Spotting and Surviving Sepsis

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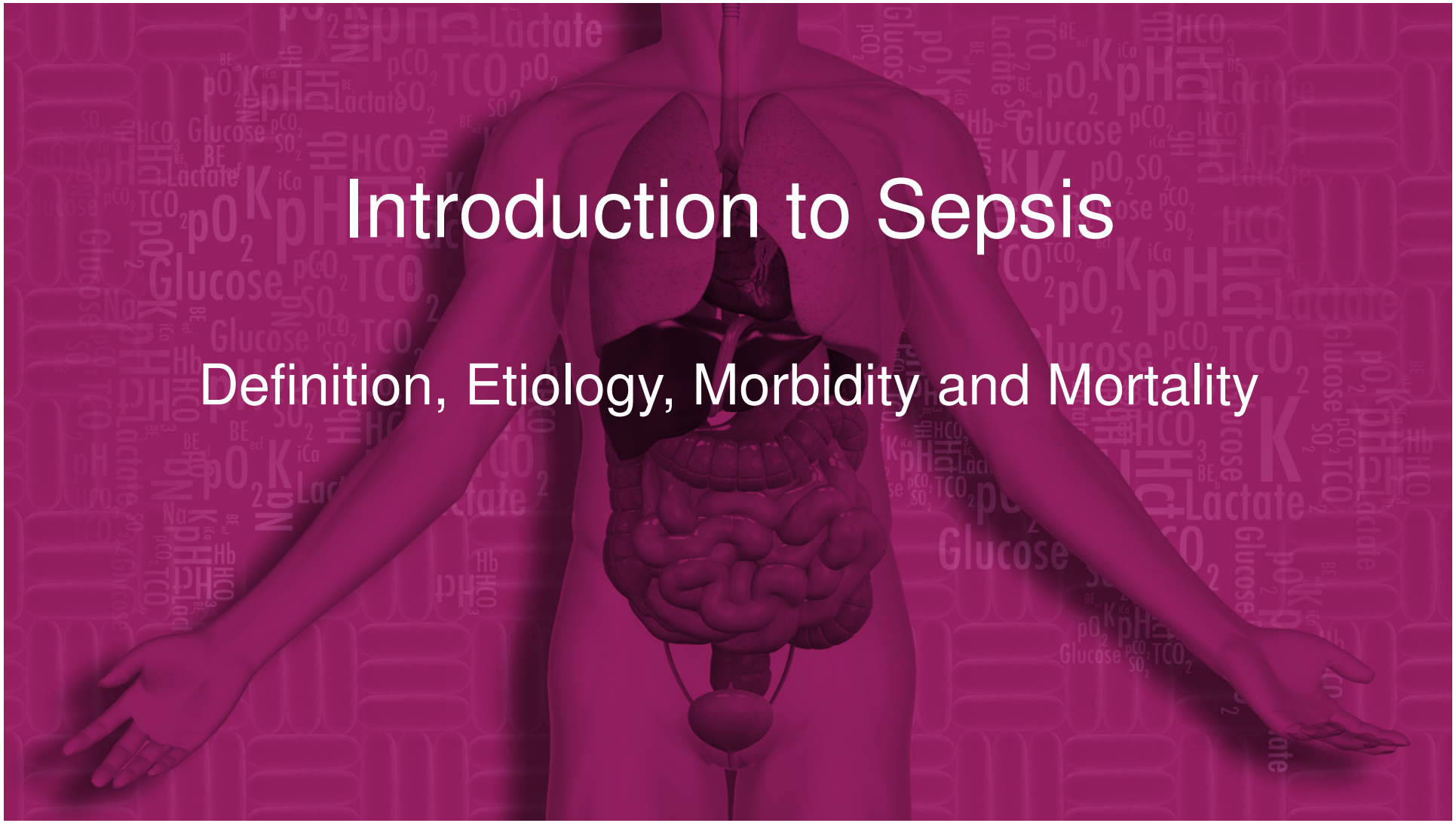
Alere

September 12, 2013

Learning Objectives

- Discuss the scope of sepsis morbidity and mortality.
- Describe the role of sepsis biomarkers in screening, diagnosis, risk stratification, and monitoring of response to therapy in sepsis.
- List factors to be considered when evaluating sepsis testing and results.
- Identify situations where point-of-care analyte testing might benefit patients with a suspected or confirmed diagnosis of sepsis.
- Apply information to assist in the identification and treatment of patients with sepsis and improve patient outcomes.


Introduction to Sepsis
Definition, Etiology, Morbidity and Mortality

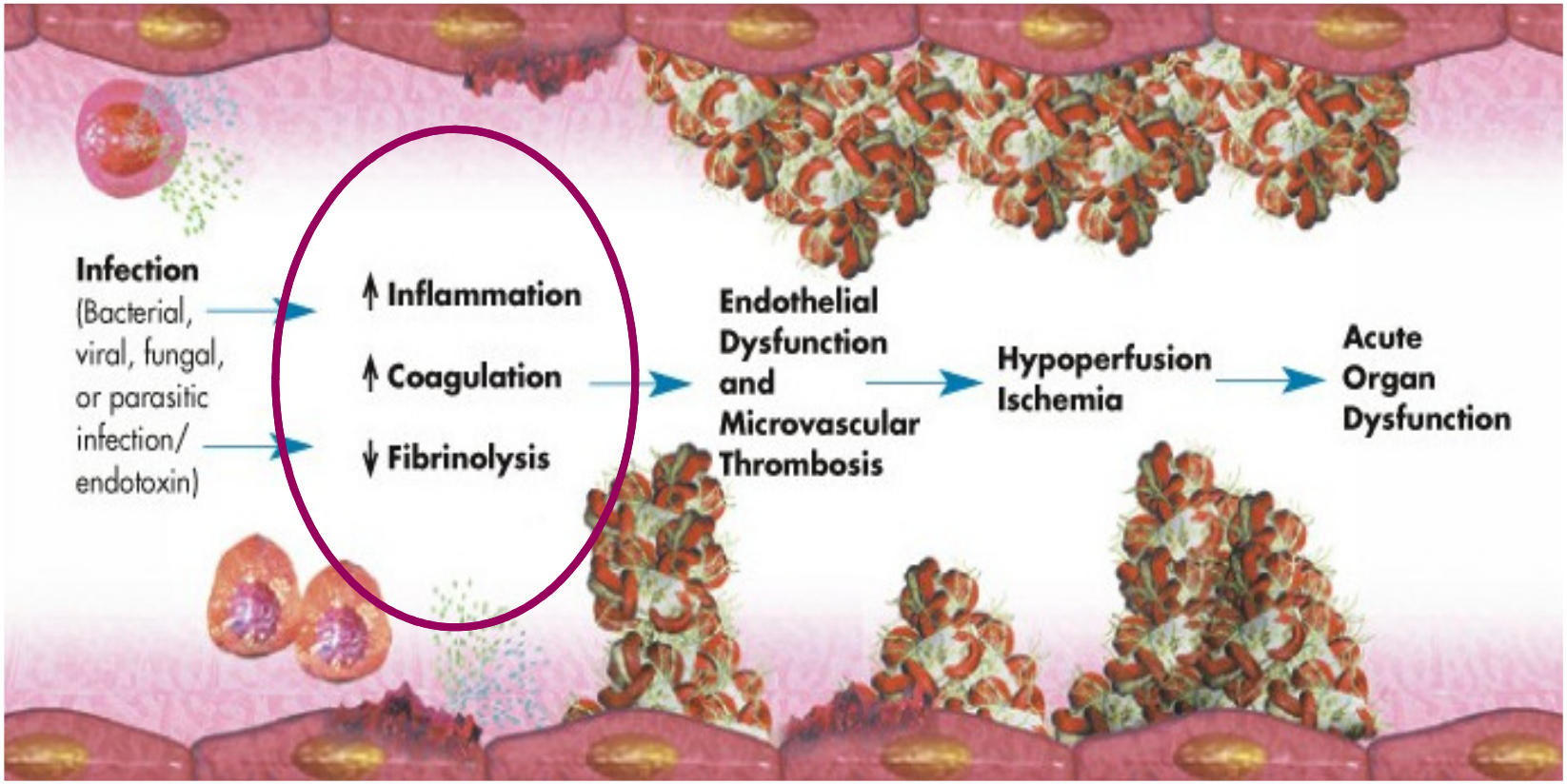
Definition of Sepsis

- Sepsis
  - Systemic, deleterious host response to infection
  - Presence (probable or documented) of infection together with systemic manifestations of infection which may include:

Fever >38.3°C or Core temp <36°C	HR >90/min or more than 2SD above normal for age	Altered Mental Status and/or Tachypnea
WBC count >12,000/mm^3 or <4,000/mm^3 or >10% immature forms	Hyperlactatemia > 1mmol/L	Plasma Procalcitonin more than 2SD above normal

Levy MM, Dellinger RP, Townsend SR et al. *Crit Care Med*. 2013;41:580-637.

Sepsis Pathophysiology

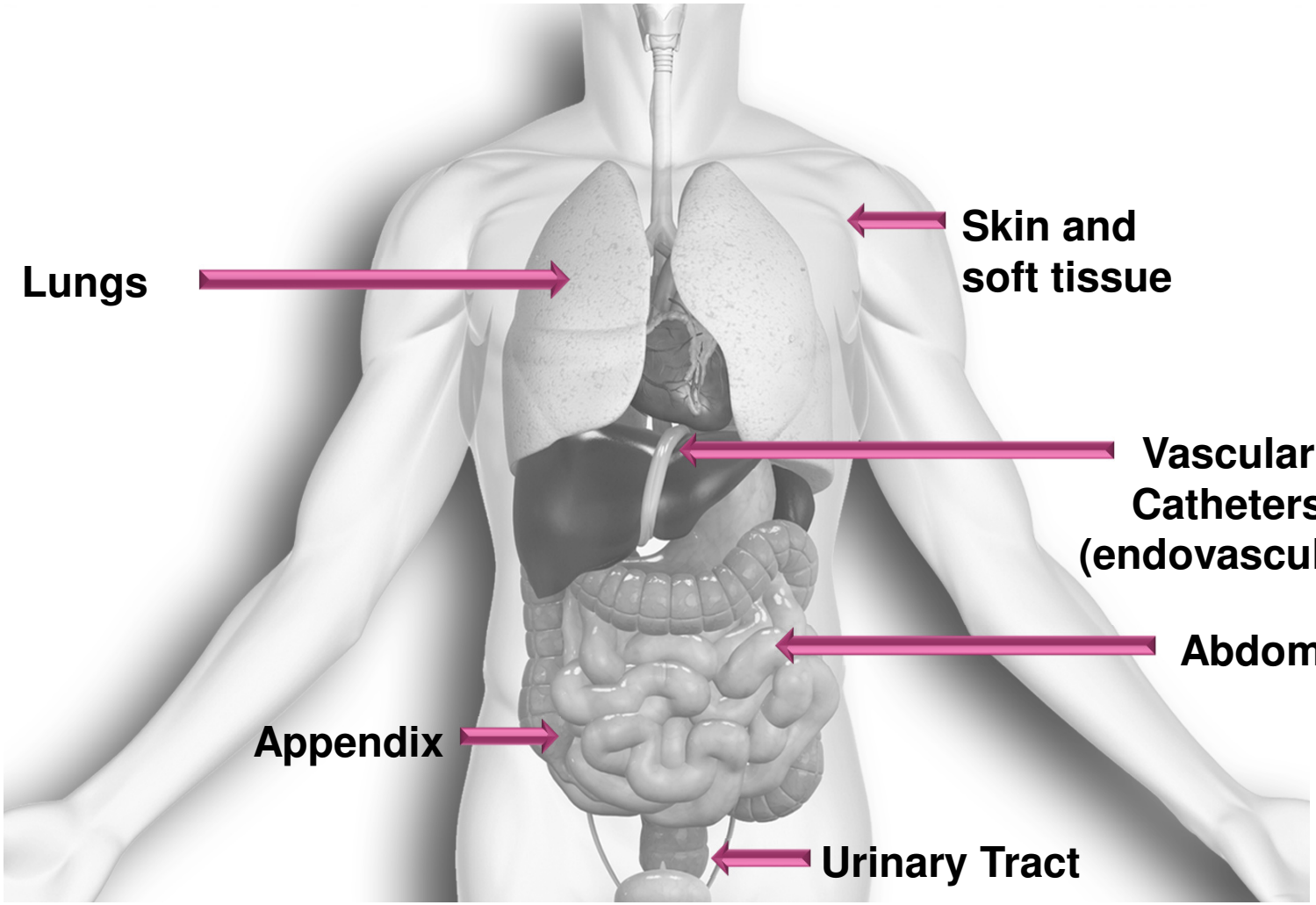


“Except on few occasions, the patient appears to die from the body's response to infection rather than from it.”

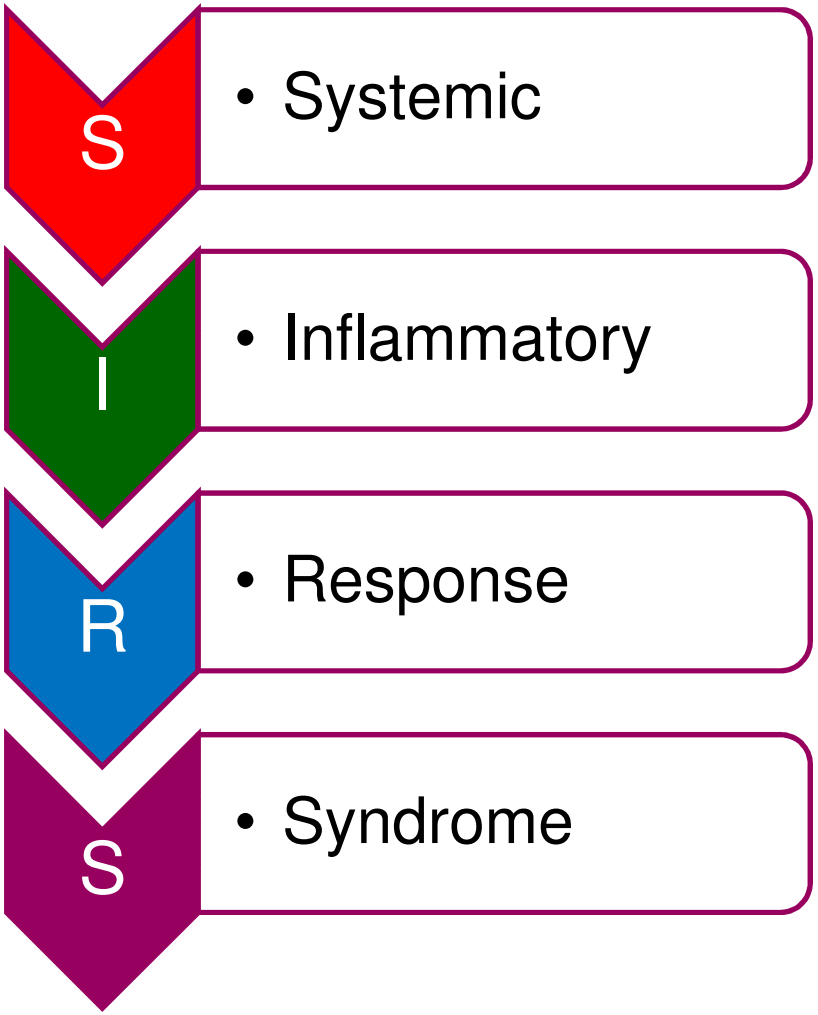
Sir William Osler, 1904

“The Evolution of Modern Medicine”

