Management of Septic Shock
Review of the Evidence and Implementation of Pediatric Guidelines at Christus Santa Rosa

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Objectives
• Review of current evidence and practice recommendations in septic shock
• Implement a set of pediatric guidelines to improve the quality of care in our patients with septic shock
• Establish quality indicators for monitoring adherence to the guidelines

Definitions - Progression of sepsis
• Sepsis
  – Systemic inflammatory response to an infection
• Severe sepsis
  – Sepsis and associated inflammatory response with organ dysfunction, hypotension, or hypoperfusion
• Septic shock
  – Sepsis-induced hypotension and inadequate organ perfusion despite adequate fluid resuscitation

Epidemiology of severe sepsis
• Incidence of 3 cases per 1000 people annually
• Overall hospital mortality rate 28.6%
  – Pediatric 10%
  – Adults 38.4% (higher in many studies)
• Average cost of $2200 per case and an annual cost 16.7 billion dollars nationally

Major goals of therapy
• Resuscitation to correct hypoxia, hypotension, and impaired tissue oxygenation
• Identify source of infection and treat to include antimicrobials and/or surgery
• Maintain organ system function and halt the development of multiorgan dysfunction

Early goal-directed therapy
• 263 adult patients with severe sepsis or septic shock
• Goal-directed therapy or standard therapy upon presentation and for initial 6 hours
• Resuscitation goals
  – Central venous pressure (CVP) ≥ 8
  – Mean arterial pressure (MAP) ≥ 65
  – Urine output ≥ 0.5 cc/kg/hr
  – Central venous oxygen saturation (ScvO₂) ≥ 70%

**Early goal-directed therapy**

- Interventions used to achieve goals
  - Aggressive fluid resuscitation to reach CVP ≥ 8
  - Vasopressors to reach MAP ≥ 65
  - Transfusion of PRBCs until Hct ≥ 30 followed by use of inotropic agents to reach ScvO2 ≥ 70%
- Early goal-directed therapy improved mortality (30.5% versus 46.5%, p=0.009)


**Early reversal of shock**

- Retrospective review of 91 children presenting to community physicians with septic shock
- Reversal of shock by community physicians within first 75 minutes improved survival by >9-fold
- Each hour of persistent shock beyond this point was associated with a >2-fold increased mortality
- Adherence to ACCM-PALS resuscitation guidelines led to improved survival: 8% vs 38% mortality

Han YY, Carcillo JA, et al, Pediatrics 2003

**Surviving Sepsis Campaign**

- Evidence-based guidelines
- Areas of management addressed include:
  - Aggressive fluid resuscitation
  - Antibiotic therapy and source control
  - Vasopressors and inotropes
  - Stress-dose and low-dose corticosteroids
  - Glycemic control
  - Mechanical ventilation
  - Pediatric considerations

**Fluid resuscitation**

- Surviving Sepsis Guidelines
  - Fluid resuscitation to CVP ≥ 8
  - Give fluid as long as hemodynamic improvement is seen
  - Decrease rate of fluid administration when increases in filling pressures are not associated with improved hemodynamics

**Antibiotic Therapy and Source Control**

- Surviving Sepsis Guidelines
  - Give Broad-spectrum antibiotic therapy **within the first hour**
  - Obtain cultures before starting antibiotics, but do not delay antibiotics for cultures
  - Start at least one antibiotic for all likely pathogens which penetrate to all likely sources

**Antibiotic Therapy and Source Control**

- Reassess antibiotics daily
- Combination therapy for pseudomonas
- Combination therapy for neutropenia
- Recommend duration of therapy be 7 to 10 days, longer for select cases
- Remember: blood cultures may be negative in up to 50% bacterial or fungal infections
Antibiotic Therapy and Source Control

- Identify sources requiring control as early as possible, ideally **within 6 hours**
- Identify abscesses that need drainage and devices (including lines) that may be infected
- When source control is required, recommend least invasive effective intervention be done
- If intravascular device is a possible source of septic shock, recommend prompt removal

**Antibiotics: Every hour counts**

- Retrospective study of 2,154 adults
- Giving antibiotics within the first hour of hypotension led to a 79.9% survival rate
- Each hour delay over the next 6 hours was associated with a 7.6% decrease in survival
- Only 50% of septic shock patients received antibiotics within the first 6 hours
  
  Kumar, et al, Crit Care Med 2006

**Antibiotics: Err on the side of caution**

- Retrospective study of 5,715 adults
- Examined appropriateness of antibiotic therapy based on infection site and relevant pathogens
- Appropriate antibiotics started in 80% of cases
- Survival rates after appropriate vs inappropriate antibiotics were 52% vs 10.3% (p<0.0001)

  Kumar, et al, Chest 2009

**Antibiotics and acute kidney injury**

- Retrospective study of 4,532 adults
- 64.4% developed some degree of AKI
- Patients who developed AKI had longer delays in antibiotics (4.3 hrs vs 6 hrs, p<0.0001)
- Increased odds of AKI per hour of delay (OR 1.14)
- AKI increased mortality (OR 1.73, p<0.0001)


