Amjad Bani Hani
Asst. Prof of Cardiac Surgery and Intensive Care

SIRS, SEPSIS, AND MODS

- In 1992, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) introduced definitions

Definitions

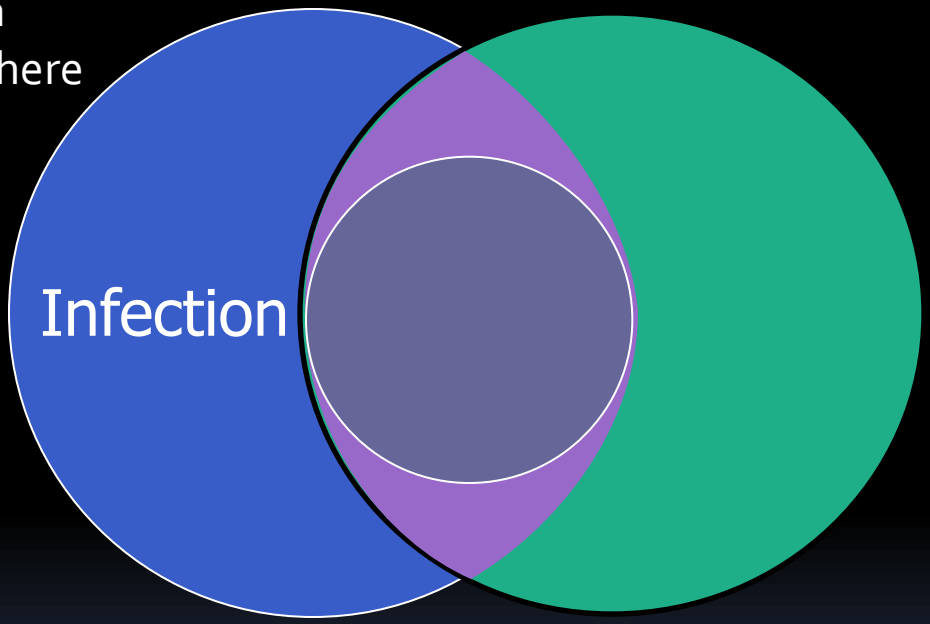
- Infection
- Systemic Inflammatory Response Syndrome (SIRS)
- Sepsis
- Severe Sepsis
- Septic Shock

Definitions (ACCP/SCCM):

- **Infection:** A microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms.

Infection: Part of a bigger picture

- Infection:
  - Presence of organisms in a closed space or location where not normally found

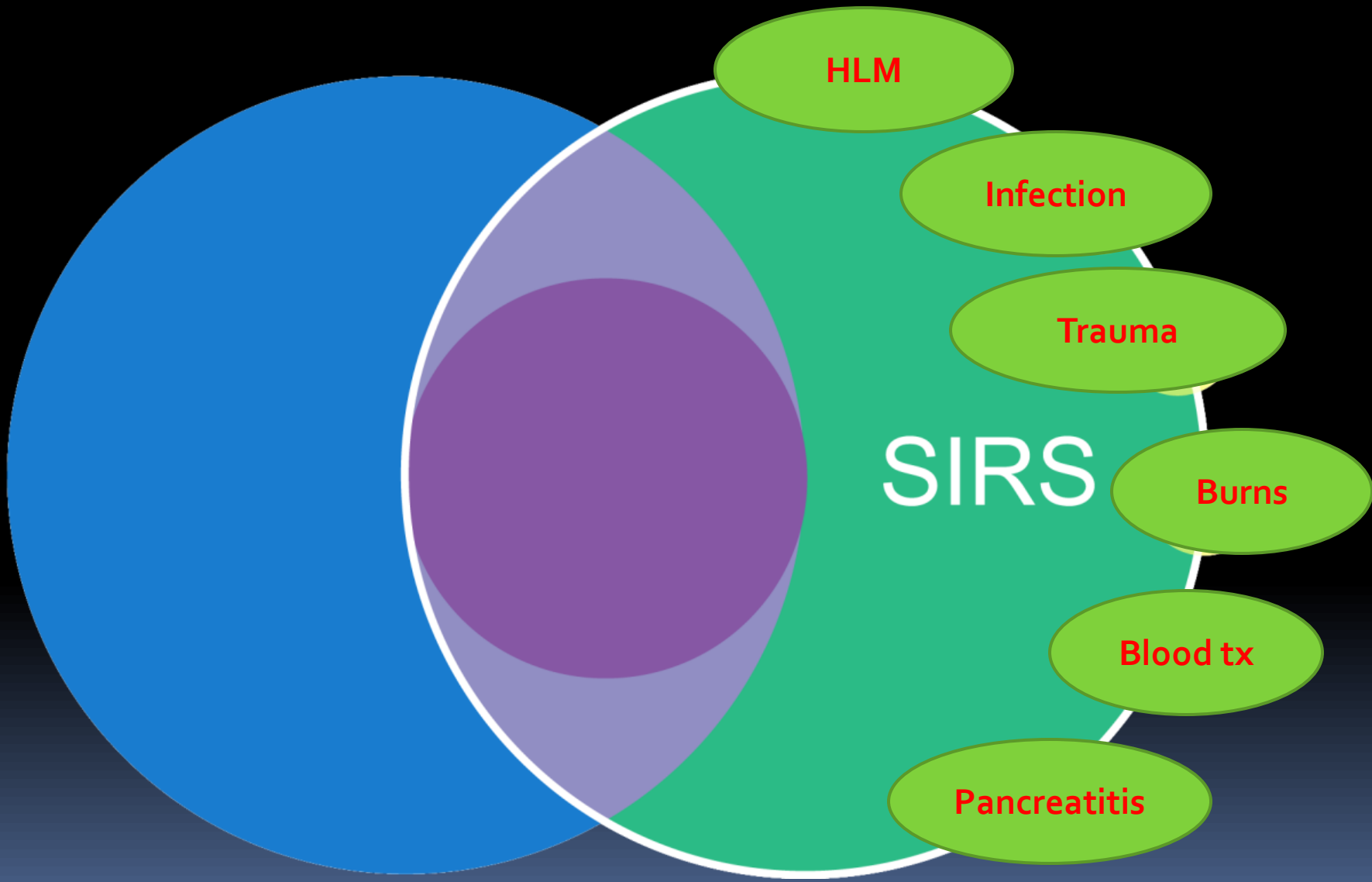


Adapted from: Bone RC et al. *Chest.* 1992;101:1644-55.
Opal SM et al. *Crit Care Med*. 2000;28:S81-2.

‘SIRS’

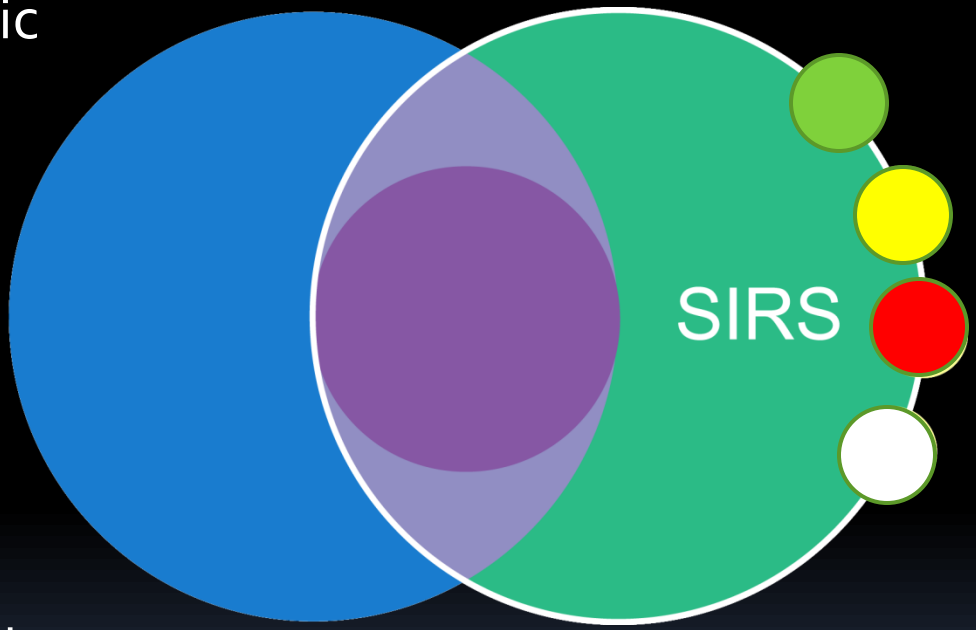
SIRS

- self-defense mechanism.
- Inflammation is the body's response to nonspecific insults that arise from chemical, traumatic, or infectious stimuli.
- The inflammatory cascade is a complex process that involves humoral and cellular responses, complement, and cytokine cascades.


HLM
Infection
Trauma
SIRS
Burns
Blood tx
Pancreatitis

SIRS: Systemic Inflammatory Response Syndrome

- SIRS: A clinical response arising from a nonspecific insult manifested by ≥2 of the following:
  - Temperature ≥38°C or ≤36°C
  - HR ≥90 beats/min
  - Respirations ≥20/min, Paco2 ≥ 32
  - WBC count ≥12,000/mL or ≤4,000/mL or >10% immature neutrophils



Adapted from: Bone RC et al. *Chest.* 1992;101:1644-55.
Opal SM et al. *Crit Care Med*. 2000;28:S81-2.

‘Sepsis’

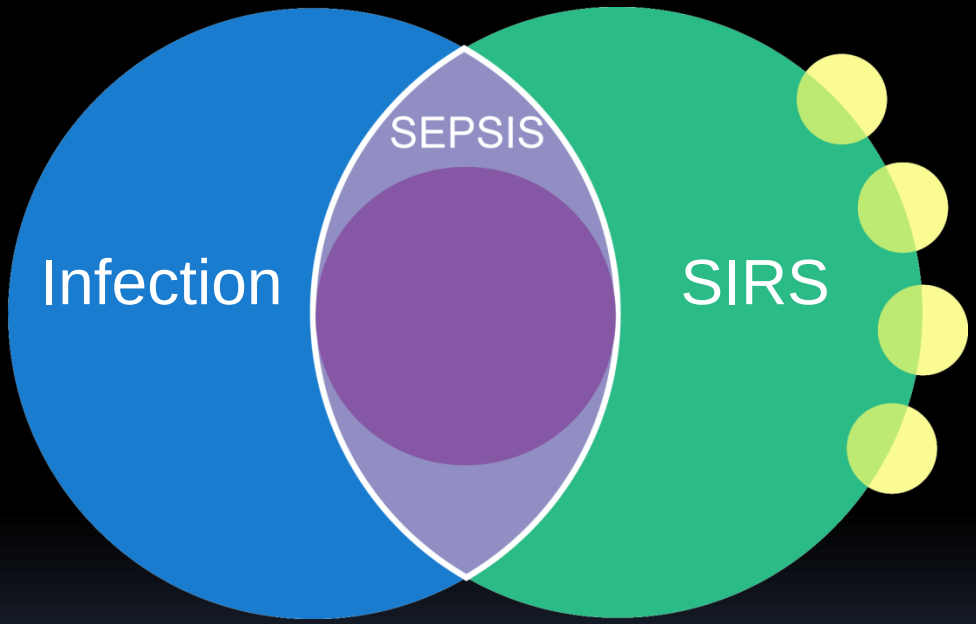
‘Sepsis’

- Sepsis is the systemic response to infection

  SIRS in the presence of proven or suspected infection

Sepsis: More Than Just Inflammation

- Sepsis:
  - SIRS criteria
  - Known or suspected infection



Adapted from: Bone RC et al. *Chest.* 1992;101:1644-55.

‘Severe Sepsis’

‘Severe Sepsis’

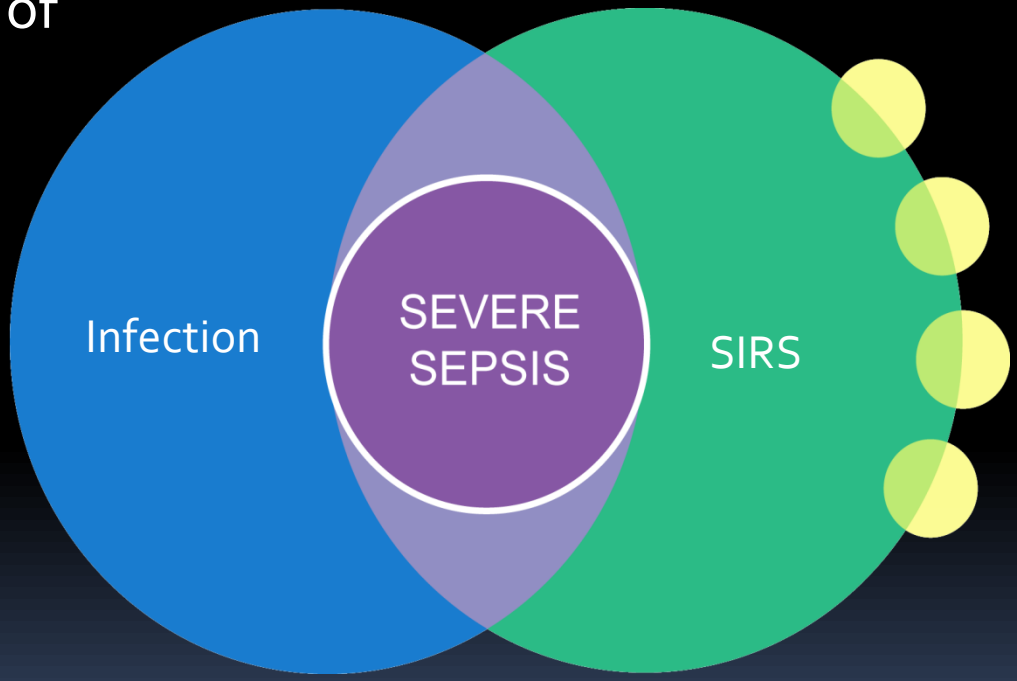
- Sepsis associated with
- Organ-dysfunction

  -Hypotension

  -Hypoperfusion

Severe Sepsis: Acute Organ Dysfunction

- Severe Sepsis =
  Sepsis with signs of ***acute*** organ dysfunction in any of the following systems:
  - Cardiovascular (septic shock)
  - Renal
  - Respiratory
  - Hepatic
  - Hemostasis
  - CNS
  - Unexplained metabolic acidosis



