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Pediatric Sepsis
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Show Notes

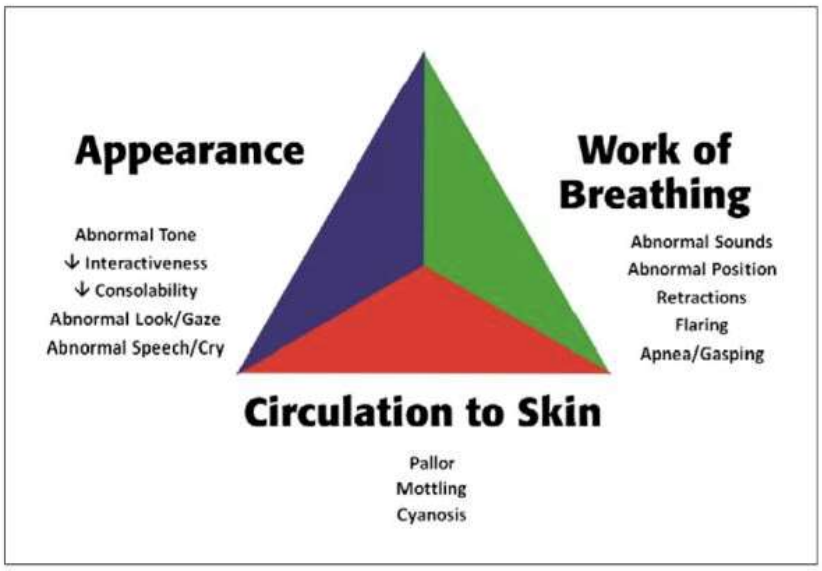
This content was largely adapted from the Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children [1]

What is sepsis?

- Currently in pediatrics we are using the definition from the 2005 International Pediatric Sepsis Consensus Conference [2].
- The diagnosis of **sepsis** requires both
    - Greater than or equal to 2 age-based systemic inflammatory response syndrome (SIRS) criteria
    - Confirmed or suspected invasive infection
- **Severe sepsis** is the above plus one of the following
    - Cardiovascular dysfunction
    - Acute respiratory distress syndrome (ARDS) or
    - Greater than or equal to 2 non-cardiovascular organ system dysfunctions
- **Septic shock** is defined as the subset of patients with severe sepsis with cardiovascular dysfunction which includes:
    - Hypotension
    - Treatment with a vasoactive medication, or
    - Impaired perfusion.
- In 2016, new adult definitions and criteria were published [3] with "sepsis" defined as life-threatening organ dysfunction caused by a dysregulated host response to infection and "septic shock" the subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality.
    - These new definitions have not yet been applied to pediatric guidelines.

What is your first step when you think a child may be suffering from sepsis?

- Consider using the pediatric assessment triangle [4] to identify the sick child.
- This is a quick visual assessment that includes the
    - General appearance
    - Work of breathing and
    - Circulation to the skin



- The pediatric assessment triangle gives us a basic understanding of our patient's neurologic, respiratory and cardiovascular status.
- If one or more abnormal findings are present that suggests the child is critically ill.
- These patients will require a structured primary and secondary assessment to address any abnormalities and prevent further decompensation.

After identifying the child as critically-ill move on to the primary assessment.

- Airway
- Breathing
- Circulation
- Disability
- Exposure

Next after the patient is stabilized, move on to the secondary assessment. This includes your history and physical exam.

For your history use the SAMPLE acronym to help guide your questions.

- S—signs and symptoms
- A—allergies
- M—medications
- P—past medical history
- L—last meal
- E—events leading up to presentation

Other helpful questions to ask on history:

- Ask the caregiver about the onset of symptoms
    - Have things gradually worsened or was there a sudden change today?
- How did the caregiver notice the fever?
    - Did she take the temperature or only a subjective fever?
    - Have they used any antipyretics that may be suppressing a fever at the time of presentation?
- Find out the patient's level of development.
    - Is there any history of seizures, developmental delay or any neurologic diseases?
- Have the caregivers noticed respiratory symptoms?
    - Rhinorrhea, cough or retractions may indicate a respiratory infection like bronchiolitis or pneumonia.
- When was the last time the baby fed?
    - If the baby has missed the past couple of feeds or if GI symptoms like vomiting or diarrhea are present then the baby is likely dehydrated and gastroenteritis may be the cause of infection.
- Take a careful past medical history.
    - Was the baby premature or require a NICU stay?
    - Does she have a history of prior infections or hospital admissions?
        - Any history of prior urinary tract infections could put this infant at risk for another.
    - Lastly, are vaccines up to date?

