

Identification & Treatment of Sepsis for the Pediatric Population

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A presentation for HealthTrust Members
March 13, 2018



Atlantic
Health System

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Pharmacist Learning Objectives

1. Define the different types of sepsis
2. Describe the pathophysiology of sepsis
3. Discuss etiology and current treatment guidelines for pediatric sepsis
4. Assess limitations of current guidelines
5. Evaluate the benefits of early goal-directed therapy
6. Assess the use of steroids in pediatric sepsis



Technician Learning Objectives

1. List the commonly used vasoactive agents in pediatric sepsis
2. Discuss preparation instructions for such agents
3. State monitoring parameters for various agents
4. Identify potential adverse effects for each agent



Sepsis

- Life-threatening organ dysfunction caused by a dysregulated host response to infection

- Different types
 - Systemic Inflammatory Response Syndrome (SIRS): ≥ 2 abnormalities of temperature, heart rate, respiratory rate, and white blood cell count
 - Sepsis: SIRS plus suspected or proven infection
 - Severe sepsis: sepsis plus organ dysfunction
 - Septic shock: sepsis plus cardiovascular dysfunction

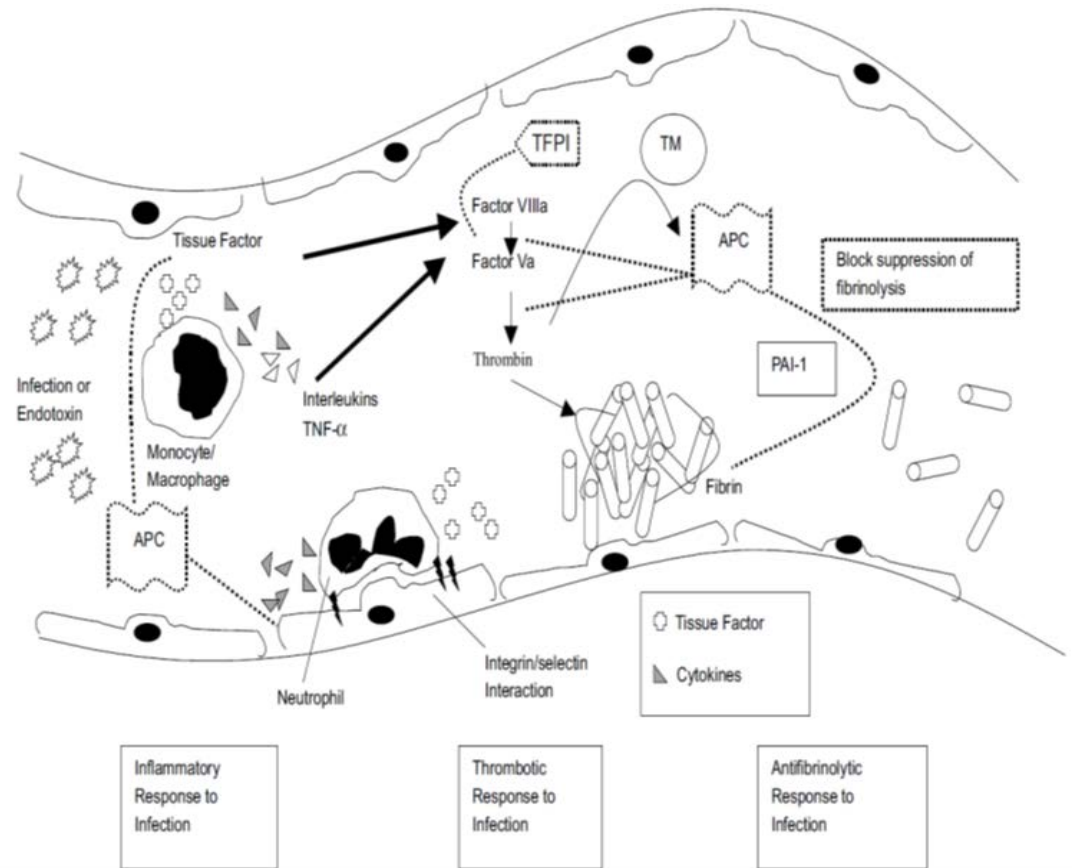
- Leading cause of mortality and critical illness worldwide

- *Streptococcus pneumoniae* is the most common pathogen



Pathophysiology

- Vascular endothelial injury
 - Causes release of tissue factor (TF) → triggers extrinsic clotting system → production of thrombin and fibrin
- Inflammation
 - Due to inflammatory insult, neutrophils are attracted to the inflammation site → adhere to vascular endothelial cells
- Coagulation



