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# Sepsis

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Fall 2008

# Overview of the Lecture

- Definition and epidemiology of sepsis
- An introduction to pathophysiology
- Diagnosis
- Treatment

# A Basic Scientist's Definition of Sepsis

A systemic response, and often a disproportionately severe one, to a poorly-controlled infection. Key features include:

- Unregulated activation the clotting and complement cascades
- Corresponding inappropriate activation of professional phagocytes (neutrophils and macrophages) and mast cells
- Global damage to endothelium, with increased permeability
- Microvascular smooth muscle failure with vasodilatation and loss of local blood flow regulation
- Organ dysfunction including but not limited to the heart, liver, gut, kidneys, and CNS, but especially the *lung.*

# A Clinician's Definition of Sepsis

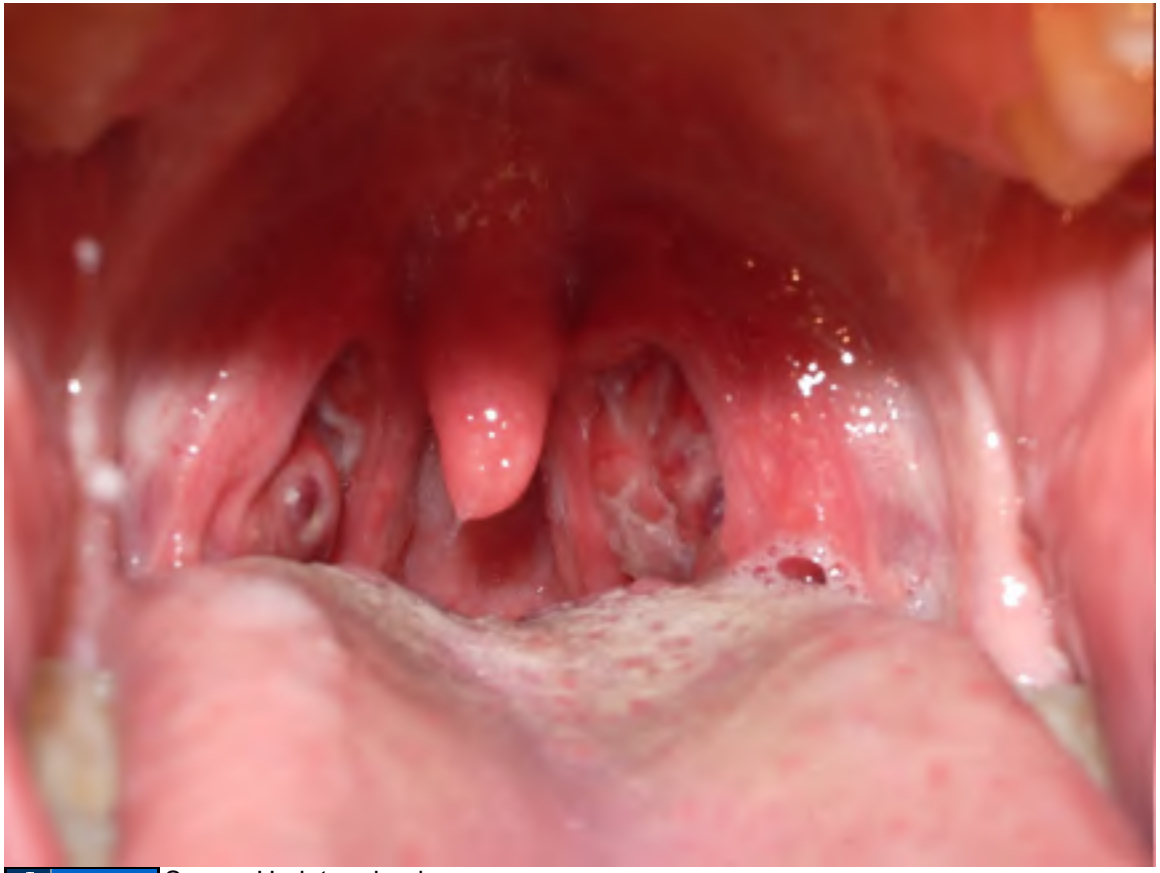
Clinically, sepsis is an illness that is characterized by:

1. The presence (or suspected presence) of an infection
2. Signs of a strong host response or, occasionally, a tepid host response when a strong one is called for
3. Hypotension
4. Signs and symptoms of poor perfusion
   - Cool, sometimes mottled, extremities
   - Oliguria
   - Confusion

# An Epidemiologist's Definition of Sepsis

- Systemic Inflammatory Response Syndrome
  - Temperature: $< 36^0$ or $> 38^o$
  - Heart Rate: $\geq$ 90 beats per minute
  - Tachypnea: 20 breaths per minute or $pCO_2 < 32$ mmHg
  - WBC count: $< 4000$ /mm$^3$ or $> 12{,}000$ /mm$^3$
- Sepsis
  - Two or more SIRS + an infectious source
- Severe Sepsis
  - Sepsis with signs of failure in at least one organ system
- Septic Shock
  - Sepsis with shock / hypoperfusion despite fluid resuscitation
- Note: Definitions vary for children and neonates