Moving on to the physical exam:

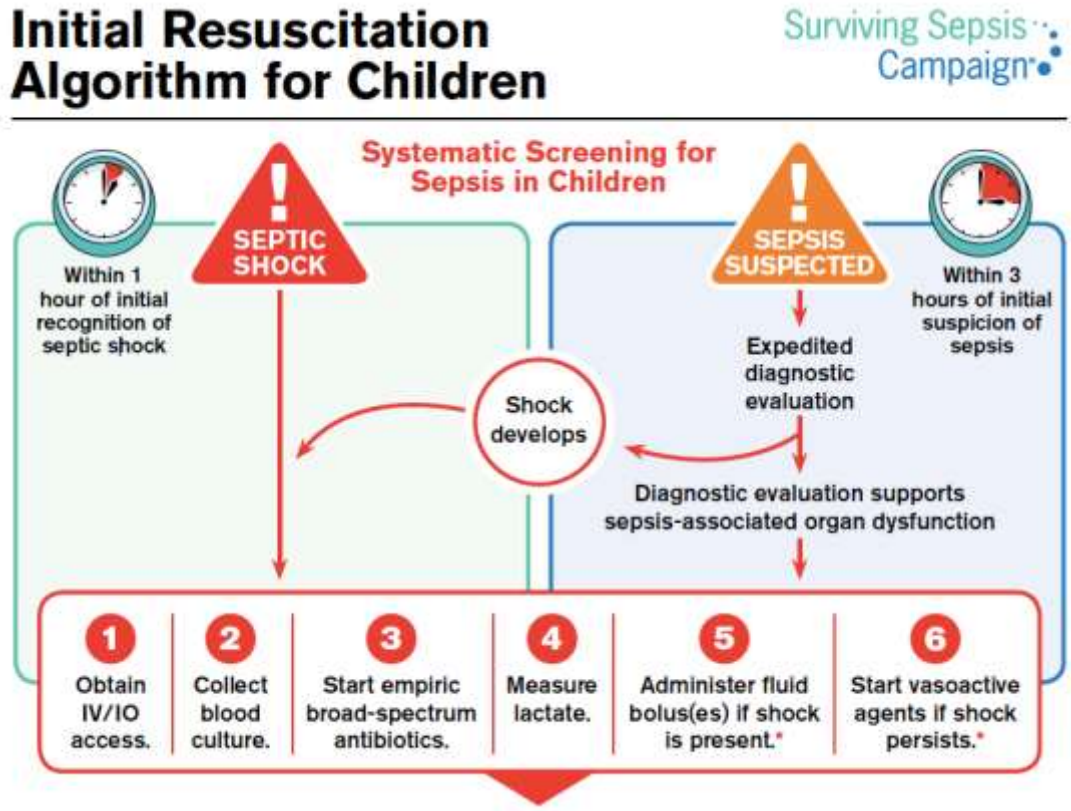
- The physical exam should be comprehensive with a careful attention to identify a site of possible infection.
- Meningeal signs are be worrisome for meningitis, but the exam is relatively insensitive.
    - Altered mental status can also be a sign of poor cerebral perfusion, commonly seen in shock.
- Look for signs of increased work of breathing and auscultate the chest. Crackles or wheezing could be a sign of lower airway disease.
- Next, the cardiovascular exam for any patient in shock is very important.
    - Access peripheral pulses and capillary refill time.
    - Weak pulses or a prolonged capillary refill time can be a sign of poor perfusion to the vital organs and should be immediately addressed.
    - Patients can also have bounding pulses and so called "flash capillary refill" due to distributive shock which also is worrisome.
    - If you are having difficulty, using a glass slide may make it easier to measure the capillary refill time.
- Moving on to the GI exam, note any signs of abdominal distention or masses that could point to an intraabdominal source.
- Be sure to complete a thorough HEENT to evaluate for otitis or throat infections

If the patient is drooling or having difficulty with managing secretions this could be a sign of a neck infection or epiglottitis.

