Sepsis Syndrome

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Case

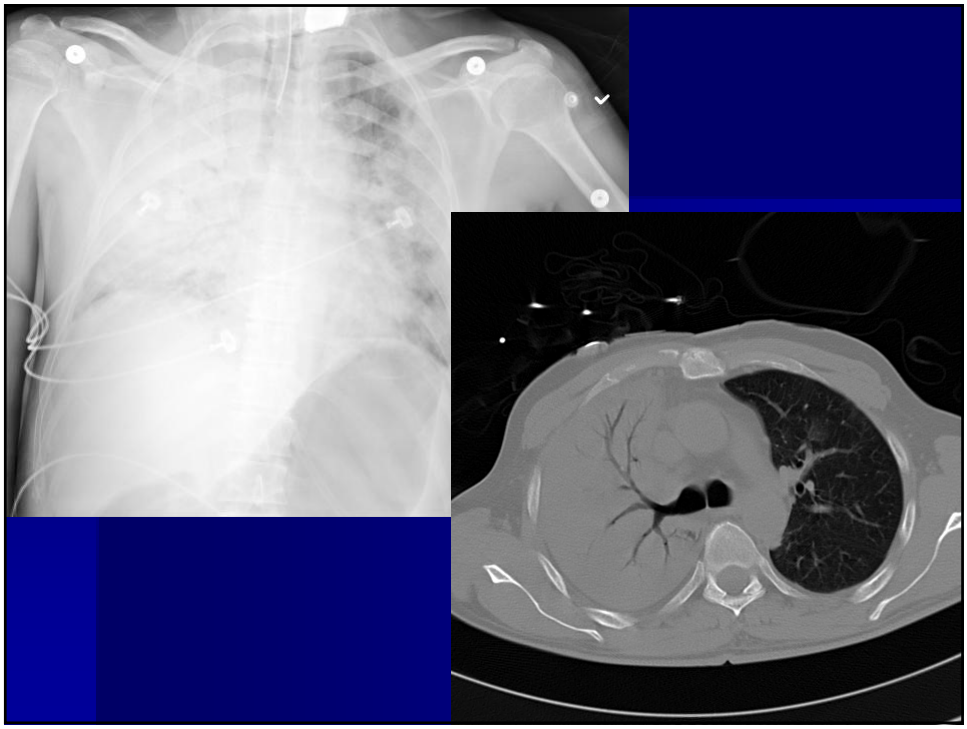
- 45 yo male Microbiology Course director with no sign prior medical history comes in cough, shortness of breath, and chills for 5 days
- He is febrile to 103 and with RR of 35-40, HR of 115, and a BP of 85/60
- On Exam he has diffuse coarse right sided crackles with mild diffuse rhonchi
- He is a little confused (He believes his name is Barack Obama and is the presumptive Democratic nominee for president) and flushed with warm extremities
- His CXR shows dense, right sided, multi-lobar infiltrates

Labs

- His ABG is 7.49/31/105 on 100% Oxygen
- WBC 25k with 25 bands, PLT 80k
- Lactate is elevated at 5, Cr. 2.5, INR 3
- D-Dimer is elevated 8, and fibrinogen is low at 120

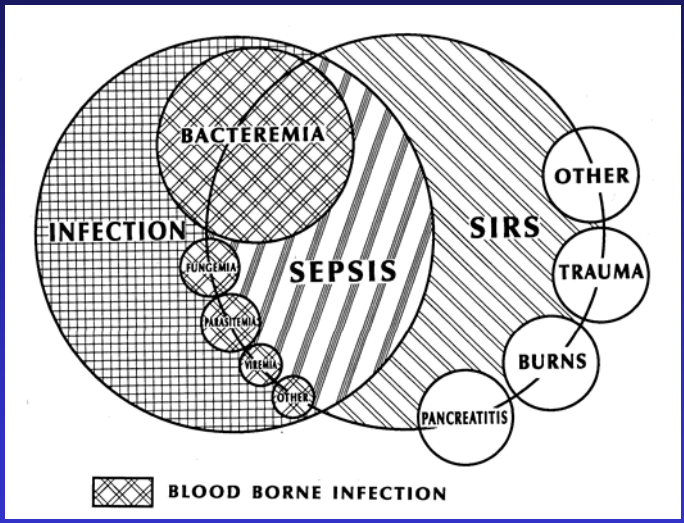
Assessment & Management

- Diagnosis?
- Differential?
- Therapy?
- Complications?
- Outcome?



Sepsis Syndrome

- Definitions
- Pathophysiology
- Clinical Manifestations
- Therapy



ACCP/SCCM Consensus Definitions

- **Infection**
  - Inflammatory response to microorganisms, or
  - Invasion of normally sterile tissues
- **Systemic Inflammatory Response Syndrome (SIRS)**
  - T >38° C (100.4) or <36°C (96.8)
  - HR >90
  - RR >20 or pCO_2 <32mm Hg
  - WBC >12K or <4K or >10% Bands
- **Sepsis**
  - Infection plus
  - ≥2 SIRS criteria
- **Severe Sepsis**
  - Sepsis
  - Organ dysfunction
    - Hypoperfusion
      - Lactic acidosis
      - Oliguria
      - Altered mental status
- **Septic shock**
  - Severe Sepsis
  - Hypotension despite fluid resuscitation
    - BP <90 or SBP decrease >40 mmHg
  - Inotropic or vasopressor agents
- **Multiple Organ Dysfunction Syndrome (MODS)**
  - Altered organ function in an acutely ill patient
  - Homeostasis cannot be maintained without intervention

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

Sepsis Syndrome

- Definitions
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Lewis Thomas

"the microorganisms that seem to have it in for us . . . turn out . . . to be rather more like bystanders. . . . It is our response to their presence that makes the disease. Our arsenals for fighting off bacteria are so powerful . . . that we are more in danger from them than the invaders."

Germs NEJM 1972;287:553-5

Determinants of the Sepsis Syndrome

- Virulence of the organism
- Inoculum of the organism
- Site of Infection
- Host response
  - Inflammatory
  - Anti-inflammatory
  - "Balance"
- Genetic factors
  - Susceptibility
  - Regulation

Organisms

- Direct Invasion
  - Bacteria
    - Aerobes
      - Gram negative rods
        - Enterobacteriaceae-like Klebsiella, Serratia
        - Pseudomonas
      - Gram positive cocci
        - Streptococcus, Staphylococcus
      - Gram negative cocci
        - Neisseria Meningitidis
  - Upper Bacteria
    - Mycobacteria tuberculosis
  - Viruses
    - Flavivirus
    - Coronaviridae
  - Rickettsia
    - Rickettsia
  - Fungi
    - Candida
    - Histoplasma
    - Aspergillus
- Intoxication

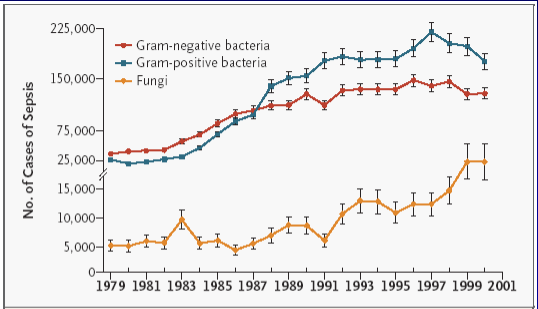
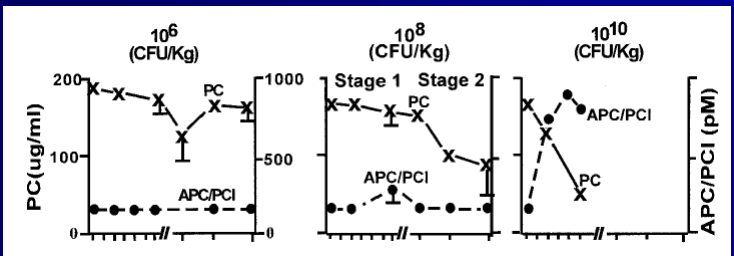
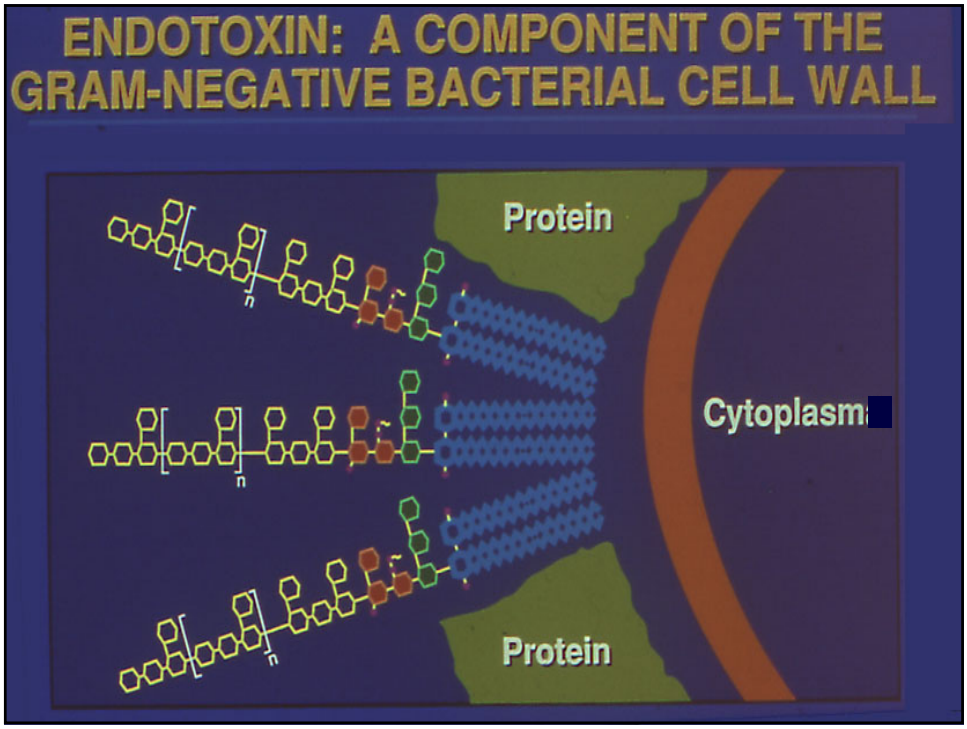


