Sepsis and Septic Shock in the Pediatric Patient: Part 2

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Introduction

Welcome to Part 2 of our podcast on sepsis and septic shock in the pediatric patient. My name is Dan Lafreniere and this podcast was developed with Dr. Christian Lehmann. Listening to this podcast should allow you to:

1. List the initial investigations and steps in managing the pediatric patient with sepsis.
2. To explain the priorities and key considerations in the management of these patients.
3. To identify common sites of infection that may lead to sepsis.

First, consider the potential foci of infection. The most common sites associated with the development of sepsis are the lungs, followed by the bloodstream. Other infections include but are not limited to: endo- and pericarditis, meningitis, or urinary tract infection (UTI). History and physical examination with help focus your investigations, and lab and imaging studies can help confirm.

Investigations

I. Laboratory Studies

Moving on to discuss investigations, the lab workup for suspected sepsis is quite broad, surveying for infective etiology and following a step-wise approach to assess organ system and metabolic function.

First, to establish the infectious etiology (1,2):

1. A **CBC w/ differential** – Where age-specific leukocytosis or leukopenia are a criterion for pediatric SIRS. In addition, neutrophilia, neutropenia, or thrombocytopenia may indicate acute infection.
2. Also **blood cultures** – Given the high prevalence of bacterial bloodstream

infections in children with sepsis. Two sets of blood cultures from two different sites, including aerobic and anaerobic bottles should be obtained from all patients prior to, but not delaying the initiation of antibiotics.

3. **Urine microscopy and macroscopy**.
4. Also **urine culture** – Where UTI is a common source of infection in children with sepsis, and catheterized urine cultures should be obtained in all patients again preferably before antibiotics are initiated.
5. A **nasopharyngeal swab** – for respiratory viruses.
6. **Other cultures** – such as cerebrospinal fluid (CSF), wound culture, aspirated fluid from an abscess, as well as viral and/or fungal cultures should be obtained as indicated by clinical findings.
    a. And a note here is that if meningitis is suspected and the patient is too unstable to undergo a lumbar puncture to obtain a sample of CSF, antibiotics should not be delayed!

Next let's cover some of the standard initial lab studies that should be run (1,2):

7. **Blood gas and oximetry**.
8. **Lactate** – Where lactate is a non-specific but useful biomarker in sepsis diagnosis, and patient stratification. As mentioned, elevated arterial lactate is one of the possible parameters used to define cardiovascular dysfunction as part of the definition of septic shock in children.
9. **Glucose** – As hypoglycemia may accompany the metabolic demands and decreased oral intake associated with sepsis in children, particularly in neonates and infants.
10. Also **electrolytes and extended electrolytes** – As electrolyte disturbances (namely hyponatremia, hyper- and hypokalemia, and hypophosphatemia) may be observed due to disease processes associated with sepsis and septic shock, such as Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH), gastroenteritis, or capillary leak. And where hypocalcemia may affect myocardial function and vascular tone, and hypomagnesemia can predispose patients to arrhythmias.
11. **Creatinine and urea** - To assess renal function and for lab signs of dehydration.
12. Also **bilirubin and alanine aminotransferase (ALT)**

And lastly, markers of coagulopathy, including (1,2):

13. **Prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR)** – Where an elevated PT and aPTT or INR point to DIC - although these can be decreased in the early hypercoagulable state.
14. **Fibrinogen and D-dimer** as well – Where decreased fibrinogen and increased D-dimer support the presence of a consumptive coagulopathy and DIC.

15. **C-Reactive Protein (or 'CRP')** – is regularly used as a non-specific marker of inflammation. In contrast, procalcitonin is not routinely used but may offer some diagnostic and prognostic value in sepsis (3,4).

II. Imaging

Typical radiography includes obtaining a chest X-ray to assess for airspace disease, pulmonary edema, or cardiomegaly in children with hypoxemia and wheezing or rales and tachypnea, or with leukocytosis (>20,000/mm^3).

