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 **I**nflammatory **R**esponse **S**yndrome (**SIRS**)

- Systemic inflammatory response to a variety of severe clinical insults manifested by 2 or more of the following conditions
- Temperature >38.5ºC or <35ºC
- Heart rate >90 beats/min
- Respiratory rate >20 breaths/min or PaCO2, <32 torr (<4.3 kPa)
- White blood 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 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

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Cardiac dysfunction and microvascular injury

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Hypotension and shock

Primary Cytokine Mediators of Septic Shock

Systemic Macrophage activation by microbes

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Systemic Interleukin-1, Tumor Necrosis Factor-α

↓

Endothelial/Leukocyte molecular activation

↓

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

↓

Vasodilation, capillary leak, endothelial damage

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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, ↑pulmonary artery pressure, ↓cardiac output)
  - PLA_2→PAF(hypotension)
  - COX-2→PGE2 (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 Drotrecognin 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).

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