Sepsis – Early goal directed therapy
An Update on current guidelines and literature in adults.
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Objectives
Pharmacists:
1. Discuss updated 2012 severe sepsis guidelines.
2. Review treatment strategies in patients presenting with severe sepsis.
3. Review recent severe sepsis publications and updates.
Technicians:
1. Understand the importance of timely medication preparation and delivery.

History
• Surviving Sepsis Campaign
  • Initiated in 2002
  • Collaboration between the Society of Critical Care Medicine and the European Society of Intensive Care Medicine
  • Goal to reduce mortality from sepsis by 25% in 5 years
    • Building awareness of sepsis
    • Improving diagnosis
    • Increasing the use of appropriate treatment
    • Educating healthcare professionals
    • Improving post-ICU care
    • Developing guidelines of care
  • Implementing a performance improvement program

Incidence/Prevalence
• More than 750,000 cases in the US each year
• 1 case per 1000 patients
  • 10% Intensive Care Patients
• Between 1979 and 2000, increase from 83 to 240 per 100,000
• May account for >34% of in-hospital deaths in United States

Prognosis
• in hospital mortality 11%-19% in patients with healthcare associated sepsis in the United States
• Mortality increases with increasing stage of sepsis
  • 25.5% in patients with Sepsis
  • 40.9% in patients with Severe Sepsis
  • 60.5% in patients with Septic Shock

Crit Care 2004 Aug;8(4):222
JAMA 2014 Jul 2;312(1):90
Arch Intern Med 2010 Feb 22;170(4):347
Am J Respir Crit Care Med 2003 Jul 1;168(1):77
Prognosis

- Longer time associated with increased mortality
  - Based on 3 cohort studies
  - Survival rate 79.9% if effective treatment within 1 hr
  - Time to antibiotics <1 hr associated with lower mortality
  - Survival rate 52% with prompt starting of appropriate therapy vs 10.3% with delayed initial of effective antimicrobial therapy

Etiology

- Infection with bacteria, fungus, virus, or parasites
  - Gram positive bacteria - 52.1%
  - Gram negative bacteria - 37.6%
  - Polymicrobial infection - 4.7%
  - Anaerobes - 1%
  - Fungi - 4.6%

Site of Infection

- Most Common
  - Lung
  - Abdomen
  - Urinary Tract

- Likely risk factors
  - Immune system deficiency due to
    - Functional or surgical asplenia
    - Hematologic malignancy
    - Infectious diseases
    - Drugs

Pathophysiology

- Host Response stimulates host defense cells, resulting in systemic inflammation and activation of pro-inflammatory mediators.

- Organ dysfunction occurs
  - Vasodilation mechanisms activated
  - Vasoconstriction pathways fail
  - Hemodynamic abnormalities
    - Decreased cardiac output
    - Inadequate arterial oxygen content
    - Reduced oxygen unloading from hemoglobin

Definitions

- Systemic Inflammatory Response Syndrome (SIRS)
  - Greater than or equal to 2 of the following:
    - Temperature greater than 38.3 degrees C or less than 36 degrees C
    - Heart Rate greater than 90 beats/min
    - Respiratory rate greater than 20 breaths/min or arterial partial pressure of carbon dioxide less than 32 mm Hg
    - White blood cell count greater than 12,000/mm3 or less than 4,000/mm3 or greater than 10% immature neutrophils (bands)

- Sepsis
- SIRS due to documented or suspected infection
- Severe sepsis
- Sepsis plus evidence of acute organ dysfunction or tissue hypoperfusion
- Septic shock
- Sepsis-induced hypotension after adequate fluid resuscitation.
Diagnosis

Sepsis
- General variables
- Inflammatory variables
- Hemodynamic variables
- Organ dysfunction variables
- Tissue perfusion variables

Diagnosis - Sepsis
- General Variables
  - Fever (>38.3 degrees C)
  - Hypothermia (core temp <36 degrees C)
  - Heart rate > 90/min or more than 2 SD above the normal value for age
  - Tachypnea
  - AMS
  - Significant edema or positive fluid balance (>20ml/kg over 24hr)
  - Hyperglycemia (>140mg/dL) in the absence of diabetes

- Inflammatory variables
  - Leukocytosis (WBC count >12,000/mm³)
    - Leukopenia (WBC count <4000/mm³)
  - Normal WBC count with greater than 10% immature forms
  - Plasma C-reactive protein more than two SD above the normal value
  - Plasma procalcitonin more than two SD above the normal value

- Hemodynamic variables
  - Arterial hypotension (SBP<90 mmHg, MAP<70 mmHg, or an SBP decrease > 40 mmHg in adults or less than two SD below normal for age)

- Organ dysfunction variables
  - Arterial hypoxemia (Pao2/Fio2<300)
  - Acute oliguria (urine output <0.5ml/kg/hr for at least 2hrs despite adequate fluid resuscitation)
  - Creatinine increase >0.5 mg/dL
  - Coagulation abnormalities (INR>1.5 or aPTT>60s)
  - Ileus (absent bowel sounds)
  - Thrombocytopenia (platelet count <100,000/mm³)
  - Hyperbilirubinemia (plasma total bilirubin>4 mg/dL)

