

SEPSIS.

new insights.

new outlooks.

**Impact and Pathophysiology
of Sepsis**



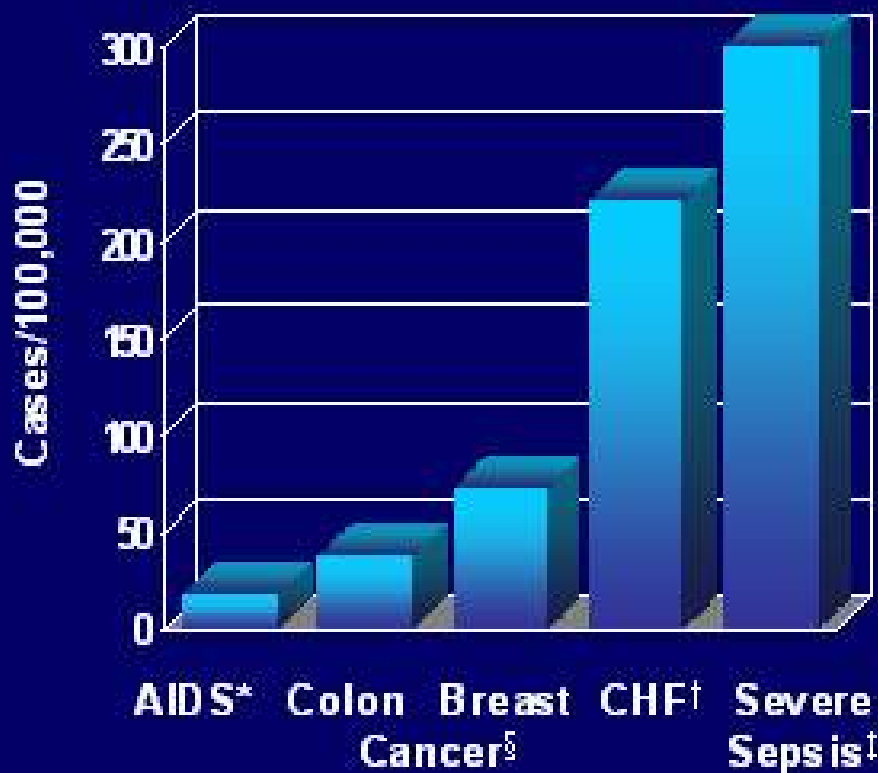
Severe Sepsis: A Significant Healthcare Challenge

- **Major cause of morbidity and mortality worldwide**
 - Leading cause of death in noncoronary ICU (US)*
 - 11th leading cause of death overall (US) †§
- **More than 750,000 cases of severe sepsis in US annually‡**
- **In the US, more than 500 patients die of severe sepsis daily‡**

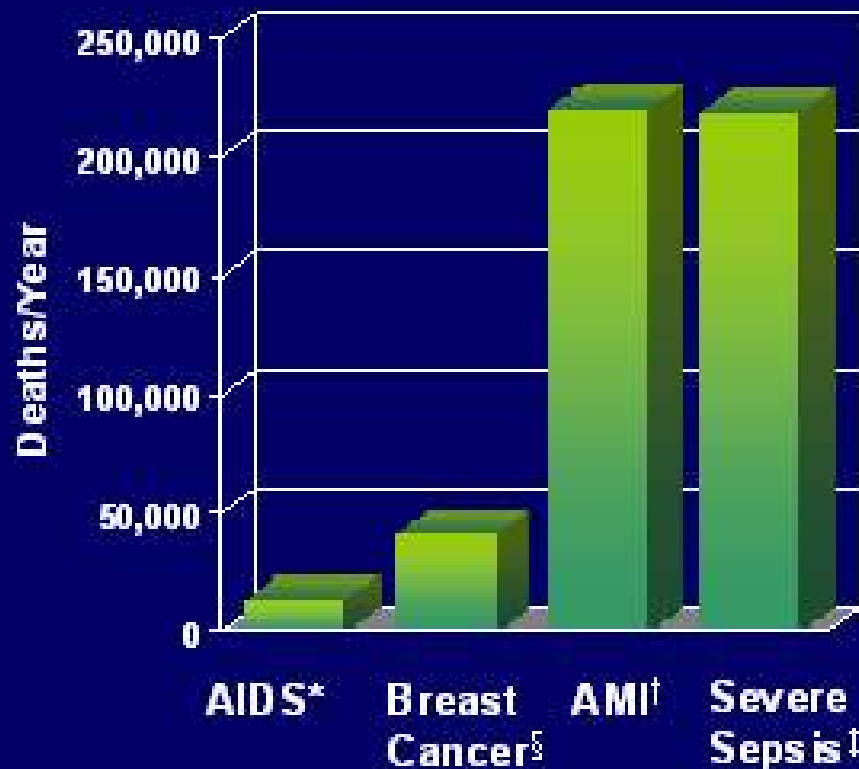
*Sands KE et al. *JAMA*. 1997;278:234-40; †Based on data for septicemia. §Murphy SL. National Vital Statistics Reports. ‡Angus DC et al. *Crit Care Med*. 2001 (In Press); reflects hospital-wide cases of severe sepsis as defined by infection in the presence of organ failure.

Severe Sepsis: Comparison With Other Major Diseases

Incidence of Severe Sepsis



Mortality of Severe Sepsis



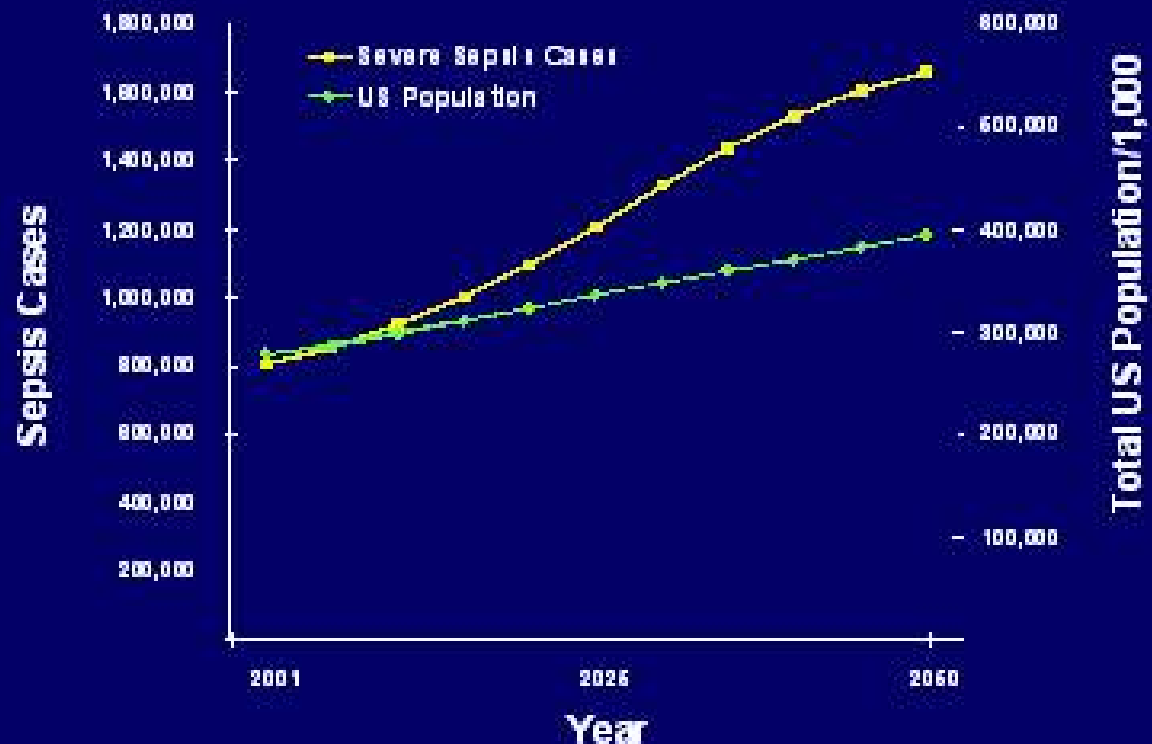
†National Center for Health Statistics, 2001. †American Cancer Society, 2001. *American Heart Association, 2000. †Angus DC et al. *Crit Care Med.* 2001 (In Press).

