

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 **S**epsis, **P**revalence, **O**utcomes and **T**herapies 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?

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- *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

Bone RC, et al. Crit Care Med. 1992

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

Bone RC, et al. Crit Care Med. 1992

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

Levy MM, et al. Intensive Care Med. 2003

The definition of sepsis?

Table 1 Diagnostic criteria for sepsis

^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 $>38.5^{\circ}\text{C}$ or $<35^{\circ}\text{C}$), 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

Infection^a

Documented or suspected *and* some of the following^b:

General parameters

Fever (core temperature $>38.3^{\circ}\text{C}$)

Hypothermia (core temperature $<36^{\circ}\text{C}$)

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 $>12,000/\mu\text{l}$)

Leukopenia (white blood cell count $<4,000/\mu\text{l}$)

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 hypotension^b (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 min^{-1} m^{-2} ^{c,d}

Organ dysfunction parameters

Arterial hypoxemia ($\text{PaO}_2/\text{FIO}_2 <300$)

Acute oliguria (urine output <0.5 ml kg^{-1} h^{-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 $<100,000/\mu\text{l}$)

Hyperbilirubinemia (plasma total bilirubin >4 mg/dl or 70 mmol/l)

Tissue perfusion parameters

Hyperlactatemia (>3 mmol/l)

Decreased capillary refill or mottling

Levy MM, et al. Intensive Care Med. 2003

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

Goldstein B, et al. *Pediatr Crit Care.* 2005

The definition of Pediatric sepsis?

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

SIRS^a

The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count:

- Core^b temperature of $>38.5^{\circ}\text{C}$ or $<36^{\circ}\text{C}$.
- 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 <10 th 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) < 5 th 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 $\mu\text{g}/\text{kg}/\text{min}$ 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 $> 3^\circ\text{C}$

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 Paco_2
OR
- Proven need^c or $> 50\%$ FiO_2 to maintain saturation $\geq 92\%$
OR
- Need for nonelective 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 $< 80,000/\text{mm}^3$ 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

Goldstein B, et al. *Pediatr Crit Care.* 2005



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

Singer M, et al. JAMA. 2016

The definition of sepsis?

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

System	Score				
	0	1	2	3	4
Respiration					
PaO ₂ /FIO ₂ , mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, ×10 ³ /μL	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular					
	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose) ^b	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1 ^b	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1 ^b
Central nervous system					
Glasgow Coma Scale score ^c	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

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.