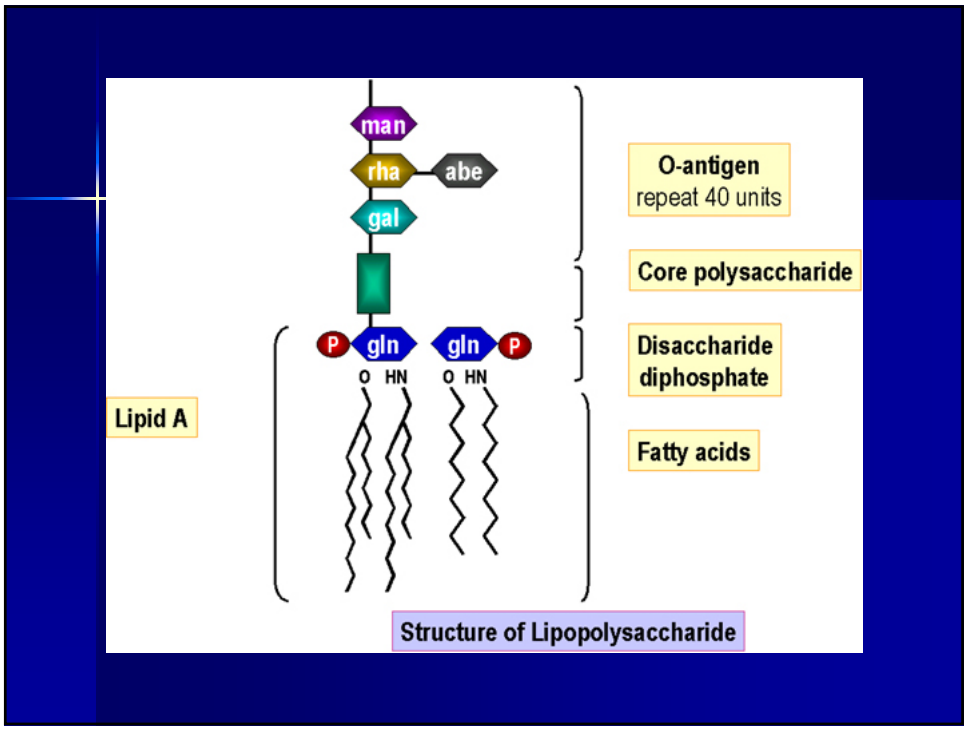
Figure 3. Numbers of Cases of Sepsis in the United States, According to the Causative Organism, 1979–2000.

Points represent the number of cases for the given year, and I bars the standard error.



Crit Care Med 2001; 29[Suppl.]:S78–S89


ENDOTOXIN: A COMPONENT OF THE GRAM-NEGATIVE BACTERIAL CELL WALL
Protein
Cytoplasm
Protein


man
rha
abe
gal
P
gln
gln
P
O HN
O HN
O-antigen
repeat 40 units
Core polysaccharide
Disaccharide
diphosphate
Lipid A
Fatty acids
Structure of Lipopolysaccharide

Systemic Activation of Inflammation in Sepsis

Inflammation is Activated in Sepsis

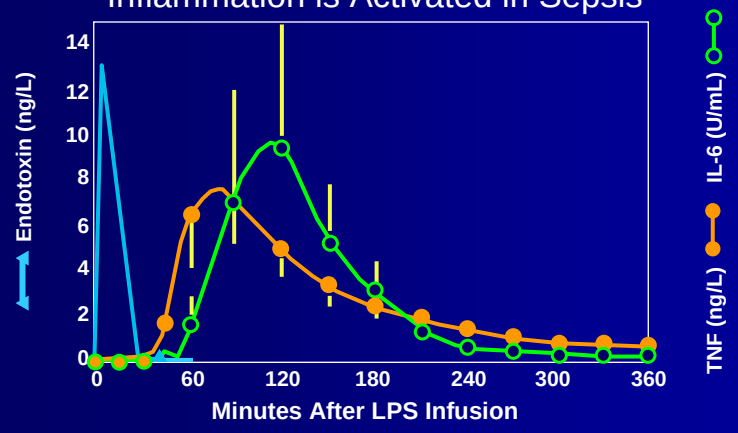


Chart adapted from: van Deventer SJ et al. *Blood.* 1990;76:2520-6.

LPS "Endotoxin" Interaction

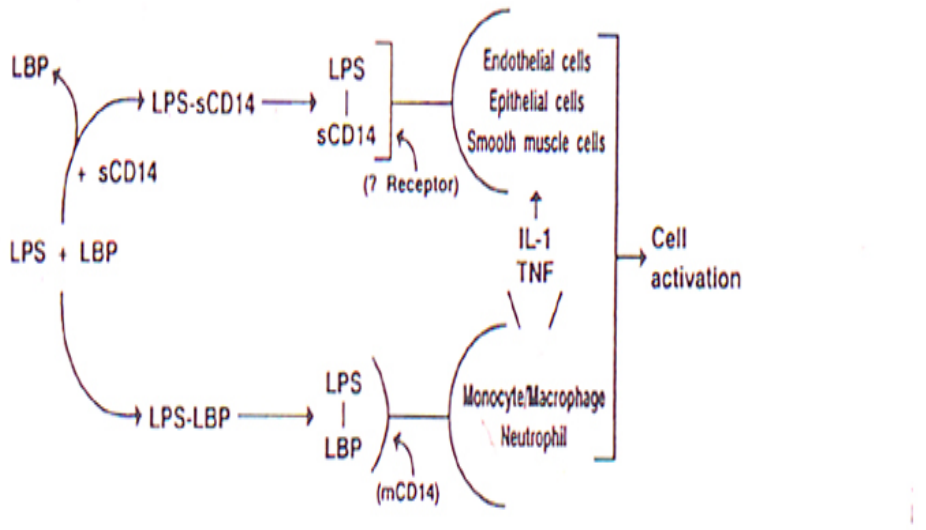
- Growth phases of the bacteria
- Cell lysis by host clearance mechanisms
  - Complement fixation
  - Antibiotic action
- Direct interaction with host tissue
- Similar mechanism for gram positive organisms
  - Peptidoglycan layer
  - Non-peptidoglycan polymers
    - Teichoic acids
      - TNF and IL1

"Exotoxins"

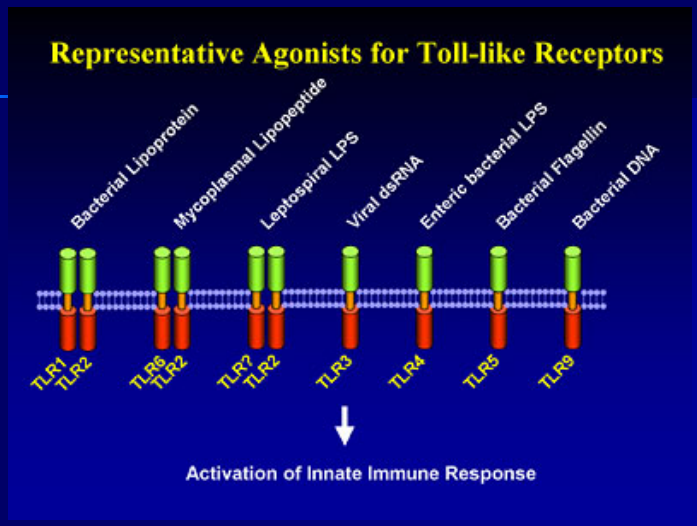
- Toxic shock syndrome toxins
  - Strains of S. Aureus
  - Group A Strep. (S. Pyogenes)
- Superantigens
  - Unconventional binding
    - Antigen presenting cells
      - "outside" the antigen presenting groove of the MHC II molecule of the macrophage
    - T Lymphocytes
      - Bind uniquely to specific family of T lymphocytes with identical V beta regions of the T-cell receptor (for example V $Beta_1$)
  - Small amounts resulting in a large T-cell and cytokine response

