Diagnosis of Sepsis in Newborn and Children

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Diagnosis of Sepsis

- What is sepsis?
- Is context dependant
- Varies depending on definitions
- Is changing based on technology and improved knowledge
- Concluding remarks
CMPA identified 327 cases involving sepsis—including 204 deaths—between 2009 and 2013.

“Inadequate patient assessment” was a factor in 75% of cases (168 lawsuits, and 159 complaints).

Forty per cent of legal actions resulted in an “unfavourable” outcome for the doctor.

Settlements often come after years of expensive litigation.

Included a nine-year-old boy with chickenpox who died of profound septic shock hours after he was discharged from an emergency department for the fourth time.
Sepsis

Core temp <36°C or >38.5°C
Tachycardia >2SD for age
Respiratory rate >2SD for age
White cell count elevated or suppressed for age

And
A suspected or proven infection caused by any pathogen OR a clinical syndrome Associated with a high probability of infection.
SIRS
SIRS + Infection
Temp. >38°C or <36°C, HR >90, RR >20 or PaCO₂ <32,
WBCs >12,000 or <4,000 or >10% bands
Sepsis
Sepsis + End Organ Damage
Severe Sepsis
Severe Sepsis + Hypotension
Septic Shock
Trajectory of Sepsis and Interventions

- Infection
- Sepsis
- Severe Sepsis
- Septic Shock

Initial assessment → expected recovery → effort required to return to recovery → time
Diagnosis of Sepsis

• What is sepsis?
• Is context dependant
• Varies depending on definitions
• Is changing based on technology and improved knowledge
• Concluding remarks
Diagnostic Criteria for Sepsis, Severe Sepsis and Septic Shock

• **General Variables**
  – Fever, hypothermia, tachycardia, tachypnoea, altered mental status, hypoglycemia, substantial edema

• **Inflammatory Variables**
  – Leucocytosis, leucopenia, > 10% immature WBC, elevated CRP or calcitonin

• **Hemodynamic Variables**
  – Arterial hypotension, elevated or decreased mixed venous O2 saturation and cardiac index
Diagnostic Criteria for Sepsis, Severe Sepsis and Septic Shock

• Organ Dysfunction Variables
  – Hypoxemia, oliguria, elevated creatinine, coagulation abnormalities, paralytic ileus, thrombocytopenia, hyperbilirubinemia

• Tissue Perfusion Variables
  – Decreased capillary refill or mottling, hyperlactatemia,

• Severe sepsis (sepsis + organ dysfunction)

• Septic shock (severe sepsis + fluid intractable hypotension or hyperlactatemia)
Suspicion of Sepsis in Community

Any Newborn

– feels feverish (hot) or cold
– peri-umbilical pus, swelling or redness
– poor or no sucking (not feeding)
– feeble or no cry
– drowsy, difficult to arose
– convulsion
– repeated vomiting

Any Child

– Not feeding
– Feeling cold
– Convulsion
– Disoriented, difficult to engage
– Repeated vomiting

Interrupting Pathways to Sepsis Project - Bangladesh
# Suspicion of Sepsis at Health Facility

## Syndromic Sepsis Case Finding Tool - Neonate

*Instruction: Please look for the danger signs listed below and (✓) Tick in appropriate box*

<table>
<thead>
<tr>
<th>Danger Signs</th>
<th>Look/Ask/Feel</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothermia</td>
<td>1. Cold/Clammy Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Blue or Pale Color Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Axillary temperature &lt; 96°F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>4. Axillary temperature &gt; 101.3°F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altered mental status</td>
<td>5. Unconscious/No movement</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>6. Lethargic/movement only when stimulated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7. Difficult to arouse/drowsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convulsion</td>
<td>8. Convulsion- by history (care giver report) or examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory Distress</td>
<td>9. Severe Chest In drawing</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10. Severe Breathing difficulty/noise breathing</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11. Respiratory rate &gt; 60 (with any other danger sign)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Umbilical infection</td>
<td>12. Pus/foul smelling discharge from umbilicus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13. Red and swollen umbilicus with discharge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Feeding properly</td>
<td>14. Stops feeding properly/sudden loss of appetite</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>15. Poor or no sucking reflex</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>16. Vomits everything out/projectile vomiting</td>
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</tr>
</tbody>
</table>
• 1101 (86%) met the sepsis criteria.
• The SIRS criteria captured 61 deaths, sensitivity 95% (95% CI, 90–100%) and specificity and 15% (95% CI, 13–17%).
• Most discriminatory individual component of the SIRS criteria was the WBC count, which alone had a sensitivity of 72% and a specificity of 56% for the identification of in hospital mortality.
• Having any two criteria had sensitivity equal to the full sepsis definition but had lower specificity (0.12).
**CAPHC SEPSIS SCREENING TOOL**

