

Sepsis in Children


**Recognizing the many faces of pediatric
sepsis and
dealing with them successfully**

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May 24,2017**

I have no disclosures and no
financial associations (sadly)

(And I really thought that George was the best looking Beatle, not Paul....)

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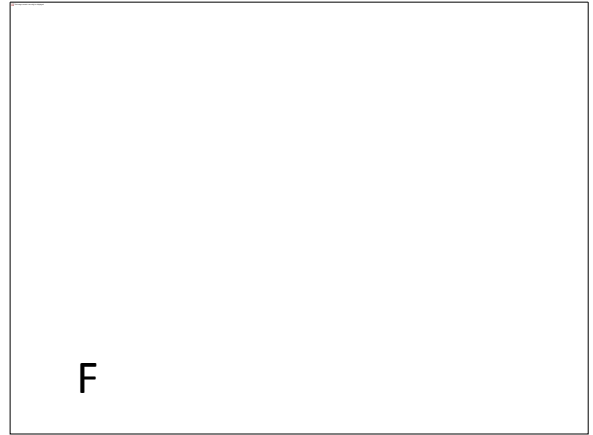
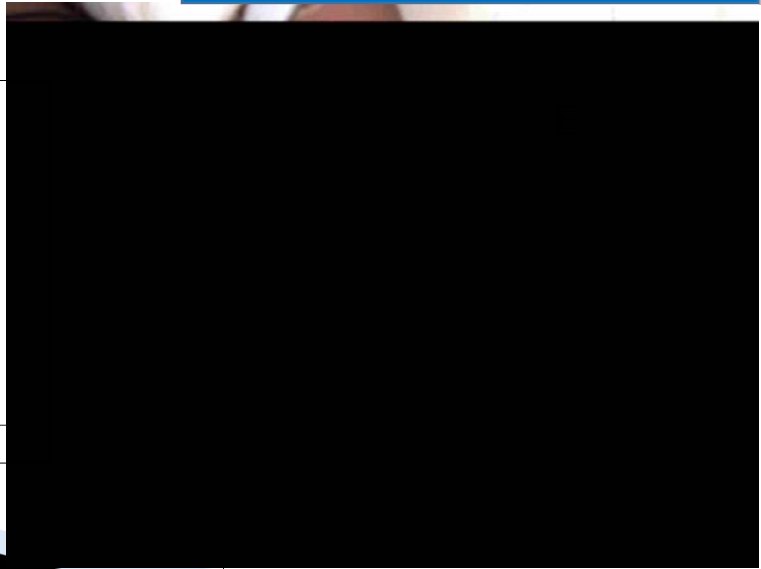
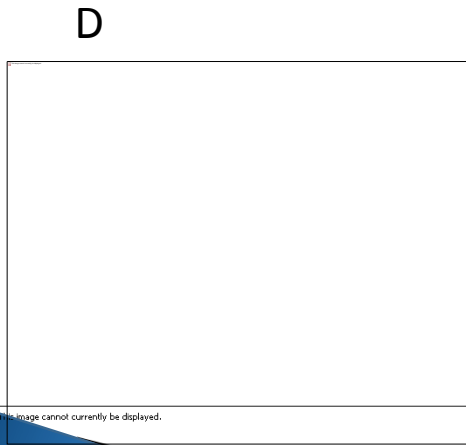
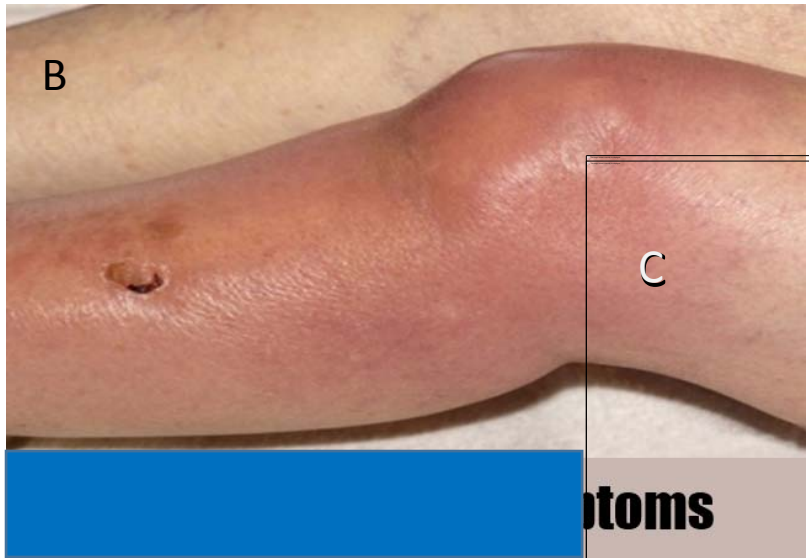


Objectives

- ▶ **Recognize the child with possible sepsis**
- ▶ **Describe the various causes of sepsis**
- ▶ **Initiate a management plan for someone suspected to have sepsis**
- ▶ **Describe the outcomes of sepsis**


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Which of these children have sepsis?



Sepsis-Historical context

- ▶ **The oldest and most elusive syndrome in medical history**
 - Described by Hippocrates as the “process by which flesh rots, swamps generate foul air and wounds fester”—sepsis is to be feared in this era (and ours still)
 - Galen describes the process as beneficial—“laudable pus” and necessary for wound healing
 - Pasteur and Semelweiss recast sepsis as the HOST response rather than the micro organism’s direct effects and this concept shapes the current thinking about the pathophysiology of sepsis with the host/pathogen interactions key to eradication
 - Sadly eradication of the pathogen does not always result in survival of the host

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Sepsis in children

- ▶ **Sepsis associated mortality has decreased from 97% in 1966 to 9% among infants in the early 90s**
- ▶ **Recent population-based study in the US found a reported mortality rate of 10.3% in children with severe sepsis (bacterial and fungal infection with at least one acute organ dysfunction)**

- ▶ **Of note incidence is highest in infants at 5.6 per 1000 population and falls as age advances (0.2 per 100 in 10-14yo)**
- ▶ **Also exhibits a sex difference being 15% higher than boys and girls (0.6 versus 0.52 per 1000, P is less than 0.001)**
- ▶ **50% of the cases had an underlying disease**
- ▶ **Over 20% below birthweight neonates**
- ▶ **Most common infections were respiratory tree (37%) and primary bloodstream infections (25%)**
- ▶ **Mean length of hospital stay was 31 days and the cost was \$40,600 per admission**

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Data taken from Watson RS, et al. Epidemiology of severe sepsis and children United States a.m. J respiratory critical care Addison 2003;167:69 5-7 1.

Scope of the problem– annual incidence, case fatality and national estimates of severe sepsis by age

Age	Incidence (per 1000 population)	National estimate of cases	Case fatality percentage	National estimate of deaths
Under 1 year	5.16	20,145	10.6	2135
0 to 28 days*	3.60	14,049	10.3	1361
29–364 days	1.56	6096	13.5	774
1–4 years	0.49	7583	10.4	786
5–9	0.22	4168	9.9	413
10–14 years	0.20	3836	9.6	368
15–19 years	0.37	6633	9.7	644
All children	0.56	42,364	0.3	4383

Additional estimates are generated from the 7 state cohort using state and national age and sex specific population estimates from the national center for health statistics and the United States Census

*Results for these ages or based on data from the 5 state AIDS (MA, M.D., and J, and Y, and the) which neonates could be identified
 Data taken from Peterson RS, et al. Epidemiology of severe sepsis and children United States a.m. J respiratory critical care Addison 2003:167:69 5–7 1.

What is SIRS?

- ▶ **SIRS- “systemic inflammatory response syndrome”—a widespread inflammatory response that may or may not be associated with infection.**

- **Requires two or more of the following criteria (one of which must be abnormal temperature or leukocyte count) defines SIRS :**

Core temperature (measured by rectal, bladder, oral, or central probe) of $>38.5^{\circ}\text{C}$ or
 $<36^{\circ}\text{C}$ --- NOT FOREHEAD MEASUREMENT


Tachycardia, defined as a mean heart rate more than two standard deviations above normal for age, or for children younger than one year of age, bradycardia defined as a mean heart rate $<10^{\text{th}}$ percentile for age

Mean respiratory rate more than two standard deviations above normal for age or mechanical ventilation for an acute pulmonary process

Leukocyte count elevated or depressed for age, or >10 percent immature neutrophils

What is sepsis?