Pathophysiology of Sepsis

- LPS initiates the stereotypic inflammatory response
- Initial targets are the macrophage and vascular endothelial cell
- Endothelial cell
  - LPS-sCD_{14} complex receptor
- Macrophage
  - LPS-LPS binding protein CD14 receptor
- Another transmembrane signaling of inflammation is TLR
  - TLR4 for gram neg. bacteria
  - TLR2 for gram positive
- Translocation of NFkB
- Transcription of TNF



2. Reference: Wenzel RP, et al. Current Understanding of Sepsis. CID 22:409, 1996.



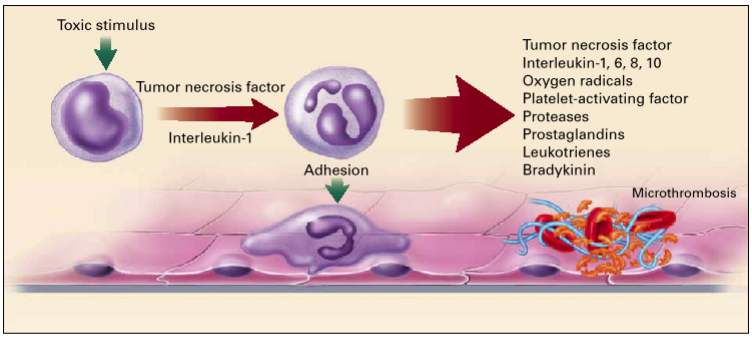
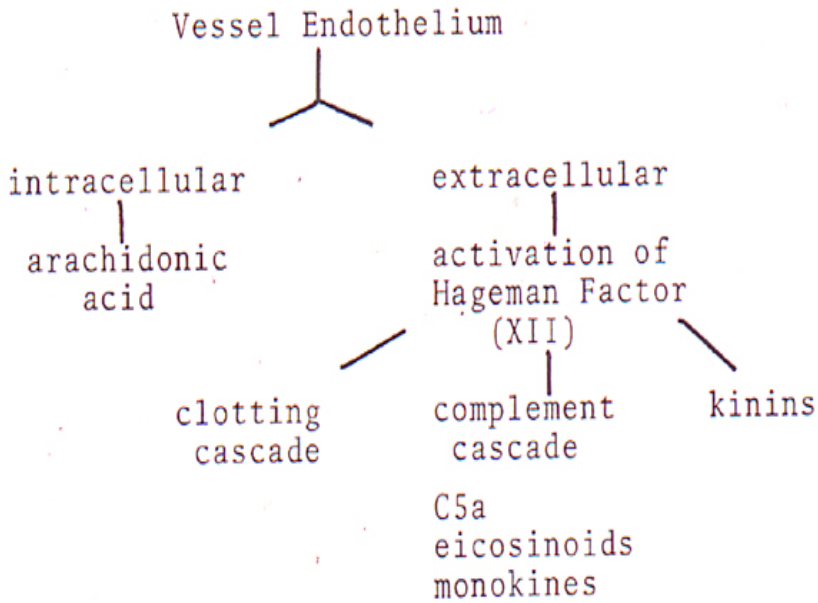
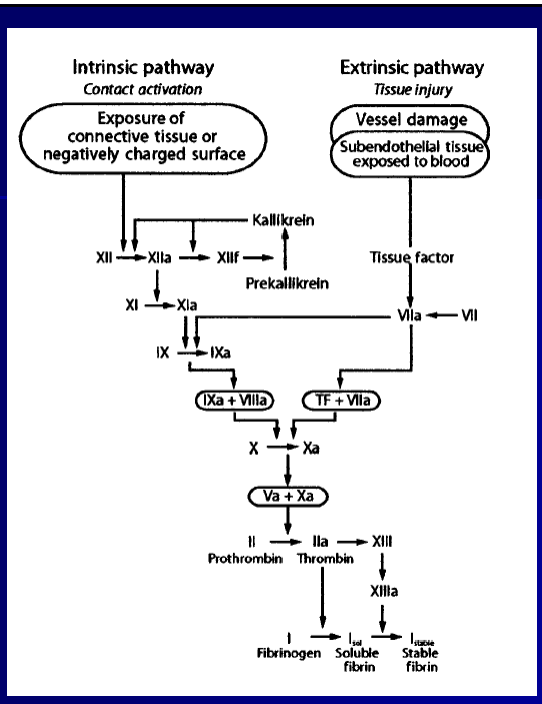
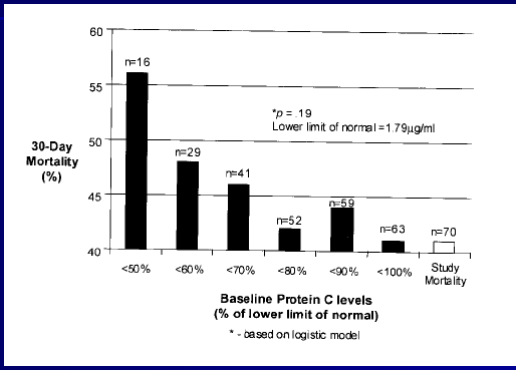


Figure 2. Early Biochemical Events in Sepsis.

An initial toxic stimulus (e.g., endotoxin) triggers the production of proinflammatory monokines (e.g., tumor necrosis factor and interleukin-1). These cytokines, in turn, result in neutrophil–endothelial-cell adhesion, activation of clotting, and generation of numerous secondary inflammatory mediators, including other cytokines, prostaglandins, leukotrienes, and proteases. Antiinflammatory compounds, such as interleukin-6 and interleukin-10, that may serve as negative feedback to the inflammatory process, are also released.







CHEST 2001; 120:915–922

Homeostasis Is Lost in Sepsis

- Proinflammatory mediators
- Endothelial injury
- Tissue factor expression
- Thrombin production

↑ Coagulation
↑ Inflammation

↓ Fibrinolysis

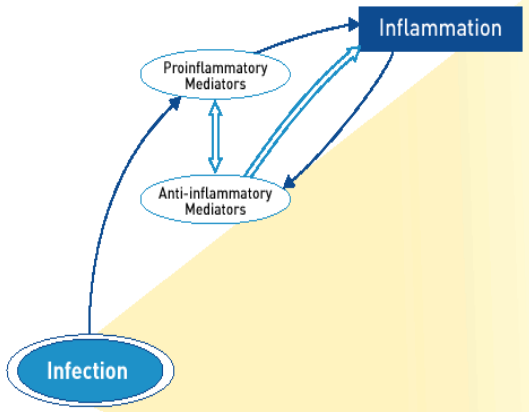
- Increased PAI-1
- Increased $TAFI_a$
- Reduced Protein C (endogenous Activated Protein C inhibits PAI-1)

Homeostasis

PAI-1= plasminogen activator inhibitor-1; $TAFI_a$= thrombin activatable fibrinolysis inhibitor. Carvalho and Freeman. *J Crit Illness* 1994;9:51; Kidokoro et al. *Shock* 1996;5:223; Vervloet et al. *Semin Thromb Hemost* 1998;24:33.

14

A Network of Cascading Events



⇒ Inhibits
→ Stimulates
→ Activates

T	Thrombin
TF	Tissue Factor
TM	Thrombomodulin
PAI-1	Plasminogen Activator Inhibitor 1
t-PA	Tissue-type Plasminogen Activator
TAFI	Thrombin Activatable Fibrinolysis Inhibitor