^c Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

Singer M, et al. JAMA. 2016

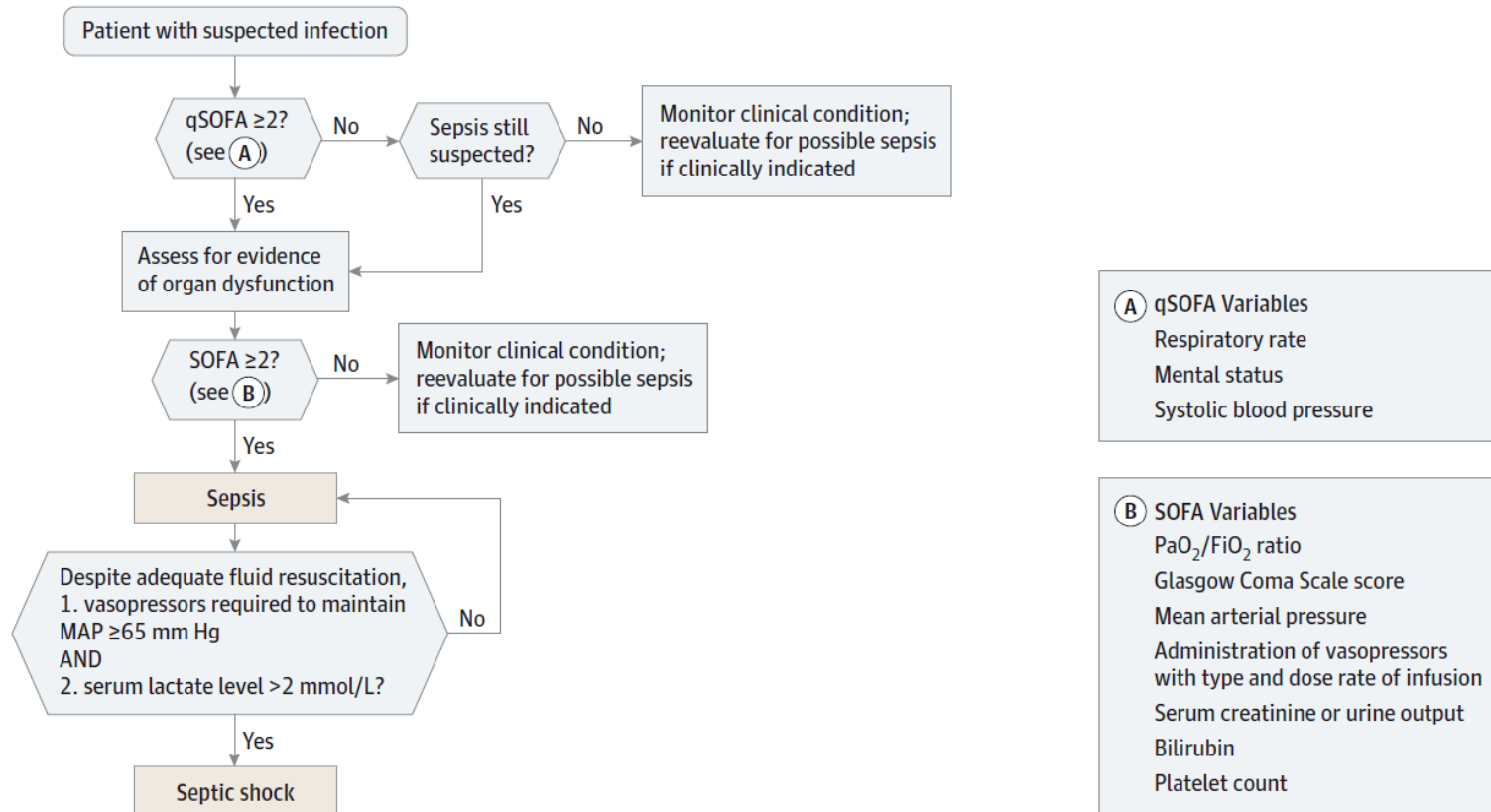
Screening for Sepsis

- 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 $\geq 22/\text{min}$
 - Altered mentation (GCS < 15)
 - Systolic blood pressure ≤ 100 mm Hg

Singer M, et al. JAMA. 2016

Screening for Sepsis

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



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 ?

JAMA Pediatrics | [Original Investigation](#) | CARING FOR THE CRITICALLY ILL PATIENT

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

Variables	Score ^a				
	0	1	2	3	4
Respiratory					
Pao ₂ :Fio ₂ ^b or Spo ₂ :Fio ₂ ^c	≥400	300-399	200-299	100-199 With respiratory support	<100 With respiratory support
	≥292	264-291	221-264	148-220 With respiratory support	<148 With respiratory support
Coagulation					
Platelet count, ×10 ³ /μL	≥150	100-149	50-99	20-49	<20
Hepatic					
Bilirubin, mg/dL	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular					
MAP by age group or vasoactive infusion, mm Hg or μg/kg/min ^d					
<1 mo	≥46	<46	Dopamine hydrochloride ≤5 or dobutamine hydrochloride (any)	Dopamine hydrochloride >5 or epinephrine ≤0.1 or norepinephrine bitartrate ≤0.1	Dopamine hydrochloride >15 or epinephrine >0.1 or norepinephrine bitartrate >0.1
1-11 mo	≥55	<55			
12-23 mo	≥60	<60			
24-59 mo	≥62	<62			
60-143 mo	≥65	<65			
144-216 mo	≥67	<67			
>216 mo ^e	≥70	<70			
Neurologic					
Glasgow Coma Score ^f	15	13-14	10-12	6-9	<6
Renal					
Creatinine by age group, mg/dL					
<1 mo	<0.8	0.8-0.9	1.0-1.1	1.2-1.5	≥1.6
1-11 mo	<0.3	0.3-0.4	0.5-0.7	0.8-1.1	≥1.2
12-23 mo	<0.4	0.4-0.5	0.6-1.0	1.1-1.4	≥1.5
24-59 mo	<0.6	0.6-0.8	0.9-1.5	1.6-2.2	≥2.3
60-143 mo	<0.7	0.7-1.0	1.1-1.7	1.8-2.5	≥2.6
144-216 mo	<1.0	1.0-1.6	1.7-2.8	2.9-4.1	≥4.2
>216 mo ^e	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	≥5