Severe Sepsis: A Growing Healthcare Challenge

Today

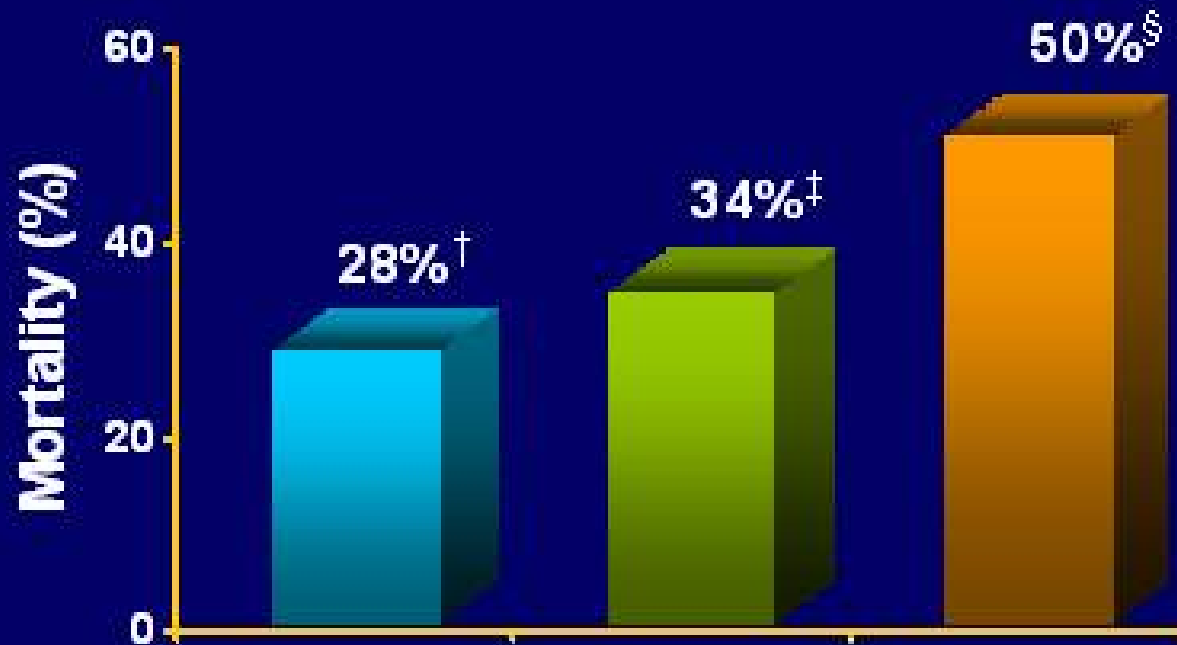
>750,000
cases of severe
sepsis/year
in the US*

Future



*Angus DC. *Crit Care Med.* 2001 (In Press).

Severe Sepsis: A Significant Healthcare Challenge



†Angus DC et al. *Crit Care Med*. 2001 (In Press).

‡Sands KE et al. *JAMA*. 1997;278:234-40.

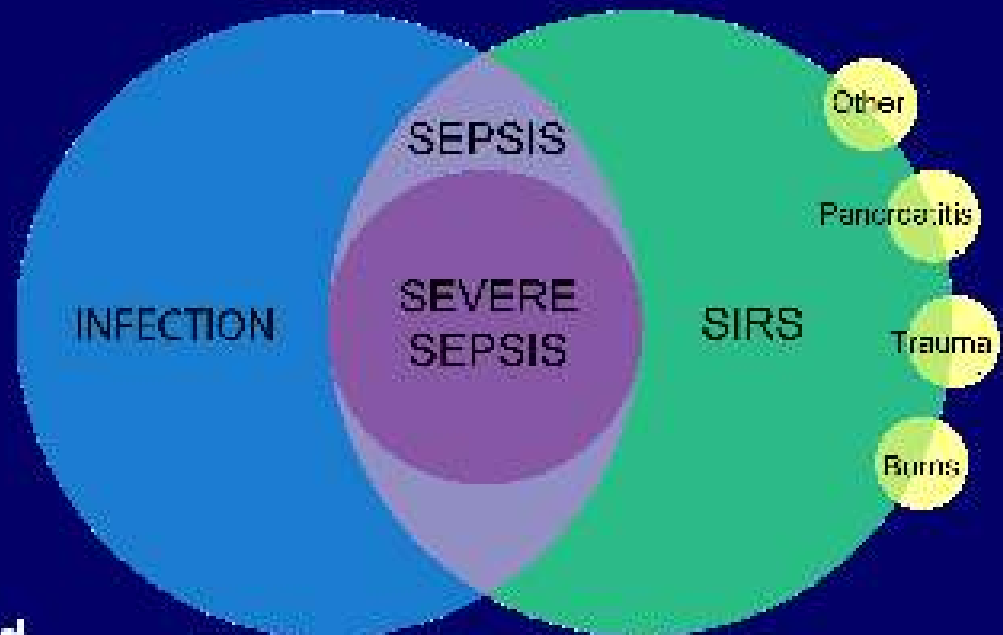
§Zeni F et al. *Crit Care Med*. 1997;1095-100.