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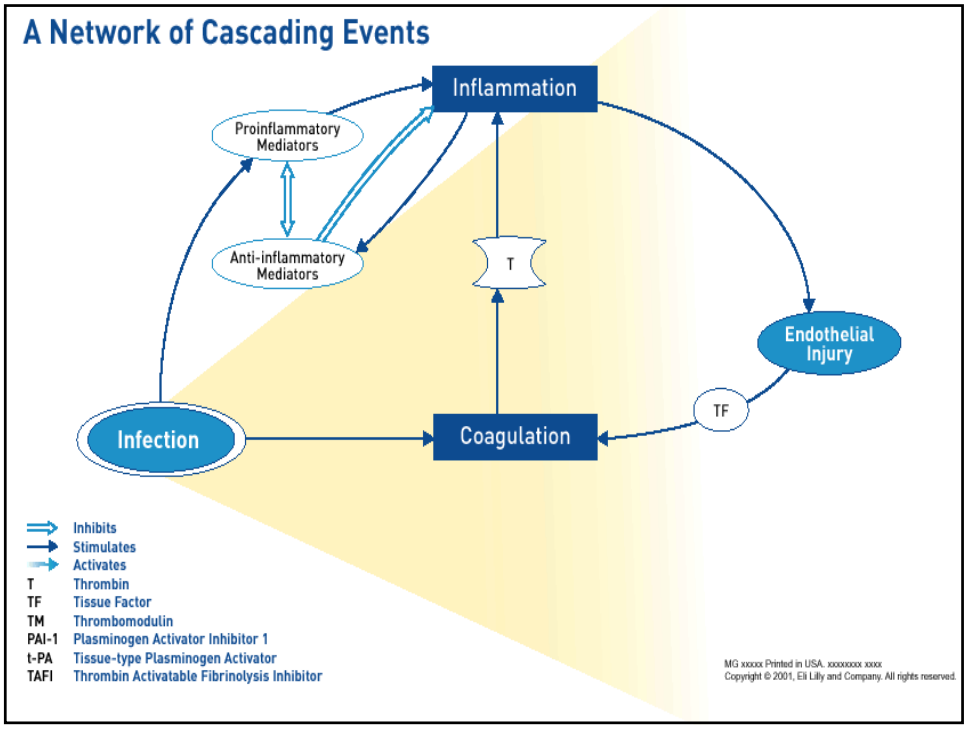
A Network of Cascading Events
Inflammation
Proinflammatory Mediators
Anti-inflammatory Mediators
T
Endothelial Injury
TF
Infection
Coagulation
Inhibits
Stimulates
Activates
T Thrombin
TF Tissue Factor
TM Thrombomodulin
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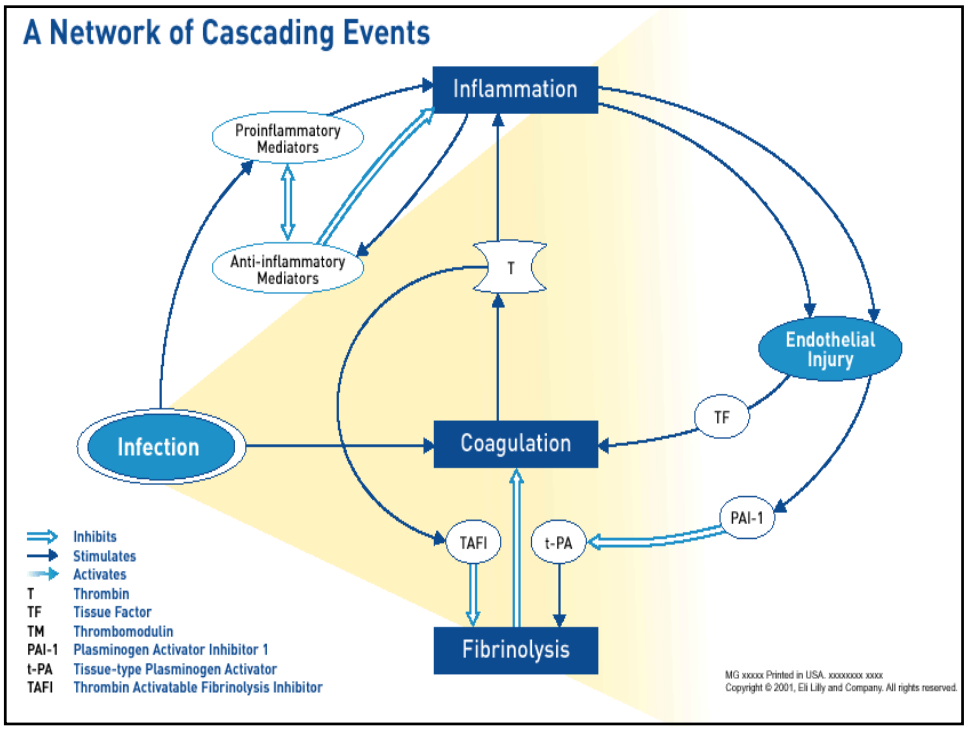
A Network of Cascading Events
Inflammation
Proinflammatory Mediators
Anti-inflammatory Mediators
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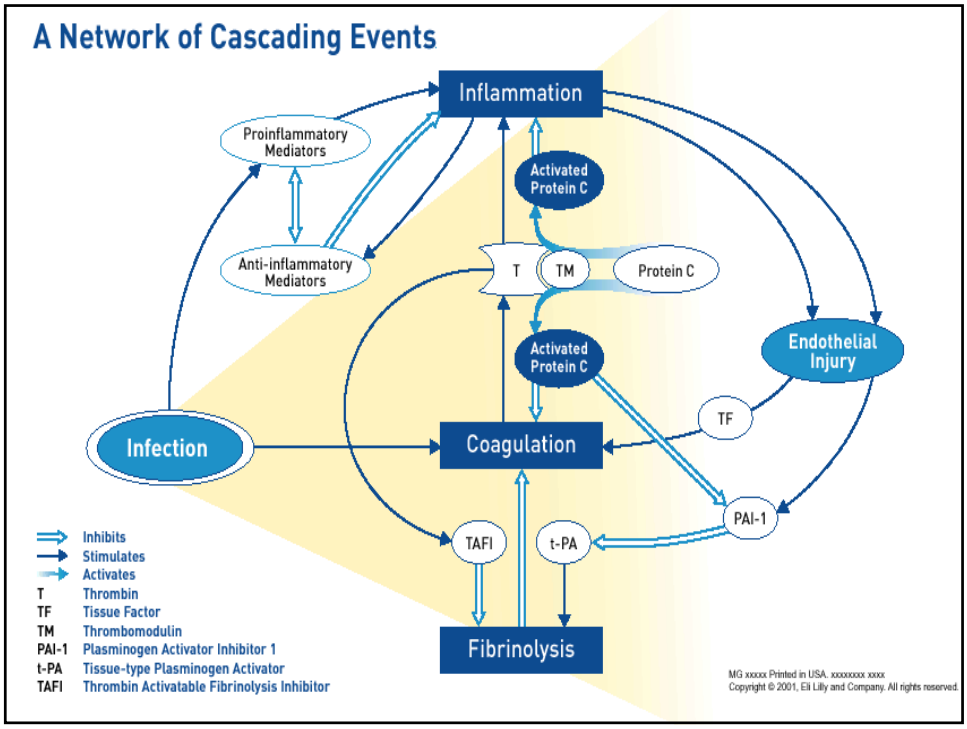


SHOCK SYNDROMES

- Hypovolemic or Oligemic
- Cardiogenic
- Vascular Obstrucive
- Distributive or Vasodilatory

Mechanisms of Vasodilatory Shock

- Activation of ATP-sensitive K channels
- Activation of the inducible form of NO synthase
- Deficiency of vasopressin

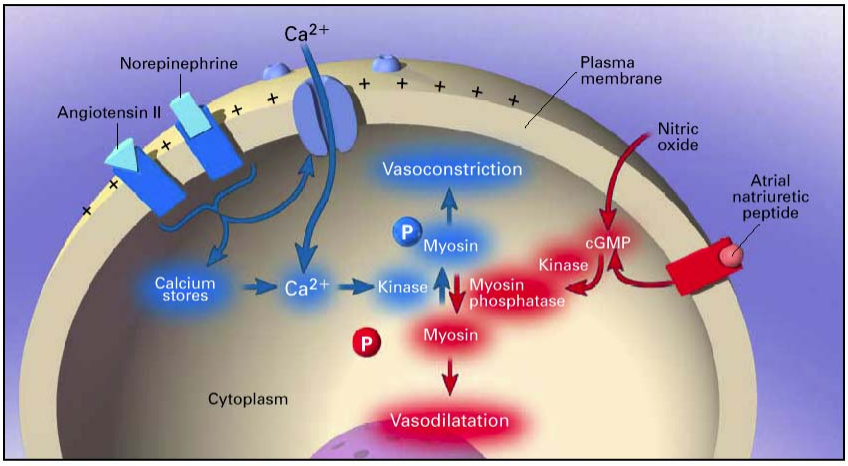
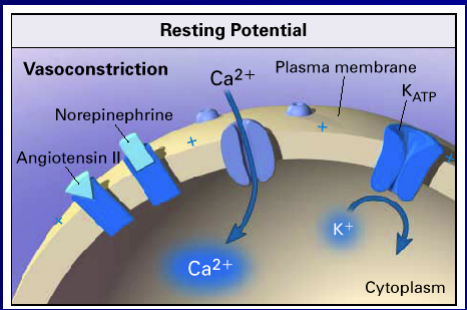
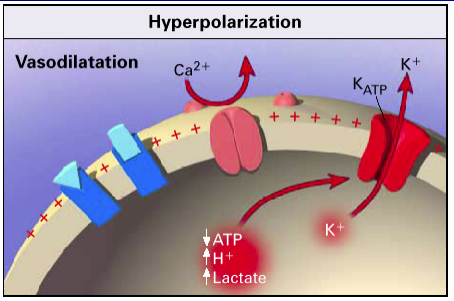


Figure 1. Regulation of Vascular Smooth-Muscle Tone.

