Pathologic Mechanisms of Septic Shock

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Topics

- Definitions: SIRS, sepsis, shock, MODS
- Morbidity/mortality of Sepsis/Shock
- Pathogenesis of shock
- Microbial triggers (endotoxin, TSSTs)
- Cytokine and non-cytokine mediators of SIRS and shock
- Pathophysiology of shock
- Therapy
Systemic Inflammatory Response Syndrome (SIRS)

- Systemic inflammatory response to a variety of severe clinical insults manifested by ≥ 2 of the following conditions:
  - Temperature: >38°C or <36°C
  - Heart rate: >90 beats/min
  - Respiratory rate: >20 breaths/min or PaCO2 <32 torr (<4.3 kPa)
  - White blood cell count: >12,000 cells/mm³, <4000 cells/mm³, or >10% immature (band) cells
Sepsis

- The presence of SIRS associated with a confirmed infectious process.
Severe Sepsis

- Sepsis with either hypotension or systemic manifestations of hypoperfusion
  - Lactic acidosis, oliguria, altered mental status
Septic Shock

- Sepsis with hypotension despite adequate fluid resuscitation, associated with hypoperfusion abnormalities
Multiple Organ Dysfunction Syndrome (MODS)

- Progressive distant organ failure (initially uninvolved) following severe infectious or noninfectious insults (severe burn, multiple trauma, shock, acute pancreatitis)
Morbidity/Mortality of Sepsis and Septic Shock

- Leading cause of death in noncoronary ICU patients
- 500,000 episodes sepsis/year in U.S. (35% crude mortality)
- 200,000 cases septic shock (40% of sepsis cases) (40-70% mortality)
- 40% hospital deaths after injury due to MODS
Pathogenesis of Shock

- Infectious or noninfectious triggers
  - Cytokine and inflammatory mediator cascade
    - Cardiac dysfunction and microvascular injury
      - Hypotension and shock
Some Characteristics of Septic Shock

- Systemic vasodilation and hypotension
- Tachycardia; depressed contractility
- Vascular leakage and edema; hypovolemia
- Compromised nutrient blood flow to organs
- Disseminated intravascular coagulation
- Abnormal blood gases and acidosis
- Respiratory distress and multiple organ failure
Microbial Triggers

- **Gram-negative bacteria:** lipopolysaccharide
- **Gram-positive bacteria:**
  - Lipoteichoic acid/cell wall muramyl peptides
  - Superantigens
    - Staphylococcal Toxic Shock Syndrome Toxin, TSST
    - Streptococcal pyrogenic exotoxin, SPE
Bacterial-Mediated Sepsis

Bacteria

Gram(-) \rightarrow LPS + LBP

Gram(+) \rightarrow LTA

dead

LBP = LPS-Binding Protein
LPS = Lipopolysaccharide
LTA = Lipoteichoic acid
TLR = Toll-like receptor

Macrophage

TLR2

CD14

Mediators of Inflammation
Superantigen activation of T Lymphocytes

TcR

V\alpha  V\beta

TSST-1

MHC class II
Gram-negative organism

LPS (endotoxin)

Gram-positive organism

Superantigen Exotoxin

T-lymphocyte

IL-2

IFN-γ

Macrophage

Interleukin-1

Tumor necrosis factor-α
EFFECTS OF EXCESS CYTOKINE RELEASE

Primary mediators (IL-1, TNFα)

Endothelial/Leukocyte molecular activation

Secondary mediators (NO, PAF, PG, LT, IL)

Vasodilation, capillary leak, endothelial damage

Shock \rightarrow MODS \rightarrow Death
IL-1 and TNF activities

- Synergistically induce genes in endothelial cells and monocytes/macrophages
  - iNOS → NO (vasodilation, ↑ pulmonary artery pressure, ↓ cardiac output)
  - PLA₂ → PAF (hypotension)
  - COX-2 → PGE₂ (fever, pain)
IL-1 and TNF activities (cont.)

- Synergistically induce genes in endothelial cells and monocytes/macrophages
  - Adhesion molecules (↑leukocyte adhesion/activation)
  - Other Cytokines (↑Acute phase proteins, recruits new phagocytes)
IL-1 and TNF activities (cont.)

