**SHOCK**

Low perfusion circulatory insufficiency leading to an imbalance between the metabolic needs of vital organs and available blood flow.

Features:
- $\downarrow O_2$ delivery to cells
- $\downarrow$ removal of wastes

Key organs affected:
- Brain
- Heart
- Lungs
- Kidneys
Shock

Systemic hypoperfusion due to:

- Reduction in cardiac output
- Reduction in effective circulating blood volume

Hypotension → Impaired tissue perfusion
Cellular hypoxia

Types of Shock

1. Hypovolemic
2. Cardiogenic* (pump failure)
3. Septic*
4. Neurogenic
5. Anaphylactic
   - IgE mediated hypersensitivity

* high mortality
CLINICAL SIGNS OF SHOCK

- hypotension
- weak, thready pulse
- cool, clammy skin
- tachycardia
- altered respirations and sensorium
- peripheral cyanosis
- oliguria

PHASES OF SHOCK

1st (Early) Phase: immediate problems due to medical, surgical or obstetrical catastrophe
- electrolytes/acidosis/respiratory difficulties

2nd Phase: renal dysfunction
- acute tubular necrosis (ATN) → urine
  - fluid overload
  - hyperkalemia
  - acidosis/uremia

3rd Phase: diuretic phase
- urine volume (3L/day) and later

(10-14 days and later)
<table>
<thead>
<tr>
<th>Stages of Shock:</th>
<th>Basic Pathology 7/e</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Progressive Stage</td>
<td>Progressive Stage</td>
</tr>
<tr>
<td>-compensatory reflex mechanisms activated (baroreceptors/ catechol. release)</td>
<td>-tissue hypoperfusion &amp; worsened circulatory metabolic imbalance</td>
</tr>
<tr>
<td>-perfusion maintained</td>
<td></td>
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</tbody>
</table>
**Significance of Hemorrhage**

<table>
<thead>
<tr>
<th>NO CLINICAL FINDINGS:</th>
<th>HYPOVOLEMIC SHOCK:</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-20% of bld. vol. lost</td>
<td>larger blood losses</td>
</tr>
<tr>
<td>OR slow blood loss</td>
<td>OR more rapid bld. loss</td>
</tr>
</tbody>
</table>

**Congestion (Hyperemia)**

Increased volume of blood in affected tissue

**Mechanism:**
- arterial and arteriolar dilatation
- bld. flow into capillaries
**Edema**

*The abnormal accumulation of fluid in the intercellular tissue spaces or body cavities*

- localized
- systemic
**Edema fluids: nomenclature**

- abdomen: ascites
- pleural cavities: effusions / hydrothorax
- pericardium: effusion
- total body: anasarca
Extravascular/Edema Fluids: Terminology

Transudate:
- low protein content
- non-inflammatory
  - ultrafiltrate of plasma (mostly albumin)
  - due to osmotic/hydrostatic imbalance
  - no increase in vasc. permeab.
- S.G. < 1.012

Exudate:
- high protein concentration
- inflammatory
  - due to altered permeab. of small bld. vessels
- S.G. > 1.020

Mechanisms of edema formation

- ↓ plasma colloid oncotic pressure
- ↑ hydrostatic pressure
- ↑ endothelial permeability
- lymphatic blockage
Thrombosis: the Virchow triad

- Endothelial injury
- Abnormal blood flow
- Hypercoagulability
Types & Fate of Thrombi

**Types**
- Arterial: coronary, cerebral, aorta + branches
- Venous: 90% in deep leg veins
  - also peri-uterine, peri-prostatic
- Mural: heart

**Fate**
- Propagation
- Embolization
- Dissolution
- Organization and recanalization

Venous thrombi ("right-sided")
Arterial thrombi ("left-sided")
Lungs
Brain
Spleen
Kidneys
Right-sided thromboemboli:
Classic example is pulmonary emboli

Left-sided thromboemboli:
Classic examples are mural thrombi in Left atrium/ventricle or endocarditis

Paradoxical embolus: through patent foramen ovale to left side

Pulmonary infarct (wedge-shaped region of necrotic lung). Seen in only approx. 10% of pulmonary emboli because of dual lung perfusion from bronchial arteries

Mural thrombus in left ventricle (e.g., after myocardial Infarction & hypokinesis)

Atrial appendage thrombi (often in mitral stenosis + atrial fibrillation)

Saddle embolus

RV

brain

spleen

kidneys

mural thrombus

mitral valve endocarditis

Atrial appendage thrombus (often in mitral stenosis + atrial fibrillation)

Saddle embolus
Acute myocardial infarction
Disseminated Intravascular Coagulation (DIC)  
(Consumption Coagulopathy)