- ▶ ***Sepsis***: Life-threatening organ dysfunction caused by dysregulated host response to infection
 - Immune dysregulation
 - Microcirculatory derangements
 - Increased vascular permeability
 - Leukocyte accumulation
- ▶ ***Septic Shock***: Subset of sepsis with circulatory and cellular/metabolic dysfunction associated with higher risk of mortality

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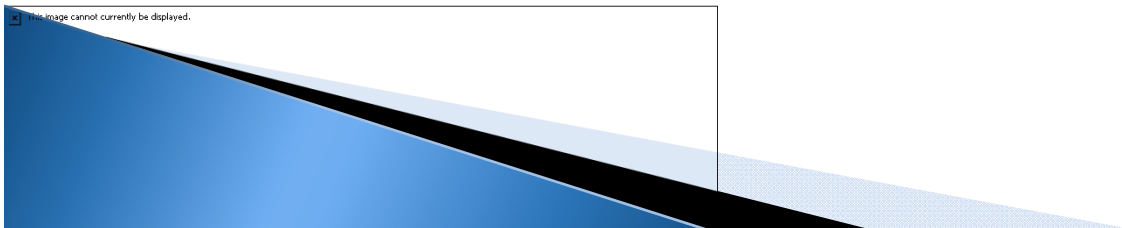
JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

What are the differences between SIRS and Sepsis?

- ▶ **Spectrum of the same pathophysiologic mechanisms.....**

BUT

- ▶ **“Sepsis” is caused by infection and SIRS may not be caused by infection –other things such as malignancy, vasculitis syndromes, toxic reactions for example**



Steps in the generation of sepsis

Infection

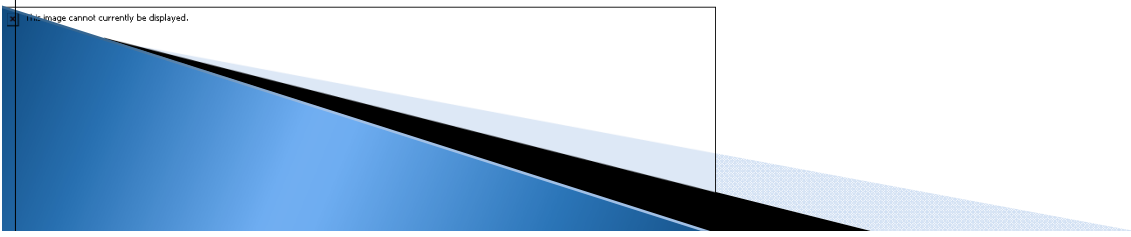
SIRS

Sepsis

Severe Sepsis

Refractory Sepsis

Multiple Organ System Dysfunction (MODS)



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Pathogens responsible for sepsis

▶ **Bacteria**

- **Staphylococcus, Streptococcus, gram negatives, especially Pseudomonas and E coli**

▶ **Fungi**

- **Candida most common, but Aspergillus, Mucor and other less common fungi can cause serious disease and death**

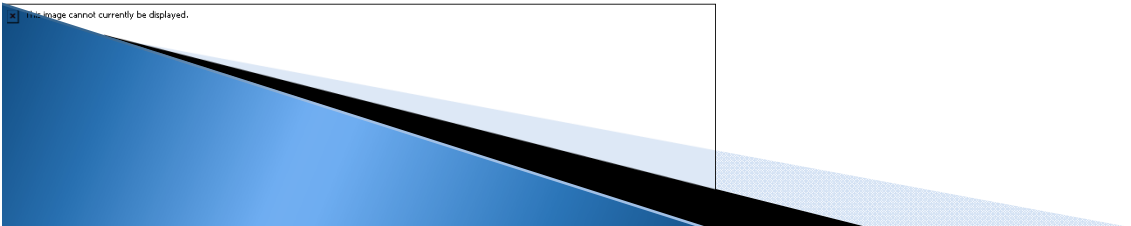
▶ **Viruses**

- **Herpes viruses, Adenoviruses, Ebola, SARS, MERS and other corona viruses, Influenza, Dengue, Chikungunya**

▶ **Other pathogens**

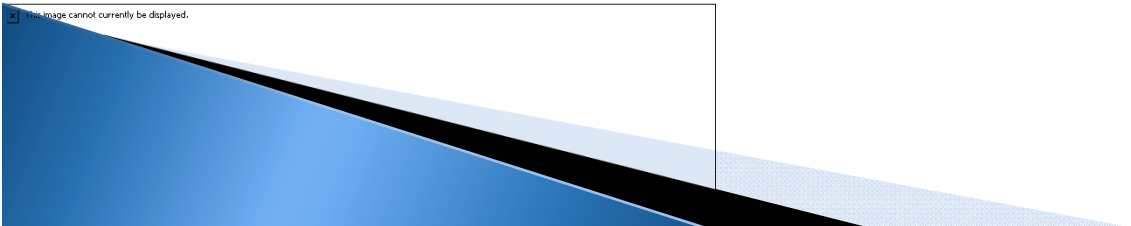
- **Malaria, Babesia (in asplenic or other compromised hosts)**

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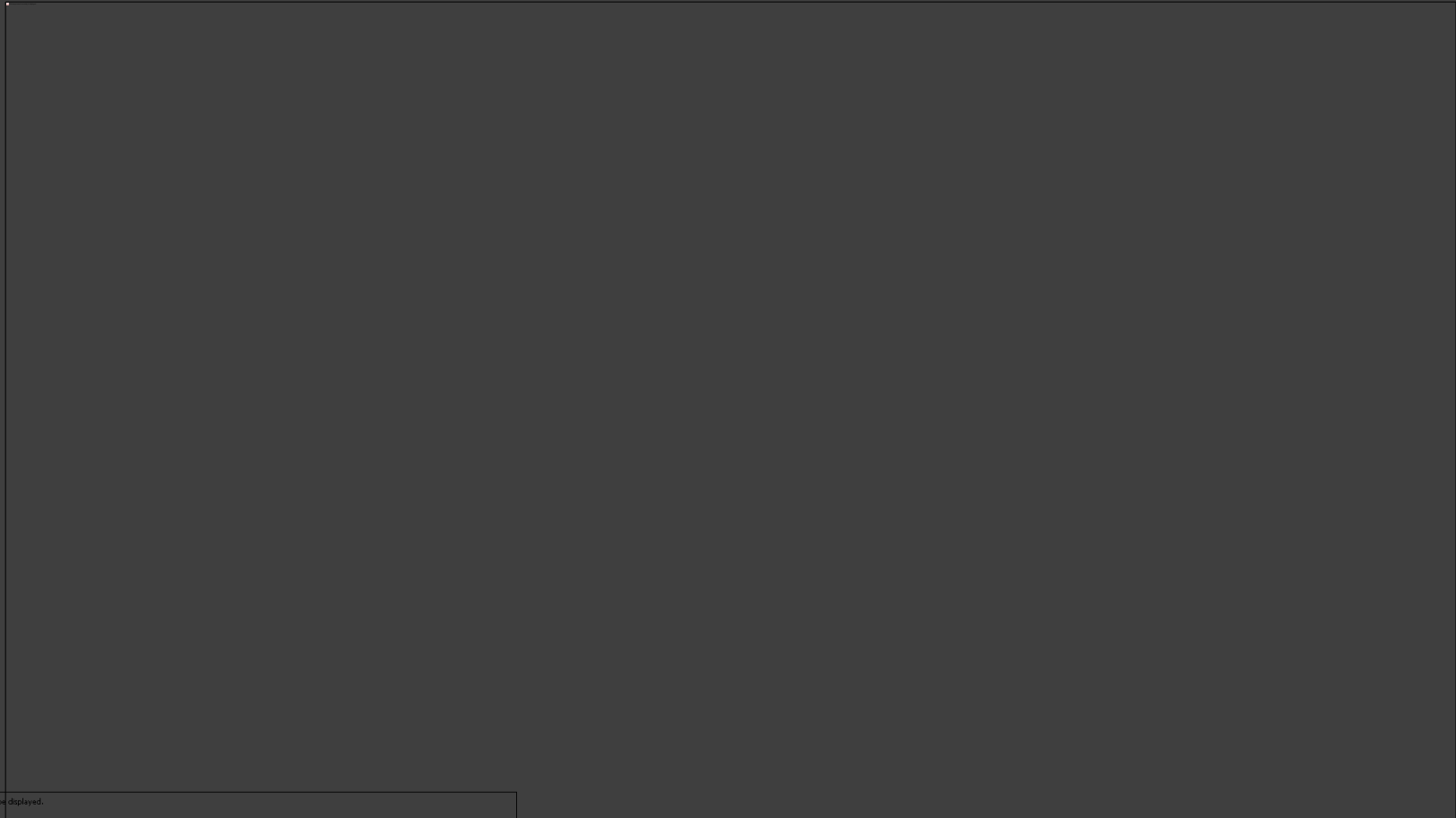


What about culture negative sepsis?