- Finish up with a head to toe musculoskeletal and skin exam looking for point tenderness that may be concerning for septic arthritis or osteomyelitis or any evidence of cellulitis.

Now that you have diagnosed a child with sepsis, what is the next step?

- Here the new Surviving Sepsis Campaign guidelines can be very helpful.
- Below we have broken up their initial algorithm that you can find here https://www.sccm.org/getattachment/SurvivingSepsisCampaign/Guidelines/Pediatric-Patients/Initial-Resuscitation-Algorithm-for-Children.pdf?lang=en-US
- Review and we can work through each step.



Start by systematically screening for sepsis in children.

- We know that early identification and treatment of sepsis is critical to optimize patient outcomes.
- If patients have signs of septic shock then we should complete the initial evaluation expeditiously and start treatment with antibiotics within 1 hour.
- If there is no evidence of shock but sepsis is still suspected then we should expedite the evaluation but antibiotics should be administered within 3 hours.

- They recommend to start by obtaining a blood culture, starting empiric antibiotics, and measuring lactate if possible, followed by giving antibiotics as soon as cultures are obtained.
- They also recommend concomitantly obtaining IV/IO access, administering fluid boluses and vasoactive agents if indicated.
- Other basic labs such as complete blood count, metabolic panel, and urine studies as appropriate should also be considered here.
- Early intervention is important because otherwise many children will develop refractory shock and multiple organ dysfunction syndrome.

We will now work though each step in the initial resuscitation algorithm.

#1 Obtain IV/IO access

- Briefly, if the child is critically ill, don't delay obtaining IV access.
- If you are unable to get a reliable IV after a couple of minutes, then one of several commercially available IO devices make placing an intraosseous line a reliable option.

#2 Collect blood culture / #3 Start empiric broad-spectrum antibiotics

- If there is evidence of shock in the appropriate clinical setting assume possible sepsis, and we should give antibiotics as soon as possible.
    - Ideally, we would like to obtain cultures prior to administration of antibiotics but antibiotics should not be delayed if cultures are unable to be quickly obtained.
    - There is evidence that delaying antibiotics in these patients with septic shock by more than few hours from initial presentation may contribute to increased mortality.
    - Therefore, in these patients, antibiotics should be administered within 60 minutes.
- For those patients not in shock, but still have high risk of sepsis, the SCCM guideline suggests completing an expedited evaluation before giving antibiotics.
- This mostly just includes history, physical and focused labs or imaging if needed.
- The guidelines recommend giving antibiotics as soon as possible if there is evidence of sepsis associated organ dysfunction but at least within 3 hours if sepsis is suspected.
- There is concern that providing broad spectrum antibiotics to every child that meets the definition of SIRS criteria plus suspected infection will lead to antibiotic overuse, medication side effects and antibiotic resistance that will outweigh the benefits of immediate antibiotic therapy.
- Remember that common complaints such as URI and otitis media may meet this definition for sepsis, so use clinical judgment in otherwise well appearing children.
- The take home point is the severity of our patient's illness directs how fast we should provide empiric antibiotics.
- Of course, if there is obvious septic shock, then those patients will be treated aggressively.
- The SCCM guidelines help provide some clarity for those patients who are not critically ill on initial presentation.
- This gives us time to gather more information about the patient before committing the patient to IV antibiotics and in many cases overtreatment.