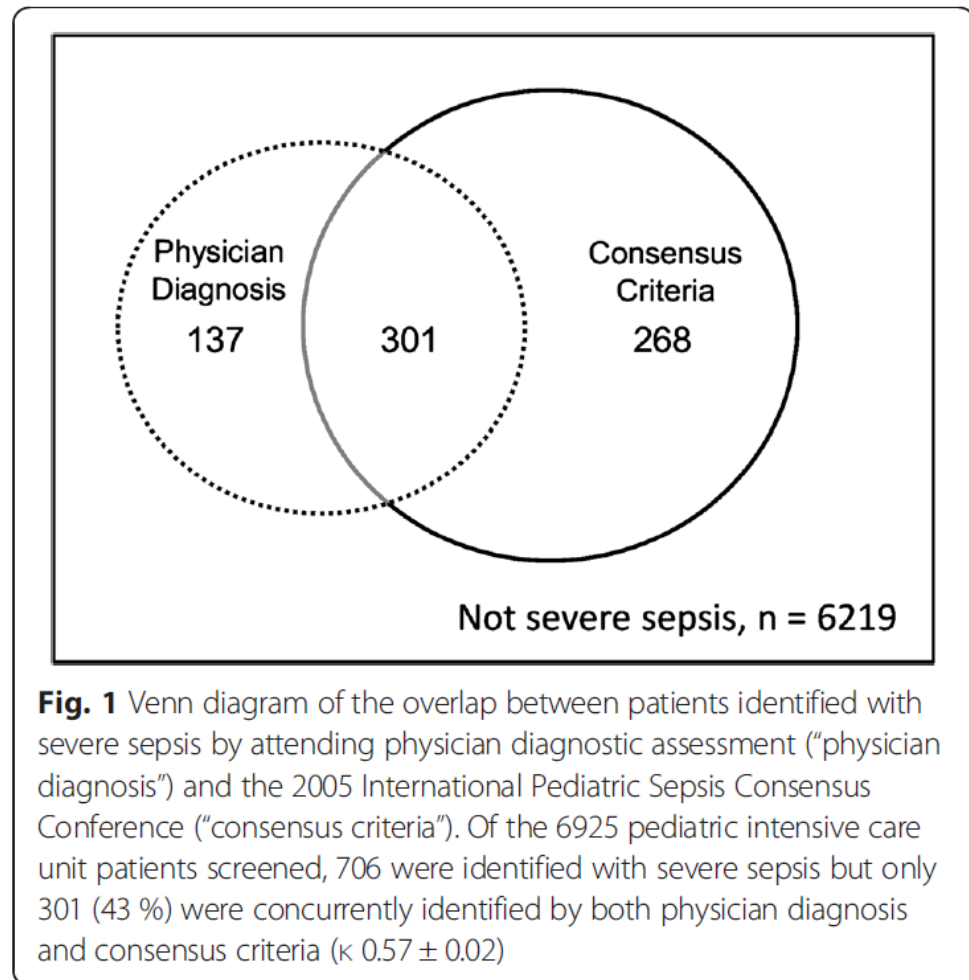
Matics TJ, et al. JAMA Pediatr. 2017

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 validate similar to qSOFA in adult
- Current recommendatio sepsis consensus defini
 - SIRS + infection
- SPROUT study showed and consensus definitio



