Figure 1. Interrelationships among systemic inflammatory response syndrome (SIRS), sepsis, and infection.
Lewis Thomas - “Lives of a Cell”

“….it is our response to their (organisms) presence that makes the disease. Our arsenals for fighting off bacteria are so powerful…. We live in the midst of explosive devices; we are mined. When we sense lipopolysaccharide, we will bomb, defoliate, blockade, seal off, and destroy all tissue in the area. Leukocytes become more actively phagocytic, release lysosomal enzymes, turn sticky, and aggregate together in dense masses, occluding capillaries and shutting off the blood supply. Complement is switched on….pyrogen is released from leukocytes, adding fever to hemorrhage, necrosis and shock. It is a shambles.”
Sepsis Facts

Despite better technology, ICU’s, invasive monitoring, better pressors, inotropes, “big gun” antibiotics and combination antibiotics
Sepsis Facts: (continued)

- Despite better technology, ICU’s, invasive monitoring, better pressors, inotropes, “big gun” antibiotics and combination antibiotics

- NO CHANGE IN MORTALITY OVER A 30 YEAR PERIOD (1971 TO 2001)
  - Until....
The greatest breakthrough

- Outcome is TIME-DEPENDENT on RESUSCITATION!

- St. Mary’s Hospital – United Kingdom reported that nonsurvivors had delayed recognition and resuscitation compared to survivors.

Pollard: *Arch Dis Child* 1999; 80:290-296
Sepsis Facts: (continued)

- The greatest breakthrough (cont.)
  - They implemented an education program in early shock recognition and resuscitation.
  - They created a specialized pediatric transport system.
  - They created a specialized pediatric intensive care unit in the receiving hospital.

Booy: *Arch Dis Child* 2001; 386-390.
Sepsis Facts: (continued)

- The greatest breakthrough (cont.)
  - The resuscitation program
    - Aggressive fluid resuscitation
    - Intubate prophylactically if > 40 ml/kg of albumin given
    - Inotropic support

Results.....

Booy: Arch Dis Child 2001; 386-390.
Sepsis Facts: (continued)

- The greatest breakthrough (cont.)
  - STUNNING
    - CASE FATALITY RATE DROPPED

  23% to 2%

Booy: Arch Dis Child 2001; 386-390.
Sepsis Facts:

- Sepsis is a clinical syndrome caused by a dysregulated systemic inflammatory response to infection.
- Characterized by a generalized pro-inflammatory cascade leading to widespread tissue injury.
Sepsis Facts: (continued)

- Sepsis encompasses a clinical spectrum of severity that includes severe sepsis, septic shock and multi-organ failure.
- Sepsis is a leading cause of morbidity and mortality in children worldwide.
Sepsis Facts: (continued)

- Infection accounts for most deaths (60%) in children under 5 years.
- WHO has stated that the 4 big causes of death are:
  - Pneumonia (1.9 million/yr)
  - Diarrhea (1.6 million/yr)
  - Malaria (1.1 million/yr)
  - Measles (550,000/yr)
Sepsis Facts: (continued)

- Annual incidence of severe sepsis is rising from 0.56 to 0.89 cases/1000 children across all age groups in the US.
- Incidence is higher in younger age and those with co-morbidities.
- Despite the rise in severe sepsis, the case fatality has fallen from 10.3% to 8.9%.
Risk Factors

- Those with indwelling devices or prosthetic material or any other breach in barrier protective function
- Congenital heart disease (risk of endocarditis)
- GU anomalies (urosepsis)
- Splenic dysfunction or absence
- Malignancies (before or during treatment)
- Burns
- Hgb SS disease have a 400 fold increase of pneumococcal sepsis
- AIDS
- Immune deficiencies
Signs and Symptoms of Sepsis

- Complete history to elicit symptoms:
  - Fever (most common presenting symptom)
  - Racing heart (tachycardia)
  - Rapid or labored breathing (respiratory distress)
  - Cool extremities
  - Color changes
Signs and Symptoms of Sepsis

- Recognize signs of poor perfusion
  - Decreased mental status
  - Delayed capillary refill
  - Weak pulses, compare central to peripheral pulse quality
  - Low urine output
  - Hypotension: Minimum BP by age:
    - < 1 month: 60 mmHg
    - 1 mo to 10 yrs: 70 + (2 X age in years)
    - > 10 years: 90 mmHg
What causes sepsis?

- Any infection may precipitate sepsis.
- The most common pathogens are bacteria, viruses, and fungi.
- Sepsis occurs when the normal, pro-inflammatory host response to infection exceeds its usual homeostatic constraints and becomes a generalized process, resulting in inflammation remote from the infection source.
What causes sepsis?