- Deciding what antibiotic to give can be complex but here are some concepts to keep in mind.
    - Choose the empiric broad-spectrum agent based on the likely pathogen.
    - Sepsis in children is most commonly due to gram-negative or gram-positive bacteria
    - Invasive fungal infections are largely restricted to immunocompromised patients and preterm infants.
    - Use your history, physical exam, labs and imaging to guide your choices
    - For a child who was previously healthy and presents with community-acquired sepsis, a third-generation cephalosporin like ceftriaxone may be appropriate for monotherapy
    - Vancomycin should be added if there is concern for resistant gram-positives like MRSA or pneumococcus.
        - Of course, vancomycin should not be used as monotherapy when the source is not known but along with another agent covering gram negatives.
- For immunocompromised patients or hospital-acquired sepsis, resistant gram-negative infection becomes much more likely.
    - There are three good empiric choices, all of which cover pseudomonas. These include
        - Cefepime
        - Meropenem, or
        - Piperacillin/tazobactam
    - The addition of an aminoglycoside such as gentamicin for additional coverage may even be appropriate depending on the clinical situation.
- Overall, ceftriaxone is the most common empiric antibiotic for undifferentiated sepsis in a previously healthy pediatric patient.
- We need to be careful to understand when ceftriaxone is not indicated.
    - Our patients that are receiving chemotherapy or frequently admitted to the hospital should most likely receive anti-pseudomonal coverage like cefepime or piperacillin-tazobactam.
    - In neonates < 4 weeks ceftriaxone is not the best choice due to the increased risk of kernicterus due to hyperbilirubinemia
        - Instead these patients typically require ampicillin to cover listeria in addition to broad-spectrum antibiotics like gentamicin or an advanced generation cephalosporin.
        - Also consider empiric acyclovir if there is a clinical concern for herpes simplex virus infection.
- Finally, remember in cases of suspected toxic shock syndrome or necrotizing fasciitis, empiric treatment should include clindamycin to limit toxin production and enhance bacterial clearance.

#4 Measure Lactate

- Lactate is used commonly in adult patients to screen for cardiovascular dysfunction in sepsis but the SCCM guideline suggested that there was not enough evidence to recommend using lactate values to stratify children with suspected shock to low or high-risk groups.
- Blood lactate levels may provide an indirect marker of tissue hypoperfusion and anaerobic metabolism due to organ dysfunction in sepsis.

    - This can be due to:
        - Systemic hypoperfusion
        - Hypoxemia or
        - May be falsely elevated due to localized hypoperfusion at blood sampling site.
- Unfortunately, there are many other causes of hyperlactatemia that occur during aerobic metabolism.
    - Albuterol is the most common drug we use that increases lactate but epinephrine and many drugs and toxins can also increase lactate.
        - Please see Josh Farkas' post on PulmCrit for more information
            - https://emcrit.org/pulmcrit/understanding-lactate-in-sepsis-using-it-to-our-advantage/
    - Hyperlactatemia is also seen in patients after a seizure or if there is an underlying metabolic, renal or liver disease.
- In adult patients, blood lactate levels greater than 2 mmol/L is included in the definition of septic shock.
- In pediatric patients, observational studies have demonstrated an association of elevated blood lactate levels with increased mortality.
- Because of all of the variability, lactate should be interpreted as part of a more comprehensive assessment of clinical status and perfusion.
- Remember that an elevated or rising lactate should get our attention, but our septic patients can be very sick and have a normal lactate level.
- If we have the ability to measure repeat lactate levels, then SCCM guideline suggests that we may trend these levels to guide the resuscitation but this is a weak recommendation and very low quality of evidence.
- There is also evidence that a bedside assessment of perfusion such as capillary refill time may be just as helpful [5].

#5 Administer fluid bolus(es) if shock is present

- Fluid resuscitation is something that all emergency and ICU physicians discuss in great detail.
- We know that fluid resuscitation can rapidly correct hypovolemia caused by capillary leak, vasodilation and fluid losses that are common in sepsis and this can provide a transient improvement in hemodynamics.
- Because of this, fluids are typically thought of as being the first line treatment of shock.
- Interestingly, fluid resuscitation in pediatric sepsis has become much more controversial in the last few years and the Surviving Sepsis guidelines reflect this.
- For patients in septic shock or who have sepsis-associated organ dysfunction and have access to intensive care, the guidelines suggest giving 10–20 mL/kg crystalloid boluses up to 40–60 mL/kg total over the first hour, titrated to clinical markers of cardiac output like heart rate, blood pressure, capillary refill time and urine output.
- Normal saline is commonly used for the initial fluid resuscitation, with lactated ringers and other balanced crystalloids becoming increasingly preferred.