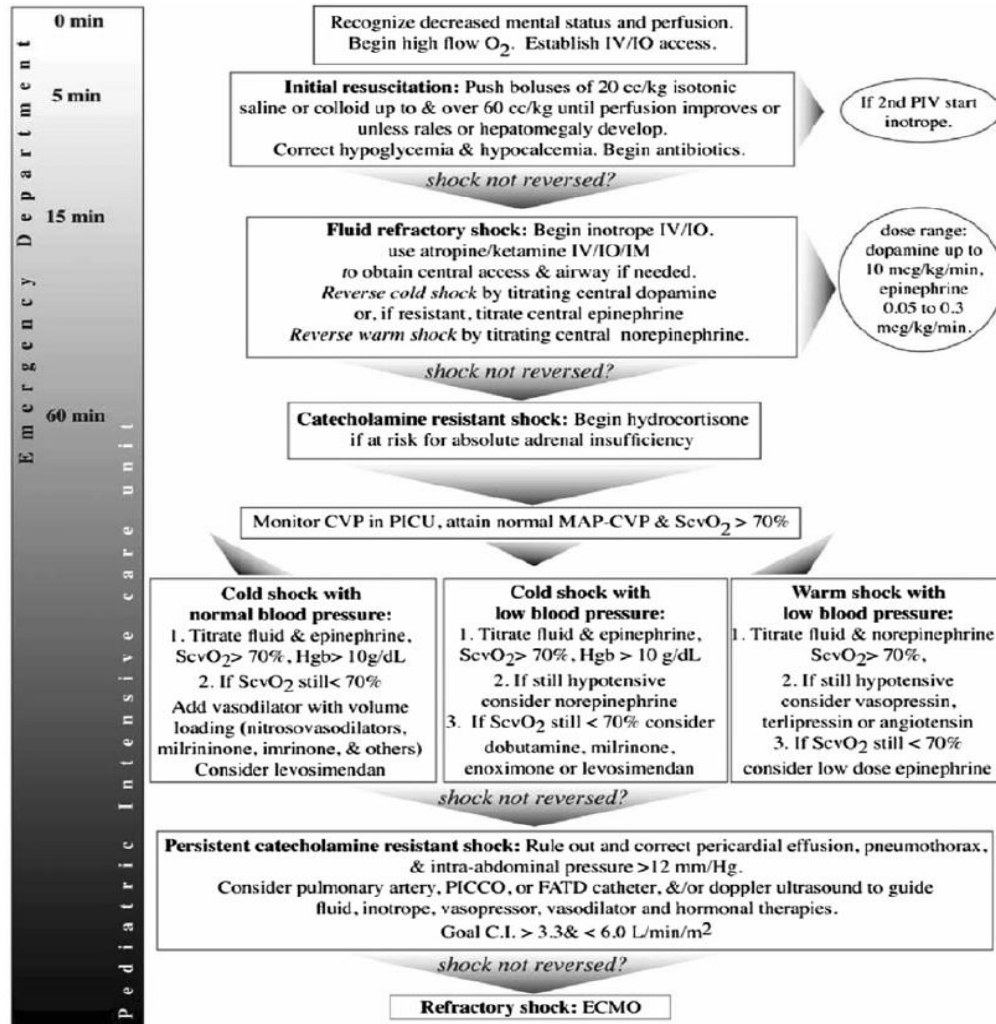
Treatment and management

- 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



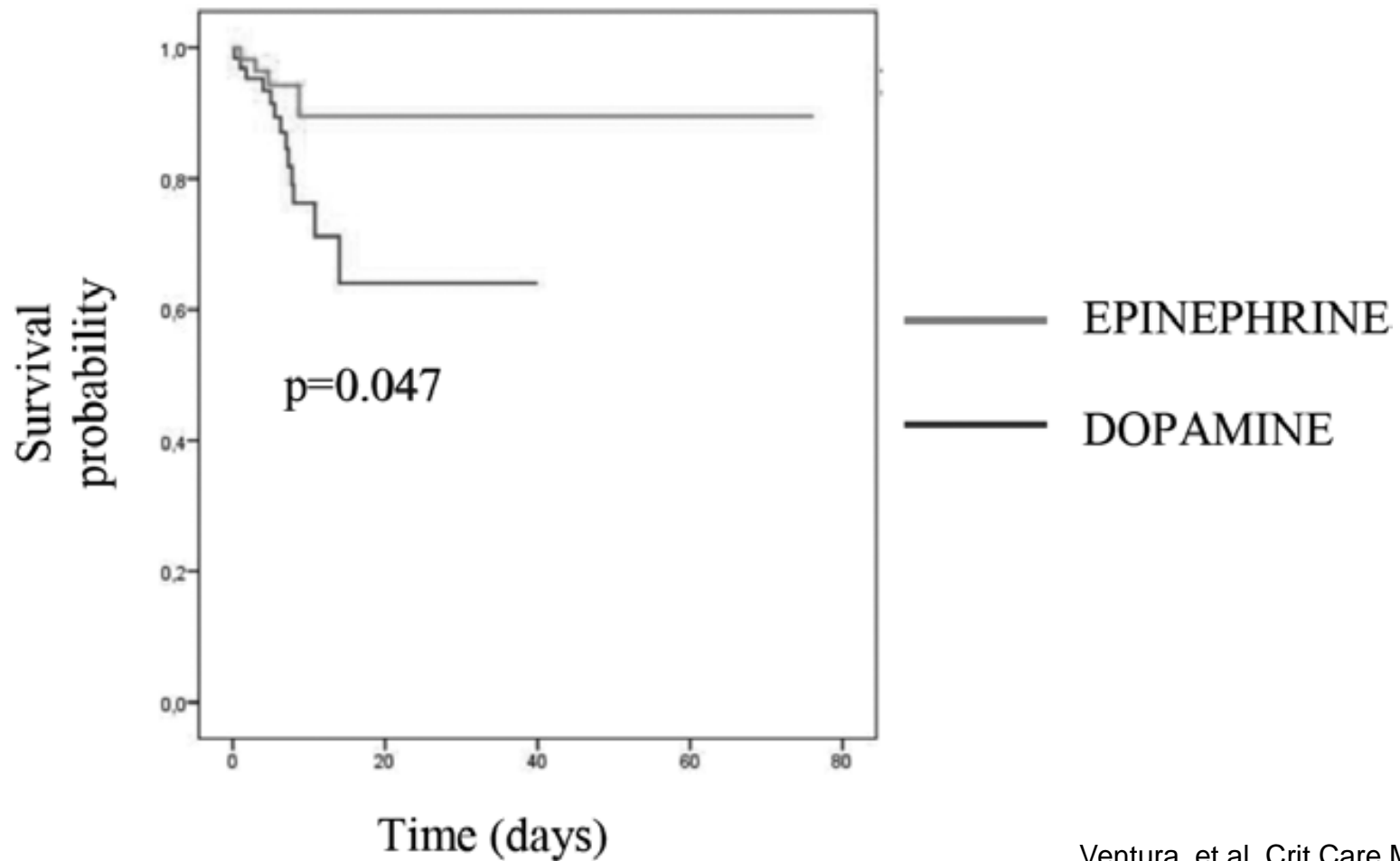
Surviving Sepsis Campaign - 2012

- 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
 - » Ramaswamy KN, et al. *Pediatr Crit Care Med*. 2016
 - » Ventura AMC, et al. *Crit Care Med*. 2015

