Sepsis and Septic Shock

Sepsis and Septic Shock Definitions

- Sepsis
- Septicemia
- SIRS
- Severe Sepsis
- Septic Shock
- MODS
- ARDS
- CARS

Septic Shock

Most common cause of death
- Human SMICU
- Large animal NICU

Fatality rate
- Human medicine 20-80%
- NBC NICU - 137 cases
  Sepsis without shock - 17%
  Septic shock - 90%

Fatilities
- Refractory hypotension
- ARDS
- MODS
Sepsis and Septic Shock

Etiology

Infectious causes
- Bacterial infections
  - Gram negative pathogens – 60%
  - Gram positive pathogens – 40%
- Viral pathogens
- Fungal pathogens

Bacteremia detected in neonate
- Sepsis < 30%
- Septic Shock > 70%

Localized infections
May never isolate causative agent
Noninfectious causes

Septic Shock

Pathogenesis

Septic shock
Inflammatory response (SIRS)
Immunosuppression (CARS)

Concept of Sepsis

Initiators
- Bacteria
- Endotoxin
- Initiators

Immunology
- SIRS
- CARS

Tissue damage
- Endotoxemia
- Shock
- MODS
- Shock

Balance
- Cessation
- Shock
- Death
Initiation of Inflammatory Reactions

Gram-positive Bacteria
Gram-negative Bacteria
Viral agents
Fungal agents
Hypoxia ischemia
Trauma/burns

Innate Immunity

Inflammatory activators (TNF, IL-1, IL-6)

CARS ↔ SIRS

Septic Shock
Initiators of mediator response

Gram negative pathogens
- Endotoxin
- Formyl peptides
- Exotoxins
- Proteases

Gram positive pathogens
- Exotoxins
- Enterotoxins
- Hemolysins
- Peptidoglycans
- Lipoteichoic acid

Septic Shock
Mediator response

Toxins → Proinflammatory Cytokines (TNF, IL-1)

Secondary mediator cascade (IL-10, IL-4, PGE2, soluble TNF receptors, IL-1 receptor antagonists)

Local mediators (NO)

Hypotension
Cardiac depression
Tissue damage
Inflammatory Cascade

Cytokines
Complement activation
Endothelial activation
Platelet Activation, PAF
Macrophage activation
PMN activation

Pro-coagulation
Anti-coagulation
Kinins
Amines
Eicosanoids
Chemokines
Natural killer cells

Septic Shock
Pathogenesis - Cardiovascular effects

• Heart rate increases
• Cardiac output increases
• Systemic vascular resistance low
  Arteriolar tone is decreases - hypotension
  Venous tone decreased - venous pooling
• Pulmonary vascular resistance is high
  Right-to-left shunt
• Despite increase cardiac output
  Tissue hypoperfusion - malperfusion
  Increased lactate
  Decreased oxygen utilization

Septic Shock
Pathogenesis - Cardiovascular effects

• Decreased sensitivity to catecholamines
  Circulating vasodilator substances
  Adrenergic receptor down-regulation
• Loss of microvascular autoregulatory mechanisms
  Microvascular damage
• Distributive shock
  Maldistribution of blood flow
  Dilation of most vascular beds
  Constriction of some
Sepsis and Septic Shock

**Portals of Entry**

- GIT - Translocation
- Respiratory tract - Aspiration
- Placenta - *in utero*
- Umbilicus

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**Predisposing factors**

- Placentitis – may be protective
- Prematurity
- Hypoxic-Ischemic disease
- Hypothermia
- FPT
- Stress
- Poor nutrition
- Poor husbandry

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**Localized Infections**

- Pneumonia
- Enteritis
- Arthritis
- Osteomyelitis
- Meningitis
- Omphalitis
- Uveitis
Sepsis and Septic Shock

Signs of Sepsis

- Fever/hypothermia
- Loss of suckle, lethargy, weakness
- Tachycardia, tachypnea
- Injection, icterus – oral, scleral
- Petechia - oral, scleral, aural
- Hyperemic coronary bands
- Linear dermal necrosis
- Increased/decreased CRT
- Shock
Systemic Inflammatory Response Syndrome **SIRS**

- Over activation of the inflammatory response
- Constellation of signs
  - Fever or hypothermia
  - Leukopenia
  - Tachycardia, Tachypnea
- Septic Shock

**SIRS** damage **MODS**

- GI tract
  - Breach of the intestinal barrier
  - Translocation of bacteria
- Lungs
  - Acute Respiratory Distress Syndrome (ARDS)
- CNS
  - Breakdown blood brain barrier
  - Inflammatory mediators
  - Neurosteroid balance
- Renal failure
  - Decreased renal blood flow – vascular damage
  - Acute tubular necrosis

