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Pediatric Sepsis: Clinical Markers

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Abstract

Pediatric sepsis can be caused by infection agents such as viruses, bacteria, protozoa, or their toxins. Clinical features cover a remarkably wide spectrum. Early recognition of the disease and prompt initiation of therapy substantially improve mortality and the outcome of potential complications. After an initial phase of very mild symptoms, the spread of microbes or toxins in the bloodstream presents as septic shock through vasoregulatory disturbance, absolute or relative intravascular volume loss, and consequential tachycardia and hypotension. The most common accompanying symptom is fever. In physical examination, features such as altered mental status, excess respiratory effort, tachycardia, and prolonged capillary refill time are present at an early stage of the disease. Laboratory tests for the assessment of early stage severity and subsequent monitoring of treatment efficacy include point-of-care arterial blood gas analysis and lactate assay. In early stage disease, it is imperative to promptly start adequate antimicrobial and supportive treatment once bacterial cultures have been taken. Despite the availability of a wide range of laboratory and imaging tests today, diagnosis and severity assessment of sepsis still primarily rely on medical history and clinical examination. In light of this, it is possible for trained care providers to detect the early signs of a septic child during repetitive physical examinations. This is still the mainstay of diagnosis and can provide in all care settings a significant reduction in therapeutic delay; this, in turn, helps to reduce sepsis-related mortality and morbidity.

Keywords
► sepsis
► physical examination
► evaluation
► septic shock
► children
► infection
► review

Introduction

Pediatric sepsis is the most common, deadly disease in both the developing and developed world. Despite modern vaccines, antibiotics, and intensive care, the number of septic patients rises year after year. However, sepsis still continues to be the most frequently underdiagnosed entity. Timely and appropriately started therapy is highly cost-effective, whereas the 3-day mortality of untreated cases is 100%. In light of all this, our fundamental goal is the early diagnosis of sepsis.[1–4]

Sepsis is a clinical syndrome resulting from a systemic inflammatory response (SIRS) evoked by severe infection.[5] Physiological changes during SIRS are consequences of pathological immune-dysregulation leading to inflammation, microcirculatory disturbance, abnormal vasodilation or vasoconstriction, increased capillary permeability, and abnormal white blood cell accumulation.

Although inflammation is vital in fighting against infections, the immune response during sepsis is abnormal, with the balance between pro- and anti-inflammatory mediators disrupted, culminating in damage to the body and multiple organ failure.[6–12] Evidence exists that hereditary or acquired immune deficiency may particularly misdirect the immune response to pathogens, thus eliciting a more severe or more rapidly progressing clinical manifestation.[10]

Age, vaccination and immunological status, medical history, and chronic diseases may help to identify vulnerable patient groups.[13–15]

In establishing the diagnosis, the so-called systemic inflammatory response syndrome (SIRS) criteria are helpful. Of course, SIRS may also develop as a reaction evoked by other than pathogenic microorganisms. The confirmation of a noninfectious origin (e.g., trauma, burn, pancreatitis) may be useful in avoiding inadequate antibiotic therapy. However, confirmation of infection through microbiological (blood, liquor, stool, or urine culture, polymerase chain reaction [PCR]) or radiological (chest X-ray) means should not delay initiation of adequate treatment (including prompt antimicrobial therapy). A delay in diagnosis and therapy significantly increases mortality.[14–17] It is also important to assess initial mental status, respiratory function, intravascular volume status, and cardiac, hepatic, renal, hematological, and coagulation functions since these parameters may assist in finding the right level of therapy aggressiveness with the goal to improve significantly prognosis.[18–21]

Diagnosis

We must remember, however, that even though countless laboratory and imaging tests are available today, sepsis essentially remains a clinical diagnosis. Even consensus criteria for diagnosis of sepsis and septic shock may fail. Only two-third of patients treated at intensive care units for severe sepsis or septic shock satisfied the consensus criteria.[22]

The systemic inflammatory response syndrome, which was first introduced by the American College of Chest Physicians and the Society of Critical Care Medicine, helps us to detect the systemic inflammatory response, its severity, and the choice of therapy.[23–25] In 2005, the International Pediatric Consensus Conference adapted the definition of SIRS, sepsis, and related diagnoses to age-specific normal values of childhood (►Tables 1–4).

