Late onset neonatal sepsis

Sarayut Supapannachart MD
Why EOS vs LOS ? 1990

• Pathogens: same (Salmonella common here)
  – GBS, Gram neg bacilli, Listeria sp
• Symptoms: septic shock, PPHN vs fever
  – Maternal antibiotic is necessary to prevent EOS
  – Lumbar puncture, Urine culture is mandatory in LOS
• Target organs: systemic vs meningitis, UTI
  – Empirical antibiotic: Amp+Gent vs Amp+ Cefotaxime
Why EOS vs LOS ? 2016

• Classic LOS is disappearing, now most LOS are nosocomial (healthcare related)

• CLABSI is the most common with CONS (Use of PICC line)

• VAP is very common here

• All are preventable !!!
Symptoms related to LOS

- Increasing Apnea or late onset apnea
- Temperature instabilities
- Hyperglycemia
- Leukocytosis or leukopenia
- Thrombocytopenia
- Increase ventilator support
- Unexplained metabolic acidosis
Epidemiology of LOS in the NICU
<table>
<thead>
<tr>
<th>Author and country</th>
<th>No. of centres</th>
<th>Birth year of cohort</th>
<th>No. of neonates</th>
<th>Definition of the onset of LOS</th>
<th>LOS, No. (%)</th>
<th>Proportion (%) of CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLBW infants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boghossian et al.² USA</td>
<td>6</td>
<td>2002–2008</td>
<td>15 178</td>
<td>72 h</td>
<td>3797 (25.0)</td>
<td>53.2</td>
</tr>
<tr>
<td>Lahra et al.⁹ Australia</td>
<td>1</td>
<td>1992–2004</td>
<td>798</td>
<td>48 h</td>
<td>220 (27.6)</td>
<td>64.4</td>
</tr>
<tr>
<td>Tröger et al.¹¹ Germany</td>
<td>46</td>
<td>2003–2011</td>
<td>5886</td>
<td>72 h</td>
<td>882 (15.0)</td>
<td>58.4</td>
</tr>
<tr>
<td>All admitted neonates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vergnano et al.³ England</td>
<td>12</td>
<td>2006–2008</td>
<td>14 225</td>
<td>48 h</td>
<td>868 (6.1)</td>
<td>54</td>
</tr>
<tr>
<td>van den Hoogen et al.⁸ Netherland</td>
<td>1</td>
<td>2003–2006</td>
<td>2278</td>
<td>48 h</td>
<td>318 (13.9)</td>
<td>77.9</td>
</tr>
<tr>
<td>Shim et al.⁷ Korea</td>
<td>1</td>
<td>1996–2005</td>
<td>1479</td>
<td>96 h</td>
<td>134 (9.1)</td>
<td>6.2</td>
</tr>
<tr>
<td>Morioka et al.¹² Japan</td>
<td>5</td>
<td>2006–2008</td>
<td>6894</td>
<td>72 h</td>
<td>42 (0.61)</td>
<td>11.9</td>
</tr>
<tr>
<td>Al-Taiar et al.¹⁰ China (Hebei), Malaysia, Hong Kong and Thailand</td>
<td>4</td>
<td>2006–2009</td>
<td>36 842</td>
<td>72 h</td>
<td>782 (2.12)</td>
<td>42.2</td>
</tr>
<tr>
<td>Tsai et al.⁴ Taiwan</td>
<td>1</td>
<td>2004–2011</td>
<td>5010</td>
<td>6 days</td>
<td>713 (14.2)</td>
<td>39.9</td>
</tr>
<tr>
<td>Hammoud et al.⁵ Kuwait</td>
<td>1</td>
<td>2005–2009</td>
<td>12 987</td>
<td>6 days</td>
<td>949 (7.3)</td>
<td>35.5</td>
</tr>
<tr>
<td>Leal et al.¹³ Mexico</td>
<td>1</td>
<td>2004–2007</td>
<td>11 790</td>
<td>72 h</td>
<td>78 (0.66)</td>
<td>47.4</td>
</tr>
</tbody>
</table>