**Recognition of SIRS**

Release of inflammatory mediators

- Fever
- Tachycardia
- Tachypnea
- Vasodilatation (warm skin)
- Mild controlled infection or systemic responses
Recognition of SIRS/Septic Shock

Bounding pulses
- Widen pulse pressure
- Increased cardiac output
- Increased systemic vascular resistance

Hypoperfusion
- Somnolence
- Fall asleep on feet
- Decreased urine output

Before endothelial damage/dysfunction
- Intervention is most dramatic

Recognition of SIRS/Septic Shock

Shock progresses

Other signs of decreased perfusion
- Cool extremities
  - Secondary to increase vasomotor tone
  - Normal or high BP
  - Cold progressing to ice cold legs

Recognition of SIRS/Septic Shock

- Homeostatic mechanisms fail
  - Hypotension occurs
  - Pulse pressure narrows
- Legs cold
- Tachycardia
- Tachypnea
- Recumbent and nonresponsive
- Decreased cardiac output
- Hypoxia and metabolic acidosis
Sepsis and Septic Shock
Therapeutic interventions

Key interventions
• Treat underlying infection
• Provide hemodynamic support
• Support during MODS and metabolic crisis
• Block proinflammatory mediators

Sepsis and Septic Shock
Antimicrobials

• Penicillin
• Amikacin
• Cephalosporins
• Ticarcillin/clavulanic acid
• Imipenem
### Septic Shock

#### Hemodynamic support

**Goals**

- Clear blood lactate
- Normalize perfusion
- Optimize cardiac output
- Increase systemic oxygen delivery

#### Hemodynamic support - Fluid therapy

**Crystalloids or colloids?**
- Crystalloid push
  - Bolus 20 ml/kg over 10-20 minutes
  - Reassess patient after every push
  - Blood pressure
  - Leg temperature
  - Peripheral pulse - arterial fill
  - Urine production
  - Mental status

**Transfusions**
- Plasma
- Whole blood

*Don’t overhydrate*

#### Pressors/Inotropes

- Therapeutic goal
  - Increase perfusion
  - Not “get good BP numbers”
- Inotropic effect most important
  - Increase cardiac output
- Pressor effect
  - Can negate inotropic effect
  - Hopefully will correct malperfusion
- Use a mix of inotropes and pressors
- Each patient - pharmacokinetic experiment
- Arrhythmias - tachycardia
Septic Shock
Pressors/Inotropes

- Dopamine
- Dobutamine
- Norepinephrine
- Epinephrine
- Vasopressin

Septic Shock
Oxygen therapy

- Optimize O2 availability
- Internasal O2 as soon as shock recognized
  - High flows 8-10 lpm
  - Utilize even if Pao2 appears adequate
- Ventilate early
  - Decrease work of breathing
    - 25% of O2 consumption to support respiration
    - Cardiovascular function improves
    - Make respiratory failure easier to manage
    - Modest PEEP
      - Decrease work of breathing, pulmonary resistance
      - Decrease hypoxia, need for high FIO2
    - Improve gas exchange with inhaled NO
Sepsis and Septic Shock

Nutritional Support

Sepsis is associated with
  • Hypermetabolism
  • Catabolism

Hyperglycemia
  • Catecholamine stimulated glycolysis
  • Catecholamine mediated insulin resistance
  • Insulin therapy
  • Strict glucose control

Hypoglycemia
  • Often profound, refractory hypoglycemia
  • Monitor blood glucose levels frequently
  • IV glucose therapy

Sepsis and Septic Shock

Inhibiting Toxic Mediators

Antitoxins - Antiendotoxin
Anti-interleukin-1 receptor
Antibradykinin, AntiPAF
AntiTNF, TNF antagonists, NSAIDs
Steroids, Interleukin-1 antagonists
Bradykinin antagonists, Modulate NO
Antiadhesion factors

Large clinical trials in man
  • Not show improvement of survival
  • Activated protein C (Xigris)
**SIRS/Septic Shock**

*Inhibiting toxic mediators*

**Why the failures?**

- Interactions are very complex
- Compensatory anti-inflammatory response syndrome (CARS)
- Genetic variations in mediators
- Timing – interactions

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**SIRS/Septic Shock**

*SIRS – CARS Balance*

Effective therapy for septic shock await

- Understanding the interaction and balance
- Understanding the timing

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**Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008**

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