Other imaging is performed as needed based on findings and includes ultrasound – such as echocardiography, as well as CT and/or MRI to assess for other foci of infection.

Differential Diagnosis

Moving on to the differential diagnosis for sepsis, while the definition of sepsis relies on confirmed or suspected infection, a range of non-infectious conditions can present similarly. These include, but are not limited to: dehydration, metabolic acidosis, heat stroke, serotonin syndrome, Kawasaki disease, Addison's, toxic ingestions – such as MDMA, methamphetamine and/or cocaine, benzodiazepine or opioid withdrawals, salicylates or anticholinergics, as well as neuroleptic malignant syndrome, or malignant hyperthermia (1,2).

Management

Now let's discuss management. Broadly, goals in the initial management of sepsis and septic shock include: obtaining vascular access, aggressive fluid resuscitation, starting broad-spectrum antimicrobials tailored based on clinical suspicions, as well as initiating vasoactive agents as needed - all of which should ideally take place within the first hour and be targeted towards therapeutic endpoints that indicate the reversal of shock and the return of tissue perfusion.

Case 2 – Diagnosis & Management

Let's discuss initial steps in management through our second case.

Amadi, a 5-year-old boy who immigrated to Canada from Nigeria with his family 4 months ago, presents to your emergency department with nausea, somnolence and fever. Amadi's parents are concerned about him and report that he has been tired and lethargic, nauseous but not vomiting, complaining of leg pain, and has had a high fever.

His mother noticed spots on his stomach and legs that first appeared 12 hours ago and are increasing in number and size. On examination he appears toxic, with a GCS of 13 - with confusion, he has a thready pulse and is tachycardic at 145 beats per minute, hypotensive with a pressure of 75/40, tachypnic with a respiratory rate of 30, febrile with a temperature of 39.9 C, and his oxygen saturation on room air is 91%. On exam you note multiple 0.5 to 2 cm diameter reddish-purple circular and well-circumscribed purpuric lesions on the legs, with similar lesions including some areas with coalesced purpura on the thorax. His capillary refill is delayed, and his extremities are cold and clammy.

At this point let's take a pause and review the initial steps in the management of the patient in septic shock. First, a minimum of two large bore peripheral IVs should be secured – however if not able to be secured in a timely manner, intraosseous (IO) access should be attempted without delay, and these should occur within 5 minutes (2). Fluid resuscitation should begin within a half-hour and antimicrobials, as well as the initiation of vasoactive agents when necessary, should occur within the first hour (5).

Fluid resuscitation is aimed at correcting relative intravascular hypovolemia, seen commonly in septic shock, which occurs secondary to leaky capillaries and peripheral vasodilation, and is guided based on clinical therapeutic endpoints. This should begin with 10-20 mL/kg of Ringer's lactate solution, or another balanced crystalloid such as Plasma-Lyte, titrated to signs of end organ perfusion or to the signs of fluid overload (6). For patients with septic shock, generally up to 60 mL/kg is required, and can be 120 mL/kg or greater within the first hours. Key within the first hour of treatment is determining if the patient is fluid responsive, where failing three boluses of 20 mL/kg (so 60 mL/kg total) can be used as a cut-off. It is common that vasoactive agents are required, and the ACCM recommends their initiation within the first hour (2,5).

Antimicrobial selection should be based on clinical presentation, age, history and comorbidities, consider local resistance patterns, and provide appropriate broad-spectrum coverage, including for atypical bacterial etiologies, as well as anti-fungal and/or anti-viral coverage when indicated. Generally, MRSA should be covered in children with septic shock, with coverage for enteric organisms when GI or GU sources are suspected, and coverage for *Pseudomonas* in patients who are immunocompromised, or have other risk factors such as those receiving total parenteral nutrition or having a recent prolonged hospitalization.