- Tissue perfusion variables
  - Hyperlactatemia (>1 mmol/L)
  - Decreased capillary refill or mottling

Diagnosis

- Severe Sepsis: Sepsis plus sepsis induced organ dysfunction or tissue hypoperfusion.
  - Sepsis induced hypotension
  - Lactate above upper limits laboratory normal
  - Urine output < 0.5ml/kg/hr for more than 2hrs despite adequate fluid resuscitation
  - Acute Lung Injury
  - Creatinine >2 mg/dL
  - Bilirubin >2 mg/dL
  - Platelet count <100,000 μL
  - Coagulopathy (INR >1.5)

Initial Resuscitation

- After identifying a patient with severe sepsis and septic shock
- Initiate Early Goal Directed Therapy (EGDT) protocol

  - Surviving Sepsis Campaign created bundles
    - 3 Hour Bundle
    - 6 Hour Bundle
Initial Resuscitation

3 Hour Bundle
- Measure Lactate Concentration
- Obtain blood cultures before administration of antibiotics
- Administer broad spectrum antimicrobials
- Administer 30mL/kg crystalloid for hypotension or lactate greater than or equal to 4 mmol/L

Initial Resuscitation

6 Hour Bundle
- If septic shock is present, complete the following within 6 hours of presentation
  - Apply vasopressors to maintain a mean arterial blood pressure greater than or equal to 65 mmHg
  - In the event of persistent arterial hypotension despite volume resuscitation or initial lactate greater than or equal to 4 mmol/L, measure central venous pressure (CVP) and central venous oxygen saturation (ScvO₂)
  - Remeasure lactate if initial lactate was elevated.

Initial Resuscitation

6 Hour Bundle Goals
- Central Venous Pressure 8-12 mm Hg
- Mean Arterial Pressure >65 mm Hg
- Urine output >0.5 mL/kg/hr
- Central venous oxygenation saturation or mixed venous oxygen saturation 70% or 65%, respectively
- Normalization of elevated lactate levels.

Initial Resuscitation

Fluid Therapy
- 30mL/kg of isotonic crystalloid as quickly as possible.
  - 0.9% Sodium Chloride
  - Lactated Ringer solution
- Avoid the use of Hydroxyethyl Starch.
- When substantial amounts of crystalloids are required, albumin may be used.

Initial Resuscitation

Broad Spectrum Antimicrobial therapy
- Within 1st hour of recognition of septic shock
- Empiric therapy of one or more drugs that have activity against all likely pathogens
- Regimen should be reassessed daily for potential de-escalation
- Use of low procalcitonin to assist the clinician in the discontinuation of empiric antibiotics

Initial Resuscitation

Broad spectrum Antimicrobial Therapy
- Combination empirical therapy for:
  - Neutropenic patients
  - Multidrug resistant bacterial pathogens such as Acinetobacter and Pseudomonas spp.
  - Pseudomonas aeruginosa bacteremia, combination therapy with an extended spectrum beta-lactam and either an aminoglycoside or a fluoroquinolone
  - Streptococcus pneumoniae bacteremia, a combination of beta-lactam and macrolide
**Initial Resuscitation**

- **Broad Spectrum Antimicrobial Therapy**
  - 3-5 days empiric combination therapy.
- **Duration of therapy typically 7-10 days.**
  - longer courses may be appropriate.
- **Antiviral therapy as early as possible if viral origin.**
  - If determined noninfectious, antimicrobial agents should not be used.

- **Vasopressors**
  - **Dopamine**
    - Removed as first choice in updated guidelines
    - No significant difference in 28 day mortality when compared with norepinephrine
    - Higher incidence of arrhythmias with dopamine
    - More vasopressor days with dopamine
  - **Dosing:**
    - 0.3-5 mcg/kg/min - dopaminergic receptors
    - 3-10 mcg/kg/min - weakly binds to beta, receptors
    - 10-20 mcg/kg/min - alpha, receptor

- **Corticosteroids**
  - ACTH
  - **Dosing:**
    - Initial 200mg
    - Dosing adjustment based on clinical response.

