Chapter 11

Sepsis

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A six-year-old female with newly diagnosed acute lymphoblastic leukemia is in day two of induction chemotherapy. She has developed fever with diarrhea and abdominal pain. An abdominal CT demonstrates typhlitis, and a short segment of necrotic large bowel and free air under the diaphragm. She requires emergent surgery for partial bowel resection.

Her current vital signs are: blood pressure 79/31, heart rate 163/min, respiratory rate 32/min, SpO_2 89% on room air, currently on nasal cannula 2L with SpO_2 increased to 93%. Weight is 26 kg.

Chest X-ray shows bilaterally increased interstitial markings. A gallop is heard on cardiac exam. Capillary refill time is three to four seconds peripherally and she is cool in the extremities. The patient has already received 80 cc/kg in crystalloid and has not produced urine since spiking the fever. A recent arterial blood gas showed a pH 7.23, pCO_2 32, pO_2 65, bicarbonate 19, base deficit −7, and a lactate of 5.1.

What Is Sepsis?

Sepsis is a syndrome caused by over-activation of the immune response secondary to an overwhelming infection. This inflammatory reaction leads to physiologic and biochemical abnormalities in the body, which define the clinical diagnosis of sepsis and septic shock. Sepsis and septic shock are leading causes of mortality in critical care medicine and can significantly raise the risk of anesthetic and surgical mortality.

What Is Systemic Inflammatory Response Syndrome (SIRS)?

Recent revisions of the definition of the systemic inflammatory response syndrome (SIRS) have simplified the definition of the inflammation associated with infection, which, when combined, define sepsis. The new definition of SIRS includes two or more of the following: temperature >38°C or <36°C, heart rate >90/min, respiratory rate >20/min or $PaCO_2$ <32 mmHg, or white blood cell count >12,000/mm^3 or <4,000/mm^3 or >10% immature bands. This definition currently applies to adults only, but similar criteria are used for children. These were set forth along with age specific vital signs and were defined in 2005 by an international consensus conference. These vital signs, listed in Table 11.1, are used to define the SIRS response for pediatrics.

SIRS

- Temperature greater than 38.5°C or less than 36°C
- Tachycardia or, for children less than 1 year of age, bradycardia, without other explanation
- Tachypnea or requirement for mechanical ventilation without underlying respiratory disease
- Leukocytosis

Sepsis

- SIRS with suspected or proven infection

Severe Sepsis

- Sepsis plus cardiovascular dysfunction, respiratory failure, or two or more other organ failures

Septic Shock

- Sepsis with multiorgan dysfunction

What Is the Definition of Septic Shock?

When patients meet the criteria for SIRS and there are signs of end-organ dysfunction, patients meet criteria for septic shock. When patients have multiple organ systems affected, they meet the criteria for multiorgan dysfunction syndrome (MODS), a syndrome which significantly increases overall mortality.

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Table 11.1 Vital sign reference by age used to define the systemic inflammatory response syndrome in children

Age	Tachycardia (beats/min)	Bradycardia (beats/min)	Respiratory rate (breaths/min)	Normal leukocyte count (x10^3/mm)	Systolic blood pressure (mmHg)
0 days – 1 week	>180	<100	>50	<34	<59
1 week – 1 month	>180	<100	>40	5–19.5	<79
1 month – 1 year	>180	<90	>34	5–17.5	<75
2 years – 5 years	>140	N/A	>22	6–15.5	<74
6 years – 12 years	>130	N/A	>18	4.5–13.5	<83
13 years – 18 years	>110	N/A	>14	4.5–11	<90

What Are Important Diagnoses to Consider in a Child with Sepsis?

The clinical presentation of sepsis emerges from a combination of host factors, such as genetics and predisposing conditions, and pathogenic factors, including virulence and pathogen load. The pathogen can be a wide range of infections, including all variety of viral, bacterial, and fungal disease. The likelihood of each different pathogen to cause infection varies by patient comorbidity. For example, the youngest children and babies are more vulnerable to viral illness and spontaneous bacterial infection, while older patients can have medical comorbidities such as rheumatologic or oncologic disease that can predispose to sepsis because of a weakened immune response.