However, clinical presentation, physical examination findings, and laboratory test results are neither specific nor sensitive. Initial symptoms such as fever, cold chills, tachycardia and elevated respiratory rate are too general and often accompany merely a trivial viral infection. Prompt antibiotic therapy started in general upon these symptoms would only aggravate antibiotic resistance, a phenomenon already significantly observed worldwide. This may also cause unnecessary hospitalizations, with financial and social demands thereof. On the other hand, starting therapy only after occurrence of obvious clinical symptoms such as hemodynamic instability or altered mental status with impeding multiple organ failure unequivocally results in drastically elevated mortality.

Table 1 Definitions of SIRS, infection, sepsis, severe sepsis, and septic shock[a]

SIRS[a,c]	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°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-h period or for children <1 y old: bradycardia, defined as a mean heart rate <10th percentile for age in the absence of external vagal stimulus, beta-blocker drugs, or congenital heart disease, or otherwise unexplained persistent depression over a 0.5-h 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 2
Septic shock	Sepsis and cardiovascular organ dysfunction as defined in ►Table 2

Abbreviations: SD, standard deviation; SIRS, systemic inflammatory response syndrome.
[a]Based on data from Goldstein et al.[5]
[b]Core temperature must be measured by rectal, bladder, oral, or central catheter probe.
[c]See ►Table 3 for age-specific ranges for physiological and laboratory variables.

Table 2 Organ dysfunction criteria[a]

Cardiovascular dysfunction	Despite administration of isotonic intravenous fluid bolus $\geq$40 mL/kg in 1 h:
	Decrease in BP (hypotension) 5th percentile for age or systolic BP < 2 SD below normal for age
	or
	Need for vasoactive drug to maintain BP in normal range (dopamine >5 µg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose)
	or two of the following:
	Unexplained metabolic acidosis: base deficit >5 mEq/L
	Increased arterial lactate more than two times upper limit of normal
	Oliguria: urine output <0.5 mL/kg/h
	Prolonged capillary refill: >5 s
	Core to peripheral temperature gap >3°C
Respiratory	PaO_2/FIO_2 < 300 in the absence of cyanotic heart disease or preexisting lung disease
	or
	$PaCO_2$ >65 Torr or 20 mm Hg over baseline $PaCO_2$
	or
	Proven need or >50% FiO_2 to maintain saturation >92%
	or
	Need for nonelective invasive or noninvasive mechanical ventilation
Neurologic	Glasgow Coma Score < 11
	or
	Acute change in mental status with a decrease in Glasgow Coma Score $\geq$3 points from abnormal baseline
Hematological	Platelet count of 80,000/mm^3 or a decline of 50% in platelet count from highest value recorded over the past 3 d (for chronic hematology/oncology patients) or
	International Normalized Ratio > 2
Renal	Serum creatinine more than two times upper limit of normal for age or twofold increase in baseline creatinine
Hepatic	Total bilirubin < 4 mg/dL (not applicable for newborn)
	or
	ALT two times upper limit of normal for age

Abbreviations: ALT, alanine aminotransferase; BP, blood pressure; SD, standard deviation.
[a]Goldstein et al.[5]

Due to the severe nature of this clinical diagnosis and the potential for complications, all care providers should use a readily available, simple, rapidly and multiply repeatable, internationally accepted system of criteria with which disease progression and therapeutic efficacy could be monitored simply. Accepted in February 2016, the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) are perfectly suitable for this.[24]

This article summarizes the most important objective clinical parameters, thus facilitating early recognition of sepsis.

Body Temperature

One of the key SIRS criteria is abnormal body temperature, be it hyperthermia or hypothermia. Fever is an adaptive response to infection. In vitro and animal experimental data confirm that cellular and humoral immunity shows increased antimicrobial activity when temperature is higher.[25]

In children, the most frequent clinical sign of a septic patient is a change in body temperature, mostly elevated core temperature. When assessing central body temperature, tympanic, rectal, urinary cystic, oral, or esophageal measurement sites can be used. Today, the tympanic temperature is most widely used during primary assessment.