CONS, coagulase-negative staphylococci; VLBW, very low birth weight.
**Pathogens Causing Nosocomial Sepsis**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>1996</th>
<th>2002</th>
<th>2008</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus-coagulase negative</td>
<td>55%*</td>
<td>47%**</td>
<td>47.9%#</td>
<td>65%##</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>9%</td>
<td>4%</td>
<td>7.8%</td>
<td>7%</td>
</tr>
<tr>
<td>Enterococcus/Group D Streptococcus</td>
<td>5%</td>
<td>3%</td>
<td>3.3%</td>
<td>6%</td>
</tr>
<tr>
<td>Gram negative enterics</td>
<td>18%</td>
<td>31%</td>
<td>18%</td>
<td>11%</td>
</tr>
<tr>
<td>Fungi</td>
<td>9%</td>
<td>11%</td>
<td>12.2%</td>
<td>9%</td>
</tr>
</tbody>
</table>

## Incidences of LOS

<table>
<thead>
<tr>
<th>Birth weight (gm)</th>
<th>CLASBI *</th>
<th>U.C.</th>
<th>VAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 750g</td>
<td>3.9 (12.7)**</td>
<td>3.9</td>
<td>2.2 (6.22)**</td>
</tr>
<tr>
<td>751- 1000g</td>
<td>3.4 (15.5)</td>
<td>2.5</td>
<td>1.8 (7.72)</td>
</tr>
<tr>
<td>1001-1250g</td>
<td>2.4 (15.9)</td>
<td>1.7</td>
<td>1.4 (8.19)</td>
</tr>
<tr>
<td>1251-1500g</td>
<td>2.4 (13.8)</td>
<td>0.9</td>
<td>0.9 (9.64)</td>
</tr>
<tr>
<td>&gt;2500</td>
<td>1.9 (11.7)</td>
<td>0.9</td>
<td>0.7 (11.82)</td>
</tr>
</tbody>
</table>

*= per 1000 catheter or 1000 ventilator days (Level III NICUs) NHSN 2006-2008

**= International Nosocomial Infection Control Consortium 2003-2008
hand hygiene compliance 54%
Peripheral Insert Central Catheter (PICC)
Peripheral Insert Central Catheter (PICC)
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Peripheral Insert Central Catheter (PICC)
Peripheral Insert Central Catheter (PICC)
Why Worry about LOS?
(Money/Mortality/Mental deficiency)

- LOS are costly; 100,000 deaths and $6.5 billion dollars in excess expenditure annually (U.S.)
- The Center for Medicare and Medicaid Services no longer reimburses hospitals for expenses associated catheter related blood stream infections
- They are responsible for up to 45% of deaths after two weeks of age
- LOS are associated with poorer neurodevelopmental outcomes.
- LOS are common events in the NICU
## Adverse Neurodevelopmental Outcome in ELBW Infants with Infections

<table>
<thead>
<tr>
<th></th>
<th>Clinical infection (n=1538)</th>
<th>Sepsis (n=1922)</th>
<th>Sepsis + NEC (n=279)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MDI &lt; 70</strong></td>
<td>1.3 (CI 1.1,1.5)</td>
<td>1.3 (CI 1.1,1.6)</td>
<td>1.6 (CI 1.2,2.2)</td>
</tr>
<tr>
<td><strong>PDI &lt; 70</strong></td>
<td>1.5 (CI 1.3,2.0)</td>
<td>1.5 (CI 1.2,1.9)</td>
<td>2.4 (CI 1.7,3.4)</td>
</tr>
<tr>
<td><strong>CP</strong></td>
<td>1.3 (CI 1.0,1.6)</td>
<td>1.4 (CI 1.1,1.8)</td>
<td>1.7 (CI 1.2,2.5)</td>
</tr>
<tr>
<td><strong>Microcephaly</strong></td>
<td>1.3 (CI 1.1,1.6)</td>
<td>1.5 (CI 1.2,1.7)</td>
<td>2.0 (CI 1.5, 2.6)</td>
</tr>
</tbody>
</table>