ACCP/SCCM Consensus Definitions

- Infection
 - Inflammatory response to microorganisms, or
 - Invasion of normally sterile tissues
- Systemic Inflammatory Response Syndrome (SIRS)
 - Systemic response to a variety of processes
- Sepsis
 - Infection plus
 - ≥ 2 SIRS criteria
- Severe Sepsis
 - Sepsis
 - Organ dysfunction
- Septic shock
 - Sepsis
 - Hypotension despite fluid resuscitation
- Multiple Organ Dysfunction Syndrome (MODS)
 - Altered organ function in an acutely ill patient
 - Homeostasis cannot be maintained without intervention

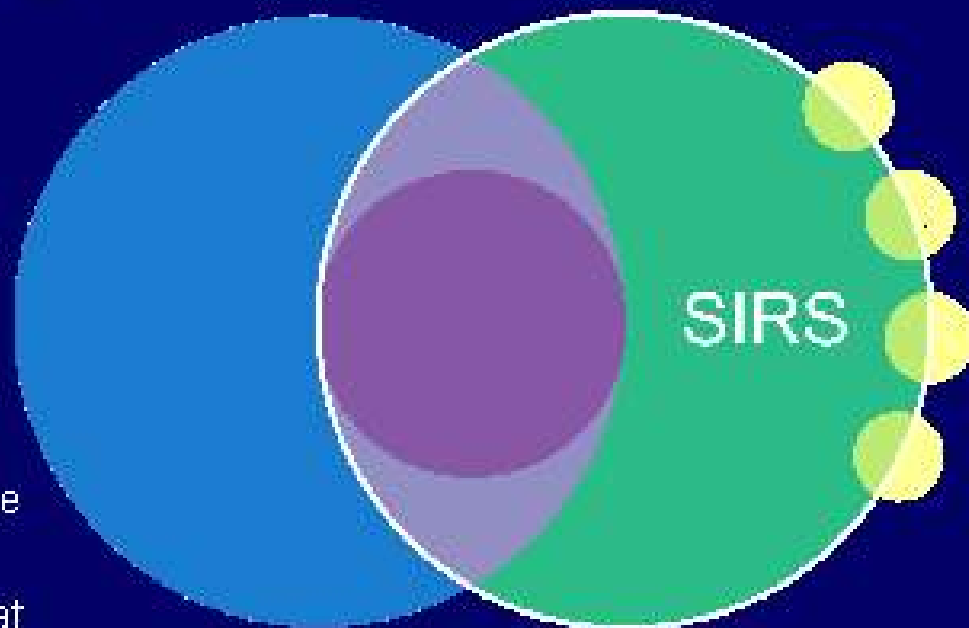
Sepsis: A Complex Disease

- This Venn diagram provides a conceptual framework to view the relationships between various components of sepsis.
- The inflammatory changes of sepsis are tightly linked to disturbed hemostasis.



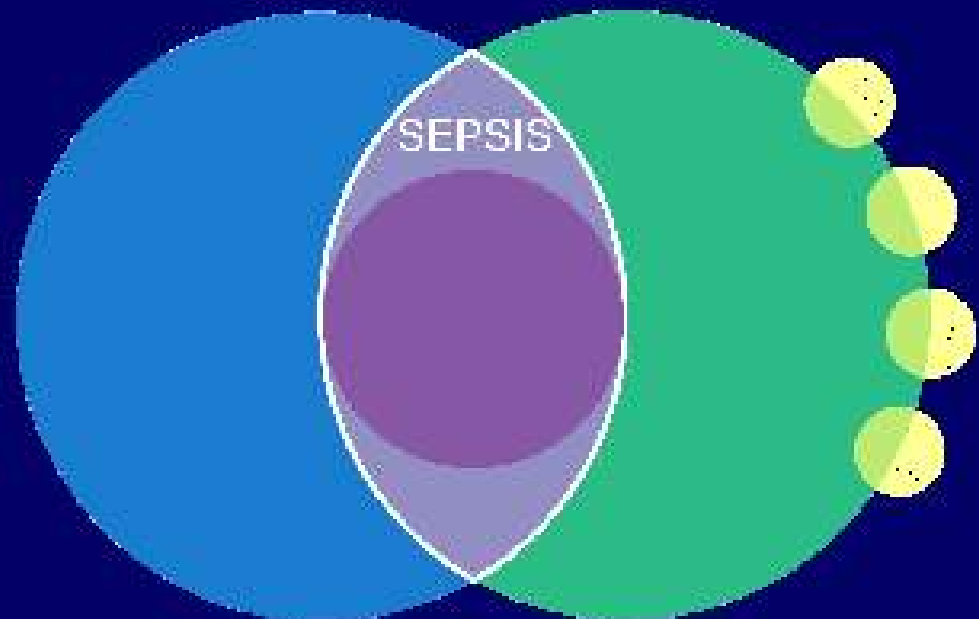
SIRS: More Than Just a Systemic Inflammatory Response

- SIRS: A clinical response arising from a nonspecific insult manifested by ≥ 2 of the following:
 - Temperature $\geq 38^{\circ}\text{C}$ or $\leq 36^{\circ}\text{C}$
 - HR ≥ 90 beats/min
 - Respirations ≥ 20 /min
 - WBC count $\geq 12,000/\mu\text{L}$ or $\leq 4,000/\mu\text{L}$ or $>10\%$ immature neutrophils
- Recent evidence indicates that hemostatic changes are also involved



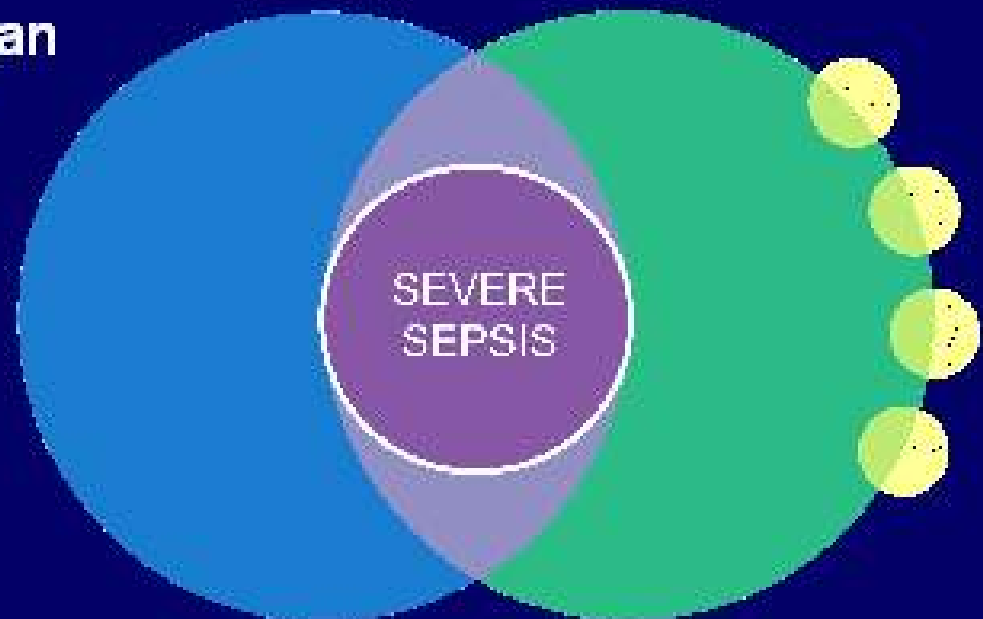
Sepsis: More Than Just Inflammation

- **Sepsis:**
 - Known or suspected infection
 - Two or more SIRS criteria
- **A significant link to disordered hemostasis**