- ▶ **Can occur if the child has had preceding antibiotics—ie organism is suppressed but still has unleashed its cytokine storm/inflammatory cascade and the host is suffering despite our inability to detect it**
- ▶ **PCR has made this better but still not perfect**
- ▶ **Can also occur in the context of viral infections, especially in young babies and immune compromised children---If we don't look for things, we won't find them**

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Culture negative sepsis—mortality versus culture positive sepsis



Shipra Gupta; Ankit Sakhuja; Gagan Kumar; Eric McGrath; Rahul S. Nanchal; Kianoush B. Kashani **Culture-Negative Severe Sepsis: Nationwide Trends and Outcomes** . Chest 2016, 150 (6).

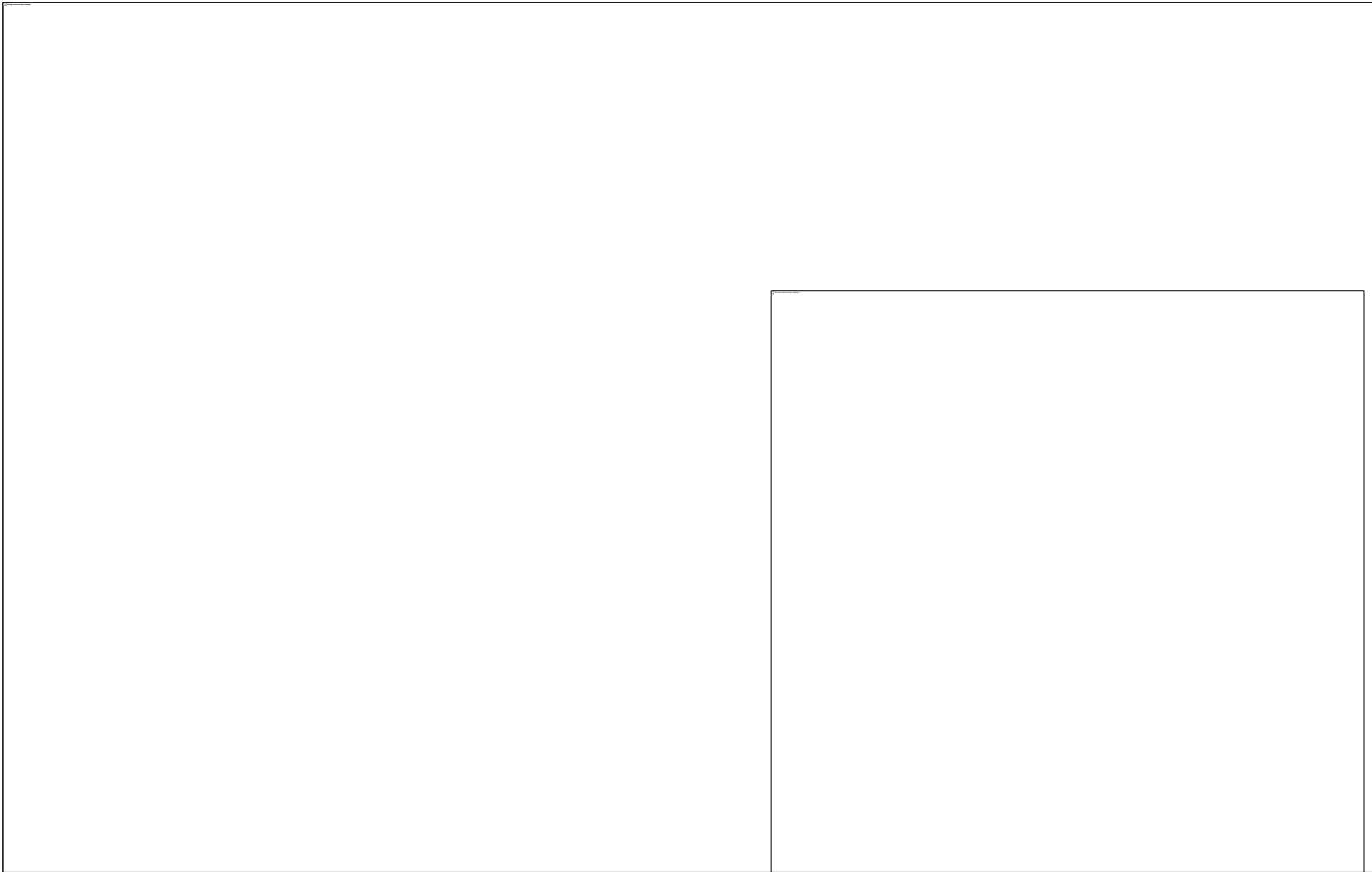
Sepsis associated with viral pathogens

- ▶ **Several recent studies including one in our own NICU demonstrated that inclusion of viral testing could identify that up to 8% of suspected bacterial sepsis was actually caused by viral pathogens, particularly in this young population**
 - **Can help better understand culture negative events**
 - **Can allow for discontinuation of antibiotics after bacteria infection is ruled out**
 - **Can allow for proper treatment to begin, if treatable non bacterial agent has a therapy**

Ronchi et al. JPeds 2014;165(4) 690-6; Kidszen et al. Am J of Perinatology, 2016; Pawar et al. Arch Ped ID April 2016; Cerone et al. Am J perinatology, 2017

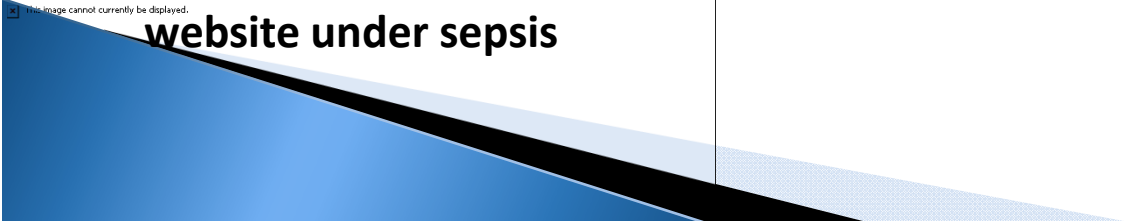
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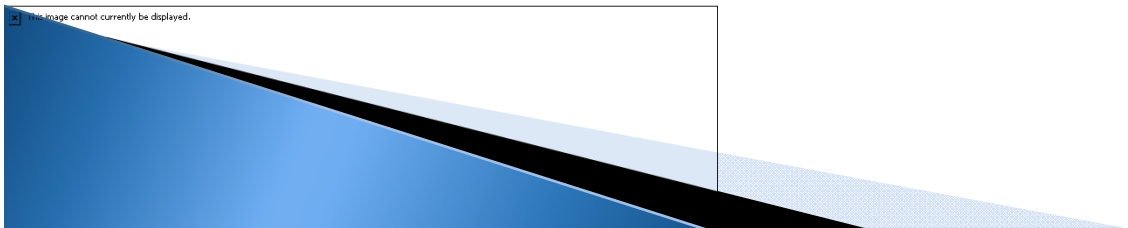
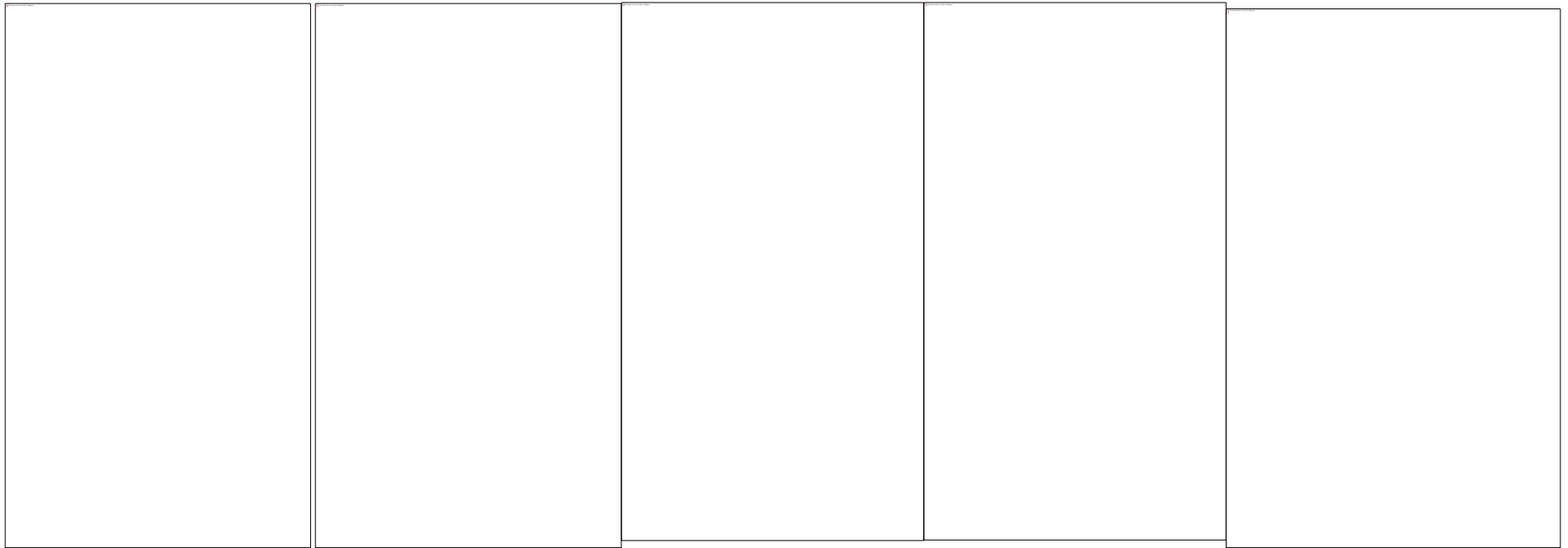
This and other guidelines and very useful information can be found on the CDC website under sepsis