The pathophysiology includes endothelium dysfunction, cell death, bioenergetic derangement and immunoparalysis.
Bacterial Etiologies

Ages 1 month to 3 months

- Group B Strep
- Listeria monocytogenes
- Streptococcus pneumoniae
- H. influenzae
- Neisseria meningitidis
- Gram Negatives
  - E. coli, Klebsiella, Pseudomonas
Bacterial Etiologies (cont.)

- Ages 3 months and older
  - Streptococcus pneumoniae
  - Neisseria meningitidis
  - Staphylococcus aureus
  - Gram Negatives
  - MRSA
Streptococcus Pneumoniae

- A lancet shaped Gram (+) diplococci
  - Most common cause of AOM
  - Most common cause of invasive bacterial infections

Epidemiology

- Most prevalent during winter months during increased viral URI season
- Mortality is highest when meningitis and/or bacteremia
Staphylococcus aureus

- A Gram (+) cocci in grape like clusters
- Epidemiology
  - Ubiquitous part of normal human flora
  - MRSA (methicillin resistant Staph aureus) increase in the community most likely the result of transmission from persons who acquired MRSA while in the hospital
Neisseria Meningitidis
- An encapsulated Gram(-) diplococcus
  - Meningitis
  - Meningococcemia

Epidemiology
- Incidence
  - 1.1/100,000 with peak in late winter and early spring
  - 60-90% cases in children
  - 46% in < 2 yrs of age
  - Peak attack < 4 months
  - Older Adolescence – College Students
Neisseria Meningitidis

Meningococcal Disease:

- Usually sporadic
- Can be endemic or epidemic (Mankato)
- High rates in Texas, Pacific NW, and SE US
- Children’s Medical Center of Dallas
  - 95 cases July’15 to June ’16
  - 56/95 with severe meningococcemia
  - 37/56 with meningitis
Can sepsis be prevented?
Figure 1. Depiction of primary, secondary, and tertiary pediatric sepsis prevention efforts (modified, with permission from Dr Bala Totapally).
Recognizing and managing sepsis at home and in the ambulance before arrival to the ED

- Medically complex children at a higher risk of infectious complications
- Signs and symptoms compared to their baseline vital signs
- If there is IV access and appropriate isotonic fluids are available then start with 20 ml/kg unless concern for underlying heart disease.
- If available provide supplemental oxygen at 100%
- Treat fever with acetaminophen
- Don’t be afraid to point out that antibiotics sooner than later is now standard of care!!
So How Can First Line Care Givers Make a Difference:

- Early recognition
- Antibiotics
- Fluid Therapy (volume resuscitation)
- Inotropes/Vasopressors
Early Recognition

“Guidelines for Hemodynamic Support of Children and Newborns with Septic Shock”

Critical Care Medicine; June 2012

Figure 1: Newborns with Septic Shock

Figure 2: Infants and Children with Septic Shock
Recommendation for stepwise management of hemodynamic support with goals of normal perfusion and perfusion pressure (MAP – CVP), and pre and post–ductal oxygen saturation difference < 5% in near term–newborns with septic shock.

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**15 min**

- **Fluid-refractory shock**
  - Establish Central Venous and Arterial Access
  - Titrate dopamine and dobutamine
  - Titrate epinephrine
  - Systemic alkalinization if PPHN is present

- **Fluid responsive**
  - Observe in NICU
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**Catecholamine – resistant shock**

60 min

Direct therapies using echocardiogram and arterial and CVP monitoring

**Cold Shock**
- Normal blood pressure
- Poor LV function,
- SVC $O_2$ sat < 70%

Titrate vasodilator with volume loading
Figure 1: Recommendation for stepwise management of hemodynamic support with goals of normal perfusion and perfusion pressure (MAP – CVP), and pre and post–ductal oxygen saturation difference < 5% in near term–newborns with septic shock. (continued)

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Titrate vasodilator with volume loading

Inhaled nitric oxide
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Cold or Warm Shock
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Inhaled nitric oxide

Warm Shock
Low Blood Pressure

Titrate volume and epinephrine
?Vasopressin
Figure 1: Recommendation for stepwise management of hemodynamic support with goals of normal perfusion and perfusion pressure (MAP – CVP), and pre and post-ductal oxygen saturation difference < 5% in near term–newborns with septic shock. (continued)

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Warm Shock
Low Blood Pressure

Titrate vasodilator
with volume loading

Inhaled
nitric oxide

Refractory Shock

ECMO

Titrate volume and epinephrine
?Vasopressin
Recommendation for stepwise management of hemodynamic support with goals of normal perfusion and perfusion pressure (MAP – CVP), in infants and children with septic shock. Proceed to next step if shock persists.