Surviving Sepsis Campaign - 2012



Ventura, et al. Crit Care Med. 2015

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
 - Masarwa, et al. Crit Care. 2017
- Updated recommendations are pending

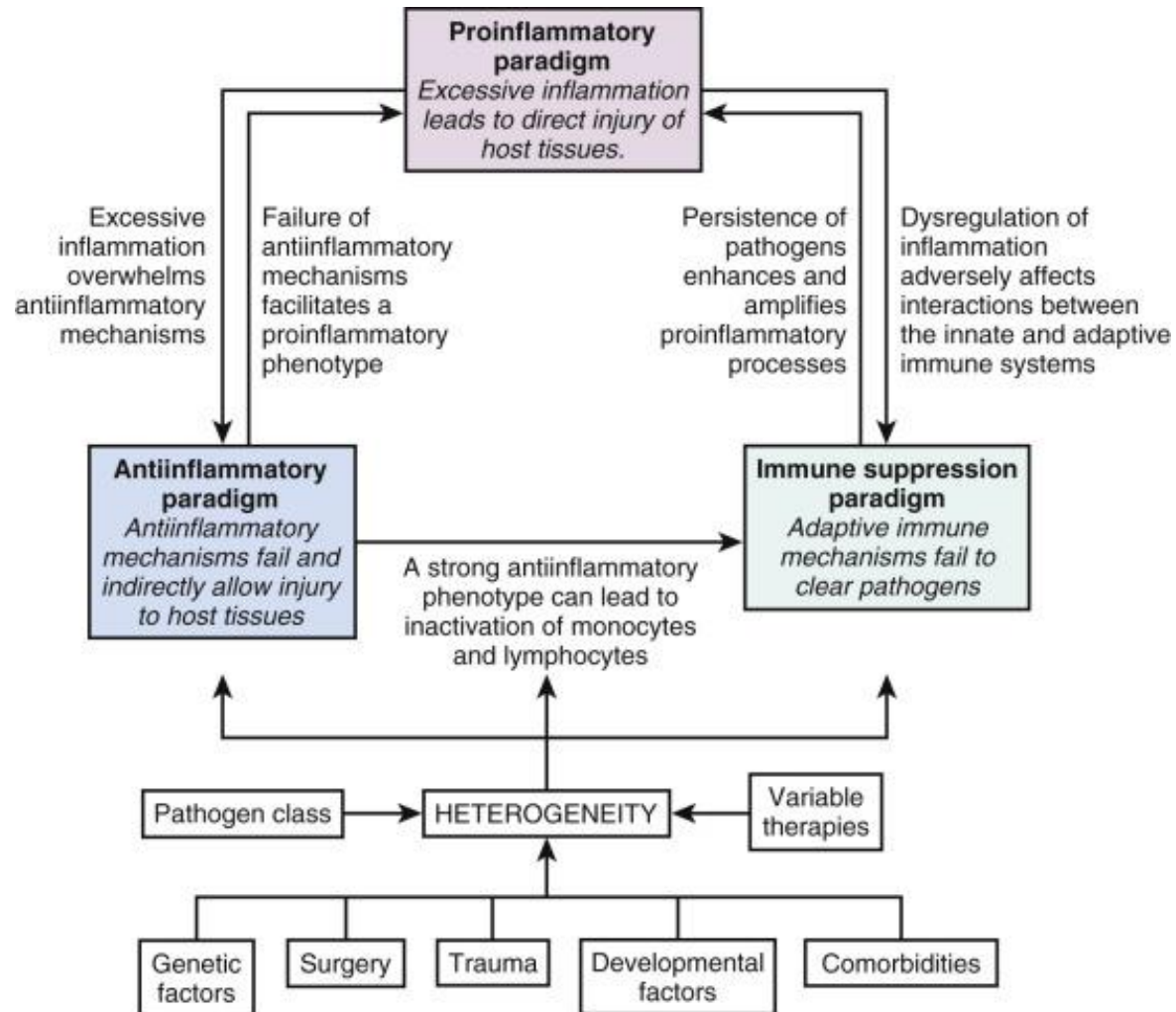
Surviving Sepsis Campaign - 2012

- 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
 - Menon, et al. *Pediatr Crit Care Med.* 2013