# The Problem with These Definitions: Most People in this Room Have Been Septic



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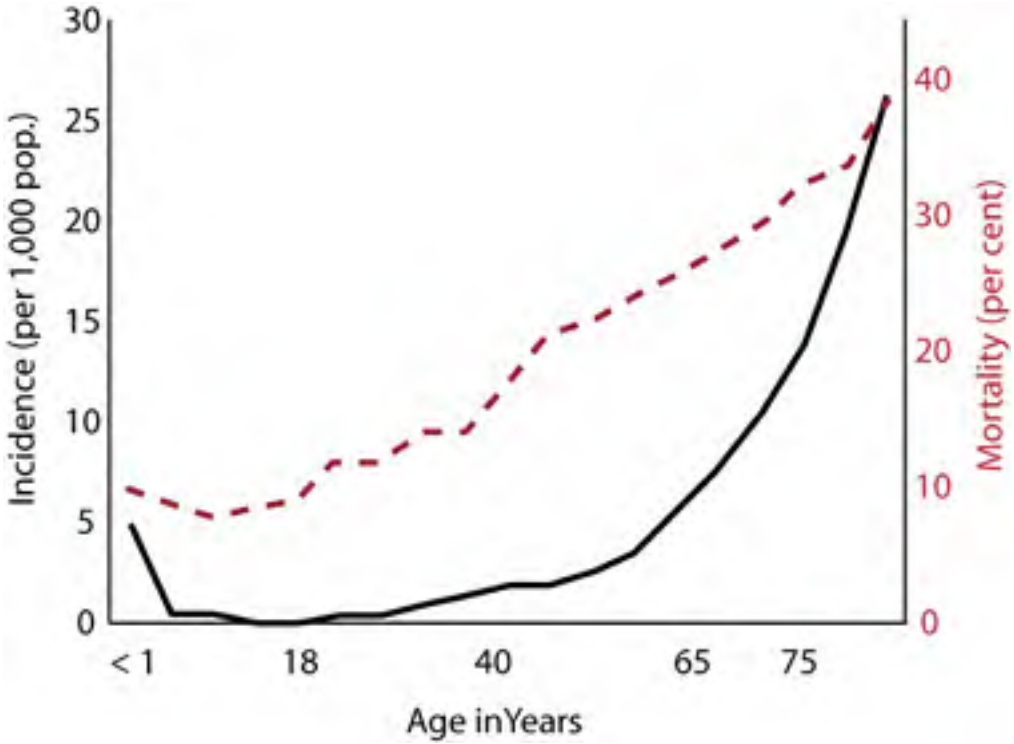
# Epidemiology of Severe Sepsis

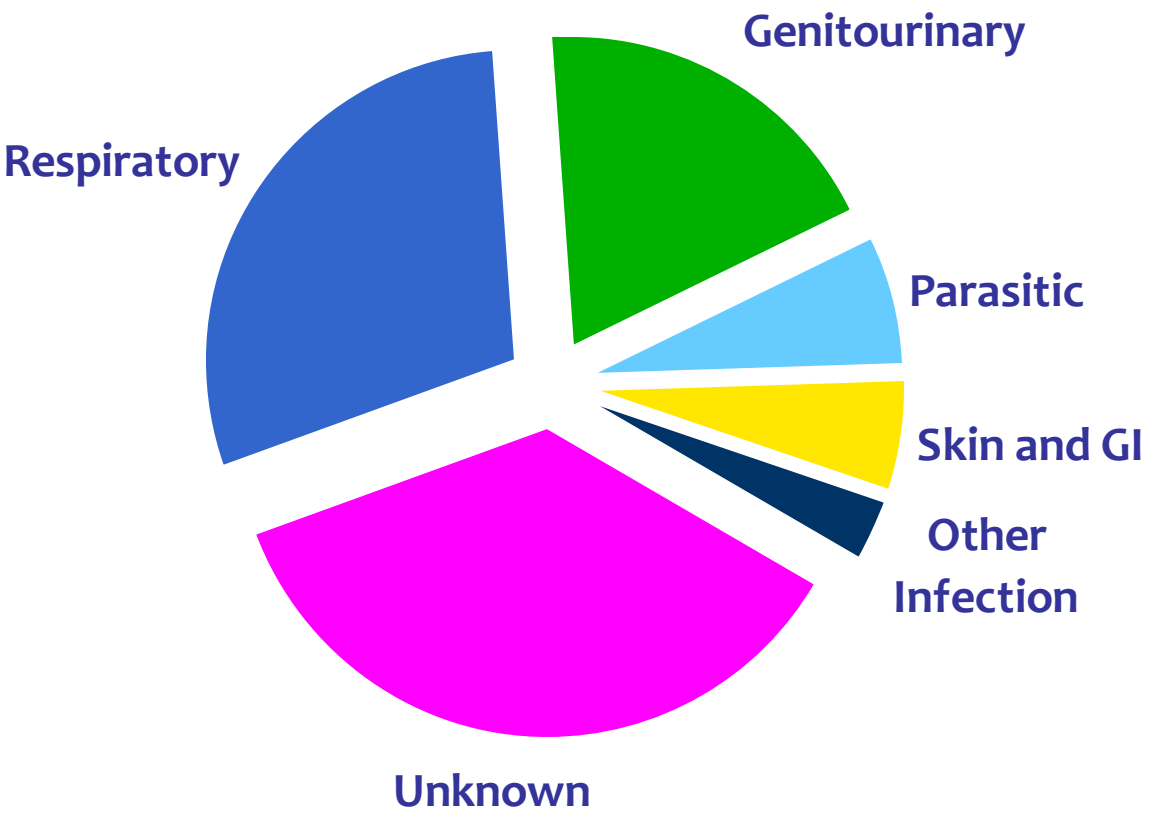
- Incidence in the United States is around 750,000 cases annually
- About 500,000 of cases are cared for initially in emergency departments
- The rest usually find themselves in ICUs following hospital admissions for other reasons
- About 215,000 cases (29%) are fatal each year
  - 2-3 fully loaded 727's crashing into the ground each day
  - Compare to COPD, with ~ 127,000 deaths annually
- Roughly 9% of deaths in the United States

