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Sepsis

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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 $> 38^0$
  – Heart Rate:  $> 90$ 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
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

Angus, et al.  CCM 2001
Sepsis Source among Patients Cared for in the ICU

- Respiratory
- Genitourinary
- Bacteremia
- Abdominal
- Wounds
- Device
- Other

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
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

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

- Widespread edema can result once aggressive fluid resuscitation begins.
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
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
Acute Lung Injury

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

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%

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 cytochrome 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 $\text{DO}_2$
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
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
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
Correction of Abnormal $\text{DO}_2$ 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.

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
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

Source Undetermined
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

Slide 8: Source Undetermined
Slide 10: Angus, et al.  CCM 2001
Slide 14: Nature Review
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