Sepsis

February 2022

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Objectives

- Definitions
- Pathophysiology
- Epidemiology
- Adult
  - Risk Factors
  - Clinical presentation
  - Management

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Objectives

- Pediatric
  - Risk Factors
  - Clinical presentation
  - Management
- Shock
- “Surviving Sepsis Campaign”

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Definitions

- Sepsis exists on a continuum of severity ranging from infection and bacteremia to sepsis and septic shock, which can lead to multiple organ dysfunction syndrome (MODS) and death.

- The Systemic Inflammatory Response Syndrome (SIRS) is no longer included.

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Definitions

- Early Sepsis
  - Infection and bacteremia may be early forms of infection that can progress to sepsis.
  - No formal definition
  - Infection = invasion of normally sterile tissue by organisms resulting in infectious pathology
  - Bacteremia = presence of viable bacteria in the blood
  - Scoring Systems - qSofa, NEWS

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Definitions

- Sepsis
  - Life-threatening organ dysfunction caused by a dysregulated host response to infection.
  - Organ Dysfunction
    - SOFA score = organ dysfunction score
    - Increase of 2 or more points in the SOFA score

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SOFA Score

- “Sequential Organ Failure Assessment”
- Superior predictor of in-hospital mortality
- Identifies patients who potentially have a high risk of dying from infection
- PaO2/FiO2, platelet count, bilirubin level, blood pressure, Glasgow Coma Score, and creatinine level
- COMPLICATED!
- Abbreviated version, qSOFA, more useful

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qSOFA Score

- Respiratory rate > or = 22/minute
- Altered mentation
- Systolic blood pressure < or = 100 mmHg
- Score > or = 2 is associated with poor outcomes due to sepsis

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Definitions

- Sepsis
  - Infection
    - No clear guidelines for identification
    - Rely on clinical suspicion derived from the signs and symptoms of infection, supporting radiologic and microbiologic data, and response to therapy

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Definitions

- Severe Sepsis - no longer used
  - Sepsis that was associated with tissue hypoperfusion or organ dysfunction

- Systemic Inflammatory Response Syndrome (SIRS) - no longer used
  - Temperature, heart rate, respiratory rate, $PaCO_2$, WBC count, and % band cells

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Definitions

- Septic Shock
  - A type of vasodilatory or distributive shock
  - Sepsis that has circulatory, cellular, and metabolic abnormalities that are associated with a greater risk of mortality than sepsis alone
  - Patient who fulfill the criteria for sepsis who, despite adequate fluid resuscitation, require vasopressors to maintain a mean arterial pressure (MAP) > or = 65 mmHg and have a lactate > 2 mmol/L
  - Higher mortality than those that do not

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Definitions

- Multiple Organ Dysfunction Syndrome (MODS)
  - Needs to be distinguished from sepsis
  - Progressive organ dysfunction in an acutely ill patient, such that homeostasis cannot be maintained without intervention
  - Applied to both infectious and non-infectious conditions

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Definitions

- Systemic Inflammatory Response Syndrome (SIRS)
  - Needs to be distinguished from sepsis
  - Criteria are present in many hospitalized patients who do not develop infection
  - Considered a clinical syndrome that is a form of dysregulated inflammation

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Definitions

- Pregnancy?
  - The usual scoring systems have excluded pregnant women because pregnancy physiology is different and normal pregnancy parameters overlap with criteria for sepsis such that some experts have proposed use of pregnancy-specific scores.
- COVID-19?
  - Patients critically ill with COVID-19 satisfy the diagnostic criteria for sepsis and exhibit a phenotype and pathology with both similarities and differences to that of sepsis caused by other pathogens.