Severe Sepsis: Acute Organ Dysfunction and Disordered Hemostasis

- **Severe Sepsis:**
Sepsis with signs of organ dysfunction in ≥ 1 of the following systems:
 - Cardiovascular
 - Renal
 - Respiratory
 - Hepatic
 - Hemostasis
 - CNS
 - Unexplained metabolic acidosis

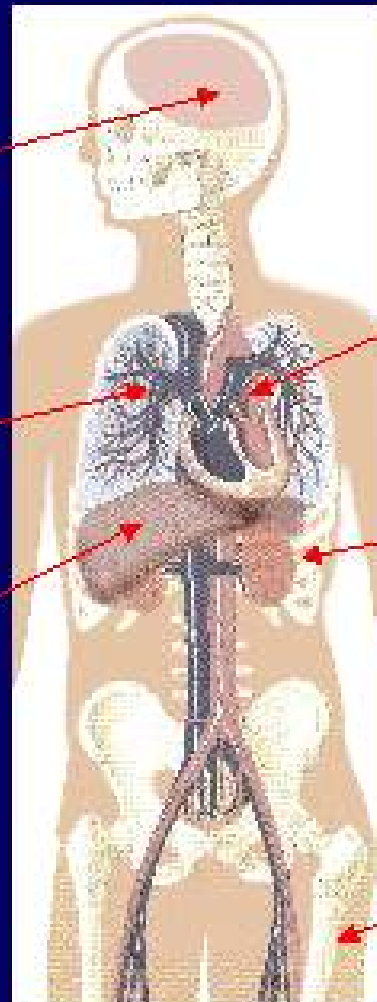


Identifying Acute Organ Dysfunction as a Marker of Severe Sepsis

Altered
Consciousness
Confusion
Psychosis

Tachypnea
 $\text{PaO}_2 < 70 \text{ mm Hg}$
 $\text{SaO}_2 < 90\%$
 $\text{PaO}_2/\text{FiO}_2 \leq 300$

Jaundice
 \uparrow Enzymes
 \downarrow Albumin
 \uparrow PT



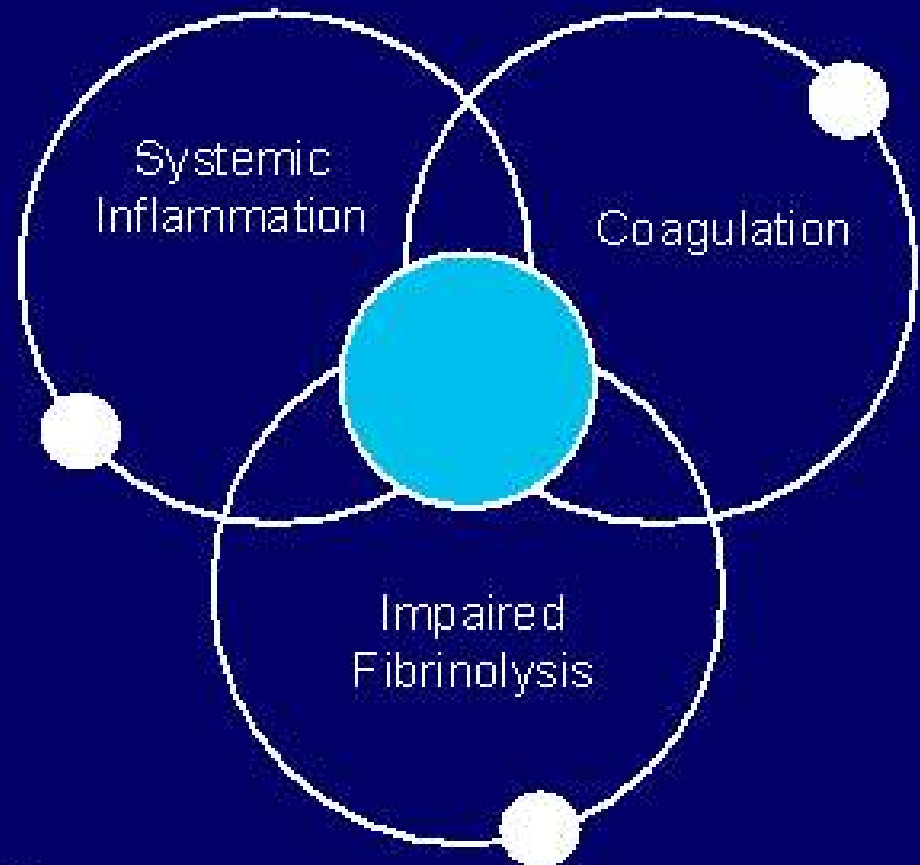
Tachycardia
Hypotension
 \uparrow CVP
 \uparrow PAOP

