



	<p>Sepsis Syndrome</p> <p>David Chong M.D. Medical Director of Critical Care Bellevue Hospital September 26, 2006</p>

	<p>Case</p> <ul style="list-style-type: none"> ■ 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 he has won the Nobel Prize and is the new Dean of the Health Sciences Campus) and flushed with warm extremities ■ His CXR shows dense, right sided, multi-lobar infiltrates
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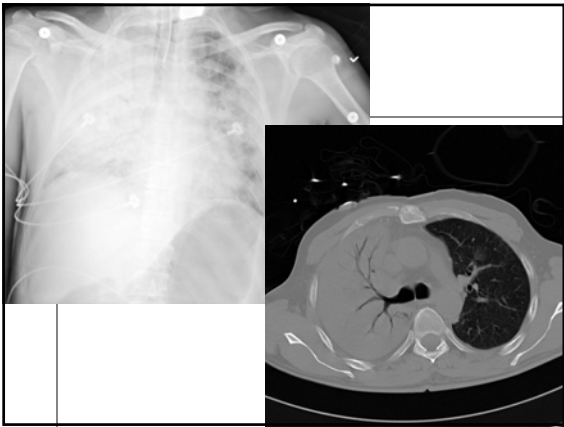
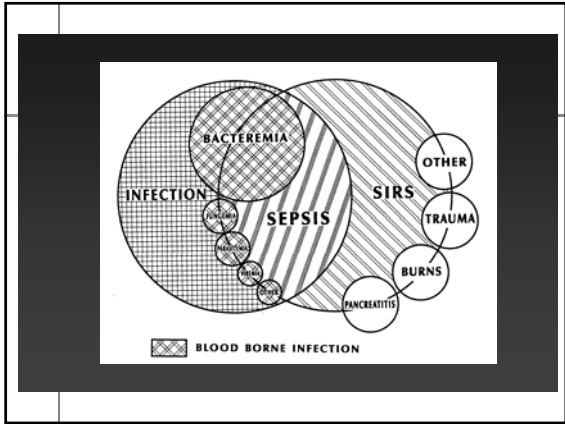
	<p>Dr. Glenda Garvey</p>
	

	
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	<p>Labs</p> <ul style="list-style-type: none"> ■ His ABG 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
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Assessment & Management
<ul style="list-style-type: none"> ■ Diagnosis? ■ Differential? ■ Therapy? ■ Complications? ■ Outcome?



ACCP/SCCM Consensus Definitions
<ul style="list-style-type: none"> ■ Infection <ul style="list-style-type: none"> - Inflammatory response to microorganisms, or - Invasion of normally sterile tissues ■ Systemic Inflammatory Response Syndrome (SIRS) <ul style="list-style-type: none"> - T > 38° C (100.4) or < 36° C (96.8) - HR > 90 - RR > 20 or pCO₂ < 32mm Hg - WBC > 12K or < 4K or > 10% Bands ■ Sepsis <ul style="list-style-type: none"> - Infection plus - ≥ 2 SIRS criteria ■ Severe Sepsis <ul style="list-style-type: none"> - Sepsis - Organ dysfunction <ul style="list-style-type: none"> ■ Hypoperfusion <ul style="list-style-type: none"> - Lactic acidosis - Oliguria - Altered mental status - Septic shock <ul style="list-style-type: none"> ■ Severe Sepsis - Hypotension despite fluid resuscitation <ul style="list-style-type: none"> ■ BP < 90 or SBP decrease > 40 mmHg - Inotropic or vasopressor agents ■ Multiple Organ Dysfunction Syndrome (MODS) <ul style="list-style-type: none"> - Altered organ function in an acutely ill patient - Homeostasis cannot be maintained without intervention
<small>Bone RC et al. Chest. 1992;101:1644-55.</small>

Sepsis Syndrome
<ul style="list-style-type: none"> ■ Definitions ■ Pathophysiology ■ Clinical Manifestations ■ Therapy

Sepsis Syndrome
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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.”