- **Epinephrine**
  - **Dosing:**
    - 0.01-0.03 mcg/kg/min
    - Higher doses should be reserved for salvage therapy
  - **Phenylephrine**
    - Not recommended in septic shock except:
      - When norepinephrine is associated with serious arrhythmias
      - Cardiac output if known to be high and blood pressure persistently low
    - As salvage therapy when combined agents have failed to achieve MAP target.
  - **Dosing:**
    - 100-180 mcg/min, titrate to MAP

**Adjunctive Therapy**

- **Transfusion** if hemoglobin (Hgb) < 7 g/dL
- **Glucose control** with insulin drip to keep serum glucose ≤ 180 mg/dL (9.99 mmol/L) and > 110 mg/dL (6.11 mmol/L)
- For intubated patients, minimize sedation use weaning protocol and avoid paralytics in absence of ARDS
- Renal replacement therapy with intermittent hemodialysis or continuous venous hemofiltration
- Deep vein thrombosis (DVT) prophylaxis is recommended
- Stress ulcer prophylaxis with H2 blocker or proton pump inhibitor recommended for severe sepsis, septic shock, or bleeding
- Nutrition - initiate oral or enteral feeding within 48 hours of severe sepsis/septic shock diagnosis

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**Initial Resuscitation**

- **Vasopressor Therapy**
  - **Norepinephrine**
    - **First Choice**
    - Beta1, alpha1, weakly binds to beta2, alpha2 activity
    - **Dosing:**
      - Usual 0.3-1.2 mcg/min, titrate to MAP
  - **Dopamine**
    - Usual 1-3 mcg/kg/min, titrate to MAP
  - **Epinephrine**
    - Added to and potentially substituted for norepinephrine

- **Stress**
  - **Renal replacement therapy**
    - Initial plus 28 days.
  - **Vasopressor**
    - For intubated patients, minimize sedation use weaning protocol and avoid paralytics in absence of ARDS
  - **Adjunctive Therapy**
    - Transfusion if hemoglobin (Hgb) < 7 g/dL
    - Glucose control with insulin drip to keep serum glucose ≤ 180 mg/dL (9.99 mmol/L) and > 110 mg/dL (6.11 mmol/L)
    - For intubated patients, minimize sedation use weaning protocol and avoid paralytics in absence of ARDS
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Guideline Issues

- Initial study (Rivers 2001)
  - Single Center Study
  - 263 patients
- 16% absolute risk reduction in hospital mortality versus standard therapy
  - Due to:
    - Goal-directed protocol?
    - Central venous oxygen saturation monitoring?
    - Both?
- Adoption of EGDT has been limited
  - Complex delivery
  - Potential risks of components
  - Resources required for implementation

Guideline Issues

Multicenter, multinational trials completed and recently published


Updates in Literature

- ProCESS
  - United States Emergency Departments randomly assigned patients with septic shock to one of 3 groups for 6 hours of resuscitation:
    - Protocol based Early Goal Directed Therapy (EGDT)
    - Protocol based standard therapy without placement of a central venous catheter, administration of inotropes, or blood transfusions.
    - Usual Care
  - Primary outcome - 60-day in hospital mortality

Updates in Literature

- ARISE
  - 51 Centers mostly in Australia or New Zealand randomized patients presenting to the emergency department with early septic shock to receive either Early Goal Directed Therapy or Usual care.
    - Primary outcome - all-cause mortality within 90 days after randomization.

Updates in Literature

- ProCESS
  - Results
    - 439 assigned to protocol based EGDT
    - 446 to protocol based standard therapy
    - 456 to usual care.
    - 60-day mortality:
      - 92 (21.1%) in the EGDT group
      - 81 (18.2%) in the protocol-based standard therapy group
      - 86 (18.9%) in the usual care group
    - 90 day, 1 year mortality showed no significant difference

Updates in Literature

- ARISE
  - Results
    - 1600 patients enrolled
      - 796 assigned to the EGDT group
      - 804 assigned to the usual care group
    - 90 day Mortality:
      - 147 (18.6%) deaths in the EGDT group
      - 150 (18.8%) deaths in the usual care group
    - No significant difference in survival time, in-hospital mortality, duration of organ support, or length of hospital stay.
Updates in Literature

• ProMISe
  • 56 hospitals in England randomly assigned patients to receive either Early Goal Directed Therapy or usual care.
  • Primary clinical outcome - all-cause mortality at 90 days.

• Results
  • 1240 patients enrolled
    • 620 in EGDT group
    • 620 in usual care group.
  • 30 day mortality
    • 184 (29.5%) deaths in the EGDT group
    • 181 (29.2%) deaths in the usual care group
  • Cost-effective analysis
    • EGDT increased costs
    • Probability of EGDT cost-effective was below 20%

Now What?!

• Surviving Sepsis Campaign responds - 04/2015
  • Bundles have been updated
    • 3 hour bundle
      • No change
    • 6 hour bundle
      • Updated
        • Apply vasopressors for hypotension that does not respond to initial fluid resuscitation to maintain a mean arterial pressure ≥ 65
        • In the event of persistent hypotension after initial fluid administration (MAP < 65 mm Hg) or if initial lactate was ≥ 4 mmol/L, reassess volume status and tissue perfusion and document findings according to Table 1.
        • Remeasure lactate if initial lactate elevated.
    • Two of the following:
      • Measure CVP
      • Measure ScvO2
      • Bedside cardiovascular ultrasound
      • Dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge

Sepsis Take Home Points

• Fluids, Fluids, Fluids
• Blood cultures before antibiotics
• Antibiotics as soon as possible
• 6 hour bundle has been updated
• Norepinephrine is the vasopressor of choice

Questions?
References