

## Lecture 33 Summary: Systemic Inflammation-Sepsis and Septic Shock (5/4/05)

### Systemic Inflammation and Sepsis

#### Sepsis

- generalized inflammatory response to infection leading to harmful, unregulated host immune response and amplification
- manifests itself as **systemic inflammatory response (SIRS)**

#### SIRS

- criteria:
  - core temperature  $> 38^{\circ}\text{C}$  or  $< 36^{\circ}\text{C}$
  - tachycardia ( $>90$  beats/min)
  - tachypnea ( $> 20$  breaths/min,  $\text{PaCO}_2 < 32$  mm Hg, or mechanical ventilation)
  - white blood cell count  $> 12\,000/\text{mm}^3$  or  $< 4\,000/\text{mm}^3$  or  $> 10\%$  mature neutrophils
- can lead to septic shock

#### Septic Shock

- characterized by low blood pressure, disseminated intravascular coagulation, and metabolic disturbances
- multiple organ failure

### Sequence of events leading to Sepsis

- 1) Structural components of bacteria interact with **pattern recognition receptors** such as Toll-like receptors
  - bacterial components that initiate sepsis include endotoxins like gram negative's LPS and exotoxins like *Staph* and *Strep* superantigens (**case #9, Toxic Shock Syndrome**)
  - recall that these molecules cross-link MHC class II molecules w/ the  $V\beta$  domains of the TCR causing massive T cell activation and consequently, activation of other leukocytes due to  $\text{IFN-}\gamma$  produced by TCs.
- 2) Widespread activation of innate immune response
  - mononuclear cells release massive amounts of classic proinflammatory molecules ( $\text{TNF-}\alpha$  and  $\text{IL-1}\beta$ ), termed "**cytokine storm**"
    - cytokine storm is counter-regulated by **compensatory anti-inflammatory response syndrome (CARS)** resulting in features resembling immunosuppression
    - CARS regulatory molecules include soluble TNF receptors, IL-1 receptor antagonists, and inactivators of complement cascade
    - initial overproduction of cytokines and the subsequent immunosuppression from CARS are both contributors to mortality in septic patients

## Severe manifestations of Sepsis

### **Hyperdynamic shock**

- characterized by increased cardiac output and loss of peripheral resistance
- due to vasodilation and vascular leakage caused by proinflammatory molecules (TNF- $\alpha$  and IL-1 $\beta$ ), nitric oxide, and prostaglandins
- caused by inadequate supply of metabolic substrate (O<sub>2</sub>), resulting in lactic acidosis and tissue damage

### **Respiratory Failure**

- due to extreme demands on lungs at a time when airway resistance is increased, respiratory system compliance decreased, and muscle efficiency is impaired
- ~85% of septic patients necessitate ventilatory support

### **Multiple Organ Failure**

- caused by tissue hyperfusion and hypoxia
- ultimate cause of death

### **Disseminated Intravascular Coagulation**

- characterized by widespread **microvascular thrombosis** and **profuse bleeding**
- thrombosis is due to the deposition of fibrin and the subsequent occlusion of capillaries
- bleeding is caused by the depletion of coagulation proteins and platelets from the constant activation of the coagulation system
- **Tissue factor** directly initiates coagulation which ultimately forms clots with fibrin. The sustained increase in plasminogen-activator inhibitor type 1 in septic patients perpetuates clotting by inhibiting fibrinolysis.
- Red skin lesions, purpura fulminans, points to DIC, a hematologic dysfunction
- **Activated Protein C** helps patients with DIC by inhibiting thrombin formation and thus coagulation activity
  - decreases inflammation by inhibiting platelet and monocyte activation, neutrophil recruitment, and mast-cell degranulation
  - 6.1% absolute reduction in mortality!!!!
  - sold as **Xigris**

## Signs and biomarkers of Sepsis

- infection coupled w/ **tachycardia** (high heart rate) and/or **tachypnea** (shortness of breath)
- lactic acidosis
- **altered state of consciousness** (confusion or psychosis) due to hypoxemia and hypotension
- reduced urinary output and abnormal bilirubin levels due to reduced kidney and liver function
- red skin lesions
- **C-reactive protein (CRP)** is an acute-phase protein released by the liver after onset of inflammation or tissue damage. Commonly used to differentiate b/t viral and bacterial infections

- **Procalcitonin** is a more valuable marker for sepsis. Its concentration highly correlates with severity of the disease and mortality.

### **Treatment of Sepsis**

Treatment regimen is a combination of antibiotic treatment, removal of the source of infection, hemodynamic respiratory, and metabolic support –

- hemodynamic tx:
  - fluid replacement therapy
  - **vasopressor** therapy using intravenous administration of **NE** or **DA** to increase vascular constriction
- respiratory tx:
  - ventilator
- metabolic tx:
  - insulin therapy helps maintain blood glucose levels and improve neutrophil phagocytosis
- **Goal-Directed Therapy** – aggressive fluid replacement, vasoactive agents, and red blood cell transfusion