*Stoll et al JAMA 292: 2357, 2004 (n=6093, 18 month follow-up)*
Strategies to Reduce the Morbidity and Mortality of LOS
Risk Factors for Catheter Line-Associated Blood Stream Infections in VLBW Infants

※ Strongest correlation with birth weight & GA
※ Use of parenteral alimentation and central lines
※ Steroids for BPD
※ Histamine blockers
※ Low serum IgG levels at birth
Risk Factors for Catheter-Associated Blood Stream Infections in VLBW Infants

- Prolonged duration of mechanical ventilation
- Overcrowding & heavy workloads
- Staffing problems (inexperienced nurses and new house staffs)
Strategies to Reduce the Mortality and Morbidity of LOS

- Identification of risk factors for nosocomial sepsis and avoidance of those care practices
- Adherence to Guidelines for catheter maintenance and insertion
- Re-emphasis of hand hygiene practices for nursery staff
- Early diagnosis of LOS (HeRO)
- Prophylactic fluconazole?
Hand Hygiene & Skin flora

- Three kinds of hand flora (transient, resident and infectious)
- Most nosocomial infections are caused by transient flora, that are located superficially.
- Hand hygiene techniques (that de-germ) are effective in eradicating transient flora
Hand Hygiene Alternatives

- Alcohol based formulations (with appropriate emollients are equivalent or superior to antiseptic detergents (in addition they require no washing & minimal drying)
- Soaps and detergents, particularly those that are anionic or cationic, are the most damaging substances (Larson Rev. Inf. Dis. 1999).
Compliance with Hand Hygiene is Poor! Monitoring is important!!
Diagnosis of Late Onset Sepsis
Diagnostic Testing for Late Onset Sepsis

- Blood culture (central + peripheral) / Urine culture
- White blood count and Differential count
- Acute phase reactants (CRP or Procalcitonin)
- CSF
- Cytokine determinations & Heart rate characteristics index
- Lumbar Puncture (selected cases)
Interpreting Positive Blood Cultures for Coagulase Negative Staphylococcus

Clinical Signs and Symptoms of Sepsis

Draw a *central and peripheral blood culture* and begin broad spectrum antibiotics which should always include vancomycin. If not CONS, line should be removed.

- Peripheral negative CONS Central negative CONS: No Sepsis
- Peripheral positive CONS Central negative CONS: Presumed contamination
- Peripheral negative CONS Central positive CONS: Presumed colonization
- Peripheral positive CONS Central positive CONS: CONS bacteremia
Interleukin-6 & Late-onset Sepsis

Sensitivity 68 (50-82)
Specificity 76 (56-90)
PPV 78 (60-91)
NPV 65 (46-80)

N= 35 infants with culture proven sepsis and 37 infants with clinical sepsis

Cumulative incidence of raised concentrations of IL-1ra, IL-6 & CRP in 28 cases between days -3 and 1

Heart Rate Monitoring and Late Onset Sepsis
Heart Rate Characteristics and Late Onset Sepsis

- In healthy humans, the interval between heart beats changes constantly.
- Chronotropic regulation of the heart occurs through autonomic innervation of the sinoatrial pacemaker cells.
The sympathetic nerve endings release norepinephrine and *increases* heart rate.

