PedsCases Podcast Scripts

This podcast can be accessed at www.pedscases.com, Apple Podcasting, Spotify, or your favourite podcasting app.

Sepsis and Septic Shock in the Pediatric Patient: Part 1

Developed by J. Daniel Lafreniere and Dr. Christian Lehmann, MD PhD FRCPC for PedsCases.com.
July 19, 2020.

Introduction

Hi, and welcome to part 1 of our podcast on sepsis. My name is Dan Lafreniere and I'm a Research Associate in the Department of Pharmacology at Dalhousie University in Halifax. This podcast was developed with Dr. Christian Lehmann, a staff anesthesiologist at the Queen Elizabeth Health Sciences Centre in Halifax. In addition to having worked clinically for many years in intensive care units, Dr. Lehmann is a Professor at Dalhousie and coordinates research labs with a focus on sepsis.

Listening to part 1 of this podcast should allow you to:

1. Describe the continuum of sepsis and identify the criteria for classifying sepsis and septic shock in children.
2. To identify challenges in the recognition and diagnosis of sepsis in children.
3. To list the initial investigations and steps in managing the pediatric patient with sepsis.
4. To explain the priorities and key considerations in the management of these patients.

And just before we start, we would like to say that our podcast aims to give a broad overview of care from identification and diagnosis to management in the non-neonatal pediatric sepsis patient. Another PedsCases podcast is available that specifically discusses the management of term infants at increased risk for early onset bacterial sepsis, which you can find under the title "Management of Early Onset Bacterial Sepsis".

Definitions

Let's begin with some definitions. Sepsis describes a clinical syndrome that involves a systemic pathologically-dysregulated host immune response to infection. The pathophysiology is complex and involves dysfunction both at the cellular metabolic level as well as at the level of the microcirculation (1). In most patients an initial hyperinflammatory phase develops in response to a systemic infection, and this may

progress to a state of immunosuppression. Ultimately, these processes can progress to organ dysfunction and to the development of multi-organ dysfunction syndrome.

In children, the incidence of sepsis has a bimodal distribution between the 'under 1 year of age' group, and early adolescents. And the burden of sepsis in children is highlighted by a variable but high mortality, ranging from 4-10% in those with severe sepsis, and 13-34% in those with septic shock – as well as how sepsis represents a leading cause of mortality in children worldwide (2,3).

It's important to note that sepsis definitions are both variable and evolving and that definitions and diagnostic & management guidelines may differ between centers. It's also important to keep in mind that **not all sepsis cases will present in a way that meets the lab and/or physiologic cut-offs that are listed in guidelines** (4).

Regarding diagnostic criteria, the International Pediatric Sepsis Consensus Conference, subsequently published by Goldstein et al. in 2005, defines sepsis as the presence of systemic inflammatory response syndrome (or 'SIRS') in the presence of suspected or proven infection, or of a clinical syndrome associated with a high probability of infection (5).

SIRS is the first criterion in their definition and describes a systemic response that may or may not be associated with infection, and to classify two or more of the following four parameters must be present (5):

1. A core temperature of <36°C or >38.5°C
2. Tachycardia – or bradycardia in children that are less than 1 year of age
3. Either leukopenia or leukocytosis, or a left shift
4. Tachypnea – or if the child is mechanically ventilated for an acute process that is unrelated to neuromuscular disease

One caveat is that in order to classify as SIRS, one of either: an abnormal temperature or leukopenia or leukocytosis needs to be present.

Sepsis has a continuum of severity, beginning with SIRS, progressing to sepsis and then to severe sepsis, followed by septic shock – which is the most severe and refractory state. The jump from sepsis to severe sepsis results from the patient developing either respiratory dysfunction – such as acute respiratory distress syndrome (ARDS), cardiovascular dysfunction, or dysfunction of two or more organ systems which include: neurologic, hepatic, renal, and hematologic (2).

Moving on to septic shock, in children it is defined as 'sepsis with cardiovascular dysfunction that persists despite administration of 40 or more mL/kg of isotonic fluid within one hour', where cardiovascular dysfunction is defined by the presence of either hypotension or reliance on a vasopressor, or two of: metabolic acidosis, oliguria, elevated arterial lactate levels, or prolonged capillary refill (5).

And this leads us to a clinical pearl: It is important to remember that unlike adults, children with sepsis have extended compensation and thus hypotension should not be expected in order to support a diagnosis of septic shock. In fact, hypotension may be indicating end-stages of shock and signal the pre-arrest patient.

At this point we would like to point out that another PedsCases podcast called 'Approach to Shock' is available and gives a more detailed approach to shock in general.