Hypothermia is an independent prognostic factor in sepsis mortality assessment. Adult studies report an increased 90-day mortality when hypothermia develops during sepsis. One-fifth of septic patients are hypothermic at hospital admission. The mortality of these patients is twice as high, independent of age, disease severity, and concomitant diseases.[26–28] Relevant studies have found no underlying etiological or unambiguously abnormal immunological

Table 3 Pediatric age groups for severe sepsis definitions[a]

Newborn	0 d to 1 wk
Neonate	1 wk to 1 mo
Infant	1 mo to 1 y
Toddler and preschool	2–5 y
School age child	6–12 y
Adolescent and young adult	13 to <18 y

[a]Goldstein et al.[5]

reasons. Elevated levels of fractalkine have been confirmed in hypothermia; it is a chemokine released upon endothelial cell damage with a possible role in the ensuing vascular dysfunction, but its clinical significance requires further research.[26] Other studies on septic patients also reported increased mortality and hypothermia-associated lymphopenia, which is an early clinical predictor of sepsis-induced immunosuppression.[29] Several studies reported on absolute leukocytopenia and lymphopenia in newborns receiving therapeutic hypothermia for hypoxic–ischemic encephalopathy.[30]

Altered Mental Status

An important part of early assessment is the evaluation of mental status. It is outstandingly important since it can be performed right upon contact with the patient, with no need for major physical, equipment-based or laboratory methods. It also lends itself to continuous, noninvasive monitoring of the mental status of the child.

In addition to the usual subjective description (irritability, nervousness, disorientation, lethargy, somnolence, stupor, coma), it can be continuously objectivized in real time using the internationally recognized Glasgow Coma Scale. Interestingly, in the emergency room, patients more frequently presented with an altered mental status (38.2%) than with excess of respiratory effort (30.2%).[31] Clinical observations indicate that Glasgow Coma Scale scores of 11 or less and acute changes in mental status of at least two points are correlated with disease severity. Changes in mental status are affected by the general effects of inadequate tissue

oxygenation in the body, insufficient tissue perfusion, potential hypoglycemia, and significant electrolyte disturbances. Of course, in septic events with an accompanying central nervous system infection (i.e., meningoencephalitis), local cerebral inflammation, circulation, and coagulation disturbances may also alter mental status.

Respiratory System

The examination and continuous monitoring of the respiratory system is indispensable when dealing with septic children. Strict observation and patency management of the airways is a key factor to ensure gas exchange. Rapid and objective assessment of the respiratory system is possible through tests such as age-specific respiratory rate, respiratory effort, auscultation, transcutaneous oxygen saturation, or blood gas analysis. Respiration rate is one of the most sensitive indicators of disease severity.[32]

Surprisingly, respiratory alkalosis of a central origin is often observable in early stage sepsis even before the onset of metabolic acidosis. As the disease progresses, the release of proinflammatory factors (cytokine storm) leads to a compromised lung compliance independent of age. In physical examination, nasal flaring, accessory respiratory muscle use, and appearance of suprasternal, subcostal, and sternal retractions may indicate, even before laboratory tests, the presence of acute lung injury (ALI) or the acute respiratory distress syndrome (ARDS), which are frequent complications confirmable by radiological (ultrasound, chest X-ray) and laboratory testing (arterial blood gas analysis).[33] Peripheral circulatory failure developing as the process continues, coupled with the onset of metabolic acidosis as its consequence, causes the respiratory rate to increase further, now as a compensatory mechanism to maintain respiratory alkalosis.

