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

The Harriet Lane Handbook

CSF parameters for preterm neonates

	Sens	Spec	(+) LR	(-) LR
CSF WBC>25	71	81	3.7	0.4
CSF glucose<24	32	94	8	0.7
CSF protein >170	61	73	2.4	0.5
All 3 abnormal	26	97	8.7	0.8
Any of the 3 abnormal	78	63	2.1	0.3

Test Performance of CSF WBC count in infants <34 weeks gestation

	Sens	Spec	(+) LR	(-) LR
CSF WBC>0	95	12	1.1	0.4
CSF WBC>10	80	67	2.4	0.3
CSF WBC>20	73	79	3.5	0.3
CSF WBC>25	71	82	3.9	0.4
CSF WBC>100	51	91	5.7	0.5
CSF WBC>1000	24	97	8	0.8

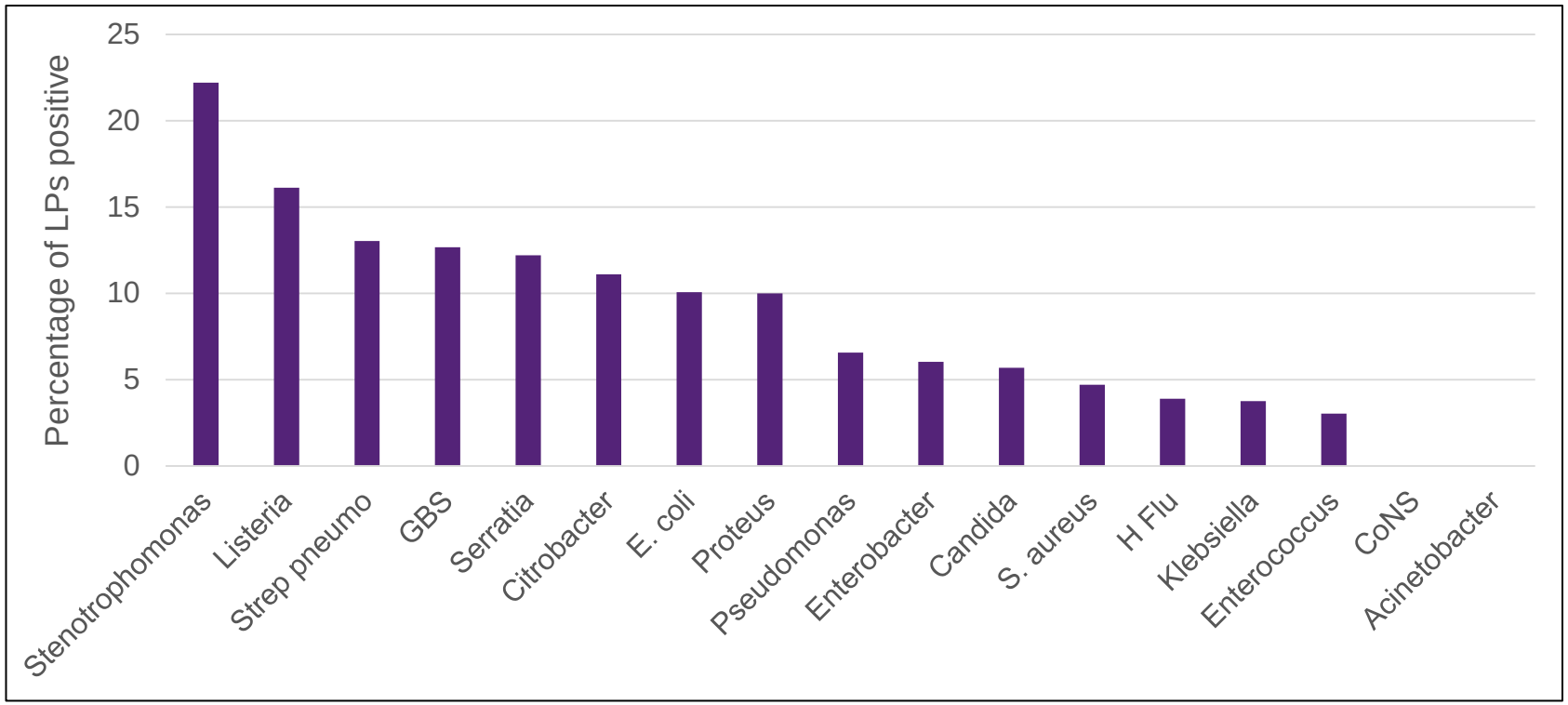
Traumatic Taps: Blood in CSF

- 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?



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)

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PEDIATRIC TRIALS NETWORK
Making drugs safer & more effective for use in the youngest patients

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

A project of the Best Pharmaceuticals for Children Act

Study Design

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

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

<u>Group 4:</u>

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

<u>Group 5</u>:

- **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