Viral illnesses such as influenza, rhinovirus, and Epstein-Barr virus can all present with symptoms that can meet clinical criteria for sepsis. The most common and obvious cause of sepsis include bacterial infections. These can occur in many different sites as manifestation of pneumonia, urogenital tract infection, and blood stream infections.

Fungal infection can also cause sepsis, though the presentation of this type of disease tends to be more indolent and is significantly more dependent on a previously weakened immune response.

The patient in the vignette at the beginning of the chapter meets clinical criteria for septic shock with end-organ dysfunction including respiratory compromise, renal dysfunction, and hemodynamic failure. She also has leukemia and has recently undergone chemotherapy, leading to significant immunosuppression. Both of these represent significant predisposing comorbidities. Typhlitis is a neutropenic colitis seen in oncologic patients leading to a dilated large bowel, with high chance of perforation, which is the likely cause of septic shock in this patient.

What Are the Most Common Sites for Infection Leading to Sepsis?

The cause of severe sepsis can vary significantly by location, age, and institution. The most common site of primary infection in severe sepsis is the respiratory system followed by bloodstream infection, genitourinary tract infections, abdominal, and central nervous system infections.

What Are the Most Common Pathogens Leading to Severe Sepsis?

Common bacterial causes include both gram-negative bacteria including *Escherichia coli, Klebsiella* species and *Pseudomonas aeruginosa* and gram-positive bacteria such as *Staphylococcus* and *Streptococcus*. It is important to consider early involvement of infectious disease specialists and to follow local antibiotic guidelines for appropriate treatment of at-risk populations to ensure broad coverage to cover all likely causative agents. Without appropriate source control, septic shock will continue to worsen and will lead to severe morbidity.

What Is the Incidence and Most Common Age of Presentation of Sepsis?

Sepsis and septic shock are leading causes of worldwide morbidity and mortality and a leading cause of critical illness. Approximately 1/3 of mortality in tertiary pediatric intensive care units (PICUs) is attributable to sepsis. A recent international survey of

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PICUs demonstrated a prevalence of 8.2% among patients admitted to a PICU with a median age of 3 years and a range from 0.7 years to 11 years.

What Is the Pathophysiology of Septic Shock?

The understanding of the cause of sepsis is incomplete, but the fundamental etiology is a significant release of vasoactive cytokines and bacterial derived products. Certain pathogens contain products such as lipopolysaccharides that have a higher potential to cause this cytokine storm. Similarly, certain individuals will have a more exaggerated response to pathogenic products, which will also lead to a higher cytokine response.

The specific response of each individual patient varies widely and depends on the pathogen load and virulence, and on the host with significant genetic variation and coexisting disease. The initial immune response also triggers several other cascades including complement and coagulation activation and catecholamine release.

What Are the Major Hemodynamic Consequences of Septic Shock?

Septic shock is most commonly seen in adults as warm shock with significant peripheral vasodilation leading to a high-output shock state. Tachycardia will increase total cardiac output to compensate for a greater volume of distribution secondary to vasoplegia caused by cytokine release. While warm shock is still the most common presentation in pediatrics, a considerable proportion of patients may also present in a cold shock state with decreased perfusion and delayed capillary refill. This version of septic shock is associated with depressed cardiac function and decreased cardiac output. The cause of this variation is incompletely understood but the consequences are the same as the majority of cases present with metabolic acidosis and end-organ dysfunction.

During early resuscitation, it is important to distinguish between warm and cold shock. Both instantaneous capillary refill and delayed capillary refill are seen in sepsis and management of septic shock should be adapted accordingly. Current guidelines for septic shock recommend initial volume resuscitation with crystalloid, up to 200 mL/kg, though most children will be given 40–60 mL/kg. Central venous pressure monitoring is useful to guide volume resuscitation with a common goal of approximately 8–12 cm H_2O, while monitoring for signs of fluid overload. There do not seem to be any advantages to colloid therapy.