This compensatory mechanism is dedicated to two possible reasons. A substantial number of septic cases have lower respiratory tract infection in the background, and gas exchange is compromised due to the primary involvement of the lungs. The most common cause of the aforementioned ALI or ARDS is sepsis. Locally released proinflammatory mediators are the underlying causes of

Table 4 Age-specific vital signs and laboratory variables[a,b]

Age group	Heart rate (beats/min)		Respiratory rate (breaths/min)	Leukocyte count (leukocytes $10^3/mm^3$)	Systolic blood pressure (mm Hg)
	Tachycardia	Bradycardia			
0 d to 1 wk	>180	<100	>50	>34	<65
1 wk to 1 mo	>180	<100	>40	>19.5 or <5	<75
1 mo to 1 y	>180	<90	>34	>17.5 or <5	<100
2–5 y	>140	NA	>22	>15.5 or <6	<94
6–12 y	>130	NA	>18	>13.5 or <4.5	<105
13 to <18 y	>110	NA	>14	>11 or <4.5	<117

[a]Goldstein et al.[5]
[b]Lower values for heart rate, leukocyte count, and systolic blood pressure are for the fifth and upper values for heart rate, respiration rate, or leukocyte count for the 95th percentile.

diffuse alveolar and pulmonary capillary injury, a process of exudative nature in the early phase. This results in an increased permeability of the alveolar–capillary barrier, upon which the alveoli get filled up with a protein-rich fluid. The process primarily affects type I pneumocytes. Type II, surfactant-producing cells are more resilient against the injury; however, damages to surfactant production lead to further deterioration of lung compliance and atelectasis. Neutrophils, tumor necrosis factor (TNF), various leukotrienes, macrophage inhibition factor, and other mediators released during sepsis have a substantial role in the process. The damaged alveolus collapses and is unable to refill with air at the next inspiration, thus escalating the ensuing atelectasis. This results in an early loss of functional residual capacity, an already limited resource in children, and, finally, global respiratory failure occurs. To compensate for the loss of lung compliance, accessory respiratory muscle effort is necessary by increasing respiration minute volume.[34–44]

The excessive respiratory effort may require up to 40% of the base metabolic rate and cardiac output. To avoid fatigue and consequential cardiorespiratory collapse in children, it is important to continuously monitor respiratory effort by physical examination and noninvasive transcutaneous saturation measurement, which is also informative of heart rate. Continuous observation helps determine when and how to start respiratory support, as well as facilitates close therapeutic efficacy monitoring once started.[39,40,45–47]

Cardiovascular System

Knowledge of age-specific heart rate, stroke volume, blood pressure, and systemic vascular resistance values, as well as their changes in response to the septic cascade triggered by infectious agents is indispensable for disease recognition and appropriate management. These are parameters with substantial differences between adults and various pediatric groups.[41–43]

Clinically informative assessment of the cardiovascular system also relies on a simultaneous evaluation of multiple parameters. During diagnosis and for rapid monitoring of therapeutic efficacy, key markers include the physical examination of heart rate and capillary refill time, and laboratory evaluation of arterial lactate levels and metabolic acidosis. Assessment of the cardiovascular system is assisted by noninvasive or invasive blood pressure measurement and continuous urinary output monitoring.

The triad triggered by inflammatory response, that is, fever, tachycardia, and altered vasoregulation, is a common set of symptoms in incipient pediatric infection. Suspicion of a septic event should be raised if these symptoms are accompanied by altered mental status, irritability, disorientation, and disturbed interpersonal contact. Similar to the respiratory system, the basis for the process is abnormal inflammation and dysregulation triggered and maintained by pathogens. The mechanisms leading to cell damage are not yet fully understood; however, postmortem data indicate a central role of endothelial damage in the evolution of the process.

Provoked by the injury, abnormal vascular tone, increased microvascular permeability, and leukocyte accumulation initially lead to relative and then absolute intravascular fluid deficit. Early symptoms of fluid deficit include an elevated heart rate and increased capillary refill time due to poor tissue perfusion. Owing to compensatory mechanisms, blood pressure drop is a late-onset symptom in most pediatric cases, together with reduced urinary output (< 1 mL/kg/hour).