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Pathophysiology

- Normal response to infection
  - Initiated when immune cells, particularly macrophages, recognize and bind to microbial components
  - Binding of immune cell surface receptors to microbial components activates genes involved in the host inflammatory response and cause polymorphonuclear leukocytes (PMNs) to migrate to the site of infection, causing local vasodilation and vascular permeability
  - This local inflammatory response leads to recruitment of additional pro- and anti-inflammatory mediators

Pathophysiology

- Transition to sepsis
  - The release of pro-inflammatory mediators in response to an infection exceeds the boundaries of the local environment, leading to a more generalized response.
  - Bacterial cell wall components spill into the bloodstream
  - Large quantities of pro-inflammatory cytokines spill into the bloodstream
  - Complement system activation
  - Genetic susceptibility of the patient

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Pathophysiology

- Systemic effects of sepsis
  - Tissue ischemia
    - Derangement in metabolic autoregulation, the process that matches oxygen availability to changing tissue oxygen needs
    - Microcirculatory and endothelial lesions
    - Erythrocytes (RBCs) lose their normal ability to deform and navigate the microcirculation

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Pathophysiology

- Systemic effects of sepsis
  - Cytopathic injury
    - Proinflammatory mediators and/or other products of inflammation may cause sepsis-induced mitochondrial dysfunction, which leads to impairment of mitochondrial electron transport, disordered energy metabolism, and cytotoxicity
    - Inability to utilize oxygen, even when present

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Pathophysiology

- Systemic effects of sepsis
  - Cell death pathways
  - Apoptosis
  - Pyroptosis
  - Autophagy
  - Immunosuppression

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Pathophysiology

- Organ-specific effects of sepsis
  - Circulation
    - Hypotension due to diffuse vasodilation
    - Hypotension due to redistribution of intravascular volume (third-spacing)
    - Decreased systolic and diastolic ventricular performance
    - Vascular hyporesponsiveness
    - Decrease in the number of functional capillaries
    - Endothelial damage/dysfunction

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Pathophysiology

- Organ-specific effects of sepsis
  - Lung
    - Endothelial injury in the pulmonary vasculature disturbs capillary blood flow and enhances microvascular permeability, resulting in interstitial and alveolar pulmonary edema
    - Creates ventilation-perfusion mismatch, which leads to hypoxemia
    - ARDS can result

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Pathophysiology

- Organ-specific effects of sepsis
  - Gastrointestinal tract
    - Translocation of bacteria and endotoxin from the gut into the systemic circulation
  - Liver
    - Previous damage or dysfunction due to sepsis leads to an inability in clearing bacteria and bacteria-derived products that have entered the portal system from the gut

Pathophysiology

- Organ-specific effects of sepsis
  - Kidney
    - Acute tubular necrosis due to hypoperfusion and/or hypoxemia leads to acute renal failure
    - Systemic hypotension, direct renal vasoconstriction, release of cytokines, and activation of neutrophils leads to acute renal failure

Pathophysiology

- Organ-specific effects of sepsis
  - Nervous system
    - Altered sensorium (encephalopathy)
    - Iatrogenic?

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Epidemiology

- Annual rate of more than 1,665,000 cases of sepsis between 1974 and 2000
- Rates of sepsis and septic shock increased yearly between 1998 and 2009
- Between 2005 and 2014 yearly rates of septic shock increased and mortality decreased
- Higher incidence of sepsis among African-American males
- Higher incidence of sepsis during the winter
- Higher incidence of sepsis in patients > or = to 65 years of age
- Bacteria are the predominant pathogen of sepsis
- Severity of disease appears to be increasing

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Risk Factors - Adult

- Intensive care unit admission
- Bacteremia
- Advanced age (>/= 65)
- Immunosuppression
- Diabetes
- Obesity
- Cancer
- Community-acquired pneumonia
- Previous hospitalization
- Genetic factors
- SARS-CoV-2

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Clinical Presentation - Adult

- Symptoms and signs of sepsis are nonspecific
- Symptoms and signs specific to an infectious source
- Arterial hypotension
  - Systolic blood pressure <90 mmHg
  - Mean arterial pressure <70 mmHg
  - Systolic blood pressure decrease >40 mmHg
  - Systolic blood pressure less than 2 standard deviations below normal for age

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Clinical Presentation - Adult

- Temperature >38.3C (100.1F) or <36C (96.8F)
- Heart rate >90 beats/min or more than two standard deviations above the normal value for age
- Tachypnea, respiratory rate >20 breaths/min

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Clinical Presentation - Adult

- Signs of end-organ perfusion
  - Warm, flushed skin in the early phases of sepsis
  - Cool skin as sepsis progresses to shock
  - Decreased capillary refill, cyanosis, or mottling may indicate shock
  - Altered mental status or obtundation
  - Oliguria or anuria
  - Ileus or absent bowel sounds

