Pathologic Mechanisms of Septic Shock

Kenneth J. Goodrum, Ph.D.
OUCOM

Topics

- Definitions: SIRS,sepsis,shock,MODS
- Morbidity/mortality of Sepsis/Shock
- Pathogenesis of shock
- Microbial triggers(endotoxin, TSSTs)
- Cytokine and non-cytokine mediators of SIRS and shock
- Pathophysiology of shock
- Therapy

Systemic Inflammatory Response Syndrome (SIRS)

- Systemic inflammatory response to a variety of severe clinical insults manifested by ≥ 2 of the following conditions
- Temperature >38ºC or <36ºC
- Heart rate >90 beats/min
- Respiratory rate >20 breaths/min or PaCO2 ,<32 torr (<4.3 kPa)
- White blood cell 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 with either hypotension or systemic manifestations of hypoperfusion
  - Lactic acidosis, oliguria, altered mental status

Septic Shock

- Sepsis with hypotension despite adequate fluid resuscitation, associated with hypoperfusion abnormalities

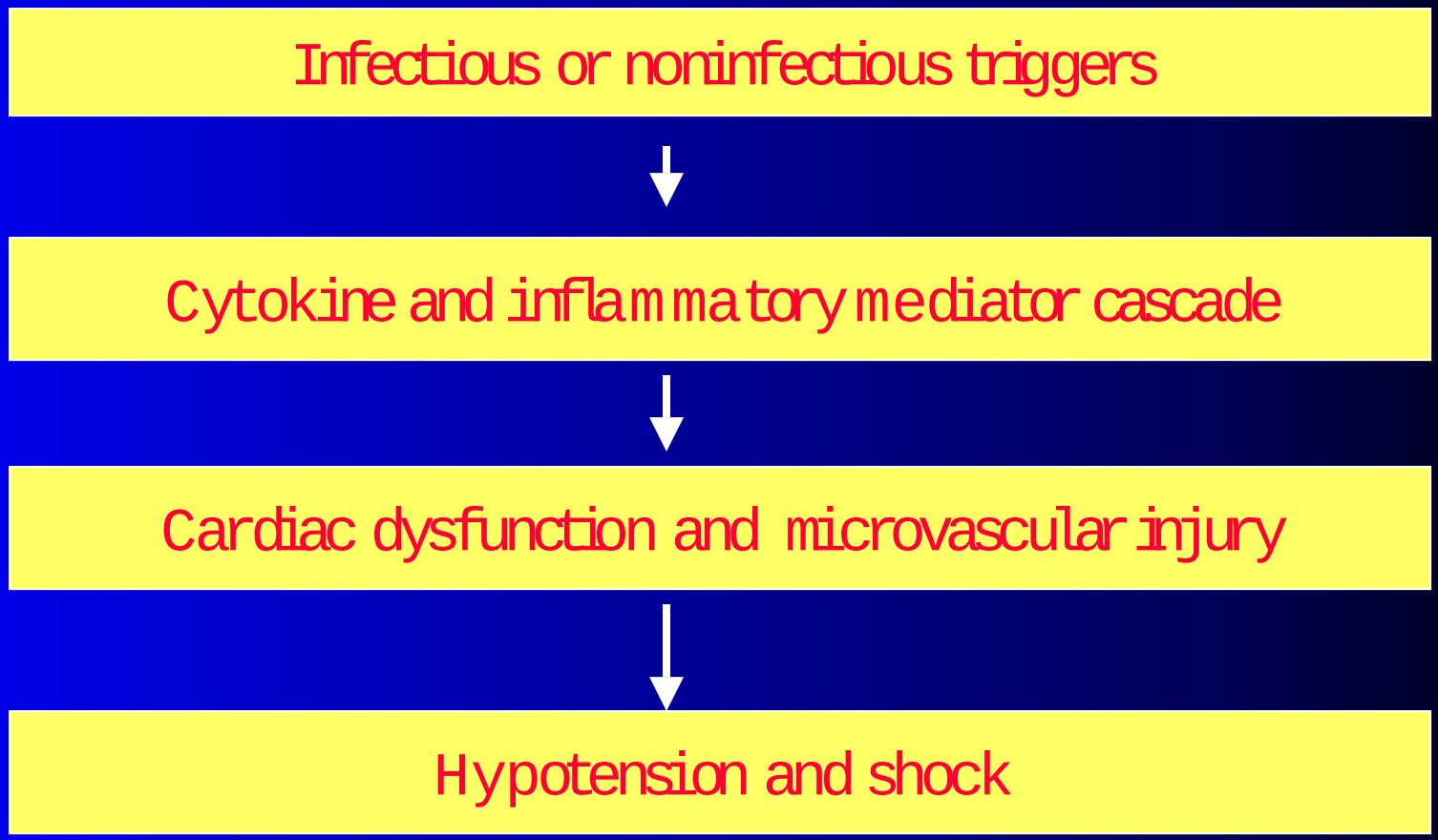
Multiple Organ Dysfunction Syndrome (MODS)