# Incidence and Mortality of Sepsis, By Age



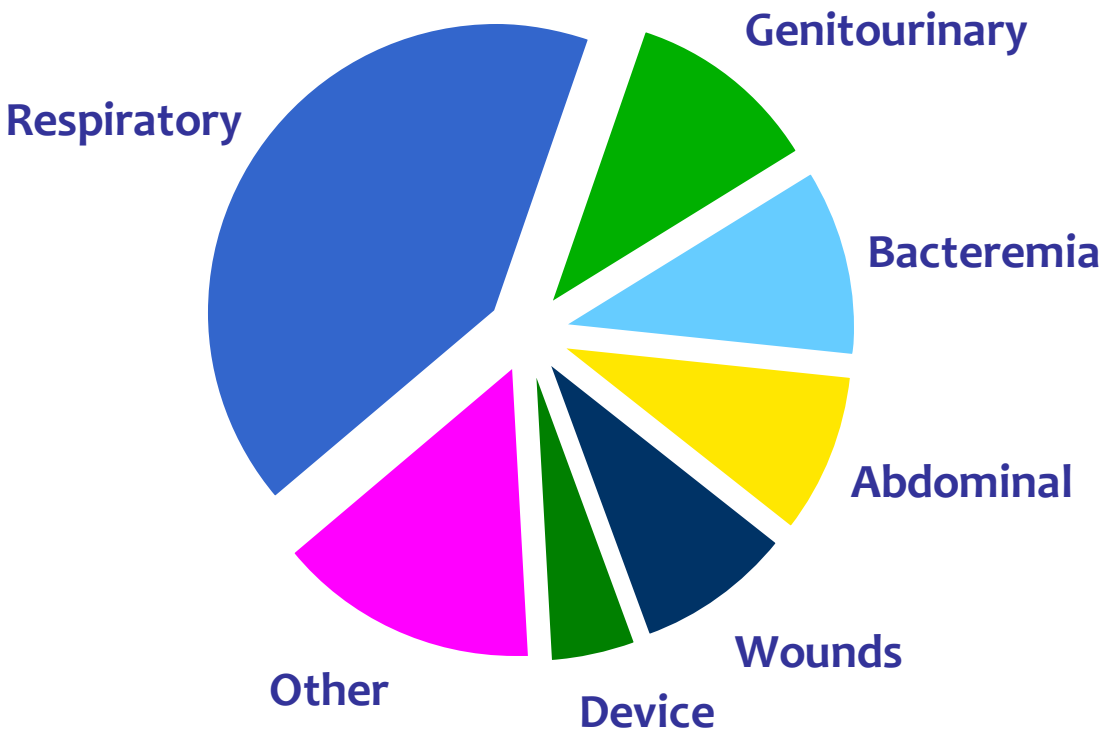

PD-INCL Angus, et al. CCM 2001

# Sepsis Source among Patients Arriving from the Community




PD-INCL Wang, et al. CCM 2007

# Sepsis Source among Patients Cared for in the ICU



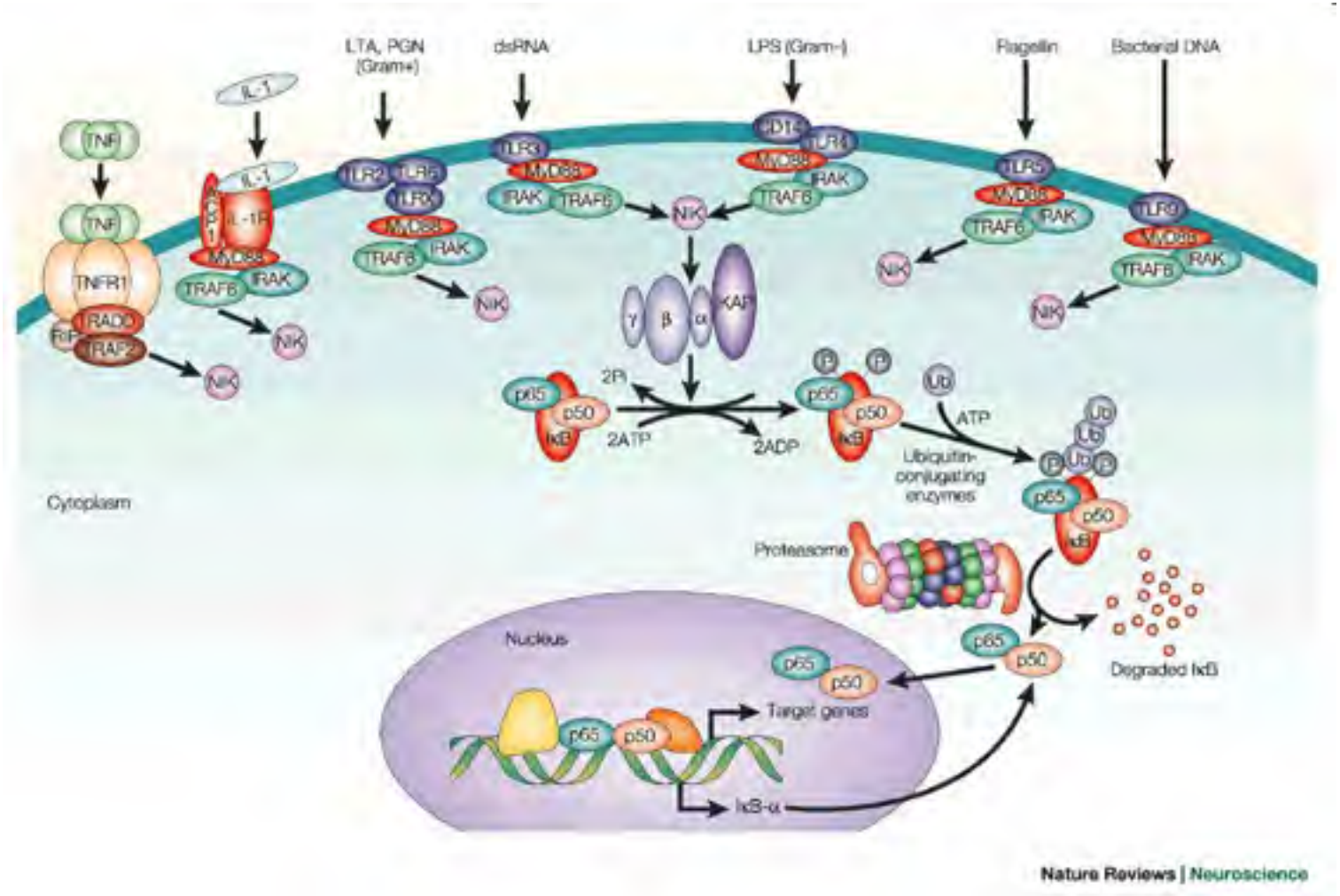

Angus, et al. CCM 2001

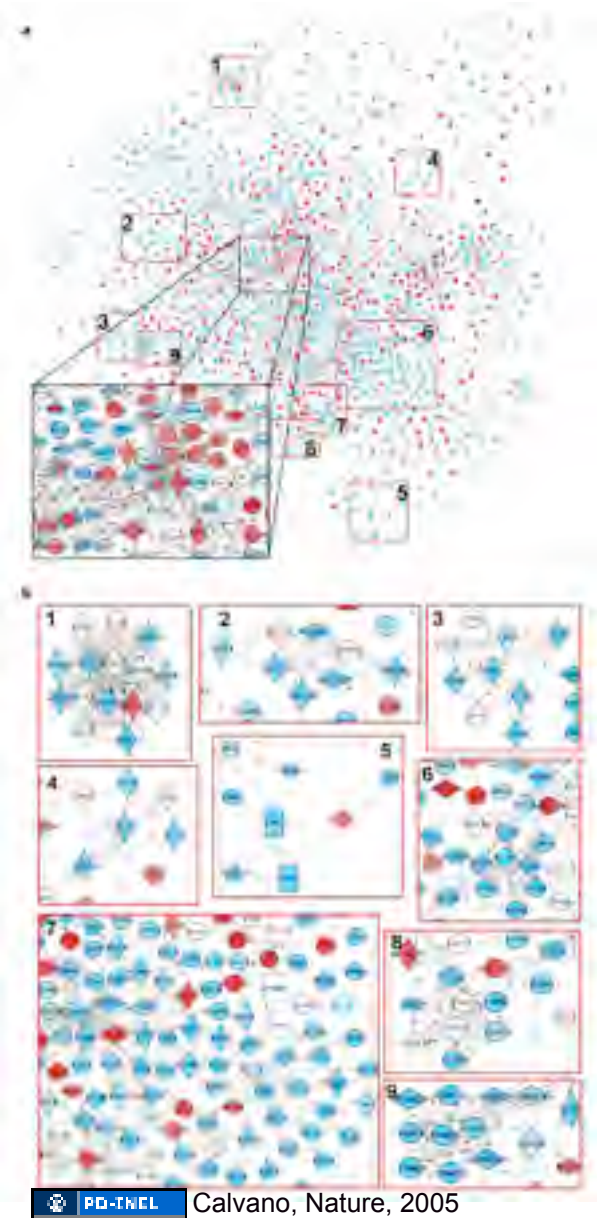
# Pathogenesis

- Sepsis is the result of inappropriate and global activation or deactivation of innate immune, inflammatory, thrombotic, and metabolic pathways

- Key culprits include:
  - Toll-like receptors and the NF-κB signaling pathway
  - Complement
