**Introduction**

Pediatric sepsis is a significant healthcare issue that can lead to devastating consequences if not managed promptly and effectively. Sepsis is one of the leading causes of mortality in children, resulting in over 75,000 pediatric deaths worldwide each year. As clinical experts in pharmacotherapy, pharmacists play a critical role in the interprofessional team caring for septic pediatric patients. This subtopic will provide an in-depth review of pediatric sepsis, including the pathophysiology, clinical presentation, diagnostic approach, and detailed pharmacologic management strategies. Key guidelines and evidence will be presented to inform clinical decision making. Scenarios and exam tips are also included to reinforce learning. Recent advancements like sepsis biomarkers and quality improvement initiatives will be discussed. The critical nature of early recognition and time-sensitive interventions make pediatric sepsis a crucial area for pharmacy expertise.

**Clinical Presentation**

Clinical Presentation:

* Fever
* Tachycardia
* Tachypnea
* Hypotension or altered mental status in severe cases
* Signs of infection (e.g. cough, vomiting, diarrhea, rash)
* Organ dysfunction (e.g. acute kidney injury, acute respiratory distress syndrome)
* Neonates: temperature instability, lethargy, poor feeding, apnea

Risk factors:

* Very young age - highest risk in infants <1 year, especially neonates
* Immunocompromised state (malignancy, transplant, immunosuppressants)
* Indwelling devices (central lines, urinary catheters)
* Recent surgery or trauma
* Underlying comorbidities (e.g. congenital heart disease, chronic lung disease)

Pediatric sepsis can present with vague, nonspecific symptoms leading to missed or delayed diagnosis. Tachycardia may be absent in approximately 10% of pediatric septic shock cases. Hypotension is a late sign in pediatric sepsis that indicates decompensation.

Early recognition is critical but challenging due to variable presentations. Maintaining a high index of suspicion in high-risk children with acute illness is key. Signs of uncompensated shock indicate severe sepsis requiring urgent management.

**Pathophysiology**

Sepsis occurs when the body's immune response to an infection becomes dysregulated, causing widespread inflammation and cellular dysfunction. The inciting infection triggers immune activation and inflammatory mediator release (cytokines, chemokines, lipid mediators) which helps localize and eradicate the infection initially.

In sepsis, this response becomes amplified and systemic. The exaggerated immune response leads to endothelial damage, increased vascular permeability, impaired vasoregulation, and coagulopathy. Widespread inflammation, cellular injury, and microvascular thrombosis result in tissue hypoperfusion, cellular hypoxia, and multiorgan dysfunction.

Cardiovascular effects include myocardial depression, vascular dilation, and intravascular volume depletion. Respiratory effects include acute lung injury, impaired gas exchange, and altered ventilation perfusion matching.

Renal effects include acute tubular injury and reduced glomerular filtration.

Metabolic effects include impaired glucose regulation and mitochondrial dysfunction.

Central nervous system effects include altered mental status, encephalopathy, and seizures.

Disseminated intravascular coagulation can occur, depleting platelets and clotting factors.

Without intervention, cellular injury progresses, leading to shock, multiorgan failure, and potentially death.

**Diagnostic Approach**

The diagnosis of pediatric sepsis involves a multifaceted approach, including clinical assessment, laboratory data, imaging, cultures, and consideration of organ dysfunction criteria.

Key aspects include:

* Clinical evaluation for signs/symptoms of infection and organ dysfunction
* Vital signs showing tachycardia, tachypnea, fever/hypothermia, hypotension in severe cases
* Detailed history of presenting illness, risk factors, comorbid conditions
* Physical exam findings like rash, respiratory distress, altered mental status
* Laboratory tests: CBC, CRP, procalcitonin, lactate, blood cultures, urinalysis/culture as indicated
* Imaging like chest X-ray, abdominal ultrasound to identify potential infection source
* Application of consensus criteria for systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis
* Evaluation for sepsis-induced organ dysfunction using pediatric SOFA score
* Bedside cardiovascular monitoring: blood pressure, echocardiography
* Other advanced monitoring like central venous oxygen saturation when indicated

A high index of suspicion is required. Diagnostic uncertainty should not delay empiric broad-spectrum antibiotics and fluid resuscitation when sepsis is suspected.

