Thinking beyond sepsis

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Clinical signs of bacterial sepsis

<table>
<thead>
<tr>
<th>Clinical Sign</th>
<th>Percent of Infants with Sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthermia</td>
<td>51</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>15</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>33</td>
</tr>
<tr>
<td>Apnea</td>
<td>9</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>16</td>
</tr>
<tr>
<td>Jaundice</td>
<td>28</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>22</td>
</tr>
<tr>
<td>Lethargy</td>
<td>25</td>
</tr>
<tr>
<td>Irritability</td>
<td>16</td>
</tr>
<tr>
<td>Anorexia</td>
<td>28</td>
</tr>
<tr>
<td>Vomiting</td>
<td>25</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>17</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11</td>
</tr>
</tbody>
</table>

Differential diagnosis

- Structural
- PDA
- PPHN

Cardiac
- Pul hypoplasia
- Pul. Hge
- BPD

Respirator
- HIE
- IVH
- ICH
- Seizure

Neurologic
- NEC
- Malrotation
- Obstruction

GIT
- Torch
- Viral

Infections
- Hypoglycemia
- IEM

Metabolic
Need for rapid and reliable tool to diagnose/exclude sepsis

Need to safely distinguish infected from uninfected newborns, especially in the early phase of the disease.

<table>
<thead>
<tr>
<th>Infected neonate:</th>
<th>Uninfected neonate:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Need early start of the antibiotic treatment</td>
<td>• to avoid the unnecessary use of antibiotics in sepsis-negative infants.</td>
</tr>
<tr>
<td>• Each hour delay matters</td>
<td></td>
</tr>
</tbody>
</table>
Problem with Broad Spectrum Antibiotics

Previous broad-spectrum antibiotic (third-generation cephalosporin or carbapenem) use was associated with an increased risk of invasive candidiasis (OR 2.2, 95% CI 1.4–3.3). (n=3702, ELBW)


Increased risk of death when infants were treated with ampicillin plus cefotaxime versus ampicillin plus gentamicin in the first 3 postnatal days (OR 1.5, 95% CI 1.4–1.7) [n=1,28,914]

Problem with prolonged use of antibiotics

Prolonged antibiotic therapy was associated with increased LOS, NEC, or death (OR 2.66, 95% CI 1.12, 6.30). (n=365, <32 weeks and <1500 gms)

• Kuppala VS et al, J Pediatr 2011;159(5):720–5

Each additional day of antibiotic therapy was associated with a 4% increase in the odds of NEC or death (19-center study, n=5693 ELBW)


Unnecessary use of broad spectrum antibiotics and prolonged use of antibiotics should be minimized.
When should we think beyond sepsis

Clinical signs/symptoms suggestive of other diagnosis

Symptomatic neonate with no risk factors for sepsis

Investigations not suggestive of sepsis
### Risk factors for early neonatal sepsis

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk Factors</th>
</tr>
</thead>
</table>
| **Mother**   | • maternal fever, UTI  
               • other systemic infections |
| **Baby**     | • Prematurity  
               • Birth asphyxia |
| **Labour**   | • spontaneous preterm onset of labor |
| **Membrane** | • Premature Rupture of membrane  
               • Prolonged rupture of membrane (>18 hrs), |
| **Infection related** | • clinical chorioamnionitis, FSL  
                    • unclean vaginal exam, >3 PV exam in labor |

Evidence based clinical practice guideline; NNF 2010
Symptomatic neonate at birth:
No antibiotics

Born without any of the known risk factors of sepsis

Chest X ray is not suggestive of pneumonia

Have alternative reasons to explain the symptoms.

These neonates need not be immediately started on antibiotics but their clinical course must be carefully monitored:

Evidence based clinical practice guideline; NNF 2010
When do we think beyond sepsis (LOS)

Symptomatic Neonate

Clinically low probability of sepsis
Do Septic screen
If positive
send blood culture and start on antibiotics
If negative
repeat septic screen after 24 hrs

Clinically high probability of sepsis
Send blood culture, do septic screen and start on antibiotics
If again negative
Think beyond sepsis
Diagnostic Markers in neonatal sepsis

- **Neutrophil indices:** I/T ratio, ANC, mESR
- **Acute phase proteins:** CRP, Procalcitonin
- **Cytokines:** (IL-6)
- **Cell surface antigens:** (CD64)
- **Molecular diagnosis:** PCR, Genomics, Proteomics

- **Early 80's:**
- **Mid 80's - Early 90's:**
- **1990's:**
- **2000's:**
- **2010s**
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- **Cell surface antigens**
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- **Molecular diagnosis:**
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- **2010s**
Sensitivity of sepsis markers

- CBC: 60%
- CRP: 70%
- PCT: 80%
- CD64: 85%
Time line for sepsis markers

For asymptomatic, at risk of EOS: antibiotic decision taken here

For symptomatic, at risk of EOS & all LOS: antibiotic decision taken here

SIRS, ie clinical signs

For asymptomatic, at risk of EOS: antibiotic decision taken here

Procalcitonin

CRP

CD64

ANC

ITR

Platelets

mESR

Hours after bacterial invasion
Sensitivity of repeat CRP as sepsis marker

Serial Serum C-Reactive Protein Levels in the Diagnosis of Neonatal Infection
William E. Benitz, Michael Y. Han, Ashima Madan and Pramela Ramachandra
Pediatrics 1998;102;e41
Blood Culture

Latest automated blood culture is very sensitive, can be positive in 8-12 hrs also.

1 ml blood gives up-to 90% positivity by 48 hrs.
Sensitivity of CRP and PCT in different types of sepsis
Referred cases on antibiotics after 72 hrs of life
(n= 115, Rani Hospital, Ranchi Feb-Aug 2015)
Sensitivity of CRP and PCT in different types of sepsis
Referred cases on antibiotics after 72 hrs of life
(n= 115, Rani Hospital, Ranchi Feb-Aug 2015)
What we do (Baby in emergency dept.)

Clinical diagnosis of sepsis.

Send sepsis profile (CBC, CRP, PCT, Blood Culture, ABG with lactate and urea)

- lab is supportive of sepsis
  - continue treatment

- lab is not supportive of sepsis
  - Do bedside screening USG-ECHO and X-ray

Cardiorespiratory
Neurological
Surgical
Others: metabolic

Admission

1 hr
2 hrs
Deterioration in premature baby

Deterioration in NICU, Examine the baby and send sepsis workup

Infective:
- Sepsis

Non-infective:
- Respiratory: Evolving BPD
- Cardiac: PDA
- CNS: IVH
- GIT: NEC
- Metabolic

Never forget to evaluate for sepsis if there is no simple explanation
Symptomatic neonate with no definite pointers for diagnosis

- No risk factors for sepsis
- Sepsis screen is negative
- Repeat sepsis screen after 24 hrs is negative
- Blood culture is sterile

Think beyond sepsis when
Thank you