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CMPeDS—a sepsis app

- ▶ **Created by MDs at Children’s Mercy Hospital in Kansas**



	Green- low risk	Amber-intermediate risk	Red—High risk
Color	Normal color of lips, skin and tongue	Pallor reported by parent or caretaker	Pale/mottled/ashen/blue
Activity	Responds normally to social cues Content/smiling Stay awake or awakens quickly Strong normal cry or not crying	Not responds normally to social cues Wakes only with prolonged stimulation Decreased activity No smile	No response to social cues Appears ill to a health professional Does not wake or if aroused does not stay awake Weak high pitched cry or continuous cry
Respiratory		Nasal flaring Tachypnea: RR > for age O2 sat <95% in room air crackles	Grunting Tachypnea RR> 60 breaths per minute Moderate to severe chest retractions
Hydration	Normal skin and eyes Moist mucosa	Dry mucous membranes poor feeding in infants CRT >3 seconds Reduced urine output	Reduced skin turgor
Other	None of the amber or red symptoms or signs	Fever for >5 days Swelling of a limb or joint Non-weight bearing/not using an extremity A new lump >2cm	Age 0-3 months, temp greater than 38C Age 3-6months, temp greater than 39 C Non blanching rash Bulging fontanelle Neck stiffness Status epilepticus Focal neurologic signs Focal seizures Bile stained emesis

If you suspect infection may be the cause of worrying clinical signs (Amber to Red) assess patient using Screening Patients for Sepsis tool—Tool used in Great Britain for “sepsis” screening

When to think about Sepsis-diagnosis

▶ **Defined or proven**

- **+ culture**
- **+PCR**
- **+tissue stain**

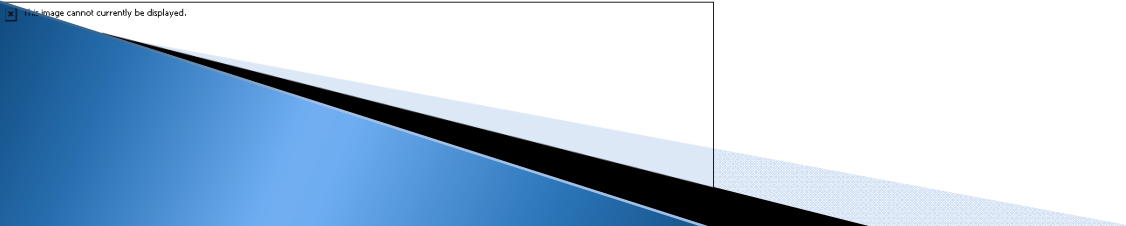


Other than PCR, these will not return in a timely enough fashion to guide the clinician's management

○ **Positive physical findings suggestive of sepsis**

- **Purpura**
- **Petechiae**
 - **Especially in conjunction with hemodynamic instability**
- **Fever, cough, hypoxia in child with infiltrates on CXR**

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Perform Initial screening for sepsis and If positive, initiate...

- ▶ **Within the first 1-3 hours (sooner the better and required within 1 hour for fluids and antibiotics)**

- **Lactate**
- **BC**
- **Broad spectrum antibiotics**
- **Crystalloid for low BP or lactate >4mg/L**

- **resuscitation from sepsis-induced hypoperfusion, at least 30ml/kg of intravenous crystalloid fluid be given within the first 3 hours.**

(Strong recommendation; low quality of evidence)

following initial fluid resuscitation, additional fluids be guided by frequent reassessment of hemodynamic status.

(Best Practice Statement)

- ▶ **6 hours**

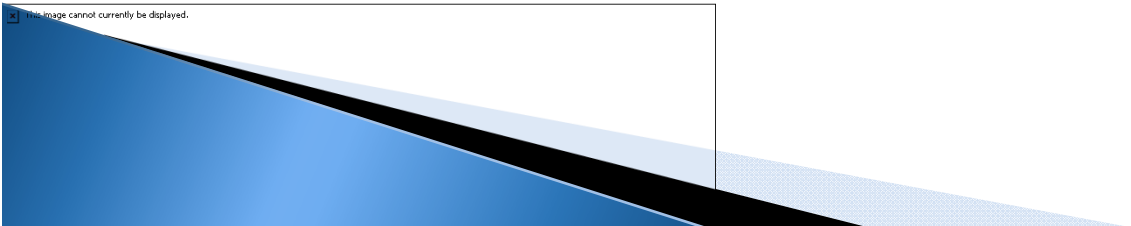
- **Pressors for hypotension that persists after fluid resuscitation to keep MAP >65mm/Hg or lactate >4mg/L**

- **Continue to reassess and re-evaluate the effectiveness of interventions**

Early Management—still the “A,B,Cs”

- ▶ **RECOGNITION AND SUSPICION ARE KEY TO MANAGEMENT**
 - Some form of resuscitation if essential and requires prompt intervention—children need BP support as they can more rapidly decompensate than adults due to less cardiac, respiratory and metabolic reserves
- ▶ **For Probable diagnosis**
 - Obtain cultures
 - Initial broad spectrum antibiotics
 - This depends on the host, circumstances of the illness, suspected source if obvious and the probable organisms
 - Go broad initially and de-escalate later after cultures are available
 - *****source control*****

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2017 changes to guidelines for pediatric sepsis management include:

- ▶ A. **Time to antibiotics** within 60 minutes for patients with sepsis (SOFA \geq 2), septic shock patients which essentially implies anyone with qSOFA and/or organ dysfunction
- ▶ B. **Lactate** measurement and targetted management in those who have an elevated as a serial marker
- ▶ C. **Blood cultures** before antibiotics (unless there is going to be significant delay)
- ▶ D. **Governance** – Use of ‘sepsis management programs’
- ▶ E. **Early Empiric broad spectrum Antibiotic** therapy for all sepsis patients (refer to local guidelines)
- ▶ F. **Procalcitonin (PCT)** in the Emergency Department (ED) finally gets in. (From an ED perspective, patients who improve quickly after first dose of antibiotics and PCT normalizes – antibiotics could be potentially be stepped down – great role for the sepsis workflow in winter and flu season). PCT was reviewed by the “PEM” blog in 2015. A possible approach to the lower risk septic patient could be to give first dose intravenous antibiotics, conduct a PCT and discharge after reassessment and period of observation with/without oral Ab if clinical improvement without raised PCT
- ▶ G. **There is no mention of C-reactive protein anywhere in document**
- ▶ H. **Fluid Challenge** for fluid resuscitation (rather than ‘drip’ method)
 - What fluid? The usual crystalloids first, albumin next (NO ‘GEL’ and NO SPECIAL COLLOIDS)
- ▶ I. **Fluid Volume** – up to 30ml/kg
- ▶ J. What about **Inotropes?** – Norepinephrine – Vasopressin – Dobutamine OR Adrenaline in that order...
- ▶ K. **No routine use of steroids** unless specific other indication(s)

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Development of various inflammatory markers in sepsis


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Comparison of PCT and CRP in early phases of sepsis

