SEPSIS: time is of the essence

A summary of pathophysiology, therapeutics, and how the pharmacy TECHNICIAN can help improve OUTCOMES

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Learning Objectives

- Define and differentiate between SIRS, sepsis, severe sepsis, and septic shock.
- Review basic pathophysiology of sepsis.
- Discuss the treatment goals for sepsis and how Early Goal Directed Therapy, antibiotics, fluids, vasopressors and ionotropes are used to reach these goals.
  - Appreciate the mechanism of actions of these specific agents.
- Be able to recognize agents used in the treatment of sepsis.
  - Identify specific combinations frequently used to treat septic patients.
- Grasp the importance of TIMING of therapy.
Epidemiology of Sepsis

- Estimated 750,000 cases in U.S. each year
- 30-60% mortality
- Costs U.S. $16.7 billion/yr (avg. $22K/case)
- More common in the elderly
  - incidence is likely to ↑ as the population ages
- Of patients diagnosed with sepsis
  - 50% will develop severe sepsis
  - 25% will develop shock

25% will develop shock

Estimated 750,000 cases in U.S. each year

> 20 mL/kg over 24h
CRP/procalcitonin
lactate, ↓

> 4 mg/dL
Hyperglycemia, hypotension, hypoxemia, acute oliguria, Coag abnormalities, Ileus,
as the population ages

SIRS + Evidence of Infection

Costs U.S. $16.7 billion/yr (avg. $22K/case)

>38° C or <36 °C
Pulse

↑

SIRS = Systemic Inflammatory Response Syndrome

2 of the following: Temperature, T 35 °C or <36 °C, Fever > 38 °C, or <36 °C, Pulse > 120 bpm, Respiratory rate > 20 breaths/min, White blood cell count (WBC) > 12,000 or <4000/mm³, or > 10% bands

↑

SIRS Sepsis Sepsis Shock

Severe Sepsis, Organ Dysfunction, hypoperfusion or hypotension:

- Renal
- Respiratory
- Hematological
- Unexplained Metabolic Acidosis
- Hepatic
- CNS

Sepsis + Organ Dysfunction, hypoperfusion or hypotension

Severe Sepsis + persistent hypotension despite fluid resuscitation + perfusion abnormalities

SIRS + Evidence of Infection

Of patients diagnosed with sepsis

SIRS Sepsis

SIRS = Systemic Inflammatory Response Syndrome
**Defining Sepsis**

Etiology

- Predisposing factors
  - Age
  - Male gender
  - Non-white ethnic origin in North Americans
  - Comorbid diseases
  - Malignancy
  - Immunodeficiency or immunocompromised
  - Chronic organ failure
  - Alcohol dependence
  - Genetic factors

Primary sites of infection

- Respiratory tract 21-68%
- Intraabdominal space 14-22%
- Urinary tract 14-18%
**Etiology**
- Gram Positive Bacteria
- Gram Negative Bacteria
- Anaerobic Bacteria
- Fungi
- Viruses

**Pathophysiology**
"The pathophysiologic sequelae resulting from the interaction between the invading pathogen and the human host are diverse, complex, and not completely understood"

Bone et al. Chest 1997;112:235-243

**Cascade of Sepsis**
Cascade of Sepsis

- Initial Infection
- Systemic Spillover of Mediators
- Coagulation System Activation
  - Exaggeration
  - Coagulation/Inhibition
  - Microvascular Thrombosis
- Inflammatory System Activation
  - ↑Coagulation
  - ↓Fibrinolysis
- Complement System Activation
- Initial Infection
- Microvascular Thrombosis
- Endothelial cell damage and capillary leak
- Vasodilation
- Shock
- Multiple Organ Dysfunction
- Death

The Slinky Theory

Healthy Person

- Vascular endothelium
- Blood Flow Oxygen Nutrients
- Blood Flow Oxygen Nutrients
- Oxygen Supply = Oxygen Demand
Sepsis

Summary of Sepsis Pathophysiology

Surviving Sepsis Campaign (SSC) Guidelines for Management of Severe Sepsis and Septic Shock

- Initiated in 2002, with updates in 2008 and 2013
  - European Society of Intensive Care Medicine
  - International Sepsis Forum
  - Society of Critical Care Medicine

- Reduce Mortality rates in severe sepsis by 25%
“Surviving Sepsis” Treatment Goals
1. Timely diagnosis and initiation of early goal-directed therapy
2. Identification of pathogen and rapid elimination of the source of infection
3. Early initiation of aggressive antimicrobial therapy
4. Interruption of pathogenic sequence leading to septic shock
5. Avoidance of organ failure

Management of Sepsis
- Early Goal Directed therapy (EGDT)
- Hemodynamic support
- Treat Infection
- Adjunctive therapies

Early Goal Directed Therapy
- Focuses on goal-oriented manipulation of cardiac preload, afterload and contractility to achieve a balance between systemic oxygen delivery and oxygen demand.
- Initiate upon presentation to the ED, diagnosis of SIRS and hypotension persisting after initial fluid challenge/or serum lactate ≥4 mmol/L
Early Goal Directed Therapy

- Benefits include:
  - decreased death due to sudden CV collapse
  - decreased activation of the sepsis cascade thereby diminishing the progression to severe disease

The Importance of Early Goal-Directed Therapy for Sepsis Induced Hypoperfusion


Protocol for EGDT

Protocol for EGDT

- Other markers identified to guide initial resuscitation

Urine Output

≥ 0.5mL/kg/hr

Lactate

Normalization of lactate

Further Evidence...