- 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 episodes sepsis/year in U.S. (35% crude mortality)
- 200,000 cases septic shock (40% of sepsis cases) (40-70% mortality)
- 40% hospital deaths after injury due to MODS

Pathogenesis of Shock



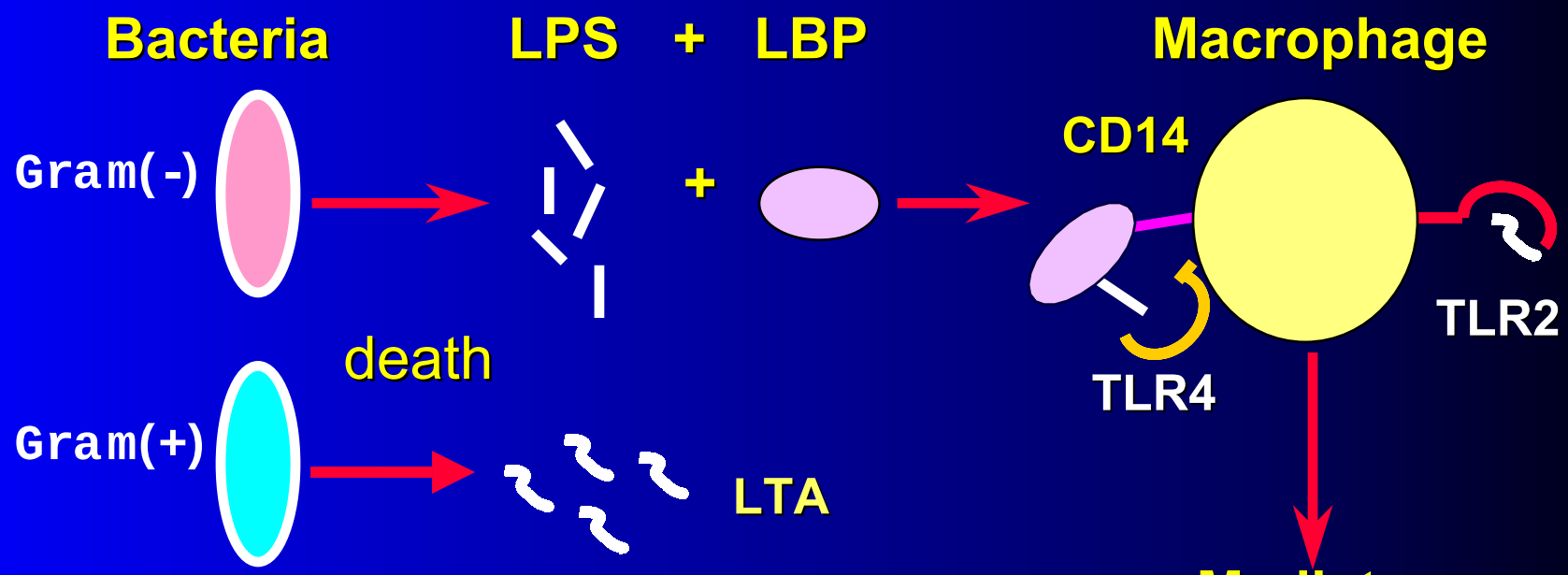
Some Characteristics of Septic Shock

- 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 and multiple organ failure