Oliguria
Anuria
 \uparrow Creatinine

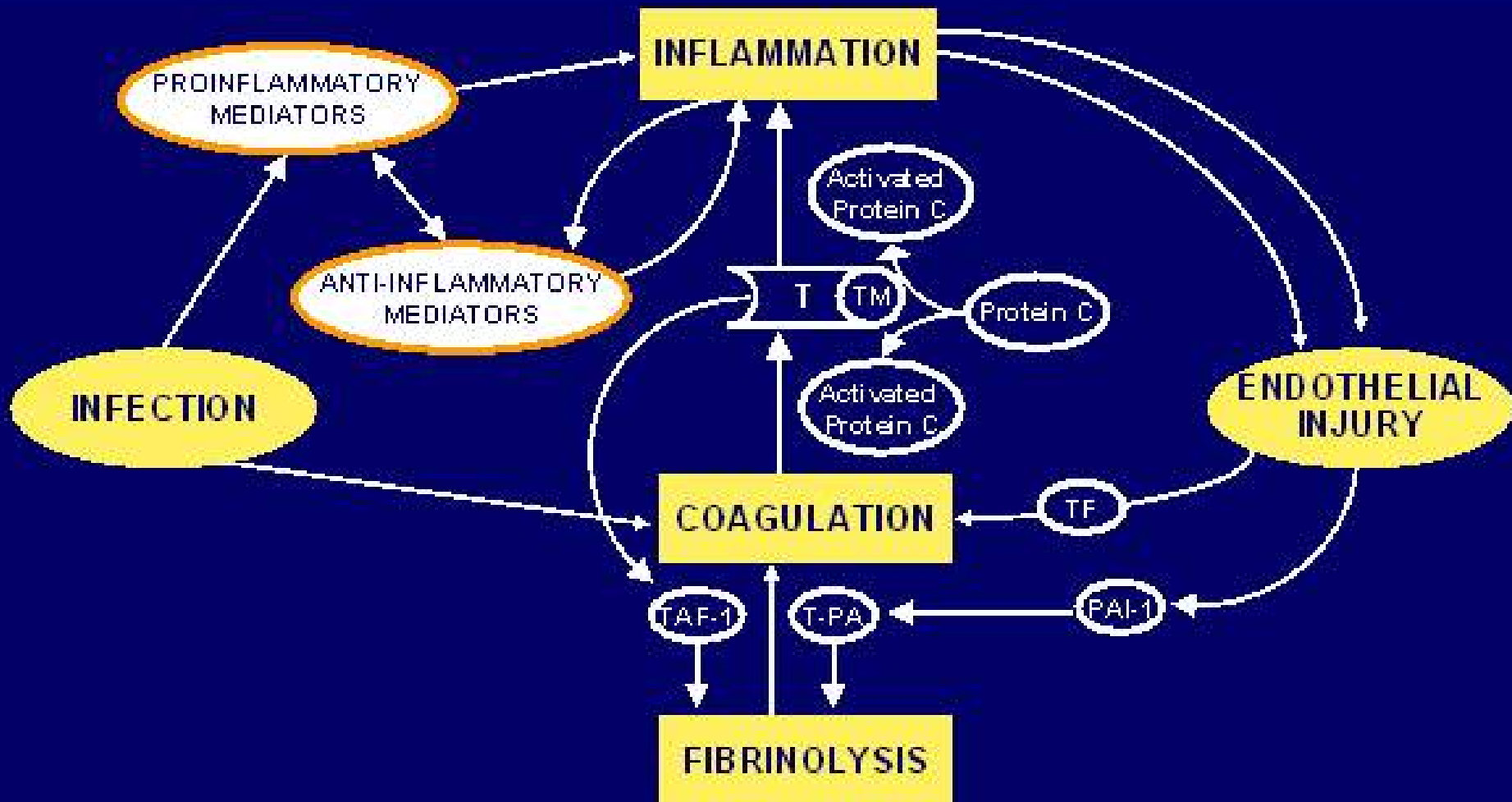
\downarrow Platelets
 \uparrow PT/APTT
 \downarrow Protein C
 \uparrow D-dimer

Severe Sepsis: A Complex and Unpredictable Clinical Syndrome

- High mortality rate (28%-50%)
- Heterogeneous patient population
- Unpredictable disease progression
- Unclear etiology and pathogenesis



Sepsis: A Network of Cascading Events



Systemic Activation of Inflammation in Sepsis

Inflammation is Activated in Sepsis

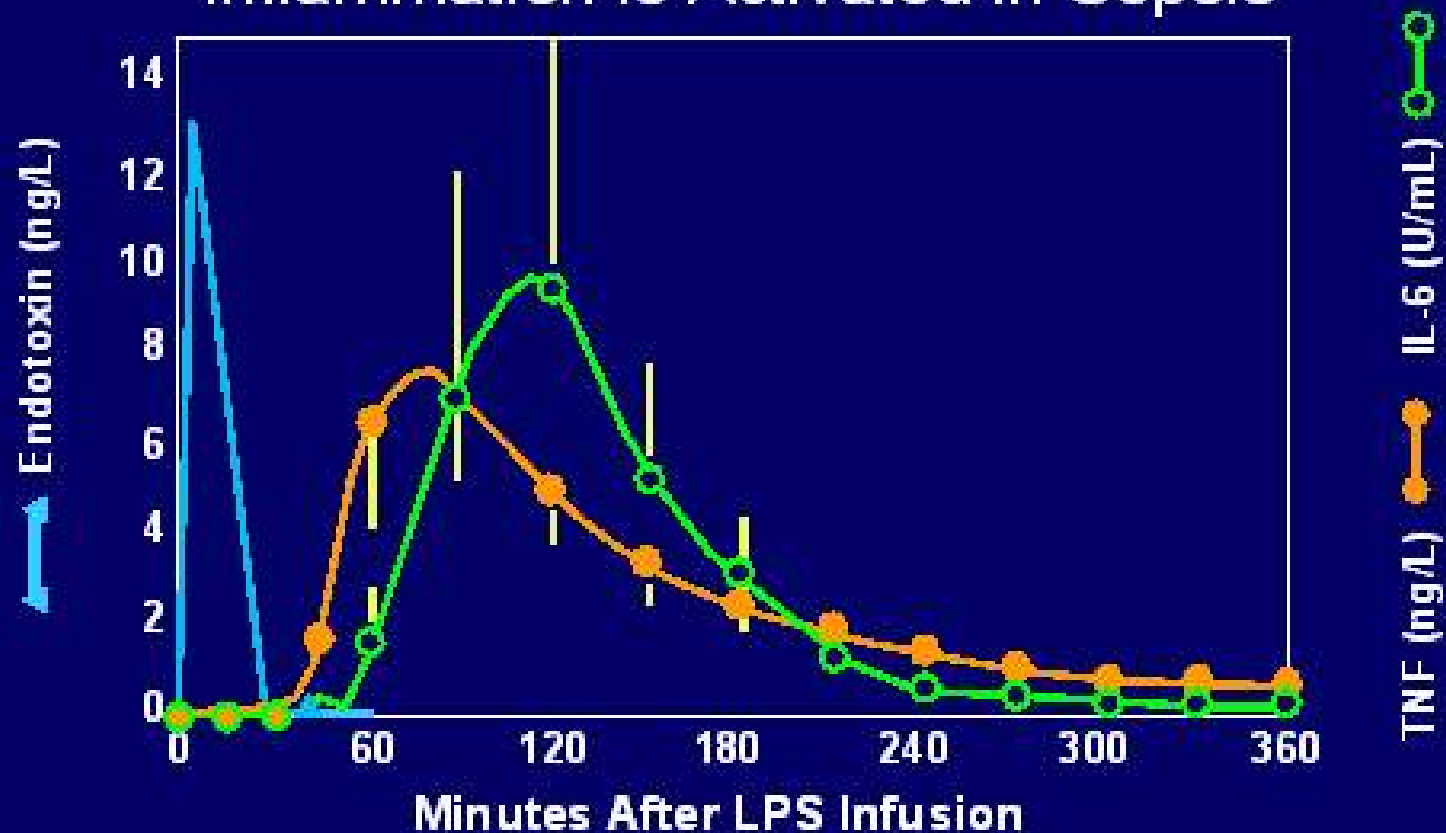
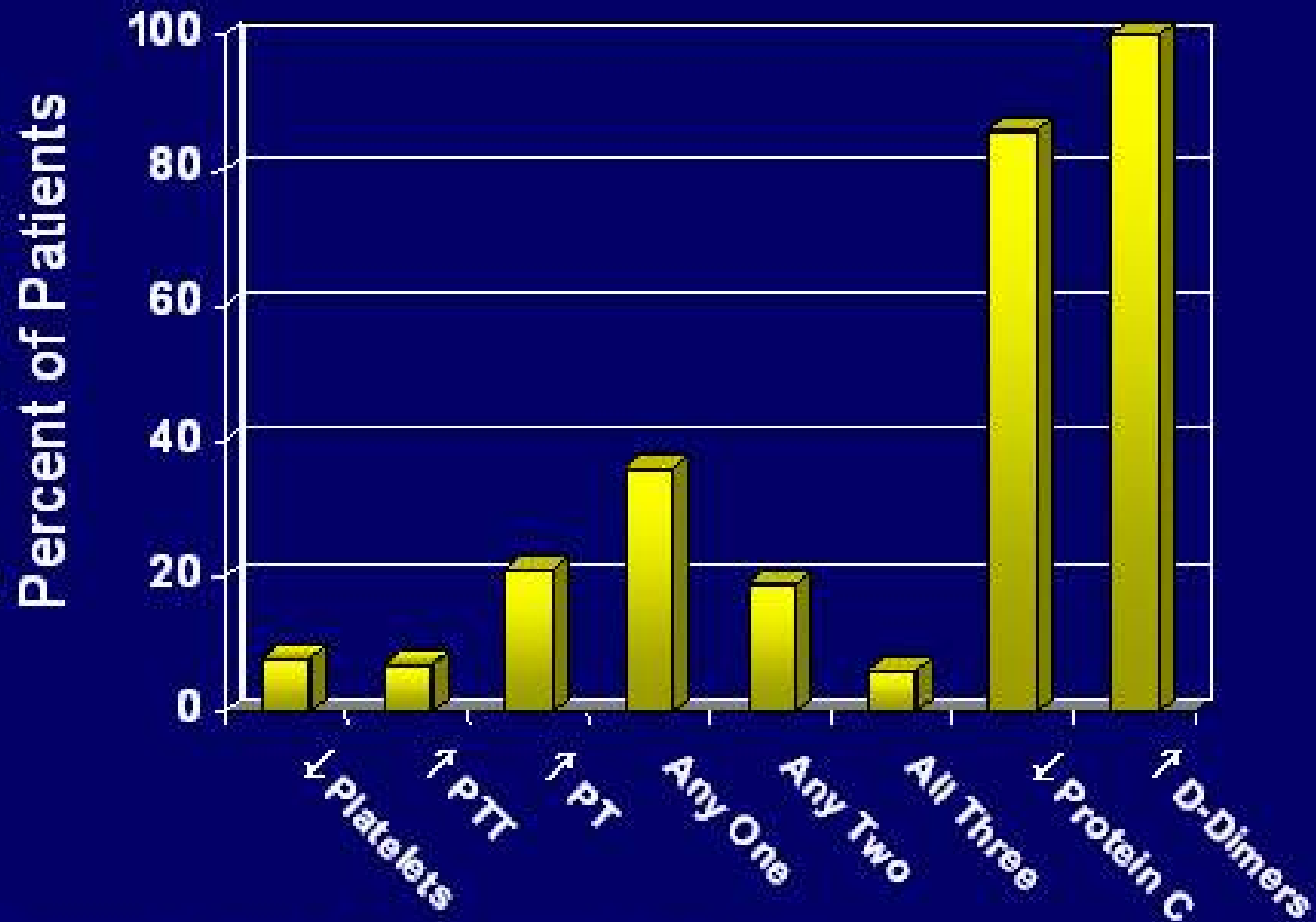