**Management - Overview**

The management of pediatric sepsis centers on early recognition, timely administration of antibiotics, and prompt fluid resuscitation and hemodynamic support. The goals are to rapidly treat the inciting infection, mitigate the exaggerated inflammatory response, preserve end-organ perfusion, and prevent progressive shock and multiorgan failure. Supportive care for organ dysfunction is provided. An interprofessional, protocol-driven approach is beneficial. Key principles include:

* Early administration of broad-spectrum IV antibiotics after cultures
* Initial fluid resuscitation with isotonic crystalloids targeting 20 mL/kg
* Vasoactive agents for fluid-refractory shock (dopamine, epinephrine)
* Adjuvant therapies like corticosteroids for refractory shock
* Oxygen supplementation and mechanical ventilation if needed
* Monitoring and management of coagulopathy and other lab abnormalities
* Limiting fluids once shock is resolved to avoid fluid overload
* Supportive management of organ dysfunction (e.g. renal replacement therapy)
* ICU monitoring and organ support if end-organ hypoperfusion persists

The priority is reversing shock, restoring perfusion, and preventing progression to multiorgan failure. An individualized approach is needed based on clinical response.

**Pharmacotherapy**

Initial Emergency Department Management

* IV fluid resuscitation
* Initial bolus of 20 mL/kg isotonic crystalloid (normal saline, Lactated Ringer's) over 30-60 mins
* May repeat up to 40-60 mL/kg in first 1-2 hours to reverse shock
* Monitor for fluid overload after shock resolves

* Vasopressors
* Begin early if fluid refractory shock persists >40 mL/kg
* First line: Dopamine or Epinephrine
* Dopamine: Start at 5-10 mcg/kg/min, titrate up to 10-20 mcg/kg/min
* Epinephrine: Start at 0.05-0.3 mcg/kg/min, titrate up to 0.3-1 mcg/kg/min
* Target MAP at 5th percentile for age

* Broad spectrum antibiotics
* Obtain cultures first
* Begin IV antibiotics within 1 hour of sepsis recognition
* Cover common bacteria based on source of infection
* Modify based on culture results when available

* Adjunctive therapies
* Hydrocortisone if fluid/catecholamine resistant shock
* Start stress dose hydrocortisone 1-2 mg/kg/dose IV q6-12h
* Drotrecogin alfa (activated) - recombinant activated protein C, controversial, not currently recommended

ICU Management

* Hemodynamic monitoring and optimization
* Central venous pressure, ScvO2 monitoring
* Echocardiography to guide fluid/pressor titration

* Judicious fluids once shock resolves
* Avoid fluid overload > 10% total body weight

* Multiple vasopressor/inotrope use if needed
* Epinephrine, norepinephrine, vasopressin, dopamine, milrinone
* Titrate to optimize blood pressure and perfusion

* Hydrocortisone for refractory shock
* Up to 50 mg/m2/day continuous infusion

* Mechanical ventilation if respiratory failure
* Lung protective strategies
* Neuromuscular blockade for refractory hypoxemia

* Renal replacement therapy for fluid overload/renal failure

* Stress ulcer and VTE prophylaxis

Key Monitoring Parameters

* Vital signs, mental status, urine output
* Serum lactate level - normalize <2 mmol/L
* Central venous oxygen saturation (ScvO2) - target >70%
* Central venous pressure - target >8 mmHg
* Echocardiography for cardiac function
* Daily fluid balance and cumulative balance