Warm vs. Cold Shock

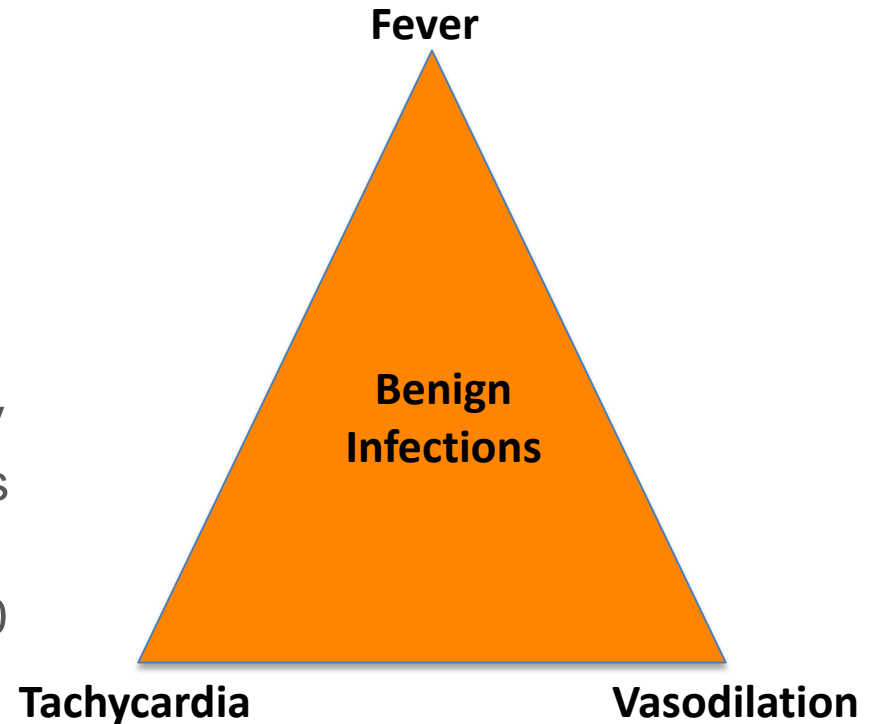
- Cold shock is most common in pediatrics
 - Late onset
 - ↓ cardiac output (CO) and ↑ systemic vascular resistance (SVR)
- Warm shock
 - Early onset
 - ↑ CO and ↓ SVR

	Warm Shock	Cold Shock
Peripheries	Warm, flushed	Cold, clammy, cyanotic
Capillary refill	< 2 sec	> 2 sec
Pulse	Bounding	Weak, feeble
Heart rate	Tachycardia	Tachycardia or bradycardia
Blood pressure	Relatively maintained	Hypotension
Pulse pressure	Widened	Narrowed



Clinical Presentation

- Signs and symptoms
 - Hypothermia or hyperthermia
 - Altered mental status
 - Peripheral vasodilation (warm shock)
 - Vasoconstriction with capillary refill greater than two seconds (cold shock)
- Threshold heart rate: less than 70 or greater than 150 associated with increased mortality



Diagnosis: Septic Shock

- Clinical diagnosis made when
 - Suspected infection manifested by hypothermia or hyperthermia
 - AND
 - Clinical signs of inadequate tissue perfusion
 - Decreased or altered mental status
 - Prolonged capillary refill greater than two seconds
 - Diminished pulses
 - Mottled cool extremities or flash capillary refill
 - Bounding peripheral pulses and wide pulse pressure
 - Decreased urine output (less than 1 mL/kg/hr)
- Hypotension is not required for diagnosis, often a late symptom