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Management - Adult

- Based on the 2021 guidelines issued by the Surviving Sepsis Campaign
- Immediate evaluation and management
  - Stabilize respiration
    - Secure the airway if indicated
    - Supplemental oxygen should be supplied to all patients with sepsis, who have indications for oxygenation, and oxygenation should be monitored continuously with pulse oximetry
    - Peripheral saturation should be maintained between 90 and 96%

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Management - Adult

- Immediate evaluation and management
  - Establish venous access
    - Peripheral access (x2), large bore preferable
    - May eventually require central venous access
    - Fluid, medications, blood products, and frequent laboratory draws
  - Cardiac monitor/Vitals
  - Draw blood if able

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Management - Adult

- Initial resuscitative therapy
  - Tissue perfusion is predominantly achieved by the aggressive administration of intravenous fluids, usually crystalloids, given at 30 mL/kg (actual body weight), started by one hour and completed within the first three hours following presentation.
    - Goal mean arterial pressure >/= 65 mmHg
    - Goal urine output >/= 0.5 mL/kg/hour
    - Evaluate and monitor for evidence of significant pulmonary edema

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Management - Adult

- Initial resuscitative therapy
  - Empiric antibiotic therapy is targeted at the suspected organism(s) and site(s) of infection and preferably administered within the first hour.

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Management - Adult

- Patients who fail initial therapy
  - Vasopressors
    - Useful in patients who remain hypotensive despite adequate fluid resuscitation or who develop cardiogenic pulmonary edema
    - Epinephrine
      - Push-dose
      - Drip

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Risk Factors - Pediatric

- Age younger than one month
- Serious injury (eg, major trauma, burns, penetrating wounds)
- Chronic debilitating medical conditions
- Host immunosuppression
- Large surgical incisions
- In-dwelling vascular catheters or other invasive devices
- Urinary tract abnormalities with frequent infection
- Immunizations?

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Clinical Presentation - Pediatric

- Core temperature of >38.5C (101.3F) or <36C (96.8F)
- Tachycardia, defined as a mean heart rate more than two standard deviations above normal for age, or for children younger than one year of age, bradycardia defined as a mean heart rate <10th percentile for age
- Mean respiratory rate more than two standard deviations above normal for age
- WBC count elevated or depressed for age

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Clinical Presentation - Pediatric

Pediatric systemic inflammatory response syndrome vital signs and laboratory values by age

Age group	Heart rate (beats/minute)		Respiratory rate (breaths/minute)	Leukocyte count (leukocytes x 10^3/mm^3)	Systolic blood pressure (mmHg)
	Tachycardia	Bradycardia			
Newborn (0 days to 1 week)	>180	<100	>50	>34	<59
Neonate (1 week to 1 month)	>180	<100	>40	>19.5 or <5	<79
Infant (1 month to 1 year)	>180	<90	>34	>17.5 or <5	<75
Toddler and preschool (>1 to 5 years)	>140	NA	>22	>15.5 or <6	<74
School age (>5 to 12 years)	>130	NA	>18	>13.5 or <4.5	<83
Adolescent (>12 to <18 years)	>110	NA	>14	>11 or <4.5	<90

Clinical Presentation - Pediatric

- Toxic or ill appearance
- Signs of dehydration (dry mucus membranes, sunken eyes, decreased urine output, prolonged capillary refill time, decreased skin turgor, and, in infants, a sunken fontanelle)
- Rigors
- Altered mental status (irritability, anxiety, confusion, lethargy, somnolence)
- Decreased tone in neonates and infants

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Clinical Presentation - Pediatric

- Seizures
- Meningismus
- Respiratory depression or failure
- Pulmonary rales or decreased breath sounds
- Distended, tender abdomen
- Costovertebral angle tenderness
- Macular erythema

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Clinical Presentation - Pediatric

- Skin cellulitis or abscess
- Peripheral edema caused by capillary leak
- Petechiae or purpura (specific infectious source vs DIC)
- Multiple nodules

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Clinical Presentation - Pediatric