  - Tissue factor (procoagulant)
  - Plasminogen Activator Inhibitor-1 (PAI-1, which prevents thrombolysis)
  - Endothelial nitric oxide
  - Lipid and carbohydrate metabolism (e.g., pyruvate dehydrogenase)
  - Apoptosis

# Toll-Like Receptors and NF-κB



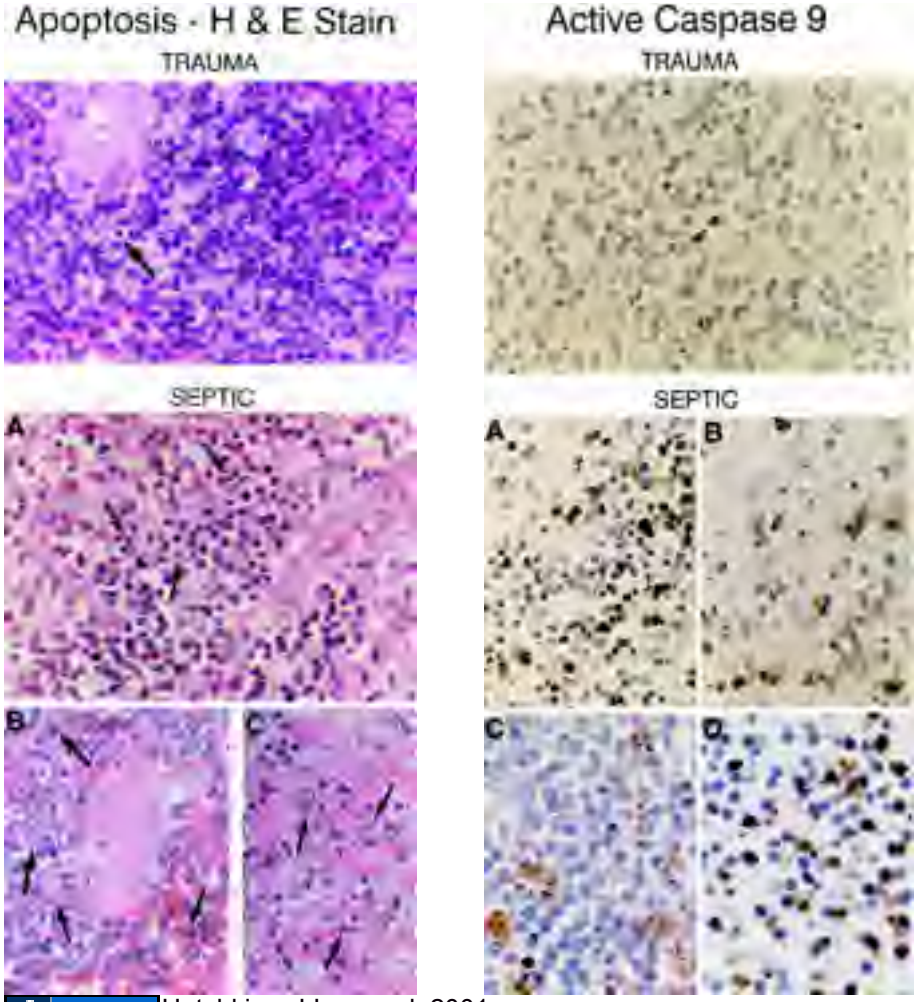



PD-INCL Calvano, Nature, 2005

Low-dose intravenous (experimental) LPS exposure in humans produces tremendous effects:

- > 1,200 genes perturbed in WBCs
- Key loci included:
  - Cytokines, chemokines, and their receptors
  - Complement proteins and receptors
  - Mitochondrial respiratory chain proteins
  - Proteasome elements