Germes NEJM 1972;287:553-5

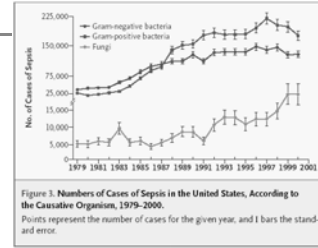
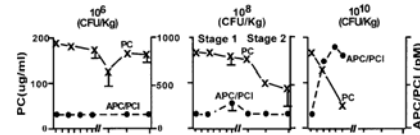


Figure 1. Numbers of Cases of Sepsis in the United States, According to the Causative Organism, 1979-2000. Points represent the number of cases for the given year, and I bars the standard error.

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

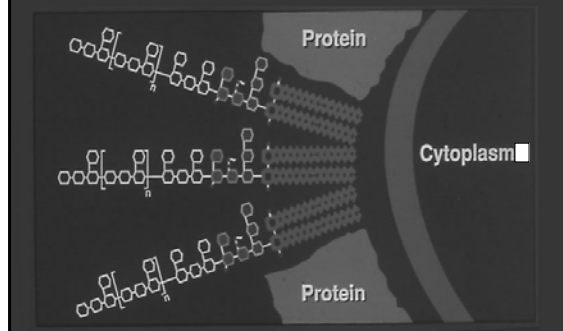


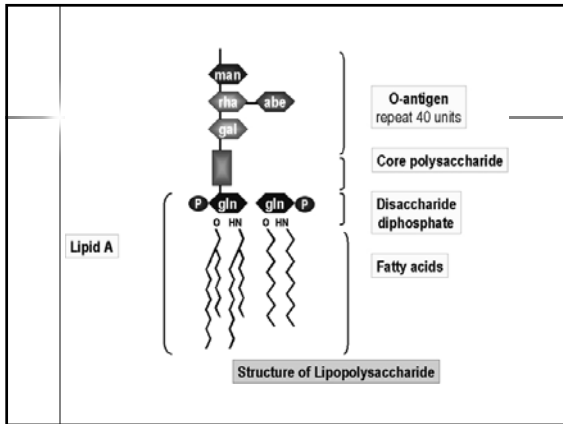
[Crit Care Med 2001; 29(Suppl.):S78-S89

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

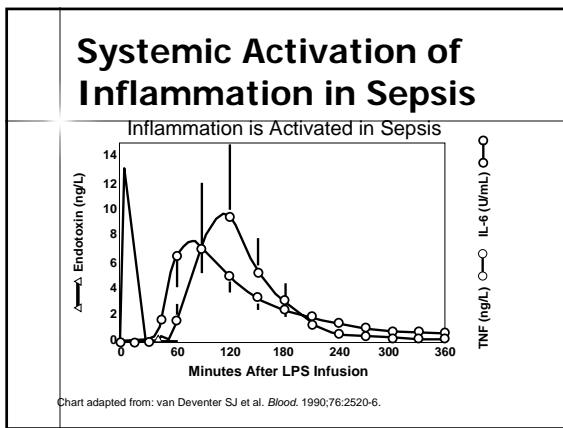
ENDOTOXIN: A COMPONENT OF THE GRAM-NEGATIVE BACTERIAL CELL WALL





“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.)
 - Small amounts resulting in a large T-cell and cytokine response