Physical findings of volume depletion in infants and children

Finding	Mild (3 to 5%)	Moderate (6 to 9%)	Severe (≥10%)
Pulse	Full, normal rate	Rapid*	Rapid* and weak **or** absent
Systolic pressure	Normal	Normal to low	Low
Respirations	Normal	Deep, rate may be increased	Deep, tachypnea **or** decreased to absent
Buccal mucosa	Tacky or slightly dry	Dry	Parched
Anterior fontanelle	Normal	Sunken	Markedly sunken
Eyes	Normal	Sunken	Markedly sunken
Skin turgor	Normal	Reduced	Tenting
Skin	Normal	Cool	Cool, mottled, acrocyanosis
Urine output	Normal or mildly reduced	Markedly reduced	Anuria
Systemic signs	Increased thirst	Listlessness, irritability	Grunting, lethargy, coma

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Management - Pediatric

- Based on the 2020 guidelines issued by the Surviving Sepsis Campaign
- Use a screening or trigger tool
- Resuscitation should be initiated within 15 minutes of confirming severe sepsis or septic shock
- Red-flag findings:
  - Fever
  - Hypothermia
  - Tachycardia
  - Tachypnea

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Management - Pediatric

- Red-flag findings:
  - Abnormal pulse (quality)
  - Abnormal capillary refill (>/= 3 sec)
  - Hypotensive (late sign)
  - Abnormal mental status
  - Purpura or petechiae
  - Macular erythema with mucosal changes (toxic shock syndrome)

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Management - Pediatric

Septic shock trigger/identification tool

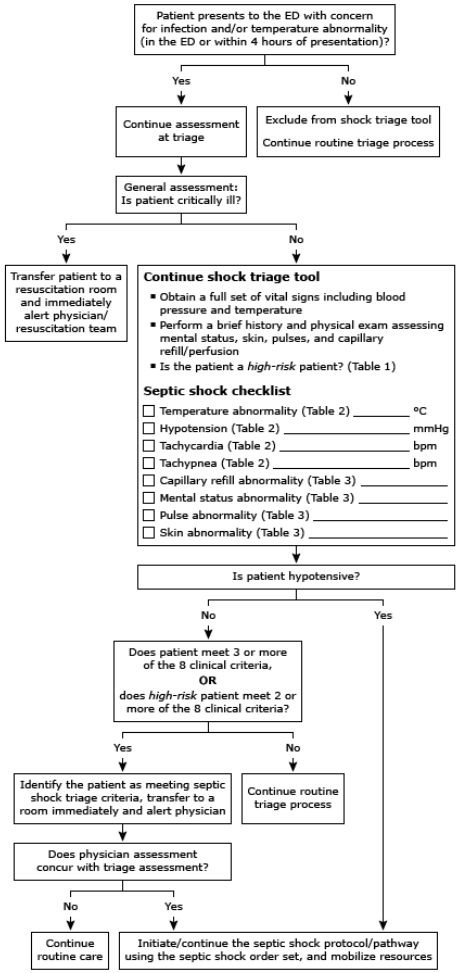

Table 1. High-risk conditions

▪ Malignancy
▪ Asplenia (including SCD)
▪ Bone marrow transplant
▪ Central or indwelling line/catheter
▪ Solid organ transplant
▪ Severe intellectual disability with cerebral palsy
▪ Immunodeficiency, immunocompromise, or immunosuppression

Table 2. Vital signs (PALS)

Age	Heart rate	Respiratory rate	Systolic BP	Temperature (°C)
0 days to 1 month	>205	>60	<60	<36 or >38
≥1 month to 3 months	>205	>60	<70	<36 or >38
≥3 months to 1 year	>190	>60	<70	<36 or >38.5
≥1 year to 2 years	>190	>40	<70 + (age in years x 2)	<36 or >38.5
≥2 years to 4 years	>140	>40	<70 + (age in years x 2)	<36 or >38.5
≥4 years to 6 years	>140	>34	<70 + (age in years x 2)	<36 or >38.5
≥6 years to 10 years	>140	>30	<70 + (age in years x 2)	<36 or >38.5
≥10 years to 13 years	>100	>30	<90	<36 or >38.5
>13 years	>100	>16	<90	<36 or >38.5

Table 3. Exam abnormalities

	Cold shock	Warm shock	Non-specific
Pulses (central versus peripheral)	Decreased or weak	Bounding	
Capillary refill (central versus peripheral)	≥3 seconds	Flash (<1 second)	
Skin	Mottled, cool	Flushed, ruddy, erythroderma (other than face)	Petechiae below the nipple, any purpura
Mental status			Decreased, irritability, confusion, *inappropriate* crying or drowsiness, poor interaction with parents, lethargy, diminished arousability, obtunded

American Academy of Pediatrics trigger tool for early septic shock recognition.

