Pathologic Mechanisms of Septic Shock

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Outline of Topics

• Definitions: SIRS, sepsis, shock, MODS
• Morbidity/mortality of Sepsis/Shock
• Microbial triggers (endotoxin, TSSTs)
• Pathogenesis/Pathophysiology of shock
• Therapy
Systemic Inflammatory Response Syndrome (SIRS)

- Systemic inflammatory response to a variety of severe clinical insults manifested by 2 or more of the following conditions
  - Temperature $>38.5^\circ C$ or $<35^\circ C$
  - Heart rate $>90$ beats/min
  - Respiratory rate $>20$ breaths/min or PaCO2, $<32$ torr ($<4.3$ kPa)
  - White blood count $>12,000$ cells/mm$^3$, $<4000$ cells/mm$^3$, or $>10\%$ immature (band) cells
Sepsis

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

- Sepsis and at least one sign of organ hypoperfusion or organ dysfunction
  - Lactic acidosis, oliguria, altered mental status, mottled skin, capillary refilling time >3s, platelet counts < 100,000/ml or DIC, acute lung injury, cardiac dysfunction
Septic Shock

- Sepsis with hypotension despite adequate fluid resuscitation, associated with hypoperfusion abnormalities
  - Systemic mean blood pressure <60 mm Hg (<80 mm Hg if previous hypertension)
  - Need for vasopressors to maintain blood pressure above 60 mm Hg
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 cases sepsis/yr in U.S. (35% crude mortality)
- 200,000 cases septic shock (40-70% mortality)
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, renal hypoperfusion & oliguria, multiple organ failure
Main Pathogens in Septic Shock

- **Gram-positive bacteria** - 30-50%
  - coagulase-negative staphylococci, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus*, other
- **Gram-negative bacteria** - 25-30%
  - *E. coli*, *Ps. aeruginosa*, *K. pneumoniae*, other
- **Fungi** - 1-3%
  - *Candida albicans*, other
- **Parasites** (1-3%) and **Viruses** (2-4%)
Common origins of sepsis

• Lung
  – bacteremia associated with nosocomial pneumonia
• Abdomen (Intraabdominal infections)
• Genitourinary tract
• Postoperative wound infections
• Primary bloodstream infection via intravascular lines
Pathogenesis of Septic Shock

Infectious Triggers

Cytokine and inflammatory mediator cascade

Cardiac dysfunction and microvascular injury

Hypotension and shock
Primary Cytokine Mediators of Septic Shock

Systemic Macrophage activation by microbes

Systemic Interleukin-1, Tumor Necrosis Factor-α

Endothelial/Leukocyte molecular activation

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

Vasodilation, capillary leak, endothelial damage

Shock → MODS → Death
Microbial Triggers = Pathogen Associated Molecular Patterns

• Gram-negative bacteria:
  - lipopolysaccharide, lipoproteins

• Gram-positive bacteria:
  - Lipoteichoic acid, peptidoglycan
  - Superantigens (TSST, SPE)

• Bacterial flagellin

• Viral and bacterial nucleic acid
Innate Cellular Receptors for Microbes

• Toll-Like Receptors (TLR) are pattern recognition receptors (PRR) that respond to pathogen-associated molecular patterns (PAMP) common to diverse microbes

• TLR ligation triggers innate immune system release of proinflammatory mediators
IL-1 and TNF activities

- Synergistically induce genes in endothelial cells and monocytes/macrophages
  - iNOS → NO (vasodilation, \( \uparrow \) pulmonary artery pressure, \( \downarrow \) cardiac output)
  - PLA\(_2\) → PAF (hypotension)
  - COX-2 → PGE\(_2\) (fever, pain)
  - Lipoxygenase → leukotrienes (neutrophil recruitment)
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)
Pathogenic Mechanisms in Septic Shock

• **Neutrophil and Vascular Endothelium activation**
  – Cytokine induced neutrophil adhesion and vascular occlusion

• **Neutrophil damage of endothelium**
  – Neutrophil release of elastase, superoxide, PLA2, PAF, LTB4
Pathogenic Mechanisms in Septic Shock (continued)

• **Endothelial procoagulant state**
  – Prothrombotic, pro-inflammatory, anti-fibrinolytic state
  • Increased tissue factor expression
  • Decreased tissue factor pathway inhibitor
  • Decreased activated protein C
Pathogenic Mechanisms in Septic Shock (continued)

• **Secondary Inflammatory Mediators**
  – Complement activation
    • C5a mediated histamine release and neutrophil recruitment
  – Pro-inflammatory cytokines
    • TNF, IL-1, IFN-γ, HMGB1
  – Prostaglandins, leukotrienes, PAF, superoxide, NO (mediates apoptosis)
Pathogenic Mechanisms in Septic Shock (continued)

- **Neuroendocrine Reflex**
  - Cytokine activated hypothalamus-pituitary axis (HPA)
  - Fever, leukocytosis, acute phase protein response
  - Metabolic alterations
    - increased catabolism of proteins, carbohydrates, and lipids
Pathophysiological Effects in the Cardiovascular System

• **Vasodilatation** (relative hypovolemia)
  – NO mediated
  – Resistance to vasopressors

• **Maldistribution of blood flow**
  – some arteriolar constriction, leukocyte and thrombotic microvascular plugs

• **Myocardial depression**
  – IL-1, TNF, and NO mediated

• **Result** = Decreased oxygen delivery, tissue hypoxia, organ failure
Treatments for Septic Shock

- **Controlling the source of infection**
  - Antibiotics (early administration)
  - Removal of infected and necrotic tissue
Treatments for Septic Shock-continued

• Management of Shock
  – Restoration of central venous pressure
    • Fluid resuscitation
    • Vasopressors
Treatments for Septic Shock-
continued

• Management of Organ Dysfunction
  – Dialysis for renal failure
  – Mechanical ventilation
Treatments for Septic Shock—continued

• Replacing/enhancing host endocrine and hemostatic Responses
  – Corticosteroids (low dose) and Drotrecogin alfa (activated protein C)
    • Reduces shock duration and mortality
  – Low dose vasopressin
    • Reduces shock duration
Controversial Current Therapies for Septic Shock

• Anti-inflammatory agents
  – Corticosteroids
  – 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
Summary Points

• Septic shock is sepsis with hypotension that persists after fluid resuscitation.
• Excessive or poorly regulated immune generation of cytokines and inflammatory compounds lead to shock.
• Pathogenic mechanisms include neutrophil and endothelial activation, complement and coagulation activation, and neuroendocrine reflexes
Summary Points - continued

• Early recognition of sepsis, antibiotic treatment and aggressive resuscitation is necessary to prevent progression to shock
• Recent randomized controlled trials support treatment approaches that replace hormones (corticosteroids) or coagulation inhibitors (activated protein C).
Summary Points- continued

• Future therapies will target both early and late mediators of septic shock (TLR, cytokines, iNOS, HMGB1).
References