- ▶ **Release of PCT into the blood stream depends on sepsis severity**
- ▶ **Dropping PCT levels indicating increased survival rates**
- ▶ **Persistent elevated PCT is predicted for an unfavorable outcome**
- ▶ **More favorable kinetic profile and other markers—levels increase 4-12 hours after onset of infection**
- ▶ **Disadvantage—can also be elevated in non sepsis conditions**
- ▶ **Both pro and anti-inflammatory effects**
- ▶ **Secretion starts 4 hours after infection and peaks at 36 hours**
- ▶ **Used to diagnose multiple infections**
- ▶ **Able to discriminate patients with and without sepsis is modest**
- ▶ **May be able to stratify early risk (day 1) but not as effective as other markers such as Procalcitonin**

PCT

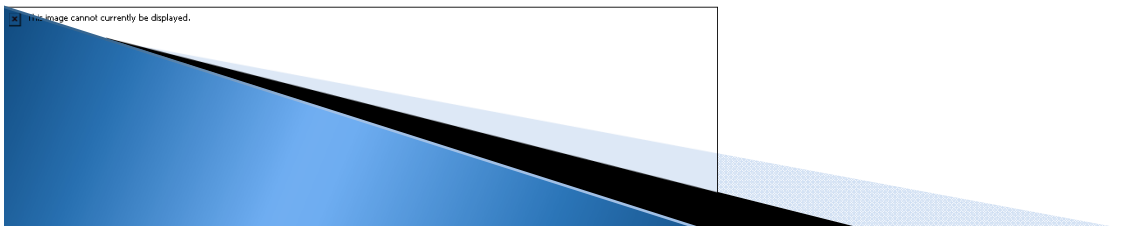
CRP

Broad spectrum antibiotics

- ▶ antimicrobials should be initiated as soon as possible after recognition and **within 1 h** for both sepsis and septic shock.
- ▶ empiric broad-spectrum therapy with one or more antimicrobials to cover all likely pathogens.

Give soon, go broad

However the consequences of abx for everyone with suspected sepsis has yet to be evaluated, some may not have sepsis



Suggested initial antimicrobial choices for empiric therapy in infants and children with suspected sepsis

Age or clinical situation	Antimicrobial agent(s)
Neonate (community onset)	Ampicillin plus gentamicin
Neonate (hospital onset)	Vancomycin plus gentamicin or cefotaxime*
Child (community onset)	Cefotaxime or ceftriaxone plus vancomycin
Child (Hospital onset)	Vancomycin or semisynthetic penicillin plus clindamycin*
Skin or soft tissue involvement	Vancomycin or semisynthetic penicillin plus clindamycin
Neonatal herpes	acyclovir
Rocky Mount spotted fever Ehrlichiosis	Doxycycline—regardless of age

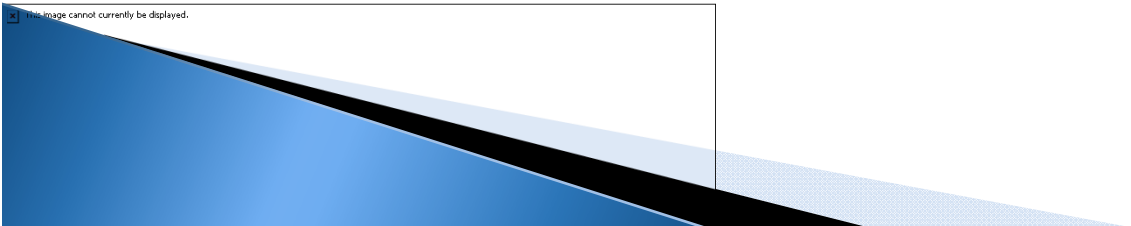
Antimicrobial should be modified when laboratory data is available based on clinical course

*Antimicrobial should be based on patient specific risk factors and local antimicrobial susceptibility trends

Source control

- **“We recommend that a specific anatomic diagnosis of infection requiring emergent source control be identified or excluded as rapidly as possible in patients with sepsis or septic shock, and that any required source control intervention be implemented as soon as medically and logistically practical after the diagnosis is made”**

Best practice statement from the Critical Care Society and European Society of Intensive Care Medicine


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Concern for Sepsis should not be limited to the criteria

- ▶ **U of Chicago PICU patients were screened for severe sepsis or septic shock using consensus guidelines (research criteria), diagnosis by healthcare professionals (clinical criteria), and International Classification of Diseases, Ninth Revision, Clinical Modification codes (administrative criteria)**
- ▶ **1729 children admitted to ICU setting 2005-2012**
- ▶ **Only 2/3 of these children who were treated for sepsis met the consensus criteria**
- ▶ **Clinical suspicion for sepsis often should occur even if the criteria from the consensus group are not met**

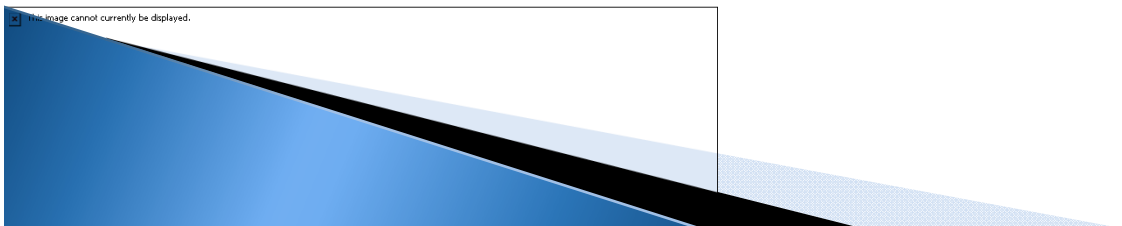
Defining pediatric sepsis by different criteria: discrepancies in populations and implications for clinical practice. Weiss SL, Parker B, Bullock ME, Swartz S, Price C, Wainwright MS, Goodman DM. *Pediatr Crit Care Med.* 2012;13(4):e219

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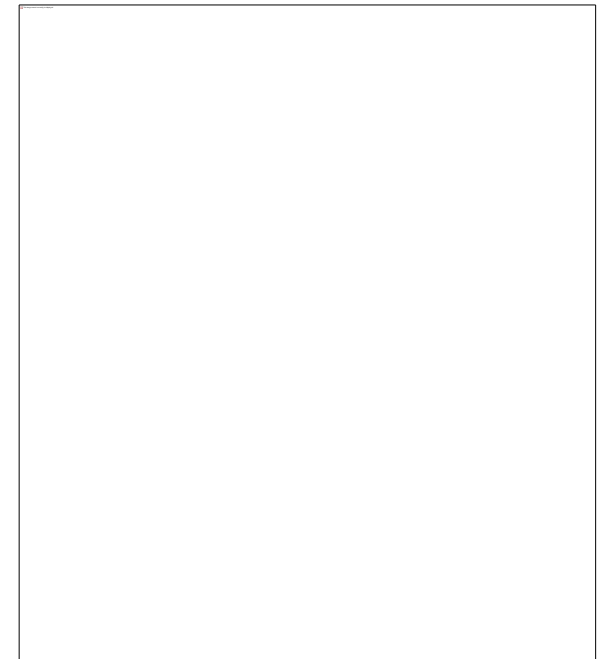
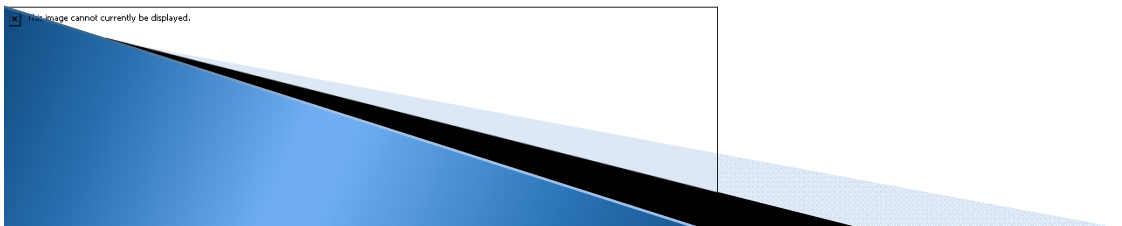
Importance of Bundles

- ▶ **To validate the importance of bundles in the management of sepsis (in adults) the Surviving Sepsis Consensus and the Institute for Healthcare Improvement initiated a joint effort with global support**
 - **30,000 patients were screened globally 2005-2012**
 - **Overall reduction in mortality was noted with the use of bundled protocols for sepsis recognition and management**
 - **Agencies with higher bundle compliance had better reduction in mortality, up to 36-39% for the highest 3 sites in the study**