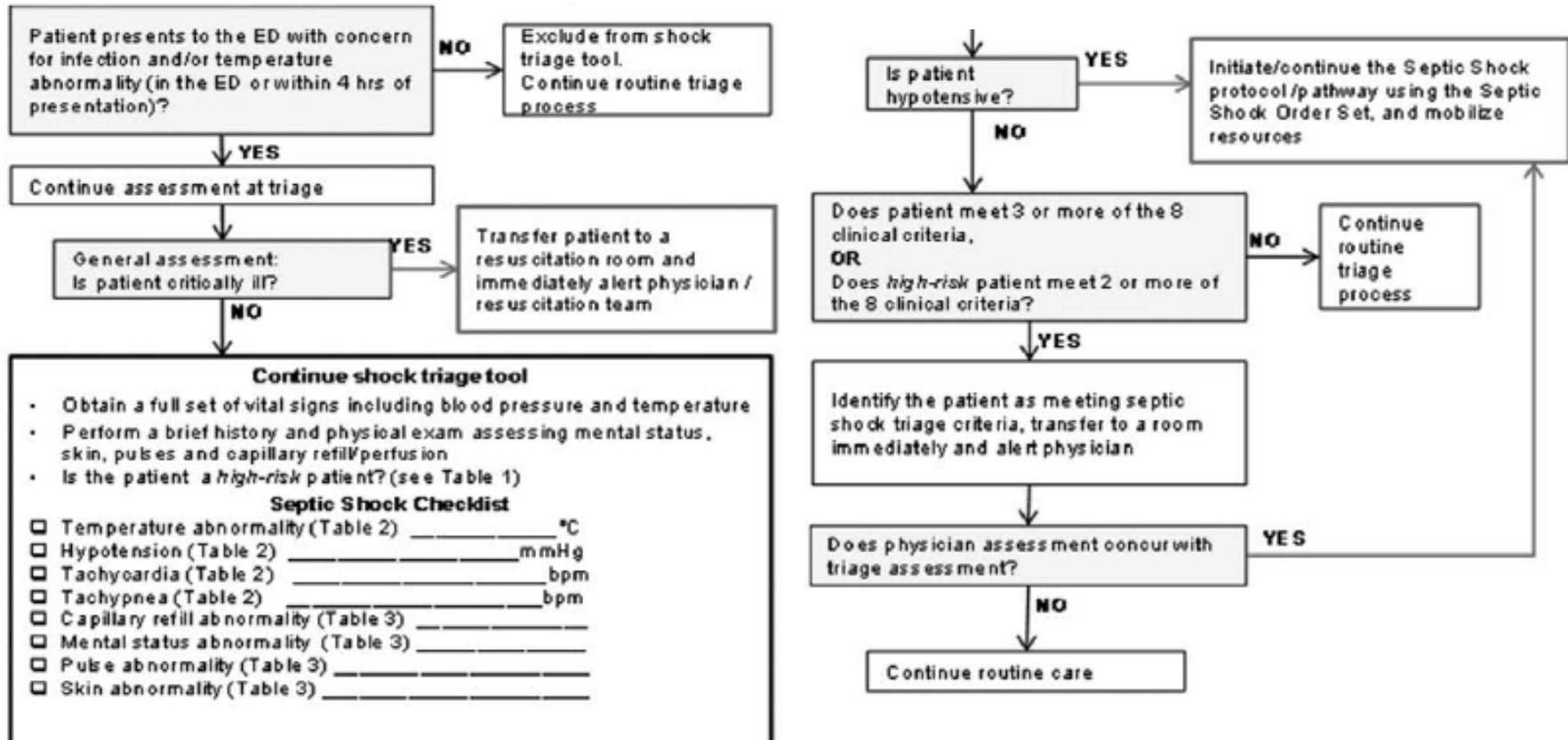


Use of Recognition Bundles to Optimize Identification

- Components
 - Trigger tool
 - Clinician assessment within 15 minutes for patients identified by the trigger tool
 - If septic shock is suspected, a resuscitation bundle should be activated



Trigger Tools



Early Septic Shock Recognition

Table 1. High Risk Conditions

- Malignancy
- Asplenia (including SCD)
- Bone marrow transplant
- Central or indwelling line/catheter
- Solid organ transplant
- Severe MR/CP
- Immunodeficiency, immunocompromise or immunosuppression

Table 2. Vital Signs (PALS)

Age	Heart Rate	Resp Rate	Systolic BP	Temp (°C)
0 d - 1 m	> 205	> 60	< 60	<36 or >38
≥ 1 m - 3 m	> 205	> 60	< 70	<36 or >38
≥ 3 m - 1 r	> 190	> 60	< 70	<36 or >38.5
≥ 1 y - 2 y	> 190	> 40	< 70 + (age in yr × 2)	<36 or >38.5
≥ 2 y - 4 y	> 140	> 40	< 70 + (age in yr × 2)	<36 or >38.5
≥ 4 y - 6 y	> 140	> 34	< 70 + (age in yr × 2)	<36 or >38.5
≥ 6 y - 10 y	> 140	> 30	< 70 + (age in yr × 2)	<36 or >38.5
≥ 10 y - 13 y	> 100	> 30	< 90	<36 or >38.5
> 13 y	> 100	> 16	< 90	<36 or >38.5

Table 3. Exam Abnormalities

	Cold Shock	Warm Shock	Non-specific
Pulses (central vs. peripheral)	Decreased or weak	Bounding	
Capillary refill (central vs. peripheral)	≥ 3 sec	Flash (< 1 sec)	
Skin	Mottled, cool	Flushed, ruddy, erythroderma (other than face)	Petechiae below the nipple, any purpura
Mental status			Decreased, irritability, confusion, <u>inappropriate</u> crying or drowsiness, poor interaction with parents, lethargy, diminished arousability, obtunded