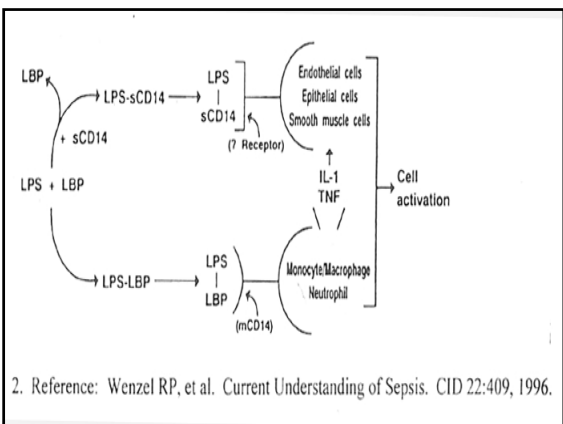


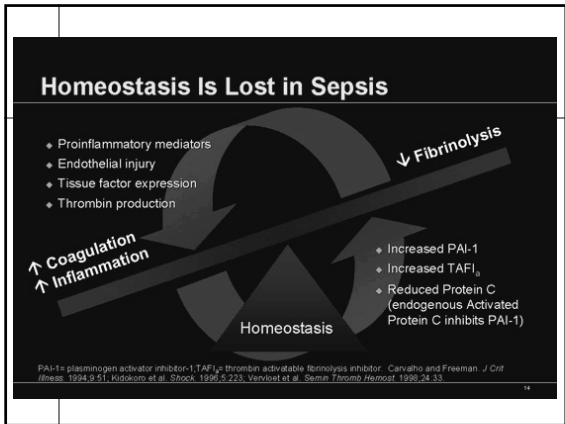
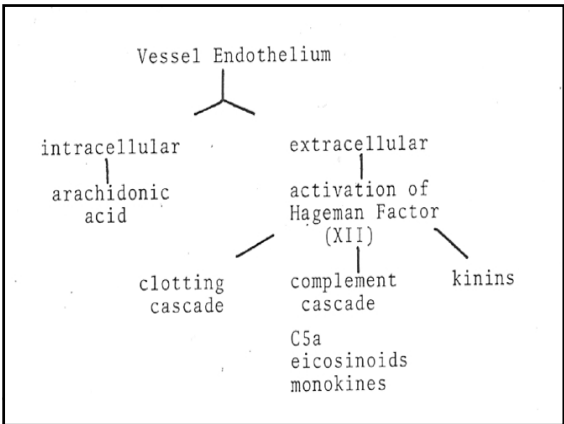
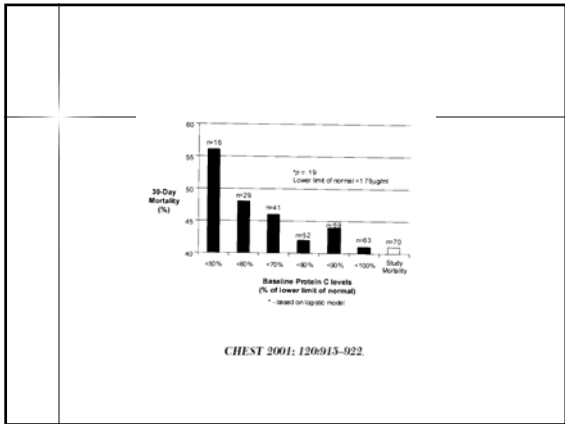
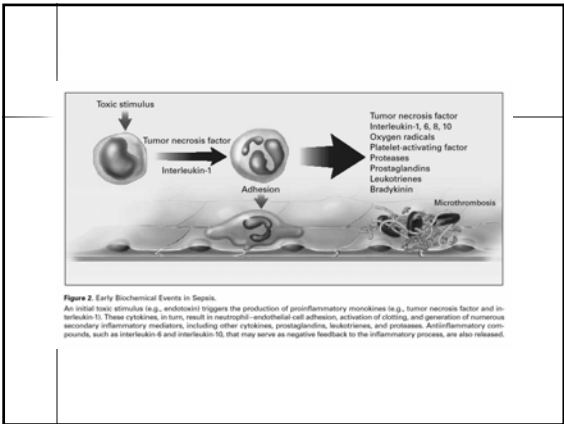
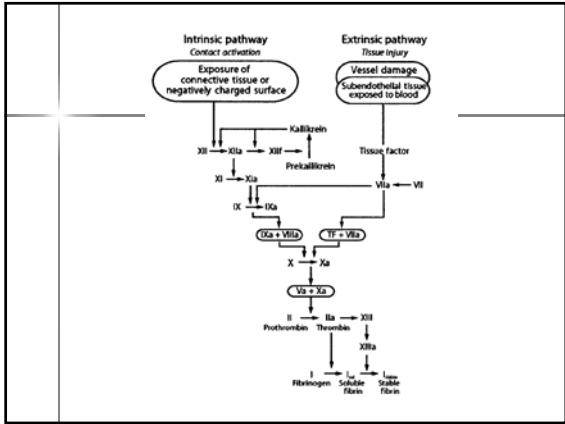
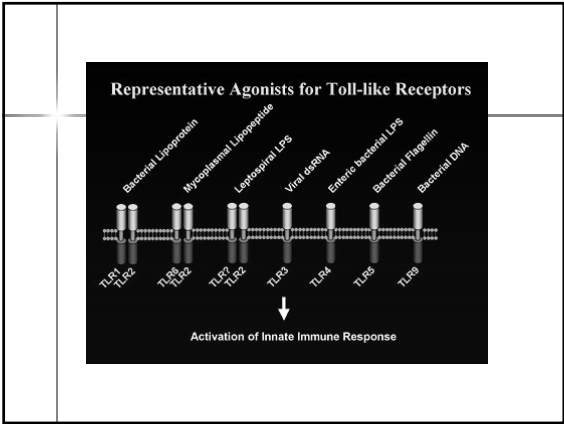
Pathophysiology of Sepsis