Common Locations for Sepsis Infections



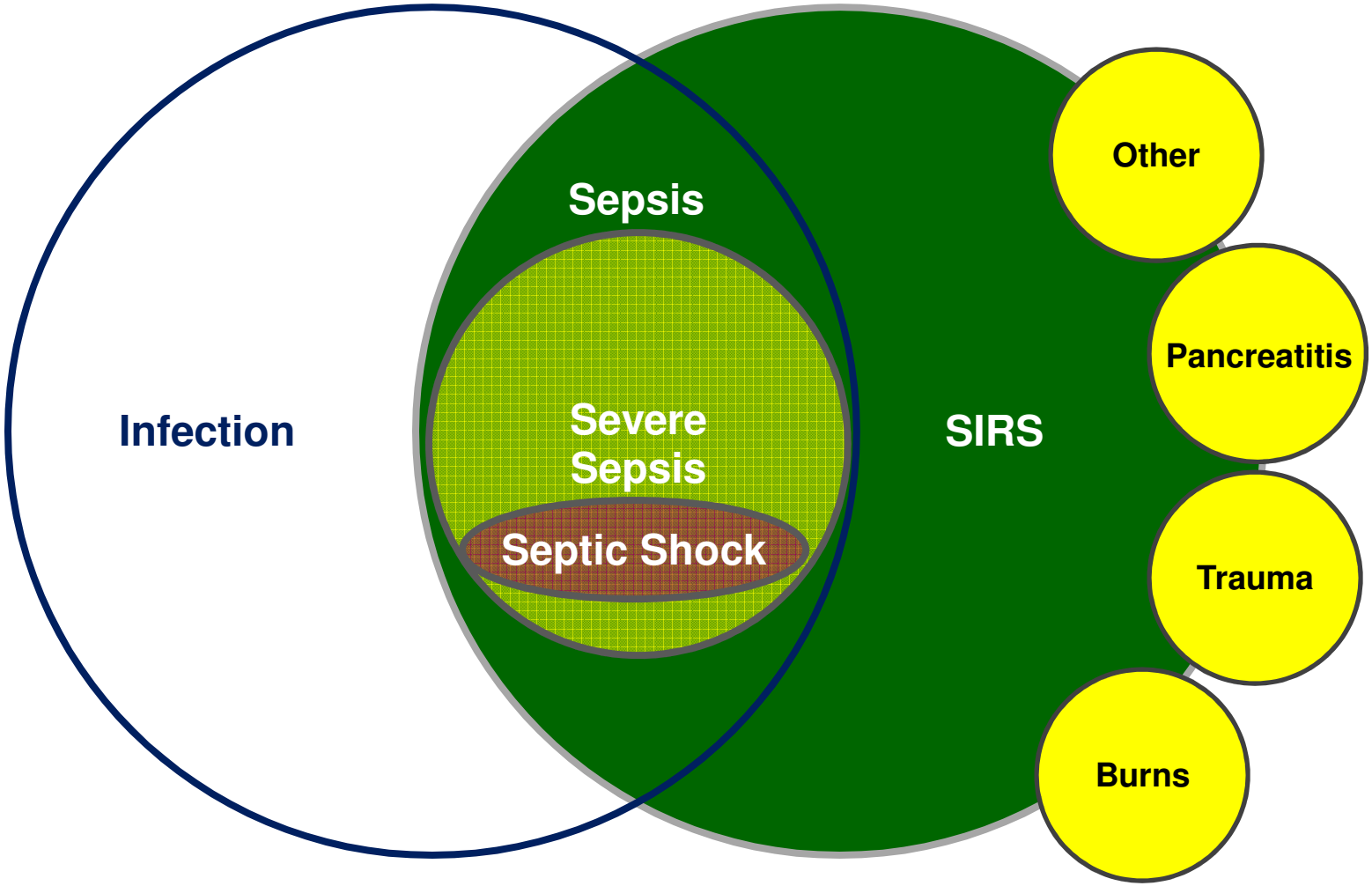
http://www.nigms.nih.gov/Education/factsheet_sepsis.htm



A clinical response arising from a nonspecific insult, including ≥ 2 of the following:

- Temperature > 38ºC or < 36ºC
- Heart rate > 90 beats/min
- Respiratory rate > 20 breaths/min or $PaCO_2$ < 32 Torr
- WBC > 12,000 cells/mm^3, < 4,000 cells/mm^3, or > 10% immature

The Relationship Between SIRS, Sepsis, and Severe Sepsis



Bone RC, Balk RA, Cerra FB et al. *Chest.* 1992;101:1644-55.

The Sepsis Continuum

Local or systemic Infection or traumatic injury

Systemic Inflammatory Response Syndrome

A clinical response arising from a nonspecific insult, including ≥ 2 of the following:

- Temperature > 38ºC or < 36ºC
- Heart rate > 90 beats/min
- Respiratory rate > 20 breaths/min or $PaCO_2$ < 32 Torr
- WBC > 12,000 cells/mm^3, < 4,000 cells/mm^3, or > 10% immature

Systemic, Deleterious host response to infection

Sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion

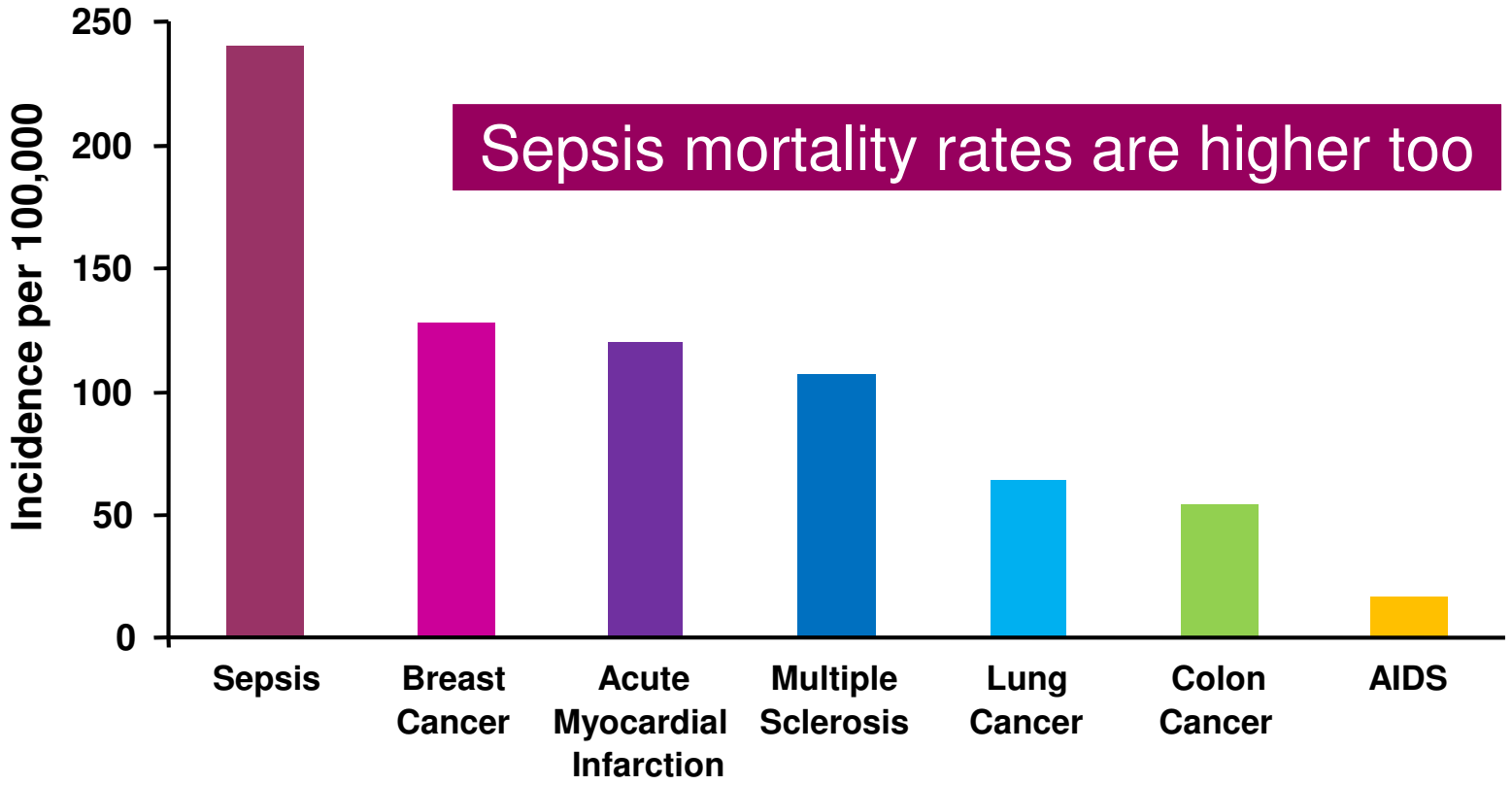
- Cardiovascular (refractory hpotension)
- Renal
- Respiratory
- Hepatic
- Hematologic
- CNS
- Unexplained metabolic acidosis

Severe sepsis plus hypotension not reversed with fluids

Immediate intervention needed to prevent death:

- Fluid resuscitation
- Reversal of hypotension
- Antibiotics

Sepsis Incidence in the United States: 2000

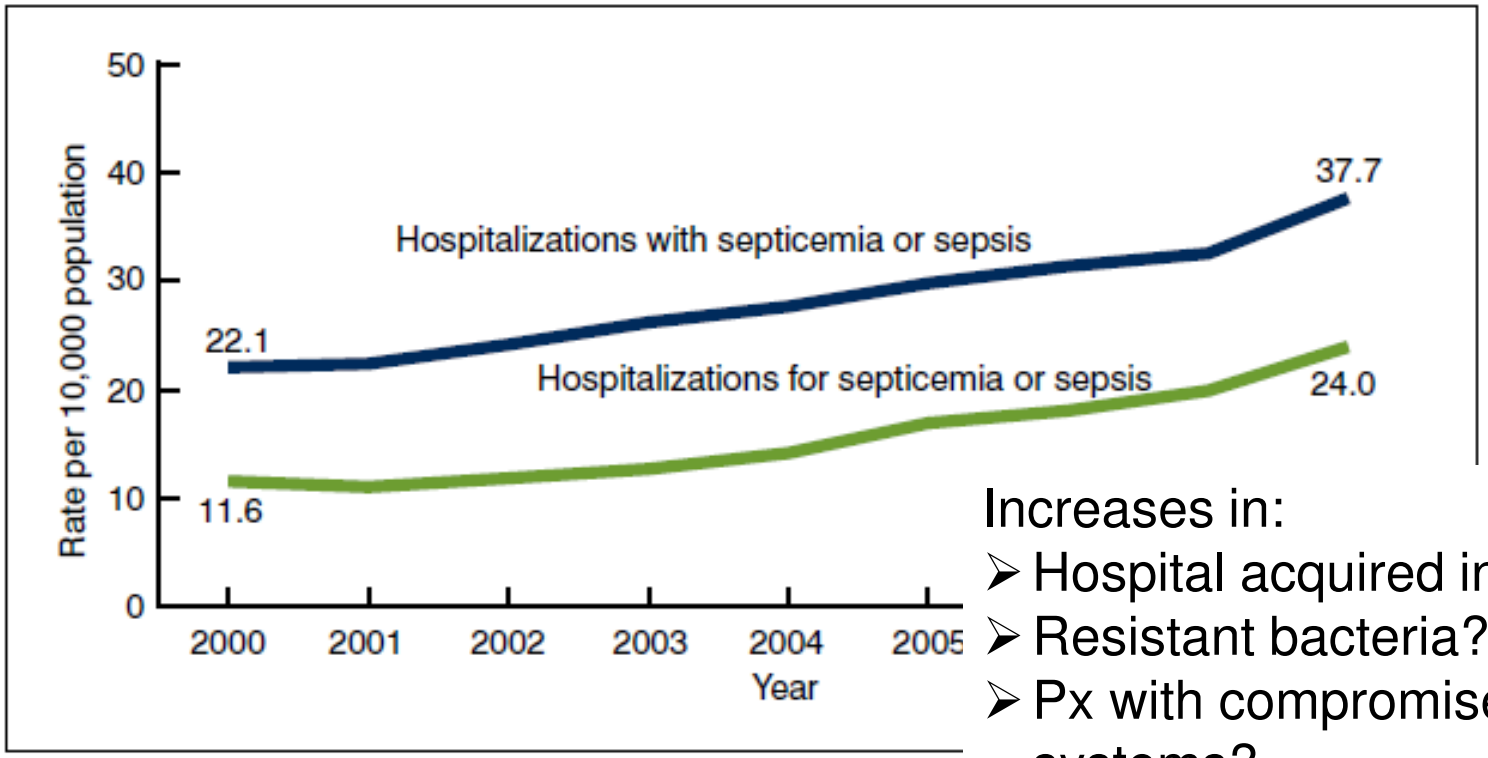


Martin GS, Mannino DM, Eaton S et al. *N Engl J Med*. 2003;348:1546-54.
SEER Cancer Statistics Review. *National Cancer Institute*. www.cancer.gov. 2007.
HIV/AIDS Surveillance Report. *Centers for Disease Control*. 2001;11.
Incidence & Prevalence: 2006 Chart Book on Cardiovascular and Lung Diseases. *NHLBI, NIH*. 2006.
Turabelidze G. *J Neurol Sci*. 2008;269:158-62.

Sepsis Incidence (cont'd)

$14.6 Billion!

Figure 1. Hospitalizations for and with septicemia or sepsis



NOTE: Significant linear trend from 2000 through 2008 for both categories.
SOURCE: CDC/NCHS, National Hospital Discharge Survey, 2000–2008.

← 2x!

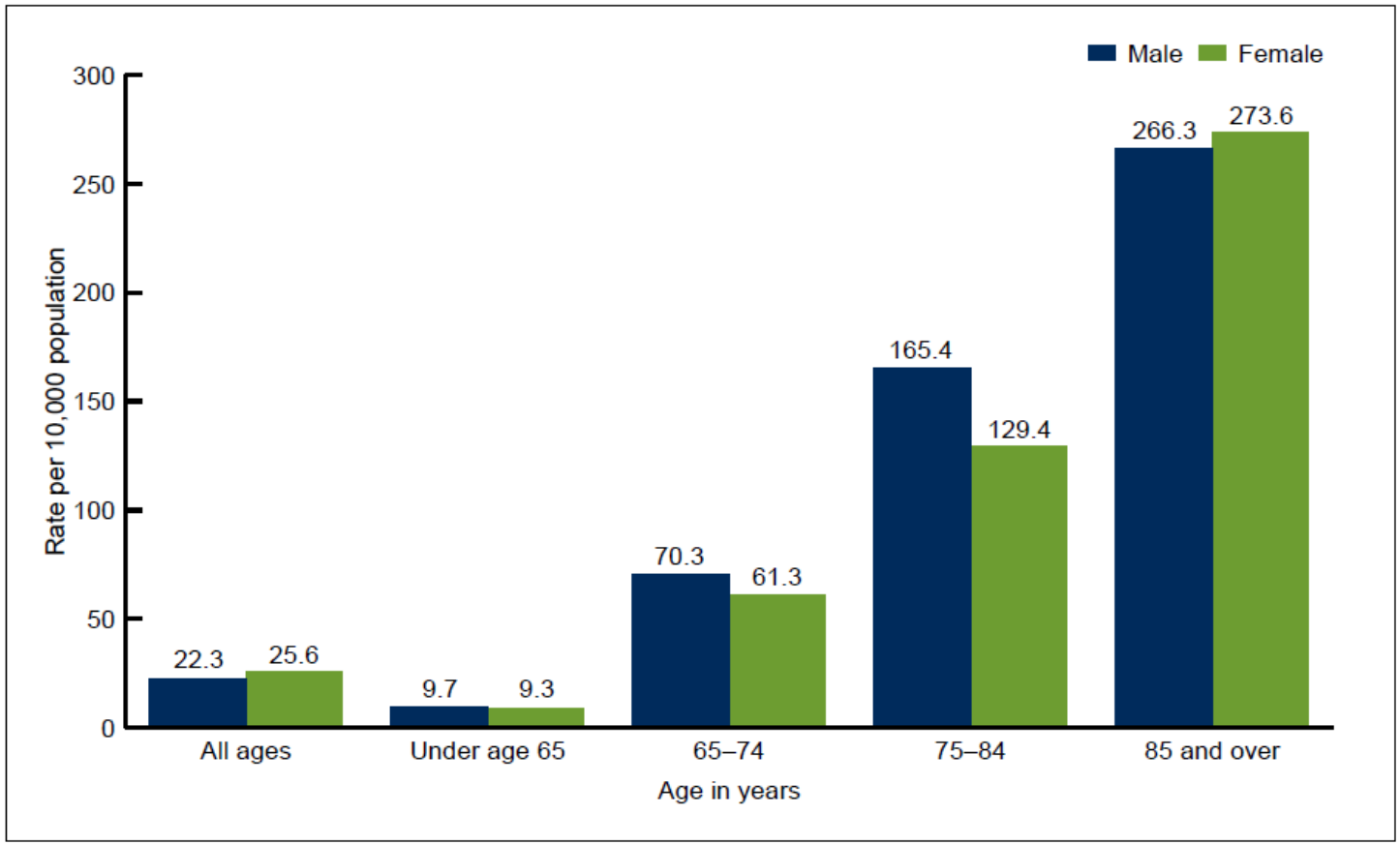
Increases in:

- Hospital acquired infections?
- Resistant bacteria?
- Px with compromised immune systems?
- Px with indwelling devices such as catheters or ventilators?