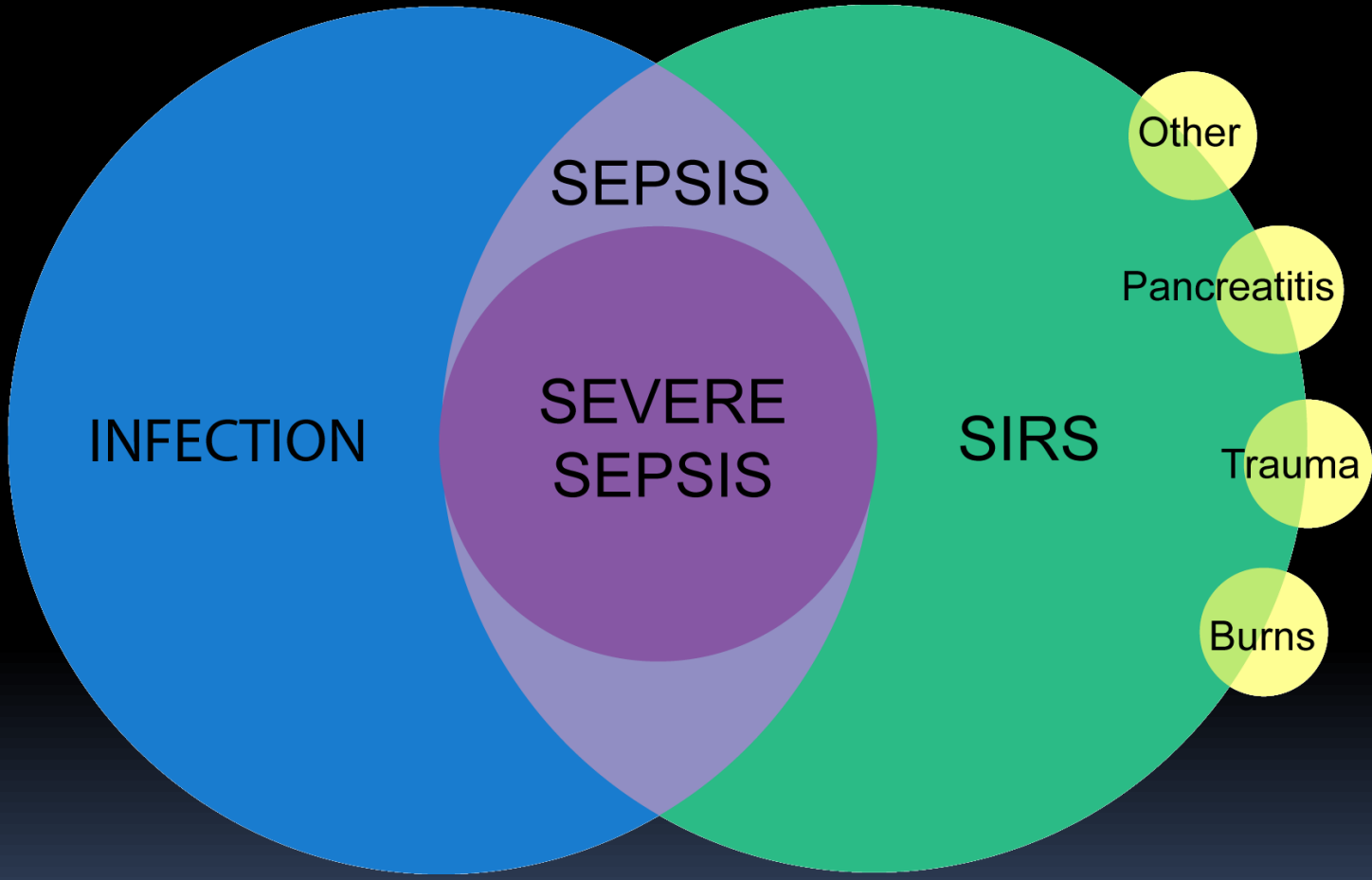
Adapted from: Bone RC et al. *Chest.* 1992;101:1644-55.

‘Septic Shock’

‘Septic Shock’

- Sepsis with hypotension despite adequate fluid resuscitation
- Include all patients on vasopressors or inotropic support

Sepsis: A Complex Disease



Adapted from: Bone RC et al. *Chest.* 1992;101:1644-55.
Opal SM et al. *Crit Care Med*. 2000;28:S81-2.

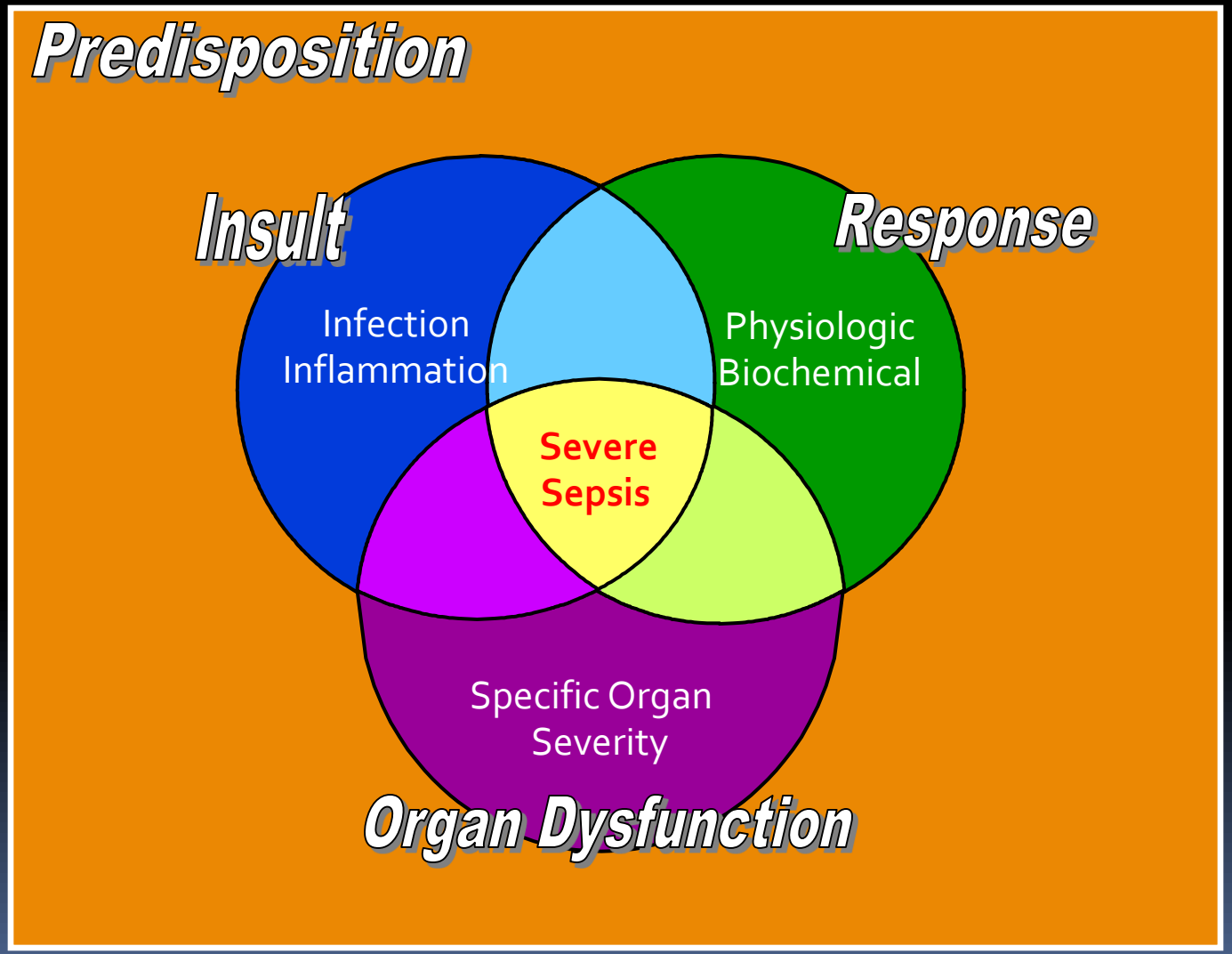
The *Multiple Organ Dysfunction Syndrome (MODS)*

- The development of potentially reversible physiologic derangement involving two or more organ systems not involved in the disorder that resulted in ICU admission

The *Multiple Organ Failure Syndrome (MOFS)*

- The development of potentially irreversible physiologic derangement involving two or more organ systems not involved in the disorder that resulted in ICU admission

Jargon 2002: PIRO



Predisposition

- Pre-existing disease
  - Cardiac, Pulmonary, Renal
  - HIV
- Age (extremes of age)
- Gender (males)
- Genetics
  - TNF polymorphisms (TNF promoter high secretor genotype)

Response

- Physiology
  - Heart rate
  - Respiration
  - Fever
  - Blood pressure
  - Cardiac output
  - WBC
  - Hyperglycemia
- Markers of Inflammation
  - TNF
  - IL-1
  - IL-6
  - Procalcitonin
  - PAF

IDENTIFYING ACUTE ORGAN DYSFUNCTION AS A MARKER OF SEVERE SEPSIS

Altered Consciousness
Reduced GCS

Tachycardia
Systolic BP ≤90, or
MAP ≤70 despite fluids
Vasopressors

Tachypnea
PaO_2/FiO_2 ≤250
Mechanical Ventilation
PEEP >7.5

Urine Output <0.5 mL/kg/hr despite fluids
↑Creatinine >50% from baseline
Acute dialysis

Liver Enzymes
>2x ULN

↓ Platelets <100,000/mm^3
↑ PT/aPTT
↑ D-dimer

Low pH with high lactate (eg, pH, 7.3 & lactate>ULN)

Balk RA. *Crit Care Clin.* 2000;16:179-192.

Organ Dysfunction

- Lungs
- Kidneys
- CVS
- CNS
- PNS
- Coagulation
- GI
- Liver
- Endocrine
- Skeletal Muscle

- Adult Respiratory Distress Syndrome
- Acute Tubular Necrosis
- Shock
- Metabolic encephalopathy
- Critical Illness Polyneuropathy
- Disseminated Intravascular Coagulopathy
- Gastroparesis and ileus
- Cholestasis
- Adrenal insufficiency
- Rhabdomyolysis

✓Specific therapy exists

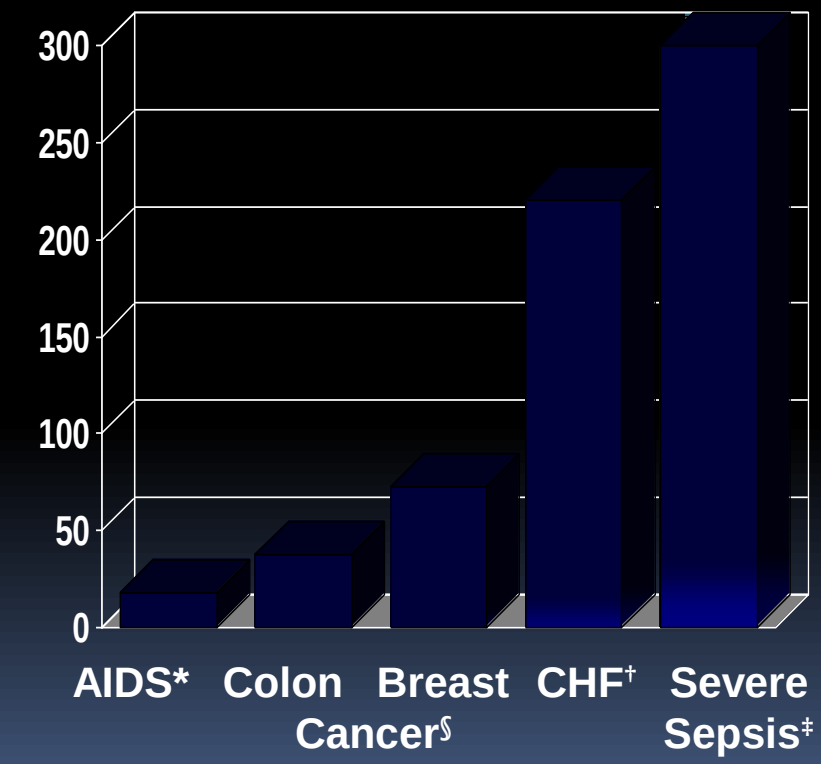
Magnitude of the Problem

- **Severe sepsis takes more lives than breast, colon/rectal, pancreatic, and prostate cancer combined.**
- **One of every three patients who develop severe sepsis will die within a month.**

