Current State of Pediatric Sepsis

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Pediatric Critical Care
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Objectives

- Review the history of pediatric sepsis
- Review the current definition of pediatric sepsis
- Review triage and management strategies
- Review current and future research areas
Epidemiology of Pediatric Sepsis

• Large variation in prevalence and mortality statistics across studies
  – Varying definitions of sepsis
  – Population differences
    • Resource-rich vs. resource poor
    • Age of cohorts
  – Heterogeneity of disease
Epidemiology of Pediatric Sepsis

• The Sepsis, Prevalence, Outcomes and Therapies Study (SPROUT)
  – Point prevalence study 2013-2014
  – 128 PICUs in 26 countries
• Using 2005 International Pediatric Sepsis Consensus Conference criteria
  – Prevalence was 8.2%
  – Mortality was 25%
    • No difference between age groups
    • No difference between developed vs. resource limited countries
The definition of sepsis?

- No gold standard definition or diagnostic test
- 1992 ACCP/SCCM Consensus Conference
- 2001 SSCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference (SEPSIS-2)
- 2016 Third International Consensus Definitions for Sepsis and Septic Shock (SEPSIS-3)
The definition of sepsis?

- No gold standard definition or diagnostic test
- 1992 ACP/SCCM Consensus Conference
- 2001 SSCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference (SEPSIS-2)
- *2005 International Pediatric Sepsis Consensus Conference*
- 2016 Third International Consensus Definitions for Sepsis and Septic Shock (SEPSIS-3)
The definition of sepsis?

• 1992 ACP/SCCM Consensus Conference
  – Attempted to address the “failures” of interventional trials
  – Inconsistent definition of the patient population
    • Infection, bacteremia, sepsis, septicemia, septic syndrome, septic shock
    • Defined as “systemic inflammatory response to an active infectious process”
  – Introduced the concept of SIRS (systemic inflammatory response syndrome)
    • Hypothermia OR hyperthermia
    • Tachycardia
    • Tachypnea
    • Leukocytosis OR leukopenia OR bandemia

The definition of sepsis?

• 1992 ACP/SCCM Consensus Conference
  – SIRS
  – Sepsis = SIRS + infectious process
  – Severe Sepsis = Sepsis + organ dysfunction, hypotension, or hypoperfusion (i.e. lactic acidosis, oliguria, encephalopathy)
  – Septic Shock = Sepsis + Hypotension despite adequate fluid resuscitation + Perfusion abnormalities OR inotrope/pressor requirement

The definition of sepsis?

- 2001 SSCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference (SEPSIS-2)
  - SIRS criteria are “overly sensitive and too nonspecific”
  - Clinical definition of sepsis remained as it was in 1991:
    - Clinical syndrome defined by the presence of BOTH infection and a systemic inflammatory response
    - Change in diagnostic criteria
      - Included adjusted criteria for pediatrics

The definition of sepsis?

Table 1 Diagnostic criteria for sepsis

<table>
<thead>
<tr>
<th>Infectiona</th>
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<tr>
<td>Documented or suspected and one of the followingb:</td>
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**General parameters**
- Fever (core temperature >38.3°C)
- Hypothermia (core temperature <36°C)
- Heart rate >90 bpm or >2 SD above the normal value for age
- Tachypnea: >30 bpm
- Altered mental status
- Significant edema or positive fluid balance (>20 ml/kg over 24 h)
- Hyperglycemia (plasma glucose >110 mg/dl or 7.7 mM/l) in the absence of diabetes

**Inflammatory parameters**
- Leukocytosis (white blood cell count >12,000/µl)
- Leukopenia (white blood cell count <4,000/µl)
- Normal white blood cell count with >10% immature forms
- Plasma C reactive protein >2 SD above the normal value
- Plasma procalcitonin >2 SD above the normal value

**Hemodynamic parameters**
- Arterial hypotensionb (systolic blood pressure <90 mmHg, mean arterial pressure <70, or a systolic blood pressure decrease >40 mmHg in adults or <2 SD below normal for age)
- Mixed venous oxygen saturation >70%
b
- Cardiac index >3.5 l/min1 m−2c,d
- Organ dysfunction parameters
  - Arterial hypoxemia (PaO2/FIO2 <300)
  - Acute oliguria (urine output <0.5 ml kg−1 hr−1 or 45 mM/l for at least 2 h)
  - Creatinine increase >0.5 mg/dl
  - Coagulation abnormalities (international normalized ratio >1.5 or activated partial thromboplastin time >60 s)
  - Ileus (absent bowel sounds)
  - Thrombocytopenia (platelet count <100,000/µl)
  - Hyperbilirubinemia (plasma total bilirubin >4 mg/dl or 70 mmol/l)