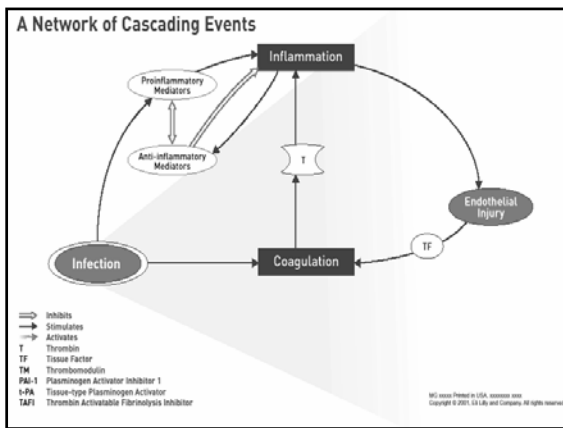
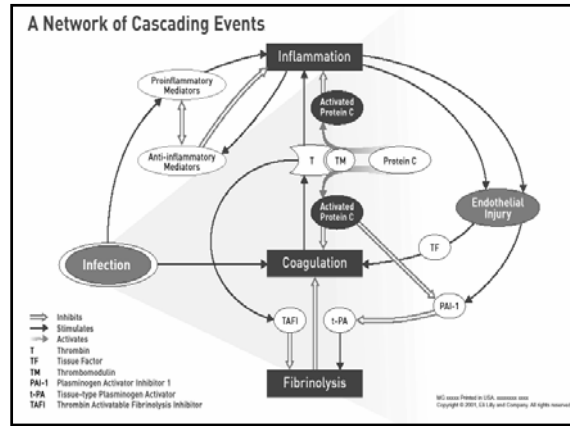
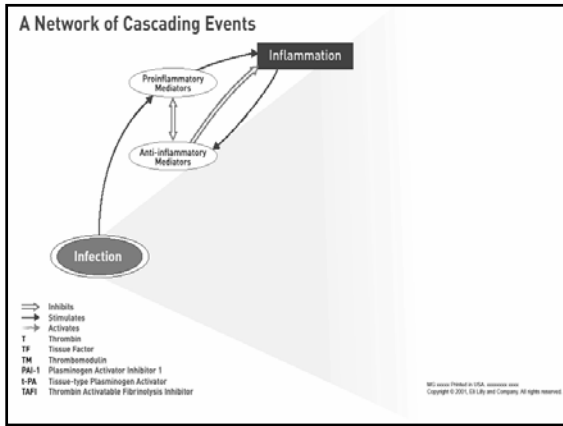
- LPS initiates the stereotypic inflammatory response
- Initial targets are the macrophage and vascular endothelial cell
- Endothelial cell
 - LPS-sCD₁₄ complex receptor
- Macrophage
 - LPS-LPS binding protein CD14 receptor
- Another transmembrane signaling of inflammation is TLR
 - TLR4 for gram neg. bacteria
 - TLR2 for gram positive
- Translocation of NFκB
- Transcription of TNF

