Introduction

Acute febrile illness is one of the most common reasons for visiting a pediatric emergency department (ED), accounting for approximately 5% to 10% of the total ED visits. It is also frequent in hospitalized children. Only a small minority of patients with acute febrile illness will develop sepsis, but any delay in recognizing this condition gives rise to worsened outcomes.

Sepsis is a leading cause of morbidity, mortality, and healthcare resources for pediatric populations use worldwide with an estimated 22 cases of sepsis per 100,000 children annually. This translates to 25.2 million cases per year in children younger than 19 years with a little less than half of these (10.6 million) resulting in death.

Sepsis and its complications, multiple organ dysfunction and septic shock, account for approximately 8% of admissions to Pediatric Intensive Care Units (PICUs). The in-hospital mortality rate ranges from less than 1% for previously healthy children to more than 7%, depending on risk factors and severity of illness. Most deaths occur within the first 48 to 72 hours of treatment due to shock and/or multiple organ dysfunction. Moreover, up to 17% of pediatric survivors of severe sepsis experience at least moderate physical or cognitive disabilities at hospital discharge.

Therefore, early identification of childhood sepsis that drives timely and appropriate patient management is crucial to improve clinical outcomes, optimize healthcare resources and minimize the social impact of long-term complications on survivors and their families.

About Sepsis

Sepsis is the body's extreme response to an infection and is a life-threatening medical emergency. Sepsis happens when an infection you already have triggers a chain reaction throughout your body.

Infections that lead to sepsis most often start in the gastrointestinal tract, lung, skin or urinary tract.

In contrast to an uncomplicated and localized infection, sepsis is a multifaceted disruption of the finely tuned balance of inflammation and anti-inflammation maintained by the immune system. In sepsis, both pro-inflammatory and anti-inflammatory pathways are activated. The resulting inflammation leads to progressive tissue damage, finally causing multi-organ dysfunction (Figure 1).

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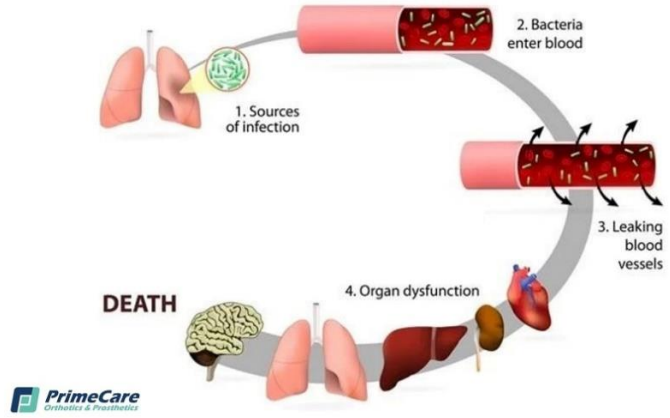

Figure 1 Progression of Sepsis: Without timely treatment, sepsis can rapidly lead to tissue damage, organ failure and death. (Image source: https://primecareprosthetics.com/es/conditions/sepsis)

Symptoms

Lay description

Clinical suspicion of sepsis is defined as positive screening in the current Sepsis Code: core temperature greater than 38.5ºC and a suspicion of infection, plus one or more of the following criteria (technical language in parenthesis):

- Shortness of breath (Tachypnoea or respiratory distress)
- High heart rate (tachycardia), low blood pressure or weak pulse
- Marbled, cold or pale skin
- Confusion or disorientation (Irritability, food rejection, altered mental status, fainting or meningeal signs)
- Reddish spots on the skin or bruises (Petechiae or ecchymosis)

At the end, the imbalance of the process causes a decrease in the perfusion and delivery of oxygen to the tissues. Finally, it causes failure of ≥ 1 organs, including the kidneys, lungs, liver, brain, and heart.

Figure 2 describes some of the clinical findings when tissue damage appears.