Guidelines

Moving on to guidelines, you may have heard the expression 'children are not little adults', highlighting the vast physiologic variations between adults and children. Pediatric sepsis guidelines have been established accordingly and the main guidelines that we will discuss in this podcast are the International Pediatric Sepsis Consensus Conference definitions published by Goldstein and colleagues in 2005, the Surviving Sepsis Campaign Guidelines published by Rhodes and colleagues in 2017, and the American College of Critical Care Medicine (the ACCM) clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock, also published in 2017 (4,5,6). In addition, the Surviving Sepsis Campaign has recently released their 2020 guidelines, published by Weiss and colleagues (7). Of the 77 statements in these guidelines, only 6 are strong recommendations, and this highlights the paucity of literature as well as the continued need for RCTs and pathophysiology studies.

Case 1 – Recognition & Protocols

For our first case, we want to share a true story.

Rory, a 12-year-old boy, was accompanied by his parents presenting to his pediatrician with an 18-hour history of leg pain, a 9-hour history of nausea and vomiting, and a fever. Rory's parents are concerned about his condition. Upon examination Rory is tachycardic at 140 beats per minute, tachypnic with a respiratory rate of 36 and febrile at 38.8°C. The pediatrician notes unilateral leg pain, abdominal tenderness, mottled skin and a superficial laceration on his elbow. Rory's parents explain that the cut was obtained the day before after Rory dove for a ball in gym class. A rapid strep test is performed and is negative. The pediatrician explains that she suspects viral gastroenteritis, which is currently going around, and advises Rory's parents to bring him to hospital for fluids. She also explains that she suspects he will develop diarrhea the next day.

ER doctors agree Rory is dehydrated and likely has gastroenteritis, he receives IV fluids and ondansetron, blood work is drawn and Rory is discharged. Over the next day Rory continues to complain of pain, develops diarrhea, is very weak and unable to eat or drink, and his fever continues despite ibuprofen and acetaminophen. Rory's parents

also notice that his nose appears blue and bring him back to the hospital, where he is admitted to the PICU with septic shock. Despite treatment Rory dies two days later due to streptococcal sepsis.

It is later found that Rory's blood work ordered upon his initial ER visit showed signs of infection, but that these were both not relayed and also that systems were not in place to trigger an alert for sepsis.

Rory's parents have since founded the Rory Staunton Foundation For Sepsis Prevention, and through their advocacy, Rory's story ignited a state and national level review of hospital policies for sepsis identification and treatment, leading to New York State being the first to introduce a statewide mandate, known as Rory's Regulations, that required hospitals to adopt sepsis protocols – with the aim being to improve early recognition and diagnosis, to identify those patients appropriate for the initiation of severe sepsis treatment protocols, as well as to provide guidelines for the early initiation of antibiotics. In fact, a recent retrospective cohort study published in JAMA reports that the implementation of these regulations was associated with significantly reduced sepsis mortality in New York state (8).

And in concluding this case, we would like to take the opportunity to extend our many thanks to Rory's parents for the opportunity to share Rory's story.

Risk Factors

Now let's discuss risk factors for the development of sepsis and septic shock – and these broadly encompass those factors that increase risk of infection or affect the ability to clear infection. There are a range of factors associated with an increased risk of progression to septic shock, and these include: an age younger than one month, immunosuppression (such as from HIV, malignancy, malnutrition, diseases involving splenic dysfunction, or treatment with immunomodulators), chronic conditions (such as short gut syndrome or uncorrected congenital heart disease), large surgical incisions, in-dwelling vascular catheters, Foley catheters, intubation, chest tubes, injury such as from penetrating trauma or burns, or urinary tract abnormalities that lead to frequent infections (2,9).

Infectious Etiologies

This leads us to the range of infectious etiologies that can lead to sepsis. First, it is important to note that, in addition to bacterial sepsis, sepsis can be triggered by fungal, viral, and parasitic microbes, and that key factors influencing pathogen prevalence include age, if the patient is immunocompromised, and the presence on an in-dwelling catheter (2,9). It is also an important consideration that studies report between 30% and 75% of children with sepsis do not have an infectious etiology identified – so called 'culture-negative sepsis' that is most commonly a result of having started antibiotics

prior to collecting blood cultures, however could also be due to a non-bacterial infectious etiology, an inflammatory host response to a bacterial component such as endotoxin (from Gram-negative organisms), or a slow-growing or fastidious bacterial organism (2).

Some common infectious etiologies include *Staphylococcus aureus* including MRSA, coagulase-negative Staph., *Streptococcus pneumoniae* and *Strep. pyogenes*, group B *Strep*. in the neonate, *Pseudomonas aeruginosa*, *E. coli*, *Enterococcus*, and *Klebsiella*. Some others that are seen less often include alpha *Strep.* in children with acute myelogenous leukemia with mucositis and neutropenia, meningococcal infections – particularly in the unimmunized population, as well as the toxic shock syndrome secondary to toxin producing strains of *Staph.* (2,9). In the pediatric sepsis patient with febrile neutropenia, both Gram-negative and Gram-positive organisms are often isolated, as well as typical nosocomial pathogens such as MRSA and multi-drug resistant Gram-negatives. Of bacterial nosocomial infections, coagulase-negative *Staph.* is the most common organism associated with sepsis, followed by Gram-negatives.