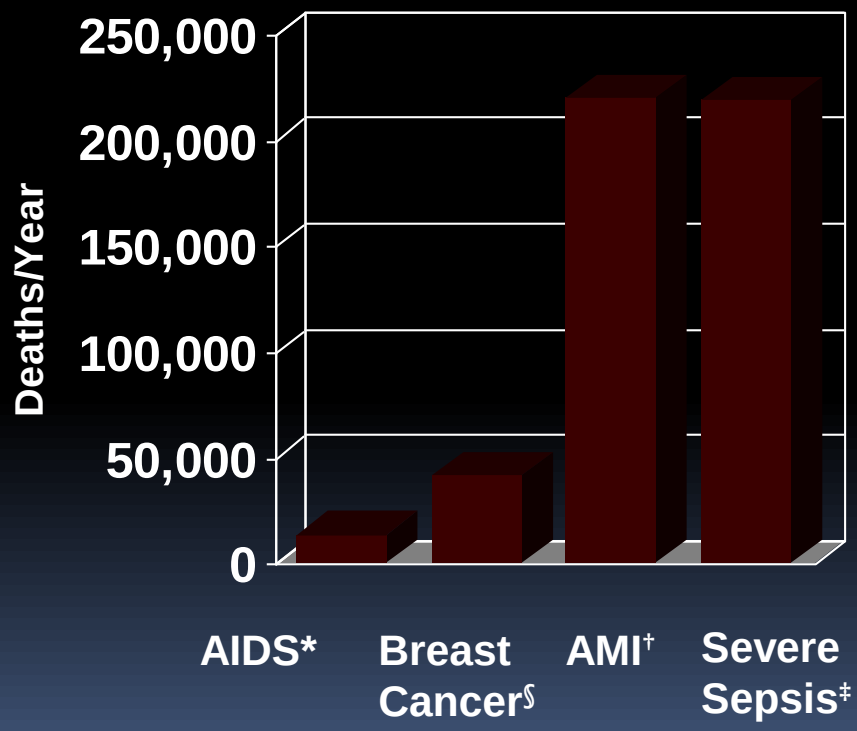
Source: Society of Critical Care

Comparison With Other Major Diseases

Incidence of Severe Sepsis



Mortality of Severe Sepsis

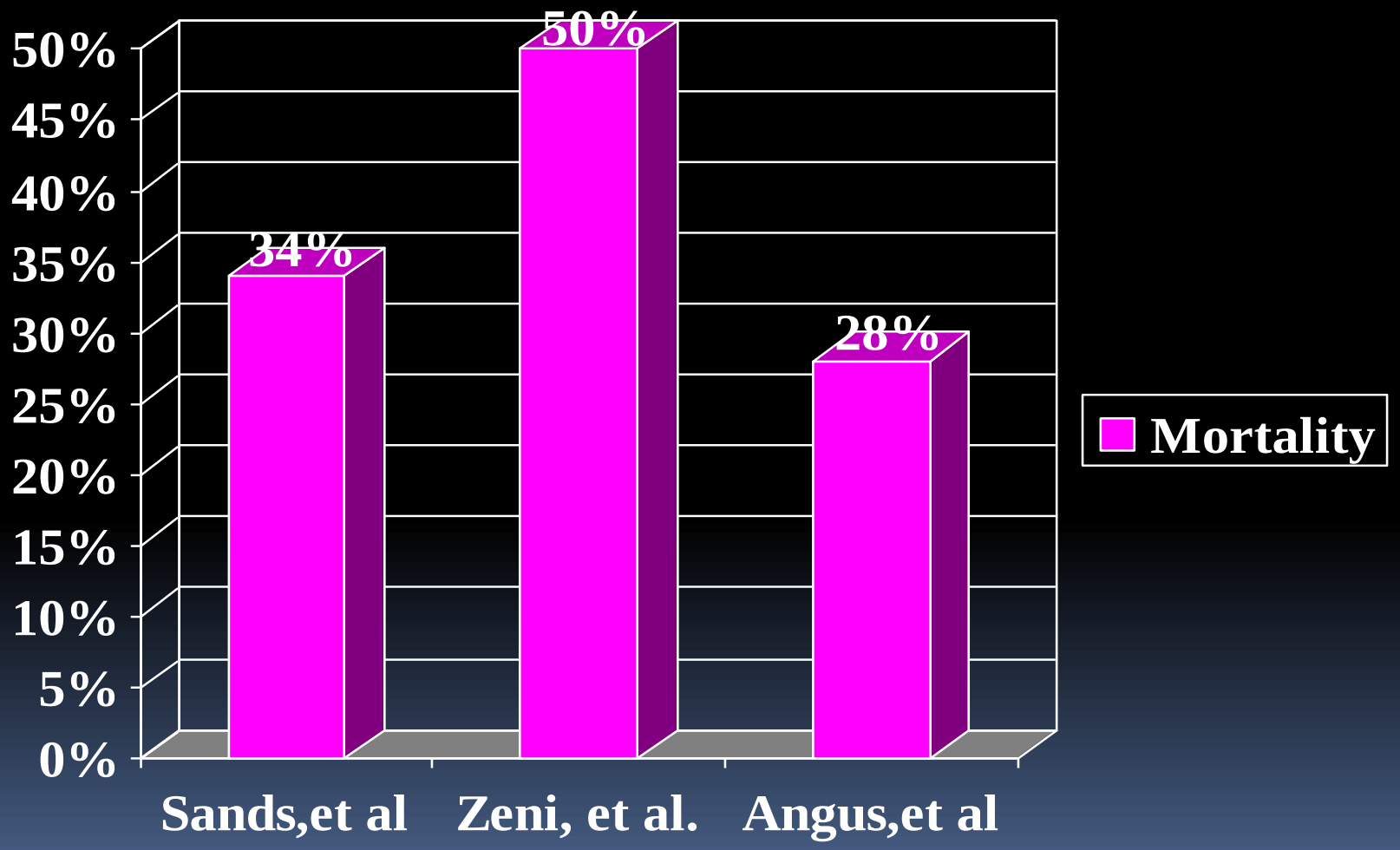


†National Center for Health Statistics, 2001. §American Cancer Society, 2001. *American Heart Association. 2000. ‡Angus DC et al. *Crit Care Med.* 2001;29(7):1303-1310.

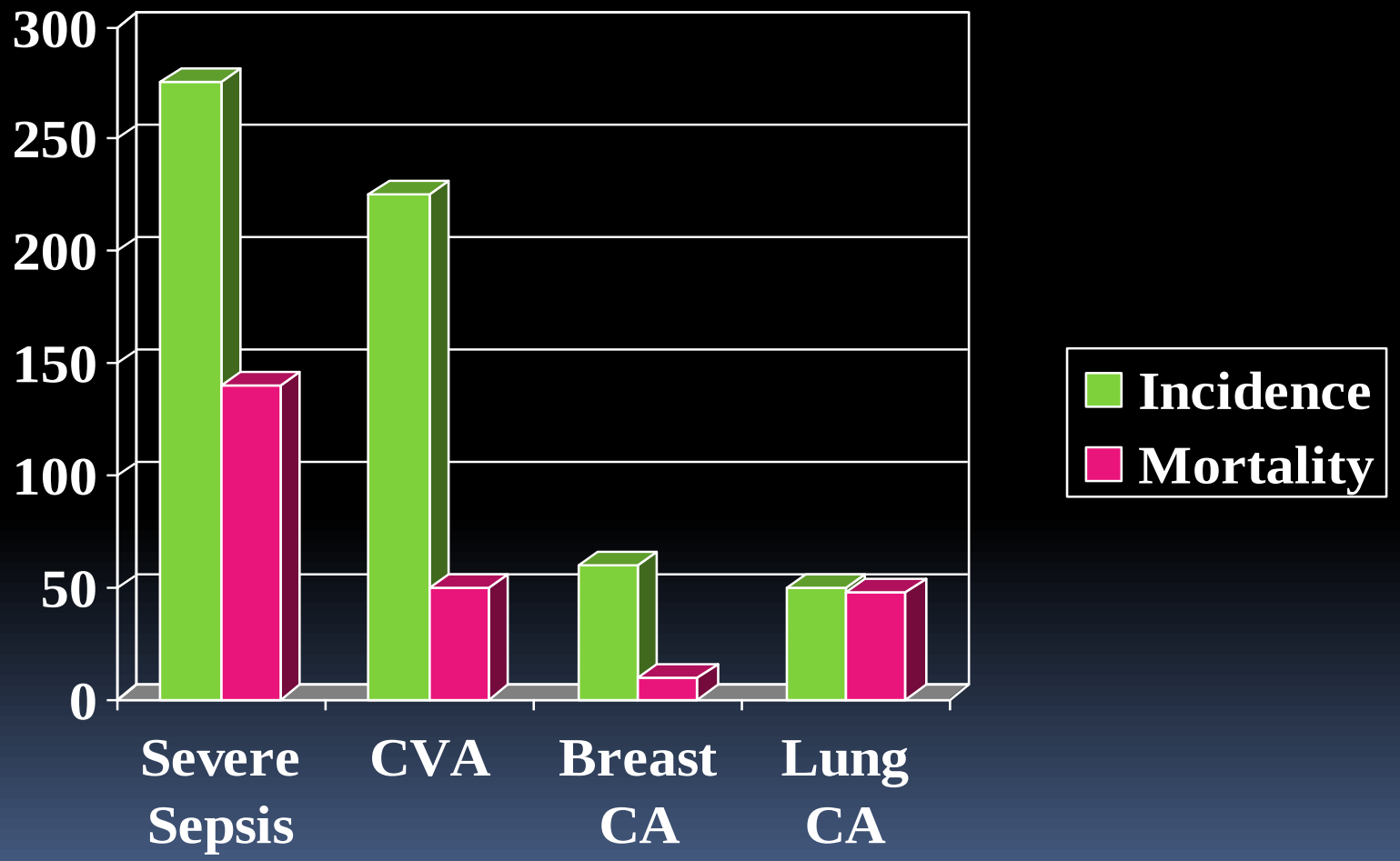
Sepsis,Mortality Rates

- Overall = 30% - 50%
- By syndrome definition:
  - SIRS = 4- 7%
  - Sepsis = 16%
  - Severe sepsis = 20%
  - Septic shock = 46%

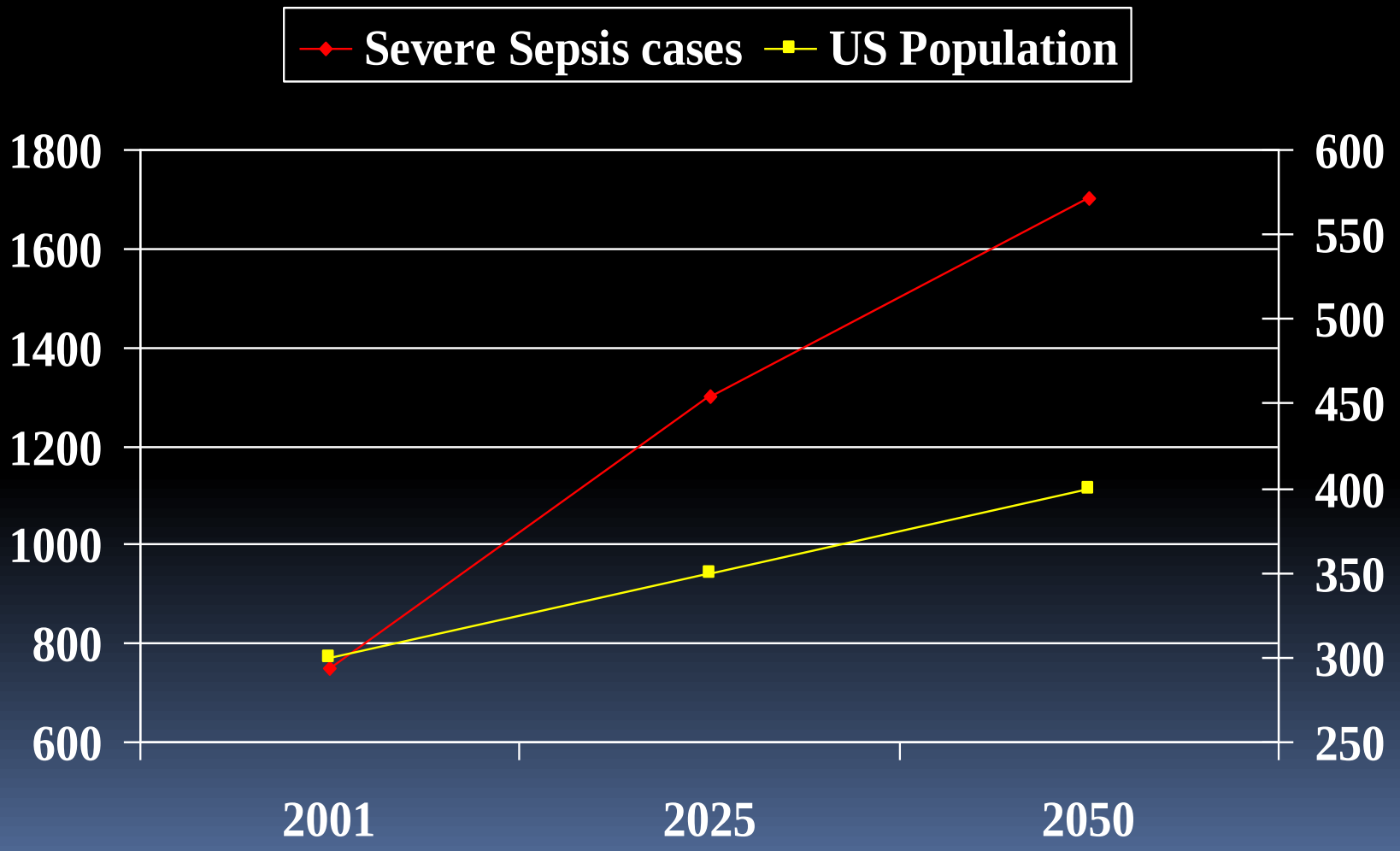
Severe Sepsis is deadly



Severe Sepsis is Common



Severe Sepsis is increasing in incidence



Epidemiology of Sepsis
The International Cohort Study

Percent of cases within each category

18	28	24	30
		35% mortality	

8353 patients with LOS > 24h
4277 infections (2696 on admission)

Alberti, Int Care Med 2002

Sources of Sepsis
The International Cohort Study

	Severe Sepsis	Septic Shock
Respiratory	66	53
Abdomen	9	20
Bacteremia	14	16
Urinary	11	11
Multiple	-	-

Microbiology of Sepsis
The International Cohort Study

	Severe Sepsis	Septic Shock
Gram-positive	44	40
Gram-negative	47	47
Fungal	9	13
Polymicrobial	-	-