**Tissue perfusion parameters**
- Hyperlactatemia (>3 mmol/l)
- Decreased capillary refill or mottling

*a Defined as a pathological process induced by a micro-organism
*b Values above 70% are normal in children (normally 75–80%) and should therefore not be used as a sign of sepsis in newborns or children
*c Values of 3.5–5.5 are normal in children and should therefore not be used as a sign of sepsis in newborns or children
*d Diagnostic criteria for sepsis in the pediatric population is signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature >38.5°C or <35°C), tachycardia (may be absent in hypothermic patients) and at least one of the following indications of altered organ function: altered mental status, hypoxemia, elevated serum lactate level, and bounding pulses

Is there a Pediatric consensus definition?
The definition of Pediatric sepsis?

- 2005 International Pediatric Sepsis Consensus Conference
  - Sought to more formally codify a definition of Pediatric Sepsis
  - SIRS concept was modified to include age-specific variations

The definition of Pediatric sepsis?

Table 2. Definitions of systemic inflammatory response syndrome (SIRS), infection, sepsis, severe sepsis, and septic shock

**SIRS**
The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count:
- Core temperature of >38.5°C or <36°C.
- Tachycardia, defined as a mean heart rate >2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5- to 4-hr time period OR for children <1 yr old: bradycardia, defined as a mean heart rate <10th percentile for age in the absence of external vagal stimulus, β-blocker drugs, or congenital heart disease; or otherwise unexplained persistent depression over a 0.5-hr time period.
- Mean respiratory rate >2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia.
- Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or >10% immature neutrophils.

**Infection**
A suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical exam, imaging, or laboratory tests (e.g., white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans).

**Sepsis**
SIRS in the presence of or as a result of suspected or proven infection.

**Severe sepsis**
Sepsis plus one of the following: cardiovascular organ dysfunction OR acute respiratory distress syndrome OR two or more other organ dysfunctions. Organ dysfunctions are defined in Table 4.

**Septic shock**
Sepsis and cardiovascular organ dysfunction as defined in Table 4.

The definition of Pediatric sepsis?

Table 4. Organ dysfunction criteria

**Cardiovascular dysfunction**
- Despite administration of isotonic intravenous fluid bolus ≥40 mL/kg in 1 hr
  - Decrease in BP (hypotension) <5th percentile for age or systolic BP <2 sd below normal for age\(^a\)
  - OR
  - Need for vasoactive drug to maintain BP in normal range (dopamine >5 \(\mu g/kg/min\) or dobutamine, epinephrine, or norepinephrine at any dose)
  - OR
  - Two of the following
    - Unexplained metabolic acidosis: base deficit >5.0 mEq/L
    - Increased arterial lactate >2 times upper limit of normal
    - Oliguria: urine output <0.5 mL/kg/hr
    - Prolonged capillary refill: >5 secs
    - Core to peripheral temperature gap >3°C

**Respiratory\(^b\)**
- \(\text{PaO}_2/\text{FiO}_2\) <300 in absence of cyanotic heart disease or preexisting lung disease
  - OR
- \(\text{Paco}_2\) >65 torr or 20 mm Hg over baseline \(\text{Paco}_2\)
  - OR
- Proven need\(^d\) or >50% \(\text{FiO}_2\) to maintain saturation ≥92%
  - OR
- Need for nonselective invasive or noninvasive mechanical ventilation\(^d\)

**Neurologic**
- Glasgow Coma Score ≤11 (57)
  - OR
- Acute change in mental status with a decrease in Glasgow Coma Score ≥3 points from abnormal baseline

**Hematologic**
- Platelet count <80,000/mm\(^3\) or a decline of 50% in platelet count from highest value recorded over the past 3 days (for chronic hematology/oncology patients)
  - OR
- International normalized ratio >2

**Renal**
- Serum creatinine ≥2 times upper limit of normal for age or 2-fold increase in baseline creatinine

**Hepatic**
- Total bilirubin ≥4 mg/dL (not applicable for newborn)
  - OR
- ALT 2 times upper limit of normal for age
The definition of sepsis?

