Rational Evaluation of the Febrile Infant

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  - Cincinnati Children’s Research Foundation
- No financial conflicts of interest

Objective
- Lessons learned
  - Epidemiology of infection in the febrile neonate
  - But he/she looks well...
  - Common strategies used to evaluate the febrile neonate
- To address current controversies
  - Who needs an LP?
  - Recognizable viral syndromes
  - Role of LP in neonates with UTI
  - Duration of hospitalization
  - Office- vs. hospital-based management
  - Role of herpes simplex virus (HSV) testing

Case: History
- 14-day-old infant
  - Rectal temperature of 38.3°C at home
  - Well until 1 day earlier when he began to feed poorly
  - Uncomplicated term vaginal birth
- What evaluation does this infant require?

Lessons Learned
- 7-13% of febrile infants have a serious bacterial infection (SBI)
- Risk of infection varies by age
- Terminology: Serious vs Invasive bacterial infection

Traditional Management if Age <60 d
- “Sepsis work-up”
  - Complete blood count
  - Blood culture
  - UA, urine culture
  - Lumbar puncture
- Empiric antibiotic therapy
- Routine hospitalization
Identification of Low Risk Patients

- Do all febrile infants <60 days require
  - a full sepsis evaluation?
  - antibiotics?
  - hospitalization?

Yale Observation Scale (1)

- Attempt to quantify physician assessment of toxicity in a systematic manner
- 6 clinical observations
  - Cry, reaction, state variation, color, hydration, response
- Scores based on degree of impairment
  1 = Normal
  3 = Moderate impairment
  5 = Severe impairment


Yale Observation Scale (2)

- Derive YOS score by adding score of each observation (range 6-30)
- Conclusion: Exam alone cannot reliably exclude SBI in infants <56 days

<table>
<thead>
<tr>
<th>Age</th>
<th>Serious Bacterial Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>YOS &lt;10</td>
</tr>
<tr>
<td>2-36 months</td>
<td>3%</td>
</tr>
<tr>
<td>29-56 days</td>
<td>22%</td>
</tr>
</tbody>
</table>

*YOS has performed similarly in other studies

Consensus

Can’t distinguish bacterial from viral illness based on observation scales or simple parameters such as height of fever or WBC count

Common strategies

- Common management strategies
  - Philadelphia protocol
  - Rochester criteria
  - Boston criteria
- Each has own definitions of high- and low-risk (or “not high-risk”) infants

Evaluation of the Febrile Infant

- Data complicated by
  - Different subpopulations studied
    - 0-3 months, 1-2 months, 1-3 months, 0-60 days, 0-56 days, 29-56 days
  - Varying definitions of
    - Fever
    - Fever without a source
    - SBI
**Protocol Components**

<table>
<thead>
<tr>
<th></th>
<th>Philadelphia</th>
<th>Rochester</th>
<th>Boston</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (days)</td>
<td>29-56</td>
<td>0-60</td>
<td>28-89</td>
</tr>
<tr>
<td>Temp (°C)</td>
<td>&gt;38.0</td>
<td>&gt;38.0</td>
<td>&gt;38.0</td>
</tr>
<tr>
<td>Exam</td>
<td>YOS</td>
<td>Well</td>
<td>YOS</td>
</tr>
<tr>
<td>WBC (per mm³)</td>
<td>&lt;15,000</td>
<td>5,000-15,000</td>
<td>&lt;20,000</td>
</tr>
<tr>
<td></td>
<td>BNR &lt;0.2</td>
<td>ABC ≤1500</td>
<td>...</td>
</tr>
<tr>
<td>UA</td>
<td>&lt;10/hpf</td>
<td>&lt;10/hpf</td>
<td>No leuk est</td>
</tr>
<tr>
<td>CSF</td>
<td>&lt;8 wbc</td>
<td>N/A</td>
<td>&lt;10 wbc</td>
</tr>
</tbody>
</table>

*BNR, band/neutrophil ratio; ABC, absolute band form count.*

**Accuracy of Common Protocols**

<table>
<thead>
<tr>
<th></th>
<th>Philadelphia</th>
<th>Rochester</th>
<th>Boston</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBI if high risk</td>
<td>13.8%</td>
<td>12.3%</td>
<td>Unknown</td>
</tr>
<tr>
<td>Management</td>
<td>Antibiotics Hospitalize</td>
<td>Antibiotics Hospitalize</td>
<td>Antibiotics Hospitalize</td>
</tr>
<tr>
<td>SBI if low risk</td>
<td>0%</td>
<td>1.1%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Management</td>
<td>No antibiotics Discharge</td>
<td>No antibiotics Discharge</td>
<td>Ceftriaxone Discharge</td>
</tr>
<tr>
<td>NPV</td>
<td>99-100%</td>
<td>88-99%</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