The parasympathetic nervous system releases acetylcholine, opening potassium channels and *decreases* heart rate.
Sepsis-Heart-Brain Interactions

Cytokines
Other mediators
↓HR variability
Decelerations
Vagal-Immune-Brain communications
Heart rate characteristics associated with neonatal sepsis

- Decreased heart rate variability
- Repetitive transient HR decelerations
HR decelerations are mediated by vagus nerve activation

Baseline

10 min after i.p. pathogen

Klebsiella

MRSA

30 sec after i.p. atropine
HRCi monitor
Observed Rates for an Adverse Event in the next 24 hours for Patients Having a HRCi Score >90th Percentile
Performance of HRCi Monitoring, Laboratory Tests and Clinical Signs for Prediction of Sepsis in the Next 24 hours
Mortality Reduction by HRCi Monitoring in VLBW Infants

- RCT using two groups of infants; one group had the HRCi monitoring masked and in the other it was visible. N = 3003
- Primary outcome was the number of days alive and ventilator free in the 120 days after randomization.
- There was a 2.3 day difference in the primary outcome favoring the group with the visible HRCi p = N.S.
- The mortality rate was reduced in the group of infants whose HRCi was displayed (10.2% > 8.1% p = .04
  (number needed to monitor = 48)
- Benefits were concentrated in infants < 1,000 g (p=.02)

Use of Prophylactic Antibiotics: Fluconazole

- There are 2000-3000 invasive Candida infections, 900-1200 survivors with neurodevelopmental impairment and 200-300 deaths annually.
- Targeting fluconazole prophylaxis to infants ≤ 27 weeks and ≤ 1000g can eliminate most infections.
- In 2006, 34% of neonatologists used antifungal prophylaxis.
- The goal of antifungal prophylaxis is to target sites of potential colonization, before invasive infection occurs.
- Fluconazole decreases colonization (without major toxicity or development of resistance).
Systemic antifungal agent vs. placebo or no drug
Outcome, *Invasive fungal infection*

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Fluconazole n/N</th>
<th>Placebo n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabrera 2002</td>
<td>0/6</td>
<td>1/5</td>
<td></td>
<td>4.6%</td>
<td>0.29 [0.01, 5.79]</td>
</tr>
<tr>
<td>Kaufman 2001</td>
<td>1/50</td>
<td>13/50</td>
<td></td>
<td>36.7%</td>
<td>0.08 [0.01, 0.57]</td>
</tr>
<tr>
<td>Kicklighter 2001</td>
<td>2/53</td>
<td>2/50</td>
<td></td>
<td>5.8%</td>
<td>0.94 [0.14, 6.44]</td>
</tr>
<tr>
<td>Manzoni 2007</td>
<td>7/216</td>
<td>10/106</td>
<td></td>
<td>53.0%</td>
<td>0.25 [0.10, 0.59]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>325</strong></td>
<td><strong>211</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>0.23 [0.11, 0.46]</strong></td>
</tr>
</tbody>
</table>
Systemic antifungal agent vs. placebo or no drug
Outcome, *Death prior to hospital discharge*

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Fluconazole n/N</th>
<th>Placebo n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaufman 2001</td>
<td>4/50</td>
<td>10/50</td>
<td></td>
<td>29.7%</td>
<td>0.40 [0.31, 1.19]</td>
</tr>
<tr>
<td>Kicklighter 2001</td>
<td>5/53</td>
<td>10/50</td>
<td></td>
<td>30.5%</td>
<td>0.47 [0.17, 1.28]</td>
</tr>
<tr>
<td>Manzoni 2007</td>
<td>18/216</td>
<td>10/106</td>
<td></td>
<td>39.8%</td>
<td>0.88 [0.42, 1.85]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>319</strong></td>
<td><strong>206</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>0.61 [0.37, 1.03]</strong></td>
</tr>
</tbody>
</table>
Common Sense Strategies to Prevent LOS in the NICU

- Avoid care practices which bypass normal skin barrier defense mechanisms (central lines, UA/UV catheters, heel sticks)
- Limit the use of drugs which are associated with nosocomial infection (steroids for BPD, H₂ blockers)
- Cohort infants colonized with resistant or invasive microorganisms (use gloves and gown)
- Limit the use of antibiotics and when needed use the simplest and most appropriate drug (antibiotic stewardship)
Common Sense Strategies to Prevent LOS in NICU