Sepsis Incidence Rises w/Age

Hospitalization rates for sepsis or septicemia were similar for males and females and increased with age.

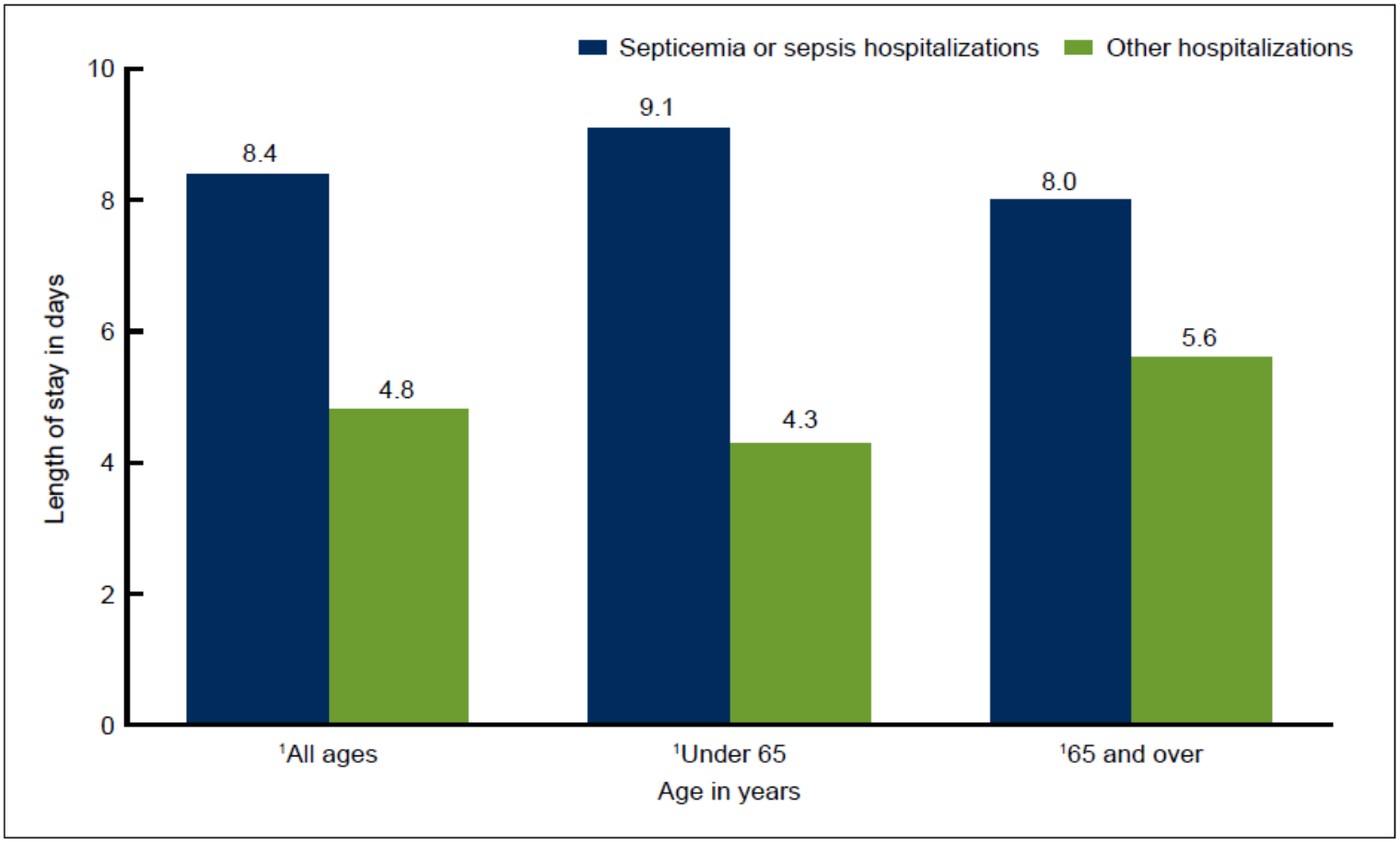
Figure 2. Rates of hospitalization for septicemia or sepsis, by sex and age, 2008



NOTES: Rates are significantly higher for males and females in each successive age group.
SOURCE: CDC/NCHS, National Hospital Discharge Survey, 2008.

Sepsis = Longer Hospital Stays

Figure 4. Average length of stay for those hospitalized for septicemia or sepsis compared with those hospitalized for other conditions, 2008



[1]Difference is statistically significant at the 0.05 level.
SOURCE: CDC/NCHS, National Hospital Discharge Survey, 2008.

Mortality Rates

- Only 2% of hospitalizations in 2008 were for septicemia or sepsis, yet they made up 17% of in-hospital deaths.

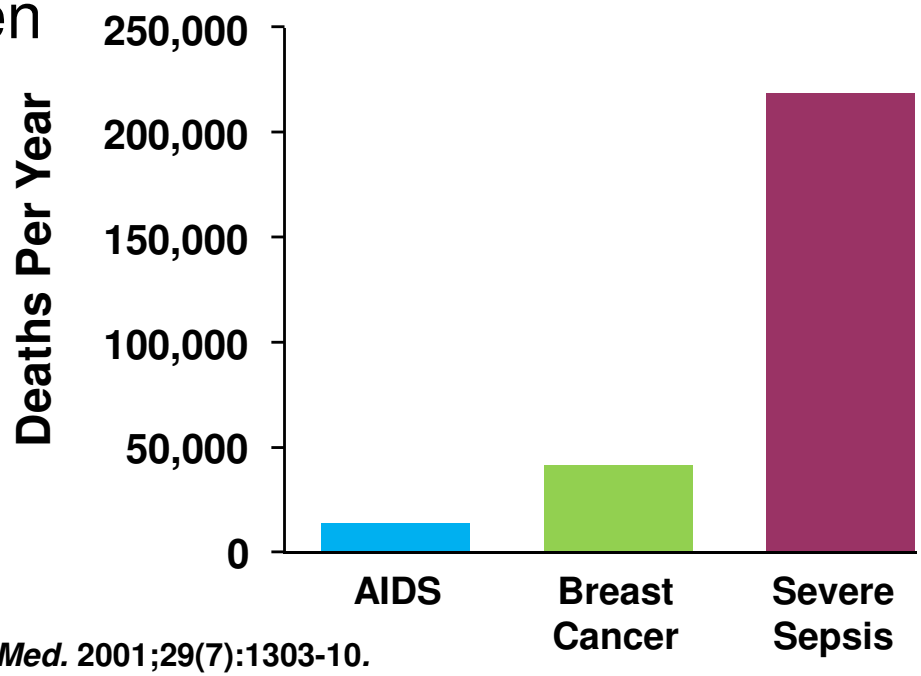
	In hospital mortality	
Population	**Sepsis**	**Other Diagnosis**
General	17%	2%
< 65 years old	13%	1%
> 65 years old	20%	3%

CDC/NCHS, National Hospital Discharge Survey, 2008..

Mortality Rates

- Sepsis remains the leading cause of death in critically ill patients in the United States.
- Each year 750,000 people will develop sepsis.
- Leading non-cardiac cause of death in ICUs
- Mortality rates between 28-50%!

Mortality rates in Med-Surg units is much higher than in EDs or Critical Care



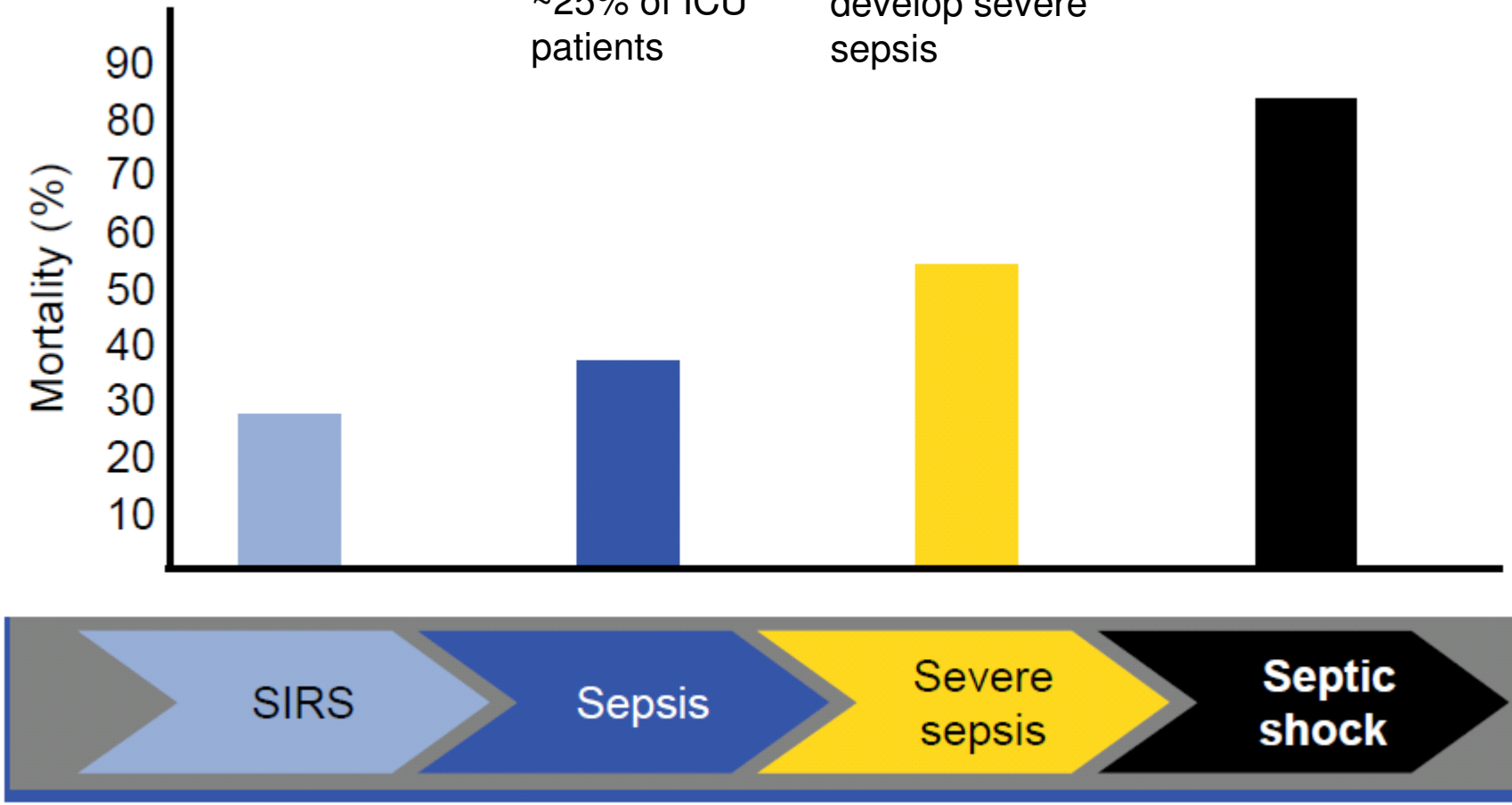
National Center for Health Statistics, 2001.
American Cancer Society, 2001.
Angus DC, Linde-Zwirble WT, Lidicker J et al. *Crit Care Med.* 2001;29(7):1303-10.

33% of SIRS patients will develop sepsis.

This is ~11% of all in-hospital patients and ~25% of ICU patients

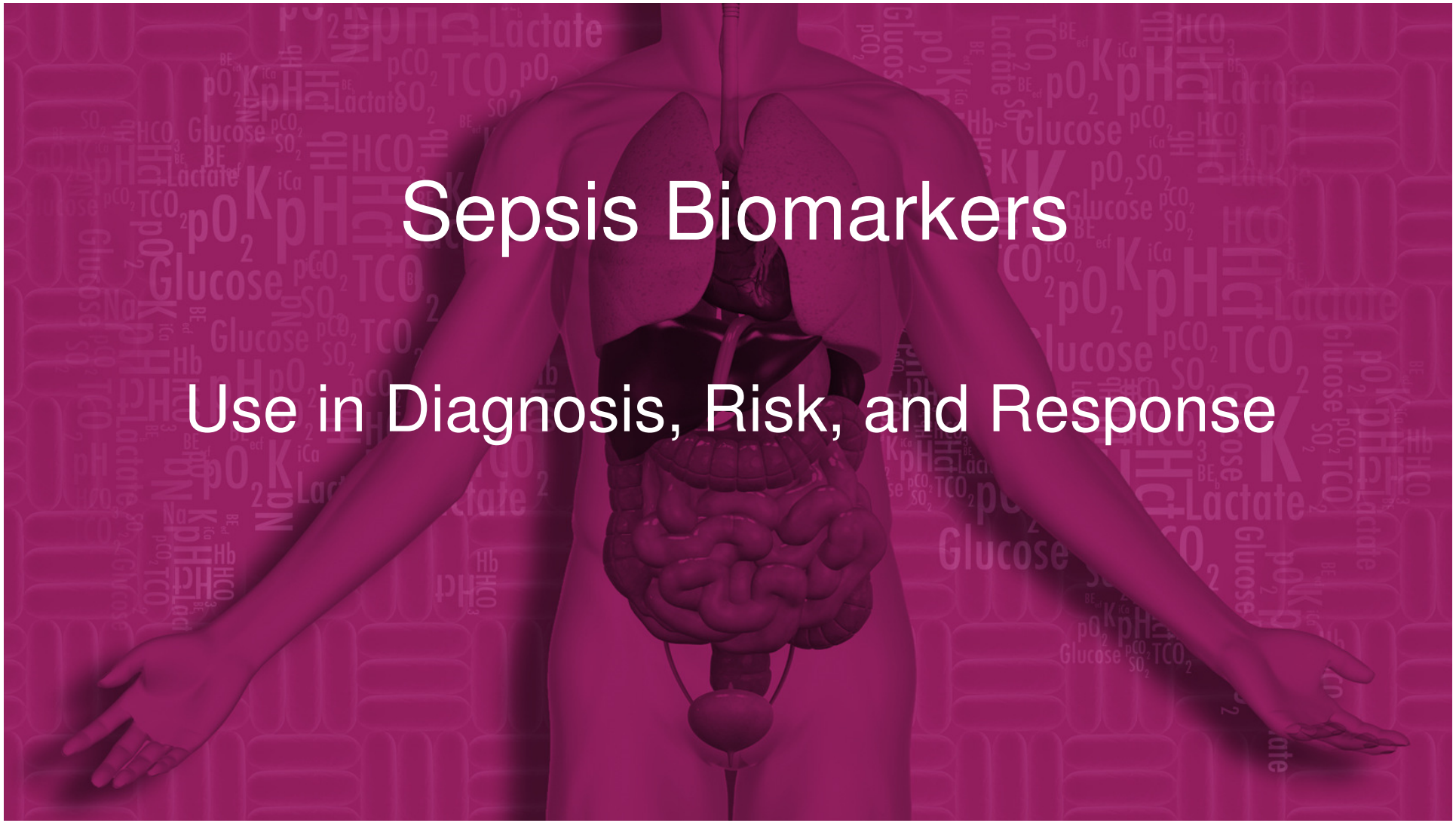
25% of septic non-ICU patients and 50% of septic ICU patients develop severe sepsis