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”

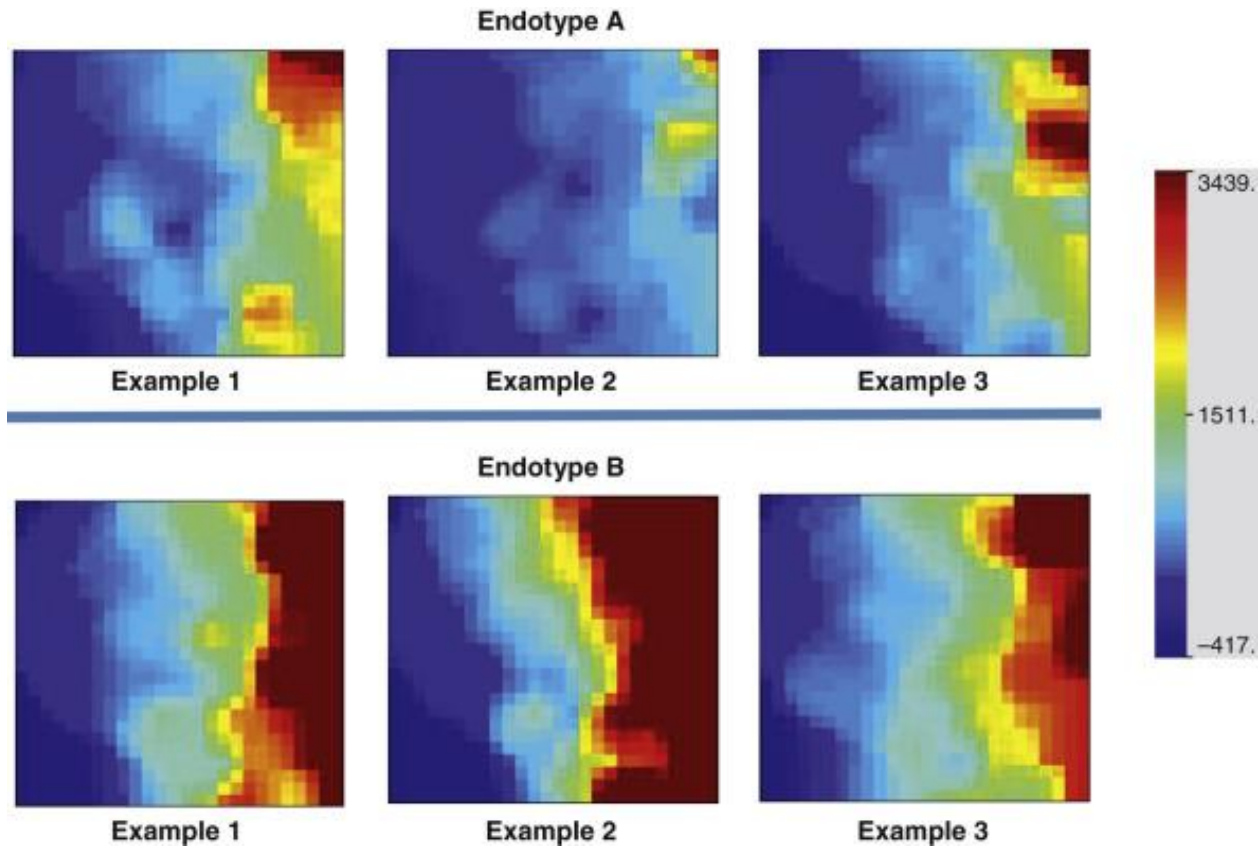
What next?



What next?

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

What next?



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!