Early initiation of inotropic support is recommended, preferably via central access if available. Epinephrine is the first-line choice for cold vasoconstricted shock, but dopamine has also been used successfully. Norepinephrine is the first-line therapy for warm vasodilatory shock. The role for other vasoactive medications in pediatrics has not been defined, though phenylephrine may provide peripheral vasoconstriction to treat hypotension secondary to warm shock, while dobutamine often provides significant inotropy.

What Treatment Options Are Available for Pressor Refractory Septic Shock?

In pressor refractory shock, consideration of adrenal insufficiency should prompt initiation of hydrocortisone stress dosing, though the evidence for or against this therapy is limited. Milrinone may effectively offload a volume overloaded heart, though this medication is long-acting and slow to titrate, making it difficult to use in rapidly changing clinical situations. Vasopressin should also be considered in pressor refractory warm shock. A final rescue therapy for pediatric septic shock is veno-arterial extracorporeal membrane oxygenation (ECMO).

Is an Arterial Line Necessary in Septic Patients?

All hemodynamic interventions should be managed with the goal of optimizing end-organ perfusion. Invasive blood pressure monitoring with arterial access should be used to obtain instantaneous determination of blood pressure, pulsatility, and pulse pressure. This also allows for repeated sampling of blood gas and lactate samples.

Lactic acidosis is a significant sign of hypoperfusion and can be used to guide blood pressure goals. Cardiac dysfunction is worsened by significant acidosis and frequent laboratory monitoring is required to detect additional end-organ dysfunction.

Is a Central Venous Line Necessary in Sepsis Patients?

Central venous access with the ability for rapid infusion of volume and blood products would be helpful for the septic patient requiring general anesthesia.

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Table 11.2 Sequential Organ Failure Assessment (SOFA). Reproduced with permission of Wolters Kluwer Health, Inc. from Jones AE, et al. Crit Care Med. 2009 May;37(5):1649–54

SOFA score	1	2	3	4
Respiration[a]				
Pao_2/Fio_2 (mm Hg)	<400	<300	<200	<100
Sao_2/Fio_2	221–301	142–220	67–141	<67
Coagulation				
Platelets × $10^3/mm^3$	<150	<100	<50	<20
Liver				
Bilirubin (mg/dL)	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular[b]				
Hypotension	MAP <70	Dopamine ≤5 or dobutamine (any)	Dopamine >5 or norepinephrine ≤0.1	Dopamine >15 or norepinephrine >0.1
CNS				
Glasgow Coma Score	13–14	10–12	6–9	<6
Renal				
Creatinine (mg/dL) or urine output (mL/d)	1.2–1.9	2.0–3.4	3.5–4.9 or <500	>5.0 or <200

MAP, mean arterial pressure; CNS, central nervous system; Sao_2, peripheral arterial oxygen saturation.
[a]Pao_2/Fio_2 ratio was used preferentially. If not available, the Sao_2/Fio_2 ratio was used; [b]vasoactive medications administered for at least 1 h (dopamine and norepinephrine mcg/kg/min).

Many of the vasoactive medications necessary for hemodynamic modulation require central access due to the risk of soft tissue damage with infiltration.

Central venous oxygen saturation can be utilized with a goal of normalization to approximately 70%. This number reflects oxygen delivery, which is a combination of cardiac output and arterial oxygen content, and oxygen consumption. Sepsis can have decreased central venous oxygen saturation because of a combination of both increased oxygen consumption, secondary to fever and metabolic stress, and decreased oxygen delivery, secondary to decreased cardiac output, anemia, and decreased oxygenation ability from lung injury. Any decrease in central venous saturation can indicate a lack of adequate oxygenation in the end-organ capillary beds, which can lead to tissue injury and must be corrected.

What Other Monitoring Devices Are Used in Sepsis Patients?

Urine output remains an important monitor of end-organ perfusion to the kidney, with a goal of at least 0.5 mL/kg/h. NIRS may have a role in monitoring cerebral oxygen delivery but evidence-based outcome studies have not been performed. Transthoracic and transesophageal echocardiography may also be useful in monitoring cardiac function.

How Is Multiorgan Dysfunction Measured in Septic Shock?