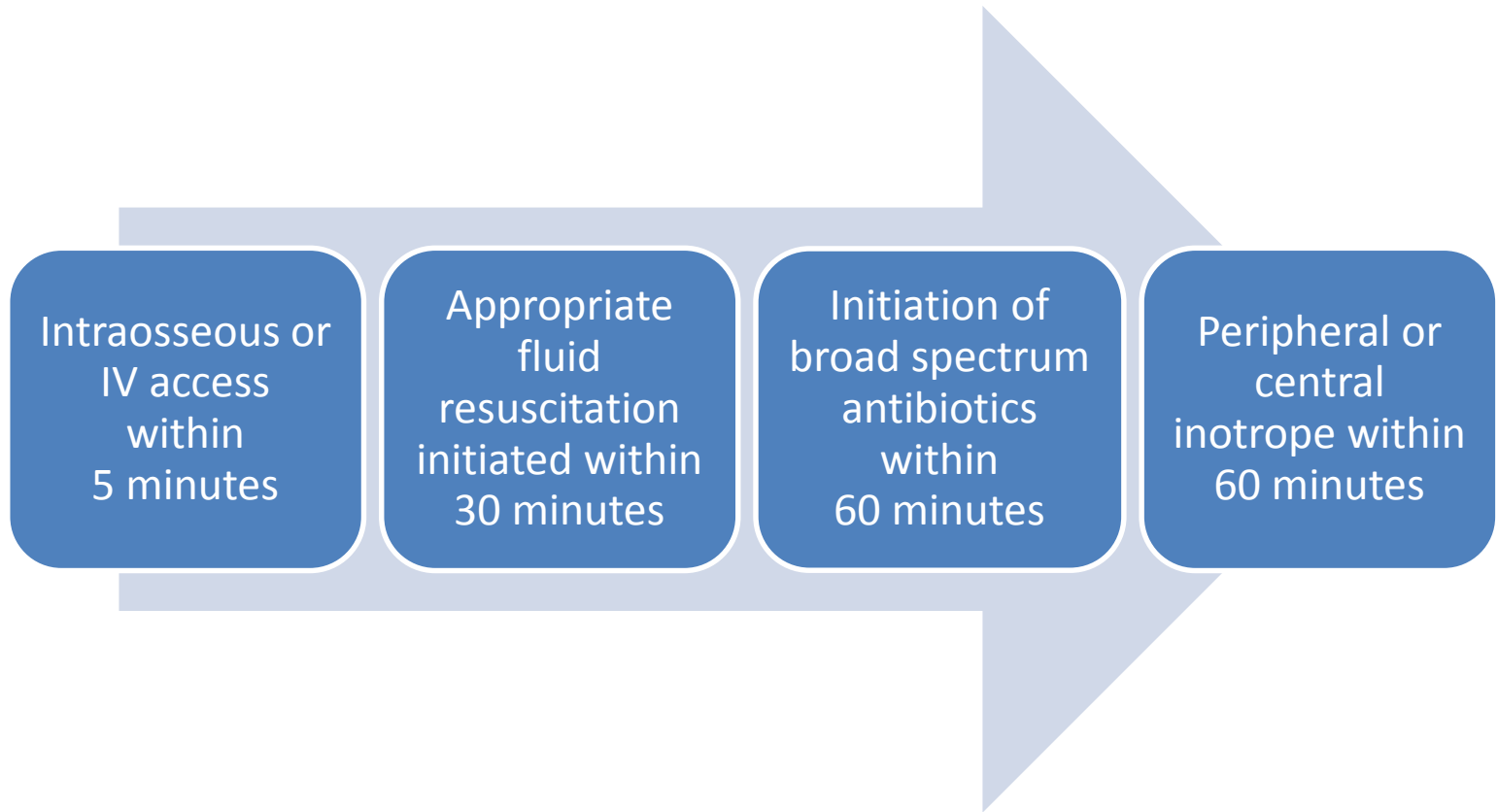


Improving Recognition of Pediatric Severe Sepsis in the Emergency Department (ED)

- Objective: evaluate performance of a sepsis recognition process, including an electronic sepsis alert and bedside assessment in a pediatric ED
- Methods: cohort study
 - Exposure: positive electronic sepsis alert
 - Prompted team assessment to determine need for sepsis protocol
 - Outcome: severe sepsis
- Results: overall, alert implementation increased ED sepsis detection from 83% to 96%
- Conclusion: implementation of the electronic sepsis alert was associated with improved recognition of severe sepsis



Resuscitation Bundles



Treatment Algorithm

0 min

Recognize decreased mental status and perfusion.
Begin high flow O₂ and establish IO/IV access according to PALS.

5 min

If no hepatomegaly or rales / crackles then push 20 mL/kg isotonic saline boluses and reassess after each bolus up to 60 mL/kg until improved perfusion. Stop for rales, crackles or hepatomegaly. Correct hypoglycemia and hypocalcemia.
Begin antibiotics.

15 min

Fluid refractory shock?

Begin peripheral IV/IO inotrope infusion, preferably Epinephrine 0.05 – 0.3 µg/kg/min
Use Atropine / Ketamine IV/IO/IM if needed for Central Vein or Airway Access

Titrate Epinephrine 0.05 – 0.3 µg/kg/min for Cold Shock.
(Titrate central Dopamine 5 – 9 µg/kg/min if Epinephrine not available)
Titrate central Norepinephrine from 0.05 µg/kg/min and upward to reverse Warm Shock.
(Titrate Central Dopamine ≥ 10 µg/kg/min if Norepinephrine not available)

60 min

Catecholamine-resistant shock?