Etiology

- Infectouse
- Non-Infectouse

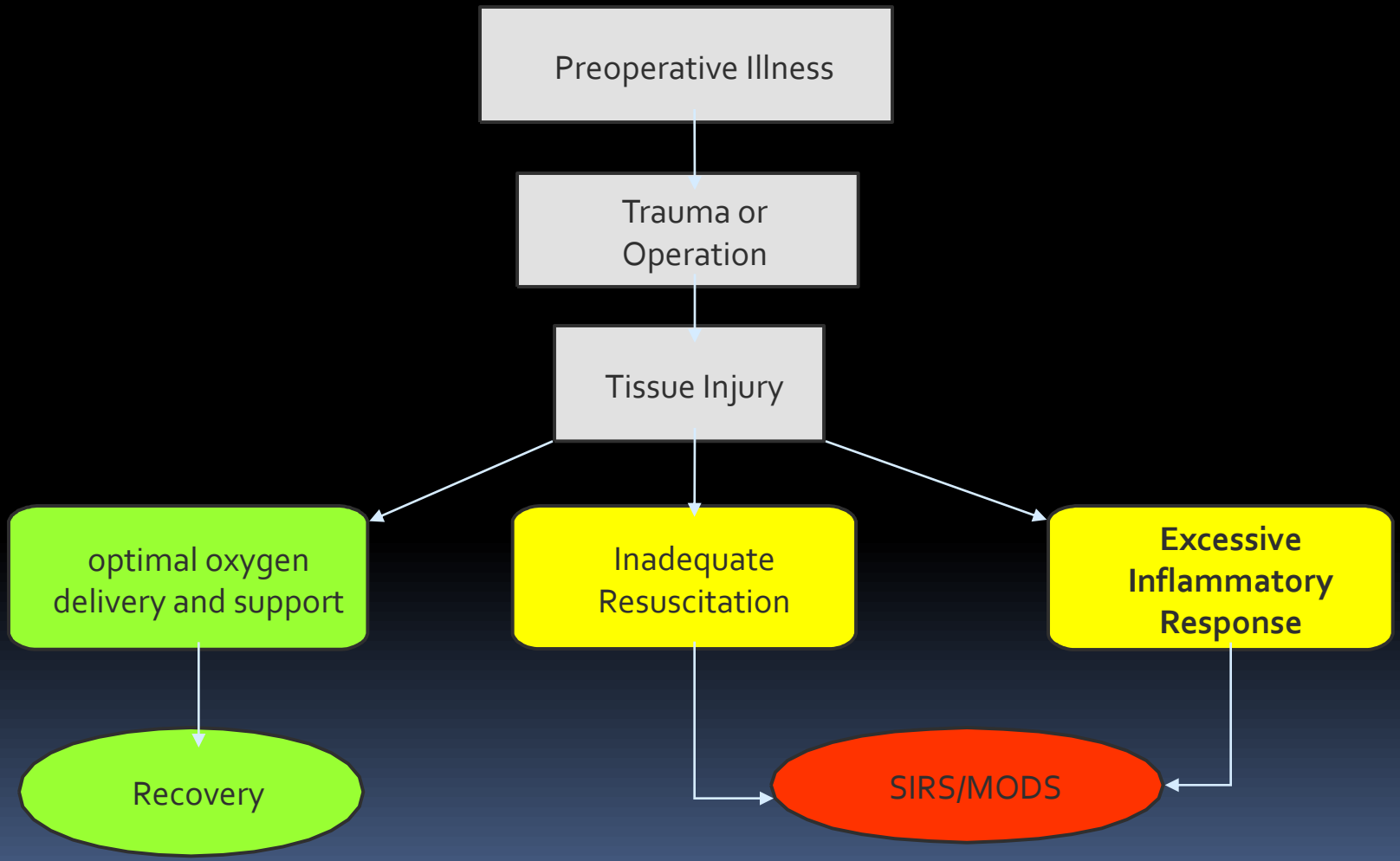
Infectouse

- Bacterial sepsis
- Burn wound infections
- Candidiasis
- Cellulitis
- Cholecystitis
- Community-acquired pneumonia[3]
- Diabetic foot infection
- Erysipelas
- Infective endocarditis
- Influenza
- Intraabdominal infections - Eg, diverticulitis, appendicitis
- Gas gangrene
- Meningitis
- Nosocomial pneumonia
- Pseudomembranous colitis
- Pyelonephritis
- Septic arthritis
- Toxic Schock Syndrom
- Urinary tract infections (male and female)

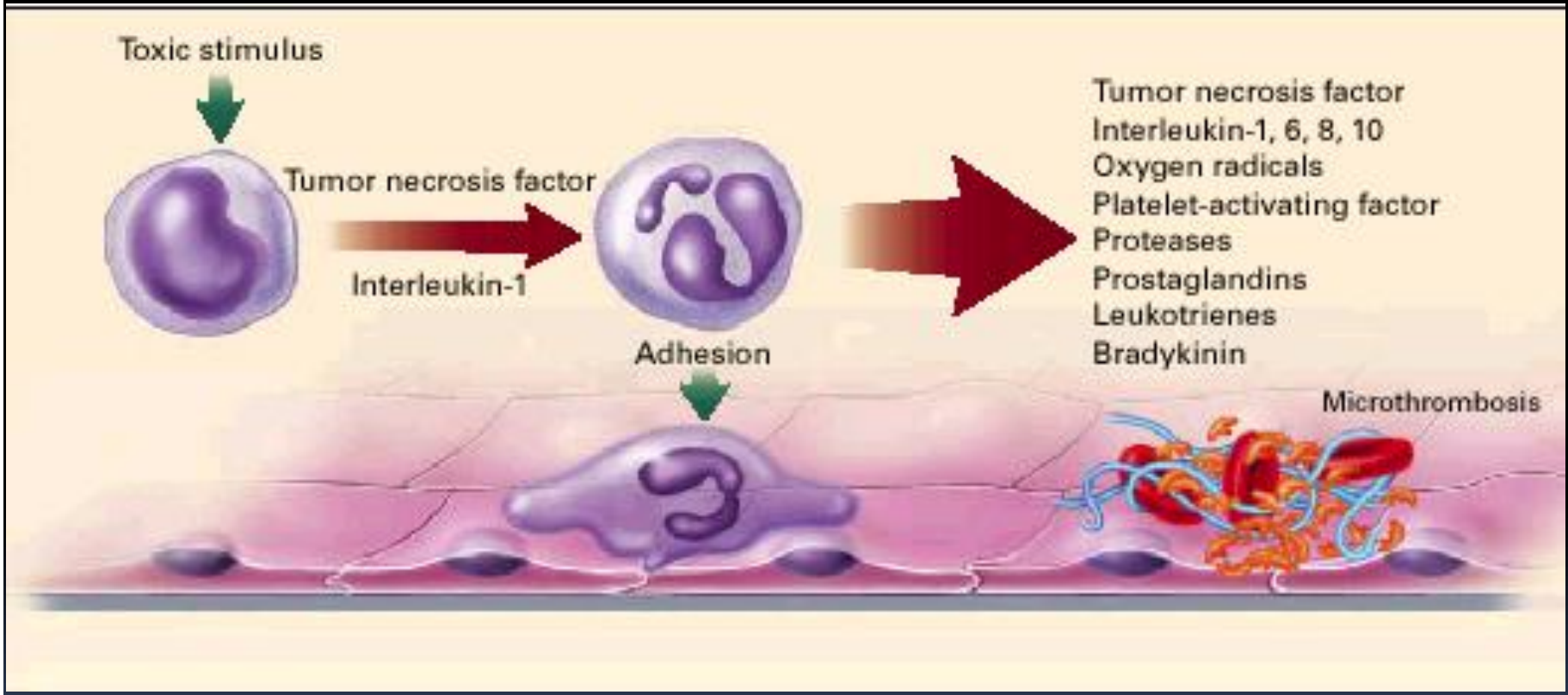
Noninfectious

- Acute mesenteric ischemia
- Adrenal insufficiency
- Autoimmune disorders
- Burns
- Chemical aspiration
- Cirrhosis
- Cutaneous vasculitis
- Dehydration
- Drug reaction
- Electrical injuries
- Erythema multiforme
- Hemorrhagic shock
- Hematologic malignancy
- Intestinal perforation
- Medication side effect - Eg, from theophylline
- Myocardial infarction
- Pancreatitis[4]
- Seizure
- Substance abuse - Stimulants such as cocaine and amphetamines
- Surgical procedures
- Toxic epidermal necrolysis
- Transfusion reactions
- Upper gastrointestinal bleeding
- Vasculitis

Pathogenesis of SIRS/MODS



Initiation of Inflammatory Response



From Wheeler & Bernard, NEJM 1999

Mediators of Septic Response

Pro-inflammatory Mediators

- Bacterial Endotoxin
- TNF-α
- Interleukin-1
- Interleukin-6
- Interleukin-8
- Platelet Activating Factor (PAF)
- Interferon-Gamma
- Prostaglandins
- Leukotrienes
- Nitric Oxide

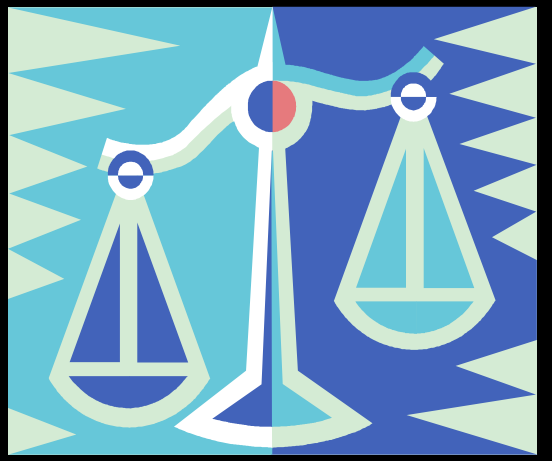
Anti-inflammatory Mediators

- Interleukin-10
- PGE2
- Protein C
- Interleukin-4
- Interleukin-12
- Lipoxins
- GM-CSF
- TGF
- IL-1RA

Pathophysiology of Sepsis

- In simple terms sepsis can be viewed as an imbalance of inflammation, coagulation, and fibrinolysis.

- In normal patients homeostasis is maintained when these are balanced.



Pathophysiology of Sepsis

During a normal response to bacteria in the blood the immune system releases inflammatory mediators to promote recovery of the tissue.

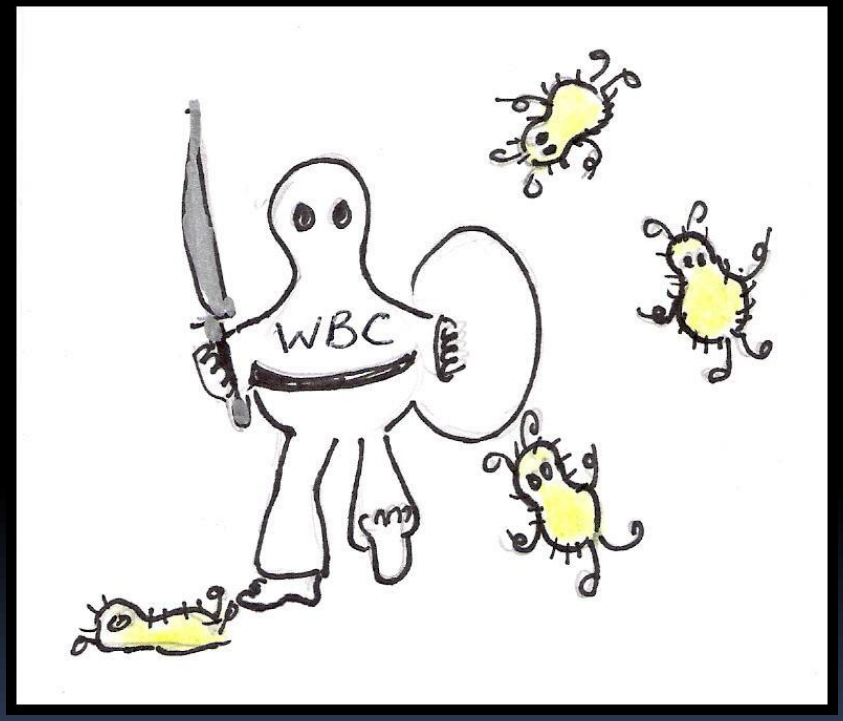
These mediators are known as:

- Tumor Necrosis Factor (TNF)
- Interleukins (IL)
- Cytokines
- Prostaglandins
- Platelet Activating Factor

Source: New England Journal of Medic

Pathophysiology of Sepsis

Once the bacteria or antigen is isolated, the pro-inflammatory mediators attract neutrophils or WBCs which attack the antigen and try to engulf it.



Graphics: Delores Zittel, 2006

Pathophysiology of Sepsis

To prevent the response from damaging normal tissue, anti-inflammatory mediators are released including transforming growth factors and interleukins (IL-4). This balance of inflammatory and anti-inflammatory mediators restricts the inflammation response to the local site of infection.

Source: Critical Care Nurse Supplement, 2004

Published in final edited form as:
Clin Chest Med. 2008 December ; 29(4): 617–viii. doi:10.1016/j.ccm.2008.06.010.