**Vasopressors**

- Surviving Sepsis Guidelines
  - Recommend that MAP be kept ≥ 65
  - Recommend either norepinephrine or dopamine as first choice
  - Suggest epinephrine, phenylephrine, and vasopressin should **not** be administered as first line

**Vasopressors**

- Surviving Sepsis Guidelines
  - Suggest epinephrine be the first chosen alternative to dopamine or norepinephrine
  - Vasopressin 0.03 units/min may be added later
  - Recommend that all patients requiring vasopressors have arterial line as soon as practical if resources are available
**Norepinephrine vs. Dopamine**

- Trial of 1679 adults with shock (all types) who received norepinephrine or dopamine first-line
- No significant difference in overall mortality
- More arrhythmias with dopamine (24 vs 12%, p<0.001)
- Dopamine showed higher mortality only in cardiogenic shock patients (p=0.03)

De Backer, et al, NEJM 2010

**Vasopressors**

- Epinephrine considered second-line due to potential for ischemia and effects on gastric blood flow
- Epinephrine vs Norepinephrine
  - Randomized trial of 280 adults with shock
  - No difference in mortality
  - 13% of patients epinephrine group patients withdrawn for lactic acidosis or tachycardia


**Inotropic therapy**

- Surviving Sepsis Guidelines
  - Recommend dobutamine be used as first-line therapy in the presence of myocardial dysfunction evidenced by elevated filling pressures and low cardiac output
  - Recommend against strategy of increasing cardiac index to some predetermined elevated value in an effort to improve oxygen delivery

**Corticosteroids**

- Multiple large RCTs in the 1980s showed that high doses of steroids were not beneficial and caused an increase in the rate of secondary infections
- More recently, lower doses have been used for “relative” insufficient stress responses
- Large randomized placebo-controlled adult study
- 7 days of low-dose steroids improved survival in nonresponders to corticotropic stimulation
  - 53% vs 63% mortality (p=0.02)

Annane, et al, NEJM 2002
### Corticosteroids

- **Surviving Sepsis Campaign**
  - Suggest IV hydrocortisone only be used in septic shock that is poorly responsive to fluid resuscitation and vasopressor therapy
  - Steroid therapy should not be guided by corticotropin stimulation test results
  - Cortisol levels or response to stimulation test do not predict who will respond clinically to steroids with hemodynamic improvement

### Recombinant activated protein C

- Mixed results in adults, but showed benefit in severe sepsis and septic shock (APACHE II >25)
- **RESOLVE trial**
  - Large clinical trial in pediatric patients with sepsis
  - Stopped early due to lack of benefit
  - Increased risk of intracranial hemorrhage, especially in infants ≤60 days

### Etomidate and septic shock

- Substudy of CORTICUS: corticotropin response and mortality in 96 adults receiving etomidate
- Higher portion of non-responders in those receiving etomidate (61 vs 44.6%, p=0.004)
- Hydrocortisone administration did not change mortality in these non-responders (45 vs 40%)
- Etomidate was associated with a higher mortality in patients with septic shock (p=0.02)

- Cuthbertson et al, Intensive Care Med 2009

### Glycemic control

- **Surviving Sepsis Guidelines**
  - Treat hyperglycemia with insulin after stabilization
  - Suggest protocol with target glucose < 150
  - Large randomized adult trial showed a reduction in ICU mortality with intensive insulin targeting glucose of 80-110 (Leuven protocol, NEJM 2001)
  - More recent trials for aggressive control showed no benefit and had higher rates of hypoglycemia

### Glycemic control

- **NICE-SUGAR study, NEJM 2009**
  - Trial of 6100 adult ICU patients randomized to intensive therapy (glucose 80-110) or conventional therapy (glucose <180)
  - Mortality of 27.5% in the intensive therapy group vs 24.9% in the conventional therapy group
  - Severe hypoglycemia of 6.8% in the intensive group vs 0.5% in the conventional group

- **COITSS study, JAMA 2010**
  - Randomized trial of intensive vs conventional insulin therapy in 509 adults with septic shock who received hydrocortisone
  - Compared with conventional therapy, intensive insulin therapy did not improve mortality
  - Patients treated with intensive insulin had significantly more episodes of hypoglycemia
### Mechanical ventilation

- **Surviving Sepsis Guidelines**
  - Tidal volumes of 6-8 ml/kg and peak pressures ≤ 30 cm H₂O
  - Elevated head of bed to 30-45° to limit risk of aspiration and ventilator-associated pneumonia
  - Recommend ventilator weaning protocol and spontaneous breathing trials
  - Recommend sedation protocols

### Pediatric considerations

- **Surviving Sepsis Guidelines**
  - Mortality much lower (10%) than in adults
  - Boluses of 20ml/kg titrated to hemodynamics
  - Use dopamine as initial pressor
    - Pediatric patients may have variable CI and SVR
    - Suggest tailoring pressor/inotropes to the patient
    - Use epinephrine or norepinephrine if fails dopamine