25% of patients with severe sepsis develop septic shock

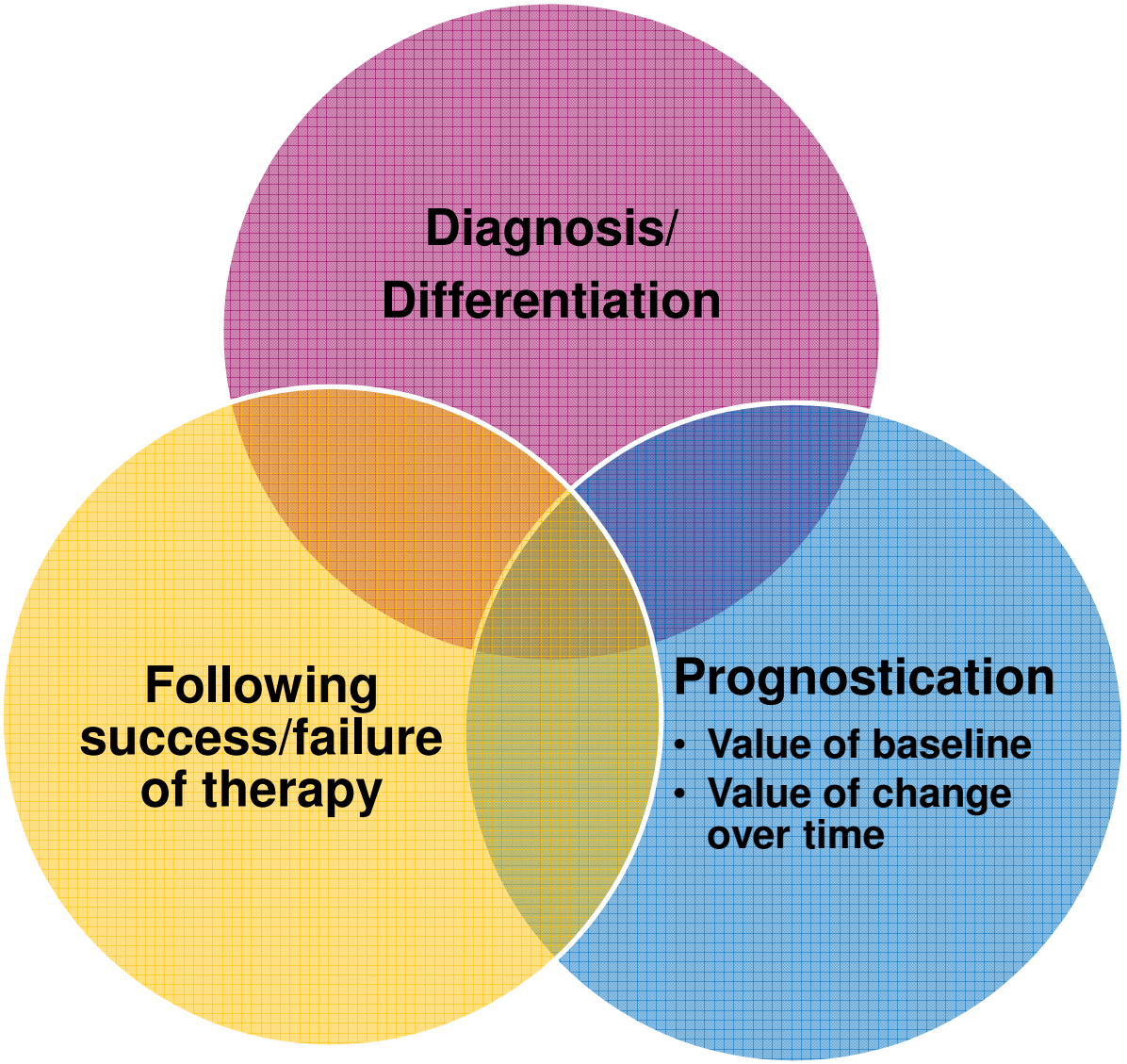


Salvo I, et al. Intensive Care Med. 1995;21 Suppl 2:S244-9.

How to Decide Who is Really Sick

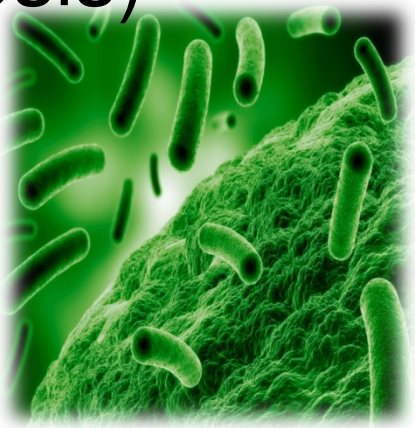

Sepsis Biomarkers
Use in Diagnosis, Risk, and Response

Utility of Biomarkers



Diagnosis of Sepsis

- Bacteria in the blood or other body fluids
  - Source of the infection
  - A high or low white blood cell count
- A low platelet count
- Low blood pressure
- Too much acid in the blood (acidosis)
- Altered kidney or liver function
- Biomarkers



Sepsis Biomarkers: Screening

Diagnosis of sepsis and evaluation of its severity is complicated by the highly variable and non-specific nature of signs and symptoms.

Distinguishing patients with localized infections or SIRS from those with sepsis is challenging.	SIRS is not specific to sepsis and can result from other conditions such as acute pancreatitis and immunodeficiencies.	Biomarkers of sepsis may improve diagnosis and therapeutic decision making.	Time is vital. Every hour of delayed diagnosis decreases survival by 7.6%*

Lever A, Mackenzie I. *Br Med J.* 2007;335:879–83.
*Kumar, et al. Crit Care Med. 2006;34(6):1593

Sepsis Biomarkers

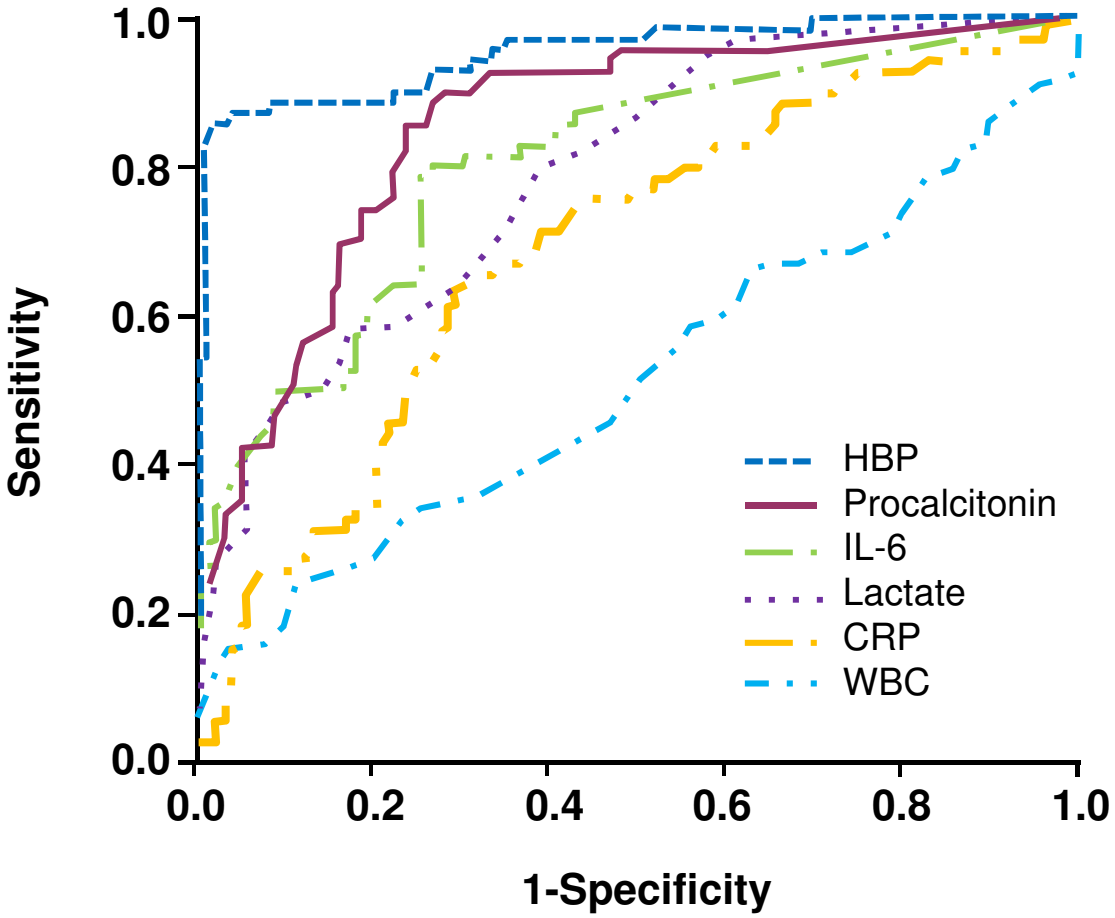
- More than 170 biomarkers have been assessed for sepsis prognosis and diagnosis

- Some common biomarkers include:

WBC	Lactate	Procalcitonin
Interleukins and other cytokines	C-reactive protein (CRP)	Procoagulant factors

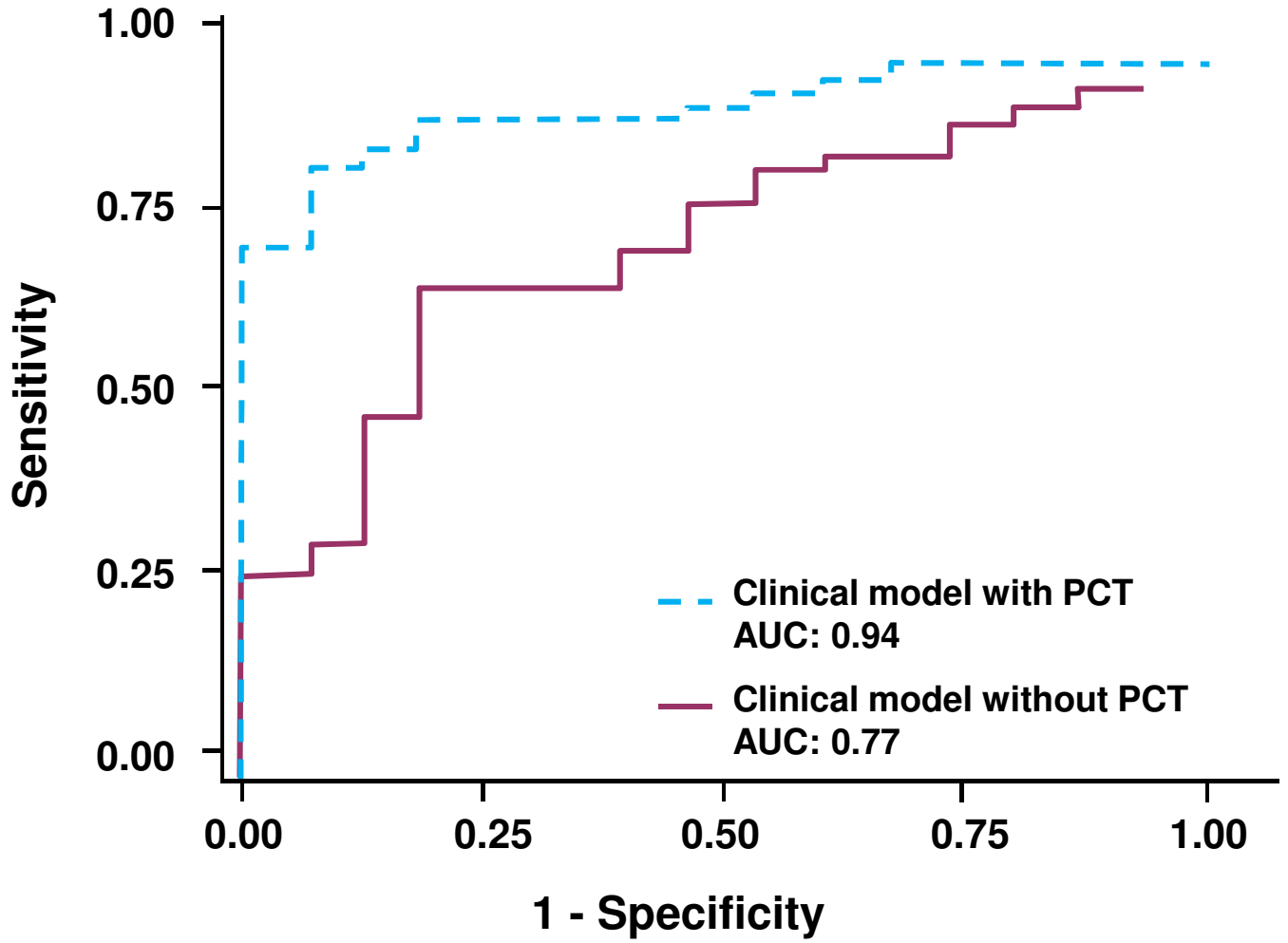
Pierrakos C, Vincent JL. *Crit Care*. 2010,14:R15.

Biomarker Performance in Severe Sepsis With or Without Septic Shock



Linder A, Christensson B, Herwald H et al. *Clin Infec Dis.* 2009;49(7):1044-50.

Procalcitonin Accuracy



Harbarth S, Holeckova K, Froidevaux C et al. *Am J Respir Crit Care Med.* 2001;164:396-402.

Procalcitonin Reference Range

Normal subjects	**< 0.5 pg/ml**
Chronic inflammatory processes and autoimmune diseases	**< 0.5 pg/ml**
Viral infections	**< 0.5 pg/ml**
Mild to moderate localized bacterial infections	**< 0.5 pg/ml**
SIRS, multiple trauma, burns	**0.5 – 2 pg/ml**
Severe bacterial infections, sepsis, multiple organ failure	**> 2 pg/ml (often 10 – 100 pg/ml)**

ACCP/ Society of Critical Care Medicine Consensus Conference. *Crit Care Med.* 1992;20:864-74.
Harbarth S, Holeckova K, Froidevaux C et al. *Am J Respir Crit Care Med*. 2001;164:396-402.
Christ-Crain M, Jaccard-Stolz D, Bingisser R et al. *Lancet*. 2004;363:600-7.

