Pathophysiology of Catheter-Related Infection

All sources of infection are potential targets for prevention

Critically ill patient: 2-4 vascular access devices

Infusates/drugs → hub/lines → Dressing → skin → hematogeneous → catheter
Lymphangitis, a sign of septicemia
Pathophysiology

- The evidence that sepsis results from an exaggerated systemic inflammatory response induced by infecting organisms is compelling; inflammatory mediators are the key players in the pathogenesis.

- Gram-positive and gram-negative bacteria induce a variety of proinflammatory mediators, including cytokines which play a pivotal role in initiating sepsis and shock.
Pro-inflammatory Mediators

- Bacterial Endotoxin
- TNF-α
- Interleukin-1
- Interleukin-6
- Interleukin-8
- Platelet Activating Factor (PAF)
- Interferon-Gamma
- Prostaglandins
- Leukotrienes
- Nitric Oxide
The bacterial cell wall components (LPS & PG) are known to release cytokines.

A major role for **TNF, IL-1** and **IL - 6** has been demonstrated.

These factors also help to keep infections localized, but, once the infection becomes systemic, the effects are detrimental.

Circulating levels of IL-6 correlate well with the outcome.
Nitric oxide plays a major role in hemodynamic alteration of septic shock.

A dual role exists for neutrophils:

- They are necessary for defense against microorganisms
- They may become toxic inflammatory mediators contributing to tissue damage and organ dysfunction.
Cellular Events During Gram Negative Bacteremia

Lipopolysacchride (LPS)

LPS binding protein (LBP)

LPS-LBP

mCD14

LR4-MD2

NF-κB + IκB

NF-κB

Promoters

Cytokines, chemokines
VCAM, ICAM MCP-1, Selectin

TNF-α, PAF, INF-γ, LT/PGs, IL-1, 6,8,12,18

Proinflammatory Phase of Sepsis-related Organ Dysfunction
Stages In the Development of SIRS

- **Stage 1:** In response to injury / infection, the local environment produces cytokines.

- **Stage 2:** Small amounts of cytokines are released into the circulation:
  - Recruitment of inflammatory cells.
  - Acute Phase Response.
  - Normally kept in check by endogenous anti-inflammatory mediators (IL-10, PGE2, Antibodies, Cytokine receptor antagonists).
Anti-inflammatory Mediators

- Interleukin-10
- PGE2
- Protein C
- Interleukin-4
- Interleukin-12
- Lipoxins
- GM-CSF
- TGF
- IL-1RA
Stages In the Development of SIRS

• **Stage 3:** Failure to control inflammatory cascade:
  - Loss of capillary integrity.
  - Stimulation of Nitric Oxide Production.
  - Maldistribution of microvascular blood flow.
  - Organ injury and dysfunction.
Molecular architecture of the IR to sepsis

**Bacterial factors**
- Cell wall components
- Extracellular products

**Effector mechanisms**
- Lymphokine storm
- Chemokine activation
- Neutrophil migration
- Vascular inflammation

**Host factors**
- Genetic susceptibility
- Innate immunity
- Acquired immunity
Sepsis and septic shock

Bacterial infection

Excessive host response

Host factors lead to cellular damage

Organ damage

Death
Pathophysiology of Sepsis-Induced Organ Injury

- Multiple Organ Dysfunction (MODS) results from diffuse cell injury / death resulting in compromised organ function.

- Mechanisms of cell injury / death:
  - Cellular Necrosis (ischemic injury).
  - Apoptosis.
  - Leukocyte-mediated tissue injury.
  - Cytopathic Hypoxia
Pathophysiology of Sepsis-Induced Ischemic Organ Injury

- Cytokine production leads to massive production of endogenous vasodilators.

- Structural changes in the endothelium result in extravasation of intravascular fluid into interstitium and subsequent tissue edema.