Remember that blood cultures and urine cultures should ideally be collected before antimicrobials are initiated, but without delaying their initiation, and that those antimicrobials that can be delivered as a bolus should be administered before those requiring infusion such as with vancomycin.

A suggested initial regimen for the **immunocompetent child** in septic shock would include vancomycin (15 mg/kg/dose) **along with** either cefotaxime (50 mg/kg/dose) OR

ceftriaxone (75-100 mg/kg/dose) (2). With the suspicion of a GI source piperacillin/tazobactam, clindamycin, or metronidazole can be added, and with the suspicion of a GU source, adding an aminoglycoside such as amikacin or gentamicin would be indicated (2). Remember that piperacillin/tazobactam does not cross the blood brain barrier so is not appropriate if there is any suspicion of meningoencephalitis.

For the **immunocompromised child**, the regimen should be tailored to include coverage for *Pseudomonas* and a suggested initial regimen would consist of vancomycin (15 mg/kg/dose) **along with** either cefepime OR ceftazidime, both of which would be at (50 mg/kg/dose) (2). With suspicion of extended spectrum beta-lactamase resistance activity or in the setting of treatment with a broad-spectrum antibiotic within the previous two weeks, a carbapenem (such as imipenem or meropenem) could be substituted for the cephalosporin. With resistance concerns, an aminoglycoside could be added to a vancomycin + cephalosporin **or** carbapenem regimen (2).

With risk factors for fungal infection, liposomal amphotericin B or an echinocandin such as caspofungin can be added (2). With risk factors for rickettsial or tropical disease infections, a tetracycline such as doxycycline would be indicated (2).

And a tip here is to not forget to quickly look through any past microbiology that is available to see what they have grown, and to screen for any drug resistant organisms in particular.

Now back to our case, the first step here is recognizing that Amadi is in septic shock (specifically presenting as cold shock) and is hypotensive. He should immediately be brought to a resuscitation area, ABCs should be assessed, he should be put on oxygen and an IV should be attempted. Establishing IV access could be quite difficult given his hypotension, and so moving on to intraosseous access would be the next step. Regarding IOs in awake children, it is important to remember that they are easy to insert and that everything that can be given IV can be given IO, and this includes the ability to administer infusions such as vasopressors.

Once access is established, blood cultures should be collected immediately before empiric antibiotics are started without delay. Following antibiotics, other blood samples can be collected. Now an appropriate antimicrobial regimen for Amadi would be cefotaxime IV/IO pushed, followed by vancomycin. As discussed, the most time critical for any child with sepsis, and especially so with hypotension, is aggressive fluid resuscitation and so within the first hour, 60 mL/kg of crystalloid should be given – which can be pushed using larger 30 or 60 cc syringes. Response to boluses of 20 mL/kg should be assessed.

In fact, experts recommend that this aggressive fluid resuscitation be performed *at a greater priority than securing the airway*, where without prior fluid resuscitation the rapid

sequence induction drugs and/or the intubation procedure itself are at a much greater risk of potentiating cardiovascular collapse.

Other initial management steps include: correction of hypoglycemia, if present, and following initial correction a dextrose infusion should be started. Regarding calcium, guidelines recommend correction of ionized hypocalcemia even without presence of clinical manifestations (5), via either calcium gluconate or calcium chloride where gluconate can be administered through a larger vein or central line, but chloride must be administered through a central line. Other electrolyte abnormalities should also be corrected as per guidelines.