The steps involved in vasoconstriction are shown in blue, and the steps involved in vasodilatation are shown in red. The phosphorylation (P) of myosin is the critical step in the contraction of vascular smooth muscle. By way of second messengers, vasoconstrictors such as angiotensin II and norepinephrine induce an increase in the cytosolic calcium concentration, which activates myosin kinase. Vasodilators such as atrial natriuretic peptide and nitric oxide activate myosin phosphatase and, by dephosphorylating myosin, cause vasorelaxation. The plasma membrane is shown at a resting potential (plus signs). The abbreviation cGMP denotes cyclic guanosine monophosphate.


Resting Potential
Vasoconstriction
Ca2+
Plasma membrane
KATP
Norepinephrine
Angiotensin II
K+
Ca2+
Cytoplasm


Hyperpolarization
Vasodilatation
Ca2+
K+
KATP
K+
ATP
H+
Lactate

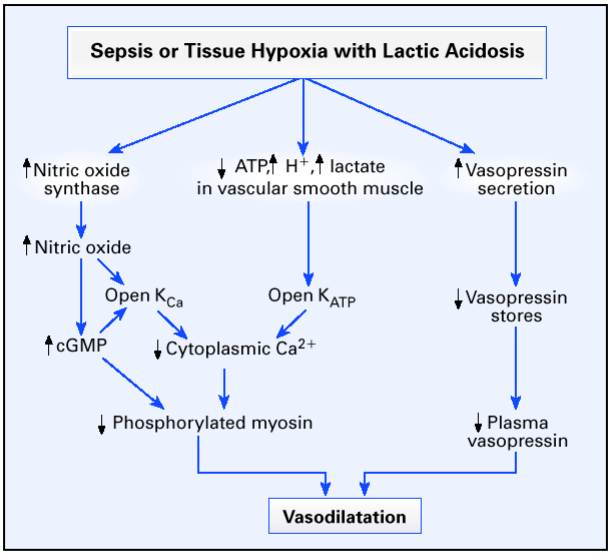


Figure 4. Mechanisms of Vasodilatory Shock.

Septic shock and states of prolonged shock causing tissue hypoxia with lactic acidosis increase nitric oxide synthesis, activate ATP-sensitive and calcium-regulated potassium channels (K_{ATP} and K_{Ca}, respectively) in vascular smooth muscle, and lead to depletion of vasopressin. The abbreviation cGMP denotes cyclic guanosine monophosphate.

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

- **Severe Sepsis**
  - Sepsis
  - Organ dysfunction
    - Hypoperfusion
      - Lactic acidosis
      - Oliguria
      - Altered mental status
- **Septic shock**
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    - BP <90 or SBP decrease >40 mmHg
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- **Multiple Organ Dysfunction Syndrome (MODS)**
  - Altered organ function in an acutely ill patient
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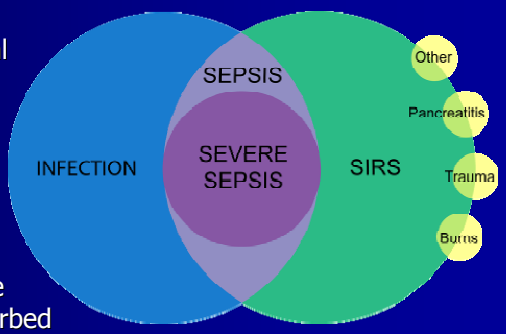
Sepsis: A Complex Disease

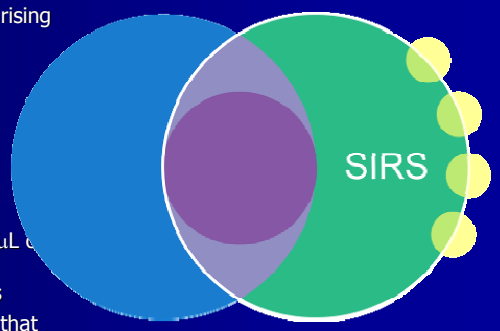
- This Venn diagram provides a conceptual framework to view the relationships between various components of sepsis.
- The inflammatory changes of sepsis are tightly linked to disturbed hemostasis.



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

SIRS: More Than Just a Systemic Inflammatory Response

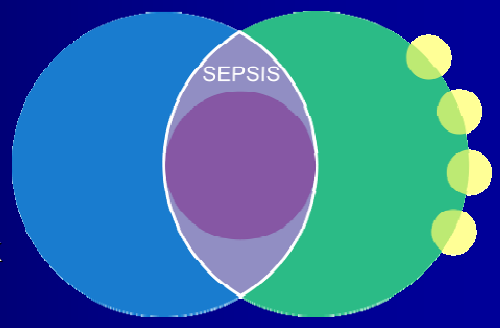
- SIRS: A clinical response arising from a nonspecific insult manifested by ≥2 of the following:
  - Temperature ≥38°C or ≤36°C
  - HR ≥90 beats/min
  - Respirations ≥20/min
  - WBC count ≥12,000/μL or ≤4,000/μL or >10% immature neutrophils
- Recent evidence indicates that hemostatic changes are also involved



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

Sepsis: More Than Just Inflammation

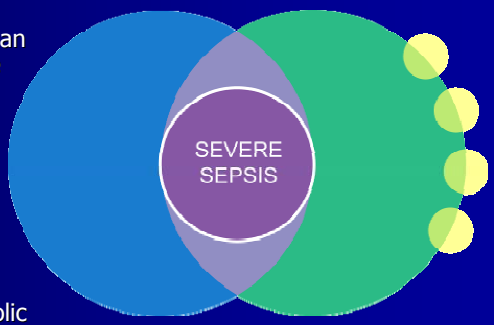
- Sepsis:
  - Known or suspected infection
  - Two or more SIRS criteria
- A significant link to disordered hemostasis



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

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



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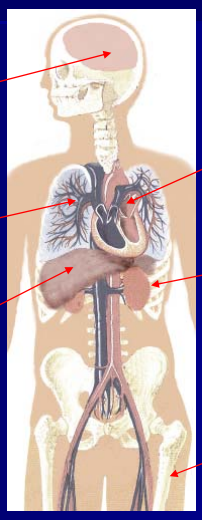
Identifying Acute Organ Dysfunction as a Marker of Severe Sepsis



Altered
Consciousness
Confusion
Psychosis

Tachypnea
PaO_2 <70 mm Hg
SaO_2 <90%
PaO_2/FiO_2 ≤300

Jaundice
↑ Enzymes
↓ Albumin
↑ PT

Tachycardia
Hypotension

Oliguria
Anuria
↑ Creatinine

↓ Platelets
↑ PT/APTT
↓ Protein C
↑ D-dimer

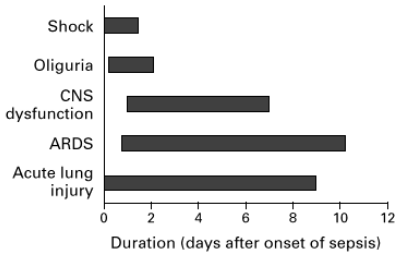


Figure 4. Onset and Resolution of Organ Failure in Patients with Severe Sepsis.

The bars show the duration of organ failure, with the timing of the onset and resolution of organ failure shown at the left and right ends of the bars, respectively. Acute lung injury — or its more severe form, the acute respiratory distress syndrome (ARDS) — develops early and is long-lived, with a mean duration of nine days. Shock and oliguria are similar in the timing of their onset, and the duration of both is brief, averaging less than two days. In contrast, central nervous system (CNS) dysfunction has a delayed onset and an intermediate duration.

SHOCK SYNDROMES

Hypovolemic or Oligemic

Cardiogenic

Vascular Obstrucive

Distributive or Vasodilatory

Hemodynamic Profiles

	Cardiac Output	Peripheral Vascular Resistance
Early	↑ ↑	↓ ↓
Late	↑ ↑ (↓)	↓ ↓ (↑)

EARLY PHASE

- Vital Signs
  - BP Modest ↓
  - Temp ↑ / ↓ / -
  - RR rapid↑
  - Pulse ↑ "bounding"
- Skin – warm, dry
- CNS – may be altered, agitation
- Urine output – usually ↓
- LAB DATA
  - ABG
    - pH↑ , pCO_2 ↓ , pO_2 mod ↓
  - Lactic acid maybe ↑
  - glucose may be ↑ or ↓
  - WBC ↑ / ↓
  - Protime prolonged
  - Platelets ↓

LATE PHASE

- Vital Signs
  - BP very ↓ or <90
  - Temp ↑ / nl /↓
  - RR ↑ / nl / ↓
  - Pulse ↑ "thready"
- SKIN – cold, "clammy"
- CNS – often confused
- URINE output – usually ↓ ↓
- LAB DATA
  - ABG
    - pH ↓, pCO_2 ↓ or nl , pO_2 mod ↓
  - Lactic acid ↑ ↑
  - glucose may be ↑ or ↓
  - WBC ↑ / ↓
  - Protime prolonged
  - Platelets ↓