Heart Rate

Similar to respiratory rate, heart rate values are strongly age-specific. Changes in heart rate are a nonspecific sign, but it is a highly sensitive early stage indicator of relative or absolute fluid deficit, a common accompanying feature of pediatric shock; it is also one of the mechanisms to compensate for ongoing cardiac dysfunction or altered vascular resistance.[43]

Heart rate variability (HRV) is an indicator of the heart's neurovegetative activity and autonomous function. It describes the heart's ability to continuously vary the time interval from heartbeat to heartbeat (RR interval) in response to changes in internal and external environmental demand; it is thus a measure of cardiac adaptability. Neither its etiology nor its exact clinical significance is clear yet; however, reduced HRV shows an association with poor outcomes in septic patients. HRV can predict the development of septic shock and multiple organ failure in sepsis.[44,48–51] In newborns, it predicts blood culture positive septic cases independent of laboratory findings.[52–54] An association is also detectable between hypercytokinemia, elevated interleukin (IL)-6, levels and reduced HRV in septic patients.[55]

Further research is needed to clarify the exact mechanisms of abnormal HRV and autonomous nervous system disorders.[56–58]

Tissue Perfusion

Microcirculation is the most important target in the septic process. Reduction in the number of functioning capillaries compromises oxygen utilization.

Several approaches exist to assess damaged microcirculation. The simplest, quickest, and most reproducible one is the measurement of capillary refill time. A capillary refill time of longer than 3 seconds is regarded as abnormal and prolonged.

Additional signs of disturbed microcirculation include altered skin temperature and skin color (paleness, mottling). Prolonged capillary refill time in incipient sepsis is a reliable indicator of vital organ microcirculation.

There are, of course, equipment-based tests available to assess the process. Spectrophotometry and sublingual/gastric assessment of orthogonal spectral polarization have not been established in daily routine diagnostics.[59–63]

Based on changes in hemodynamic response, cardiac output, and systemic vascular resistance, two forms of shock can be distinguished.[64]

Clinical manifestation may identify shock as being of the warm (hyperdynamic) type, characterized by low systemic vascular resistance, quick and prompt capillary refill time, warm skin all over the body, Corrigan's pulse, and wide pulse pressure (difference between systolic and diastolic blood pressure).

Children's heart rates are physiologically higher than those of adults. So there is much less opportunity to further increase heart rate as a compensatory mechanism than in adults. Children therefore tend to raise their systemic vascular resistance in response to blood pressure decrease and to maintain it in the normal range.

In cold (hypodynamic) shock, systemic vascular resistance is high, the skin is cold and damp, a so-called cold–warm boundary can be detected, the capillary refill time is prolonged, the pulse is suppressible, and the pulse amplitude is narrow. There is, of course, a limit beyond which further vasoconstriction leads to a decrease in cardiac output, hypotension, circulatory failure, and eventually death, unless appropriate intervention is made. Earliest possible recognition and treatment of cold shock persisting in spite of normal blood pressures is therefore a key outcome factor.[65]

Tissue perfusion, capillary refill time, and cold–warm boundary assessment are excellent markers in both shock severity evaluation and therapeutic efficacy monitoring.[66–71]

Blood Pressure
Blood pressure drop is a very late-phase manifestation in pediatric shock; therefore, normal age-specific blood pressure values early in the process do not help to exclude the diagnosis. They do help, however, differentiate between cold and warm shock in a noninvasive way. Treatment goals include restoring an age-specific normal blood pressure within the golden hour. Each hour spent outside the age-specific normal blood pressure range and with a capillary refill time of at least 3 seconds will double the mortality.[72]

Various hemodynamic values measured at emergency departments are characterized by various mortality estimates: normal heart rate, 1%; tachycardia/bradycardia, 3%; hypotension and capillary refill time <3 seconds, 5%; normotension and prolonged capillary refill time, 7%; hypotension and prolonged capillary refill time, 33%. When hemodynamic values are normalized by treatment based on ACCM/PALS (American College of Critical Care Medicine-Pediatric Advanced Life Support) guidelines, a 40% reduction in mortality can be observed, independent of the patient's group assignment at treatment initiation.[40,73]

Subcutaneous Bleeding
Skin changes, that is, color and temperature described previously, mainly depend on shock type. In either type, thrombocytopenia developing as part of the septic process causes petechiae, and an early physical symptom of disseminated intravascular coagulation is the appearance of purpura. All patients developing purpurae should be considered potentially severe cases. When suspecting invasive meningococcal infection, parenteral antibiotic treatment must be started immediately, even before arrival at the hospital.

Likewise, upon detection of grave thrombocytopenia, extensive, cause-finding examinations and coagulation tests must be performed.

