Central Nervous System Infections and The Young Infant

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Preterm Infants: Obtaining Cerebrospinal Fluid

- 1998-2001; NICHD NRN centers, 9,641 VLBW infants
- 1.4% meningitis
- 30% had LP (22%-85%)
- Of infants with meningitis, 1/3rd (45/134) had positive cerebrospinal fluid (CSF) culture but negative blood culture (excluding CoNS, 47%)
- 67% (90/134) had repeat CSF culture: 12% positive
- Findings consistent with prior study (Wiswell et al, and subsequent study by Garges, Benjamin et al)
- Bacteremia, CNS penetration, secondary bacteremia

Stoll et al. *Pediatrics* 2004; Garges & Benjamin et al *Pediatrics* 2006
Term Infants

Obtaining Cerebrospinal Fluid

- 1997-2004; 150 NICUs (Pediatrix)
- 9,111 infants ≥34 weeks had a lumbar puncture
- 1% of infants had culture-proved meningitis
- 38% (35/92) had positive CSF culture but negative blood culture
- CSF indices (cell count, protein, glucose) had modest sensitivity and specificity

Garges et al. *Pediatrics* 2006:117;1094
### CSF parameters for preterm neonates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sens</th>
<th>Spec</th>
<th>(+) LR</th>
<th>(-) LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF WBC &gt; 25</td>
<td>71</td>
<td>81</td>
<td>3.7</td>
<td>0.4</td>
</tr>
<tr>
<td>CSF glucose &lt; 24</td>
<td>32</td>
<td>94</td>
<td>8</td>
<td>0.7</td>
</tr>
<tr>
<td>CSF protein &gt; 170</td>
<td>61</td>
<td>73</td>
<td>2.4</td>
<td>0.5</td>
</tr>
<tr>
<td>All 3 abnormal</td>
<td>26</td>
<td>97</td>
<td>8.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Any of the 3 abnormal</td>
<td>78</td>
<td>63</td>
<td>2.1</td>
<td>0.3</td>
</tr>
</tbody>
</table>
Test Performance of CSF WBC count in infants <34 weeks gestation

<table>
<thead>
<tr>
<th>CSF WBC</th>
<th>Sens</th>
<th>Spec</th>
<th>(+) LR</th>
<th>(-) LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0</td>
<td>95</td>
<td>12</td>
<td>1.1</td>
<td>0.4</td>
</tr>
<tr>
<td>&gt;10</td>
<td>80</td>
<td>67</td>
<td>2.4</td>
<td>0.3</td>
</tr>
<tr>
<td>&gt;20</td>
<td>73</td>
<td>79</td>
<td>3.5</td>
<td>0.3</td>
</tr>
<tr>
<td>&gt;25</td>
<td>71</td>
<td>82</td>
<td>3.9</td>
<td>0.4</td>
</tr>
<tr>
<td>&gt;100</td>
<td>51</td>
<td>91</td>
<td>5.7</td>
<td>0.5</td>
</tr>
<tr>
<td>&gt;1000</td>
<td>24</td>
<td>97</td>
<td>8</td>
<td>0.8</td>
</tr>
</tbody>
</table>
Traumatic Taps: Blood in CSF

- From one house officer to the next
- Do not ‘adjust’
  - Ratio (e.g., 500:1 or 1000:1)
  - Observed to predicted
- Test performance CSF parameters poor
- Culture when you do LOS workup

Greenberg Smith Benjamin *Pediatr Infect Dis J* 2008;27:1047-1051
Concordance of lumbar punctures with blood cultures

- If an infant undergoes LP on the day before, the day of, or the day after a positive blood culture for an organism, what % of LPs are positive for the same organism?

![Graph showing percentage of LPS positive for various organisms](image-url)
Meningitis

• Most common pathogens are typical late onset sepsis (LOS)

• Meningitis occurs in 1-2% in those who get the LP

• Diagnosis of meningitis
  • You need the culture
  • No set of clinical parameters can exclude meningitis in a neonate
  • Meningitis occurs in the absence of bacteremia and in the presence of normal CSF parameters
  • Cannot use peripheral WBC or bacteremia to determine need for LP
  • Cannot “rule out” meningitis based on CSF parameters; need reliable culture
  • Can a combination of blood culture plus CSF parameters to provide estimate that the probability of bacterial meningitis is < 1% or even <0.5%
MULTIPLE DOSE PHARMACOKINETIC STUDY OF MEROPENEM IN YOUNG INFANTS (<91 DAYS) WITH SUSPECTED OR COMPLICATED INTRA-ABDOMINAL INFECTION

Phase I/II Study
Sponsor: NICHD
Study Design

• Multi-center multi-dose dose escalation study
• Open-label
• Infants <32 weeks:
  • ≤ 14 days PNA: 20mg/kg q 12hr
  • ≥ 15 days PNA: 20mg/kg q 8hr
• Infants ≥32 weeks:
  • ≤ 14 days PNA: 20mg/kg q 8hr
  • ≥15 days PNA: 30mg/kg q 8hr
CSF samples

- 50-200 µL of CSF will be collected from infants when CSF is obtained as part of clinical care.
- CSF may be obtained by the following methods
  - Lumbar puncture
  - Ventricular tap
  - CSF reservoir tap
- Record specimen number, date/time sample obtained, date/time of sample freezing, dose given (mg), actual and dosing patient weight (g).
MPODS

- 20 centers,
- 200 participants
- Enrollment took 16 months
- 6 infants with CSF samples
Protocol: Antibiotic Safety in Infants with Complicated Intra-Abdominal Infections (SCAMP)
(Version 4.0, 24-Sept-2015)
Study Design

- Phase 2/3 - safety
- Prospective
- Open-label
- Partially Randomized
- Multi-center

A project of the Best Pharmaceuticals for Children Act
Study Population

• **210** premature infants (≤33 weeks gestation at birth):
  - Group 1 (N~70): ampicillin, gentamicin, and metronidazole
  - Group 2 (N~70): ampicillin, gentamicin, and clindamycin
  - Group 3 (N~70): piperacillin-tazobactam and gentamicin

Group 4:
• **50** late preterm and term infants (≥34 weeks gestation at birth)
  - Group 4: metronidazole in addition to the antibiotic regimens prescribed per SOC

Group 5:
• **24** infants (any gestational age) with suspected or confirmed infection
  - Group 5a (N~8): metronidazole
  - Group 5b (N~8): clindamycin
  - Group 5c (N~8): piperacillin-tazobactam
CSF PK Sampling

• Only if performed per routine medical care
• Can occur any day of treatment period
• Sources: lumbar puncture, ventriculoperitoneal shunt, or externalized ventricular device
• **Group 5:** At least 1 dose of the drug of interest will be administered prior to (if possible ≥1 hour) CSF PK sample
• One blood PK sample within 1 hour after CSF collection
• Maximum of 5 CSF/blood PK samples per infant up to 24 hours after last dose of study drug
SCAMP – Cohort 5

- The trial is still enrolling as of September, 2016
- Sites activated - 46
- Enrollment began in May 2014
- Number CSF samples - 23