### Hemodynamic support of pediatric and neonatal septic shock

- **Practice parameters from the American College of Critical Care Medicine (Crit Care Med 2009)**
  - Address the following:
    - Resuscitation goals for children
    - Fluid resuscitation (proportionally more than adults)
    - Inotropic, vasopressor, and vasodilator therapies
    - Hydrocortisone for adrenal insufficiency
    - ECMO for refractory shock

### Pediatric practice parameters

- **Use cardiac output and perfusion pressure**
- **Urine output** estimates adequacy of perfusion pressure in absence of invasive monitoring
- **Multiple methods to measure cardiac output**, but not routinely available and can be unreliable
- **SvO₂ can estimate whether cardiac output meets tissue metabolic demands**

### Pediatric practice parameters

- **Recommend that diagnosis of septic shock rely on clinical examination, but lactate may be useful**
- **Hemodynamic parameters and mortality**
  - Tachycardia/bradycardia (3%)
  - Hypotension with cap refill <3 sec (5%)
  - Normotension with cap refill >3 sec (7%)
  - Hypotension with cap refill >3 sec (33%)

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### Validating SvO₂ use in pediatrics

- 102 children with septic shock treated by ACCM/PALS guidelines
  - Half randomized to SvO₂ monitoring for first 6 hrs
    - Volume, PRBCs, +/- inotropes to reach SvO₂ ≥ 70
  - Lower 28-day mortality: 11.8 vs 39.2%, p=0.002
  - Lower incidence of new organ dysfunction as well

**Pediatric practice parameters**

- No advantage to colloids over crystalloids
- Blood transfusions
  - Goal hemoglobin >10 in septic shock
- Vasopressors
  - Typically recommend use of dopamine first-line
  - Agree with using norepinephrine alone with low SVR and wide pulse pressure, DBP < ½ SBP

**Pediatric practice parameters**

- 2002 guidelines discouraged use of vasoactive agents until central access was in place
- Newer guidelines recommend use of peripheral inotropes (not vasopressors) until central access is attained
  - Low-dose dopamine or epinephrine
- Obtain arterial access when able, but this should not delay use of vasopressors

**Bundled care for septic shock**

- Prospective 2-year interventional study
- The second year added an early goal-directed therapy protocol to ED management
- 79 patients pre-intervention, 77 post-intervention
- Patients in the post-intervention year:
  - Received significantly greater fluid volumes
  - Had increased use of early vasopressors
  - Had reduction in mortality (18% vs 27%)

**Bundled care for septic shock**

- Septic shock bundle used over 2-year period
  - Initiate CVP/SvO2 monitoring within 2 hrs
  - Broad-spectrum antibiotics within 4 hrs
  - Complete early goal-directed therapy within 6 hrs
  - Give corticosteroids if indicated
  - Monitor lactate clearance
- 330 total patients; mortality 20.8% if bundle completed vs 39.5% if not completed (p<0.01)

**Bundled care for septic shock**

- Surviving Sepsis Campaign, Crit Care Med 2010
  - 6-hr resuscitation and 24-hr management bundles
  - Data collected from 2005-2008 for hospitals enrolled
  - Data from 165 sites and over 15,000 patients analyzed
  - Full bundle compliance increased from 10.9% initially to 31.3% by the end of two years
  - Overall mortality decreased from 37% to 30.8% over two years (p=0.001), and survival improved the longer a center was in the campaign

**Bundled care for septic shock**

- Meta-analysis of 8 trials of bundled care for septic shock
  - Sepsis bundles associated with a consistent increase in survival (odds ratio 1.91, p < 0.0001)
  - All studies reported decreases in time to antibiotics and increased appropriateness of antibiotics
  - All other elements were inconsistently reported

Barochia, et al, Crit Care Med 2010
Pediatric guidelines for initial management of septic shock

- Recognize decreased mental status and perfusion
- Maintain or establish airway and IV access per PALS
- Fluid challenges: 20cc/kg boluses up to and over 60cc/kg unless clinically worse due to fluids
- Obtain cultures and start broad-spectrum antibiotics within 1 hour (do not delay for cultures)
- Assess for and treat hypoxia, hypoglycemia, and hypocalcemia
- Notify PICU if requiring >40ml/kg in boluses
- Consider intubation for persistent shock and/or respiratory distress
- Fluid-refractory shock: Start dopamine and obtain central and arterial access as able
- Consider norepinephrine alone for warm shock if central access is in place

Pediatric guidelines for initial management of septic shock

- Dopamine-resistant shock: Add epinephrine for cold shock or norepinephrine for warm shock
- If at risk for adrenal insufficiency, consider baseline cortisol level and give hydrocortisone 100mg/m² loading dose
- Titrate pressors; give additional volume as needed
- Monitor CVP, arterial blood pressure, lactates, and SVO₂ as able

Quality Indicators

- Time to antibiotics
- Time to achieve CVP ≥ 8
- Time to achieve adequate age-adjusted BP
- Time to achieve SVO₂ ≥ 70

Questions???
References


References