# Lymphocyte Apoptosis: Another Key Pathogenic Feature in Sepsis




Hotchkiss, J Immunol, 2001

# In What Context are All of These Responses Intended?

- Long-distance signals
  - IL-1 (to the hypothalamus for thermogenesis)
  - Colony Stimulating Factors (to the marrow for increased leukocyte production)
  - To the pulmonary vascular bed (for neutrophil demargination)
- Short-distance signals
  - Chemoattractants (e.g., C5a)
  - Phagocyte activators
- A key part of the pathogenesis of sepsis is the ‘nonsensical’ systemic availability of signals meant for local communication only
  - Proinflammatory signal may overcome antiinflammatory regulatory mechanisms

# The Septic Trajectory

- Early, uncontained proinflammatory response
  - Local response gets out of the barn
  - Other organs susceptible to damage as innocent bystanders
- Late, immunocompromised phase
  - Proinflammatory initiation gives way to impaired host defense networks
  - Ability to handle infection lessens over the course of the illness
  - Secondary infections are common
- Resolution
  - In survivors, normal host response may take months to recover

# Key Clinical Features of Sepsis:  Hypotension

- Initially produced by C3a and C5a, leukotrienes, and histamine by way of mast cell degranulation
- Once the illness is firmly established, widespread inappropriate production of inducible nitric oxide synthase (iNOS) causes persistent vasodilation
- Both mechanisms lead to increased intravascular volume and relative hypovolemia

# Key Clinical Features of Sepsis: Hypotension

- Endothelial injury and histamine release result in loss of capillary integrity
- Remember: Starling's Law

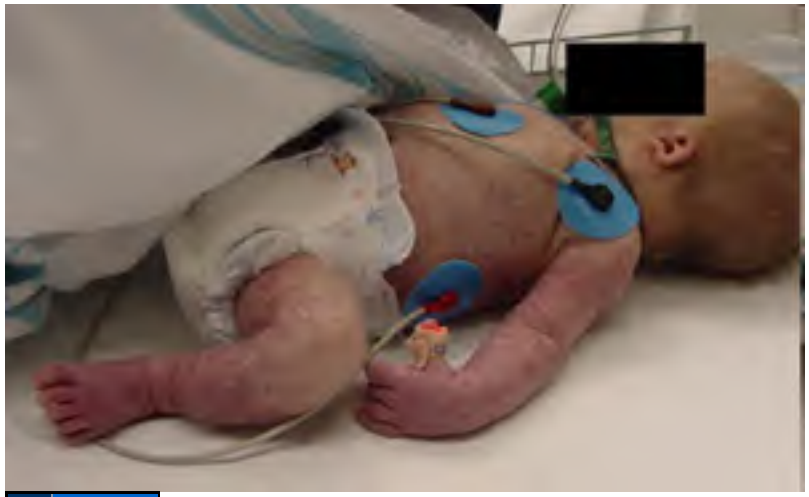
$$Q = L_P S\left[\left(P_C - P_{IF}\right) - \sigma\left(\pi_C - \pi_{IF}\right)\right]$$

- Widespread edema can result once aggressive fluid resuscitation begins

PD-EXP Journal of Endocrinology (Wikipedia)

# Key Clinical Features of Sepsis: Hypotension

- Hypotension is more than just vasodilatation.
- Local blood flow is dysregulated
  - Some areas that need it don't get it
  - Some areas get too much
- Evidence of organ ischemia can be widespread
  - Elevated liver enzymes
  - Elevated creatinine
  - Elevated troponin



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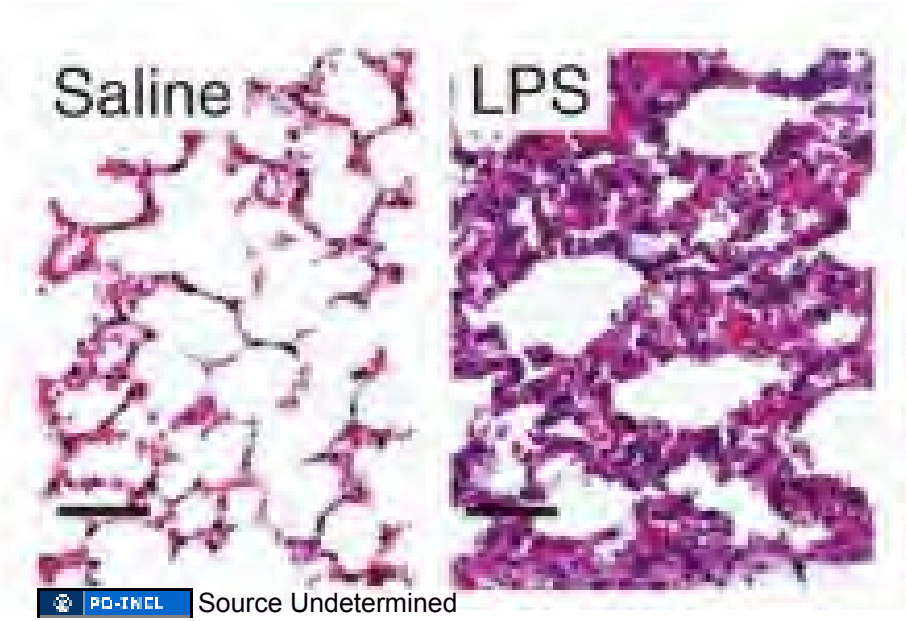
# The Lung as a Target in Sepsis

A sitting duck

- The only organ that sees the entire cardiac output and then some
  - Pulmonary arterial flow
  - Bronchial flow
- The lung is the first tissue bed to see all of the mediators that are washing out of a infectious focus somewhere out in the periphery
- The lung has to filter infectious debris (bacteria, biofilms, etc.) dropping into the blood stream from infected devices
- The lung's function is exquisitely sensitive to capillary leak