Technical description

Initially, arteries and arterioles dilate, decreasing peripheral arterial resistance; cardiac output typically increases. Later, cardiac output may decrease, blood pressure falls (with or without an increase in peripheral resistance), and typical features of hypoperfusion appear.

Even in the stage of increased cardiac output, vasoactive mediators cause blood flow to bypass capillary exchange vessels (a distributive defect). Poor capillary flow resulting from this shunting, along with capillary obstruction by microthrombi, decreases delivery of oxygen and impairs removal of carbon dioxide and waste products. Decreased perfusion causes dysfunction and sometimes failure of ≥ 1 organs, including the kidneys, lungs, liver, brain, and heart.

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Coagulopathy may develop because of intravascular coagulation with consumption of major clotting factors, excessive fibrinolysis in reaction thereto, and more often a combination of both.[6]

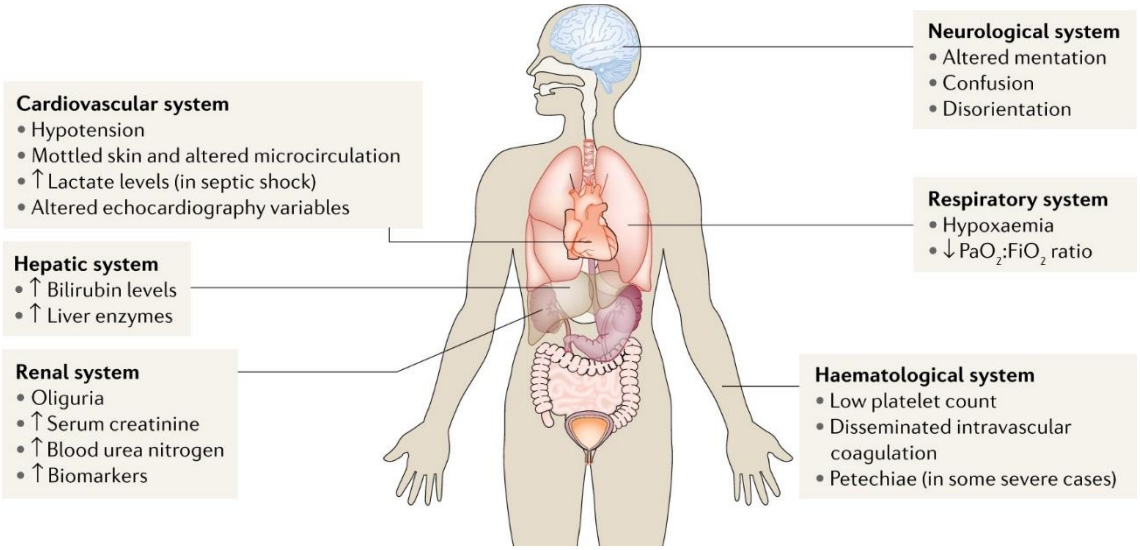

Figure 2. System damage resulting from sepsis (Image source: Lelubre, C., Vincent, JL. Mechanisms and treatment of organ failure in sepsis. Nat Rev Nephrol 14, 417–4272018). https://doi.org/10.1038/s41581-018-0005-7)

Predisposing factors

Predisposing factors include:

- Neonatal period
- Diabetes mellitus
- Cirrhosis
- Leukopenia (especially that associated with cancer or treatment with cytotoxic medications)
- Invasive devices (including endotracheal tubes, vascular or urinary catheters, drainage tubes, and other foreign materials)
- Prior treatment with antibiotics or corticosteroids
- Recent hospitalization (especially in an intensive care unit)

Complementary examinations

Healthcare providers also perform tests that check for signs of infection or organ damage. Some of these tests are used to identify the germ that caused the infection that led to sepsis (this testing might include blood cultures looking for bacterial infections or fungal infections, or tests for viral infections, like COVID-19 or influenza).

Other tests are also done to determine signs of infection including proadrenomedullin, procalcitonine, C-reactive protein, high leukocyte count.