The Compensatory Anti-inflammatory Response syndrome (CARS) in Critically ill patients

Nicholas S. Ward, MD[a,*], **Brian Casserly, MD**[a], and **Alfred Ayala, PhD**[b]

[a]Division of Pulmonary, Critical Care, and Sleep Medicine, The Warren Alpert Medical School of Brown University, 593 Eddy Street, APC 707, Providence, RI 02912, USA

[b]Division of Surgical Research, Department of Surgery, The Warren Alpert Medical School of Brown University, Providence, RI 02912, USA

Cellular/molecular elements

Lymphocyte dysfunction (ie, reduced proliferative and/or type 1 helper T-cell [Th1] cytokine production in response-defined antigens or specific T-cell stimuli)

Lymphocyte Apoptosis

Down-regulation of monocyte HLA receptors Monocyte deactivation (ie, reduced Th1/ proinflammatory cytokine production in response stimuli)

IL-10 production

Transforming growth factor-beta production Prostaglandin E2 production

Molecular Mediators in Pathophys

- Parallel to SIRS is CARS
  - Compensatory Anti-inflammatory Response System
    - Attempts to down regulate the SIRS response
    - IL-4, IL-10, transforming growth factor beta, CSF, soluble receptors to TNF, antagonists to TNF-alpha and IL-1
    - If CARS reaction is severe it will manifest as anergy and infection susceptibility

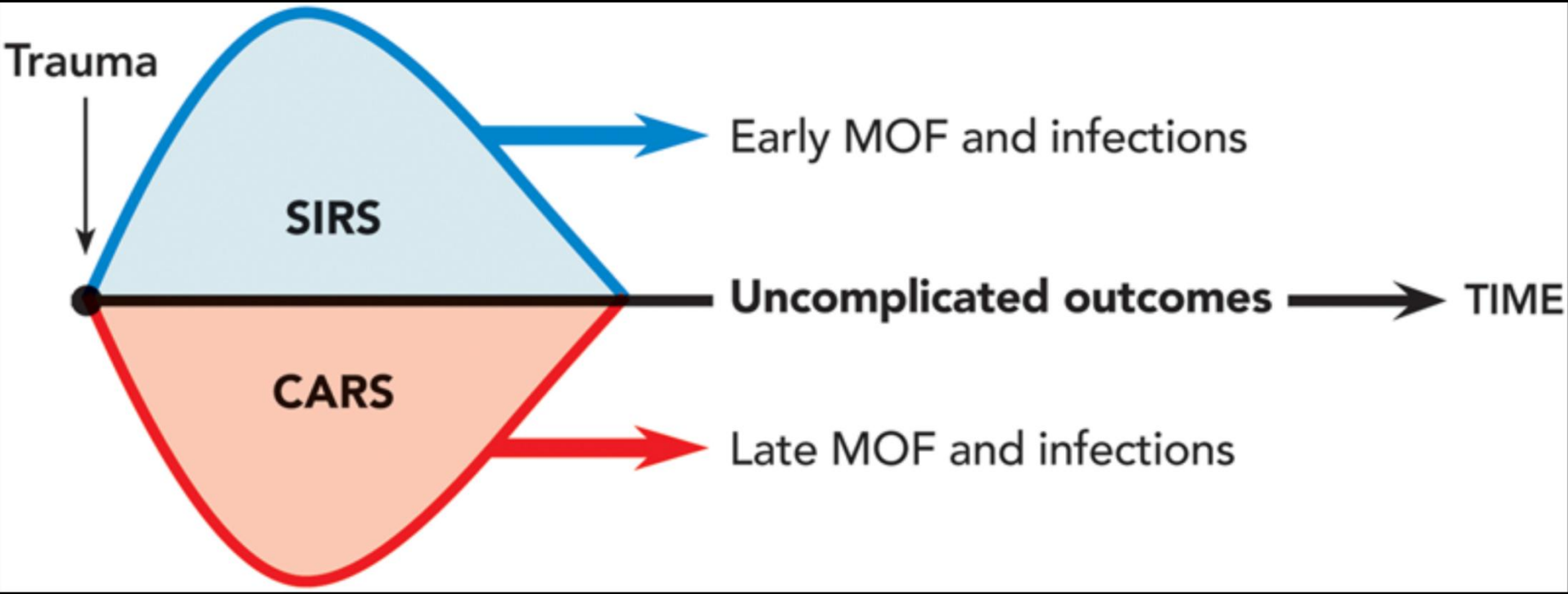


Figure Legend:

Fig. 2. Trauma-induced injury actives innate immune responses to produce pro- and antiinflammatory cytokines. Imbalance between the systemic inflammatory response syndrome and the compensatory antiinflammatory response (immunosupression) increases morbidity of trauma patients. In the first hours, the magnitude of the systemic inflammatory response syndrome is correlated with early multiple organ failure and infections. In the following days, immunosupression contributes to the increased incidence of nosocomial infections and late sepsis. CARS = compensatory anti-inflammatory response; MOF = multiple organ failure; SIRS = systemic inflammatory response syndrome.

Pathophysiology of Sepsis

When the body is unable to maintain the appropriate balance, the immune response is no longer local but becomes systemic.

Inflammation and altered clotting quickly spread through the body.

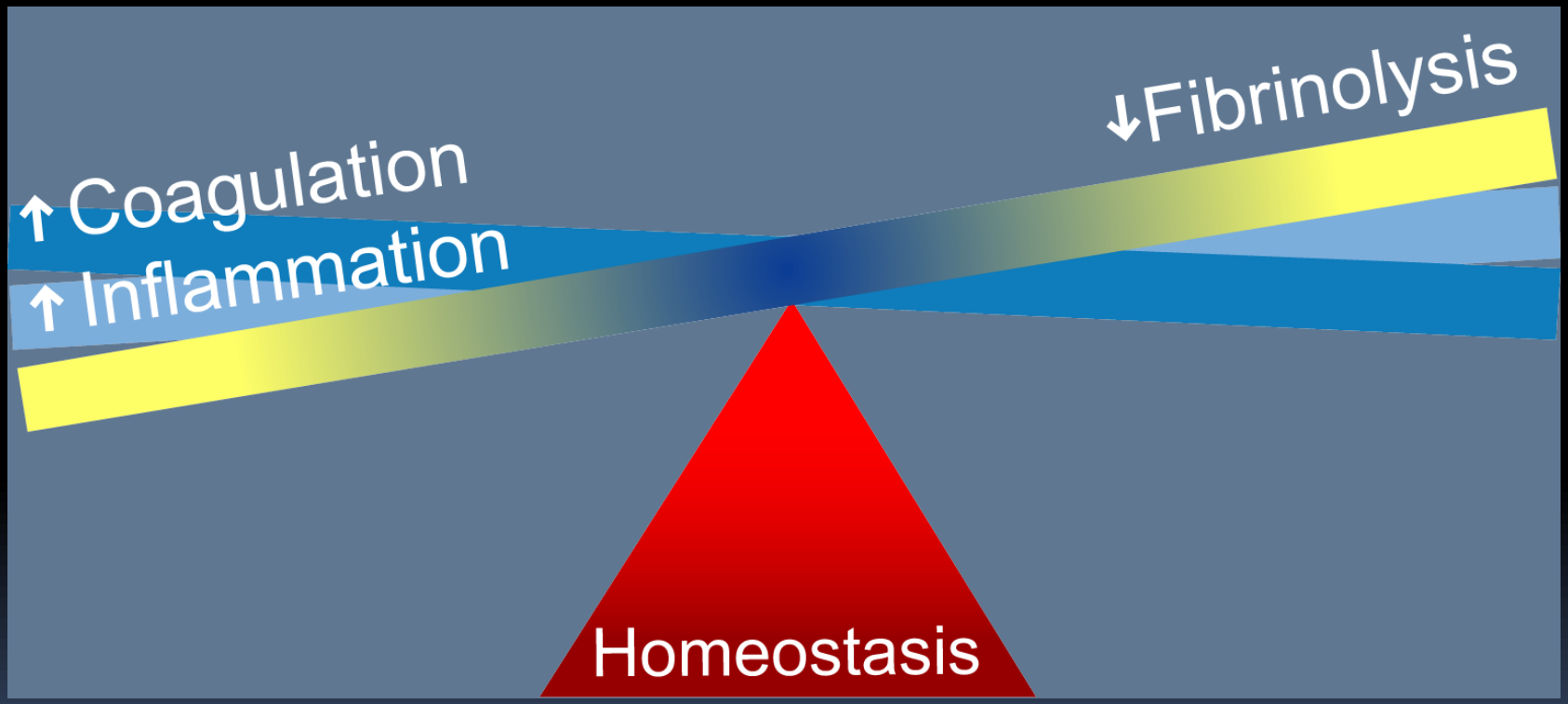
Source: Critical Care Nurse Supplement, 2004

Pathophysiology of Sepsis

- The release of the inflammatory mediators starts the Coagulation Cascade leading to the development of a clot.
- To maintain this clot, inhibitors are released to suppress fibrinolysis or breakdown. This is necessary to have time for the body to destroy the bacteria before the clot is gone.

Source: Critical Care Nurse Supplement, 2004

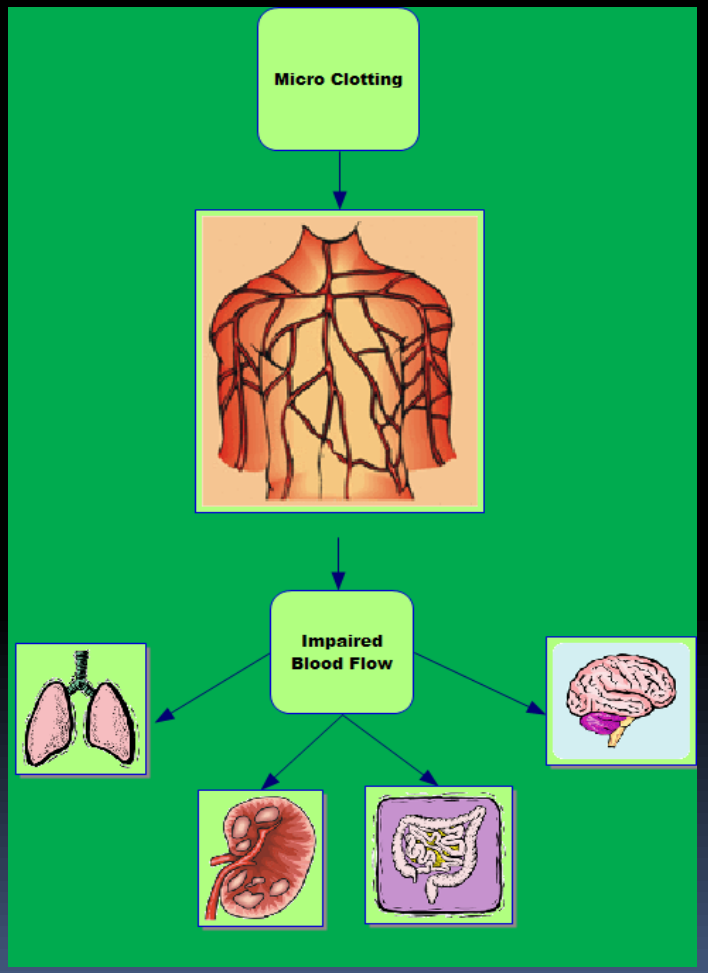
Homeostasis Is Unbalanced in Severe Sepsis



Carvalho AC, Freeman NJ. *J Crit Illness.* 1994;9:51-75; Kidokoro A et al. *Shock.* 1996;5:223-8; Vervloet MG et al. *Semin Thromb Hemost.* 1998;24:33-44.

Activation of Coagulation

The enhanced clotting continues making tiny clots or "microthrombi" in the vascular system which impairs blood flow and organ perfusion.



Activation of Fibrinolysis

Fibrinolysis, or the breakdown of clots, is the body's response to the increased clotting and inflammation.

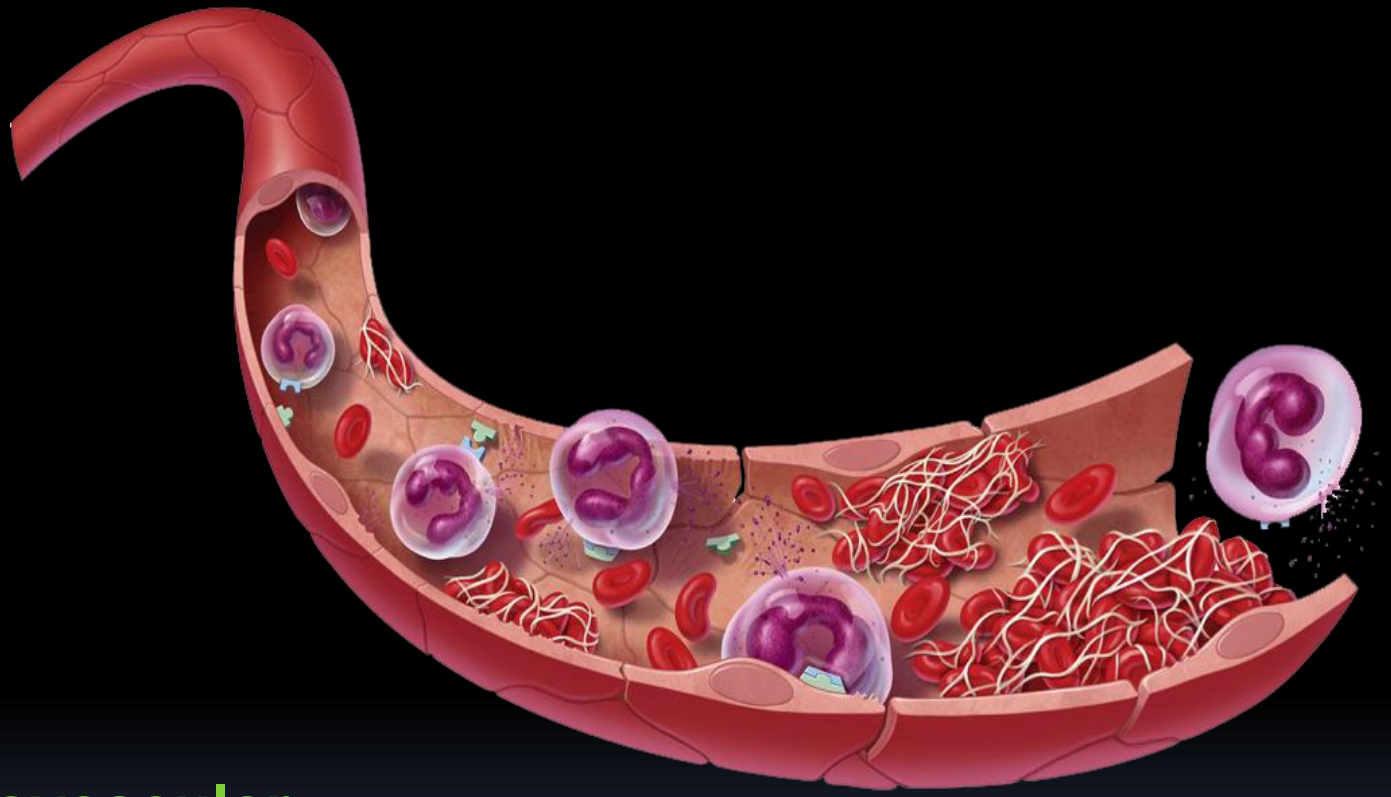
In sepsis this breakdown is inhibited or slowed through

- Plasminogen Activator Inhibitor-1 (PAI-1)
- Thrombin Activatable Fibrinolysis Inhibitor (TAFI)

Activation of Fibrinolysis

The increase levels of these two inhibitors, Plasminogen Activator Inhibitor-1(PAI-1) and Thrombin Activatable Fibrinolysis Inhibitor (TAFI), suppress fibrinolysis even more creating a state of “coagulopathy”.