Microbial Triggers

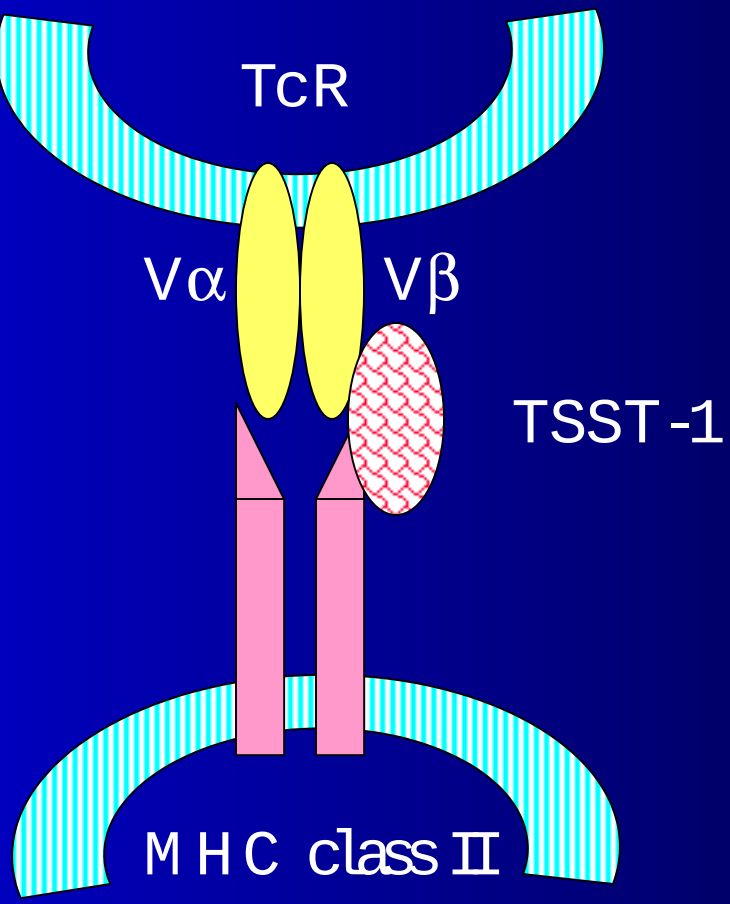
- Gram-negative bacteria:**lipopolysaccharide**
- Gram-positive bacteria:
  - **Lipoteichoic** acid/cell wall **muramyl peptides**
  - Superantigens
    - **Staphylococcal Toxic Shock Syndrome Toxin,** TSST
    - **Streptococcal pyrogenic exotoxin**, SPE