- Plugging of microvascular beds with neutrophils, fibrin aggregates, and microthrombi impair microvascular perfusion.
Infection → Vasodilatation → Hypotension
Infection → Inflammatory Mediators → Microvascular Plugging → Maldistribution of Microvascular Blood Flow → Ischemia
Infection → Inflammatory Mediators → Vasodilatation
Infection → Inflammatory Mediators → Edema
Infection → Endothelial Dysfunction
Infection → Endothelial Dysfunction → Vasoconstriction
Infection → Endothelial Dysfunction → Edema
Endothelial Dysfunction → Vasoconstriction
Infection → Endothelial Dysfunction
Endothelial Dysfunction → Edema
Maldistribution of Microvascular Blood Flow → Ischemia
Ischemia → Cell Death
Cell Death → Organ Dysfunction
Pathogenesis of Vasodilatation in Sepsis

- Loss of Sympathetic Responsiveness:
  - Down-regulation of adrenergic receptor number and sensitivity, possible altered signal transduction.

- Vasodilatory Inflammatory Mediators.

- Endotoxin has direct vasodilatory effects.

- Increased Nitric Oxide Production.
Vasodilatory Inflammatory Mediators

- Vasoactive Intestinal Peptide
- Bradykinin
- Platelet Activating Factor
- Prostanoids
- Cytokines
- Leukotrienes
- Histamine
- NO
Microvascular Plugging in Sepsis

- Decreased red cell deformability in inflammatory states.

- Microvascular sequestration of activated leukocytes and platelets.

- Sepsis is a Procoagulant State.
  - The extrinsic pathway may be activated in sepsis by upregulation of Tissue Factor on monocytes or endothelial cells.
  - Fibrinolysis appears to be inhibited in sepsis by upregulation of Plasminogen Activator Inhibitor.
  - A variety of pathways result in reduced Protein C activity in sepsis.
Sepsis Pathogenesis

Unbalanced Immune Reaction

- Tissue Factor
  - Procoagulant State
    - Microvascular Thrombosis

Mediators of Inflammation

- ROS
  - Vasodilation
  - Capillary Leak
Endothelial Dysfunction in Sepsis

- Endothelial cell expression of Selectins and ICAM is upregulated in Sepsis due to inflammatory activation.

- Selectins bind carbohydrate ligands on the surfaces of PMN’s.

- ICAM binds Integrins on the surfaces of PMN’s.

- The Selectins initiate a weak bond between the PMN and the endothelial cell causing PMN’s to tumble along the vessel wall.
Apoptosis in Sepsis

• A physiologic process of homeostatically-regulated programmed cell death to eliminate dysfunctional or excessive cells is activated.

• A number of inflammatory cytokines, NO, low tissue perfusion, oxidative injury, LPS, and glucocorticoids all are known to increase apoptosis in endothelial and parenchymal cells.

• Levels of circulating sfas (circulating apoptotic receptor) and nuclear matrix protein (general cell death marker) are both elevated in MODS.
Leukocyte-Mediated Tissue Injury

- Transmigration and release of elastase and other degradative enzymes can disrupt normal cell-cell connections and normal tissue architecture required for organ function.

- Reactive oxygen species cause direct cellular DNA and membrane damage and induce apoptosis.
Cytopathic Hypoxia

• A defect of cellular oxygen utilization.

• May be due to activation of PARP (poly-ADP-ribosepolymerase-1).

• Oxidative DNA damage activates PARP which consumes intracellular and mitochondrial NAD+.

• NAD+ depletion leads to impaired respiration and a shift to anaerobic metabolism.

• Affected cells may suspend normal cell-specific activities in favor of preservation of cell viability.
Abnormalities of coagulation and fibrinolysis homeostasis in sepsis

- An imbalance of homeostatic mechanisms lead to disseminated intravascular coagulopathy (DIC) and microvascular thrombosis causing organ dysfunction and death.

- Inflammatory mediators instigate direct injury to the vascular endothelium; the endothelial cells release tissue factor (TF), triggering the extrinsic coagulation cascade and accelerating production of thrombin.
The coagulation factors are activated as a result of endothelial damage, the process is initiated via binding of factor XII to the subendothelial surface.

This activates factor XII, and then factor XI and, eventually, factor X are activated by a complex of factor IX, factor VIII, calcium, and phospholipid.

The final product of the coagulation pathway is the production of thrombin, which converts soluble fibrinogen to fibrin.

The insoluble fibrin, along with aggregated platelets, forms intravascular clots.
Circulatory pathophysiology of septic shock

- The predominant hemodynamic feature of septic shock is arterial vasodilatation.