ED: emergency department; SCD: sickle cell disease; bpm: beats per minute; PALS: Pediatric Advanced Life Support; BP: blood pressure.

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Management - Pediatric

- Airway and Breathing
  - Initiate supplemental oxygen therapy to maintain a saturation between 90 and 97%
  - Escalate to noninvasive ventilation as needed
  - Endotracheal intubation is frequently necessary in children with fluid-refractory, catecholamine-resistant septic shock to protect the airway, assist with ventilation, and/or promote oxygenation
  - When performing RSI in a child with septic shock, it is important to choose agents that do not worsen cardiovascular status

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Management - Pediatric

- Circulation
  - Establish venous access
    - Preferably two sites and of the largest caliber that can be reliably inserted
- Treat hypoglycemia
- Fluid resuscitation
  - Patients without signs of fluid overload should receive 10 to 20 mL/kg of balanced crystalloid solution, up to 40 to 60 mL/kg within the first hour, as long as hemodynamic improvement is determined

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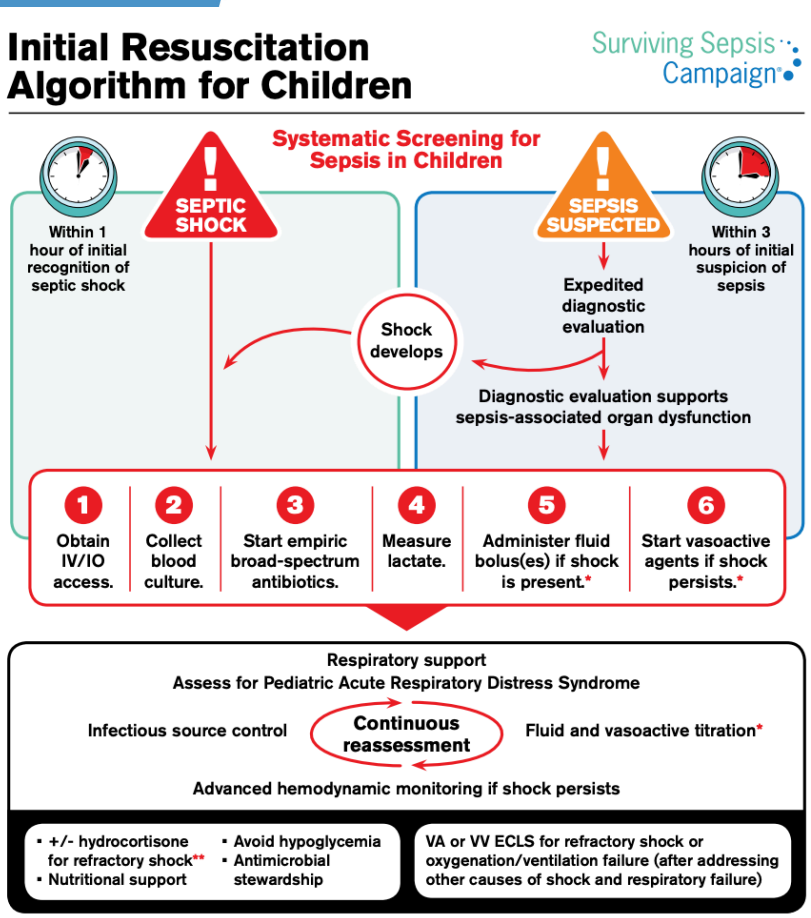
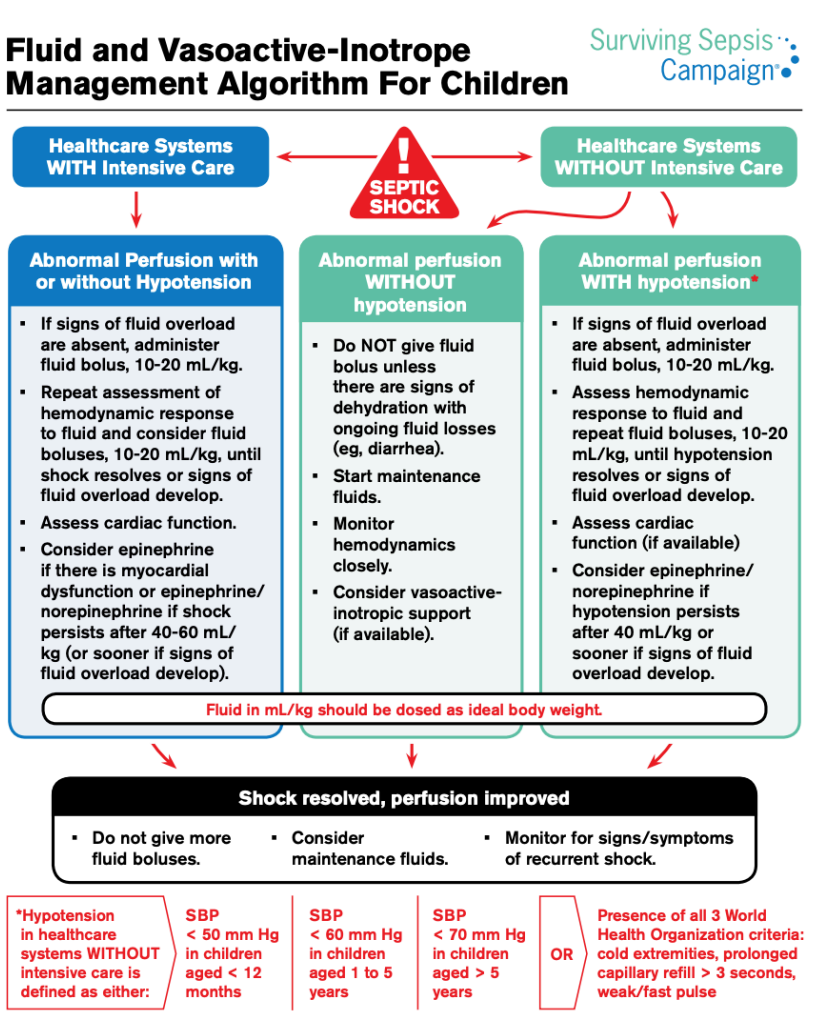
Management - Pediatric