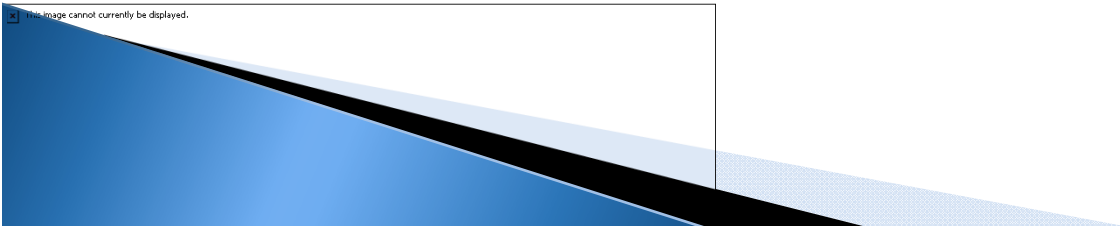
Newest article and commentary just published in NEMJ May 21, 2017


- ▶ **Protocol initiation and Bundle compliance in NYS from 2014 -2016 increased for adults from about 72% and 41% to 85% and 55% respectively. During the same time frame, sepsis mortality fell from ~ 30% to 26%.**
- ▶ **In pediatric patients, protocol initiation was high initially at around 80% while 1 hour bundle compliance was low at ~5% and fluctuated with a high of ~ 25%. However, the mortality during this time was relatively flat ~ 10%.**
 - **Could argue that the bundle compliance matters and was not followed well, hence limited improvement OR that regulations cannot mandate clinical judgement—ie the protocol initiation was the driver of the low mortality rate , not bundle compliance**



Summary

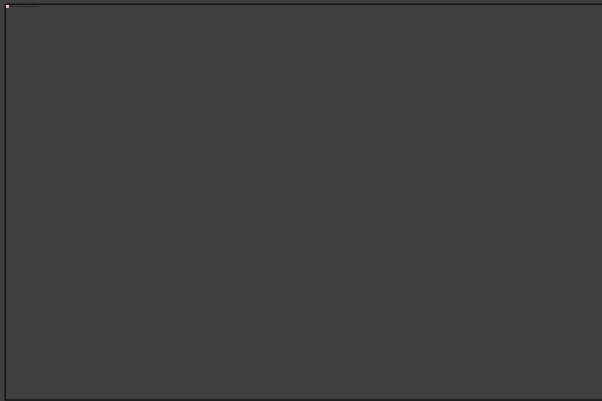
- ▶ **SUSPICION AND RECOGNITION ARE KEY**
- ▶ **Start resuscitation early with source control, intravenous fluids and antibiotics.**
- ▶ **Frequent assessment of the patient's volume status is crucial throughout the resuscitation period.**
- ▶ **guide resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion**



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Case A

3 year old with rapidly progressive rash,
fever, lethargy



Initial BP <60/40

HR 160s

RR40s

WBC 3.0 with 30% bands

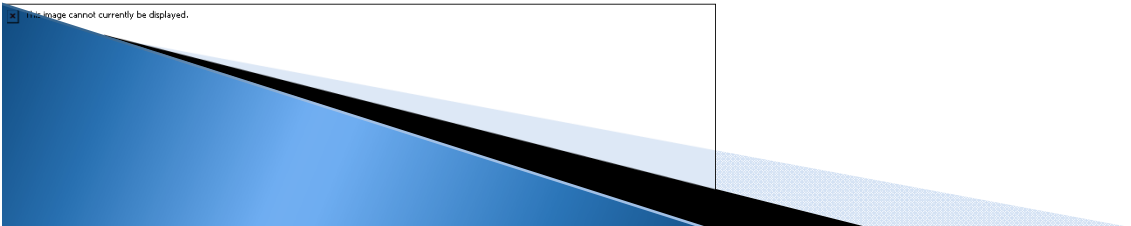
Lactate 4.5mg/L

CRP 150ug/dL

Diagnosis?? Sepsis??

Neisseria meningitis—meningococemia with purpura fulminans

- ▶ **Remember not all purpura fulminans is due to Neisseria, any bacterial pathogen can produce severe sepsis**
- ▶ **Outcome for this type of presentation is very grave with high morbidity and mortality**

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Case B 9 yo with swollen knee, pain,
inability to ambulate, fever to 103



BP 90/60

HR 120

RR 30

**WBC 15K with 75% PMN
and 12% bands**

Lactate 2.3

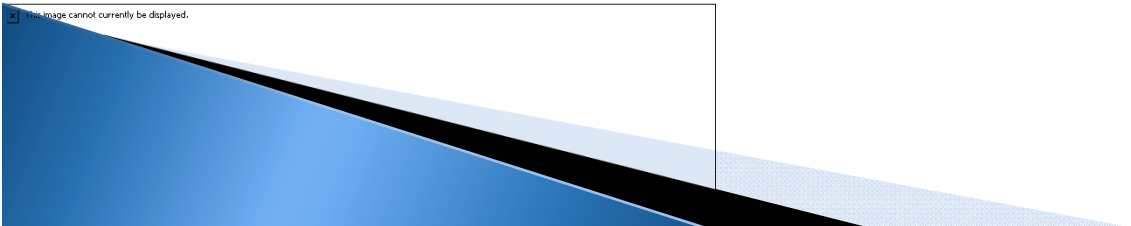
CRP 150ug/dL

Sepsis???

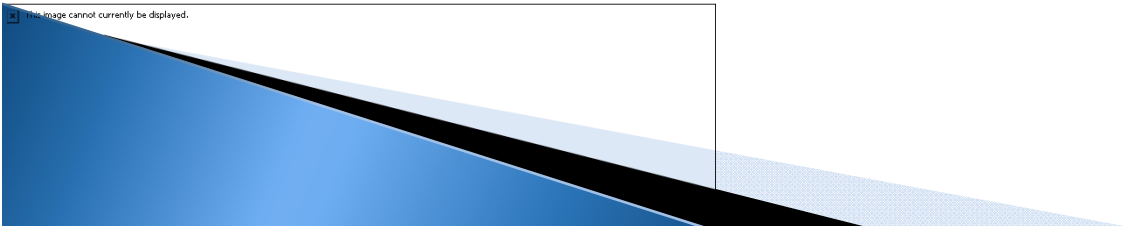
Further data

- ▶ **Knee aspiration with 189,000 WBC, 25,000 RBCs, gram positive cocci in clusters**
- ▶ **Taken to the OR for knee washout. Frank pus encountered in the joint space and in the surrounding tissues**
- ▶ **12 hours after the initial blood culture was drawn, the lab notified the floor that the blood culture was positive for *Staphylococcus aureus***

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Sepsis with Septic arthritis due to *Staphylococcus aureus*, non MRSA

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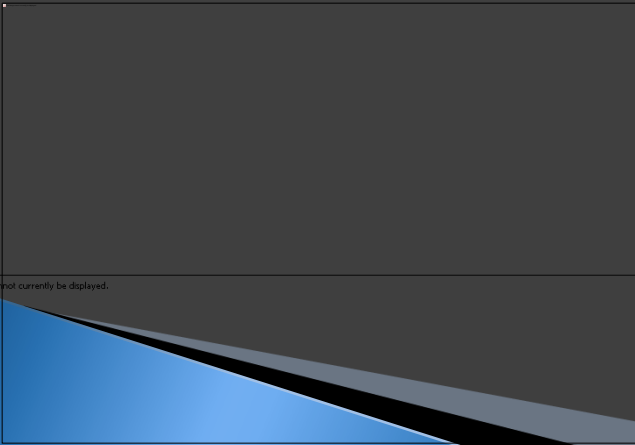
Case C

Ill appearing 4 year old with increasingly swollen hands, erythema, warmth and tenderness. Refuses to move hands or allow touching. Very irritable, febrile to 104, tachycardic. Developed an evanescent rash over the trunk since admission to the ED

BP 110/55 HR 140s RR 40 (taken while screaming)

WBC 25,000 with left shift
CRP 210 ug/dL
Lactate 2.5mg/L

Sepsis????