- Widespread thrombosis in microcirculation
- Platelets & fibrin in capillaries
- **Mechanism:** Activate *intrinsic* pathway
- **Clinical:** sepsis—obstetrical catastrophe—cancer—extensive tissue damage
- **Hematologic:** rapid consumption of fibrinogen, platelets, prothrombin, V, VIII, X
  - Generation of d-dimers (“fibrin split products”)
Sepsis & Septic shock: definitions

1. SEPSIS: suspected or proven infection + systemic inflammatory response syndrome: fever, tachycardia, tachypnea, leukocytosis

2. SEVERE SEPSIS: sepsis + ORGAN DYSFUNCTION: hypotension, hypoxemia, oliguria, metabolic acidosis, thrombocytopenia, obtundation

3. SEPTIC SHOCK: severe sepsis + ORGAN DYSFUNCTION, HYPOTENSION, despite adequate fluid resuscitation

750,000 cases of sepsis / yr. in U.S.
Sources:
- pneumonia
- meningitis
- inflam. bowel dis.
- GU tract (urosepsis)

Immune cell “cross-talk” in sepsis

NEJM 2003; 348: 138-150
Toll-like receptors (TLR)
• Family of PPR’s (pattern recognition receptors)
  • TLR2: peptidoglycan Gram+ org’s
  • TLR 4: LPS (endotoxin) Gram- org’s

Role of innate immune response in sepsis: proinflam. cytokines

- edema
- vasc. permeab.

systemic acute-phase response

upregulate adhesion molecules

vasodilation
Role of adaptive immune response in sepsis

PROINFLAM. cytokines:
- TNF
- IL-1

ANTI-INFLAM. cytokines:
- IL-4
- IL-10

Roles of procoagulant-anti-coagulant balance

- LPS
- Tissue factor (thromboplastin)
- Levels of:
  - Protein C
  - Protein S
  - Antithrombin III
  - Tissue factor-pathway inhibitor

Damage
- Coagulation
- Fibrin
- Thrombus
- Thrombus

anti

anti-inflam. shift in sepsis
Organ Dysfunction in Septic Shock

**Circulatory shock**

↓ myocardial contractility

↓ vascular resistance + hypovolemia

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Mediators</th>
<th>Treatment</th>
<th>Results of RCTs</th>
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</thead>
<tbody>
<tr>
<td>Superantigens: TSST-1</td>
<td>Anti-TSST-1</td>
<td>Not evaluated</td>
<td></td>
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<tr>
<td>Streptococal exotoxins (e.g., streptococcal pyrogenic exotoxin A)</td>
<td>Antistreptococcal exotoxins</td>
<td>Not evaluated</td>
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<tr>
<td>Lipopolysaccharide (endotoxin)</td>
<td>Antilipopolysaccharide</td>
<td>Negative</td>
<td></td>
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<tr>
<td>Innate immunity</td>
<td>TLR-2, TLR-4</td>
<td>TLR agonists and antagonists</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Monocytes, macrophages</td>
<td>GM-CSF, interferon gamma</td>
<td>Not evaluated</td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>G-CSF</td>
<td>Not evaluated</td>
<td></td>
</tr>
<tr>
<td>Adaptive immunity</td>
<td>B cells (plasma cells and immunoglobulins)</td>
<td>IgG</td>
<td>Not evaluated</td>
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<tr>
<td>Proinflammatory pathway</td>
<td>CD4+ T cells (Th1, Th2)</td>
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<tr>
<td>TNF-α</td>
<td>Anti-TNF-α</td>
<td>Negative</td>
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<tr>
<td>Interleukin-1β</td>
<td>Interleukin-1β receptor antagonist</td>
<td>Negative</td>
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<tr>
<td>Interleukin-6</td>
<td>Interleukin-6 antagonist</td>
<td>Not evaluated</td>
<td></td>
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<tr>
<td>Prostaglandins, leukotrienes</td>
<td>Ibuprofen, high-dose corticosteroids</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Bradykinin</td>
<td>Bradykinin antagonist</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Platelet-activating factor</td>
<td>Platelet-activating factor acetyl hydrolase</td>
<td>Negative</td>
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<tr>
<td>Proteases (e.g., elastase)</td>
<td>Elastase inhibitor</td>
<td>Negative</td>
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<tr>
<td>Oxidants</td>
<td>Antioxidants (e.g., N-acetylcysteine)</td>
<td>Not evaluated</td>
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<tr>
<td>Nitric oxide</td>
<td>Nitric oxide synthase inhibitor</td>
<td>Negative</td>
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*NEJM 2006; 355: 1699-1713*