Management - Pediatric

- Monitoring
  - Improvement in quality of central and peripheral pulses
  - Improvement in skin perfusion
  - Improvement in mental status
  - Urine output >/= 1 mL/kg/hr
  - Blood pressure improvement to at least the 5th percentile for age
  - Mean arterial blood pressure maintained at >5th percentile for age
    - Estimated as 1.5 x age (years) + 40

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Management - Pediatric

- Empiric antibiotic therapy
  - Should begin within one hour of presentation
- Vasoactive therapy
  - For patients with fluid-refractory septic shock and/or continued evidence of abnormal perfusion
  - Epinephrine
    - Push-dose
    - Drip

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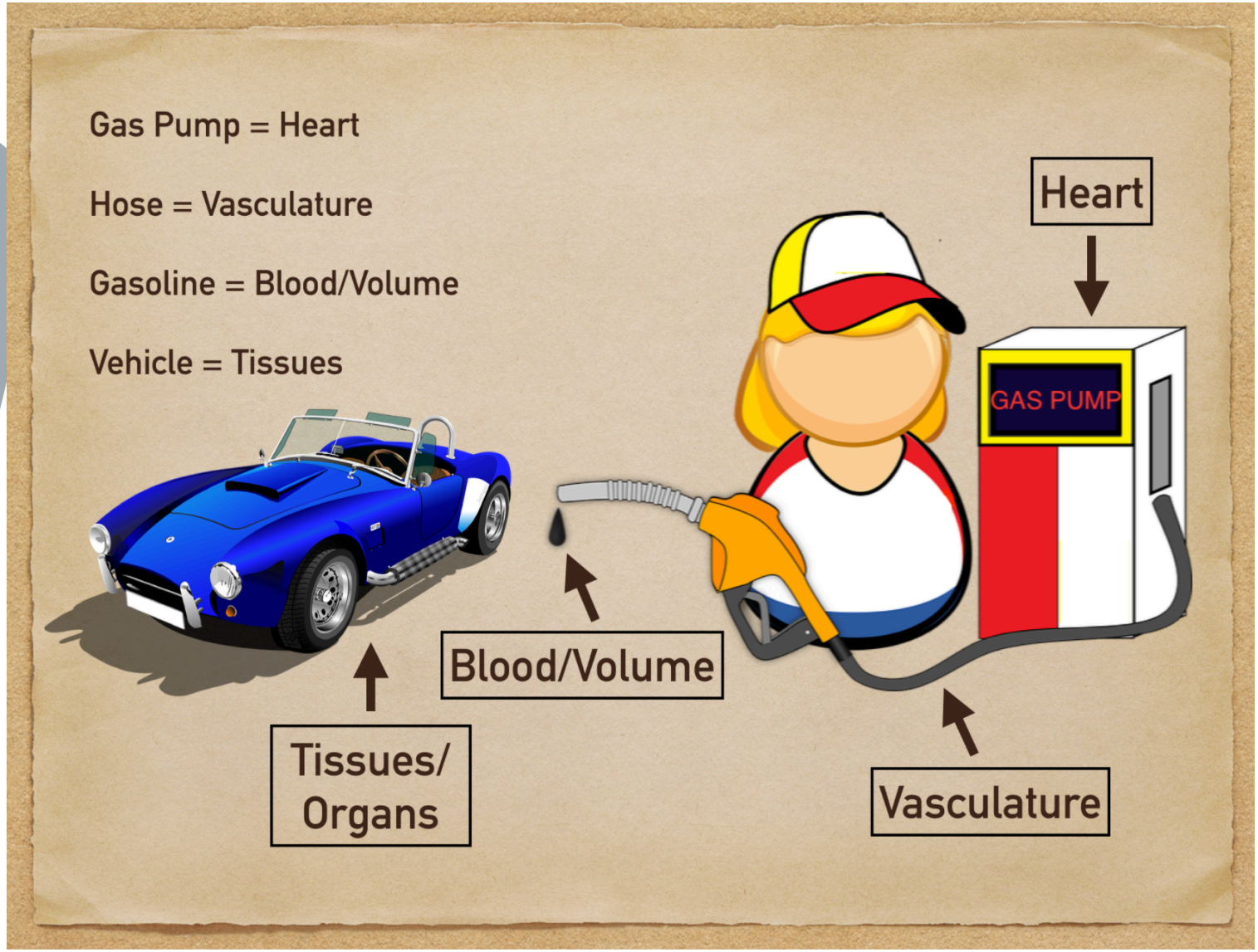
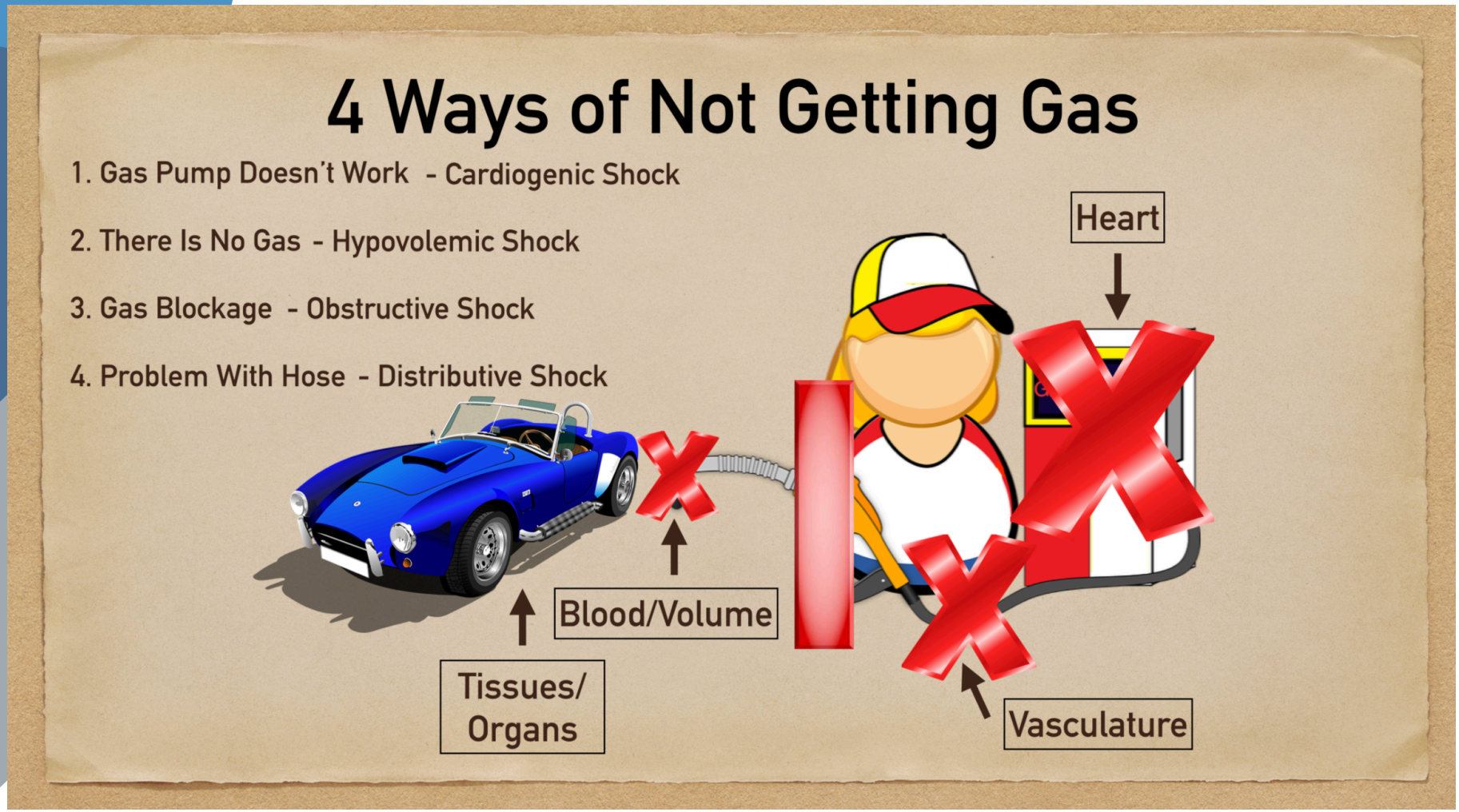
Distributive Shock