**Emergency Department**

Patient Age: _______ days/months/years  
Date/Time: ______________

**This is a screening tool to identify patients with severe sepsis. No screening tool can identify all patients with severe sepsis. If you are concerned that a patient might have severe sepsis or another serious condition, notify the responsible physician immediately regardless of whether they meet the criteria in this tool.**

**TACHYCARDIA**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Critical HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 6 m</td>
<td>&gt; 150</td>
</tr>
<tr>
<td>6 &lt; 12 m</td>
<td>&gt; 160</td>
</tr>
<tr>
<td>1 &lt; 4 y</td>
<td>&gt; 145</td>
</tr>
<tr>
<td>4 &lt; 10 y</td>
<td>&gt; 125</td>
</tr>
<tr>
<td>≥ 10 y</td>
<td>&gt; 105</td>
</tr>
</tbody>
</table>

**CONTINUE TO MONITOR AS PER CTAS GUIDELINES**

**ARE THERE ANY SIGNS OF INFECTION?**
- Fever (> 38.0 C)
- Hypothermia (< 36.0 C)
- Cough /chest pain/respiratory distress
- Abdominal pain /& or distention
- Vomiting/Emerges
- Skin or joint (pain/swelling/redness)
- Other signs of infection

**ARE THERE ANY HIGH RISK MEDICAL CONDITIONS?**
- Age < 3 months
- Immunocompromised (Malignancy, Transplant, Asplenia/Sickle Cell, Medications)
- Cardiac, Respiratory or Neuromuscular Disease
- Indwelling Vascular Access/ Medical Device
- Recent Surgery/hospitalization
- Significant Developmental Delay
- Other high risk conditions

**AND/OR**

**Assess for signs of SEVERE SEPSIS/SEPTIC SHOCK. ARE THERE SIGNS OF?**
- Perfusion Changes (capillary refill > 2 sec, low SpO2, mottled skin, cold extremities)
- Mental Status Changes (confusion, lethargy, irritability)

**NOTIFY MOST RESPONSIBLE PHYSICIAN. PROCEED TO SEVERE SEPSIS/SEPTIC SHOCK GUIDELINES**

**This child may have early signs of sepsis. Complete assessment. Triage Appropriately. Continue to monitor as per CTAS guidelines.**

**RN Reviews Vital Signs**

Patient has temperature >101.3F or <96.8F AND 1 of the 2:

1) Heart Rate Abnormality
(From Goldstein et al. with correction for age of fever by Cruz et al.)

<table>
<thead>
<tr>
<th>Temperature (F)</th>
<th>&lt;6 mo</th>
<th>6 mo-1y/o</th>
<th>1-3 y/o</th>
<th>3-10 y/o</th>
<th>&gt;10 y/o</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;109</td>
<td>160</td>
<td>140</td>
<td>130</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>&gt;109, &lt;101</td>
<td>185</td>
<td>145</td>
<td>135</td>
<td>115</td>
<td></td>
</tr>
<tr>
<td>&gt;101, &lt;102</td>
<td>190</td>
<td>150</td>
<td>140</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td>&gt;102, &lt;103</td>
<td>195</td>
<td>155</td>
<td>145</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>&gt;103, &lt;104</td>
<td>200</td>
<td>160</td>
<td>150</td>
<td>130</td>
<td></td>
</tr>
<tr>
<td>&gt;104, &lt;105</td>
<td>205</td>
<td>165</td>
<td>155</td>
<td>135</td>
<td></td>
</tr>
<tr>
<td>&gt;105</td>
<td>210</td>
<td>170</td>
<td>160</td>
<td>140</td>
<td></td>
</tr>
</tbody>
</table>

2) Respiratory Rate Abnormality
(From Warren et al.)