- Fluids should be discontinued if signs of fluid overload develop such as signs of pulmonary edema or hepatomegaly.
- Despite the wide adaption of aggressive fluid resuscitation in sepsis there is very little prospective evidence supporting this practice.
- In healthcare systems without intensive care, patients are at much higher risk from suffering side effects of aggressive fluid resuscitation.
- There have been no large randomized-controlled trials in high-resources settings, and we largely rely on small retrospective studies that showed a correlation of IV fluid resuscitation with improved mortality.
- Interestingly there is one large randomized-controlled trial, the FEAST trial [6], of septic pediatric patients in resource-poor settings that showed an **increased** mortality associated with IV fluid boluses.
- Because the FEAST trial is the best quality evidence available, the SCCM recommended against the use of IV fluid boluses for normotensive pediatric patients with suspected sepsis if there not access to intensive care.
- It's important to note that the FEAST trial took place in Africa where there was no access to ICU care, so it is unknown if this data directly applies to our current practice in the United States.
- The hope is that in high-resource settings, patients can be protected from the harms of IV fluid boluses by using mechanical ventilation, diuretics and renal replacement therapy as needed.
- On the other hand, in healthcare systems that don't have access to ICU level of care, there is probably more evidence that fluid boluses harm rather than help.
- It is unclear how to manage hypotensive patients in poor resource settings and currently the SCCM guidelines recommend giving up to 40 mL/kg of crystalloid if there is no evidence of fluid overload but there is very limited evidence.

When thinking about what type of fluid to use…

- There's good evidence that crystalloids are superior to colloids for initial resuscitation of septic patients.
- The SCCM guidelines suggest using a balanced or buffered crystalloid like Lactated Ringers as opposed to saline.
- There are some concerns that high chloride concentrations in 0.9% saline may contribute higher rates of acute kidney injury but this not clear [7].
- We do know that large volume normal saline resuscitation will cause a hyperchloremic metabolic acidosis and this can be prevented by using a balanced crystalloid.
- Saline may be more appropriate if there is known hyponatremia, severe vomiting with a metabolic alkalosis or concern for intracranial pathology.
- For patients in undifferentiated sepsis, an initial bolus with saline may be reasonable if that is what is most on hand, but lactated Ringer's makes more sense as you continue your resuscitation.

#6 Start vasoactive agents if shock persists

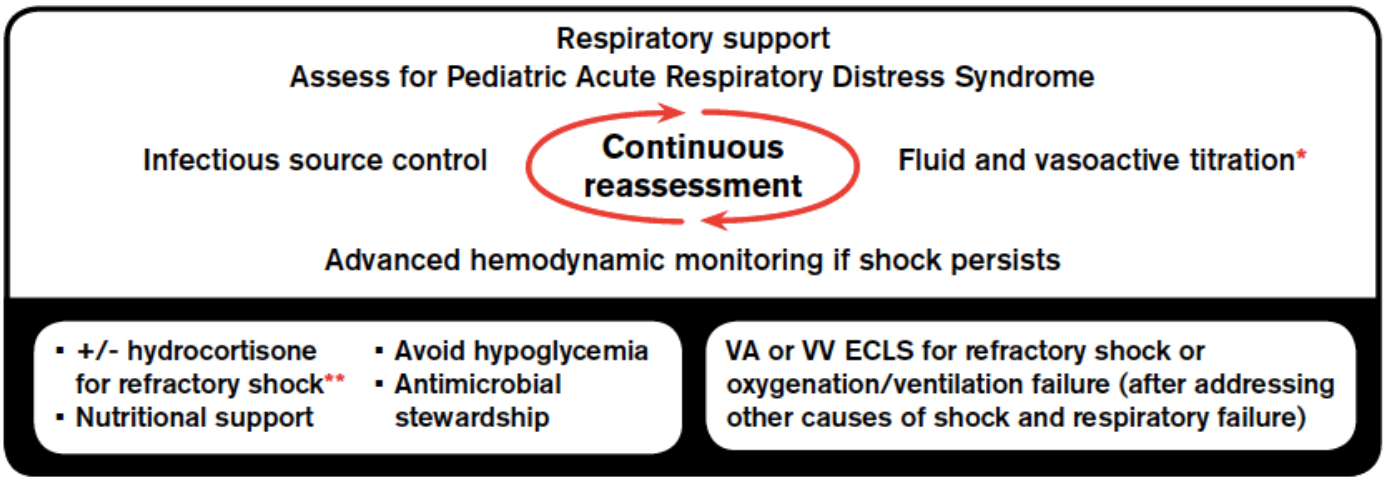
- Blood pressure goals should be appropriate for the patient's age and many providers recommend the blood pressure target to be at least the 5th percentile.
- For children older than 1 month, the systolic pressure should be at least 70 mmHg.