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

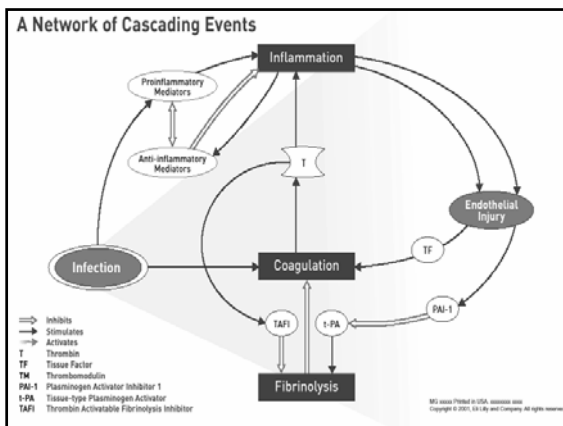






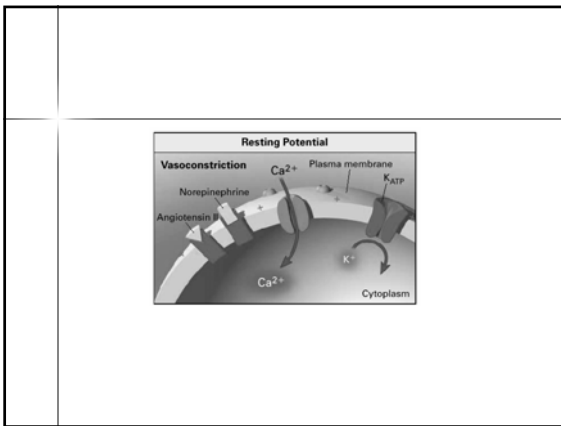
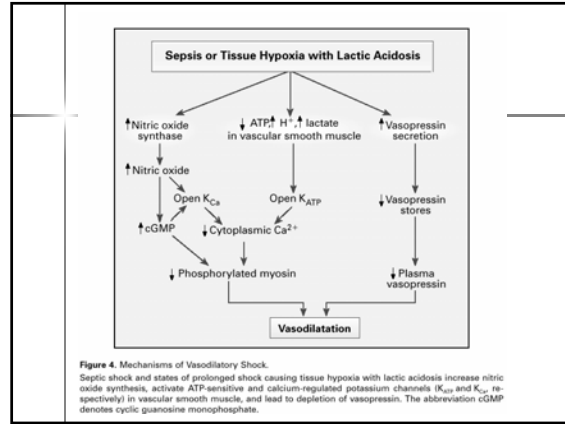
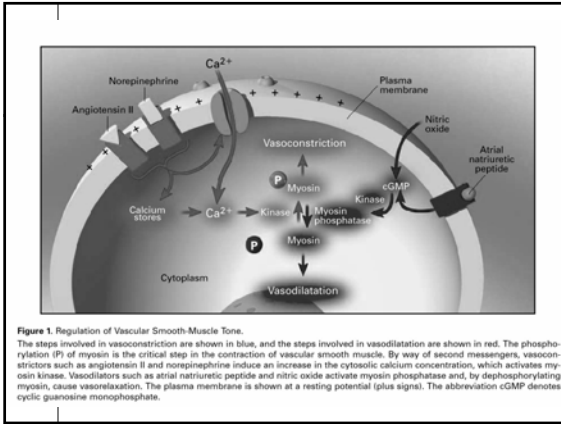
SHOCK SYNDROMES