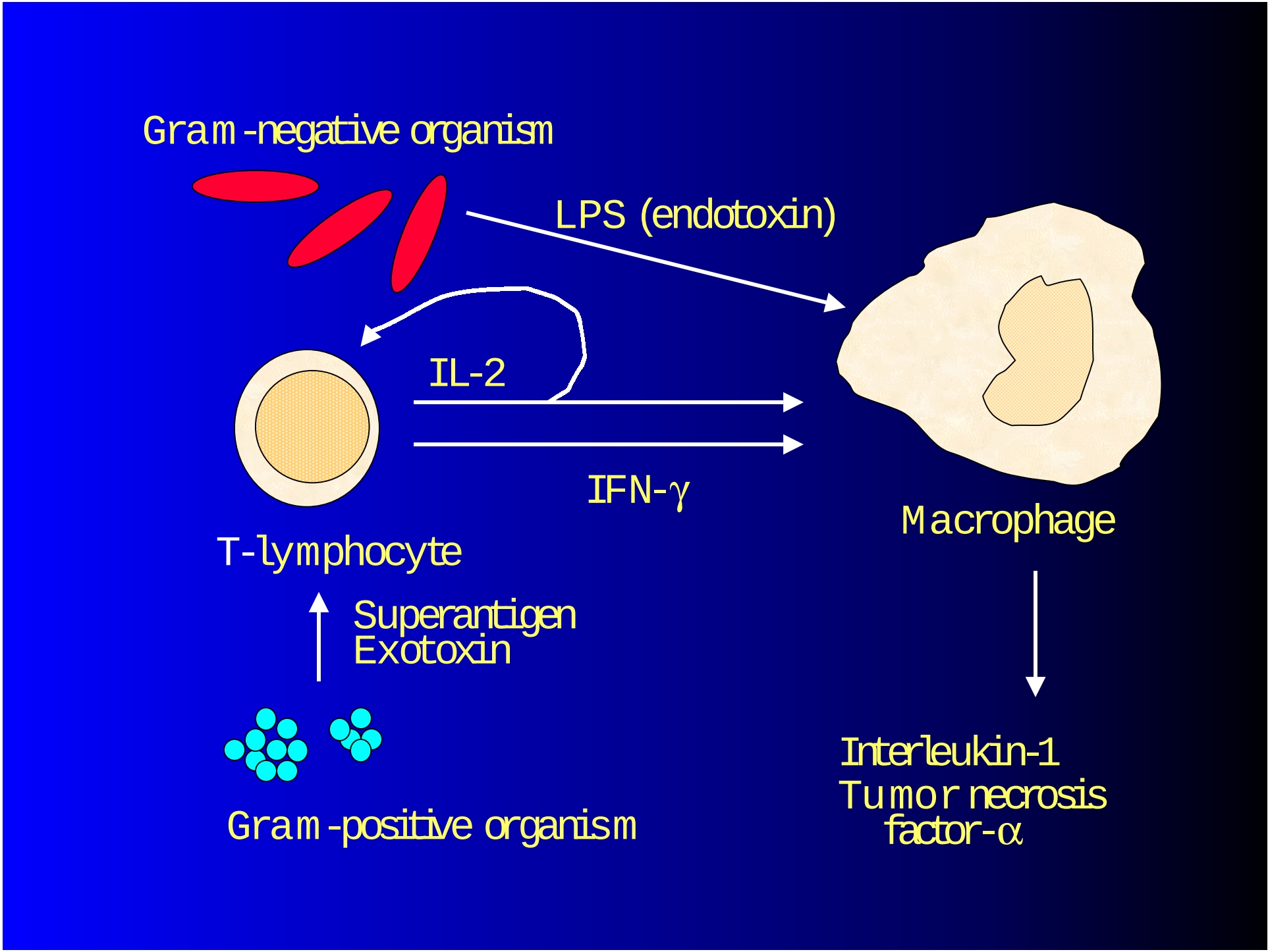
Bacterial-Mediated Sepsis



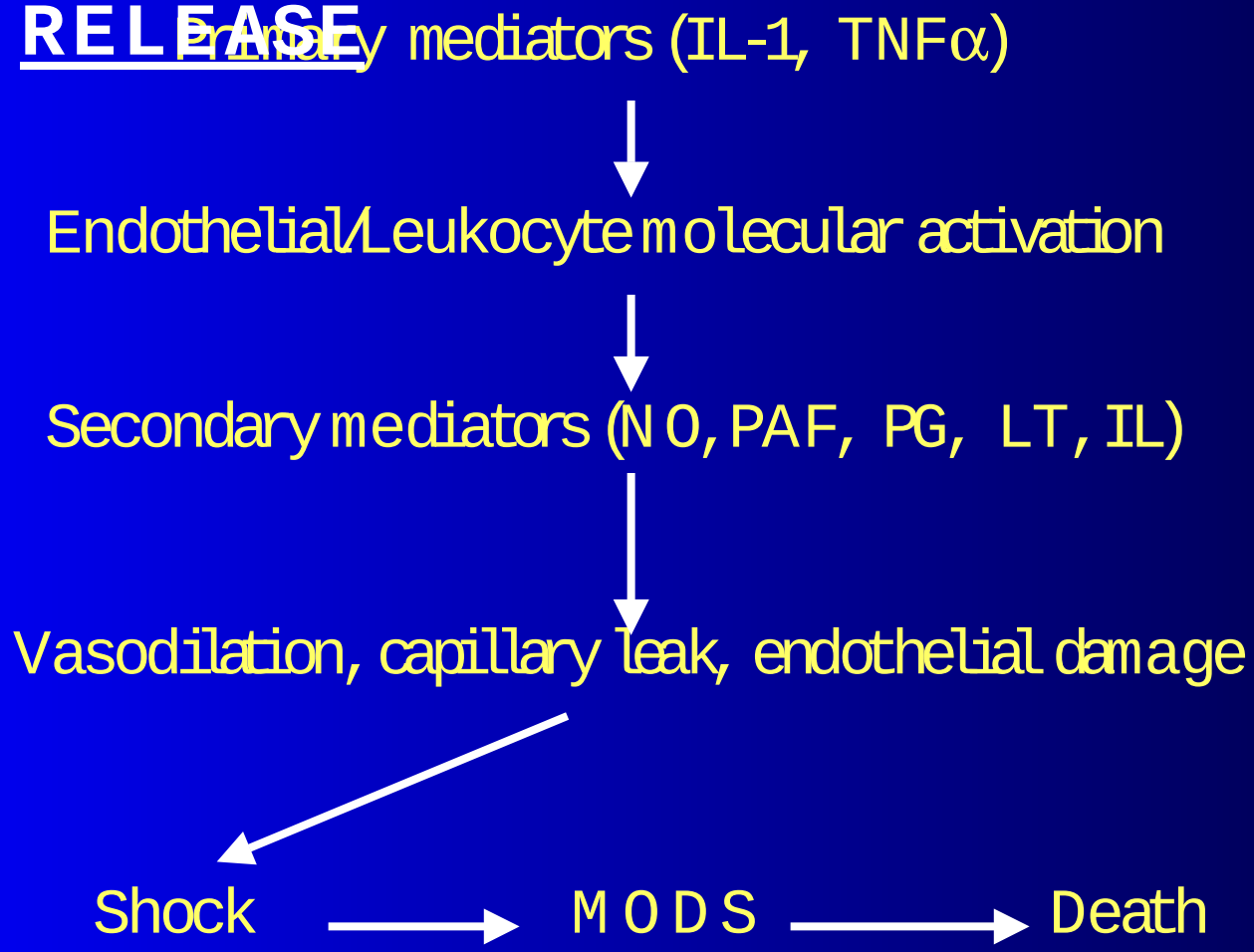
LBP = LPS-Binding Protein
LPS = Lipopolysaccharide
LTA=Lipoteichoic acid
TLR= Toll-like receptor

Superantigen activation of T Lymphocytes




Gram-negative organism
LPS (endotoxin)
IL-2
IFN-γ
T-lymphocyte
Macrophage
Superantigen
Exotoxin
Gram-positive organism
Interleukin-1
Tumor necrosis
factor-α