**Key Guidelines and Evidence**

Key Recommendations for Management of Pediatric Sepsis

|  |  |  |  |
| --- | --- | --- | --- |
| **Guideline/ Source** | **Key** **Recommendations** | **Level of Evidence** | **Strength of**  **Recommendation** |
| Surviving Sepsis Campaign Guidelines (2021) | Administer antimicrobials within 1 hour of sepsis recognition | Moderate | Strong |
| Surviving Sepsis Campaign Guidelines (2021) | Provide fluid resuscitation with 20 mL/kg crystalloid boluses over 30-60 mins to reverse hypotension | Low | Weak |
| Surviving Sepsis Campaign Guidelines (2021) | Begin vasoactive agents if fluid refractory shock persists after 40-60 mL/kg | Low | Weak |
| Surviving Sepsis Campaign Guidelines (2021) | Target threshold MAP of 5th percentile for age | Moderate | Strong |
| American College of Critical Care Medicine Guidelines (2009) | Use protocol-driven management approach with sepsis bundles | Low | Strong |
| American College of Critical Care Medicine Guidelines (2009) | Measure serum lactate level; normalize lactate <2 mmol/L | Moderate | Strong |

**Clinical Scenarios**

Clinical Scenario 1:

A 6-year-old girl with a history of leukemia on chemotherapy presents with fever, tachycardia, and respiratory distress. She is diagnosed with chemotherapy-induced neutropenia and early septic shock based on blood cultures positive for Pseudomonas aeruginosa. She receives an initial fluid bolus and is started on meropenem, vancomycin, and micafungin empirically. Despite 60 mL/kg of fluids and initiation of dopamine and vasopressin for persistent hypotension, her blood pressure remains low.

Clinical Scenario 2:

A previously healthy 18-month-old boy presents with a 2-day history of vomiting, diarrhea, and fever. He is tachycardic, tachypneic, and ill-appearing on exam. His serum lactate is elevated at 5 mmol/L. He is diagnosed with septic shock and started on vancomycin and ceftriaxone after blood cultures are obtained. He receives an initial 30 mL/kg fluid bolus and started on dopamine for hypotension. Within 6 hours, his lactate normalizes to 1 mmol/L and his shock resolves after 40 mL/kg total fluids.

Clinical Scenario 1 Answer Key:

This scenario of fluid/catecholamine refractory shock in an immunocompromised pediatric patient indicates the potential need for hydrocortisone. Stress-dose steroids can help reverse vasopressor-dependent shock in sepsis through their hemodynamic effects. The risk of immunosuppression is outweighed by the potential mortality benefit in this critically ill child.

Clinical Scenario 2 Answer Key:

This scenario highlights the importance of serial lactate levels in pediatric sepsis. Although his hypotension responded to fluids and vasopressors, his normalized lactate provided evidence that his tissue hypoperfusion had resolved with resuscitation. This helps guide the decision to avoid further fluid boluses and additional therapies once the shock has reversed.

**Tips for Board Exam Questions**

* Know the diagnostic criteria for SIRS, sepsis, and septic shock in pediatric patients based on pediatric consensus guidelines. Recognizing sepsis severity is key.
* Be familiar with age-specific vital sign reference ranges and thresholds for hypotension to identify shock.
* Remember the steps in the 1-hour pediatric sepsis bundle: labs/cultures, antibiotics, fluids, and vasopressors.
* Recall the agents commonly used for fluid-refractory shock (dopamine, epinephrine, norepinephrine).
* Understand the rationale behind adjuvant steroid use in refractory shock cases. Consider risk/benefit.
* Emphasize avoiding fluid overload once shock is reversed to prevent worse outcomes.

**Summary**

Pediatric sepsis is a major healthcare challenge requiring prompt recognition and treatment to prevent devastating outcomes. Pharmacists play a pivotal role in managing these high-risk patients. Key learning points include pathophysiologic processes leading to shock and organ failure, recognizing sepsis presentations, rapidly initiating antibiotics and fluids, tailoring hemodynamic support, and preventing secondary injury from fluid overload or prolonged treatments.

Landmark trials and guidelines have shaped evidence-based care protocols. However, uncertainties remain regarding optimal fluid volumes, vasopressor choices, steroid use, and adjunctive therapies. Ongoing research and quality improvements are still needed. Using clinical judgment and a meticulous, patient-centered approach is essential. With their pharmacotherapy expertise and perspective, pharmacists crucially impact care across the sepsis management spectrum.

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