If at risk for Absolute Adrenal Insufficiency consider Hydrocortisone.
Use Doppler US, PICCO, FTD or PAC to Direct Fluid, Inotrope, Vasopressor, Vasodilators
Goal is normal MAP-CVP, ScvO₂ > 70%* and CI 3.3 – 6.0 L/min/m²



The First Hour of Resuscitation: ABC

- Goals
 - Maintain or restore airway, oxygenation and ventilation
 - Maintain or restore circulation
 - Maintain or restore threshold heart rate
- Airway and breathing
 - Initial therapy: supplemental oxygen or high-flow nasal cannula
 - Progression of sepsis can lead to hypoxemia and metabolic acidosis followed by respiratory alkalosis
 - Intubation
 - Dependent on clinical assessment
 - Ketamine plus atropine pretreatment is the preferred combination for induction during intubation



Initial Management: First hour

- Circulation
 - Vascular access should be obtained within minutes, otherwise intraosseous placement should be conducted
 - Begin fluid resuscitation immediately unless hepatomegaly, rales or cardiac gallop are present
 - If fluid refractory, a peripheral inotrope should be started
- Antibiotics
 - Cultures should be collected and broad spectrum antibiotics started within the first hour



Initial Fluid Resuscitation

- Goals
 - Attain normal perfusion and blood pressure
 - Prevent or correct hypoglycemia
- Administer 20 mL/kg fluid boluses, observe for fluid overload
 - Can be administered by push or pressure bag
 - First hour usually requires 40-60 mL/kg if the child is not fluid overloaded
- Hypoglycemia
 - Administer 10% dextrose containing isotonic IV solution



Initial Hemodynamic Support and Refractory Therapy

- Options for hemodynamic support include DOPamine, EPINEPHrine, or norepinephrine
- EPINEPHrine or norepinephrine are preferred
 - EPINEPHrine can be started for “cold” shock
 - Norepinephrine can be started for “warm” shock
- Refractory treatment
 - Hydrocortisone
 - Place in therapy: used if child is refractory despite vasopressors, and at risk for absolute adrenal insufficiency



Therapeutic Endpoints for the First Hour

- Capillary refill less than or equal to two seconds
- Normal pulses with no differential between the quality of peripheral and central pulses
- Warm extremities
- Urine output greater than 1 mL/kg/hr
- Normal mental status
- Normal blood pressure for age
- Normal glucose concentration
- Normal ionized calcium concentration



Patient Case

- 13-year-old female presents to the ED from home
- Chief Complaint (CC): fever, abdominal pain
- History of Present Illness (HPI):
 - 7 days PTA → presented to pediatrician, given course of amoxicillin for suspected mesenteric adenitis
 - 3 days PTA → presented to ED, lab work within normal limits, diagnosed with constipation and sent home
 - 2 days PTA → seen by pediatric GI who requested additional lab work
 - 1 day PTA → persistent fevers and worsening pain
 - Day of arrival (DOA) → presents to ED due to persisting symptoms



Patient Case

Past Medical History

- No significant past medical history

Past Surgical History

- None

Social History

- Homeschooled
- Lives with parents and older sister

Family History

- Noncontributory

Home medications

- Pediatric multivitamin
- Probiotic



Patient Case – ED Presentation

Vital Signs	
Temperature (°C)	39.6
Heart Rate (bpm)	130
Blood Pressure (mmHg)	85/48
Respiratory Rate (bpm)	42
O ₂ Saturation	98% on room air

Physical Exam	
Cardiovascular	Tachycardia, capillary refill 3-4 secs in lower extremities, bounding pulses
Pulmonary	Tachypneic with shallow breaths, decreased aeration
Abdominal/GI/ Renal	Pain, tender in bilateral flanks, L>R



Patient Case – ED Management

- Fluid resuscitation
 - 20 mL/kg fluid bolus of 0.9 % sodium chloride administered
 - Weight: 64 kg
 - $64 \text{ kg} \times 20 \text{ mL/kg} = 1,280 \text{ mL}$ of 0.9% sodium chloride
 - Repeat exam
 - HR: 117 bpm
 - RR: 36 bpm
 - T: 39.4°C
 - BP: 90/50 mmHg
 - O₂ saturation: 99% on 2 L NC
 - Capillary refill: < 2 secs
 - Additional 20 mL/kg fluid bolus administered



Patient Case – ED management

- Blood cultures drawn and antibiotics initiated
 - Piperacillin/tazobactam: 4 g piperacillin component (adult dose)
 - Vancomycin 1 g (15 mg/kg) IV once
- Abdominal x-ray: **bilateral renal abscesses**
- Patient in fluid refractory shock
 - Norepinephrine 0.05 mcg/kg/min started for warm shock
 - What makes our patient a candidate for treatment for warm shock?
- Diagnosis: septic shock 2/2 bilateral renal abscesses
- Patient transferred to the pediatric ICU (PICU)



Meanwhile, in the PICU...