# Organs Injured as Innocent Bystanders

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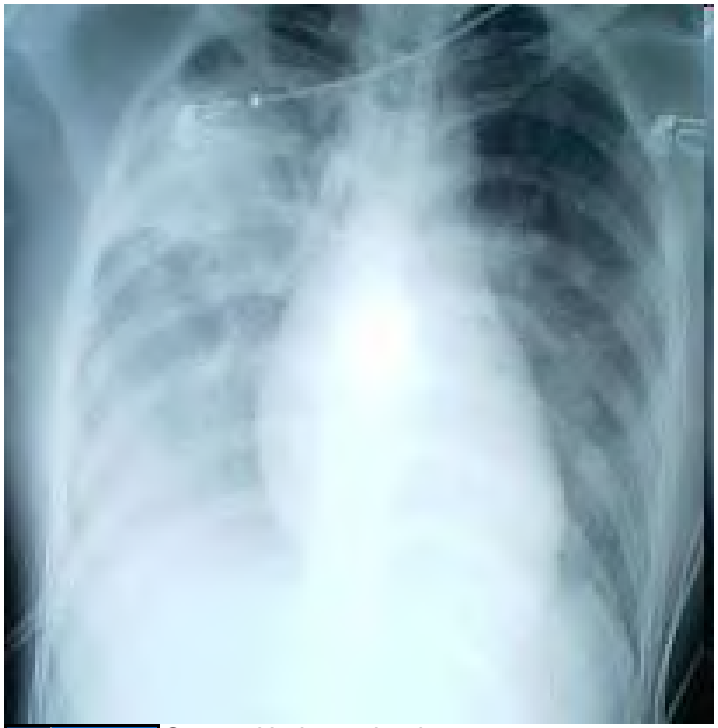
# Acute Lung Injury



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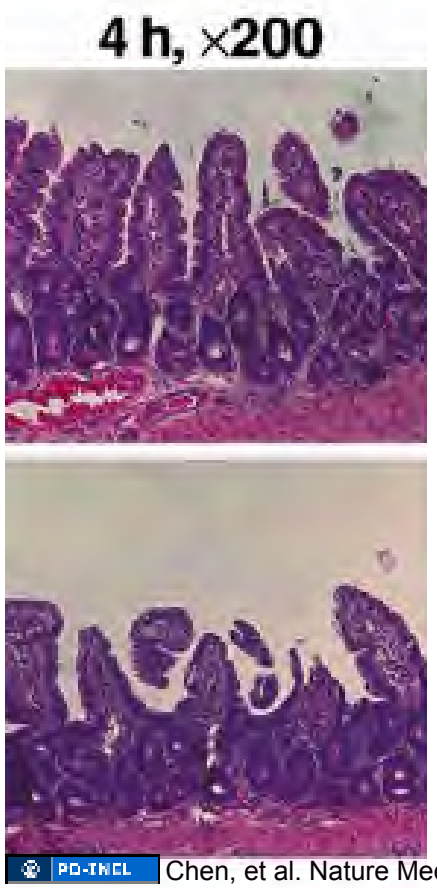
The differential diagnosis for this x-ray includes illnesses far removed from the lung

- Infections such as pyelonephritis
- Ischemic injury to the gut or an extremity
- Hemorrhagic shock
- The list goes on

# Other Organs That Take a Hit

The Gut

- Increased permeability may worsen problems by allowing gut flora into the portal vein
- Edema and ischemia lead to loss of villi and poor adsorption
- Mediators released by the gut hit the liver, then the lung

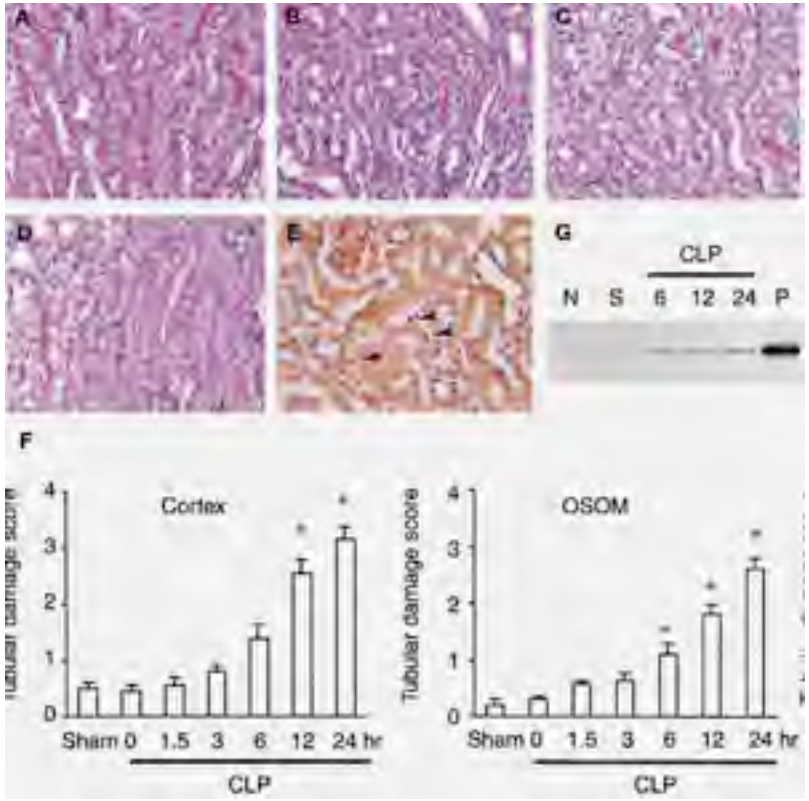



PD-INCL Chen, et al. Nature Med 2003

# Other Organs That Take a Hit

The Kidney

- Acute renal failure
- Injury mechanisms similar to other organs – ischemia + circulating mediators
- Pyelonephritis is a frequency underlying cause of sepsis
- Mortality of sepsis + acute renal failure is very high (up to 75%)




PD-INCL Miyaji, et al. Kidney Intl 2003

# Other Organs that Take a Hit

- The Heart
  - Tissue edema
  - Microvascular thrombosis
  - Decreased contractility
  - Decreased compliance
- The Liver
  - Diminished synthetic function
  - Diminished clearance of systemically generated lactate
  - Injured Kupffer cells contribute to general pro-inflammatory state
  - Decreased clearance of occasional microorganisms from the portal circulation

# The Net Impact on $DO_2$

- Pulmonary edema leads to VQ mismatch and hypoxia
- Decreased cardiac contractility leads to diminished cardiac output
- Peripheral vasodilatation leads to hypovolemia and diminished cardiac output
- 'Hypermetabolic state' in the periphery reduces venous $pO_2$ and content, stressing the ability of remaining functioning lung to oxygenate blood
- In short, $DO_2$ goes down.