- Diminished peripheral arterial vascular tone may result in dependency of blood pressure on cardiac output.

- Vasodilatation results in hypotension and shock if insufficiently compensated by a rise in cardiac output.
Gram negative bacteremia

\[ \text{Lipopolysaccharide (LPS)} \]

Cytokines

\[ \text{Inducible NO synthase (iNOS)} \]

\[ \text{Peroxynitrite} \]

\[ \text{Tubular damage} \]

\[ \text{Systemic vasodilation, } \downarrow \text{renal eNOS} \]

\[ \text{Glomerular microthrombi} \]

\[ \uparrow \text{Reactive oxygen species} \]

\[ \uparrow \text{NO} \]

\[ \text{Oxygen radical scavenger} \]

\[ \text{ACUTE RENAL FAILURE} \]
An elevation of cardiac output occurs; however, the arterial-mixed venous oxygen difference is usually narrow, and the blood lactate level is elevated.

This implies that low global tissue oxygen extraction is the mechanism that may limit total body oxygen uptake in septic shock.

The basic pathophysiologic problem seems to be a disparity between the uptake and oxygen demand in the tissues, which may be more pronounced in some areas than in others.
This is termed misdistribution of blood flow, either between or within organs, with a resultant defect in capacity to extract oxygen locally.

During a fall in oxygen supply, cardiac output becomes distributed so that most vital organs, such as the heart and brain, remain relatively better perfused than nonvital organs.

However, sepsis leads to regional changes in oxygen demand and regional alteration in blood flow of various organs.
The peripheral blood flow abnormalities result from the balance between local regulation of arterial tone and the activity of central mechanisms (eg, autonomic nervous system).

The regional regulation, release of vasodilating substances (eg, nitric oxide, prostacyclin), and vasoconstricting substances (eg, endothelin) affect the regional blood flow.

Development of increased systemic microvascular permeability also occurs, remote from the infectious focus, contributing to edema of various organs, particularly the lung microcirculation and development of acute respiratory distress syndrome (ARDS).
Pulmonary dysfunction

- Endothelial injury in the pulmonary vasculature leads to disturbed capillary blood flow and enhanced microvascular permeability, resulting in interstitial and alveolar edema.

- Neutrophil entrapment within the pulmonary microcirculation initiates and amplifies the injury to alveolar capillary membrane.

- ARDS is a frequent manifestation of these effects. As many as 40% of patients with severe sepsis develop acute lung injury.
Prognosis

- Septic shock has a high death rate, exceeding 50%, depending on the type of organism involved.

- Mortality from Gram-negative septic shock ranges from 40 to 70%.

- The organism involved and the immediacy of hospitalization will determine the outcome.

- Survival depends on rapid institution of broad-spectrum antimicrobial therapy, intravenous fluids, and other supportive measures.

- Elderly patients and those with severe underlying surgical or medical diseases are less likely to survive.
Treatment

- Septic shock is a medical emergency, and patients are usually admitted to intensive care units.

- The objectives of treatment are to:

  - Provide oxygen, and relieve respiratory distress (if present)
  - Administer intravenous fluids to restore blood volume, and vasoactive drugs to treat low blood pressure
  - Treat underlying infections with antibiotics
  - Support any poorly functioning organs
Ensuring adequate nutrition, if necessary by parenteral nutrition, is important during prolonged illness.

Activated protein C has been shown to decrease mortality in severe Sepsis.

Low dose cortisol treatment has shown promise for septic shock patients with relative adrenal insufficiency.
Prevention

- Appropriate treatment of localized infections.

- HIB vaccine for children has already reduced the number of cases of Hemophilus septicemia.

- Children who have had their spleen removed or who have diseases that damage the spleen should receive pneumococcal vaccine.

- Close contacts of septic children with certain organisms such as pneumococci, meningococci, and Hemophilus may require preventive antibiotic therapy.
Evidence-Based Measures to Reduce Infections Associated with Catheter Insertion.

- Hand hygiene
- Maximal sterile barrier precautions
- Chlorhexidine skin antisepsis
- Optimal site care (device selection and site of insertion)
- Education
- Catheter removal
- Monitoring of practices
- Leadership