- Initiated on maintenance fluids
 - D5NS at 105 mL/hr
- Full course of antibiotics initiated
 - Cefepime 2 g IV q12h (adult dose)
 - Vancomycin 1 g (15 mg/kg) IV q12h
- Norepinephrine still running at 0.05 mcg/kg/min
- Remaining question
 - Should our patient be started on steroid therapy?



Role of Steroids in Septic Shock

- Refractory therapy
 - Used during risk of absolute adrenal insufficiency or adrenal pituitary axis failure when shock persists regardless of EPINEPHrine or norepinephrine infusion
- Hypothesis for use of hydrocortisone
 - Relative adrenal insufficiency
 - Changes in the hypopituitary adrenal axis, glucocorticoid receptor, and cortisol metabolism
- Baseline cortisol levels should be obtained prior to starting hydrocortisone



Reasoning Behind Abnormal Cortisol Levels

- Hypoproteinemia
 - Decreases total cortisol concentration
- Adrenocorticotrophic hormone (ACTH) stimulation
 - Elevated serum cortisol levels = lower ACTH concentrations
- Absolute adrenal insufficiency
 - Basal serum cortisol level of less than 7 mcg/dL and peak serum cortisol of less than 18 mcg/dL after stimulation
- Relative adrenal insufficiency
 - Basal serum cortisol level of less than 20 mcg/dL and a change of less than 9 mcg/dL after cortisol stimulation



Steroid Recommendations

- Patients at risk for inadequate cortisol/aldosterone production
 - Purpura fulminans and Waterhouse-Friderichsen syndrome
 - Previously received steroid therapy for chronic illness
 - Pituitary or adrenal abnormalities
- May be beneficial to administer stress dose hydrocortisone in the early course of illness for these patients
- Whether separate mineralocorticoid replacement is needed, remains unclear



CORTICUS Study

- Purpose: evaluate the survival benefit of hydrocortisone in septic shock patients
- Design: multicenter, double-blind, randomized, placebo-controlled trial
- Intervention: 50 mg IV hydrocortisone q6h x 5 days or placebo
- Primary outcome: mortality at 28 days in patients who did not have a response to the corticotropin test



Results and Conclusion

- At 28 days, no difference in mortality between patients who did not have a corticotropin response in the two study groups ($p=0.69$)
 - 46.7% did not have a response to corticotropin
- 34% of patients died in the steroid group vs 31% in the placebo group ($p=0.51$)
- Duration of shock was shorter in the steroid group, but greater incidence of recurrent sepsis and septic shock
- Conclusions
 - Hydrocortisone was not efficacious in improving survival or reversal of shock in adults



RESOLVE Study

- Purpose: determine whether corticosteroids used as adjunctive therapy for pediatric severe sepsis is associated with improved outcomes
- Design: retrospective cohort study which examined the clinical database in the RESOLVE trial
- Population: 477 children with severe sepsis

Baseline Characteristics			
	Received CS (n=193)	Did not receive CS (n=284)	P-value
Age, years	5.45 +/- 5.54	4.68 +/- 5.10	0.1229
Male sex, %	51.8	55.6	0.4112
Organ dysfunctions, n	3.8 +/- 1.2	3.6 +/- 1.2	0.0602
PRISM III, 12-hr score	17.2 +/- 8.1	16.5 +/- 8.2	0.4040
CS: corticosteroid, PRISM: pediatric risk of mortality All values are mean +/- standard deviation unless stated otherwise			



Results and Conclusion

- In children with severe sepsis and similar severity of illness, the use of corticosteroids did not improve risk of mortality
- Conclusion
 - Outcomes were similar in patients who received corticosteroids versus those who did not
- Limitations
 - No protocol for administration and dosing of steroids
 - Lack of ACTH stimulation testing

Results			
	Received CS	Did not receive CS	P-value
Mortality, %	15.1	18.8	0.2971
MV, days	8.3 +/- 6.4	7.7 +/- 7.5	0.3750
V-I support, days	4.5 +/- 4.1	4.3 +/- 4.7	0.5891
PICU, LOS	12.1 +/-8.0	11.0 +/- 8.5	0.1562

MV: mechanical ventilation; V-I: vasopressor-inotropic, PICU: pediatric ICU; LOS: length of stay
All values are mean +/- SD unless stated otherwise