Sepsis-induced disseminated intravascular coagulation may result in complement-mediated thrombotic microangiopathy. The process may culminate in necrotizing fasciitis requiring a surgical solution.[74–76]

The most severe manifestation of the process is purpura fulminans, a life-threatening condition characterized by disseminated dermal and systemic thrombosis, skin bleeding and dermal necrosis, systemic microcirculation disorder, and multiple organ failure. The pathogenesis of the process is rooted in intrinsic coagulation cascade disorders and hereditary or acquired protein C deficiency.[77–80]

Laboratory Investigations
Owing to the nature of the septic process, laboratory tests are run in parallel with treatment initiation while diagnosis is still being established. In full-blown septic shock, antimicrobial treatment and golden-hour therapy must not be delayed by laboratory tests (blood panel, inflammatory parameters, liver and kidney function tests).

Microbiology
Microbiological tests should take place before the onset of antimicrobial treatment, if possible, but must in no way cause significant delay (longer than 45 minutes).

It is recommended to collect an aerobic and an anaerobic blood culture sample from at least one sampling site, but preferably from two different sampling sites.[81–85] From older children, volumes of 3 to 10 mL should be sampled, which reduces incidence of false-negative cases.[86–96]

In addition to conventional microbiological diagnosis, an alternative way of pathogen identification is PCR. Multiple PCR is well-known to deliver faster results, but requires a greater volume of blood, and is more prone to false-positive results and does not facilitate antibiogram assessment.[96–102]

White Blood Cell Count
Age-specific white blood cell count deviations and a percentage of immature forms higher than 10% are included in SIRS criteria as well. In suspicion of sepsis, the most fundamental laboratory test is total white blood cell count. Bacterial infection may entail both neutrophilia and neutropenia. The greater the proportion of immature white blood cells, the greater the chance of an infectious origin behind SIRS.[103]

Inflammatory Markers
Additional inflammatory markers recommended for use are sedimentation rate, C-reactive protein, IL-1b, IL-6, IL-8, TNF-α, leukotriene B4, and procalcitonin (PCT). Because early disease symptoms are nonspecific, combined use of biomarkers is recommended for quick diagnostic judgment, rapid treatment initiation, and therapeutic efficacy monitoring, thereby significantly improving specificity and sensitivity.[103–106]

Inflammatory marker assessment is useful in predicting severe bacterial infection in infants and children with no clinically definite focal infectious lesions on hospital admission.[107,108]

In children aged 2 to 17 years, combined use of metabolic and inflammatory parameters helps identify patients who require intensive care. Information on multiple laboratory parameters is especially helpful in determining disease

severity also in situations where care providers are less experienced in pediatric care.[109]

Patients who satisfy SIRS criteria and have elevated IL-6 levels are more likely to develop complications (pneumonia, multiple organ failure) and have a greater mortality risk.[110] On the other hand, declining levels are a good indicator of therapeutic efficacy as early as day 2 of antibiotic treatment and have a positive predictive value in SIRS with an infectious origin.[111]

The soluble form of the CD14 cellular surface antigen is called presepsin (P-SEP). CD14 is a diagnostic and prognostic marker in adult sepsis. According to a prospective study, P-SEP in late-onset sepsis of premature babies is a potentially useful biomarker in both establishing diagnosis and treatment monitoring.[105]

Repeat assessment of markers with various half-lives helps confirm diagnosis and is suitable for disease activity monitoring; on a longer run, it also assists in judging the duration of antimicrobial therapy. PCT is more likely to help distinguish between viral and bacterial pathologies, but has a limited significance in determining the septic process in children as compared with adults.[103,106–121]

Platelet Count and Hemostasis

Disseminated intravascular coagulation developing during sepsis is affected not only by basic coagulation factors but also by endothelial injury caused by thrombocytes and proinflammatory factors. Coagulation system assessment is imperative in critically ill patients. The most important tests include platelet count, partial thromboplastin time, international normalized ratio, and activated partial thromboplastin time.

In sepsis, thrombocytopenia is well correlated with disease severity and is an early predictor of poor outcomes. Of various other biomarkers, elevated levels of soluble thrombomodulin were associated with higher 90-day mortality and multiple organ failure.