The risk of mortality with septic shock increases with multiorgan dysfunction. A common scoring algorithm used to define organ dysfunction in septic shock is the Sequential Organ Failure Assessment (SOFA), shown in Table 11.2. This assessment tool takes into account end-organ dysfunction and demonstrates increased mortality with higher scores. The trend of this score also correlates with higher or lower mortality. This assessment tool has been shown to be effective in small cohorts of pediatric patients and is useful to monitor severity of illness. Practitioners must be prepared for severe end-organ dysfunction during progression of severe sepsis and patients undergoing surgical procedures will be at higher risk

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of more end-organ involvement. The cause of progression to multiorgan dysfunction syndrome is unknown, but it is likely a combination of severe inflammatory products, hypoperfusion, acidosis, hypoxemia and alterations in coagulation.

What Are the Respiratory Symptoms of Advanced Sepsis?

Acute respiratory distress syndrome (ARDS) is defined as acute hypoxemia with a P:F<300 with bilateral pulmonary infiltrates on chest radiograph not due to congestive heart failure. This is further divided into mild (P:F 200–300), moderate (P:F 100–200) and severe (P:F<100). ARDS is observed in about 6% of adult and pediatric sepsis patients.

What Is the Ventilatory Strategy for Patients with ARDS?

The ventilatory strategy for ARDS is to increase the level of positive end-expiratory pressure (PEEP) and adjust the FiO_2 to maintain SaO_2 >90%. The target FiO_2 is below 60%. An ARDSNet study published in 2000 demonstrated lung protection with low tidal volumes around 6 mL/kg compared to 12 mL/kg. Permissive hypercapnia with pH>7.25 is usually the goal to minimize barotrauma and volutrauma. Once mean airway pressure increases beyond 20 cm H_2O, consideration of advanced modes of ventilation such as oscillation is usually warranted. Nitric oxide also has a role in treating severe hypoxemia and high FiO_2, though there is a rare association with renal failure with this treatment. This can assist in ventilation/oxygenation matching and can also alleviate pulmonary hypertension, which can complicate cardiac function.

What Are Other End-Organ Manifestations of Severe Sepsis?

Renal dysfunction is another common comorbidity with severe sepsis. Fluid overload is a common manifestation following volume resuscitation and if the renal system cannot compensate for the volume, continuous renal replacement therapy (CRRT) may be warranted. CRRT is also indicated in severe refractory acidosis, uremia, or hyperkalemia. All of these can result from tumor lysis syndrome in leukemia patients such as the one discussed in the vignette. This syndrome occurs when patients with a high tumor burden have many of their tumor cells lyse at the same time, possibly secondary to treatment or severe stress. Unfortunately, the use of CRRT can be limited secondary to hemodynamic instability secondary to the fluid shifts necessary to complete dialysis.

Patients with severe sepsis also will occasionally present with disseminated intravascular coagulation. This is a syndrome secondary to release of tissue factor from endothelia and inflammatory cells, which leads to activation of the clotting cascade and consumption of intravascular endogenous anticoagulants. The lack of these endogenous anticoagulants leads to uncontrolled micro-thrombi formation, causing intravascular and intra-organ clots along with a predisposition to bleeding due to consumption of pro-coagulant factors and platelets. This is an important consideration prior to surgical intervention as many septic patients will require correction of coagulopathy represented by abnormal prothrombin and partial thromboplastin times and abnormal fibrinogen levels with fresh frozen plasma and cryoprecipitate.

Thrombocytopenia should be corrected prior to surgery. Anemia may be present, secondary to intravascular lysis secondary to DIC or hemodilution, and this should also be corrected prior to operation as it will lead to improvement in hemodynamics and oxygenation. Transfusion is indicated for hemoglobin level <7 mg/dL though some guidelines recommend transfusion when <10 mg/dL.

What Are the Anesthetic Considerations for Sepsis Patients?