Steroid Meta-Analysis

- Objective: evaluate efficacy of steroid use versus placebo in children with fluid or vasopressor dependent shock
- Design: meta-analysis of randomized controlled trials (RCTs)
- Primary outcome: mortality or duration of shock
- Secondary outcome: duration of hospitalization
- Interventions
 - 5 trials used IV hydrocortisone
 - 2 trials used IV methylPREDNisolone
 - 1 trial used IV dexamethasone



Results and Conclusion

- Comparison group
 - Four trials compared steroids with placebo
 - Four trials compared steroids vs. no steroids, as adjunct to standard therapy
- Results
 - Two studies showed a statistically significant effect of steroids on decreasing mortality in dengue shock syndrome ($p=0.007$)
 - No difference in mortality rates between those who did and did not receive steroids in remaining studies ($p=0.078$)
 - No difference in shock duration between steroid and no steroid group
 - No difference in hospital duration between steroid and no steroid group
- Conclusion
 - No clear evidence of mortality benefit or modification of shock duration with steroid use in pediatric shock



Role of Fludrocortisone

- Purpose: determine whether the addition of fludrocortisone to a hydrocortisone based protocol leads to a decrease in vasopressor duration
- Methods: retrospective chart review
- Population: 97 children with SIRS and shock

Hypotension requiring
60 mL/kg fluid resuscitation
and initiation of vasopressors

If no improvement

Empirically start hydrocortisone
100 mg/m²/day (max dose 50 mg)
IV q6h x 7 days

Dependent on discretion of
attending physician

Fludrocortisone 50 mcg po/ng
daily if < 35 kg OR fludrocortisone
100 mcg po/ng daily if ≥ 35 kg



Results and Conclusion

- Overall mortality was 7%
 - 5 out of 7 children who experienced mortality received hydrocortisone plus fludrocortisone
 - Septic children who received hydrocortisone plus fludrocortisone required a shorter duration of norepinephrine
- Conclusion
 - No difference found in the SIRS subgroup
 - Addition of corticosteroids resulted in a shorter duration of vasopressors
- Limitations
 - Lack of routine ACTH stimulation testing
 - Lack of criteria guiding timing of steroid initiation and fludrocortisone addition



Pros and Cons of Stress Dose Steroids

Pros	Cons
Decrease in catecholamine duration	Increased rates of infection
Decrease in catecholamine amount	Increased bleeding risk
	Hyperglycemia
	Worsening of sepsis/septic shock



Back to our patient...

- No history of chronic illness requiring steroid therapy
- No risk of adrenal insufficiency
- Vasopressor running at recommended initial rate
- Is it wise to start hydrocortisone therapy at this point?
 - No benefit in steroid therapy if not at risk for adrenal insufficiency



Stabilization

- Goals
 - Normal perfusion, capillary refill, and threshold heart rates
 - Perfusion pressure appropriate for age
 - Cardiac index (CI) greater than 3.3 and less than 6.0 L/min/m²

Threshold Heart Rates and Perfusion Pressure

	Heart Rate (bpm)	Mean Arterial Pressure (mmHg)
Newborn	110-160	(55 + age x 1.5) = 55
Infant (2 yr)	90-160	(55 + age x 1.5) = 58
Child (7 yr)	70-150	(55 + age x 1.5) = 65



Fluid Resuscitation

- Fluid losses may be persistent for days
- Replacement should align with clinical endpoints
- Crystalloid: fluid of choice if hemoglobin > 10 g/dL
- If prolonged INR, infusion of fresh frozen plasma (FFP) is recommended
- Hypoglycemia
 - D10% isotonic IV solution should be run at a fluid maintenance rate
 - Glucose concentrations should be greater than 80 mg/dL and less than 150 mg/dL



Hemodynamic Support

- Catecholamine resistant shock
 - Clinical presentation
 - Low cardiac output (CO) and high systemic vascular resistance (SVR)
 - High CO and low SVR
 - Low CO and low SVR



Shock: Low CI, Normal BP, High SVR

- Situation: resistance to EPINEPHrine
- First line treatment: milrinone
- Second line treatment: nitroprusside or nitroglycerin
- Monitoring parameters: cyanide or isothiocyanate toxicity



Shock: Low CI, BP, and SVR

- Norepinephrine can be added to or substituted for EPINEPHrine to increase diastolic blood pressure and SVR
- After resolution of hypotension, DOBUTamine or a type III phosphodiesterase inhibitor may be added to norepinephrine to improve CI and central venous oxygen saturation (Scvo₂)



Shock: High CI and Low SVR

- If hypotension exists regardless of norepinephrine and fluid titration, low-dose vasopressin, angiotensin, or terlipressin may be useful
- Frequent reevaluation of hemodynamic parameters is recommended during vasopressor therapy