EFFECTS OF EXCESS CYTOKINE RELEASE



IL-1 and TNF activities

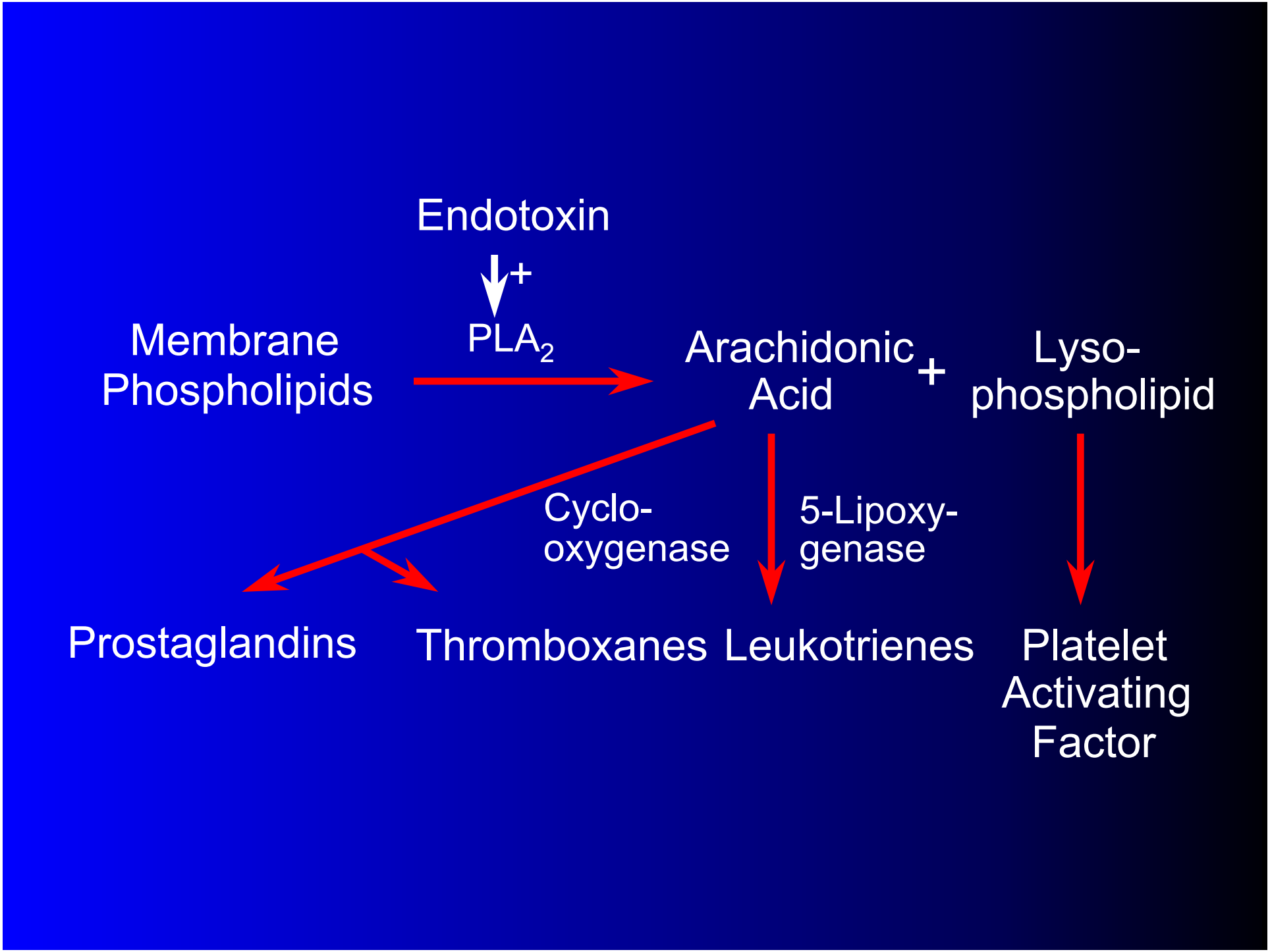
- Synergistically induce genes in endothelial cells and monocytes/macrophages
  - iNOS→NO (vasodilation, ↑pulmonary artery pressure, ↓cardiac output)
  - PLA_2→PAF(hypotension)
  - COX-2→PGE2 (fever,pain)