SEVERE SEPSIS PATHOPHYSIOLOGY



Microvascular dysfunction

- ↑ Inflammation
- ↑ Coagulation
- ↓ Fibrinolysis

→ **Hypoperfusion/hypoxia** → **Organ dysfunction**

Microvascular thrombosis
Endothelial dysfunction

Global tissue hypoxia
Direct tissue damage

Making Matters Worse
The Role of Endothelium in Sepsis

Normal endothelium has anticoagulant abilities and plays a role in the body's homeostasis abilities including:

- Vasomotor tone
- Movement of cells and nutrients
- Maintaining blood fluidity

When activated, endothelium also plays a role in the inflammatory, coagulation, and fibrinolytic components of sepsis.

Making Matters Worse

- In sepsis the endothelium becomes damaged which makes the "inflammatory process" worse by releasing more cytokines (TNF-a and IL-1) causing neutrophils to stick to its' lining.
- The "activation" of the capillary endothelium leads to increased permeability causing fluid to "leak" out of the capillaries and into the extracellular spaces.

Source: http://www.xigris.com/Learning_Modules/course_01/module_02/index.htm

Question: Why do Septic Patients Die?

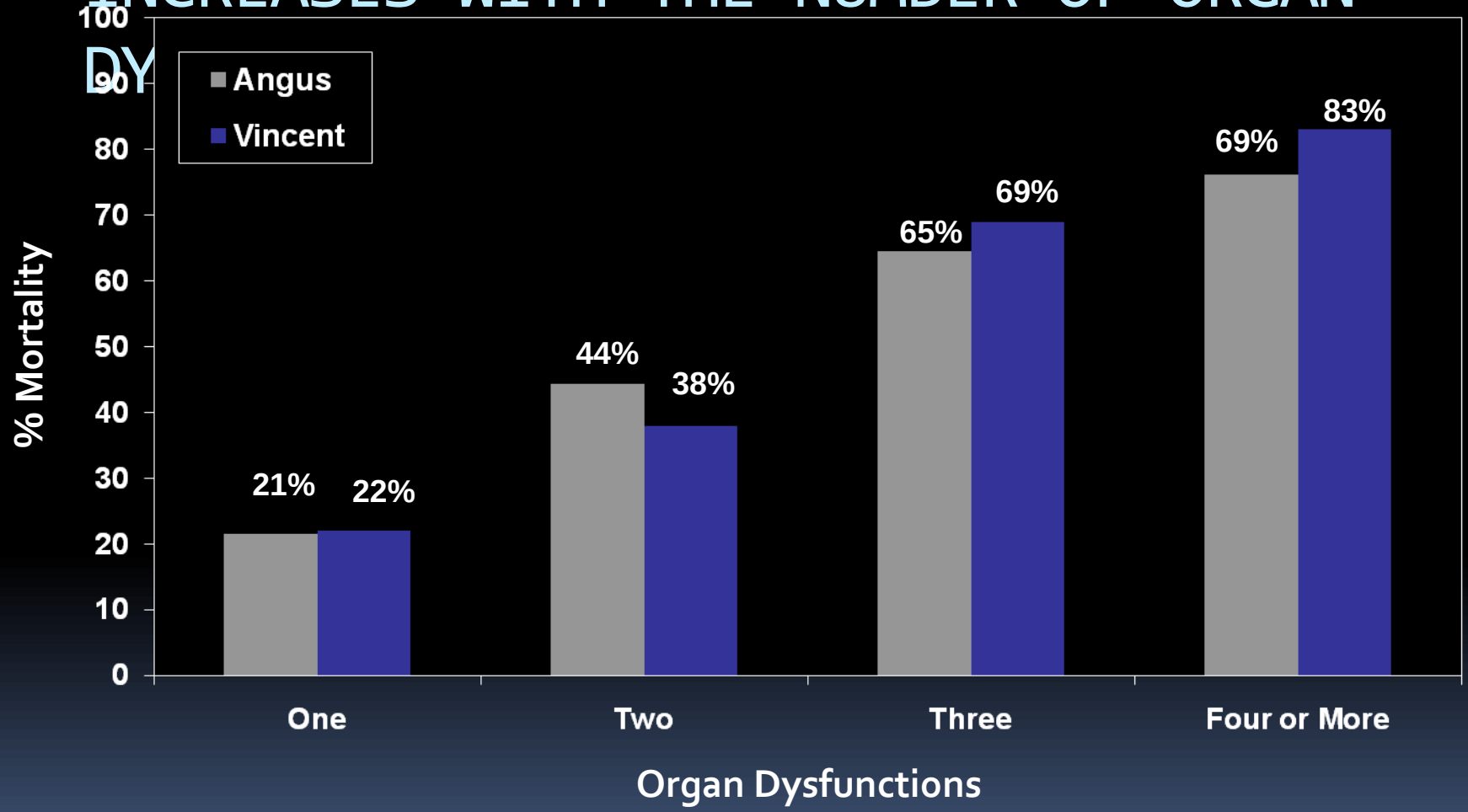
- Answer: Organ Failure

Organ Failure and Mortality

- Knaus, et al. (1986):
  - Direct correlation between number of organ systems failed and mortality.
  - Mortality Data:

#OSF	D1	D2	D3	D4	D5	D6	D7
1	22%	31%	34%	35%	40%	42%	41%
2	52%	67%	66%	62%	56%	64%	68%
3	80%	95%	93%	96%	100 %	100 %	100 %

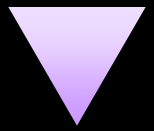
SEVERE SEPSIS-ASSOCIATED MORTALITY INCREASES WITH THE NUMBER OF ORGAN DY



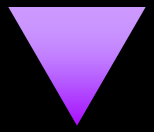
Angus DC, et al. *Crit Care Med.* 2001;29:1303-1310.
Vincent JL, et al. *Crit Care Med.* 1998;21:1793-1800.

Severe Sepsis: The Final Common Pathway

Endothelial Dysfunction and Microvascular Thrombosis



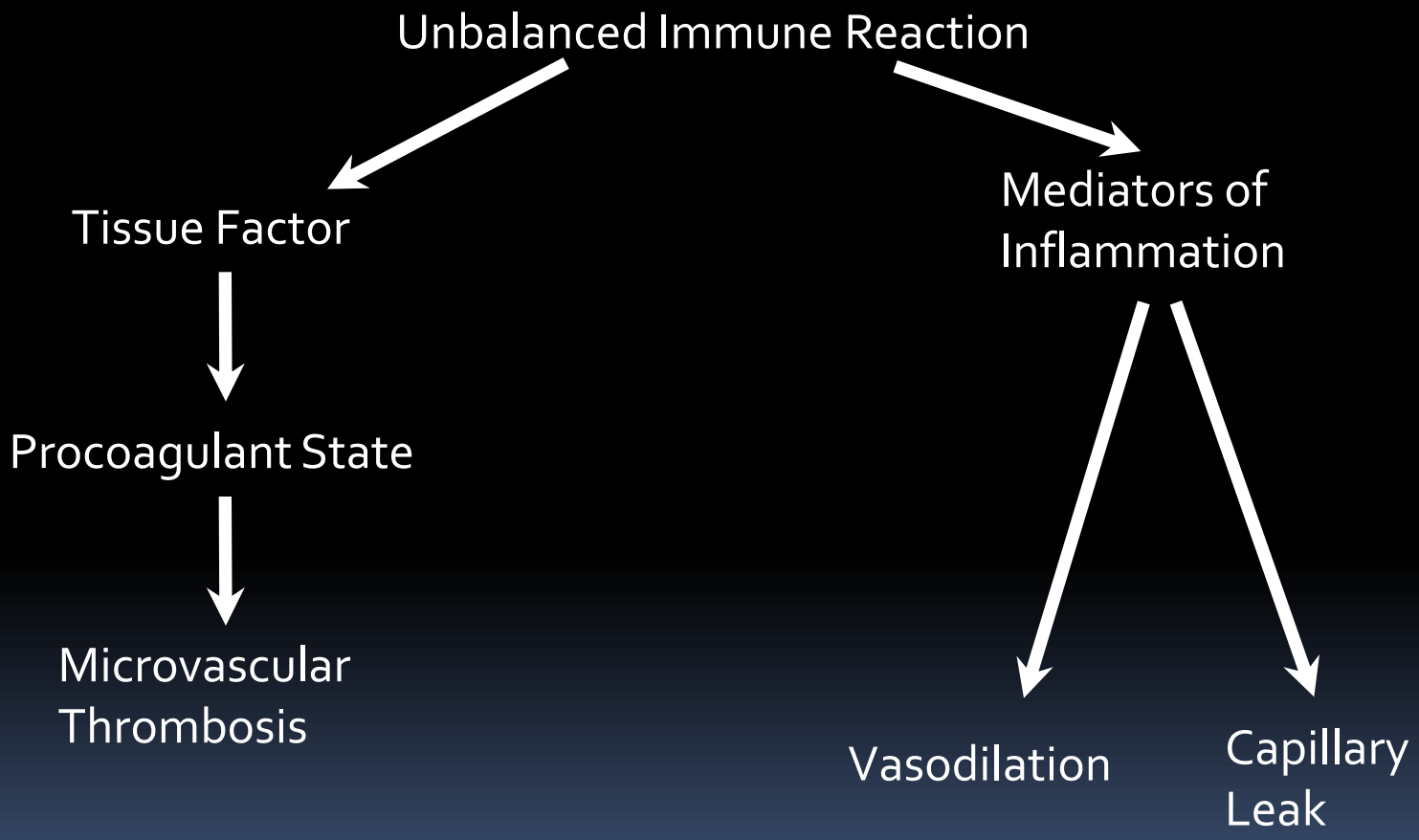
Hypoperfusion/Ischemia



Acute Organ Dysfunction (Severe Sepsis)

Death

Sepsis Pathogenesis



Evolution of Sepsis care

Established Core Rx:
Source Control
Antibiotics
Resuscitation
Supportive Care

Established Core Rx:
Source Control
More Antibiotics
Faster Resuscitation
Better Supportive Care

In general the process of care has improved

Steroids

No Steroids
Endotoxin Antagonists
LPS/LPS receptor antagonists
anti-TNF
NSAIDs
Nitric Oxide Synthase Inhibitors
Tissue Factor Pathway Inhibitors
anti-TLR4

Xigris
Tight Glycemic Control
Looser Glycemic Control

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, 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.

How do you Quickly deliver complex care?

Mobilization and coordination of people and resources.

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*

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.

System-based Approaches to sepsis

Early-Goal Directed Therapy

- INCLUSION = SEPSIS AND [BP < 90 after fluid OR Lactate > 4]

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

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.

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*

Used to promote:

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

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.

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)

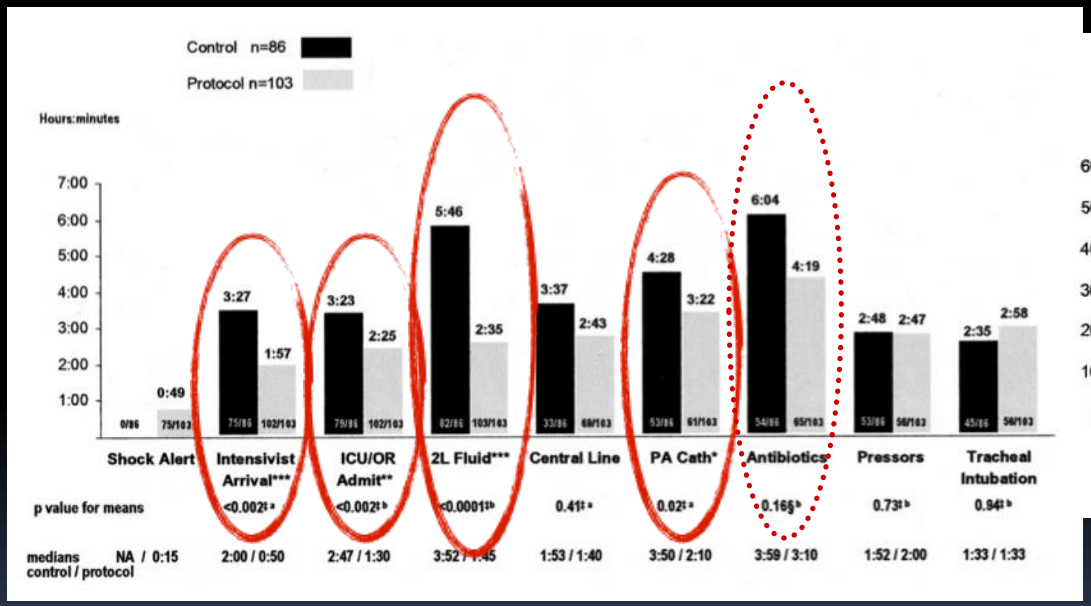
Do what you normally do. We will be watching.

AFTER (protocol)

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.