  - This is the systolic, so don't confuse this with the mean arterial pressure commonly discussed for adults.
- Children older than 10 years of age, a systolic of 90 is preferred similar to adults.
- For children less than 10 years, the lower limit of the systolic pressure can be estimated by multiplying the age in years x 2 plus 70.
  - That can be confusing at first so here's an example.
    - If your patient is 5 years old, that's 5 x 2 = 10, add that to 70 which equals 80
    - So, the systolic pressure for a 5-year-old should be greater than 80.
  - Double check your values using a Broselow tape or trusted app on your phone. Now is not the time to make a math error.
- Remember that blood pressure is just one marker of cardiac output.
- We also need to monitor peripheral perfusion, mental status, urine output and lactate if available.
- The previous pediatric shock guideline [8] recommended using a bedside assessment of peripheral perfusion to categorize the patient as warm shock and cold shock.
  - Warm shock is a vasodilatory distributive shock with warm extremities that is more common in septic adult patients.
  - Cold shock is characterized by cold extremities and poor peripheral perfusion.
- Typically, vasopressors are preferred for warm shock and inotropes for cold shock
- Studies have shown that it is very difficult to reliably access cardiac output by our exam.
- If you have access to point of care ultrasound you can get a better idea of cardiac function which may better direct our choice of vasoactive agents.
- One thing that we do know is that we should not use dopamine as our first line vasoactive agent in septic shock as there is good evidence that using dopamine increases mortality in these patients [9].
- Both epinephrine and norepinephrine are appropriate first line agents.
- Remember that epinephrine acts on both alpha and beta receptors and is best used to treat poor perfusion that is due to myocardial dysfunction and low cardiac output.
- Norepinephrine acts mostly on peripheral alpha receptors to increase systemic vascular resistance.
- If cardiac function seems appropriate on exam and bedside ultrasound then norepinephrine may be indicated.
- If cardiac function seems suppressed then epinephrine might be a better choice.

Peripheral vs. central access for vasoactive agents

- Giving peripheral pressors is controversial.
- We would always prefer having central access but this is not practical early in the resuscitation.
- If needed, consider administering a dilute concentration of the initial vasoactive medication through a reliable peripheral IV until you have more definititive access as delays in therapy will likely harm the patient.
- You will need to work closely with your nursing staff and closely monitor the IV site for signs of extravasation.

- If you are lucky enough to have a clinical pharmacist, ask them to make a dilute concentration in case the IV infiltrates.
- Vasopressors can be given through a secure IO if you are unable to obtain IV access. This hasn't been well studied in children but is likely safe.
- Remember to check an ionized calcium on your patients requiring hemodynamic support, especially in infants where the sarcoplasmic reticulum of the myocardium is not fully matured and very reliant on calcium.
- Adequate calcium levels are necessary for cardiac contractility and vasomotor tone.
- Patients in septic shock commonly have hypocalcemia and may benefit from replacement.



After the initial resuscitation the care of patients with sepsis requires continuous reassessment. This involves:

- Respiratory support & assessing for pediatric ARDS
- Fluid and vasoactive titration
- Advanced hemodynamic monitoring
- Infectious source control
- Steroids
- Nutritional support
- ECMO

Below we will introduce a few of these concepts

Source control

- Remember if there is an infected central line, abscess or necrotizing fasciitis, get your surgeons involved early.
- In these situations, patients will only improve after we remove the source of infection and ongoing inflammation.

How do you provide respiratory support for patients suffering from sepsis?

- If our patient responds to our initial resuscitation then we may be able to avoid intubation.
- Noninvasive ventilation with high flow nasal canula, CPAP or BiPAP may allow us to reduce the work the of breathing and improve oxygenation.
- Remember that noninvasive ventilation is only appropriate for children who don't have evidence of ongoing end organ dysfunction.
- These patients require close monitoring for possible worsening shock and need for intubation.
- There is not great evidence about early intubation of children with refractory septic shock that are otherwise maintaining their airway.
- It's reasonable to intubate these patients if they fail to respond to the initial resuscitation to reduce some of the high metabolic demand and work of breathing.
- This also is way to prevent emergent intubation if the patient's condition worsens.
- Remember that the peri-intubation time is high-risk for decompensation, especially in patients who are intravascularly dehydrated or are already hypotensive.
- The conversion to positive pressure ventilation that occurs during intubation reduces venous return to the right heart.
- Sedation may also worsen hemodynamics and cause further hypotension or even cardiac arrest.