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Case C

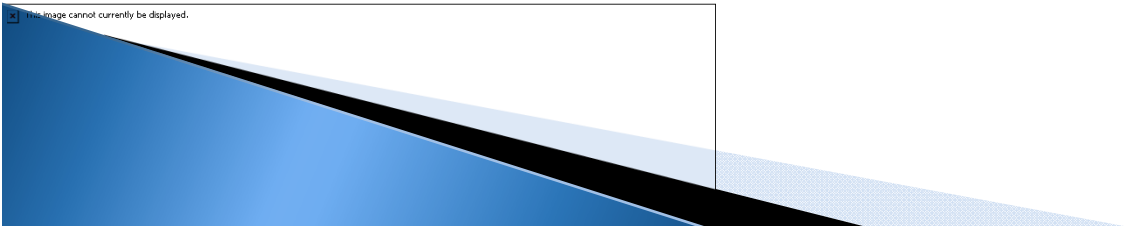
- ▶ **Cultures done**
- ▶ **Given fluids and antibiotics**
- ▶ **Continued spiking fevers**

- ▶ **Day 2**

- **Still very ill appearing**
- **Cultures negative**
- **CPR has risen to 249ug/dL**
- **Rash persists**
- **Serum ferritin drawn**

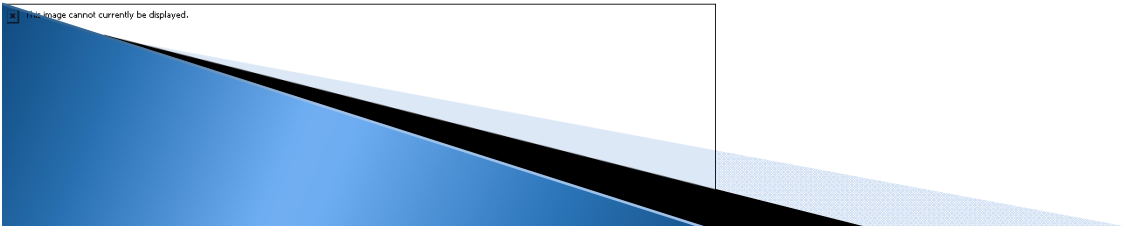
Sepsis??

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Case C

- ▶ **Serum ferritin was over 6000**
- ▶ **Diagnosis of new onset of systemic JIA with macrophage activation syndrome (MAS) strongly considered**
- ▶ **Responded to a dose of Inflixumab**
- ▶ **Not sepsis but this is not clear at presentation so always need to SUSPECT sepsis due to high mortality associated with untreated disease**
- ▶ **MAS is also a medical emergent condition but not in the same way as sepsis—still needs rapid diagnosis and treatment**

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Case D

3 year old with a high fever for 3 days and increasing groin node with overlying erythema and tenderness to palpation. Very irritable and hard to examine. Groin node greater than 3 cm in size. Had been on antibiotics from pediatrician for lymphadenitis



HR 155 RR 45 BP 65/35

WBC 19.5 K with 75% neutrophils, 5% bands

CRP 195ug/dL

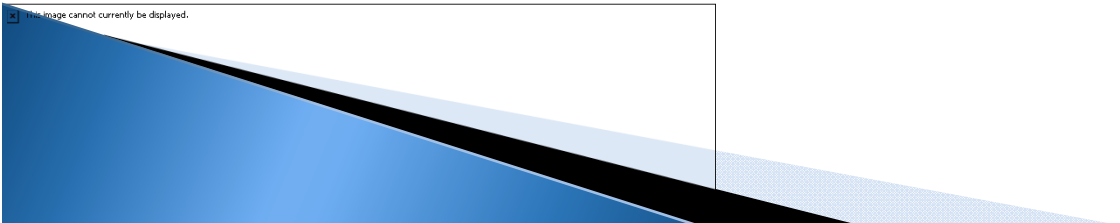
Lactate 2.5

Sepsis??



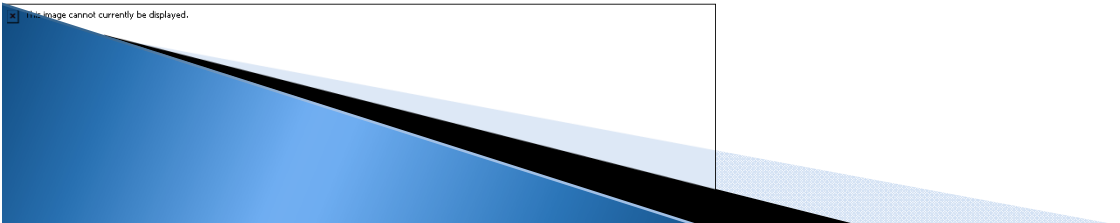
Case D

- ▶ **Given fluids**
 - ▶ **Cultures done**
 - ▶ **Antibiotics given**
 - ▶ **U/S of groin node—no drainable focus**
-
- ▶ **Sepsis????**



Case D

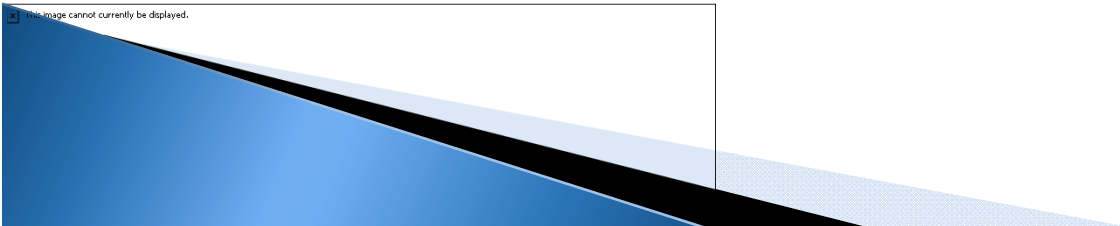
- ▶ **Following day**
- ▶ **Tachycardic to 200 with gallop rhythm**
- ▶ **BP in the 50s systolic**
- ▶ **Hands and feet cool and poorly perfused**
- ▶ **New rash in groin, trunk and extremities**
- ▶ **Blood cultures negative**
- ▶ **Node still enlarged**
- ▶ **WBC now 25,000 and CRP over 200ug/dL**
- ▶ **Sepsis??**



Case D

- ▶ **Transferred to the PICU**
- ▶ **Cardiac echo with mitral and tricuspid insufficiency and regurgitation, cardiac output ~ 23%**
- ▶ **Started pressors**

- ▶ **Diagnosed with...?**

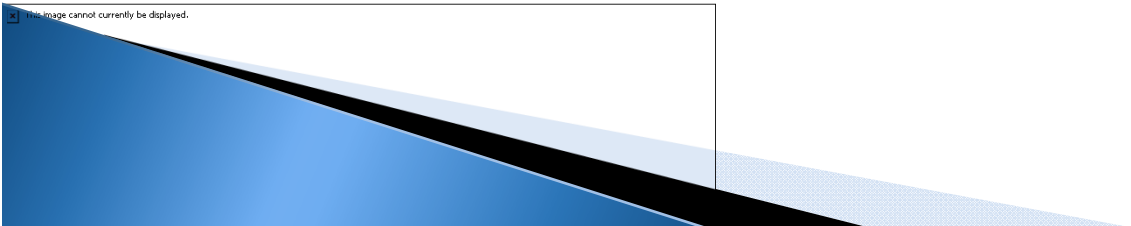


Case D--Kawasaki Disease

Sepsis-like presentation seen in less than 3% of all cases of Kawasaki disease

- ▶ **MOST likely is an infectious disease trigger to this syndrome but not yet known to be**
- ▶ **“technically” not sepsis as there is not a clear infectious cause and antibiotics will not alter the disease**
- ▶ **Given IVIG and during the infusion his cardiac insufficiency began to abate and within 24 hours he was markedly improved and recovered slowly without cardiac sequelae**

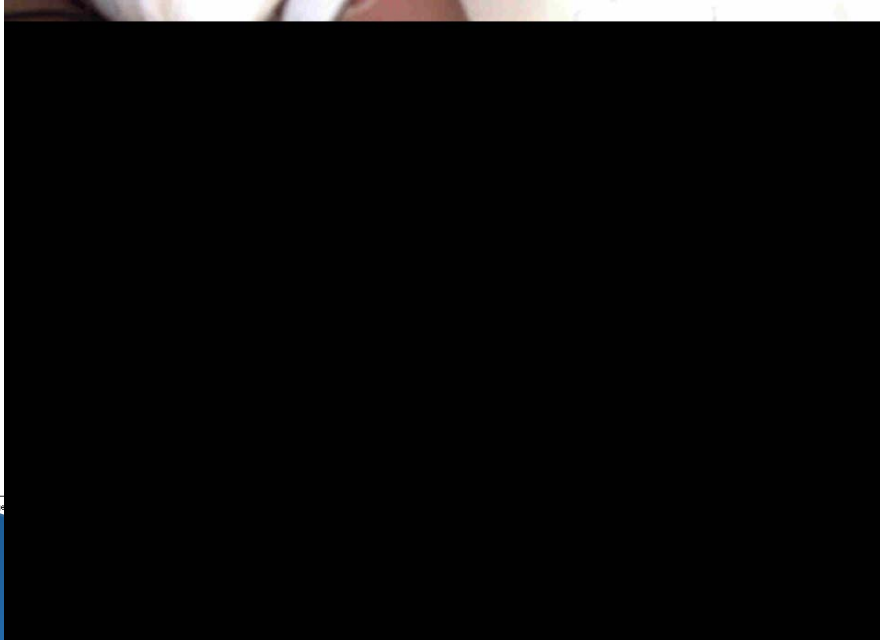
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CASE E

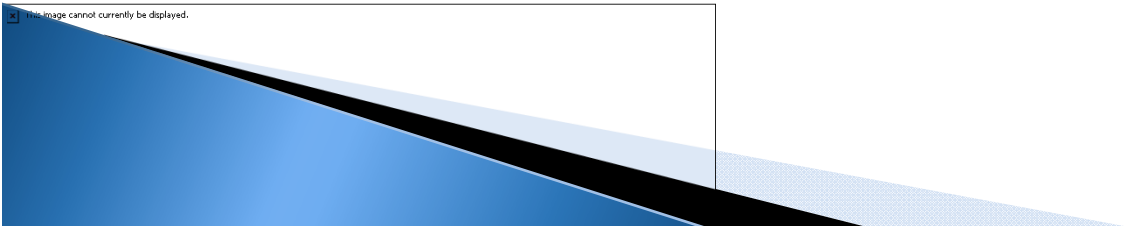
3 week old male with “UTI” and elevated WBC (>50,000) who just did not get better with antibiotics for his UTI. Transferred when WBC reached 90,000 after 4 days of antibiotics and fever was still around 104.