Endothelial injury and consequential coagulopathy play a central role in sepsis pathogenesis and facilitate prognostic judgment.[122–130]

Acid–Base Tests

In critically ill patients, the most common bedside laboratory test is blood–gas analysis to assess acid–base homeostasis. If we define sepsis as a malignant intravascular inflammatory reaction, it is easy to see how an uncontrolled release of inflammatory mediators and complement activation lead to tissue oxygen deficit and consequential metabolic acidosis through increased oxygen consumption due to altered metabolic autoregulation and through reduced oxygen availability.[131] The process is only aggravated by microcirculatory and endothelial dysfunction, and an initially relative, and later absolute, fluid deficit. Testing for pH and base deficit provides a quick and easy-to-represent picture of the body's metabolic status and therapeutic efficacy.

Lactate

Tissue lactate assessment is a good indicator of both appropriate tissue supply and aerobic glucose utilization. Elevated lactate levels are a good predictor of shock and tissue hypoperfusion even in normotensive patients. In suspicion of septic shock, it is recommended to test for lactate level at the time of diagnosis because it is known to be elevated in early stage shock. It is an excellent therapy monitoring marker; in the presence of elevated levels, therapeutic objectives include restoring a physiological lactate level.[132–134]

Pediatric evidence is limited, but one study has found that children satisfying SIRS criteria and having a venous lactate level greater than 4 mmol/L at diagnosis are more likely to develop organ dysfunction in the first 24 hours of treatment.[135]

Blood Glucose

Blood glucose testing is of fundamental importance in all critically ill children. Hypoglycemia, especially in infants, can be explained by altered metabolic utilization and a decline in enteral intake due to a poor general condition. Hypoglycemia, of course, needs immediate correction to avoid potential harmful neurologic outcomes. On the other hand, a disturbed glucose homeostasis, peripheral insulin resistance, and stress hormone release can lead to hyperglycemia as well.[136,137] Stress-induced hyperglycemia has been reported in cases of meningococcemia.[138,139]

Both hypoglycemia and hyperglycemia have been reported to be associated with higher mortality in newborns.[140] Since a correlation exists between hypercytokinemia and blood glucose levels in septic patients, adequate glycemic control is important during therapy. Under tight control, it is possible to avoid hypoglycemia induced by intensive insulin therapy.[141–143]

Calcium

Intracellular calcium has a major role in maintaining vascular tone and also affects myocardial function. Its assessment is important in any shock processes including septic shock. Reduced calcium levels are a frequent symptom in critically ill patients, most likely due to hormonal milieu alterations, but with a pathophysiology not yet fully understood.[144–146] In sepsis, reduced calcium levels may contribute to a decreased myocardial function.[147,148] Upon detecting a low ionized calcium level (< 1.1 mmol/L) or symptomatic hypocalcemia (positive Chvostek or Trousseau sign, spasms, prolonged QT interval) during the septic process, immediate correction of the hypocalcemia is recommended.[45,149]

Conclusion

In summary, sepsis continues to play a significant role in childhood mortality today. In developed countries, a half of all premature and newborn mortality is originated from this disease. Sepsis mortality declines as children get older. Its significance is made even greater by a potential for serious long-term consequences in survivors due to tissue perfusion disturbance and subsequent multiple organ failure. Establishing the diagnosis of sepsis is not simple in any age. However, the nature of the process classifies it as what we call a time-factor disease, making sepsis diagnosis and treatment a real emergency task. Early recognition is the

first step down the road toward reduced mortality rates. This requires continuous education of patients and their relatives to recognize early warning signs in vulnerable populations. Despite the availability of a wide range of laboratory, microbiological, and imaging tests today, sepsis continues to be a primarily clinical diagnosis. Medical history and a thorough physical examination are indispensable for diagnostic judgment. Owing to the dynamic nature of sepsis pathophysiology, evaluation and reevaluation of physical examination findings and bedside laboratory tests are indispensable not only in early diagnosis but also in controlling the therapeutic process. Most importantly, sepsis must be kept in mind as a potential diagnosis in almost every child in the emergency room when an infection cannot be excluded.

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