Procalcitonin Accuracy in the ED

Fig. 1

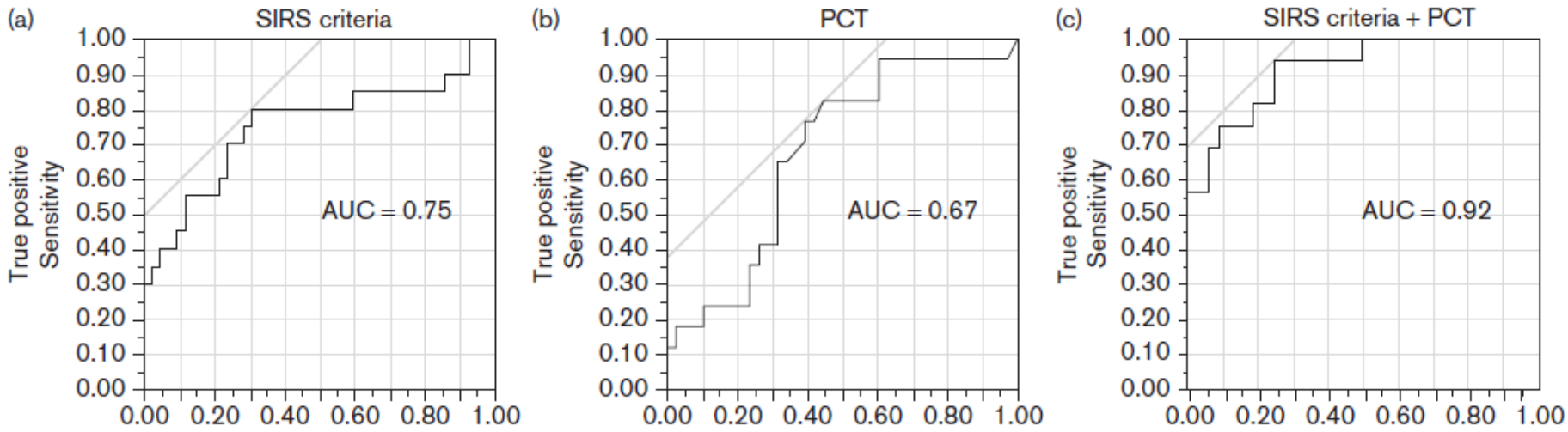


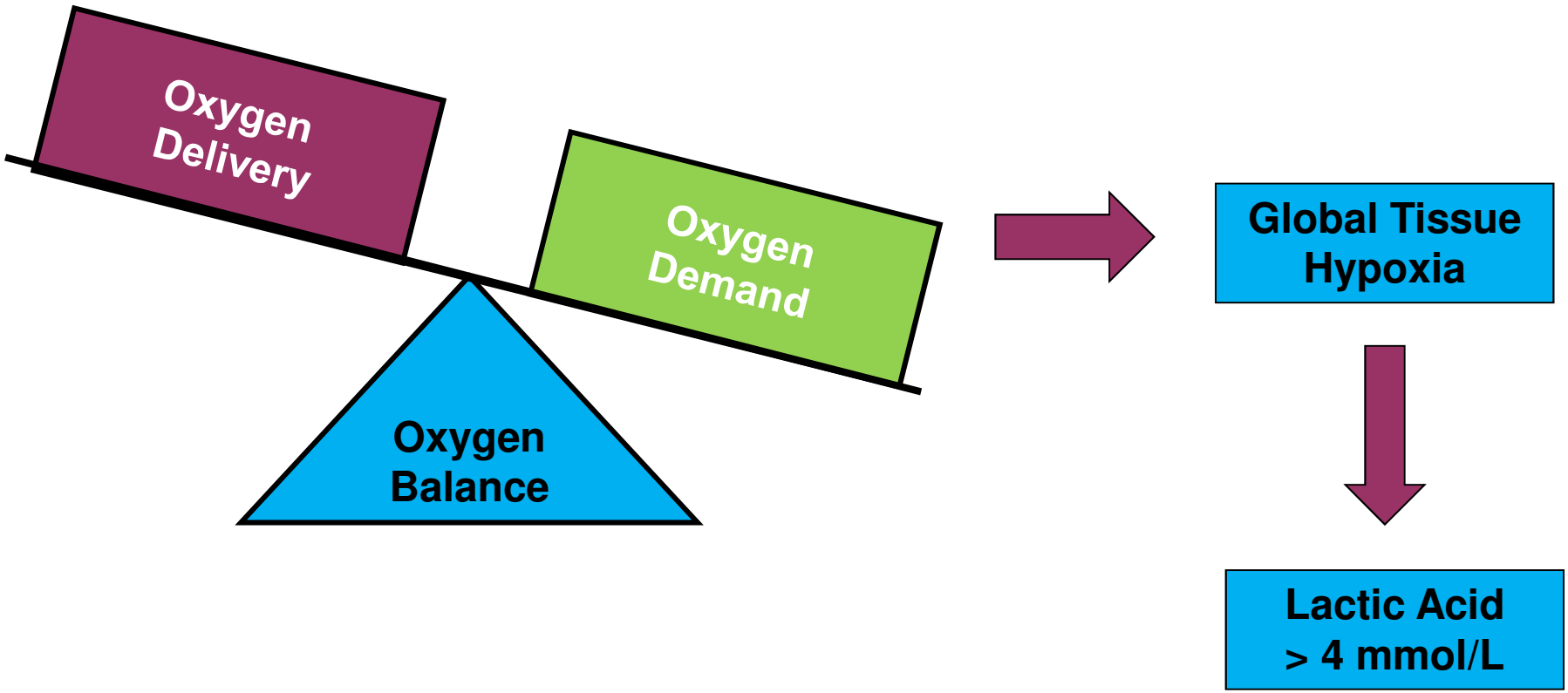
Table 2 Laboratory assays for sepsis

Assay	Septic shock ($n=2$)	Uncomplicated sepsis ($n=19$)	No sepsis ($n=45$)	P-value
Lactate (mg/dl)[a]	2.8	1.70 (1.40–2.20)	1.10 (0.73–1.55)	0.06
MRproADM (nmol/l)	1.05 (1.05–1.05)	0.91 (0.55–1.26)	0.82 (0.52–1.18)	0.78
MRproANP (pmol/l)	201 (102–300)	178 (91.6–232)	143 (77.2–349)	0.98
PCT (ng/ml)	0.34 (0.26–0.43)	0.32 (0.19–1.17)	0.18 (0.07–0.54)	0.04
Copeptin (pmol/l)	13.4 (13.1–13.7)	13.2 (6.29–34.1)	17.1 (8.2–34.8)	0.61
proET-1 (pmol/l)	118 (104–132)	75.0 (36.9–111)	80.0 (51.5–106)	0.53

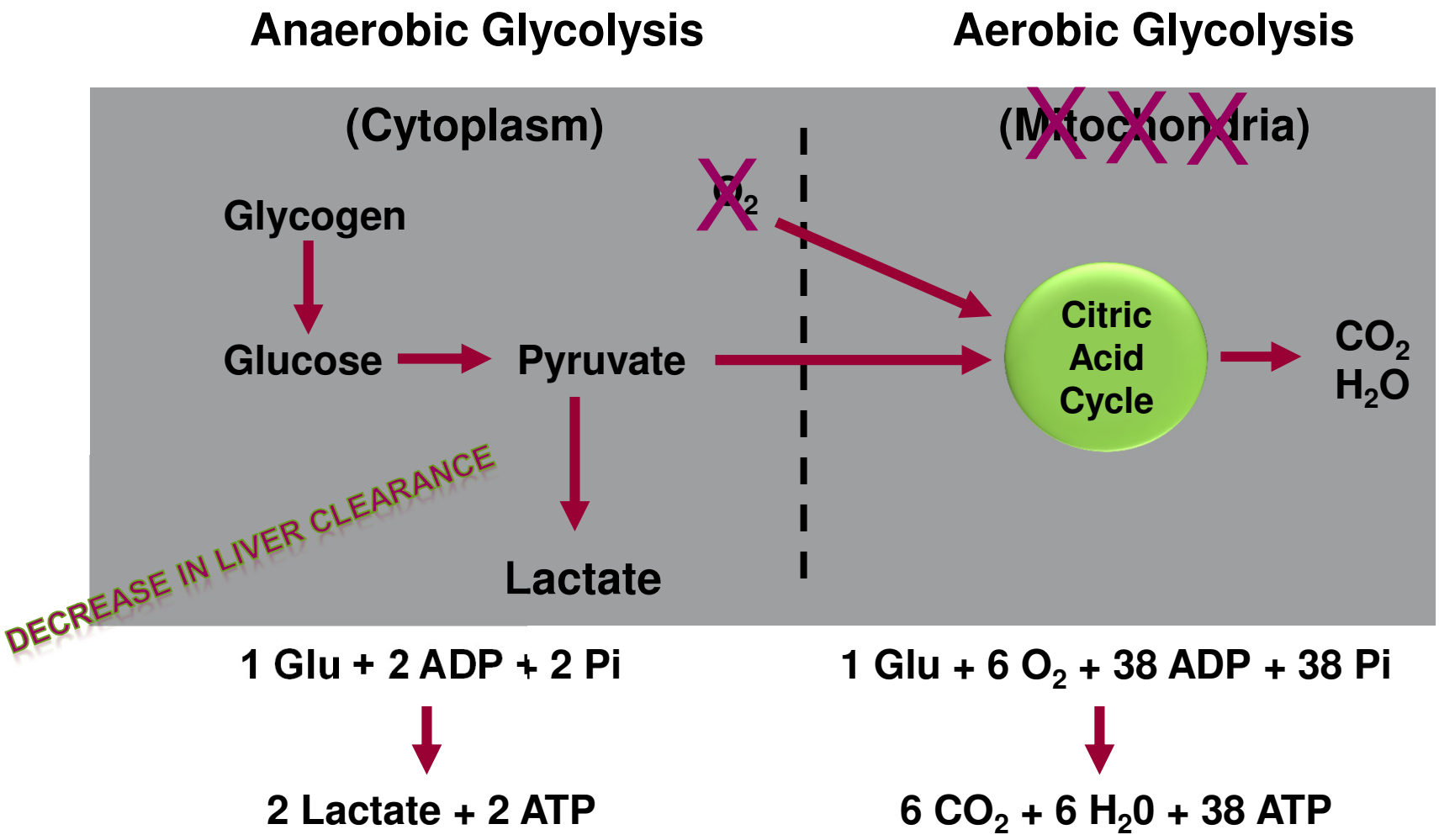
All values are expressed as median (interquartile range) or % (number) accordingly.
MRproADM, midregional proadrenomedullin; MRproANP, proatrial natriuretic peptide; PCT, procalcitonin; proET-1, proendothelin-1.
[a]Only available in 14 patients (septic shock=1, uncomplicated sepsis=7, no sepsis=4).

Hicks *et al*. Eur. J Em Med. 2013, May 10;xxx:xxx-xxx.

Global Tissue Hypoxia
A More Sensitive Measure of Shock

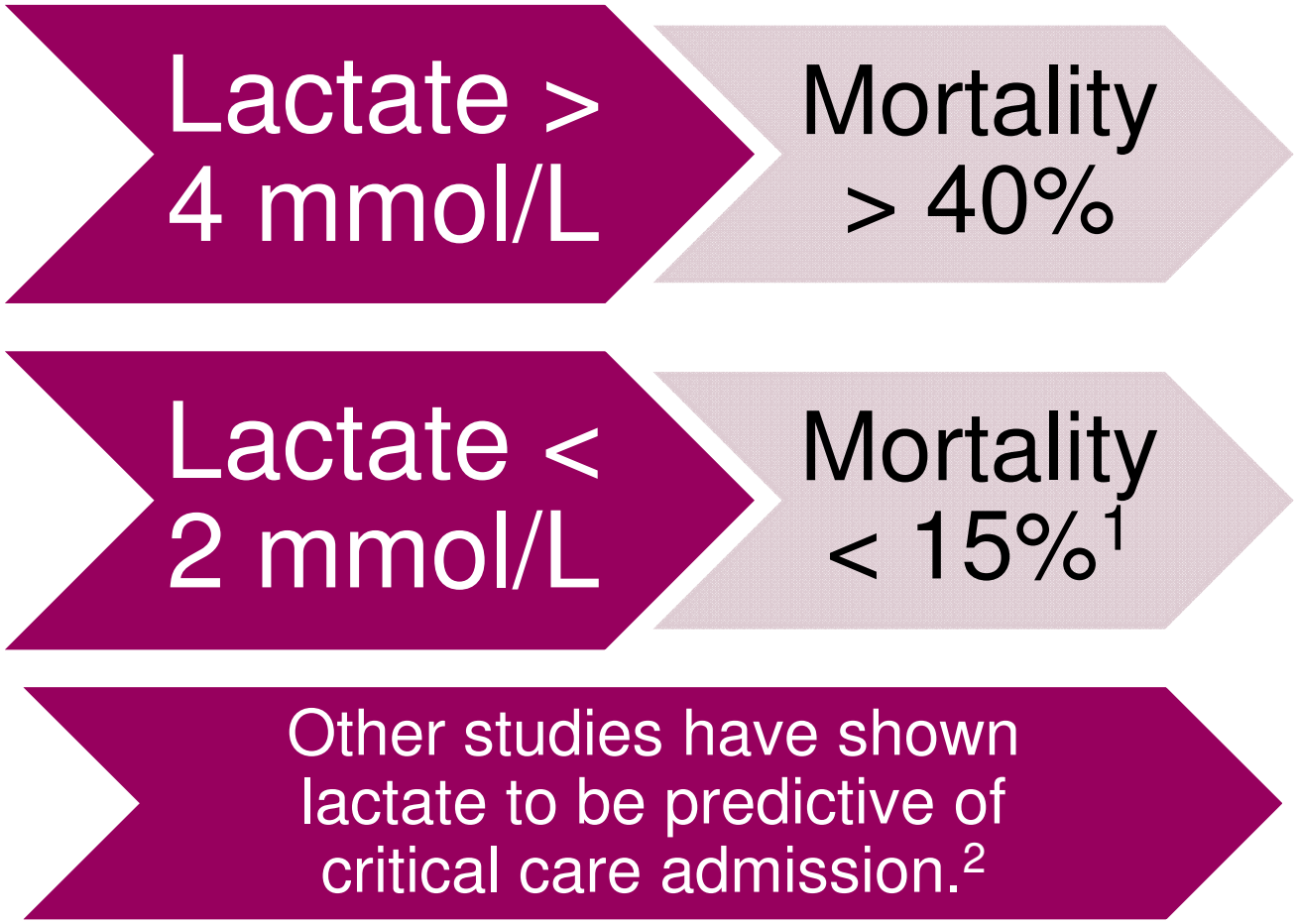


Lactic Acidosis



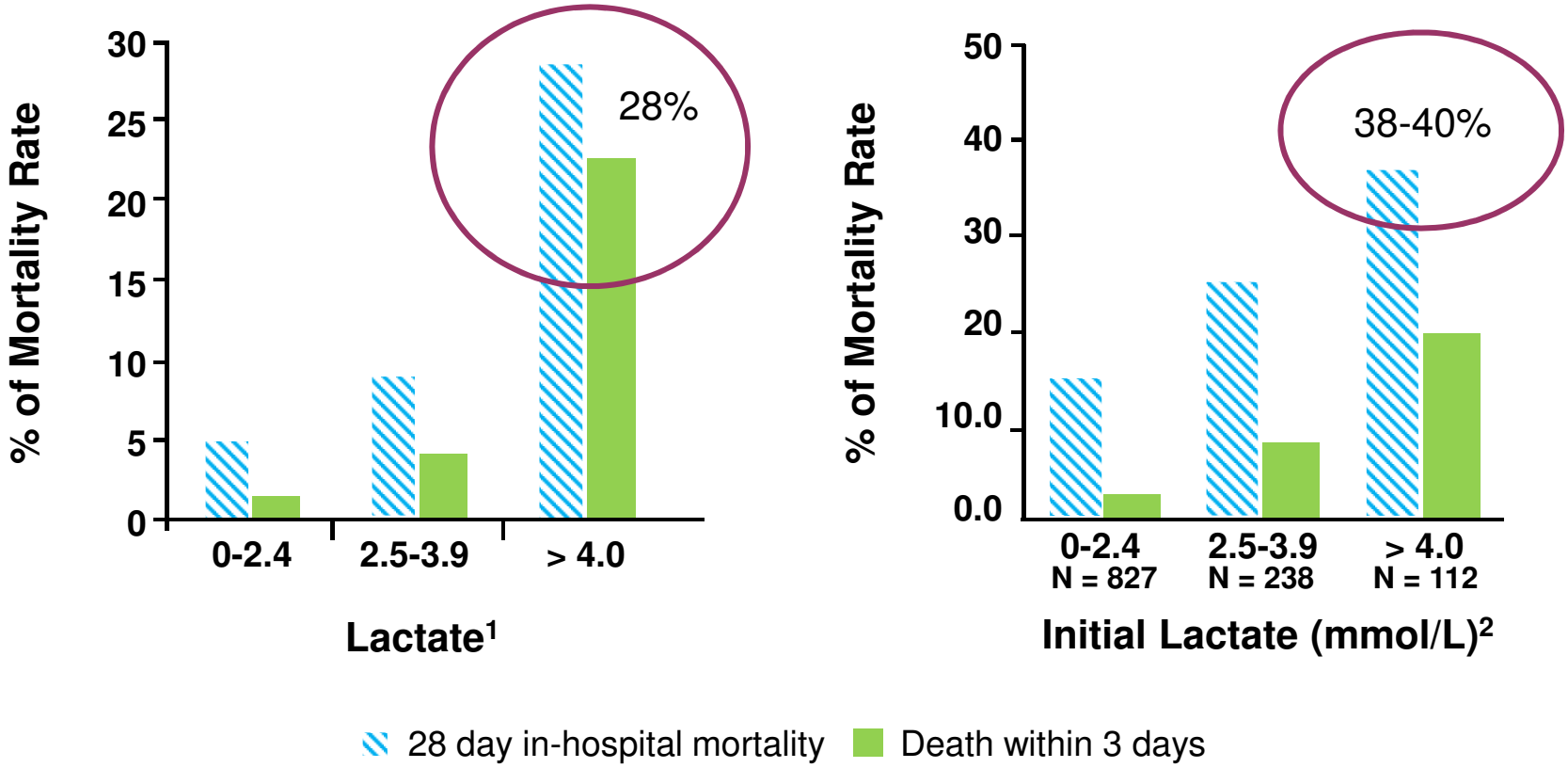
Mizock BA, Falk JL. *Crit Care Med*. 1992;20:80-95.