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



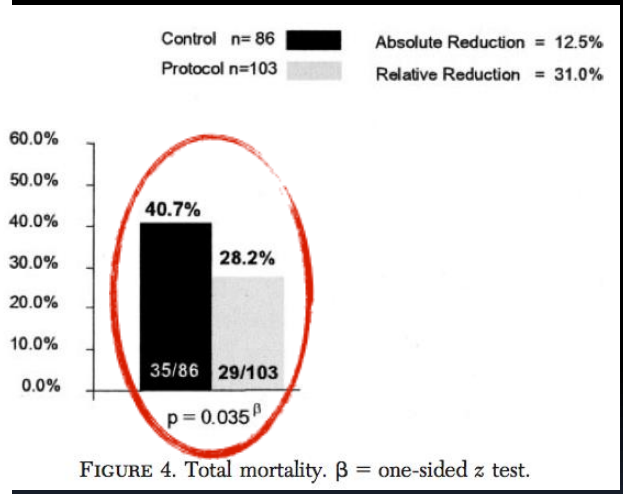
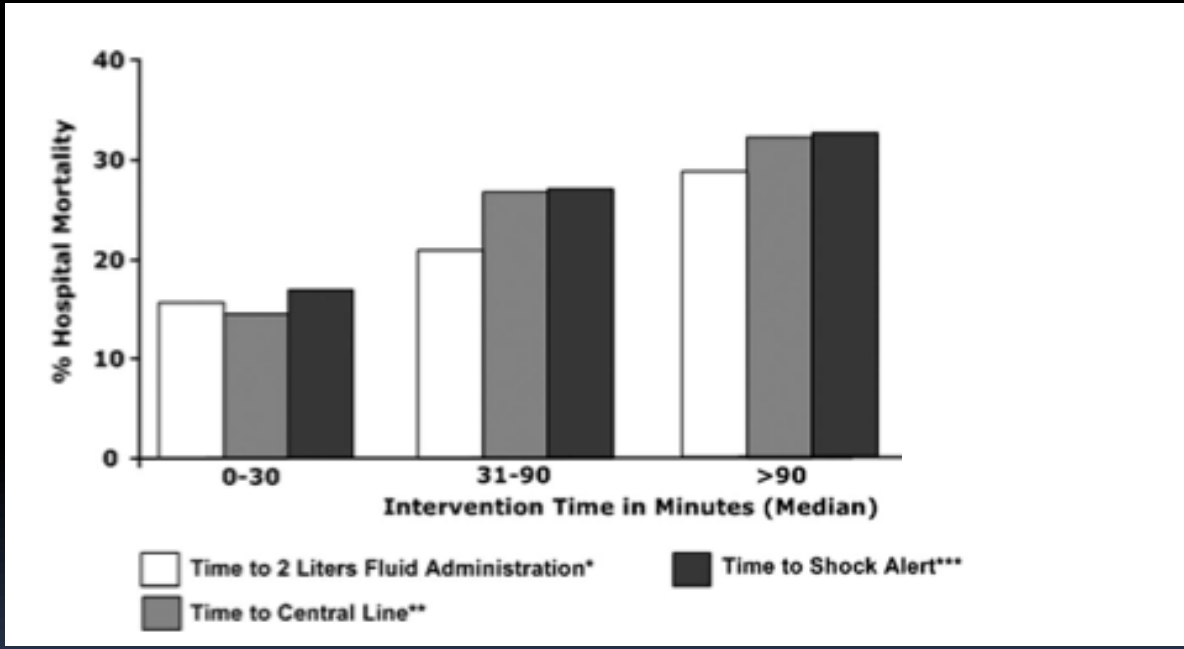


FIGURE 4. Total mortality. β = one-sided z test.

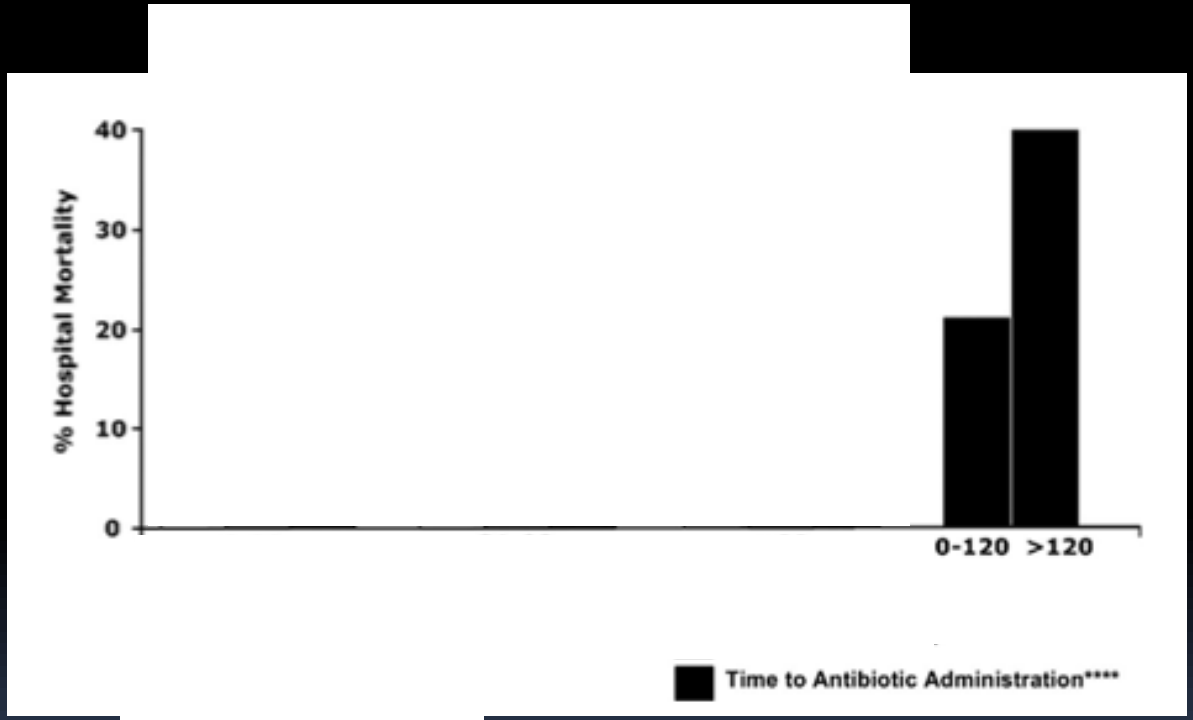
Sebat, F., Johnson, D., Musthafa, A. A., Watnik, M., Moore, S., Henry, K., & Saari, M. (2005). A multidisciplinary community hospital program for early and rapid resuscitation of shock in nontrauma patients. *Chest*, *127*(5), 1729–1743.

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



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.

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



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.

BEFORE

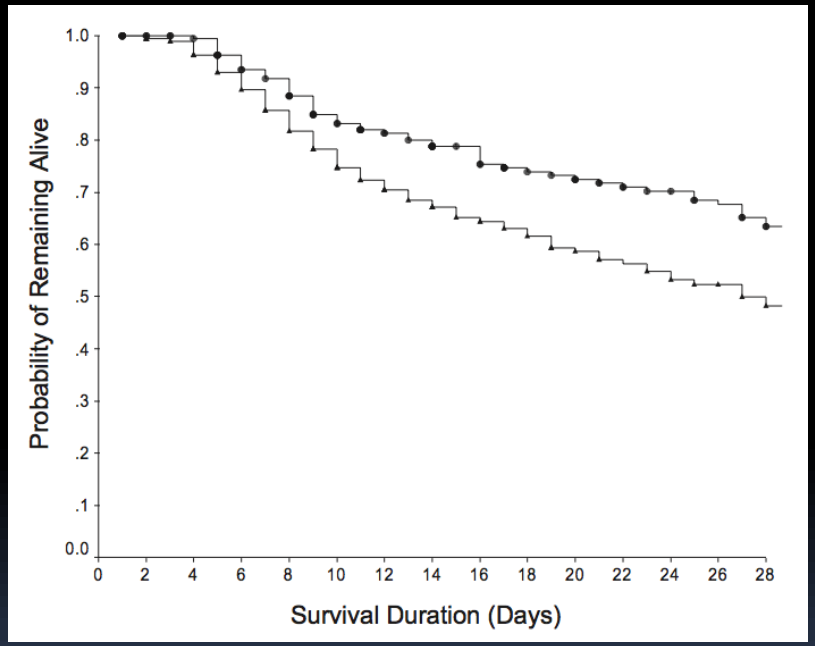
Do whatever it is that you normally do. We will be watching.

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.

Thiel, S. W., Asghar, M. F., Micek, S. T., Reichley, R. M., Doherty, J. A., & Kollef, M. H. (2009). Hospital-wide impact of a standardized order set for the management of bacteremic severe sepsis*. *Critical Care Medicine*, *37*(3), 819–824. doi:10.1097/CCM.0b013e318196206b



After

Before

Thiel, S. W., Asghar, M. F., Micek, S. T., Reichley, R. M., Doherty, J. A., & Kollef, M. H. (2009). Hospital-wide impact of a standardized order set for the management of bacteremic severe sepsis*. *Critical Care Medicine*, *37*(3), 819–824. doi:10.1097/CCM.0b013e318196206b

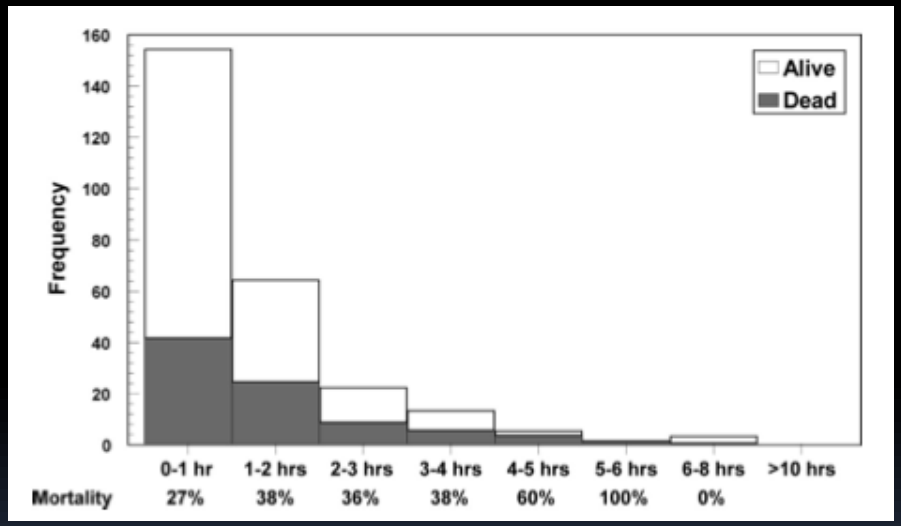
	Rivers 2001 RCT	Sebat 2005 Before-After	Nguyen 2007 Complete or Not	Thiel 2009 Before-After	Levy 2011 Before-After
Goals	CVP >8 MAP > 65 ScVO2 >70% HCT >30	MAP > 70 SaO2 > 92 UOP > 30ml/h SvO2 > 60 CI > 2.5	ABX in 4 h CVP > 8, MAP > 65, ScVO2 > 70%, HCT > 30 Check Lactate Steroids	Appropriate ABX in 4 h, CVP > 8, MAP > 65, ScVO2 > 70%	Early ABX, Blood Cultures, Appropriate ABX, CVP > 8, MAP > 65, SvO2 > 70%
Specific Interventions	Fluids, Blood, Pressors	ABX, Fluids Pressors	ABX, Fluids Blood, Pressors	ABX, Fluids, Pressors, Steroids, Xigris, Other Supportive Care	ABX, Fluids, Pressors, Steroids, Xigris, Other Supportive Care
System Interventions	ED-based Sepsis Team	Screening, Education, Shock Team, Protocols	Education, In-services, Protocols	Education, In-services, Order Set, Protocols	Screening, Education, Order Sets
Absolute Change in Mortality	-16%	-12%	-19%	-16%	-7%

- Identify Sepsis as early as possible
- Broad Spectrum antibiotics ASAP and Identify source(s) of infection
- Identify severity: Vitals, mental status, UOP, LACTATE, other labs.
- Volume and physiologic resuscitation ASAP with GOALS.
- Tweak your system so these things happen FAST

- Train all providers
- Vital sign/Laboratory alerting systems
- ?Biomarkers

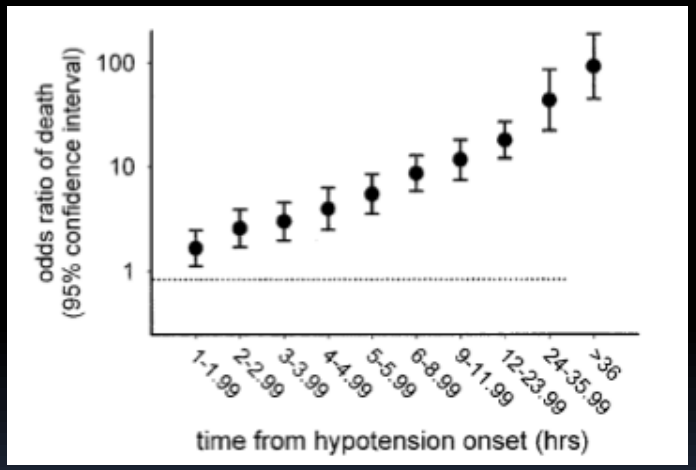
No randomized-controlled data

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.

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.

Defining the severity of sepsis

- Importance of looking for organ failure is self evident.

- Identification of “shock” dramatically alters the treatment and mortality.
  - Blood Pressure, Response to Fluid, LACTATE

- 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.

Surviving Sepsis targets of fluid resuscitation

What are they?

- SBP
- MAP
- CVP
- U/o
- Lactate
- $ScvO_2$
- HCt

Surviving Sepsis targets of fluid resuscitation

What are they?

- SBP > 90
- MAP > 65
- CVP 8 - 12
- U/o > 0.5 ml/kg/hr
- Lactate < 1
- $ScvO_2$ >70
- HCt > 30

- Crystalloids are favored as the initial fluid
- Hydroxyethyl starches are likely harmful
- Albumin may have a role, particularly if alot of fluid is given

Chronic Phase

- Monitor for and prevent recurrence of sepsis
  - VAP, CLABSI, UTI. Infection Control Practices.
- Lung Protective Ventilator Strategies
- Protocolized Sedation, Daily Awakenings
- Nutritional Support
- Early Mobilization
- Success with these measures is most likely with a multi-disciplinary approach.

- 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 chronic phase of care to ensure compliance

How do we manage sepsis and septic shock?

1) Investigate and treat sepsis
   - Try and find and treat source
   - Early blood cultures
   - Start antibiotics asap ideally within 1 hour and after cultures taken
2) Assess extent of end organ hypoperfusion and improve oxygen delivery (early goal directed therapy)

Oxygen delivery

What does it mean?

Oxygen delivery

What does it mean?

Delivery (DO_2) = O_2 content x cardiac output

= ([Hb] x SpO_2 x 1.34) x (HR x SV)

Oxygen content = [Hb] x SpO_2 x 1.34

Cardiac output = HR x SV

Fluid Challenge

What is the difference between an infusion and a challenge?

Fluid Challenge

What is the difference between an infusion and a challenge?