<table>
<thead>
<tr>
<th>RR</th>
<th>&lt;30</th>
<th>&gt;60</th>
<th>&lt;25, &gt;65</th>
<th>&lt;20, &gt;30</th>
<th>&gt;14, &gt;24</th>
<th>&lt;14, &gt;20</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>

Contact MD/NP to Evaluate RN to document notification of MD/NP
*MD/NP is responsible to respond in 10 minutes*

**MD/NP evaluates patient at the bedside:**
Are the vital sign abnormalities explained by pain, medication, anemia, dehydration or other external stimuli?
(Adapted from Goldstein et al.)

No

Your patient has SIRS.
**SIRS** with a suspected or proven infection, is **Sepsis.**

MD/NP: Are there signs of organ dysfunction?
(Adapted from Brierley et al.)

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>Respiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capillary refill &gt; 2 seconds, decreased pulses, cool extremities, mottling, flush capillary refill, bounding pulses, or wide pulse pressure? Hypotension?</td>
<td>Escalating respiratory support? If congenital heart disease, new oxygen requirement above baseline?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Renal</th>
<th>Neurological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low urine output: &lt; 1 cc/kg/hour?</td>
<td>Irritable, agitated, drowsy, confused, lethargic, not arousable?</td>
</tr>
</tbody>
</table>

**Sepsis without organ dysfunction**
- MD/NP must reassess patient in 1 hour
- Continuous monitor
- Confirm IV access
- Strongly consider fluid resuscitation
- Consider whether current antibiotics are appropriate
- Discuss with attending
- Consider whether ICU consult is needed

Yes

**INITIATE SEVERE SEPSIS PROTOCOL**
Sepsis

Paediatric Sepsis

Severe sepsis is a CLINICAL EMERGENCY. Signs and symptoms of sepsis in children can be subtle and deterioration to shock rapid. Early initiation of simple treatment improves outcomes.

Recognition:
If a child with suspected or proven infection AND has at least 2 of the following:
- Core temperature < 36°C or > 38.5°C
- Inappropriate tachycardia (Refer to local criteria / APLS guidance)
- Altered mental state (including sleepiness, irritability, lethargy, flappiness)
- Reduced peripheral perfusion / prolonged capillary refill

Think: could this child have SEPSIS or SEPTIC SHOCK? If in doubt, consult a senior clinician.

Complete all elements within 1 hour

Respond with Paediatric Sepsis 6:

1. Give high flow oxygen:

2. Obtain intravenous / intraosseous access & take blood tests:
   a. Blood cultures
   b. Blood glucose - treat low blood glucose
   c. Blood gas (+ FBC, lactate & CRP as able for baseline)

3. Give IV or IO antibiotics:
   - Broad spectrum cover as per local policy

4. Consider fluid resuscitation:
   - Aim to restore normal circulating volume and physiological parameters
   - Titrate 20 ml/kg Isotonic Fluid over 5 - 10 min and repeat if necessary
   - Caution with fluid overload > Examine for crepitations & hepatomegaly

5. Involve senior clinicians / specialists early:

6. Consider inotropic support early:
   - If normal physiological parameters are not restored after ≥ 40 ml/kg fluids
   - NB adrenaline or dopamine may be given via peripheral IV or IO access

Record any reasons for variation from Paediatric Sepsis 6 overleaf
Diagnosis of Sepsis

- What is sepsis?
- Is context dependant
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Defining Pediatric Severe Sepsis

PICU – 42 beds, 1729 patients

Consensus guidelines (research criteria) N= 90 (5.2%)

Diagnosis by healthcare professionals (clinical criteria) n= 92 (5.6%)

ICD 9 (administrative criteria) N=103 (6.0%)
Discordant Identification of Severe Sepsis

- Only 301/706 patients (42.6%) were identified by both criteria (κ 0.57 ± 0.02).
- The 137/438 of patients (31%) who did not meet consensus criteria were younger, had a lower severity of illness, and a lower PICU mortality than those who met consensus criteria or both definitions.