Serum lactate levels may carry prognostic value in sepsis



[1] Drumheller B, Goyal M, Pines J et al. *Ann Emerg Med.* 2007;50:S21-2.
[2] Chan YL, Tseng CP, Tsay PK et al. *Crit Care Med.* 2004;8:R12-20.

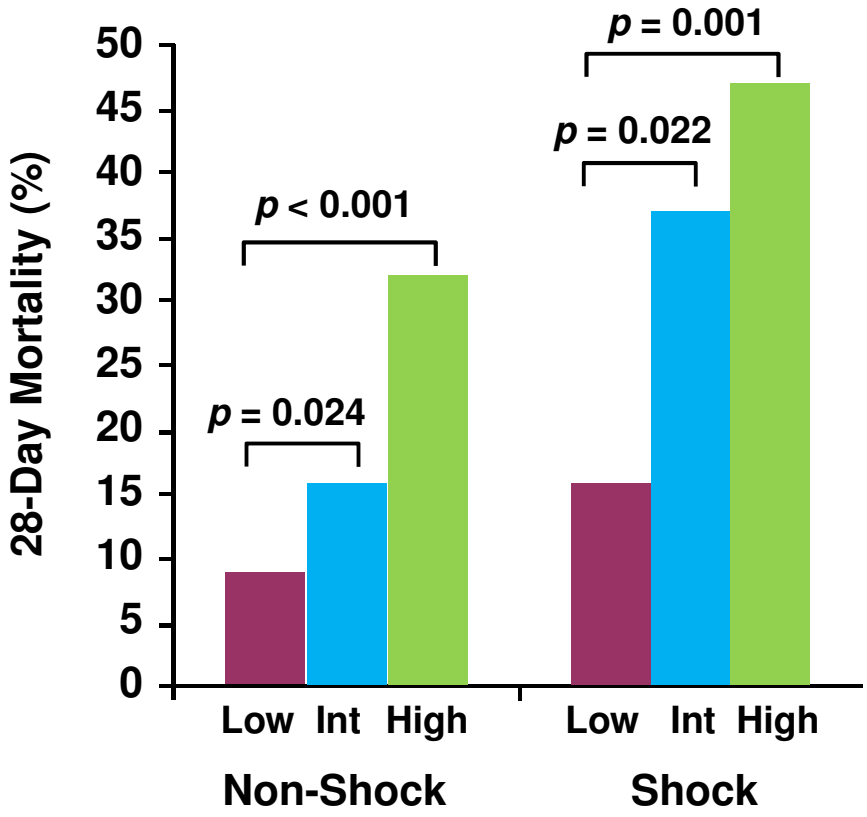
Serum Lactate as a Predictor of Mortality



[1] Trzeciak S, Dellinger RP, Chansky ME et al. *Intensive Care Med*. 2007;33:970-7.
[2] Shapiro NI, Howell MD, Talmor D et al. *Ann Emerg Med*. 2005; 45:524-8.

Serum Lactate and Mortality in Severe Sepsis

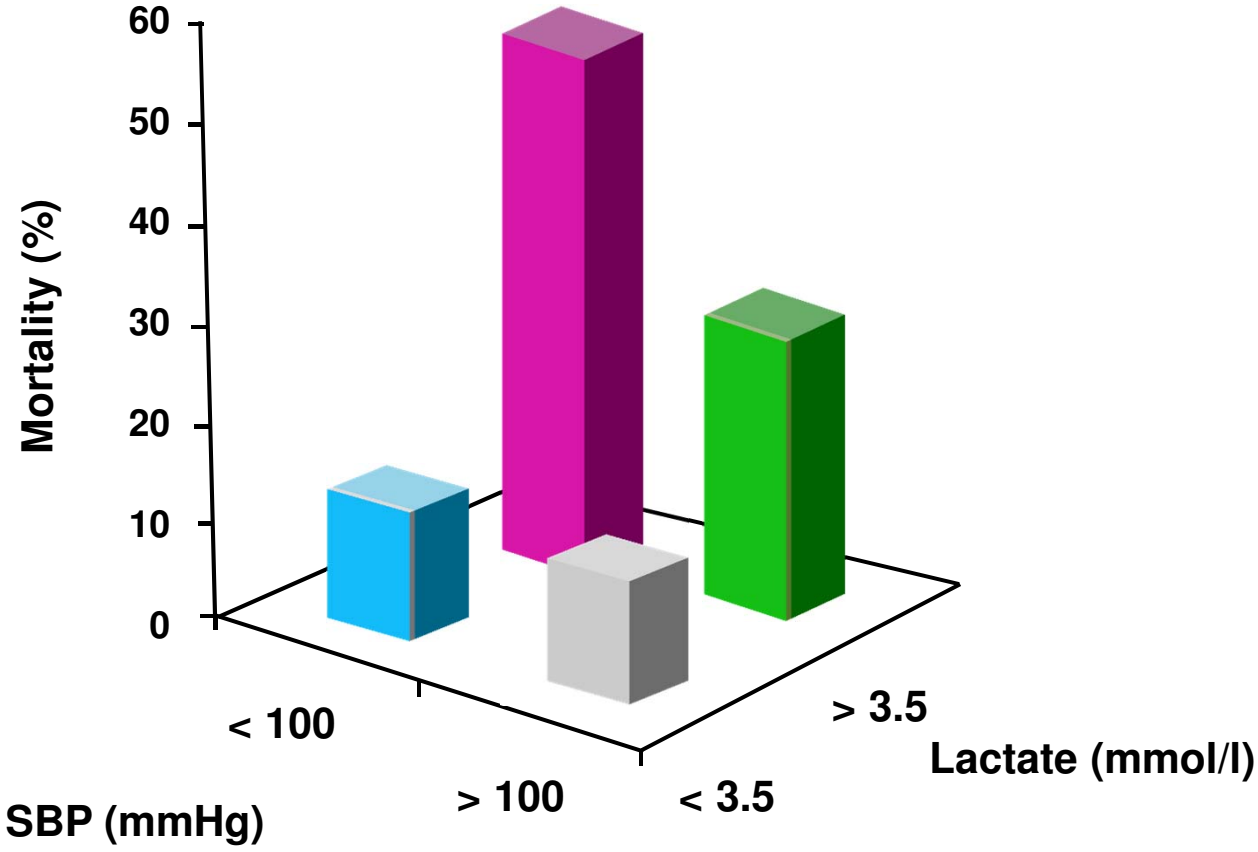
- Initial serum lactate evaluated in 839 adults admitted with severe sepsis.
- High initial serum lactate associated with ↑ mortality regardless of presence of shock or MODS.



MODS=Multiple Organ Dysfunction Syndrome, also MSOF; Multisystem Organ Failure.

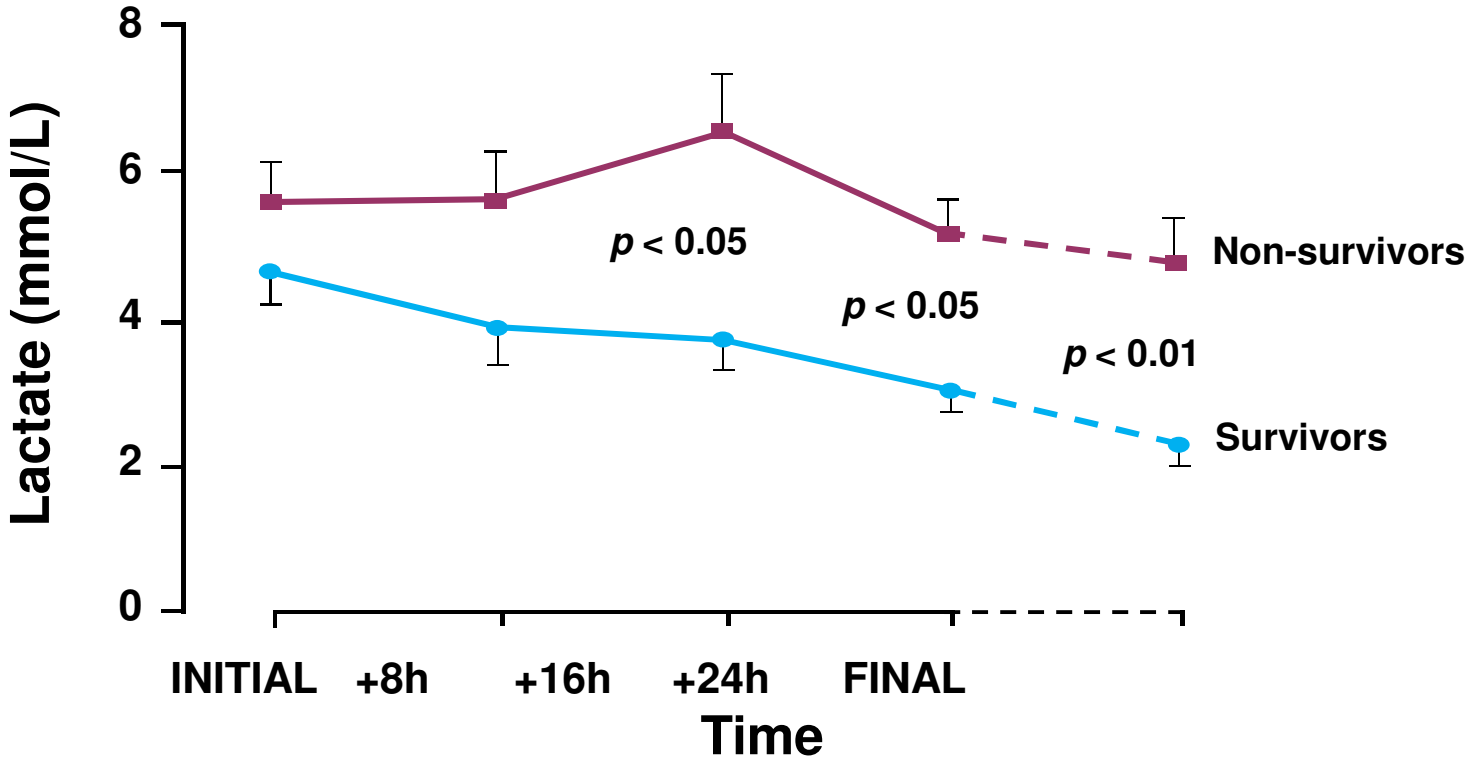
Mikkelsen ME, Miltiades AN, Gaieski DF et al. *Crit Care Med.* 2009;37:1670-7.

Lactate, SBP, and Mortality



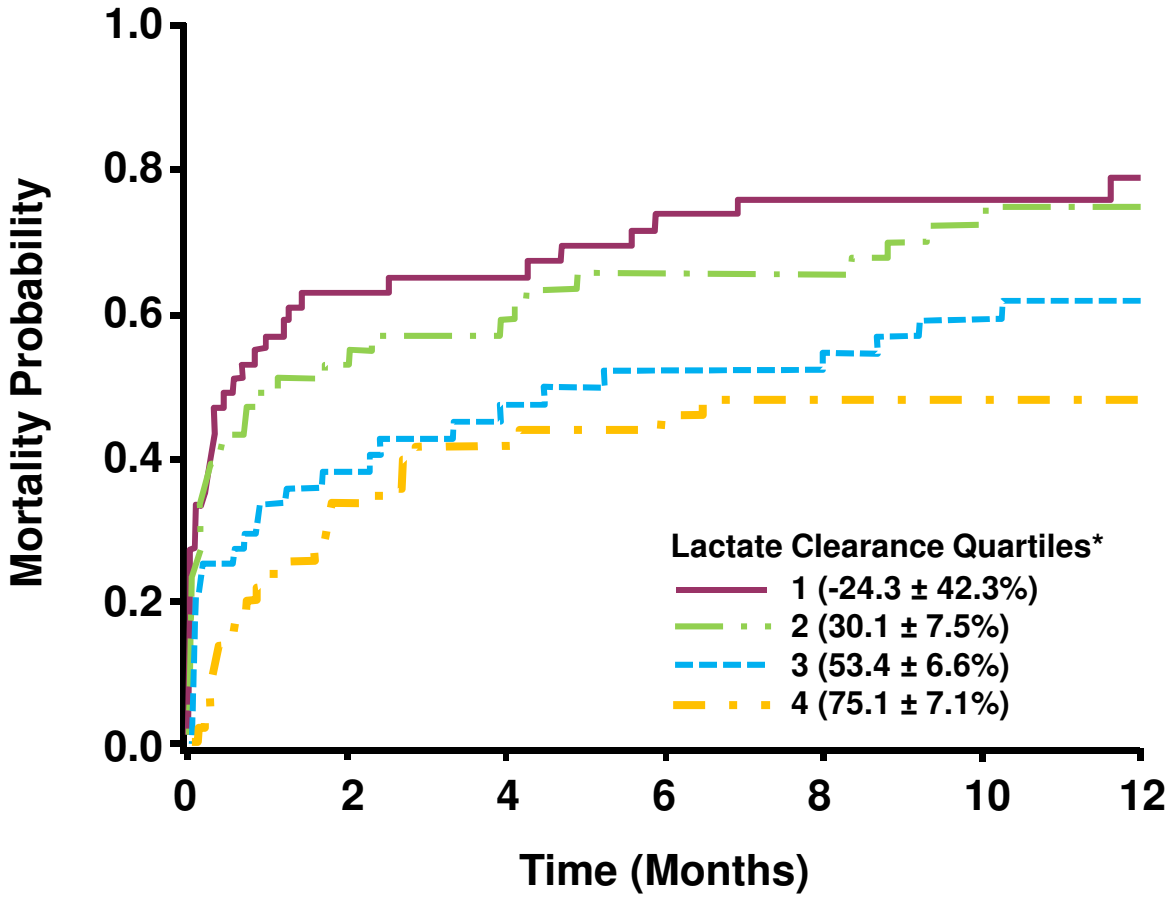
Jansen TC, van Bommel J, Mulder PG et al. *Crit Care.* 2008,12:R160.

Improving Lactate a Good Prognostic Sign



Bakker J, Gris P, Coffernils M et al. *Am J Surg*. 1996;171:221-6.

12-Month Survival Based on Lactate Clearance Quartile



*During the first 6 hours in the emergency department ($p < 0.01$).

Nguyen HB, Loomba M, Yang JJ et al. *J Inflam.* 2010;7:6.

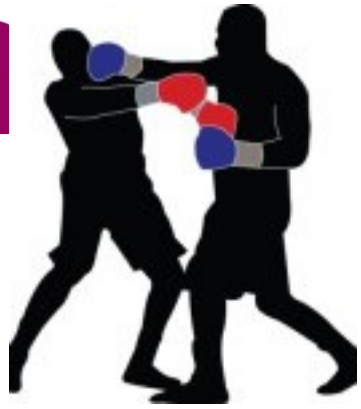
Sepsis Biomarkers: Monitoring Response to Therapy

Lactate levels are particularly useful when measured serially, to guide response to resuscitation and fluid therapy.

Lactate clearance (≥ 10% decrease in lactate concentration between initial and repeat measurements) has been shown to be a better prognostic factor than a single lactate determination.[1,2]

Early goal-directed therapy targeting global tissue hypoxia may be more effective than standard care in decreasing lactate during the first six hours of intervention.[3]

[1] Nguyen HB, Rivers EP, Knoblich BP et al. *Crit Care Med*. 2004;32(8):1637-42.
[2] Becker KL, Snider R, Nylen ES. *Crit Care Med*. 2008;36(3):941-52.
[3] Nguyen HB, Loomba M, Yang JJ et al. *J Inflam.* 2010;7:6.