- 2016 Third International Consensus Definitions for Sepsis and Septic Shock (SEPSIS-3)
  - NEW definition of Sepsis
    - Life-threatening organ dysfunction caused by a dysregulated host response to infection
    - “Severe sepsis” becomes superfluous
    - Organ dysfunction is identified as an acute change in SOFA score ≥ 2
  - Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities increase mortality
    - Persisting hypotension requiring vasopressors to maintain MAP ≥ 65 and with serum lactate > 2 mmol/L

The definition of sepsis?

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score

<table>
<thead>
<tr>
<th>System</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td><strong>Respiration</strong></td>
<td></td>
</tr>
<tr>
<td>PaO₂/FIO₂, mm Hg (kPa)</td>
<td>≥400 (53.3)</td>
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<tr>
<td><strong>Coagulation</strong></td>
<td></td>
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<tr>
<td>Platelets, ×10³/µL</td>
<td>≥150</td>
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<tr>
<td><strong>Liver</strong></td>
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<tr>
<td>Bilirubin, mg/dL (µmol/L)</td>
<td>&lt;1.2 (20)</td>
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<tr>
<td><strong>Cardiovascular</strong></td>
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<td>MAP ≥70 mm Hg</td>
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<td><strong>Central nervous system</strong></td>
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<tr>
<td>Glasgow Coma Scale score</td>
<td>15</td>
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<tr>
<td><strong>Renal</strong></td>
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<tr>
<td>Creatinine, mg/dL (µmol/L)</td>
<td>&lt;1.2 (110)</td>
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<td>Urine output, mL/d</td>
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<td>&lt;500</td>
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Abbreviations: FIO₂, fraction of inspired oxygen; MAP, mean arterial pressure; PaO₂, partial pressure of oxygen.

a Adapted from Vincent et al.²⁷
b Catecholamine doses are given as µg/kg/min for at least 1 hour.

Screening for Sepsis

• Need to identify the septic patient early and quickly implement therapy to decrease risk of mortality
  – quick SOFA (qSOFA) offered similar predictive validity as SOFA outside of the ICU
  – 2 out 3 criteria
    • Respiratory rate ≥ 22/min
    • Altered mentation (GCS < 15)
    • Systolic blood pressure ≤ 100 mm Hg

Screening for Sepsis

Figure. Operationalization of Clinical Criteria Identifying Patients With Sepsis and Septic Shock

- Patient with suspected infection
  - qSOFA ≥ 2? (see A)
    - Yes: Assess for evidence of organ dysfunction
      - SOFA ≥ 2? (see B)
        - Yes: Sepsis
          - Despite adequate fluid resuscitation, 1. vasopressors required to maintain MAP ≥ 65 mm Hg AND 2. serum lactate level > 2 mmol/L?
            - Yes: Septic shock
            - No: Monitor clinical condition; reevaluate for possible sepsis if clinically indicated
        - No: Monitor clinical condition; reevaluate for possible sepsis if clinically indicated
    - No: Sepsis still suspected?
      - Yes: Monitor clinical condition; reevaluate for possible sepsis if clinically indicated
      - No: Monitor clinical condition; reevaluate for possible sepsis if clinically indicated

A qSOFA Variables
- Respiratory rate
- Mental status
- Systolic blood pressure

B SOFA Variables
- $\text{PaO}_2/\text{FiO}_2$ ratio
- Glasgow Coma Scale score
- Mean arterial pressure
- Administration of vaspressors with type and dose rate of infusion
- Serum creatinine or urine output
- Bilirubin
- Platelet count

The baseline Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score should be assumed to be zero unless the patient is known to have preexisting (acute or chronic) organ dysfunction before the onset of infection. qSOFA indicates quick SOFA; MAP, mean arterial pressure.
Updated Pediatric sepsis definition?
Updated Pediatric Definition?

Adaptation and Validation of a Pediatric Sequential Organ Failure Assessment Score and Evaluation of the Sepsis-3 Definitions in Critically Ill Children

Travis J. Matics, DO; L. Nelson Sanchez-Pinto, MD, MBI
Updated Pediatric Definition?