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



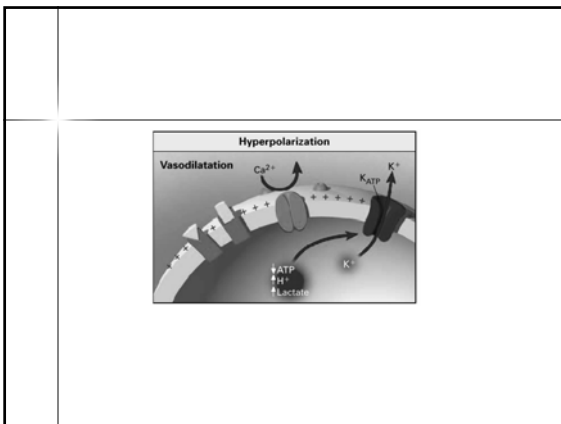
Mechanisms of Vasodilatory Shock

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



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)
 - $T > 38^\circ$ or $< 36^\circ C$
 - HR > 90
 - RR > 20 or $pCO_2 < 32$ mm 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: 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.

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

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

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

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

Identifying Acute Organ Dysfunction as a Marker of Severe Sepsis

- Altered Consciousness, Confusion, Psychosis
- Tachycardia, Hypotension
- Tachypnea, $\text{PaO}_2 < 70$ mm Hg, $\text{SaO}_2 < 90\%$, $\text{PaO}_2/\text{FiO}_2 \leq 300$
- Oliguria, Anuria, \uparrow Creatinine
- Jaundice, \uparrow Enzymes, \downarrow Albumin, \uparrow PT
- \downarrow Platelets, \uparrow PT/APTT, \downarrow Protein C, \uparrow D-dimer

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.

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	

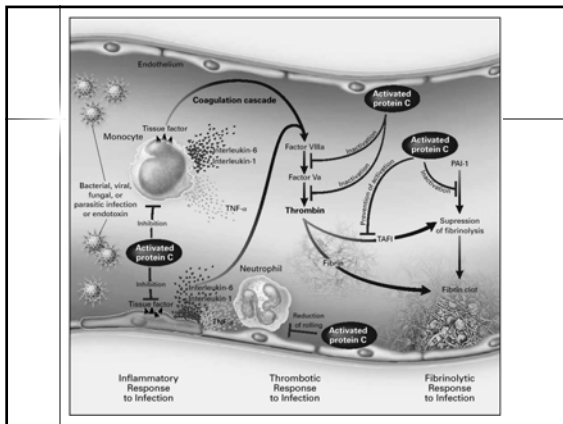
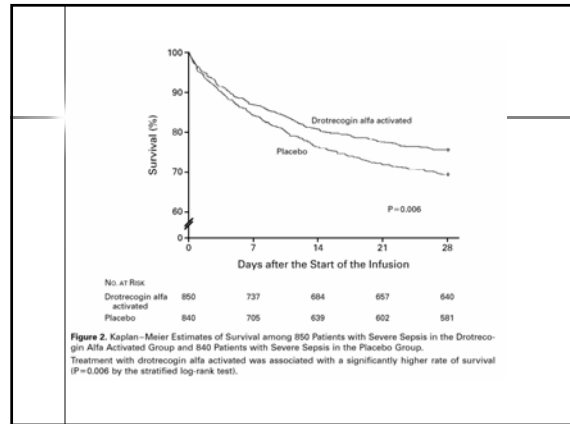
Diagnosis	
<ul style="list-style-type: none"> ■ Cultures ■ Empiric Antibiotics <ul style="list-style-type: none"> - Likely site of infection "where?" (Source Control) - Likely Organisms - Specific Epidemiology from the environment <ul style="list-style-type: none"> ■ Antibigram - Early ■ Clinical Response 	