- Use of alcohol based emollients (improved compliance)
- Avoid skin damage (e.g., scrubbing with brushes)
- Encourage use of breast milk
- Minimize central venous catheter days
- Use sterile barriers for central venous line insertion and line maintenance
Columbia’s NICU Bundle

- Follow AAP recommendations for hand hygiene compliance & CDC guidelines for catheter insertion and maintenance
- Standardized protocol for line insertion and dressing changes (q 7 days).
- Use of a checklist for line insertion
- Use of Chloraprep® after age 48 hours for line insertion and dressing changes (controversial)
Columbia’s NICU Bundle

- Removal of central lines when enteral intakes are 80-100 ml/kg
- Entry into the central line restricted to once/day
- Use of a separate port for infusion of TPN and lipids
- Dressing changes are done every seven days.
- Tubing is changed every third day.
2006-2009 MSCHONY NICU
Annual Mean CLABSI* Rates

* No. of blood stream infections divided by total central line days X 1000
<table>
<thead>
<tr>
<th>Trial of example</th>
<th>Birth year of cohort</th>
<th>Therapy</th>
<th>No. of infants</th>
<th>Outcome</th>
<th>Results (intervention vs control)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intervention</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>Immune replacement therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carr et al(^{52})</td>
<td>2000–2006</td>
<td>GM-CSF</td>
<td>139</td>
<td>141</td>
<td>Sepsis-free survival rate</td>
</tr>
<tr>
<td>Kuhn et al(^{51})</td>
<td>2002–2006</td>
<td>G-CSF</td>
<td>102</td>
<td>98</td>
<td>Sepsis-free survival rate</td>
</tr>
<tr>
<td>Fanaroff et al(^{53})</td>
<td>1988–1991</td>
<td>IVIG</td>
<td>1204</td>
<td>1212</td>
<td>Incidence of sepsis</td>
</tr>
<tr>
<td>De Jonge et al(^{55})</td>
<td>2004–2006</td>
<td>INH-A21</td>
<td>994</td>
<td>989</td>
<td>Incidence of sepsis</td>
</tr>
<tr>
<td>Feeding strategies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jacobs et al(^{52})</td>
<td>2007–2011</td>
<td>Probiotics*</td>
<td>548</td>
<td>551</td>
<td>Incidence of sepsis</td>
</tr>
<tr>
<td>Flidel-Rimon et al(^{46})</td>
<td>1995–2001</td>
<td>Enteral feeding</td>
<td>385†</td>
<td></td>
<td>The relationship between the initiation of feeding and sepsis</td>
</tr>
<tr>
<td>Manzoni et al(^{49})</td>
<td>2007–2008</td>
<td>BLF alone</td>
<td>153</td>
<td>168</td>
<td>Incidence of sepsis</td>
</tr>
<tr>
<td>Manzoni et al(^{49})</td>
<td>2007–2008</td>
<td>BLF plus LGG</td>
<td>151</td>
<td>168</td>
<td>Incidence of sepsis</td>
</tr>
<tr>
<td>Skin care with antiseptics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quach et al(^{27})</td>
<td>2009–2013</td>
<td>CHG bathing</td>
<td>195†</td>
<td></td>
<td>Incidence of sepsis</td>
</tr>
</tbody>
</table>

*F. infantis, S. thermophilus and B. lactis.*
†Grouping of neonates was based on the presence of sepsis.
‡The study used a before-and-after quasiexperimental design.
BLF, bovine lactoferrin; CHG, chlorhexidine gluconate; CVC, central venous catheter; GM-CSF, granulocyte-macrophage colony-stimulating factor; IVIG, intravenous immunoglobulins; LGG, Lactobacillus rhamnosus; G-CSF, granulocyte colony-stimulating factor; RR, relative risk.
Conclusions

- LOS are an immense problem (worldwide) that increase mortality and morbidity and adds billions of dollars to the costs of NICU care
- The frequency of catheter related blood stream infections can be reduced by multidisciplinary, collaborative quality improvement
- The use of prophylactic fluconazole should await the results of large randomized clinical trials.
THANK YOU