- Single-center, retrospective cohort study
- Conducted from 2009 – 2016
- Pediatric SOFA score was developed by adapting SOFA with pediatric age-specific cut-offs
- 8711 patient encounters
- pSOFA correlated well with in-hospital mortality
- SEPSIS-3 + pSOFA
  - 14.1% met sepsis criteria with 12.1% mortality
  - 4.0% met septic shock criteria with 32.3% mortality
- Requires further validation in larger, prospective studies

Table 1. Pediatric Sequential Organ Failure Assessment Score

<table>
<thead>
<tr>
<th>Variables</th>
<th>Score²</th>
<th>0</th>
<th>1</th>
<th>2</th>
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<td>Respiratory</td>
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<td>PaO₂/FIO₂ or SpO₂/FIO₂</td>
<td>≥400</td>
<td>300-399</td>
<td>200-299</td>
<td>100-199 With respiratory support</td>
<td>&lt;100 With respiratory support</td>
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<td>Coagulation</td>
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<td>Platelet count, x10⁹/µL</td>
<td>≥150</td>
<td>100-149</td>
<td>50-99</td>
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<td>&lt;20</td>
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<td>Bilirubin, mg/dL</td>
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<td>Infusion, mm Hg or µg/kg/min</td>
<td>&lt;1 mo</td>
<td>≥46</td>
<td>&lt;46</td>
<td>Dopamine hydrochloride ≤5 or dobutamine hydrochloride (any)</td>
<td>Dopamine hydrochloride &gt;5 or epinephrine ≤0.1 or norepinephrine bitartrate ≤0.1</td>
<td>Dopamine hydrochloride &gt;15 or epinephrine &gt;0.1 or norepinephrine bitartrate &gt;0.1</td>
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<td>24-59 mo</td>
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<td>144-216 mo</td>
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<td>Renal</td>
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<td>Creatinine by age group, mg/dL</td>
<td>&lt;1 mo</td>
<td>&lt;0.8</td>
<td>0.8-0.9</td>
<td>1.0-1.1</td>
<td>1.2-1.5</td>
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<td>1-11 mo</td>
<td>&lt;0.3</td>
<td>0.3-0.4</td>
<td>0.5-0.7</td>
<td>0.8-1.1</td>
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<td>12-23 mo</td>
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<td>&lt;0.6</td>
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Future for defining Pediatric Sepsis

- Still no updated validated tool to quickly identify pediatric sepsis similar to qSOFA in adults
- Current recommendations are to use 2005 International pediatric sepsis consensus definitions
  - SIRS + infection
- SPROUT study showed discordance between physician diagnosis and consensus definition
Future for defining Pediatric Sepsis

• Still no updated validated tool to quickly identify pediatric sepsis similar to qSOFA in adults
• Current recommendations are to use 2005 International Pediatric Sepsis Consensus Definitions
  – SIRS + infection
• SPROUT study showed discordance between physician diagnosis and consensus definition

Fig. 1 Venn diagram of the overlap between patients identified with severe sepsis by attending physician diagnostic assessment (“physician diagnosis”) and the 2005 International Pediatric Sepsis Consensus Conference (“consensus criteria”). Of the 6925 pediatric intensive care unit patients screened, 706 were identified with severe sepsis but only 301 (43%) were concurrently identified by both physician diagnosis and consensus criteria (κ 0.57 ± 0.02)
Treatment and management

• Key is early recognition and prompt institution of therapy as the single most important step in sepsis management
  – EMR triggers to identify abnormal vital signs and laboratory values
• Management was extrapolated from adult sepsis studies
  – Few prospective pediatric studies
• Protocol driven resuscitation bundles
  – Decrease time to initiation of therapy (fluids, antibiotics, vasoactives)
  – Improve outcomes
Surviving Sepsis Campaign - 2012

• Initial resuscitation
  – Apply oxygen: NC, HFNC, CPAP, intubation
  – Establish IV/IO access for fluid resuscitation
    • Cap refill < 2 seconds
    • Normal BP
    • Normal pulses
    • Urine output > 1ml/kg/hr
    • Normal mental status
  – Treat septic shock per PALS algorithm
Surviving Sepsis Campaign - 2012

• Antibiotics and source control
  – Empiric antibiotics to be administered within 1 hour
    • Ideally after cultures are drawn
    • Delays in therapy are associated with poor outcomes

• Fluid resuscitation
  – Rapid fluid boluses (isotonic crystalloid) over 5-10 minutes
    • SPROUT study identified albumin use to increase risk of mortality
  – Target reversal of hypotension, increasing urine output, normal capillary refill and peripheral pulses, and normal level of consciousness
  – If hepatomegaly or rales occurs, limit additional fluids and start vasopressor/inotropic support
Surviving Sepsis Campaign - 2012