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

Management	
<ul style="list-style-type: none"> ■ Ventilatory Support (ABC's) ■ Antibiotics <ul style="list-style-type: none"> - Early - Appropriate ■ Resuscitation <ul style="list-style-type: none"> - Fluid <ul style="list-style-type: none"> ■ Crystalloid ■ Colloid - Blood - Vasoactive agents ■ Intensive Monitoring ■ Assess for cause ■ Modulate the host response (restore balance) ■ Minimize complications 	

EARLY PHASE LATE PHASE	
<ul style="list-style-type: none"> ■ Vital Signs <ul style="list-style-type: none"> - BP Modest ↓ - Temp ↑ / ↓ / - - RR rapid ↑ - Pulse ↑ "bounding" ■ Skin - warm, dry ■ CNS - may be altered, agitation ■ Urine output - usually ↓ ■ LAB_DATA <ul style="list-style-type: none"> - ABG <ul style="list-style-type: none"> ■ pH ↑, pCO₂ ↓, pO₂ mod ↓ - Lactic acid may be ↑ - glucose may be ↑ or ↓ - WBC ↑ / ↓ - Prottime prolonged - Platelets ↓ 	<ul style="list-style-type: none"> ■ Vital Signs <ul style="list-style-type: none"> - BP very ↓ or <90 - Temp ↑ / nl / ↓ - RR ↑ / nl / ↓ - Pulse ↑ "thready" ■ SKIN - cold, "clammy" ■ CNS - often confused ■ URINE output - usually ↓ ↓ ■ LAB_DATA <ul style="list-style-type: none"> - ABG <ul style="list-style-type: none"> ■ pH ↓, pCO₂ ↓ or nl, pO₂ mod ↓ - Lactic acid ↑ ↑ - glucose may be ↑ or ↓ - WBC ↑ / ↓ - Prottime prolonged - Platelets ↓

Early Goal-Directed Therapy In The Treatment of Severe Sepsis and Septic Shock	
<small>Rivers et al. NEJM 2001;345:1368-77</small>	
<ul style="list-style-type: none"> ■ 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 ScvO₂ >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 O₂ 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 	



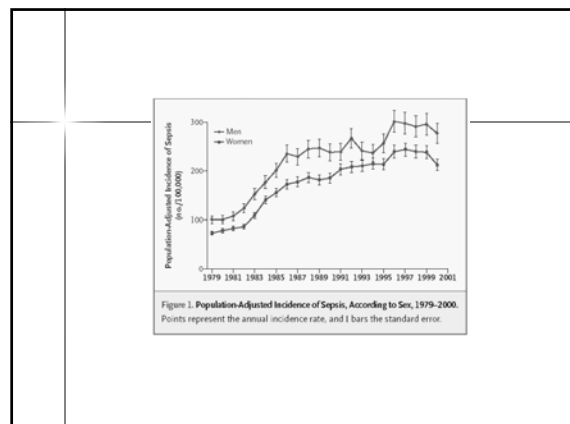
Epidemiology

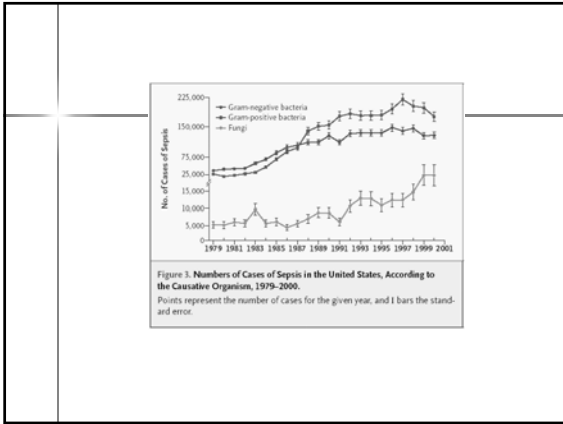
- Accounts for about 2% of admissions but 59% require intensive care
- \$ 17 billion dollars in the US alone
- Mortality is 20-50%
- 2nd leading cause of death in noncoronary ICU's
- 10th leading cause of overall death
- More common in men and in non-whites
- Patients are now older (57 to 60)
- Incidence 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 organisms 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