Diagnosis

- Cultures
- Empiric Antibiotics
  - Likely site of infection "where?" (Source Control)
  - Likely Organisms
  - Specific Epidemiology from the environment
    - Antibiogram
  - Early
- Clinical Response

Management

- Ventilatory Support (ABC's)
- Antibiotics
  - Early
  - Appropriate
- Resuscitation
  - Fluid
    - Crystaloid
    - Colloid
  - Blood
  - Vasoactive agents
- Intensive Monitoring
- Assess for cause
- Modulate the host response (restore balance)
- Minimize complications

Early Goal-Directed Therapy In The Treatment of Severe Sepsis and Septic Shock

Rivers et al. NEJM 2001;345:1368-77

- Patients with severe sepsis or septic shock were randomly assigned to get early goal directed therapy vs. standard therapy for the first 6 hours; the physicians were "blinded"
- EGDT and standard therapy included CVP (8-12 mmHg), MAP (>65 mmHg), and UO (>0.5/hr) but EGDT added $ScvO_2$ >70, Hct 30 and DBA to increase CI to achieve the saturation goal
- There was a 16% absolute mortality reduction (46.5% vs. 30.5%)
- In the EGDT group O_2 saturation was higher, lactate was lower, base deficit was lower, pH higher, APACHE II lower and there was less severe organ dysfunction
- The EGDT got more fluid (3.49 vs. 4.98L), blood (18.5 vs. 64.1%), and Dobutamine (0.8 vs. 13.7%)
- The number needed to treat was 6

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EFFICACY AND SAFETY OF RECOMBINANT HUMAN ACTIVATED PROTEIN C FOR SEVERE SEPSIS

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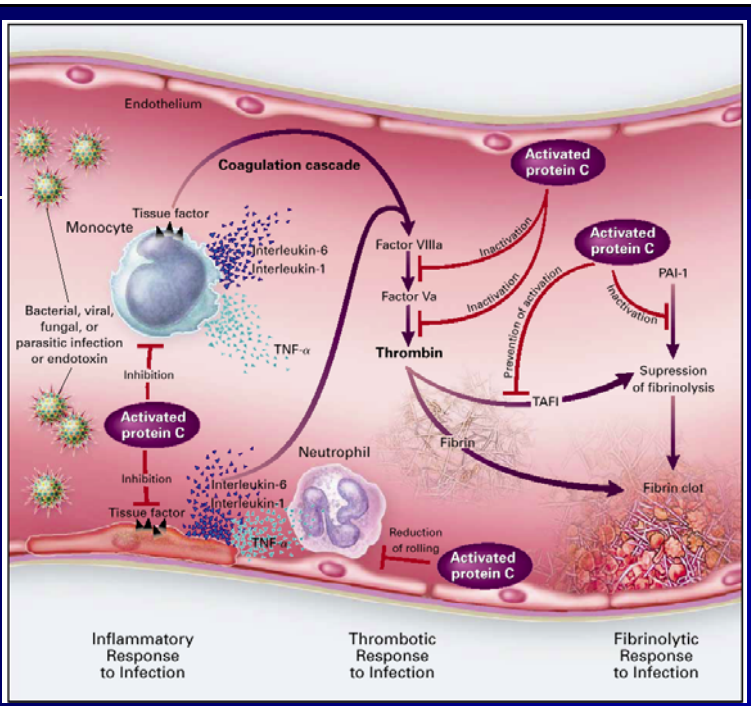
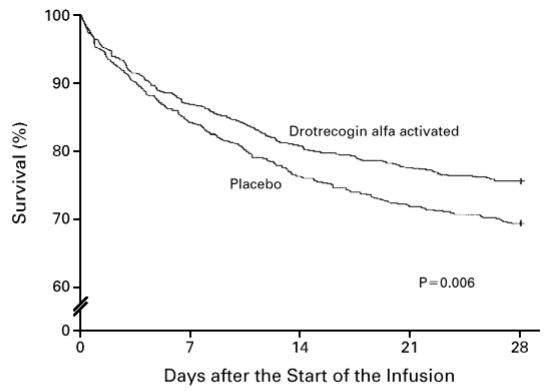


Results

- The study was halted at the 2nd interim eval.
- Reduction in the relative risk of death by 19.4%
- Absolute reduction was 6.1% (30.8 vs. 24.7)
- Incidence of serious bleeding was higher in the treatment group
- 3.5% vs. 2%
- The mortality difference was greatest in the sickest patients
- 1 additional life saved for every 16 treated
- 1 additional serious bleed for every 66 treated



No. at Risk					
Drotrecogin alfa activated	850	737	684	657	640
Placebo	840	705	639	602	581

Figure 2. Kaplan–Meier Estimates of Survival among 850 Patients with Severe Sepsis in the Drotrecogin Alfa Activated Group and 840 Patients with Severe Sepsis in the Placebo Group.

Treatment with drotrecogin alfa activated was associated with a significantly higher rate of survival (P=0.006 by the stratified log-rank test).

Epidemiology

- Accounts for about 2% of admissions but 59% require intensive care
- $ 17 billion dollars in the US alone
- Mortality is 20-50%
- 2nd leading cause of death in noncoronary ICU's
- 10th leading cause of overall death
- More common in men and in non-whites
- Patients are now older (57 to 60)
- Incidence has increased from 1979 (164,000 cases) to 2000 (660,000)-Annualized increase of 8.7%
- Deaths have increased from 43,579 to 120,491
- Gram positive organism are the predominant pathogens since 1987
- Mortality has decreased from 27% to 17%
- But only 56% go home vs. 78%

NEJM 2003;346:1546-54

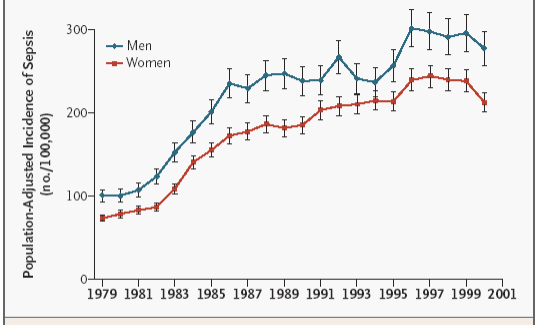


Figure 1. Population-Adjusted Incidence of Sepsis, According to Sex, 1979–2000.
Points represent the annual incidence rate, and I bars the standard error.

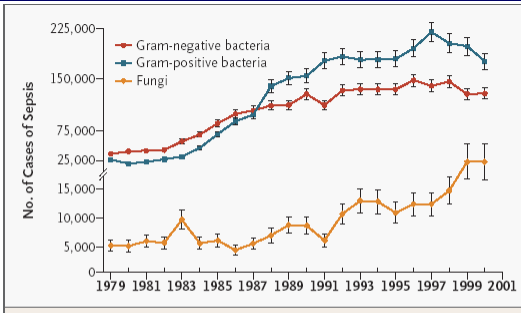


Figure 3. Numbers of Cases of Sepsis in the United States, According to the Causative Organism, 1979–2000.
Points represent the number of cases for the given year, and I bars the standard error.

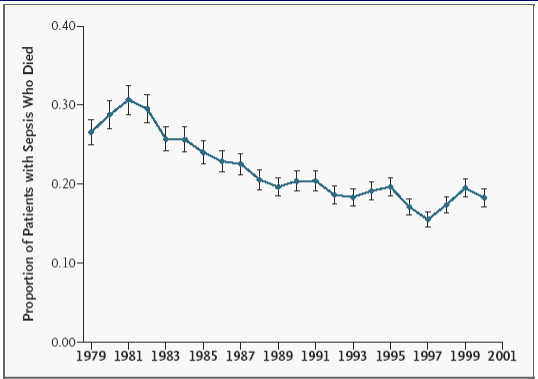


Figure 4. **Overall In-Hospital Mortality Rate among Patients Hospitalized for Sepsis, 1979–2000.**

Mortality averaged 27.8 percent during the first six years of the study and 17.9 percent during the last six years. The I bars represent the standard error.

Future Directions

- Intensive Insulin Therapy?
- Stress Dose Steroids?
- New Immunomodulators?
- New Paradigm?
- New Process ?