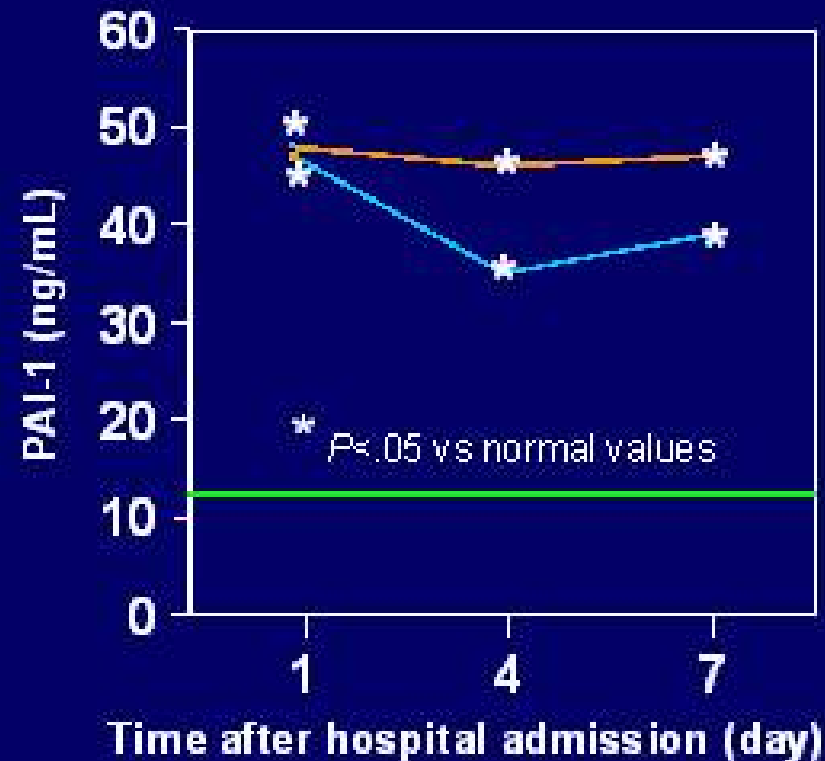
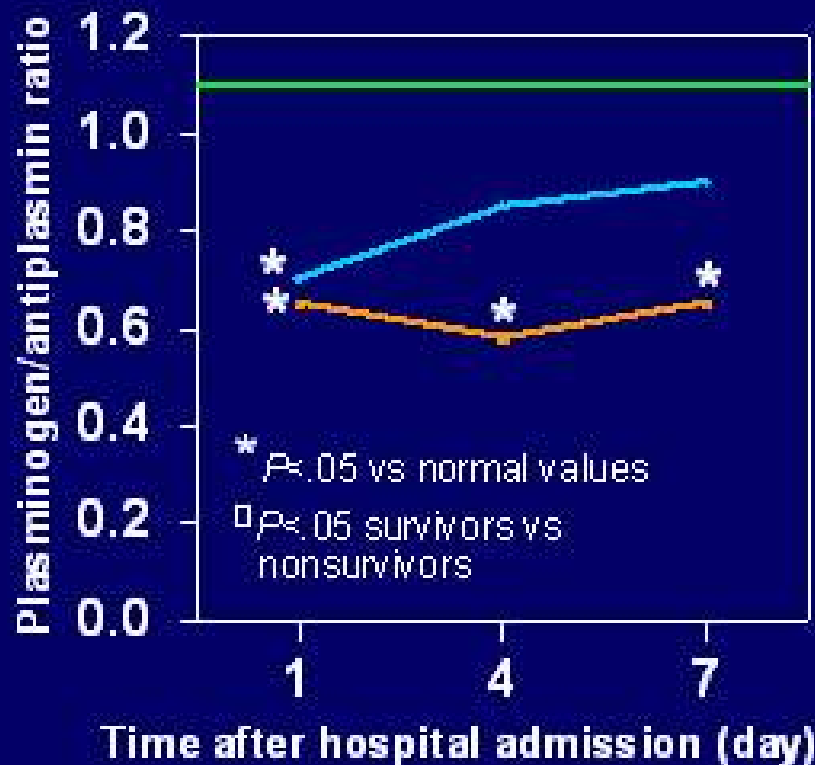
Chart adapted from van Deventer SJ et al. *Blood*. 1990;76:2520-6.