Agreement was lowest in North America (31%) moderate in Australia and New Zealand (45%) and Europe (51%); and highest in Asia (72%), Africa (72%), and South America (85%).

Diagnosis of Sepsis

- What is sepsis?
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# Sepsis Detection Methods
## Algorithmic Alert vs. Physician Judgement


Test characteristics of sepsis screening tests.

<table>
<thead>
<tr>
<th>Test</th>
<th>Algorithmic Alert</th>
<th>Physician Judgment</th>
<th>Combined Method</th>
<th>Sequential Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>92.1 (91.67–92.43)</td>
<td>72.73 (72.1–73.35)</td>
<td>96.6 (96.3–96.9)</td>
<td>68.2 (67.5–68.8)</td>
</tr>
<tr>
<td>Specificity</td>
<td>83.4 (82.91–83.95)</td>
<td>99.51 (99.41–99.61)</td>
<td>83.3 (82.8–83.8)</td>
<td>99.6 (99.6–99.7)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>2.5 (2.24–2.67)</td>
<td>40.25 (39.56–40.94)</td>
<td>2.6 (2.3–2.8)</td>
<td>47.6 (46.9–48.3)</td>
</tr>
<tr>
<td>Positive likelihood ratio</td>
<td>5.6 (5.18–5.95)</td>
<td>148.79 (117.2–1900)</td>
<td>5.8 (5.5–6.1)</td>
<td>200.8 (151.8–266.7)</td>
</tr>
<tr>
<td>Negative likelihood ratio</td>
<td>0.09 (0.05–0.19)</td>
<td>0.27 (0.19–0.39)</td>
<td>0.04 (0.01–0.12)</td>
<td>0.32 (0.24–0.43)</td>
</tr>
<tr>
<td>Receiver operative characteristic curve area</td>
<td>0.88 (0.85–0.91)</td>
<td>0.86 (0.81–0.91)</td>
<td>0.90 (0.88–0.92)</td>
<td>0.84 (0.79–0.89)</td>
</tr>
</tbody>
</table>

Severe sepsis/septic shock prevalence: 88 (0.45%)
What is the probability this patient is septic?
Lactate Normalization and Organ Dysfunction in Sepsis

Lactate normalization was associated with decreased risk of persistent organ dysfunction (RR 0.46, 0.29-0.73).

Lactate clearance was not (RR 0.70, 0.35-1.41).

Table VI. Absolute and relative change in lactate level from the first to the final lactate level, by clearance and normalization status

<table>
<thead>
<tr>
<th></th>
<th>Lactate clearance (n = 70)</th>
<th>Lactate nonclearance (n = 7)</th>
<th>Lactate normalization (n = 62)</th>
<th>Lactate non-normalization (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute change in lactate level</td>
<td>-0.73 mmol/L [-0.3, -1.55]</td>
<td>0.55 mmol/L [0.47, 1.69]</td>
<td>-0.58 mmol/L [-0.27, -1.44]</td>
<td>-0.33 mmol/L [-0.19, -0.58]</td>
</tr>
<tr>
<td>% change in lactate level</td>
<td>-32.1% [-19.5, -55.2%]</td>
<td>35.3% [16.0, 61.9%]</td>
<td>-33.4% [-19.4, -56.1%]</td>
<td>-11.9% [35.2%, -30.6%]</td>
</tr>
</tbody>
</table>

Results presented as median [IQR].

Still Laborious and Slow?