Intensive Insulin Therapy

Van den berghe et al. NEJM 2001;345:1359-67

- Prospective, randomized controlled study of SICU patients on mechanical ventilation
- intensive insulin therapy: maintenance of blood glucose at a level between 80 and 110 mg per deciliter
- conventional treatment: infusion of insulin only if the blood glucose level exceeded 215 mg per deciliter and maintenance of glucose at a level between 180 and 200 mg per deciliter
- 1548 patients over 12 months
- Reduced mortality from 8% to 4.6%
  - Benefit was due to its effect on patients who stayed in the SICU >5 days (20.2% vs. 10.6%)
- The greatest reduction in mortality were in those patients that had MODS from a septic focus
- **Reduced In-hospital mortality by 34%**
  - **Blood stream infections by 46%**
  - **ARF requiring HD or CVVH by 41%**
  - **Median number of RBC transfusions by 50%**
  - **CIPN by 44%**
  - **Less likely to require prolong ventilation and intensive care**

Intensive Insulin Therapy II

Van den berghe et al. NEJM 2006;454:449

- Intention-to-treat analysis of 1200 patients, intensive insulin therapy reduced blood glucose levels but did not significantly reduce in-hospital mortality (40.0 percent in the conventional-treatment group vs. 37.3 percent in the intensive-treatment group, P=0.33).
- However, morbidity was significantly reduced by
  - the prevention of newly acquired kidney injury,
  - accelerated weaning from mechanical ventilation
  - accelerated discharge from the ICU and the hospital.
- Length of stay >3 days in the ICU could not be predicted on admission
- Among 433 patients who stayed in the ICU for less than three days, mortality was greater among those receiving intensive insulin therapy.
- In contrast, among 767 patients who stayed in the ICU for three or more days
  - In-hospital mortality in the 386 who received intensive insulin therapy was reduced from 52.5 to 43.0 percent (P=0.009) and morbidity was also reduced.
- *Conclusions* Intensive insulin therapy significantly reduced morbidity but not mortality among all patients in the medical ICU.
- Although the risk of subsequent death and disease was reduced in patients treated for three or more days, these patients could not be identified before therapy.

Steroids and Septic Shock

Annane et al. JAMA 2002;288:862-871

- Septic shock may be associated with relative adrenal insufficiency; replacement therapy with low doses has been proposed (50 mg of Hydrocortisone q6h plus 50 μg of fludrocortisone po)
- Placebo-controlled, randomized, double-blind, parallel group trial in 19 ICU's in France from 1995-1999
- Replacement steroids (n=151) or matching placebo (n=149) were given for 7 days; 28 day mortality in the nonresponders was the main outcome measure
- All the patients had to be septic and in shock and were randomized from 3-8 hours from the onset of shock
- The patients were then given a 250 μg IV bolus and cortisol levels were measures at time 0, 30min, and 60 min after
- Relative adrenal insufficiency was defined as a response of 9 μg/dL or less
- There were 229 nonresponders (115 placebo and 114 steroid) and 70 responders
- The mortality in the placebo group was was 63% and 53% in the steroid group
- Vasopressors were withdrawn in the 57% in the steroid group vs. 40% in the placebo
- However, the analysis was done correcting for baseline cortisol, cortisol response, McCabe Classification, LOD score, arterial lactate, and P/F ratio

Corticus

Sprung et al. N Engl J Med 2008;358:111-24.

- Multicenter, randomized, double-blind, placebo-controlled trial
- 251 patients received 50 mg of intravenous hydrocortisone and 248 patients received placebo every 6 hours for 5 days; then the dose was then tapered during a 6-day period.
- At 28 days, the primary outcome was death among patients who did not have a response to a corticotropin test.
- Of the 499 patients in the study, 233 (46.7%) did not have a response to corticotropin (125 in the hydrocortisone group and 108 in the placebo group).
- At 28 days, there was no significant difference in mortality between patients in the two study groups who did not have a response to corticotropin (39.2% in the hydrocortisone group and 36.1% in the placebo group, P = 0.69)
- No difference in patients who had a response to corticotropin (28.8% in the hydrocortisone group and 28.7% in the placebo group, P = 1.00).
- At 28 days, 86 of 251 patients in the hydrocortisone group (34.3%) and 78 of 248 patients in the placebo group (31.5%) had died (P = 0.51).
- In the hydrocortisone group, shock was reversed more quickly than in the placebo group.
- However, there were more episodes of superinfection, including new sepsis and septic shock.
- Of note the original plan was to recruit 800 patients but had to stop at 500; however it is still the largest study to date
- Recruitment from 52 centers over 44 months, on average each center took approx 5 months to recruit each patient. The question of clinical equipoise was raised.

VASST

Russell et al. N Engl J Med 2008;358:877-87.

- In this multicenter, randomized, double-blind trial, patients who had septic shock and were receiving a minimum of 5 µg of norepinephrine per minute to receive either low-dose vasopressin (0.01 to 0.03 U per minute) or only norepinephrine (5 to 15 µg per minute) in addition to open-label vasopressors.
- The primary end point was the mortality rate 28 days after the start of infusions.
- A total of 778 patients underwent randomization (396 patients received vasopressin, and 382 norepinephrine), and were included in the analysis.
- There was no significant difference between the vasopressin and norepinephrine groups in the 28-day mortality rate (35.4% and 39.3%, respectively; P = 0.26) or in 90-day mortality (43.9% and 49.6%, respectively; P = 0.11).
- There were no significant differences in the overall rates of serious adverse events (10.3% and 10.5%, respectively; P = 1.00).
- In the prospectively defined stratum of less severe septic shock, the mortality rate was lower in the vasopressin group than in the norepinephrine group at 28 days (26.5% vs. 35.7%, P = 0.05)
- in the stratum of more severe septic shock, there was no significant difference in 28-day mortality (44.0% and 42.5%, respectively = 0.76). A test for heterogeneity between these two study strata was not significant (P = 0.10).
- Low-dose vasopressin did not reduce mortality rates as compared with norepinephrine among patients with septic shock who were treated with catecholamine vasopressors.
- ***This was not a primary vasopressor trial***
- ***These patients were not refractory to vasopressors.***

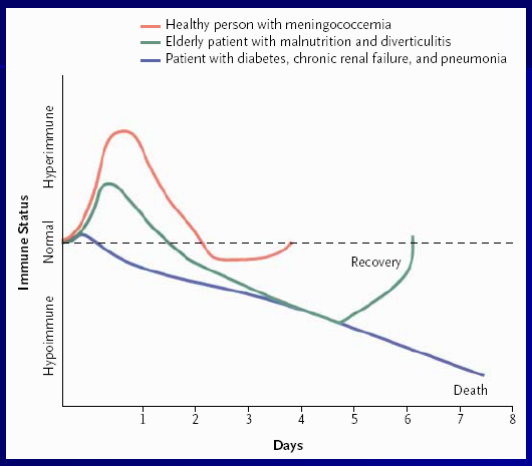
Table 1. Investigational Treatments of Sepsis.

Compound	Therapeutic Rationale
Antiendotoxin antibodies	Neutralize endotoxin, a compound that triggers sepsis
Antioxidant compounds	Neutralize effects of oxidant-mediated tissue injury
Anticoagulants	Inhibit formation of microthrombi and injury due to tissue ischemia and reperfusion
Bactericidal permeability-increasing protein	Kill bacteria and neutralize endotoxin
Tumor necrosis factor antibodies	Block action of tumor necrosis factor at the tissue level
Constructs of tumor necrosis factor soluble receptor	Block action of tumor necrosis factor at the tissue level
Interleukin-1–receptor antagonists	Inhibit action of interleukin-1 on cellular receptors
Interleukin-1 antibodies	Prevent interleukin-1–receptor interactions
Bradykinin-receptor antagonists	Prevent vasoactive effects of bradykinin
Cyclooxygenase inhibitors	Block inappropriate pyrogen, thromboxane, and prostacyclin production
Thromboxane antagonists	Inhibit inappropriate vasoconstriction and platelet aggregation
Platelet activating factor antagonists	Block platelet activation and inflammatory lipid release
Inhibitors of leukocyte-adhesion molecules	Prevent endothelium–leukocyte interaction
Nitric oxide antagonists	Restore appropriate vasoregulation

Lewis Thomas

"the microorganisms that seem to have it in for us . . . turn out . . . to be rather more like bystanders. . . . It is our response to their presence that makes the disease. Our arsenals for fighting off bacteria are so powerful . . . that we are more in danger from them than the invaders."

Germs NEJM 1972;287:553-5



A new approach?

A new process of care?