Activation of Coagulation in Severe Sepsis



Data from: Bernard et al. The Ibuprofen in Sepsis Trial (In Press).

Impairment of Fibrinolysis in Severe Sepsis

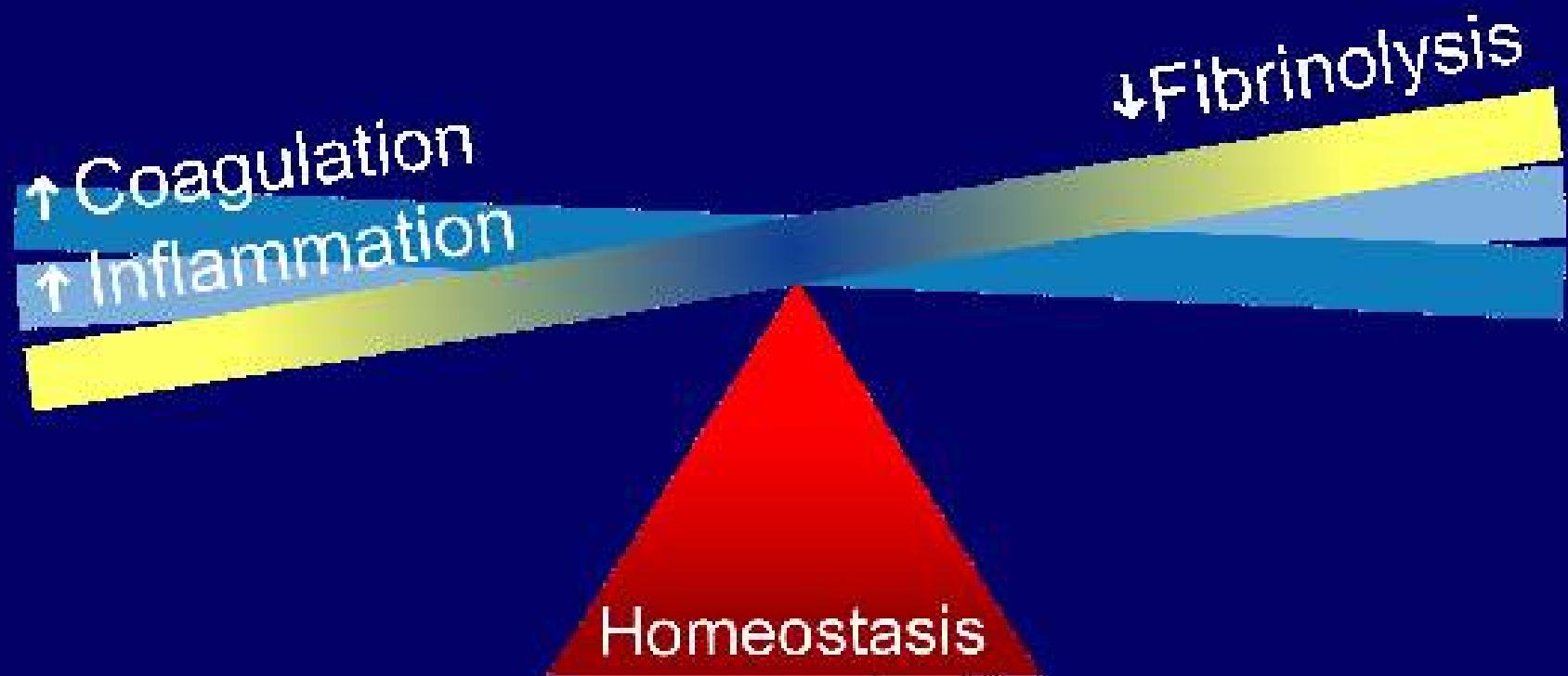


Survivors (n=23)

Nonsurvivors (n=25)

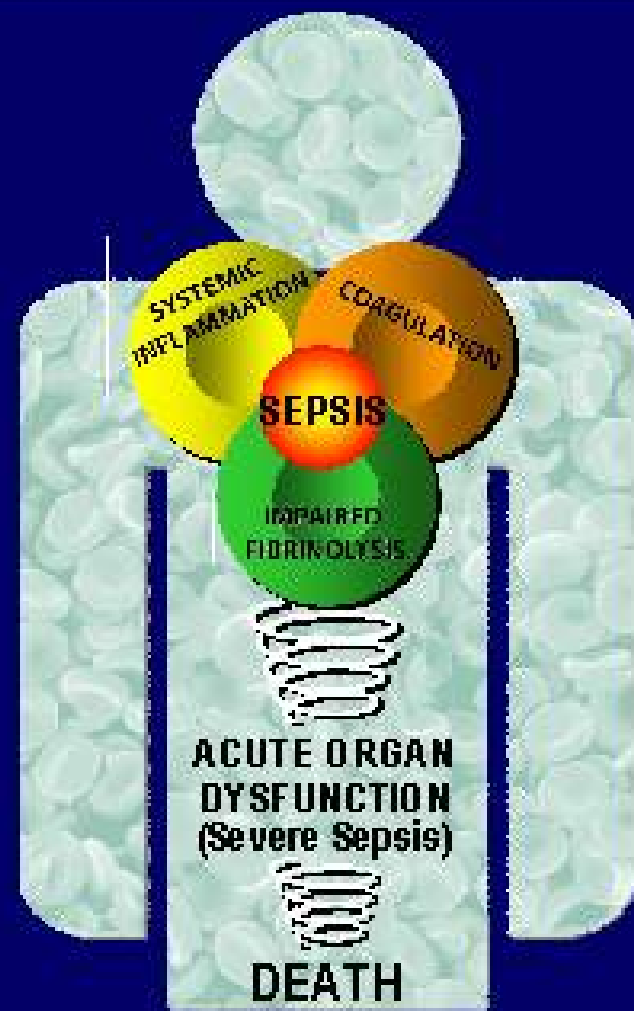
Normal Values

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.