- Cachexia (↓lipoprotein lipase, disrupts glucose metabolism)
- Activates coagulation (↑intravascular thrombi, DIC, ↑tissue factor, ↑ activated factor X, ↑ TFPI, ↓activated protein C)
Endotoxin

PLA$_2$

Arachidonic Acid

Cyclooxygenase

5-Lipoxygenase

Lyso-phospholipid

Prostaglandins

Thromboxanes Leukotrienes

Platelet Activating Factor
Actions of Leukotrienes

- Vasoconstriction
- Bronchoconstriction
- Chemotaxis
- Leukocyte-Endothelial Cell Adhesion
- Leukocyte Emigration
- Vascular Leakage
- Stimulate Leukotriene and Oxygen Free Radical Release
Actions of PAF

- Vasoconstriction/Vasodilation
- Hypotension & Cardiac Depression
- Bronchoconstriction
- Chemotaxis
- Leukocyte-Endothelial Cell Adhesion
- Leukocyte Emigration
- Vascular Leakage
- Platelet Aggregation
- Stimulates Leukotriene, PAF, Cytokine and Oxygen Free Radical Release
**Actions of Nitric Oxide**

- Vasodilation
- Inhibits leukocyte-endothelial cell adhesion
- Inhibits platelet adhesion/aggregation
- Decreases vascular permeability
- Scavenges superoxide radicals
- High concentrations are cytotoxic
PATHOPHYSIOLOGY

General Clinical Signs

- Flu-like symptoms
  - fever, chills
  - general malaise, irritability, lethargy
- Tachycardia and hypotension
- Hyperventilation
- Site of infection may or may not be evident
PATHOPHYSIOLOGY

Cardiovascular

● Systemic vasodilation and hypotension ($P_{sys} < 90$ mmHg)
● Tachycardia (>100 beats/min)
● Increased cardiac output (hyperdynamic), although contractility is depressed; hypodynamic in late shock
● Ventricular dilation; decreased ejection fraction
● Loss of sympathetic responsiveness
PATHOPHYSIOLOGY

Cardiovascular

- Hypovolemia due to vascular leakage; central venous pressure may be decreased or increased depending upon fluid resuscitation
- Compromised nutrient blood flow to organs; decreased organ oxygen extraction
Pulmonary & Renal

- Hyperventilation with respiratory alkalosis
- Pulmonary hypertension and edema
- Hypoxemia (arterial pO₂ < 50 mmHg)
- Reduced pulmonary compliance; increased work
- Respiratory muscle failure
- Renal hypoperfusion; oliguria
- Acute tubular necrosis and renal failure
PATHOPHYSIOLOGY Cont.

Other

- Disseminated intravascular coagulation (DIC)
- Blood dyscrasias
  - leukopenia
  - thrombocytopenia
  - polycythemia
- Central and peripheral nervous dysfunction
- Increased lactate occurs early
Therapies of Sepsis/Septic Shock

- Antibiotics (early administration)
- Hemodynamic support
  - (fluid resuscitation)
    - Restore tissue perfusion
    - Normalize cellular metabolism
  - Vasopressor agents
    - Dopamine, norepinephrine, dobutamine
Therapies of Sepsis/Septic Shock (cont.)

- Source control
  - Surgical debridement of infected, devitalized tissue
  - Catheter replacement
- Supplemental oxygen (treatment of acute respiratory distress syndrome, ARDS)
- Nutritional support
Controversial Current Therapies for Septic Shock

● Anti-inflammatory agents
  – Cortocosteroids
  – Ibuprofen
  – Prostaglandin E1
  – Pentoxifylline

● Oxygen Scavengers
  – N-acetylcysteine
  – selenium
Controversial Current Therapies for Septic Shock (cont.)

- Drugs modifying coagulation
  - Anti-thrombin III
- Drugs enhancing host defenses
  - Intravenous immunoglobulin (IVIG)
  - Interferon-gamma
  - GM-CSF
  - Immunonutrition
Controversial Current Therapies for Septic Shock (cont.)

- Other drugs
  - Growth hormone, antibiotics, fresh frozen plasma, anesthetic sedative and analgesic agents, catecholamines

- Hemofiltration, plasma filtration, plasma exchange
Experimental Therapies of Sepsis/Septic Shock

- Anti-endotoxin therapies
  - IVIG, BPI protein
- IL-1Ra
- Anti-TNF-alpha, soluble TNFR
- PLA2 inhibitors, PAF inhibitors
- iNOS inhibitors
- Anti-coagulants (APC)
References