What medications do you typically use for induction prior to intubation?

- The SSCM guidelines recommend using ketamine and fentanyl because of its favorable hemodynamic profile in the setting of shock.
- It's important to mention that etomidate should probably not be used.
- There is nothing conclusive but some evidence suggests that patients in septic shock may be at high risk of adrenal insufficiency after receiving even one dose etomidate.

What about steroids?

- Steroids are another controversial topic and there is a lot of variability between providers.
- The Surviving Sepsis guidelines recommend against using steroids routinely if patients respond to our initial resuscitation.
- There was not sufficient evidence to recommend for or against steroids for patients in refractory shock despite fluid and vasoactive support.
- What we do know is that if our patient was previously receiving chronic corticosteroids or has any reason to be at high risk for adrenal failure, steroids are likely indicated.
- Remember patients in adrenal failure may present with a combination of hypoglycemia, hyponatremia, hyperkalemia but these are not required to empirically treat.
- Also keep in mind that a large portion of pediatric patients presenting with septic shock are chronically ill.
- They may have a history of an organ or stem cell transplant, malignancy, renal disease or chronic lung disease.

- These patients are very commonly treated with courses of steroids and may need additional stress dosing due to their acute illness.
- If you decide to give steroids then choosing an agent with both glucocorticoid and mineralocorticoid activity like hydrocortisone is a good idea.
- Hydrocortisone improves myocardial contractility and vascular smooth muscle tone.
- Well known side effects to keep in mind include hyperglycemia and muscular weakness and increase risk of hospital-acquired infections with prolonged use.
- There is just no definitive evidence that steroids improve outcomes.

What to do about persistent, refractory shock?

- Much of these next steps are not totally evidence based and depend on individual clinician preference and best practices.
- If there is continued hypotension you can either add vasopressin or further titrate up to high-dose catecholamines.
- If there is evidence of persistent cardiac dysfunction an inodilator like milrinone or dobutamine could be trialed.
    - Inodilators help increase cardiac output by improving cardiac filling and reducing afterload.
    - But be careful because this can worsen hypotension.

What about ECMO?

- Remember that ECMO stands for extracorporeal membrane oxygenation.
- This is a way to support patients who have developed either respiratory or cardiac failure.
- EMCO is only a supportive therapy and should only be used in children that are suffering from a reversible cause.
- In patients with septic shock this is commonly ARDS or sepsis induced myocardial dysfunction.
- The patient's physiology dictates if either VA or VV ECMO is offered.
- VV or veno-venous ECMO is can be considered in PARDS—that is pediatric acute respiratory distress syndrome and refractory hypoxia.
- In VV ECMO deoxygenated blood is removed from the venous circulation, is oxygenated and typically delivered back in to the vena cava and right atrium.
- This requires our patient to have adequate heart function.
- In VA or veno-arterial ECMO deoxygenated blood is removed from a large vein, oxygenated and bypasses the heart by being pumped directly into the arterial system.
- VA EMCO is reserved for patients with cardiac failure or in some small infants
- Remember that sepsis is a hypermetabolic condition and these patients typically require supraphysiologic blood flow on ECMO which can be difficult to achieve in some patients.

Take home points/pitfalls:

- Remember to always review age adjusted vital signs on every patient and don't dismiss any unexplained tachypnea or tachycardia as this may be a sign of significant illness.
- Be very worried about any ill-appearing child, and use a structured approach to effectively care for each critically ill patient.
- Have a low threshold to evaluate for sepsis in any child who looks unwell.
- Remember that pediatric sepsis is 2 age adjusted SIRS criteria plus suspected infection.
- Use your history and exam to guide your initial resuscitation.
- Patients with suspected sepsis all need an IV access, blood cultures, empiric antibiotics and lactate measured if available.
- Many will likely need some amount of fluid resuscitation and further support guided by your bedside exam.
- Interpret labs in light of the clinical picture. A single white count or lactate level isn't very helpful unless it is tied to the clinical picture. If a kid looks really sick, the labs may be normal despite critical illness.
- Remember that children may look okay but can decompensate quickly as they run out of their physiologic reserve.
- It is important that once you recognize a child is critically ill to quickly get your referring pediatric intensivist on the phone to facilitate transfer.

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