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)


Endotoxin
+
Membrane Phospholipids
PLA2
Arachidonic Acid
+
Lyso-phospholipid
Cyclo-oxygenase
5-Lipoxy-genase
Prostaglandins
Thromboxanes
Leukotrienes
Platelet Activating Factor

Actions of Leukotrienes

- Vasoconstriction
- Bronchoconstriction
- Chemotaxis
- Leukocyte-Endothelial Cell Adhesion
- Leukocyte Emigration
- Vascular Leakage
- Stimulate Leukotriene and Oxygen Free Radical Release

Actions of PAF

- Vasoconstriction/Vasodilation
- Hypotension & Cardiac Depression
- Bronchoconstriction
- Chemotaxis
- Leukocyte-Endothelial Cell Adhesion
- Leukocyte Emigration
- Vascular Leakage
- Platelet Aggregation
- Stimulates Leukotriene, PAF, Cytokine and Oxygen Free Radical Release

Actions of Nitric Oxide

- Vasodilation
- Inhibits leukocyte-endothelial cell adhesion
- Inhibits platelet adhesion/aggregation
- Decreases vascular permeability
- Scavenges superoxide radicals
- High concentrations are cytotoxic

PATHOPHYSIOLOGY

General Clinical Signs

- Flu-like symptoms
  - fever, chills
  - general malaise, irritability, lethargy
- Tachycardia and hypotension
- Hyperventilation
- Site of infection may or may not be evident

PATHOPHYSIOLOGY

Cardiovascular

- **Systemic vasodilation and hypotension (P_{sys} < 90 mmHg)**
- **Tachycardia (>100 beats/min)**
- **Increased cardiac output (hyperdynamic), although contractility is depressed; hypodynamic in late shock**
- **Ventricular dilation; decreased ejection fraction**
- **Loss of sympathetic responsiveness**

PATHOPHYSIOLOGY Cont.

Cardiovascular Cont.

- Hypovolemia due to vascular leakage; central venous pressure may be decreased or increased depending upon fluid resuscitation
- Compromised nutrient blood flow to organs; decreased organ oxygen extraction

PATHOPHYSIOLOGY Cont.

Pulmonary & Renal

- Hyperventilation with respiratory alkalosis
- Pulmonary hypertension and edema
- Hypoxemia (arterial $pO_2 < 50$ mmHg)
- Reduced pulmonary compliance; increased work
- Respiratory muscle failure
- Renal hypoperfusion; oliguria
- Acute tubular necrosis and renal failure

PATHOPHYSIOLOGY Cont.

Other

- Disseminated intravascular coagulation (DIC)
- Blood dyscrasias
  - leukopenia
  - thrombocytopenia
  - polycythemia
- Central and peripheral nervous dysfunction
- Increased lactate occurs early

Therapies of Sepsis/Septic Shock

- Antibiotics (early administration)
- Hemodynamic support
  - (fluid resuscitation)
    - Restore tissue perfusion
    - Normalize cellular metabolism
  - Vasopressor agents
    - Dopamine, norepinephrine, dobutamine

Therapies of Sepsis/Septic Shock (cont.)

- Source control
  - Surgical debridement of infected, devitalized tissue
  - Catheter replacement
- Supplemental oxygen (treatment of acute respiratory distress syndrome,ARDS)
- Nutritional support

Controversial Current Therapies for Septic Shock

- Anti-inflammatory agents
  - Cortocosteroids
  - 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
- Anti-coagulants (APC)

References

- Immunological therapy of sepsis:experimental therapies. P. Arndt and E. Abraham. Intensive Care med (201)27:S104-115.
- Immunological therapy in sepsis:currently available. J.Carlet. Intensive Care Med (2001)27:S93-S103.