The goal in choosing anesthetic induction agents is to provide pharmacologic agents with the least hemodynamic perturbation possible. Patients in septic shock are at high risk for cardiac arrest with secdation and initiation of positive pressure ventilation. Ketamine tends to slightly increase blood pressure through release of endogenous catecholamines, though in septic patients, these catecholamines can be depleted and can lead to a decrease in blood pressure, as well as a secondary myocardial depression effect of the agent. Fentanyl and midazolam have good analgesic and hypnotic properties, but can cause some decrease in myocardial output, though the amount of decrease seen with this can be minimal. Propofol tends to provide excellent intubating conditions quickly but

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can cause hemodynamic instability. Etomidate has a black-box warning in pediatrics due to adrenal suppression and increased mortality in septic patients and should not be used in pediatric sepsis patients.

Many of these procedures are emergent and a modified rapid sequence induction technique should be strongly considered. The likelihood of aspiration may also be higher due to a stress-induced ileus in severe sepsis. The choice of paralytic between succinylcholine and rocuronium likely depends on comorbidities including pre-existing renal dysfunction, hyperkalemia, or liver injury. Careful monitoring of induction should be used as end-organ dysfunction including hepatic and renal dysfunction may lead to significantly less need for drug dosing than commonly used. Remifentanil is a good choice as a primary agent for analgesia. Dexmedetomidine can blunt the tachycardic response desirable for pediatric patients and may cause hemodynamic instability. The effect of heart rate on cardiac output in pediatrics is important to consider given the smaller stroke volume from a smaller heart. Inhaled anesthetics cause significant peripheral vasodilation and will cause worsened hemodynamic instability.

Other anesthetic considerations for pediatric patients include a higher risk for hypothermia, which will worsen hemodynamic instability and can worsen coagulopathy. Hypoglycemia must also be avoided and severe stress associated with sepsis may lead to a requirement for a higher glucose infusion rate than usually needed. Preparation for all of these issues should be considered prior to taking a patient with sepsis to the operating room. Regular arterial blood gases, coagulation testing, lactate levels, and glucose testing are necessary. Blood counts and electrolyte levels should also be closely monitored.

What Types of Surgical Procedures Are Often Required in Patients with Septic Shock?

Septic pediatric patients may require surgical debridement of abscesses or necrotic wounds. Empyemas may require drainage following a severe pneumonia. Though many of these may occur in stable patients, there is the possibility that drainage could release bacterial products into the bloodstream and lead to a transient bacteremia and SIRS. Trauma patients can suffer infectious processes and require surgical intervention for foreign body removal or repair of intraabdominal injury or long bone fracture. Occasionally, septic shock patients will develop significant fluid overload with abdominal compartment syndrome requiring surgical decompression. Infected tunneled central lines also will require removal if the infection cannot be cleared.

What Are Common Postoperative Considerations in Sepsis Patients?

Any patient with significant ventilatory requirement or hemodynamic instability during operative procedures should be monitored in a pediatric intensive care unit until the hemodynamic instability has resolved. These patients require continued monitoring for end-organ dysfunction and intervention if necessary. Antibiotic therapy must be continued and monitored for toxicity. Nutrition should be started, though there has been some recent controversy as to the appropriate timing for this. Glycemic control should be initiated with insulin if levels are continually high, though the true benefit of this is still unknown and studies are ongoing. Children are at higher risk for hypoglycemia and this must be avoided. Patients recovering from severe illness are also at increased risk for secondary infection, which can lead to significant mortality, and this also must be monitored with indwelling central lines and catheters.

What Is Propofol Infusion Syndrome (PIS)?

While commonly used for sedation in adult ICUs, propofol for continuous sedation in pediatric patients has been issued a black-box warning by the Food & Drug Administration (FDA) after numerous reports of patient deaths. These deaths were directly attributed to the PIS in children. PIS is a complex, multifactorial constellation of symptoms. The exact etiology of PIS is unknown but postulated to result from impaired fatty acid metabolism in mitochondria.

Symptoms of PIS include acidosis, bradyarrhythmia, and rhabdomyolysis of cardiac and skeletal muscle leading to multi organ failure. In patients with PIS, a high incidence of lipemia, hypertriglyceridemia, and fatty liver changes has been noted.

Patients with prolonged infusion of propofol greater than 4 mg/kg/h or 67 mcg/kg/min are highest risk for development of PIS. Treatment requires stopping the propofol infusion and initiation of supportive therapies.

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Suggested Reading

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