0 min
Recognize decreased mental status and perfusion, cyanosis,
Maintain airway and establish access according to PALS guidelines.

5 min
Push 20 ml/kg isotonic saline or colloid boluses up to and over 60 ml/kg
Correct hypoglycemia and hypocalcemia
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- Fluid-responsive
  - Establish central venous access, begin dopamine and establish arterial monitoring.

- Fluid refractory – dopamine resistant shock
  - Titrate epinephrine for cold shock, norepinephrine for warm shock to normal MAP – CVP and SVC O₂ sat > 70%

Observe in PICU
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**Catecholamine – resistant shock**

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Normal Blood Pressure  
Cold Shock  
SVC O\textsubscript{2} sat < 70%  

Add vasodilator with Type III PDE inhibitor with volume loading
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**Catecholamine – resistant shock**

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**Normal Blood Pressure**
- Cold Shock
- SVC O₂ sat < 70%
  - Add vasodilator with Type III PDE inhibitor with volume loading

**Low Blood Pressure**
- Cold shock
- SVC O₂ sat > 70%
  - Titrate Volume and Epinephrine
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**Catecholamine – resistant shock**

At risk for adrenal insufficiency?  
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**Normal Blood Pressure**  
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Add vasodilator with Type III PDE inhibitor with volume loading

**Low Blood Pressure**  
**Cold shock**  
SVC $O_2$ sat > 70%

Titrate Volume and Epinephrine

**Low Blood Pressure**  
**Warm Shock**

Titrate Volume and Norepinephrine Vasopressin / angiotensin
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**Low Blood Pressure**  
Cold shock  
SVC O₂ sat > 70%

Tritrate Volume and Epinephrine

**Low Blood Pressure**  
Warm Shock

Tritrate Volume and Norepinephrine / Vasopressin / angiotensin

**Persistent Catecholamine – resistant Shock**

Place pulmonary artery catheter and direct fluid, inotrope, vasopressor, vasodilator and hormonal therapies to attain normal MAP – CVP and CI > 3.3 and < 6.0 L/min/M²

**Refractory Shock**

Consider ECMO
Therapeutic Interventions

Antimicrobials of Choice

- **Neonates > 2 kg**
  - Ampicillin 50 mg/kg IV/IO/IM Q 6-8 hrs plus
  - Gentamicin 2.5 mg/kg IV/IO/IM Q 12 hrs
  - Or Ampicillin plus Cefotaxime 50 mg/kg Q 8hrs
Antimicrobials of Choice

- **Ages 1 month and older**
  - Ceftriaxone 50 mg/kg (max 2 g) IV/IO/IM Q 12 hrs plus
  - Vancomycin 15 mg/kg (max 1 g) IV/IO/IM Q 8 hrs
Immunosuppressed patients

- Vancomycin 15 mg/kg (max 1 g) IV/IO Q 8 hrs plus
- Cefepime 50 mg/kg (max 2 g/dose) IV/IO Q 8 hrs and consider antifungal therapy
Therapeutic Interventions: (cont.)

- **Fluid Therapy (volume resuscitation)**
  - 20 ml/kg of NS or LR

- **Inotropes/Vasopressors**
  - Epi 0.3 – 2 mcg/kg/min
  - Dopamine 10-20 mcg/kg/min
  - Norepinephrine 0.3 – 2 mcg/kg/min

- **Vasodilators**
  - Nipride 0.5 – 4 mcg/kg/min
  - Milrinone 0.25 – 1 mcg/kg/min
Steroids

- Evidence supports insufficient adrenal reserve in over 50% of pediatric patients.
- Low dose hydrocortisone and fludrocortisone therapy reduces mortality in adults with septic shock and adrenal insufficiency.
- Adult literature is robust to extrapolate to the pediatric population.
Vasopressin

- Vasopressin levels initially high in shock then decrease below normal
- Enhances the sensitivity of the vasculature to the effects of other pressors
- Vasodilation in some regional vasculature – Circle of Willis
- Pulmonary vasodilation
- Stimulation of cortisol secretion
Complications of Sepsis

- Critical illness polyneuropathy
- Necrotizing myopathy
- Brain injury from HIE
- Sleep disturbance
- Decrease cognitive function
- Amputations of limbs
- Organ dysfunction (lung, liver, kidney, and pancreas)
- Anxiety, panic attacks and PTSD
Conclusion

- Early Recognition
- Airway, Breathing and Circulation
- Fluids and Inotropes/ Vasopressors
- Antimicrobial therapy in the first hour

Pediatric Intensive Care Unit

- Steroids if catecholamine resistant
- Vasopressin
- ECMO
Bibliography