Tachycardia for age with elevated respiratory rate but BP was WNL for his age. Hands and feet swollen red and tender.... CRP very elevated over 200ug/dL. Does he have sepsis?



Case E-Congenital leukemia with cutis leukemia

- ▶ **Flow cytometry revealed a clonal Acute myelogenous leukemia (type MM3)**
- ▶ **He was started on chemotherapy and rapidly defervesced**
- ▶ **Outcome for this type of presentation is better in children than in adults**

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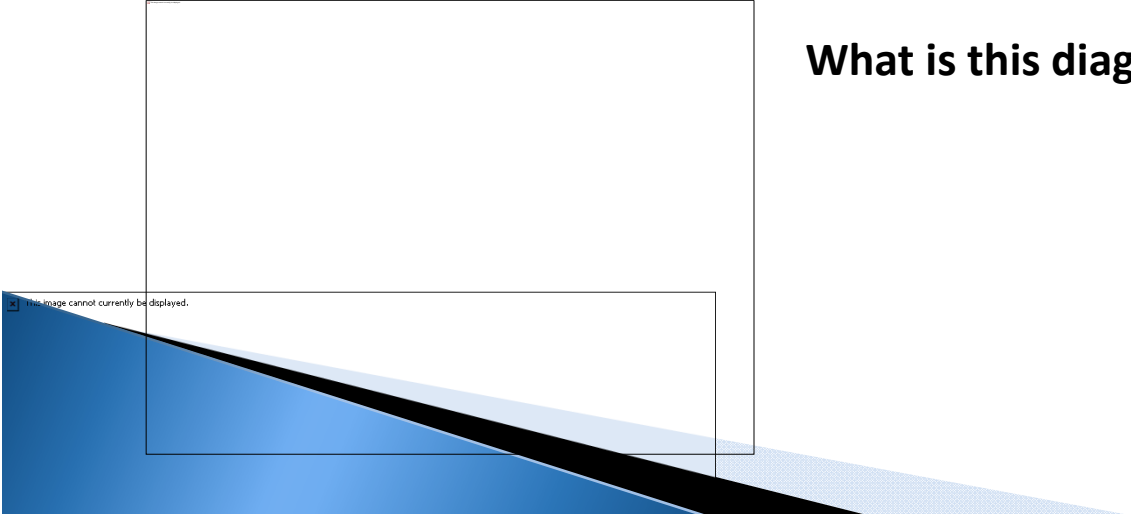
Case F

3 month old former 32 week preemie twin with past history of necrotizing enterocolitis (NEC)

- surgical intervention and ostomy/stoma creation in first week of life
 - Reanastomosis 1 month ago.
- Presented to outlying hospital in extremis with respiratory and circulatory collapse.
- Initially felt to have gram negative sepsis-abdominal origin.
- Within 24 hours after admission, noted to have small (1cm) “purple” splotch—within hours this blossomed into....

What is this diagnosis?

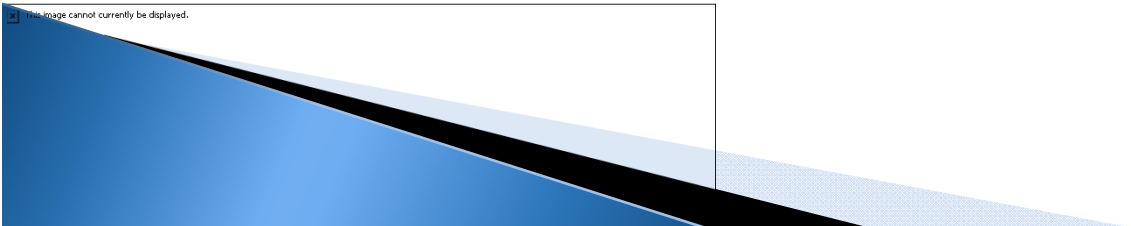
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Case F- NECROTIZING SKIN AND SOFT TISSUE INFECTION

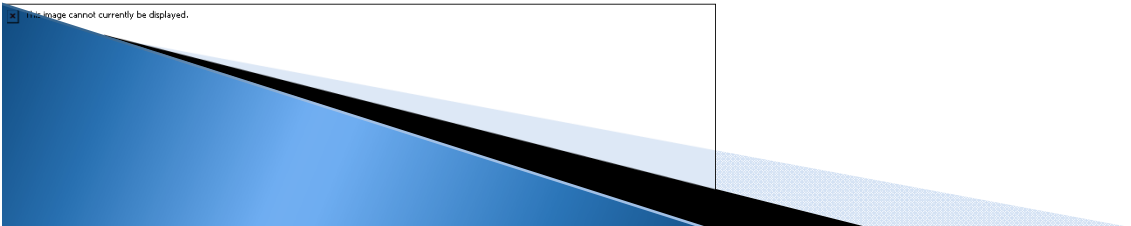
- ▶ “stool” recovered from OR intervention
 - *E coli*, Enterococcus, Bacteroides,
 - *Staphylococcus epidermidis*, *Streptococcus*
 - *viridans*
 - Most likely this was a synergistic infection
 - Polymicrobial (anaerobes and
 - *E coli*+/- enterococcus) in a
 - compromised host (due to age and
 - multiple surgeries)

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Sepsis summary

- ▶ **Early recognition**
- ▶ **Early fluid and antibiotics**
- ▶ **Identification and correction of source, if warranted**
- ▶ **On going evaluations and re-evaluations, especially if patient remains unstable**
- ▶ **Protocols can help children (and adults) survive sepsis—but only if we use them often—better to do “too much” than “not enough” in the context of sepsis (maybe)**

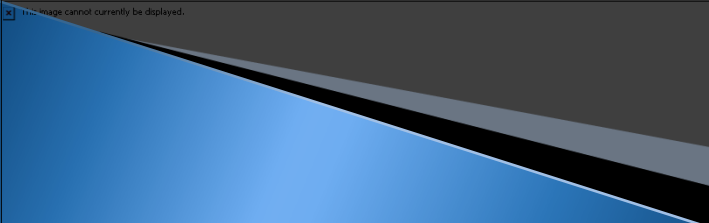
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You too can survive sepsis

I just did!!

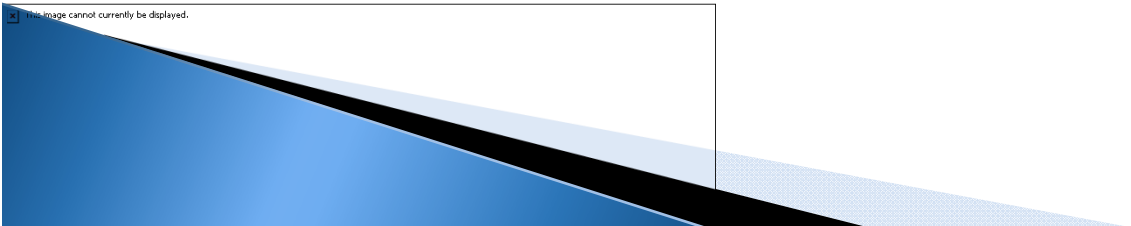
THANKS

Questions?

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References not otherwise cited

- ▶ **CDC.gov for “sepsis and septic shock”**
- **C.W. Seymour et al. Time to Treatment and Mortality in mandated Emergency Care. NEJM may 2017**
- **T.B. Hershey and J.M. Kahn State Sepsis Mandates---A New Era for Regulation of Hospital Quality. NEJM May 2017**

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