- Multi-center, prospective, randomized, controlled trial based in China
- 314 severe sepsis/septic shock patients
- Assessed efficacy of EGDT
- Primary Outcomes:
  - 28-day mortality
  - ICU mortality

Results
Fluid Therapy

- **Goal:** Maximize cardiac output to restore tissue perfusion
  - Crystalloids
    - Normal saline
    - Typically patient requires up to sol. in first 24h
    - 25% will remain in intravascular space
  - Colloids
    - 5% albumin and plasma protein
    - Offer more rapid restoration of intravascular volume
    - Less peripheral edema
    - May be preferred if albumin is less than 2 g/dL.
  - Complications
    - Pulmonary and systemic edema

Ionotrope & Vasopressor Therapy

- Utilize when fluid resuscitation fails to reverse hypotension, or during fluid resuscitation to maintain minimally adequate blood pressure
- Levophed (norepinephrine)
  - 1st line vasopressor
  - Do **not** use low-dose dopamine for renal protection

Vasopressor & Ionotrope Therapy

- Dopamine
  - Useful in hypotension & compromised systolic dysfunction
  - More tachycardia & arrhythmias
- Dobutrex (dobutamine)
  - Consider in patients with measured low cardiac output despite fluid resuscitation
- Neosynephrine (phenylephrine)
  - Useful when tachycardia limits the use of others
- Adrenaline (epinephrine)
  - For refractory hypotension, last line
- Pitressin (vasopressin)
  - Endogenous vasopressin deficiency in sepsis
  - Controversial – adjunct to norepinephrine or dopamine
Ionotrope & Vasopressor Complications

- Tachycardia
- Myocardial Infarction
- Organ and tissue ischemia

Treat Infection

- Obtain culture specimens
- Eliminate source of infection
  - Remove catheters and culture if indicated (intravascular and urinary)
  - Surgical debridement, Drain abscesses

Antimicrobial Therapy

- Start within 1st hour of recognition of severe sepsis
- Empiric Broad Spectrum Therapy with IV antibiotics
- Select Based on:
  - Site of infection
  - Most likely pathogens
  - Community or hospital acquired
  - Patient’s immune status
  - Antibiotic susceptibility & resistance patterns
Critical GOLDEN hour

- 2,154 septic shock patients studied
- Main outcome measure: survival to hospital discharge

Main outcome measure: Survival to hospital discharge

Potential Antibiotic Therapy

- **Empiric**
  - Often single therapy with BROAD-SPECTRUM antibiotics
  - Common examples:
    - Ertapenem, imipenem, meropenem
    - Zosyn (piperacillin + tazobactam)
  - If MRSA is a concern
    - Adding vancomycin, linezolid, or daptomycin

Mechanisms of Action

- Zosyn
Mechanisms of Action
- Vancomycin

Duration of Therapy
- Generally 7-10 days
- Step down to oral therapy if patient is
  - hemodynamically stable
  - afebrile 48-72 hours,
  - normalizing WBC count
  - able to take PO medications

Adjunctive Therapies
- Low dose steroids
- Glycemic Control
- DVT and Stress Ulcer Prophylaxis
- Previous Recommendation
  - Activated Protein C
Low Dose Steroids
- Sepsis associated with Relative adrenal insufficiency
- Consider if hypotension is resistant to aggressive fluid therapy + vasopressors
- Drug of Choice:
  - hydrocortisone 200 mg/day
  - Optional: add fludrocortisone 50 ug daily
- No ACTH stimulation test
- DO NOT use in absence of shock

Low Dose Steroids
- Likely MOAs of steroids use in sepsis
  - ↓ systemic inflammation
  - Limits the generation of vasodilatory and procoagulant factors
    - Ex. nitric oxide
  - Increased sensitivity to vasopressors
  - Improved cardiac index

Glycemic Control
- Insulin therapy
- Start After initial stabilization
  - Initiate when blood glucose levels exceed 180 mg/dL
  - Goal Glucose ~150 mg/dL
ICU Prophylaxis
- Deep Vein Thrombosis (DVT) prophylaxis
  - Heparin or low molecular weight heparin
  - Thromboguards
  - Sequential compression devices
- Stress Ulcer Prophylaxis
  - H2 blockers
  - Proton pump inhibitors

Drotrecogin alpha (Xigris™)

Previous Indication
- For the reduction of mortality in adult patients with severe sepsis who have a high risk of death as determined by APACHE score (>24)
- NOT indicated for pediatrics, or adults with low risk of death

Drotrecogin Alpha (Xigris)
- MOA
  - inhibits coagulation and inflammation
  - promotes fibrinolysis
- Major side effect
  - Bleeding
  - Hold before and after procedures
Drotecogin Alpha (Xigris)

- Cost
  - ~ $7000 for course of treatment
- After PROWESS SHOCK trial showed no benefit in 2011, Lilly discontinued its production

Future Therapies

- Research is focused on biomarkers and their pathways
  - i.e. TNF, IL-6, etc.
  - Modulating these pathways

Technician’s Role

- Recognize agents that could potentially be ordered for a septic patient
- Ensure PROMPT and ACCURATE delivery of antibiotics and other therapies associated with sepsis
  - THIS REALLY CAN SAVE SOMEBODY’S LIFE!
  - TIME IS OF THE ESSENCE
- Participate in developing institutional protocols that may help overcome barriers to instituting Early Goal Directed Therapy
Questions?