250 to 500 ml colloid (or blood products)

500 to 1000ml Hartmann's

[NOT 5% dextrose]

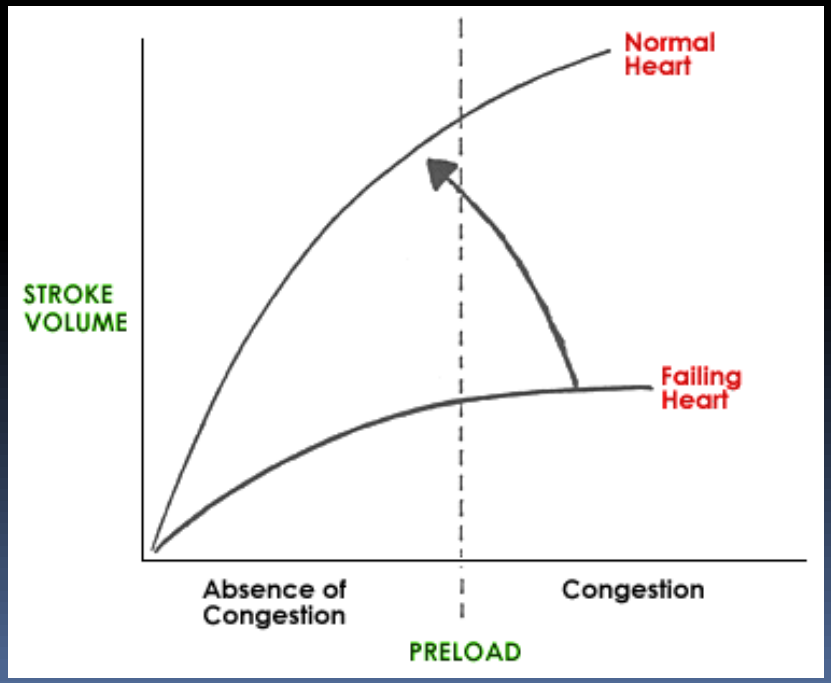
As fast a possible (with pressure bag)

You at the bedside

Fluid Challenge

Aim is to improve SV (and hence CO) by increasing preload

Frank-Starling mechanism



Markers of perfusion

What are they?

Markers of perfusion

What are they?

- Clinical signs
  - Warm skin, conscious level, u/o
- Haemodynamic variables
  - CVP
- Bloods
  - Serum Lactate
  - $ScvO_2$

CVP

What does it mean?

CVP

What does it mean?

Starling's Law

Estimate of LVEDV (i.e. preload)

Not always a good correlation with volume-responsiveness

However if low strongly suggestive of hypovolaemia

Lactate

What does it mean?

Lactate

What does it mean?

- Increased production (anaerobic glycolysis)
  - Tissue hypoperfusion
  - Tissue dysoxia
- Reduced metabolism
  - Hepatic
  - Renal
- <1 is normal, 1-2 is a concern, >2 is bad, >4 is very bad

Scv02

What does it mean?

ScvO2

What does it mean?

- Balance between oxygen delivery and consumption (VO_2)
- $ScvO_2 = SaO_2 - \frac{VO_2}{CO}$
- Target > 70%

Scv02

What can I do if it's low?

ScvO2

What can I do if it's low?

Delivery = [Hb] x SpO_2 x 1.34 x HR x SV

ScvO2

What can I do if it's low?

Delivery = [Hb] x SpO_2 x 1.34 x HR x SV

Fluid optimise

Transfuse packet cells

HCt > 30%

Inotropes

Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2012

R. Phillip Dellinger, Mitchell M. Levy, Andrew Rhodes, Djillali Annane, Herwig Gerlach, Steven M. Opal, Jonathan E. Sevransky, Charles L. Sprung, Ivor S. Douglas, Roman Jaeschke, Tiffany M. Osborn, Mark E. Nunnally, Sean R. Townsend, Konrad Reinhart, Ruth M. Kleinpell, Derek C. Angus, Clifford S. Deutschman, Flavia R. Machado,Gordon D. Rubenfeld, Steven A. Webb, Richard J. Beale, Jean-Louis Vincent, Rui Moreno, and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup.

Crit Care Med. 2013; 41:580-637

Intensive Care Medicine 2013; ..

Current Surviving Sepsis Campaign Guideline Sponsors

- American Association of Critical-Care Nurses
- American College of Chest Physicians
- American College of Emergency Physicians
- Australian and New Zealand Intensive Care Society
- Asia Pacific Association of Critical Care Medicine
- American Thoracic Society
- Brazilian Society of Critical Care(AIMB)
- Canadian Critical Care Society
- Chinese Society of Critical Care Medicine
- Emirates Intensive Care Society
- European Respiratory Society
- European Society of Clinical Microbiology and Infectious Diseases
- European Society of Intensive Care Medicine
- European Society of Pediatric and Neonatal Intensive Care
- Infectious Diseases Society of America
- Indian Society of Critical Care Medicine
- International Pan Arab Critical Care Medicine Society
- Japanese Association for Acute Medicine
- Japanese Society of Intensive Care Medicine
- Pediatric Acute Lung Injury and Sepsis Investigators
- Society Academic Emergency Medicine
- Society of Critical Care Medicine
- Society of Hospital Medicine
- Surgical Infection Society
- World Federation of Critical Care Nurses
- World Federation of Pediatric Intensive and Critical Care Societies
- World Federation of Societies of Intensive and Critical Care Medicine

Participation and endorsement:

German Sepsis Society

Latin American Sepsis Institute

"Time Zero"

- Time Zero = time of presentation
  - ED, Medical Floors, ICU
- Both bundles time based
- Most important time based elements:
  - Antibiotic timing
  - Resuscitation timing (EGDT)

Antibiotic therapy

1. We recommend that intravenous antimicrobial therapy be started as early as possible and within the first hour of recognition of septic shock (1B) and severe sepsis without septic shock (grade1C).

Hospital Mortality by Time to

Time to ABX[1], hrs	OR[2]	95% CI		*p*-value	Probability of mortality[3]	95% CI	
0 (ref)	1.00	---	---	---	18.7	17.5	19.9
1	1.05	1.02	1.07	< 0.001	19.3	18.3	20.4
2	1.09	1.04	1.15	< 0.001	20.0	19.1	21.0
3	1.14	1.06	1.23	< 0.001	20.8	19.7	21.8
4	1.19	1.08	1.32	< 0.001	21.5	20.3	22.8
5	1.25	1.11	1.41	< 0.001	22.3	20.7	23.9
6	1.31	1.13	1.51	< 0.001	23.1	21.2	25.1

[1]Time to ABX is based on 15,948 observations that are greater than or equal to zero

[2]Hospital mortality odds ratio referent group is 0 hours for the time to ABX and is adjusted by the number of baseline organ failures, infection type (community vs. nosocomial), and geographic region (Europe, North America, and South America)

Fluid therapy

4. We recommend that initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemnic be started with ≥ 1000 mL of crystalloids (to achieve a minimum of 30ml/kg of crystalloids in the first 4 to 6 hours).

   (Grade 1B).

Logistic Regression Model

Compliance indicator	Hospital mortality odds ratio[1]	95% CI	*p*-value
1. Serum lactate within 6 hours	0.71	0.67 – 0.75	< 0.001
2. Blood cultures before antibiotics	0.81	0.76 – 0.86	< 0.001
3. Broad spectrum antibiotics	0.83	0.79 – 0.88	< 0.001
4. Fluids and vasopressors	0.57	0.54 – 0.61	< 0.001
5. CVP ≥ 8 mm Hg within 6 hours	0.74	0.69 - 0.79	< 0.001
6. $ScvO_2$ ≥ 70% within 6 hours	0.73	0.67 – 0.78	< 0.001
7. Resuscitation bundle	0.77	0.72 – 0.83	< 0.001
8. Low-dose steroids policy	0.82	0.77 - -0.88	< 0.001
9. Drotrecogin alfa policy	0.93	0.88 – 0.98	0.008
10. Glucose control maintained	0.70	0.69 – 0.74	< 0.001
11. IPP < 30 cm H_20	0.78	0.71 – 0.86	< 0.001
12. Management bundle	0.72	0.68 – 0.77	< 0.001
High resuscitation performance	0.79	0.75 – 0.83	< 0.001
High management performance	0.84	0.80 – 0.88	< 0.001

SSC Bundle:

TO BE COMPLETED WITHIN 3 HOURS OF TIME OF PRESENTATION [†]:

1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30ml/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 severe sepsis or septic shock ascertained through chart review.

SSC Bundle:

TO BE COMPLETED WITHIN 6 HOURS OF TIME OF PRESENTATION:

5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation to maintain a mean arterial pressure (MAP) ≥65mmHg)
6. In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36mg/dl):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation (ScvO2)*
7. Remeasure lactate*

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

The Importance of Early Detection

- Efforts to **just treat recognized sepsis** alone are incomplete

- A critical aspect of mortality reduction in the Campaign has been pushing practitioners to identify sepsis early.
  - Levy MM, Dellinger RP, Townsend SR ,et al. The Surviving Sepsis Campaign: Results Of An International Guideline-Based Performance Improvement Program Targeting Severe Sepsis. Crit Care Med. 2010 Feb;38(2):367-74.

- It may well be that earlier recognition accounts for much of the signal in mortality reduction and partially explains sharply increasing incidence.
  - Gaieski DF, Edwards JM, Kallan MJ, et al. Benchmarking the Incidence and Mortality of Severe Sepsis in the United States. Crit Care Med. 2013 Feb 25. [Epub ahead of print]

- Without recognition that the clock is ticking, there is simply no incentive to recognize a challenging diagnosis early.

6 Hour Resuscitation Bundle

- Early Identification
- Early Antibiotics and Cultures
- Early Goal Directed Therapy

VOLUME 345 NOVEMBER 8, 2001 NUMBER 19

The New England Journal of Medicine

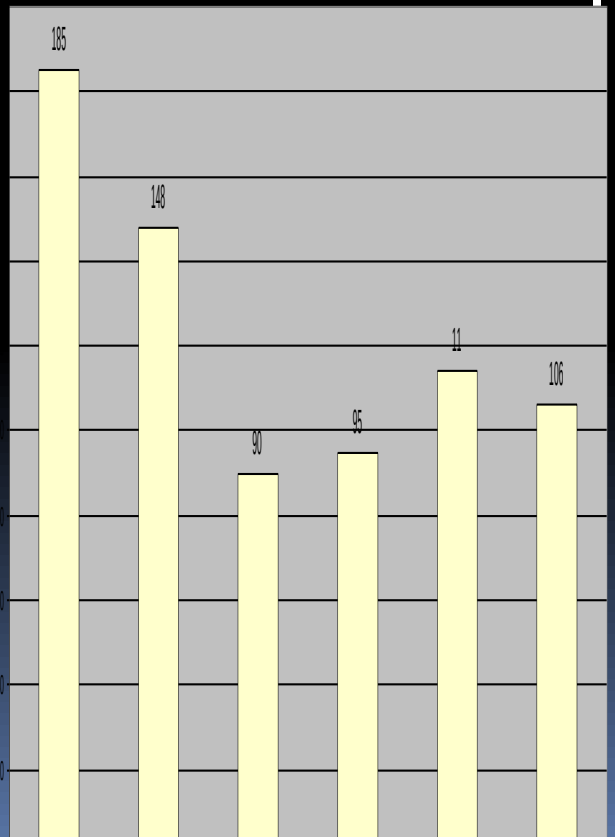
EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

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*

Rhode Island Hospital EGDT Data

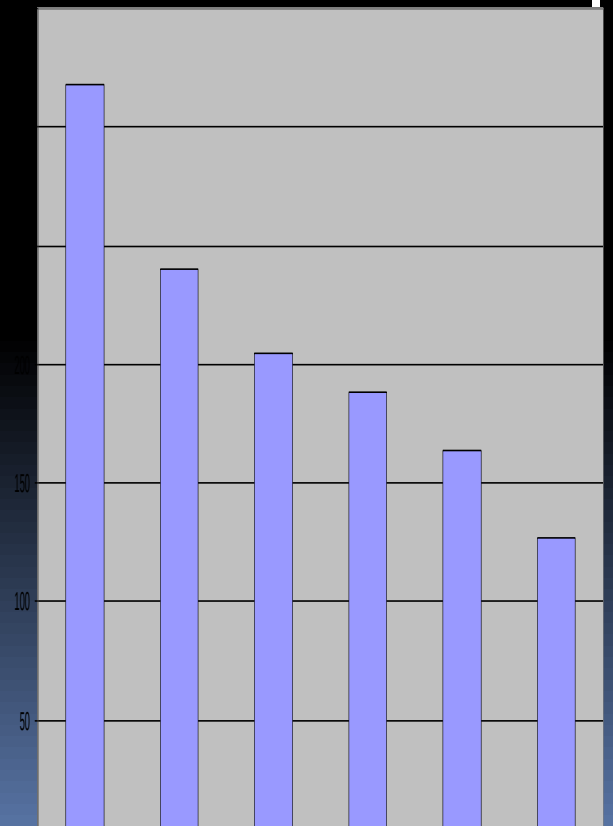
Time from Entering ED to Receiving Antibiotics

Reduced by 42%



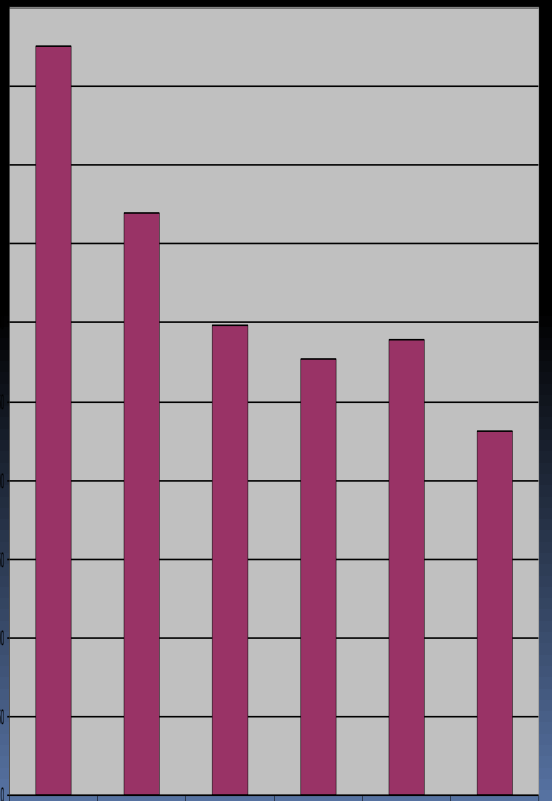
Time from Entering ED to Catheter Insertion

Reduced by 60%



Time from Entering ED to Transfer to MICU

Reduced by 51%



THANK YOU