Viral etiologies of sepsis include respiratory viruses such as influenza, parainfluenza, adenovirus, human metapneumovirus or respiratory syncytial virus (RSV), as well as Dengue (2,9). In the immunocompromised patient, infection with Epstein-Barr Virus (EBV), cytomegalovirus (CMV) or adenovirus can lead to sepsis. And it is also important to note that infection with HSV, enterovirus, and adenovirus in neonates and young children may not be distinguishable from bacterial sepsis (2,9). Remember that many of these viral causes will not be readily detectable by classic lab investigations and blood cultures and to always maintain a high degree of suspicion based on symptomatology and exposures, even in the presence of negative blood cultures.

Fungal etiologies of sepsis are reported in 10% of pediatric patients with severe sepsis and septic shock, and of these cases, candida species are the leading cause (2). Risk factors for the development of fungal sepsis include: In-dwelling vascular catheters, prolonged periods of neutropenia, immunocompromised status, as well as the recent use of broad-spectrum antibiotics (2).

History & Physical

Now let's move on to discuss history and physical exam, it is a first good idea to familiarize yourself with the vital sign reference ranges for patients of different sizes and ages, which can be found in the pediatrics vitals chart on PedsCases.com.

In addition to signs of infection, SIRS, and possibly the presence of warm or cold shock, other physical findings in the sepsis patient may include, *on general inspection*: a toxic appearance, rigors, altered mental status, seizures, and signs of dehydration, *on head and neck exam*: meningismus and bulging fontanelle, *on examination of the limbs and*

abdomen: a distended and/or tender abdomen, or a decreased tone in infants and neonates, *on respiratory exam*: pulmonary rales or a decrease in breath sounds (secondary to bronchopneumonia), *and on examination of the skin*: cellulitis and/or lymphangitis, skin abscess, macular erythema (suggesting toxic shock syndrome), peripheral edema due to capillary leak, nodules indicative of disseminated Staph. aureus or fungal infection, petechiae or purpura suggesting a particular infectious source (such as meningococcemia or rickettsial infection) or of disseminated intravascular coagulopathy (DIC) (2).

Clinical Manifestations

Potential clinical manifestations of sepsis in children include: SIRS, evidence of infection, shock, lab findings, or other physical findings.

And to give a brief summary of the types of shock and how they present in children: Distributive shock (otherwise known as warm shock) is characterized by a hyperdynamic physiology – with an increase in cardiac output and decrease in systemic vascular resistance (SVR), leading to findings that include: bounding pulses, warm dry extremities, a wide pulse pressure, and flash capillary refill. On the other hand, cold shock, which is more commonly seen in children, is characterized by an increase in SVR and decreased cardiac output, leading to decreased perfusion, where signs include: diminished pulses, a delay in capillary refill, as well as mottled and/or cool extremities (2,9). It should be noted that the 2020 SSC guidelines recommend against using bedside clinical signs alone to characterize between warm and cold shock, suggesting the use of advanced hemodynamic monitoring where available. Examples include arterial blood pressure, central venous oxygen saturations, ultrasonography of the heart as well as of the ascending and descending thoracic aorta with Doppler – possibly using point of care ultrasound if available, and these can be used to guide resuscitation (7).

This concludes Part 1 of our two-part podcast. Thank you for listening! In Part 2, we will cover investigations, microbiology, the differential diagnosis, and conclude by discussing management through our second case. We would also like to mention that the full transcript for this podcast is available through PedsCases.com.

Developed by J. Daniel Lafreniere and Dr. Christian Lehmann, MD PhD FRCPC for PedsCases.com.
July 19, 2020.

References – Part 1

1. De Backer D, Orbegozo Cortes D, Donadello K, Vincent JL. Pathophysiology of microcirculatory dysfunction and the pathogenesis of septic shock. Virulence. 2014;5(1):73-9.
2. Pomerantz WJ & Weiss SL. Systemic inflammatory response syndrome (SIRS) and sepsis in children: Definitions, epidemiology, clinical manifestations, and diagnosis. UpToDate – Online. Page updated April 2019.
3. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41(2):580-637.
4. Davis AL, Carcillo JA, Aneja RK, et al. American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. Crit Care Med. 2017;45(6):1061-1093.
5. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005;6(1):2-8.
6. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017;43(3):304-377.
7. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children. Pediatr Crit Care Med. 2020;21(2):e52-e106.
8. Kahn JM, Davis BS, Yabes JG, et al. Association Between State-Mandated Protocolized Sepsis Care and In-hospital Mortality Among Adults With Sepsis. JAMA. 2019;322(3):240-250.
9. Weiss SL & Pomerantz WJ. Septic shock in children: Rapid recognition and initial resuscitation (first hour). UpToDate – Online. Page updated October 2019.

Developed by J. Daniel Lafreniere and Dr. Christian Lehmann, MD PhD FRCPC for PedsCases.com.
July 19, 2020.