- Colonies or or a positive blood culture bottle!
- Plate Innoculated
- Instrument Loaded
Matrix Assisted Laser Desorption/Ionization (MALDI)

From Sauer, Nature Review Methods 2010
PCR Followed by Mass Spec

• Whole samples and paired blood cultures (247 from 175 patients)

• Blood Culture
  – Agreement between PCR-MS and conventional method (blood culture) = 94%
  – Sensitivity 97%, specificity 99% for PCR-MS

• PCR-MS identified 13 more pathogens not found by conventional means

Elena Jordana-Lluch et al PLOS One 2013
Rapid Molecular Diagnostics

• Biomarkers - characteristics that can be measured and evaluated as an indicator of pathological processes or responses to a therapeutic intervention

• Ideal for all biomarkers
  – sensitivity, specificity, predictive value

• Ideal for acute conditions
  – readily obtainable from body fluids or tissue samples
  – test results available in a relatively short period

Gene Expression Profiles

Transcriptional Profiling: Ready for prime time

New Diagnostic Biomarkers in Pediatric Sepsis

Table 1. Association of study measurements with severity of illness, organ dysfunction, and clinical outcome in septic patients.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>MMP-9/TIMP-1</th>
<th>MrProANP</th>
<th>A-FaBP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rs</td>
<td>P</td>
<td>rs</td>
</tr>
<tr>
<td>Severity of illness and Organ Dysfunction</td>
<td>-0.57</td>
<td>&lt;0.001</td>
<td>0.60</td>
</tr>
<tr>
<td>PELOD</td>
<td>-0.74</td>
<td>&lt;0.001</td>
<td>0.62</td>
</tr>
<tr>
<td>Clinical Outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU LOS</td>
<td>-0.68</td>
<td>&lt;0.001</td>
<td>0.69</td>
</tr>
<tr>
<td>Hospital LOS</td>
<td>-0.66</td>
<td>&lt;0.001</td>
<td>0.62</td>
</tr>
<tr>
<td>Inotrope-free days</td>
<td>0.23</td>
<td>0.299</td>
<td>-0.07</td>
</tr>
<tr>
<td>Ventilator-free days</td>
<td>-0.242</td>
<td>0.277</td>
<td>-0.16</td>
</tr>
<tr>
<td>GOS b</td>
<td>0.45</td>
<td>0.036</td>
<td>-0.19</td>
</tr>
</tbody>
</table>

Sidestream Dark-Field Images of Sublingual Microcirculation

Vincent JL and De Backer D NEJM 369;18;2013
Persistent low microcirculatory vessel density in nonsurvivors of sepsis

Figure 2. The functional capillary density (FCD) improved in survivors. Day 1: 1.7 cm/cm² (0.8–3.4); day 2: 4.3 cm/cm² (2.1–6.9) (p = .001). The FCD in nonsurvivors did not change. Day 1: 3.2 cm/cm² (0.8–3.8); day 2: 1.9 cm/cm² (1.0–2.1). The median FCD on day 2 was lower in nonsurvivors: 1.9 cm/cm² (1.0–2.1) vs. 4.3 cm/cm² (2.1–6.9) (p = .009).

Top A et al Crit Care Med 2011;39:8
Mortality Prediction in PICU

- Septic shock (2005 consensus) was sensitive but not specific (AUC = 0.69; 95% CI 0.65–0.72).
- Oxygenation markers, ventilator support, hypotension, cardiac arrest, serum lactate, pupil responsiveness, and immunosuppression were the best-performing predictors (0.843; 0.811–0.875).
- The sepsis score performed comparably when applied to all children admitted with invasive infection (0.810; 0.781–0.840).

Schlapbach L J et al  Intensive Care Med 2017;
Mortality Prediction in PICU

Every one-point increase was associated with a 28.5% (23.8–33.2%) increase in the odds of death.

Children with a score ≥6 had 19.8% mortality and accounted for 74.3% of deaths.

Schlapbach L J et al Intensive Care Med 2017;
• Intuition that something was wrong despite the clinical assessment of non-severe illness substantially increased the risk of serious illness (LR 25.5, 95% CI 7.9 to 82.0)
• Strongly associated with gut feeling: children’s overall response (drowsiness, no laughing), abnormal breathing, weight loss, and convulsions.
• Strongest contextual factor was the parents’ concern that the illness was different from their previous experience (OR 36.3, 95% CI 12.3 to 107).
Conclusions

• Sepsis is a life threatening organ dysfunction caused by a dysregulated host response to infection
• Present definitions and methods of diagnosis are imperfect
• Approaches are context dependent and should be pragmatic
• Move afoot to change the current state.