# To Make Matters Worse

- Oxygen consumption is abnormal
  - Tissue edema increases the diffusion path from capillaries to mitochondria
  - Local microthrombosis reduce the number of capillaries participating in blood flow to any particular organ
  - Increased levels of nitric oxide (from iNOS) directly poison cyctochrome C oxidase on the inner mitochondrial membrane
- The net result is poor oxygen utilization even in areas where delivery may be intact
- These abnormalities limit the effectiveness of resuscitation aimed at restoring $DO_2$

# Therapeutic Basics

Reliable identification of cases early in their course

- Easier said than done
- Entry points (clinics, hospitals) are busier than ever, wait times are long
- Some patients are sicker than ever, some are less sick than ever
- In-patients can go several hours between visits by nursing or physician staff (think nights, weekends)

- Early findings are hard to distinguish from a lot of other problems
- In elderly patients, the findings can be very subtle and masked by underlying illnesses

- Screening methods suffer from low specificity – capturing ‘all cases’ results in capturing a bunch of folks as well who are not septic

# Therapeutic Basics

Reliable identification of cases early in their course

- Laboratory Tests:
  - WBC (it's one of the SIRS criteria)
  - Measures of other organ function (SaO2, liver function tests, renal function tests)
  - Measures of disordered coagulation (PT, aPTT, fibrinogen, D-dimer, etc.)

  - Blood lactic acid levels
    - In and out of vogue over the past 40 years.
    - Back in fashion now
    - A marker of anaerobic metabolism
    - Few false positives (exercise, grand mal seizures – these are usually not confused with sepsis)

  - Other markers not very useful
    - Inflammatory markers
      - » E.g., TNF, IL-6 much more reflective in the lab than in clinical application

# Therapeutic Basics

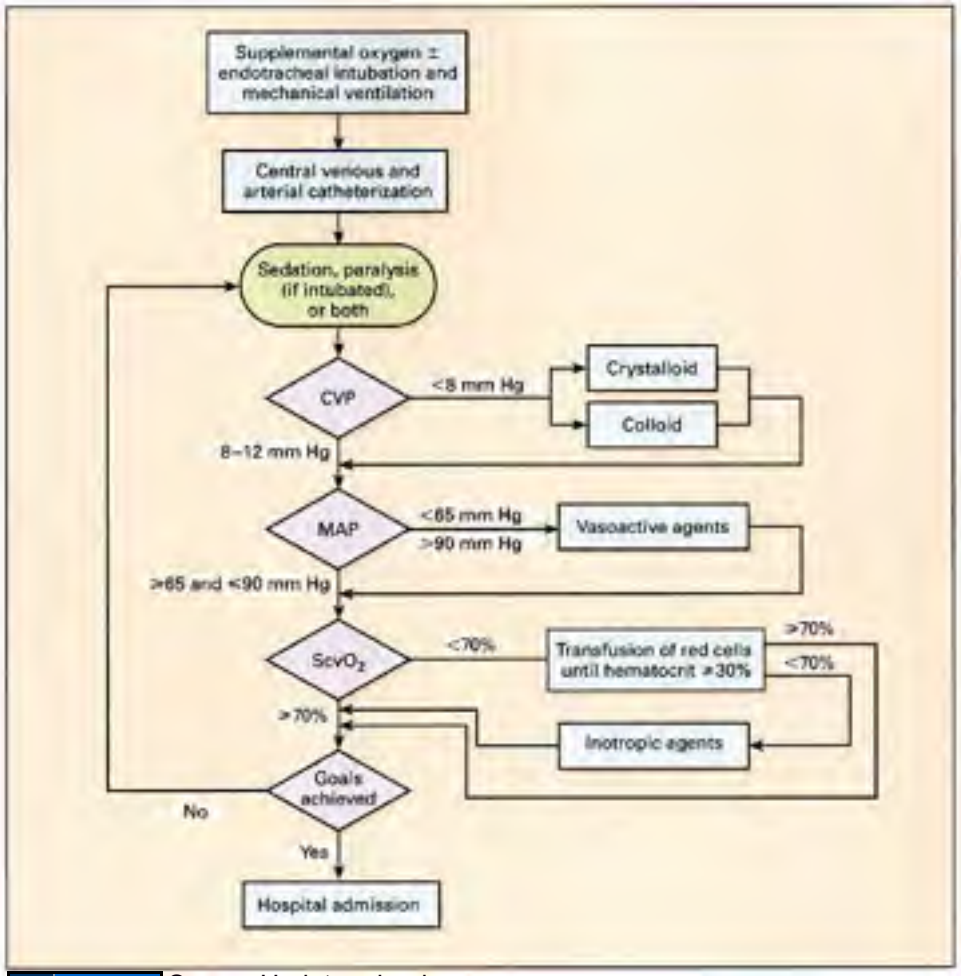
- Correct Hypoperfusion
  - Volume resuscitation
  - Packed red cells
  - Pressors and Inotropes
- Antibiotics
- Lung support
- Specific Therapy

# Therapeutic Basics

Before you get started, how should you monitor the success of your early resuscitation:

- Arterial blood pressure -> an arterial catheter is reasonable
- Central venous pressure -> many treatment algorithms require one
- Urine output
- Arterial oxygen saturation
- Central or mixed venous oxygen saturation
- Serial lactate measurements

# Therapeutic Basics: An Organized Approach to Resuscitation

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# Therapeutic Basics

## Correction of Abnormal $DO_2$ Step 1: Volume Resuscitation

- Intravenous Fluids
  - Normal saline or lactated Ringers frequently used (LR typically a surgical intervention)
  - In a critically ill adult, several *liters* of IVF are commonly required
  - Downside is that patients with a pre-existing leaky microvasculature will not keep this fluid in their circulation for more than a few hours
  - Pulmonary edema as part of volume resuscitation is not uncommon and often contributes to the need to initiate mechanical ventilation
  - Most protocols base volume resuscitation on central venous pressure measurements