Severe Sepsis: A Vicious Cycle of Inflammation and Coagulopathy



Severe Sepsis Therapy: Standard Care

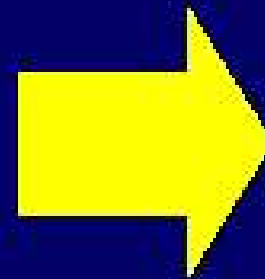
- Source control
- Antibiotics
- Hemodynamic support
- Mechanical ventilation
- Renal replacement therapy
- Sedation/analgesia
- Ensure adequate nutrition
- Provide hematological support
- Other supportive measures

Severe Sepsis Therapy: Numerous Investigational Approaches

- **Bacterial modulators**
 - Antiendotoxin, BPI
- **Anticytokines**
 - IL-1ra, anti-TNF, sTNF-r
- **Antiinflammatory agents**
 - Glucocorticoids, leukocyte adhesion molecule inhibitors
- **Hemostatic agents**
 - Recombinant Human Activated Protein C, ATIII, TFPI, heparin
- **Other**
 - iNOS inhibition, antioxidants, thromboxane antagonists, bradykinin receptor antagonists

Endogenous Modulators of Inflammation

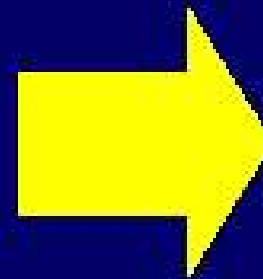
- **Antiinflammatory cytokines**
- **Activated Protein C**
 - Inhibits thrombin-mediated inflammatory activities
 - Inhibits attachment of leukocytes to endothelium



**Decrease
inflammatory
response**

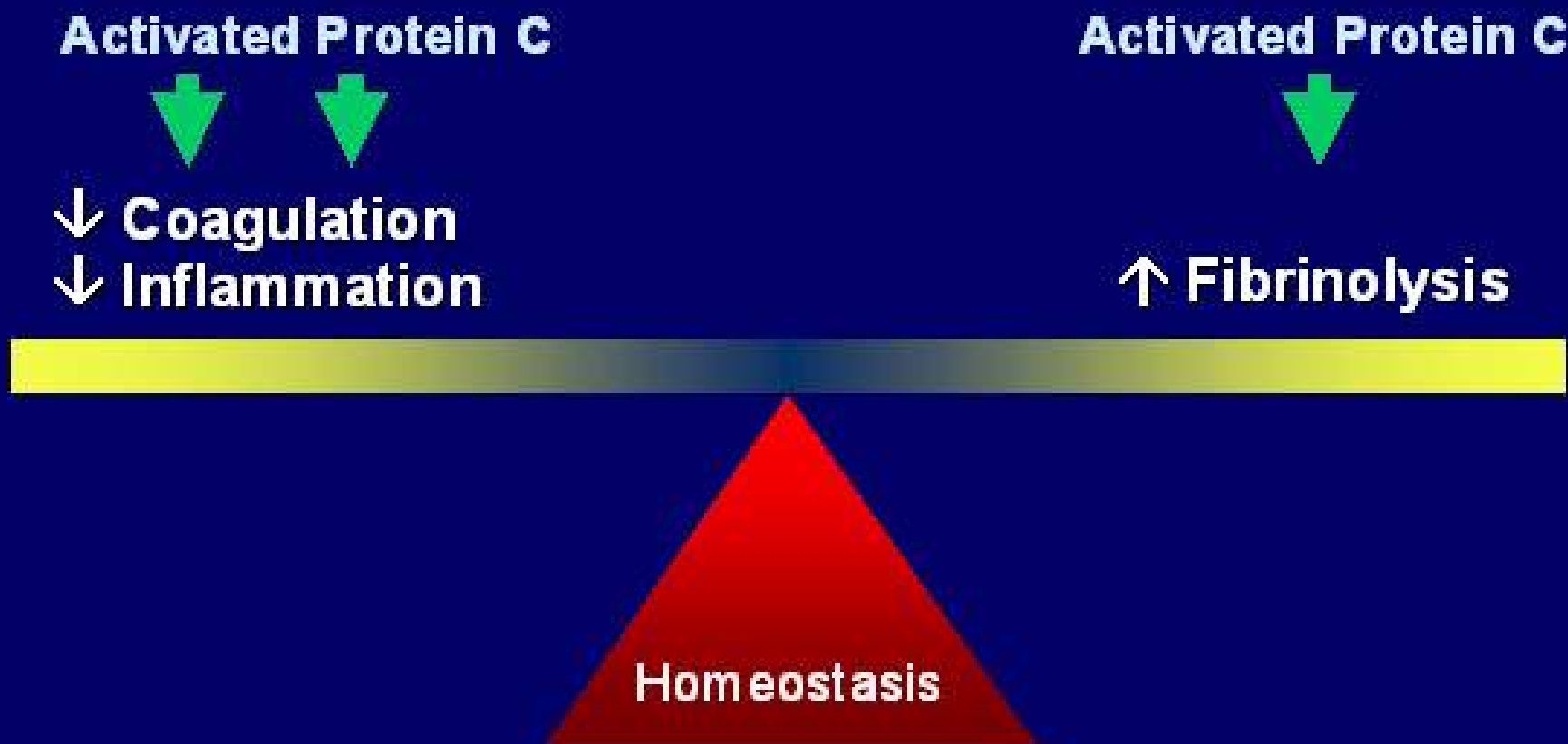
Endogenous Modulators of Thrombosis

- Activated Protein C
- Antithrombin III-heparan sulfate
- Tissue factor pathway inhibitor (TFPI)



**Prevent
coagulation
from
becoming
generalized**

Endogenous Activated Protein C Modulates Coagulation, Fibrinolysis, and Inflammation in Severe Sepsis



Severe Sepsis: The Final Common Pathway

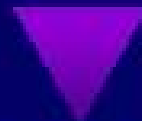
***Endothelial Dysfunction and
Microvascular Thrombosis***



Hypoperfusion/Ischemia



***Acute Organ Dysfunction
(Severe Sepsis)***



Death

Conclusions

- Sepsis is a significant healthcare challenge with major morbidity, mortality, and health economic implications
- Patients with severe sepsis (acute organ dysfunction) are at high risk for mortality
- Systemic inflammation, coagulation, and impaired fibrinolysis are key components of disordered homeostasis in patients with severe sepsis
- With increased knowledge of sepsis pathophysiology, researchers have identified potential investigational agents that may interrupt the sepsis cascade

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Answers that Matter