• Inotropes/vasopressors
  – Choice depends on “type” of shock
    • Dopamine, per the current PALS guidelines, is suggested as the first line in “cold shock”
      – Higher mortality and longer duration/less resolution of shock when compared to epinephrine
Surviving Sepsis Campaign - 2012

Survival probability

Time (days)

p=0.047

EPINEPHRINE

DOPAMINE

Surviving Sepsis Campaign - 2012

- Inotropes/vasopressors
  - Community septic shock is typically “cold shock”
    - Epinephrine is the first line
  - Hospital-associated shock is typically “warm shock”
    - Norepinephrine is the first line
  - Vasopressin?
    - Systematic Review suggests no mortality benefit when compared to conventional therapy

- Updated recommendations are pending
Surviving Sepsis Campaign - 2012

- Hydrocortisone
  - Grade IA evidence to use in fluid-refractory, catecholamine-resistant septic shock
    - Lack of well-powered RCTs to support steroids
    - SPROUT study suggest risk of mortality with steroid use
      - OR 1.58 (95% CI: 1.01-2.49)
  - Design and implementation of an RCT is difficult
    - Recent survey suggests >90% of pediatric intensivists would administer steroids in fluid-refractory, catecholamine-resistant shock
What next?

- Sepsis is a heterogeneous syndrome, which lacks a “Gold standard”
  - Stratification and study design is difficult
    - Equivocal results on new therapies
- Not just a “pro-inflammatory state”
  - Failure of the compensatory anti-inflammatory response syndrome (CARS)
  - Acquired immune deficiency leading to “immunoparalysis”
What next?

- **Proinflammatory paradigm**
  - Excessive inflammation leads to direct injury of host tissues.
  - Excessive inflammation overwhelms antiinflammatory mechanisms.
  - Failure of antiinflammatory mechanisms facilitates a proinflammatory phenotype.
  - Persistence of pathogens enhances and amplifies proinflammatory processes.
  - Dysregulation of inflammation adversely affects interactions between the innate and adaptive immune systems.

- **Antiinflammatory paradigm**
  - Antiinflammatory mechanisms fail and indirectly allow injury to host tissues.

- **Immune suppression paradigm**
  - Adaptive immune mechanisms fail to clear pathogens.
  - A strong antiinflammatory phenotype can lead to inactivation of monocytes and lymphocytes.

- **Heterogeneity**
  - Pathogen class
  - Genetic factors
  - Surgery
  - Trauma
  - Developmental factors
  - Comorbidities
  - Variable therapies
What next?

• Different phenotypic presentations → Different treatment algorithms
• “-omic” revolution (genomics, transcriptomics, proteomics, metabolomics)
What next?

Endotype A

Example 1  Example 2  Example 3

Endotype B

Example 1  Example 2  Example 3

Wong, et al. Am J Respir Crit Care Med. 2015
What next?

- Different phenotypic presentations → Different treatment algorithms
- “-omic” revolution (genomics, transcriptomics, proteomics, metabolomics)
  - Identify new pathways and therapeutic targets
    - Zinc homeostasis is deranged
      - Phase I trial of zinc supplementation
    - MMP-8 is highly upregulated
      - Inhibition confers survival advantage in mouse models
  - Identify new sepsis biomarkers
    - IL-27 outperforms pro-calcitonin in identifying pediatric sepsis
  - Identify new sepsis phenotypes
What next?

• Pediatric sepsis consensus conference update
  – New definitions utilizing modified SOFA score
• Surviving Sepsis Campaign update
  – Updates regarding resuscitation fluid choice, empiric antibiotic choice, vasopressor/inotrope choice, use of adjunctive therapies
Bottom Line

• Definition of Pediatric Sepsis is based on 2005 Consensus definition
  – Suspected Infection + 2 of 4 SIRS criteria = SEPSIS
  – SEPSIS + organ dysfunction = SEVERE SEPSIS
  – Cardiovascular dysfunction + SEPSIS = SEPTIC SHOCK

• Treatment and Management is based on 2012 Surviving Sepsis Campaign
  – Prompt recognition
  – Aggressive fluid resuscitation (prefer crystalloid)
  – Early broad-spectrum antibiotic administration
  – Early inotrope/vasopressor administration in fluid refractory shock (prefer epinephrine or norepinephrine)
  – Adjunctive steroid use in catecholamine resistant shock
Thank You!