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

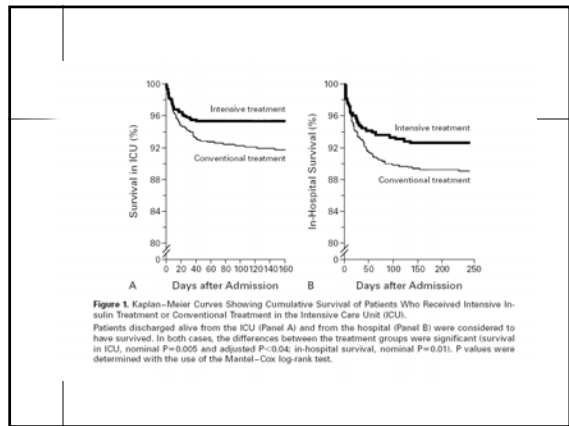
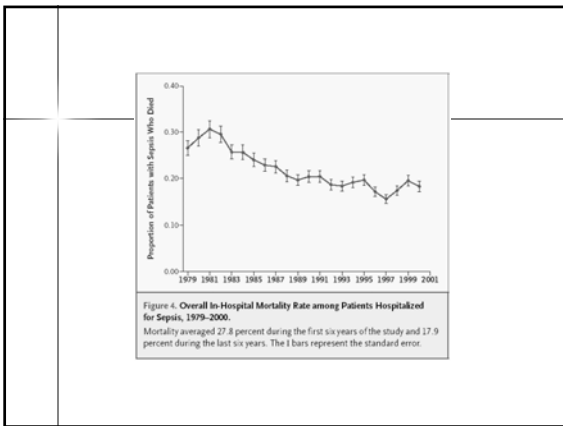




Intensive Insulin Therapy

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



Future Directions

- Intensive Insulin Therapy
 - Van den berghe et al. NEJM 2001;345:1359-67
 - Van den berghe et al. NEJM 2006;454:449
- Stress Dose Steroids
 - Annane et al. JAMA 2002;288:862-871
- New Immunomodulators?
 - Abraham et al. OPTIMIST Trial JAMA 2003;290:238-247
- New Paradigm?
 - Hotchkiss NEJM 2003;348:138-150
- New Process ?
 - Bundles

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.
- Although length of stay 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 from the onset of shock
- The patients were then given a 250 µg IV bolus and cortisol levels were measured at time 0, 30min, and 60 min
- 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 63% and 53% in the steroid group
- Vasopressors were withdrawn in the 57% in the steroid group vs. 40% in the placebo

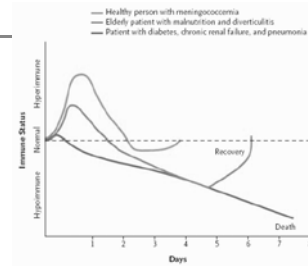


TABLE 1. INVESTIGATIONAL TREATMENTS OF SEPSIS.

Compound	Therapeutic Rationale
Antiendotoxin antibodies	Neutralize endotoxin, a compound that triggers sepsis
Antioxidant compounds	Neutralize effects of oxidant mediators and 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 prostaglandin, thromboxane, and prostacyclin production
Thrombosane 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

Bundles

- All or nothing
- Changing our approach and processes
- Bundled together is profoundly better than any of the individual elements
- Decreasing hospital infection rates to 0
- Can be a wonderfully successful and joyous

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."

Germes NEJM 1972;287:553-5



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 still in shock and perform Cortrosyn stim test (d/c if >9 pre to post)
 - Consideration for Activated Protein C (Xigris) [APACHE >25]
 - Insulin drip if glucose is >150



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