As mentioned, children with sepsis generally present in cold shock and an infusion of epinephrine is recommended as the first line pressor in the fluid-refractory hypotensive patient with cold shock, with dopamine being an acceptable alternative, and a second pressor can be initiated if the patient hasn't responded following titration of the dose (2). If the patient is normotensive but has fluid-refractory cold shock, there is a weak recommendation with low quality evidence for a low-dose epinephrine infusion, where adding a vasodilatory agent would follow if the patient did not respond (2). For warm shock, the ACCM recommends norepinephrine as a first line agent (5). The 2020 SSC guidelines outline that they were unable to recommend one of epinephrine or norepinephrine as a first-line agent for septic shock, and outline that in their practice they select one of the two based on the patient's physiology and clinician preference (6). In patients with fluid-refractory catecholamine-resistant shock the 2020 guidelines state that stress doses of steroids may or may not be used, without clear evidence supporting one specific approach (6).

A conservative approach to airway management should be employed in children with septic shock, where intubation is a last resort and preparation and drug selection are considered. It is important to not rush the decision to intubate, and CPAP/BiPAP should always be considered first. Potential benefits to intubation include establishing a patent and protected airway and supporting ventilation, as well as decreasing the work of breathing (2). Now, once the decision to intubate has been made, it's important to make sure that fluid resuscitation is given prior to RSI as well as during and after, and that the value of fluid resuscitation should not be overlooked. It may in fact be valuable to delay RSI for fluids when appropriate in order to prevent the risk of potentiating cardiovascular collapse.

Regarding induction agents, propofol should be avoided as it leads to pronounced cardiovascular depression and hypotension. Instead, the induction agent of choice in this setting is ketamine when not contraindicated, and if it is, then etomidate should be considered – though while keeping in mind that etomidate administration leads to marked and prolonged inhibition of cortisol synthesis.

Take-Home Points

We've covered quite a bit through these two parts of the podcast and so now is a great time to review some take home points.

Moving through what we've covered chronologically, regarding definitions and recognition of sepsis:

1. Sepsis is a dysregulated host response to infection and leads to a range of immunologic/cellular metabolic/and microcirculatory perturbations, which contribute to the development of shock, organ dysfunction and progression to MODS.
2. Remember that not all cases of sepsis will present in a way that meet the lab and/or physiologic cut-offs listed in guidelines.

Regarding management for sepsis:

1. The initial goals include: obtaining vascular access, aggressive fluid resuscitation with crystalloids, initiating broad-spectrum antimicrobials tailored based on clinical suspicions and factors such as age and history, as well as initiating vasoactive agents as needed - all of which should ideally take place within the first hour and that are targeted towards therapeutic endpoints that indicate the reversal of shock and the return of tissue perfusion.
2. Recall that it is important to collect bloods for culture before, but not delaying, the immediate initiation of empiric antimicrobials – and similarly their administration should not be delayed in a patient with suspected meningitis who is too unstable to undergo a lumbar puncture for CSF.

Key points regarding initial management specifically for septic shock:

1. First, recall that children will compensate and remain normotensive, thus hypotension should not be expected when making the diagnosis of sepsis or septic shock. Also that hypotension in the pediatric sepsis patient can indicate that they are pre-arrest.
2. For septic shock, immediately establish access, start the patient on oxygen, initiate broad-spectrum antimicrobials, and begin aggressive fluid resuscitation (with 60 mL/kg crystalloid within the first hour).
3. Assess the patient's fluid responsiveness, where failing 3 boluses of 20 mL/kg of isotonic fluids within the initial hour can be used as a cut-off and begin vasopressors when indicated. For cold shock, which is more common in children,

epinephrine is recommended as the first line agent, and for warm shock norepinephrine is recommended.
4. Recall that it may be important to consider fluid resuscitation at a higher priority than the airway, and when airway management is required, use conservative strategies first such as CPAP/BiPAP. If intubation is indicated, fluid resuscitate the patient prior to during and after RSI and consider ketamine as a first-choice induction agent.
5. Use lab and imaging studies as discussed in an attempt to identify the source of infection, as well as to perform a sequential assessment of organ system function.

This concludes our two-part podcast on the diagnosis and management of pediatric sepsis and septic shock. Thank you for listening! As a reminder the full transcript for this podcast is available through PedsCases.com.

References – Part 2:

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