Distributive Shock



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Distributive Shock

Hemodynamic profiles of shock on pulmonary artery catheter in adults

Physiologic variable	Preload	Pump function	Afterload	Tissue perfusion
Clinical measurement	**Pulmonary capillary wedge pressure**	**Cardiac output***	**Systemic vascular resistance**	**Mixed venous oxyhemoglobin saturation¶**
Hypovolemic	↔ (early) or ↓ (late)	↔ (early) or ↓ (late)	↑	>65% (early) or <65% (late)
Cardiogenic	↑	↓	↑	<65%
Distributive	↔ (early) or ↓ (late)	↑ or ↓ (occasionally)	↓	>65%
Obstructive				
PE, PH, tension pneumothorax	↔ (early) or ↓ (late)	↔ (early) or ↓ (late)	↑	>65%
Pericardial tamponadeΔ	↑	↓	↑	<65%

PE: pulmonary embolus; PH: pulmonary hypertension; PAC: pulmonary artery catheter.
* Cardiac output is generally measured using the cardiac index.
¶ Mixed venous oxyhemoglobin saturation cutoff measured on PAC is 65%, but on triple lumen catheter is 70%.
Δ Equalization of right atrial, right ventricular end-diastolic and pulmonary artery wedge pressures is classic in pericardial tamponade and distinguishes it from primary cardiogenic shock.

“Surviving Sepsis Campaign”

Adult:

https://journals.lww.com/ccmjournal/Fulltext/2021/11000/Surviving_Sepsis_Campaign__International.21.aspx

Pediatric:

https://journals.lww.com/pccmjournal/Fulltext/2020/02000/Surviving_Sepsis_Campaign_International_Guidelines.20.aspx

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Thank You!

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