The Great Debate

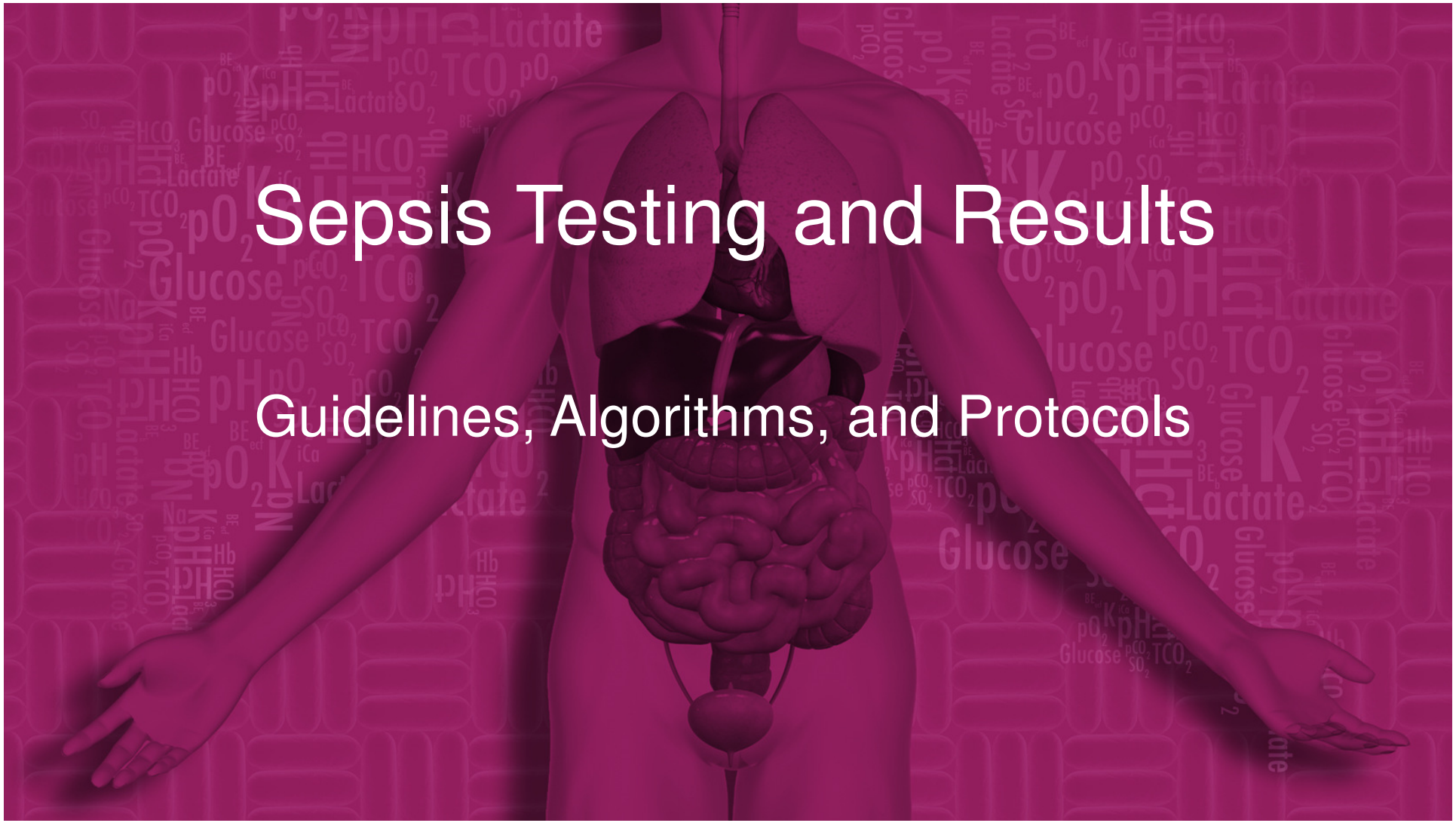
Lactate vs $ScvO_2$

Should Lactate Clearance Be Substituted for Central Venous Oxygen Saturation as Goals of Early Severe Sepsis and Septic Shock Therapy?

- Yes: Jones AE, CHEST (2011) **140:**1406-1408.
- No: Rivers EP et al, CHEST (2011) **140:**1408-1413.

Clinical Takeaway: All the combatants agree that ScvO2 and lactate provide complementary information. The forthcoming Pittsburgh Study may light our way.

http://pulmccm.org/2013/critical-care-review/should-lactate-clearance-replace-scvo2-in-egdt-procon-chest/


Sepsis Testing and Results
Guidelines, Algorithms, and Protocols

Sepsis is No Longer Just an ICU Disease

The Surviving Sepsis Campaign: Results of an international guideline-based performance improvement program targeting severe sepsis *

Levy, Mitchell M. MD; Dellinger, R Phillip MD; Townsend, Sean R. MD; Linde-Zwirble, Walter T.; Marshall, John C. MD; Bion, Julian MD; Schorr, Christa RN, MSN; Artigas, Antonio MD; Ramsay, Graham MD; Beale, Richard MD; Parker, Margaret M. MD; Gerlach, Herwig MD, PhD; Reinhart, Konrad MD; Silva, Eliezer MD; Harvey, Maurene RN, MPH; Regan, Susan PhD; Angus, Derek C. MD, MPH; on behalf of the Surviving Sepsis Campaign

Levy MM, Dellinger RP, Townsend SR et al. *Crit Care Med*. 2010;38:367-74.

2012 Update

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

R. Phillip Dellinger, MD[1]; Mitchell M. Levy, MD[2]; Andrew Rhodes, MB BS[3]; Djillali Annane, MD[4]; Herwig Gerlach, MD, PhD[5]; Steven M. Opal, MD[6]; Jonathan E. Sevransky, MD[7]; Charles L. Sprung, MD[8]; Ivor S. Douglas, MD[9]; Roman Jaeschke, MD[10]; Tiffany M. Osborn, MD, MPH[11]; Mark E. Nunnally, MD[12]; Sean R. Townsend, MD[13]; Konrad Reinhart, MD[14]; Ruth M. Kleinpell, PhD, RN-CS[15]; Derek C. Angus, MD, MPH[16]; Clifford S. Deutschman, MD, MS[17]; Flavia R. Machado, MD, PhD[18]; Gordon D. Rubenfeld, MD[19]; Steven A. Webb, MB BS, PhD[20]; Richard J. Beale, MB BS[21]; Jean-Louis Vincent, MD, PhD[22]; Rui Moreno, MD, PhD[23]; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*

Dellinger RP et al. *Crit Care Med*. (2013) 41:580-637.

Diagnostic Criteria for Sepsis

Infection, documented or suspected, and some of the following:

- General
- Inflammatory
- Hemodynamic
- Organ Dysfunction
- Tissue Perfusion

Dellinger RP et al. *Crit Care Med*. (2013) 41:580-637.

Diagnostic Criteria for Sepsis

General Variables

Fever

- >38.3° C

Hypothermia

- Core temperature < 36° C

Elevated heart rate

- >90 bpm or >2 SD normal value for age

Tachypnea

Edema or + fluid balance

- >20 mL/kg over 24 hours

Hyperglycemia

- Plasma glucose > 140 mg/dL without diabetes

Diagnostic Criteria for Sepsis

Inflammatory Variables

- Leukocytosis (WBC >12,000)
- Leukopenia (WBC < 4000)
- Normal WBC but >10% immature forms
- CRP > 2 SD above normal
- PCT > 2 SD above normal

Dellinger RP et al. *Crit Care Med*. (2013) 41:580-637.

Diagnostic Criteria for Sepsis

Hemodynamic Variables

Arterial Hypotension	SBP < 90 mm Hg
	MAP < 70 mm Hg
	SBP decrease > 40 mm Hg (adults)

Dellinger RP et al. *Crit Care Med*. (2013) 41:580-637.

Diagnostic Criteria for Sepsis

Organ Dysfunction Variables

Arterial hypoxemia

- $Pao_2/F_{IO2} < 300$

Acute oliguria

- Urine output < 0.5 mL/kg/hr for 2 hours with adequate fluids

Creatinine increase

- >0.5 mg/dL

Ileus

- No bowel sounds

Thrombocytopenia

- Platelet count < 100,000

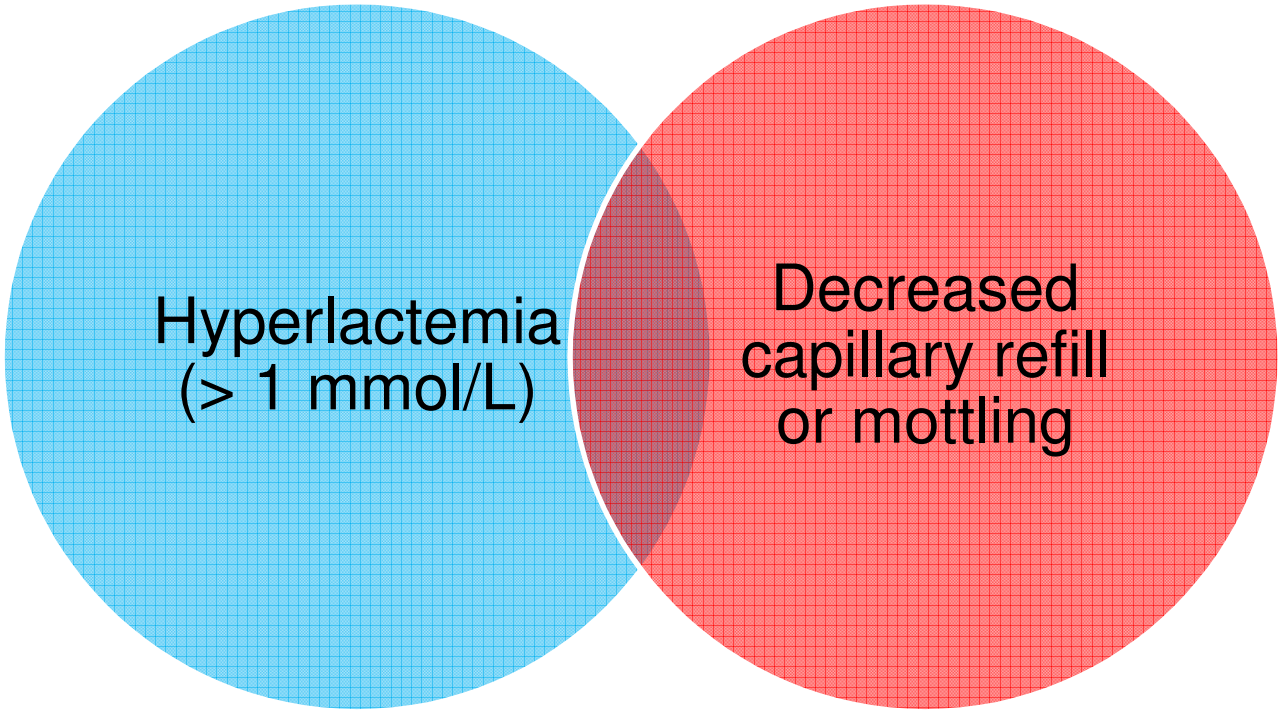
Hyperbilirubinemia

- Total bilirubin > 4 mg/mdL

Dellinger RP et al. *Crit Care Med*. (2013) 41:580-637.

Diagnostic Criteria for Sepsis

Tissue Perfusion Variables



Dellinger RP et al. *Crit Care Med*. (2013) 41:580-637.

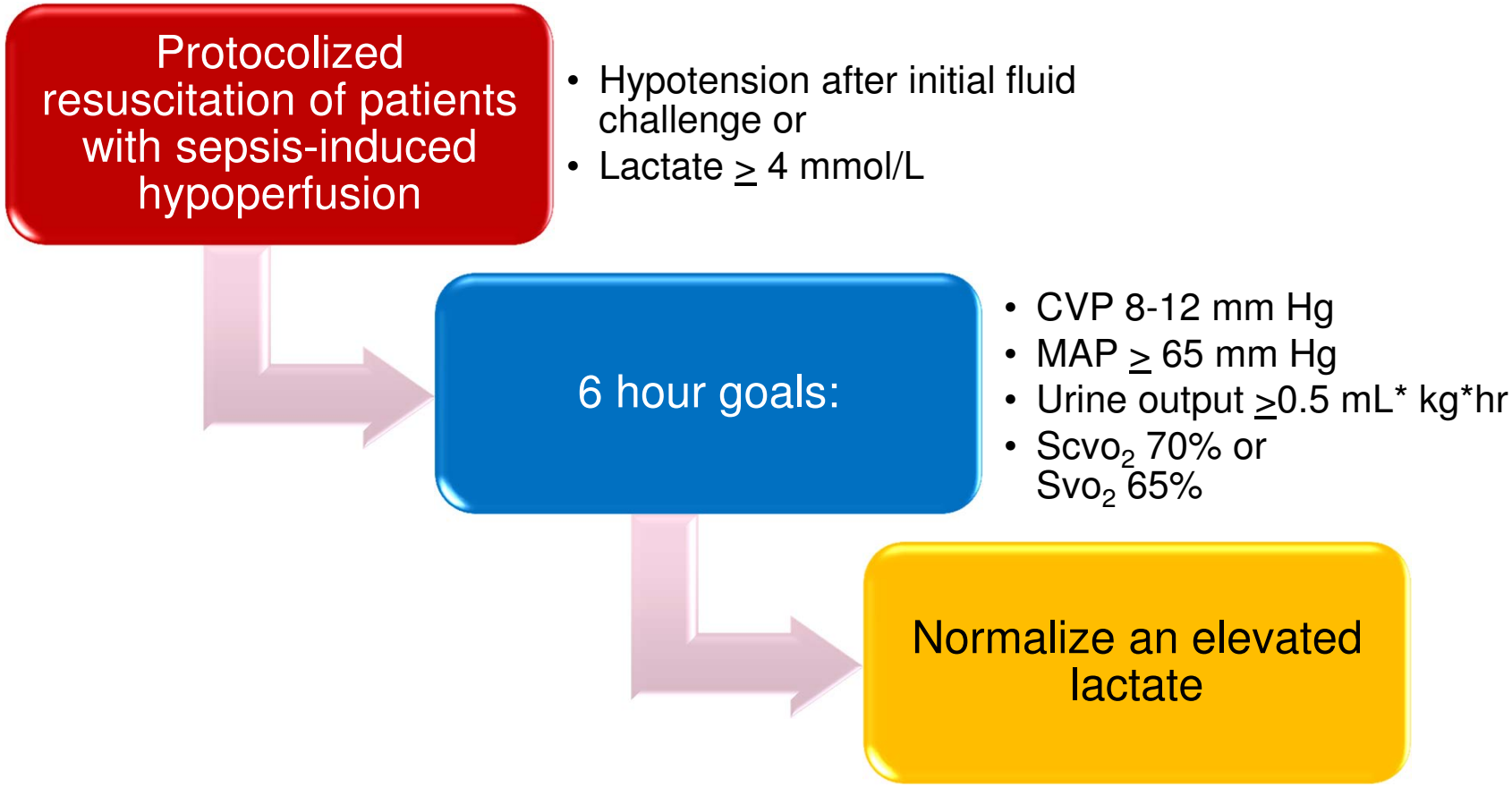
Sooner, smarter, new strategies against sepsis

"We suggest using lactate normalization as a target for resuscitation," Dr. Dellinger explains. "If someone has severe sepsis and their initial serum lactate is elevated, you want to resuscitate them with fluids, normalize their blood pressure, ensure good oxygen levels, and increase tissue perfusion to totally normalize lactate—that's a new recommendation for 2012."

To better accommodate the new recommendation, laboratories will need to use a rapid and robust lactate assay; some emergency departments may prefer the use of blood gas analyzers to measure lactate levels closer to the bedside.

***CAP Today* July 2013 Feature Story Ann Griswold, PhD**

Initial Resuscitation and Infection Issues-The Big Picture



Dellinger RP et al. *Crit Care Med*. (2013) 41:580-637.

2013 Resuscitation Bundles

To be completed within 3 hours:

- Measure lactate level
- Obtain blood cultures prior to administration of antibiotics
- Administer broad spectrum antibiotics
- Administer 30 mL/kg crystalloid for hypotension or lactate 4mmol/L

To be completed within 6 hours:

- Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) 65 mm Hg
- In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate 4 mmol/L (36 mg/dL):
  - Measure central venous pressure (CVP)*
  - Measure central venous oxygen saturation (ScvO2)*
- Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of 8 mm Hg, ScvO2 of 70%, and normalization of lactate.