# Therapeutic Basics

## Correction of Abnormal $DO_2$ Step 2: Correction of Oxygen Carrying Capacity

- Transfusion
  - More controversial than intravenous fluids
  - Many published guidelines suggest keeping Hct > 30 %
  - Upside is that transfused red cells are a nice intravascular volume expander and tend to stay in the blood stream for much longer than IV fluids
  - Down sides include cost, availability, possibility of transfusion reactions
  - Concerns about blood product transmission of things like Hepatitis C are really misplaced in this setting – the mortality of the acute illness wildly out-strips the risk of communicable diseases in the blood supply

# Therapeutic Basics

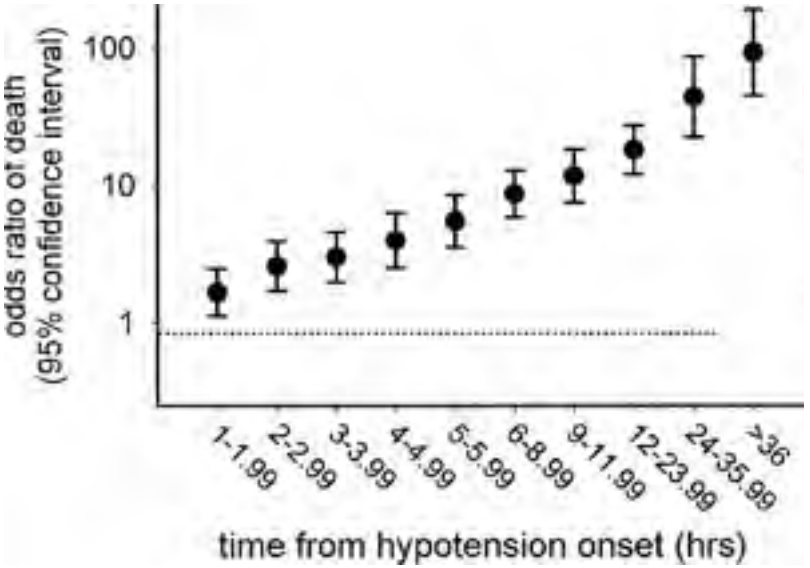
Correction of Abnormal $DO_2$ Step 3:  Maximizing blood flow

- Volume resuscitation often corrects much of the problem with hypotension
- Vasopressors and inotropes can be added to improve blood pressure and venous oxygen saturations once volume has been replaced

# Therapeutic Basics

Early, appropriate antibiotics are *key*

- Unless a specific site of infection, and a specific organism, are known, initial approach is very broad spectrum.
- Gram$^{+}$ and Gram$^{-}$ organisms should be covered, and antibiotic resistance to standard agents should be assumed until proven otherwise




PD-INCL Kumar, CCM 2006

# Therapeutic Basics

## Respiratory Support

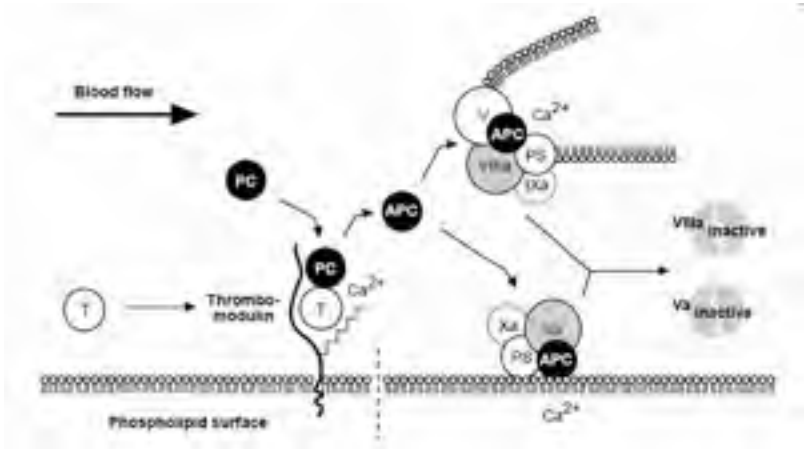
- Supplemental oxygen to overcome gas exchange abnormalities. Goal is hemoglobin saturation as close to 100% as possible

- Readiness to intubate and mechanically ventilate
  - Improves gas exchange
  - Importantly, removes work of breathing from the patient's metabolic 'to do list'
    - This can be substantial – 25-30% of metabolic demands commonly

# Therapeutic Basics

Specific Therapy

- Despite so much being known about the biochemistry of sepsis, there's only one agent that's been shown to be of clear benefit
- Activated protein C
- Acts by degrading factor Va and factor VIIIa
- *Anticoagulant and antiinflammatory*
- Marketed as Drotecogin alfa (Xigris)
- Best results so far: ~ 5-6% reduction
- Expensive: $8,000 per patient

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# Longer Term Management of Sepsis

Key Goals

- Minimize ongoing damage from the inciting event
- Support respiratory function until recovery
- Do no harm in supporting respiratory function
- Support failed organ systems until function returns

# Additional Source Information

for more information see: http://open.umich.edu/wiki/CitationPolicy

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Slide 10: Angus, et al.  CCM 2001
Slide 11: Wang, et al.  CCM 2007
Slide 12: Angus, et al.  CCM 2007
Slide 14: Nature Review
Slide 15: Calvano, Nature, 2005
Slide 16: Hotchkiss, J Immunol, 2001
Slide 20: Journal of Endocrinology (Wikipedia) http://en.wikipedia.org/wiki/File:Ernest_Starling.jpg  PD-EXP
Slide 21: Source Undetermined
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Slide 24: Source Undetermined
Slide 25: Chen, et al. Nature Med 2003
Slide 26: Miyaji, et al. Kidney Intl 2003
Slide 34: Source Undetermined
Slide 38: Kumar, CCM 2006
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