Refractory Shock

Condition	Treatment
Pericardial effusion	Pericardiocentesis
Pneumothorax	Thoracentesis
Hypoadrenalism	Adrenal hormone replacement
Hypothyroidism	Thyroid hormone replacement
Ongoing blood loss	Blood replacement/hemostasis
Increased Intra-arterial Pressure	Peritoneal catheter or abdominal release
Necrotic tissue	Nidus removal
Excessive immunosuppression	Wean immunosuppressants



Extracorporeal Membrane Oxygenation (ECMO) and Continuous Renal Replacement Therapy (CRRT)

- Once potential reversible causes have been addressed, ECMO may be the next option
- Reasoning: mitigates differential cyanosis, allows for highest possible flow rates → resolution of shock
- Monitoring parameters
 - Prevention of hemolysis
 - Plasma free hemoglobin concentrations should be maintained at less than 0.05 g/L
- Continuous renal replacement therapy (CRRT)
 - Consider for fluid overload or patients with purpura



Therapeutic Endpoints for Stabilization

- Capillary refill less than or equal to two seconds
- Threshold heart rate
- Normal pulses with no differential between quality of peripheral and central pulses
- Warm extremities
- Urine output greater than 1 mL/kg/hr
- Normal mental status
- CI greater than 3.3 and less than 6.0 L/min/m² with normal perfusion pressure for age
- Scvo₂ > 70%



Patient Case – Stabilization

- Hypotension resolved, norepinephrine drip discontinued
- Interventional Radiology (IR) consult obtained
- Blood cultures still negative to date
- Plan for drainage of abscesses on HD 3

Vital Signs: HD 2	
Temperature	Afebrile
HR	76 bpm
RR	23 bpm
BP	111/76 mmHg
O ₂ Saturation	98% RA



Patient Case – Stabilization

- Fluid drained from abscesses and sent for culture
 - Total amount drained = 12 mL
- Transferred to the general pediatrics floor

Vital Signs: HD 3	
Temperature	Afebrile
HR	80 bpm
RR	17 bpm
BP	119/80 mmHg
O ₂ Saturation	98% RA



Patient Case – Stabilization

- Surgical cultures result as gram positive cocci
- HD 5-7
 - Vital signs remain stable
 - Blood culture results as methicillin resistant staphylococcus aureus (MRSA), vancomycin continued and cefepime discontinued
 - Day 7, patient discharged with four week course of clindamycin 600 mg po q8h

Vital Signs: HD 4	
Temperature	Afebrile
HR	80 bpm
RR	17 bpm
BP	119/80 mmHg
O ₂ Saturation	98% RA



Adverse Effects and Monitoring of Vasoactive Agents

- DOBUTamine
 - Tachyarrhythmias
 - Hypotension
 - Hypertension
 - Extravasation
 - Monitor: blood pressure, heart rate, electrolytes, and cardiac output
- EPINEPHrine
 - Anxiety
 - Dizziness
 - Arrhythmias
 - Extravasation
 - Monitor: blood pressure and heart rate
- DOPamine
 - Arrhythmias
 - Hypertension
 - Ischemia
 - Extravasation
 - Monitor: EKG, heart rate, MAP, and urine output
- Norepinephrine
 - Tachycardia
 - Bradycardia
 - Arrhythmias
 - Extravasation
 - Monitor: blood pressure, heart rate, and urine output



Vasoactive Preparations

Name	Weight	Concentration (mcg/mL)	Mixing instructions	Range (mcg/kg/min)	Starting Rate (mcg/kg/min)
DOPamine	< 10 kg	1,600	400 mg in total volume of 250 mL D5W	2-20	5
DOPamine	> 10 kg	3,200	800 mg in total volume of 250 mL D5W	2-20	5
DOBUTamine	< 20 kg	2,000	500 mg in total volume of 250 mL D5W	2-20	5
DOBUTamine	> 20 kg	4,000	1,000 mg in total volume of 250 mL D5W	2-20	5



Vasoactive Preparations

Name	Weight	Concentration (mcg/mL)	Mixing instructions	Range (mcg/kg/min)	Starting Rate (mcg/kg/min)
EPINEPHrine	< 10 kg	50	12.5 mg in total volume of 250 mL NS	0.05-1	0.05
EPINEPHrine	> 10 kg	100	25 mg in total volume of 250 mL NS	0.05-1	0.05
Norepinephrine	< 10 kg	50	5 mg in total volume of 100 mL D5W	0.05-2	0.05
Norepinephrine	> 10 kg	100	10 mg in total volume of 100 mL D5W	0.05-2	0.05



Summary

- Sepsis is a life threatening form of organ dysfunction caused by a dysregulated host response to infection
- Treatments within the first hour should focus on maintenance of airway, breathing, and circulation
- The timeline for the first hour includes IV access, fluid resuscitation, initiation of antibiotics, initiation of vasopressors (if needed), and drawing cultures
- Steroids are an option as refractory therapy, overall no clinical benefit shown
- Treatment with steroids should be tailored to individual cases