Initial Resuscitation and Infection Issues-The Details

- Initial Resuscitation
- Screening for Sepsis Performance and Improvement
- Diagnosis
- Antimicrobial Therapy
- Source Control
- Infection Prevention

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Initial Resuscitation and Infection Issues

Initial Resuscitation

Protocols to resuscitate tissue hypoperfusion. Goals in the first 6 hours-

- Central venous pressure mm Hg
- Mean arterial pressure $\geq$ 65 mm Hg
- Urine output $\geq$ 0.5 mL/kg/hr
- CVO2 sat 70% or MVO2 sat 65%

If lactate is elevated, target resuscitation to normalize

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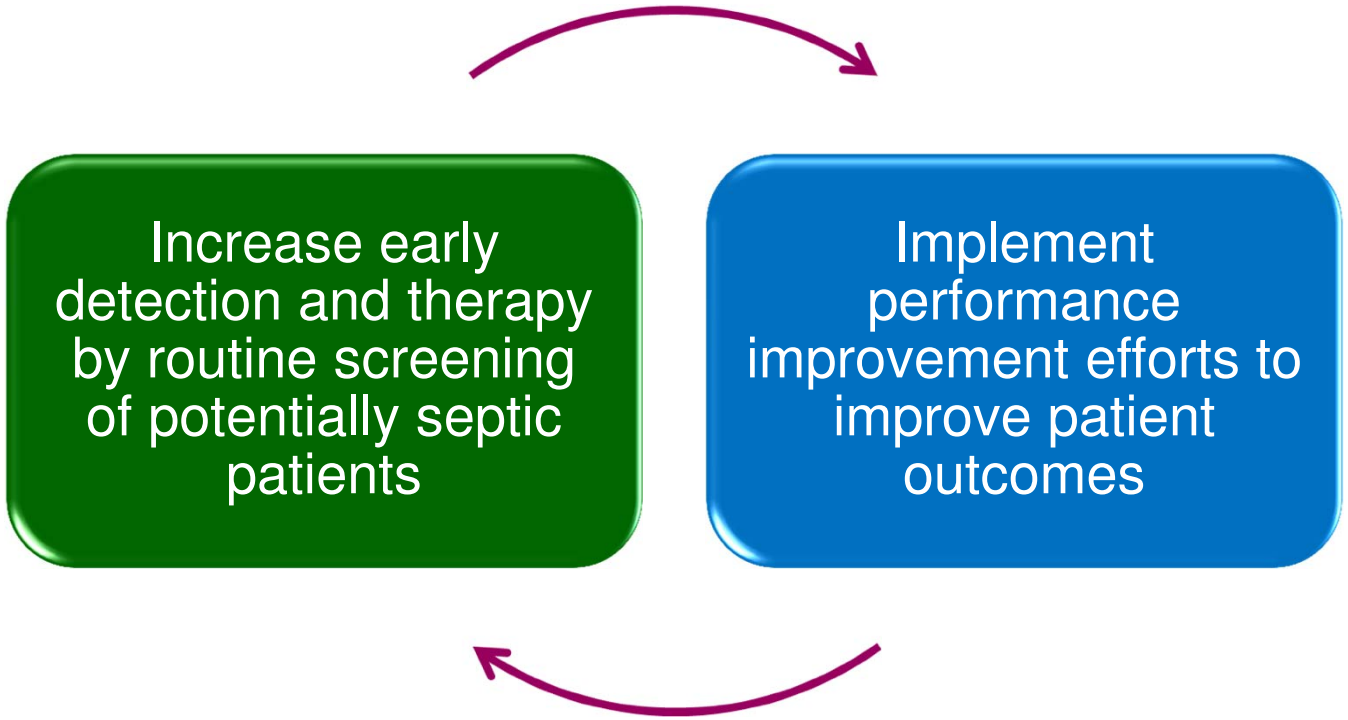
Initial Resuscitation and Infection Issues

Screening for Sepsis Performance and Improvement



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Initial Resuscitation and Infection Issues

Diagnosis

Cultures before antimicrobials	• Don't delay AMs >45 min. • Aerobic and anaerobic
Candidiasis suspected?	• 1,2 beta-beta-D-glucan assay • Mannan and anti-mannan assay
Imaging studies	• To confirm the possible source of infection

Initial Resuscitation and Infection Issues

Antimicrobial Therapy

- AMs in the 1st hour after septic shock or severe sepsis is identified
- Pick AM that is most effective against all likely pathogens
  - Reassess AM regimen daily for possible deescalation
- If sepsis suspicion lessens, low PCT (or other biomarkers) can assist discontinuation decision
- Combination empirical therapy for neutropenic patients

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Initial Resuscitation and Infection Issues

Antimicrobial Therapy (cont'd)

- 7-10 day courses are typical
- Switch to AV ASAP
- No AM for those with non-infectious severe inflammation

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Initial Resuscitation and Infection Issues

Source Control

Infection Prevention

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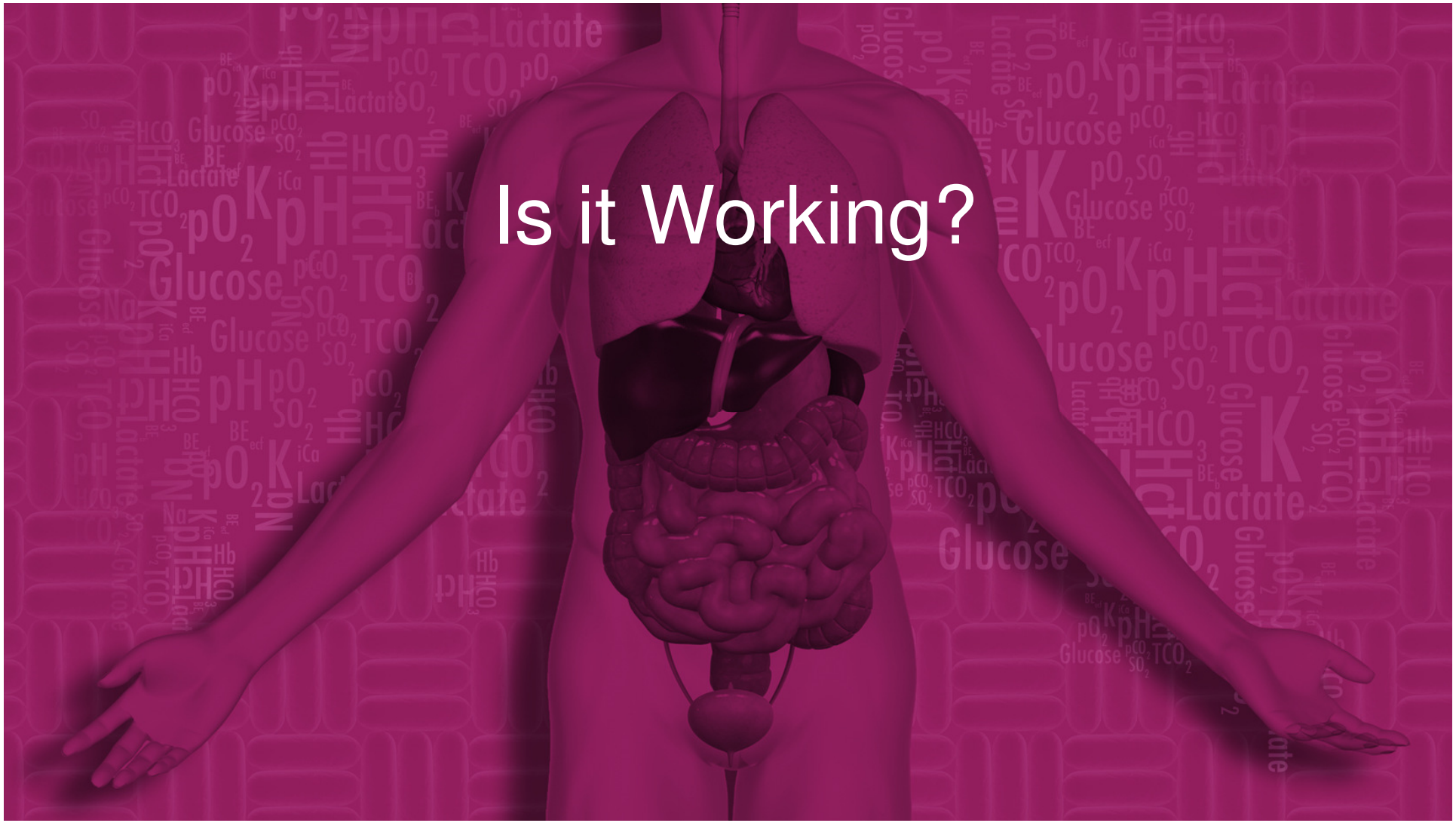

Is it Working?

15,775 patients at 252 participating Surviving Sepsis sites[1]

Unadjusted hospital mortality decreased from 37% to 30.8% over a 2 year period

33-month study period at Mayo-MN[2]

Bundle compliance rose from 12.7% to 52.7%

Mortality declined from 30.3% to 22%

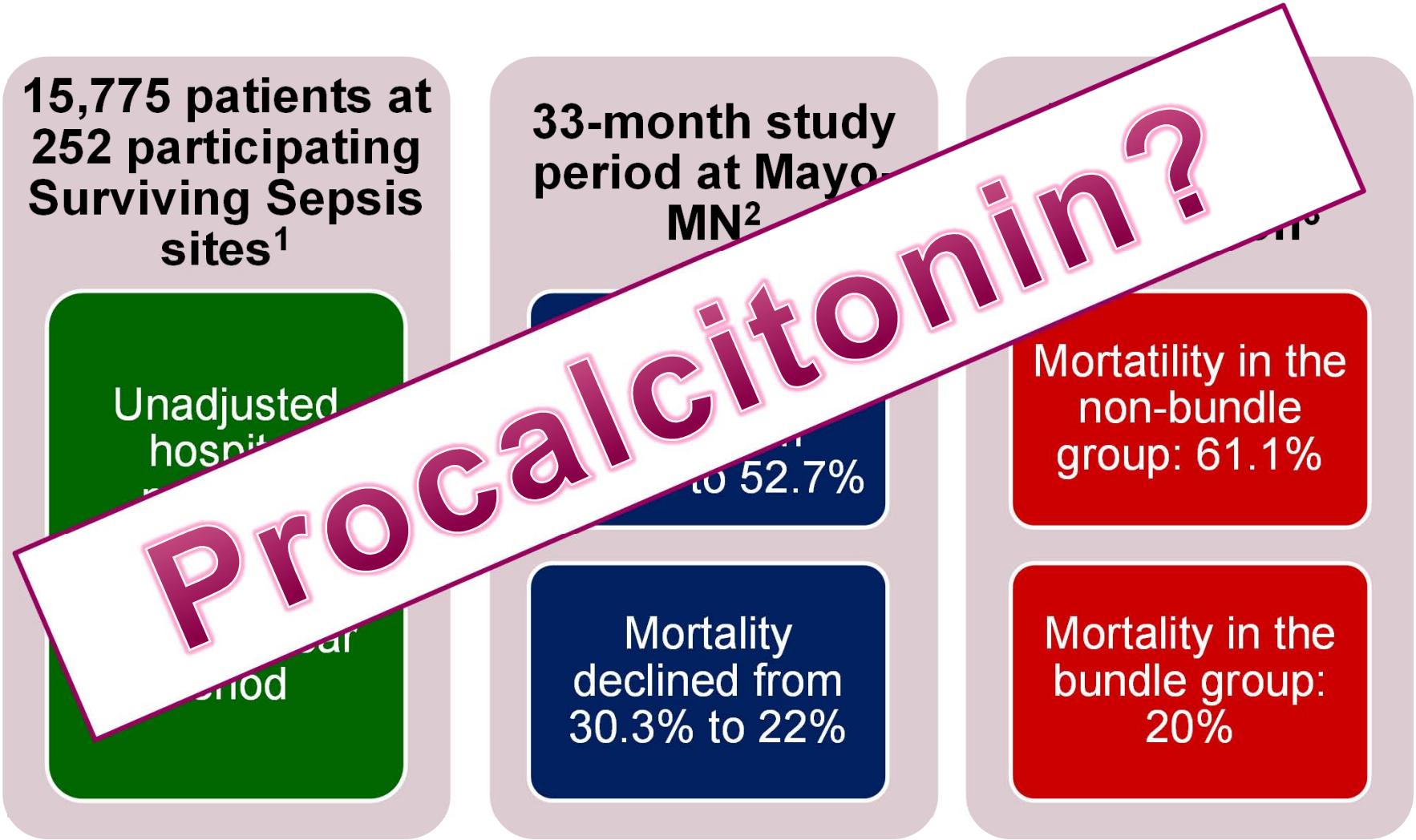
Medical City Plano (TX) evaluation[3]

Mortatility in the non-bundle group: 61.1%

Mortality in the bundle group: 20%

1. Intensive Care Med (2010) **36**:222-231, 2. Crit Care Med (2011) **39**:252-258, 3. Ann Pharmacother (2010) **44:**1733-1738

Is it Working?



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Point-of-Care Analyte Benefits

- A 2010 study published in the *Journal of Emergency Medicine* found that point-of-care testing provided a reliable and feasible way to measure serum lactate at the bedside.[1]
  - Base excess (BE)
    - Some studies suggest BE is an accurate marker for the prediction of elevated lactate in the emergency department (ED).[2]
    - Some studies also show poor correlation due to effects of other conditions.[3]
  - Point-of-care lactate is useful in the diagnosis of sepsis at the bedside
    - Recommended for institutions where clinical decisions are limited by lack of laboratory infrastructure or reliability.[4]

[1] **Shapiro NI, Fisher C, Donnino M et al. *J Emerg Med.* 2010;39:89-94.**
[2] **Montassier E, Batard E, Segard J et al. *Am J Emerg Med.* 2010. Epub ahead of print.**
[3] **Martin MJ, FitzSullivan E, Salim A et al. *Am J Surg*. 2006;191:625-30.**
[4] **Moore CC, Jacob ST, Pinkerton R et al. *Clin Infect Dis*. 2008;46:215-22.**

Turnaround Time

- Serum lactate must be available with rapid turnaround time (within minutes) to effectively treat severely septic patients.
- An arterial blood gas analyzer located in the clinical laboratories usually accomplishes this.
- Hospitals should invest in adequate equipment in to meet present standards of care for septic patients.
- If a central analyzer is not efficient in a particular hospital setting, point-of-care analyzers should be evaluated for faster turnaround time.

http://www.survivingsepsis.com/bundles/individual_changes/serum_lactate.
www.emcrit.org/wp-content/uploads/lactate-faq.pdf.


In Summary…
Identification, Treatment, and Outcomes

Treatment of Patients With Sepsis

- Early goal-directed therapy: standard operating procedure
  - Apply with critical care/sepsis team *if patient remains hypotensive or lactate remains high following fluid challenges*
    1. Site central venous catheter using ultrasound guidance where practicable, according to proper procedures for infection control
    2. If central venous pressure (CVP) < 8 mmHg, give further fluid challenges to achieve a target CVP of > 8 mmHg (> 12 mmHg if ventilated) unless the patient shows signs of fluid overload
    3. If patient remains hypotensive, start a norepinephrine infusion to target SBP > 90 mmHg or MBP > 65 mmHg.

Daniels R. *J Antimicrob Chemother*. 2011;66(Suppl 2):ii11–ii23.

Improve Patient Outcomes

- Lactate clearance is associated with improved patient outcome.
- Lactate measurement is associated with increased risk of death independent of other aspects of sepsis bundle guidelines.
- Point-of-care measurements of lactate are faster than central laboratories.
  - May be beneficial for serial measurements.

Nguyen HB, Rivers EP, Knoblich BP et al. *Crit Care Med.* 2004;32(8):1637-42.
Afessa B, Keegan MT, Schramm GE et al. *Crit Care Med.* 2011;15(Suppl 1): P286.
Boldt J, Kumle B, Suttner S et al. *Acta Anaesthesiol Scand.* 2001;45:194–9.

Questions?

Thank You!

Today is the youngest you'll be for the rest of your life. Act like it.