Central Line Bundle

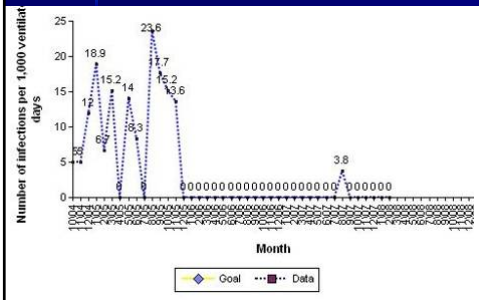
- Hand Hygiene
- Maximal Barrier Precautions Upon Insertion
- Chlorhexidine Skin Antisepsis
- Optimal Catheter Site Selection
- Daily Review of Line Necessity with Prompt Removal of Unnecessary Lines

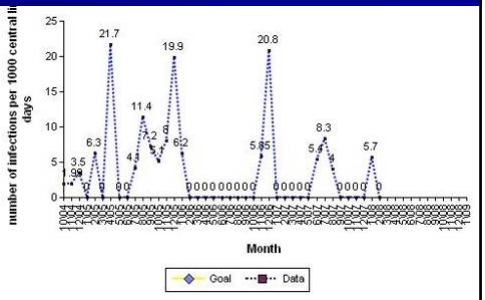
Ventilator Associated Pneumonia (VAP) Bundle

- Elevation of the Head of the Bed
- Daily "Sedation Vacations" and Assessment of Readiness to Extubate
- Peptic Ulcer Disease Prophylaxis
- Deep Venous Thrombosis Prophylaxis

BELLEVUE MICU

VAP CRBSI





Sepsis Bundle

- **Resuscitation**
  - Lactate if >4 mmol/L give at least 20ml/kg in the first 6 hours until the CVP >8 mmHg or lactate <4
  - Blood cultures prior to abx
  - Abx within 3 hours in ED or within 1 hour on the floor
  - Pressors if MAP >65 if BP cannot be maintained with IVF (NE then Vasopressin)
  - Consider SvO2 sat (>65% is the goal)
- **Management (24hours)**
  - Stress steroids if the patient is "poorly responsive to fluid and vasopressor therapy"
  - Documentation of the consideration for Activated protein C (APACHE>25)
  - Insulin drip if glucose is >150
  - Plateau Pressure <30 cmH20

Improvement in Process of Care and Outcome After a Multicenter Severe Sepsis Educational Program in Spain

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Context Concern exists that current guidelines for care of patients with severe sepsis and septic shock are followed variably, possibly due to a lack of adequate education.

Objective To determine whether a national educational program based on the Surviving Sepsis Campaign guidelines affected processes of care and hospital mortality for severe sepsis.

Design, Setting, and Patients Before and after design in 59 medical-surgical intensive care units (ICUs) located throughout Spain. All ICU patients were screened daily and enrolled if they fulfilled severe sepsis or septic shock criteria. A total of 854 patients were enrolled in the preintervention period (November-December 2005), 1465 patients during the postintervention period (March-June 2006), and 247 patients during the long-term follow-up period 1 year later (November-December 2006) in a subset of 23 ICUs.

Intervention The educational program consisted of training physicians and nursing staff from the emergency department, wards, and ICU in the definition, recognition, and treatment of severe sepsis and septic shock as outlined in the guidelines. Treatment was organized in 2 bundles: a resuscitation bundle (6 tasks to begin immediately and be accomplished within 6 hours) and a management bundle (4 tasks to be completed within 24 hours).

Main Outcome Measures Hospital mortality, differences in adherence to the bundles' process-of-care variables, ICU mortality, 28-day mortality, hospital length of stay, and ICU length of stay.

Results Patients included before and after the intervention were similar in terms of age, sex, and Acute Physiology and Chronic Health Evaluation II score. At baseline, only 3 process-of-care measurements (blood cultures before antibiotics, early administration of broad-spectrum antibiotics, and mechanical ventilation with adequate inspiratory plateau pressure) we had compliance rates higher than 50%. Patients in the postintervention cohort had a lower risk of hospital mortality (44.0% vs 39.7%; $P=.04$). The compliance with process-of-care variables also improved after the intervention in the sepsis resuscitation bundle (5.3% [95% confidence interval [CI], 4%-7%] vs 10.0% [95% CI, 8%-12%]; $P<.001$) and in the sepsis management bundle (10.9% [95% CI, 9%-13%] vs 15.7% [95% CI, 14%-18%]; $P=.001$). Hospital length of stay and ICU length of stay did not change after the intervention. During long-term follow-up, compliance with the sepsis resuscitation bundle returned to baseline but compliance with the sepsis management bundle and mortality remained stable with respect to the postintervention period.

Conclusions A national educational effort to promote bundles of care for severe sepsis and septic shock was associated with improved guideline compliance and lower hospital mortality. However, compliance rates were still low, and the improvement in the resuscitation bundle lapsed by 1 year.

JAMA. 2008;299(19):2294-2303 www.jama.com

Sepsis is one of the most prevalent diseases and one of the main causes of death among hospitalized patients.[1] Severe sepsis accounts for 1 in 5 admissions to intensive care units (ICUs) and is a leading cause of death in noncardiac ICUs.[2,3] In Spain, the incidence of severe sepsis is 104 cases per 100 000 adult residents per year with a hospital mortality of 20.7%, and the incidence of septic shock is 31 cases per 100 000 adult residents per year with a mortality of 45.7%.[4] In the United States, the incidence of severe sepsis is higher (300 cases per 100 000 population) as is the mortality rate (28.6%), which represents 215 000 deaths annually.[1]

Early appropriate antibiotic therapy,[5,7] early goal-directed therapy (EGDT),[8] corticosteroids,[9] recombinant human activated protein C or drotrecogin alfa (activated),[10] and lung protective strategies[11] have all been associated with survival benefits. These and other therapeutic advances led to the development of the Surviving Sepsis Campaign (SSC) guidelines[12] as part of a plan

For editorial comment see p 2322.

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Caring for the Critically Ill Patient Section Editor: Derek C. Angus, MD, MPH, Contributing Editor, JAMA.

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Table 2. Performance of Process-of-Care Measurements

Type of Measure	Preintervention Cohort (n = 854)	Postintervention Cohort (n = 1465)	*P* Value
	No. (%) [95% CI]		
Sepsis resuscitation bundle (first 6 h after presentation)			
Measure lactate	334 (39.0) [36-42]	736 (50.1) [48-53]	<.001
Blood cultures before antibiotics	465 (54.4) [51-58]	914 (62.4) [60-65]	<.001
Broad-spectrum antibiotics	568 (66.5) [63-70]	1009 (68.9) [67-71]	.24
Fluids and vasopressors	329 (40.9) [37-44]	630 (46.7) [44-49]	.008
Central venous pressure ≥8 mm Hg	167 (21.4) [19-24]	344 (26.7) [24-29]	.007
Central venous oxygen saturation ≥70%	49 (6.3) [5-8]	147 (11.4) [10-13]	<.001
All resuscitation measures	45 (5.3) [4-7]	147 (10.0) [8-12]	<.001
Sepsis management bundle (first 24 h after presentation)			
Consideration of low-dose steroids for septic shock according to ICU policy	320 (45.4) [42-49]	662 (54.7) [51-57]	<.001
Consideration of drotrecogin alfa (activated) according to ICU policy	378 (44.3) [41-48]	760 (51.9) [49-54]	<.001
Glucose control	381 (44.6) [41-48]	726 (49.6) [47-52]	.02
Plateau-pressure control	424 (85.7) [83-89]	712 (82.7) [80-85]	.15
All management measures	93 (10.9) [9-13]	230 (15.7) [14-18]	.001
Administration of medication			
Low-dose steroids	311 (36.4) [33-40]	611 (41.7) [39-44]	<.001
Drotrecogin alfa (activated)	51 (6.0) [4-8]	74 (5.1) [4-6]	.20
	Mean (SD) [95% CI]		
Time from presentation, min			
Serum lactate measured	152.5 (146.5) [137.4-167.5]	140.4 (137.4) [130.8-150.1]	.18
Blood culture obtained	136.5 (165.5) [120.0-153.0]	116.4 (146.3) [106.2-126.6]	.03
Antibiotics administered	156.0 (167.0) [139.9-172.0]	129.4 (136.8) [120.2-138.6]	.003
Central venous pressure ≥8 mm Hg achieved	238.4 (188.6) [219.4-257.3]	241.6 (193.4) [226.7-256.5]	.79
Central venous oxygen saturation ≥70% achieved	245.0 (212.0) [203.9-286.3]	258.9 (200.5) [235.4-282.5]	.55

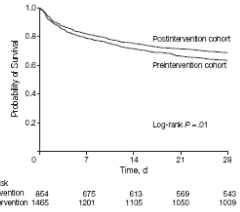
Abbreviations: CI, confidence interval; ICU, intensive care unit.

Table 3. Performance of Outcome Measurements

	Preintervention Cohort (n = 854)	Postintervention Cohort (n = 1465)	*P* Value
Mortality, No. (%) [95% CI]			
Hospital	376 (44.0) [41-47]	580 (39.7) [37-42]	.04
28-d	311 (36.4) [33-40]	456 (31.1) [29-33]	.009
ICU	315 (36.9) [34-40]	474 (32.4) [30-35]	.03
Hospital stay, d[a]			
Mean (SD) [95% CI]	28.7 (23.4) [26.6-30.8]	30.7 (25.7) [29.0-32.4]	.16
Median (IQR)	20.9 (13.5-35.7)	22.8 (13.3-41.4)	.25
ICU stay, d[a]			
Mean (SD) [95% CI]	13.4 (16.0) [11.9-14.0]	13.6 (16.3) [12.5-14.7]	.87
Median (IQR)	7.6 (4.5-15.0)	7.7 (4.0-15.9)	.83

Abbreviations: CI, confidence interval; ICU, intensive care unit; IQR, interquartile range.
[a] Deaths are excluded.

Figure. Probability of Survival in Patients With Severe Sepsis in the Preintervention and Postintervention Cohorts According to the Length of Survival



When you are on the wards as a third year student and you have a patient with sepsis…