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And finally, blood tests for organ damage are also done. These include lactate, ALT, AST, bilirubin, blood urea, serum creatinine, International normalized ratio (INR), platelet count, fibrinogen, D-dimer, oxygen level –partial pressure of arterial oxygen PaO2-, carbon dioxide level –partial pressure of carbon dioxide PCO2-, and bicarbonate.

Treatment

Healthcare providers should immediately evaluate and treat people who might have sepsis. Research shows that rapid, effective sepsis treatment includes:

- Giving appropriate treatment, including antibiotics, as soon as possible.
- Maintaining blood flow to organs (fluids or vasoactive medication).
- Operating, when necessary, to remove tissue damaged by the infection.

Importance of early recognition

Early recognition and treatment of sepsis is key for improving outcomes. Currently, this is challenging as clinical judgment and abnormal vital signs lack sufficient sensitivity. Some blood test markers can indicate a suspected infection, but these do not necessarily define sepsis and some, like middle region of proadrenomedullin or lactate, may only be altered in seriously ill patients. Several attempts have been made to define different scores to identify sepsis, but their application to the early detection of sepsis is limited. The most recent attempt is the International Consensus for Pediatric Sepsis and Septic Shock[7] (the Phoenix Sepsis Score, Figure 3). Published in 2024, the aim of the Phoenix Sepsis Score is to update and evaluate sepsis and septic shock criteria in children. However, the proposed criteria are not predictive of early sepsis and only establish a diagnosis with an evolved patient.

Given these challenges, we aim to develop machine learning based algorithms for early recognition and prediction of sepsis in pediatric patients admitted to Pediatric Intensive Care Units (PICUs).

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Table. The Phoenix Sepsis Score[a]

Variables	0 Points	1 Point	2 Points	3 Points
Respiratory, 0-3 points				
	Pao_2:FIo_2 ≥400 or Spo_2:FIo_2 ≥292[b]	Pao_2:FIo_2 <400 on any respiratory support or Spo_2:FIo_2 <292 on any respiratory support[b,c]	Pao_2:FIo_2 100-200 and IMV or Spo_2:FIo_2 148-220 and IMV[b]	Pao_2:FIo_2<100 and IMV or Spo_2:FIo_2 <148 and IMV[b]
Cardiovascular, 0-6 points				
		1 Point each (up to 3)	2 Points each (up to 6)	
	No vasoactive medications[d]	1 Vasoactive medication[d]	≥2 Vasoactive medications[d]	
	Lactate <5 mmol/L[e]	Lactate 5-10.9 mmol/L[e]	Lactate ≥11 mmol/L[e]	
Age based[f]				
	Mean arterial pressure, mm Hg[g]			
<1 mo	>30	17-30	<17	
1 to 11 mo	>38	25-38	<25	
1 to <2 y	>43	31-43	<31	
2 to <5 y	>44	32-44	<32	
5 to <12 y	>48	36-48	<36	
12 to 17 y	>51	38-51	<38	
Coagulation (0-2 points)[h]				
		1 Point each (maximum 2 points)		
	Platelets ≥100 × 10^3/μL	Platelets <100 × 10^3/μL		
	International normalized ratio ≤1.3	International normalized ratio >1.3		
	D-dimer ≤2 mg/L FEU	D-dimer >2 mg/L FEU		
	Fibrinogen ≥100 mg/dL	Fibrinogen <100 mg/dL		
Neurological (0-2 points)[i]				
	Glasgow Coma Scale score >10; pupils reactive[j]	Glasgow Coma Scale score ≤10[j]	Fixed pupils bilaterally	
Phoenix sepsis criteria				
Sepsis	Suspected infection and Phoenix Sepsis Score ≥2 points			
Septic shock	Sepsis with ≥1 cardiovascular point(s)			

Figure 4. The Phoenix sepsis score laboratory values

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