**Philadelphia Protocol**

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>YOS</td>
<td>&lt;10</td>
</tr>
<tr>
<td>CBC</td>
<td>&lt;15,000 WBC/mm³ Band/Neutrophil &lt;0.2</td>
</tr>
<tr>
<td>UA</td>
<td>&lt;10 WBC/hpf</td>
</tr>
<tr>
<td>LP</td>
<td>&lt;8 WBC/mm³ Gram stain: no bacteria</td>
</tr>
</tbody>
</table>

**Summary: Philadelphia Protocol**

- Infants ≤28 days
  - Complete evaluation (including LP)
  - Empiric antibiotics
  - Hospitalization
- Infants 29-56 days
  - Complete evaluation (including LP)
  - If low risk, discharge with follow-up
  - If high risk, empiric antibiotics & hospitalization

**Philadelphia: Age 29-56 days**

<table>
<thead>
<tr>
<th>Age</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>747</td>
<td>422</td>
</tr>
<tr>
<td>SBI- Not High Risk</td>
<td>0/286</td>
<td>0/101</td>
</tr>
<tr>
<td>SBI- High Risk</td>
<td>65/461</td>
<td>43/321</td>
</tr>
<tr>
<td>NPV</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>NPV 95% CI</td>
<td>98-100%</td>
<td>96-100%</td>
</tr>
</tbody>
</table>

*Conclusion: A subset of infants 29-56 days old (40%) can be managed as outpatients without antibiotics.*


**Philadelphia: Cautionary Tale (1)**

- 422 Febrile Infants
- 101 low risk
- 321 high risk
- 94 per protocol
- 7 off protocol
- 21 off protocol
- 300 per protocol
- 11 inpatients, no abx
- 10 outpatients, no abx

Philadelphia: Cautionary Tale (2)

- SBI in 0/101 low risk patients
- 28 children (6.6%) not managed in accordance with protocol
  - Band/neutrophil ratio >0.2 (11)
  - WBC >15,000/mm³ (7)
  - Ill appearance (2)
  - Bacteria on UA (1)
- Conclusion: Poor compliance affects usefulness


Philadelphia: Age <28 days

- Performance in 254 infants
  - SBI in 5/109 (4.6%) of low risk infants
  - Sensitivity =84% (95% CI:67-95%)
  - NPV =95% (95% CI: 90-99%)
- Interpretation by the field: Philadelphia protocol lacks sensitivity to identify neonates (<28 days) at low risk of SBI for outpatient management


Prospective Studies, No Antibiotics if Low-Risk

<table>
<thead>
<tr>
<th>Year and Reference</th>
<th>Criteria Type</th>
<th>Age d</th>
<th>No. of Low Risk Patients</th>
<th>Cases of SBI in Low Risk Patients</th>
<th>Rate of SBI in Low Risk Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993(1) Rochester 2</td>
<td>0-56</td>
<td>148</td>
<td>0</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>1993(1) Philadelphia</td>
<td>20-56</td>
<td>287</td>
<td>1</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>1994(2) Rochester 2</td>
<td>0-50</td>
<td>203</td>
<td>4</td>
<td>1.97</td>
<td></td>
</tr>
<tr>
<td>1997(3) Modified Rochester</td>
<td>4-30</td>
<td>131</td>
<td>1</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>1996(3) Philadelphia 2</td>
<td>20-60</td>
<td>101</td>
<td>0</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>870</td>
<td>6</td>
<td>0.67</td>
<td></td>
</tr>
</tbody>
</table>

Huppler AR. Pediatrics 2010;125:228-233

Current Controversies #1

- Does a recognizable viral syndrome obviate the need for an LP?

Recognizable Viral Syndromes

- Does presence of a recognizable viral syndrome alter management of the febrile infant?
  - Several studies demonstrate that infants with viral syndromes are at low risk of concurrent SBI
  - Limited by biased sample populations
  - Sickest infants are least likely to be tested for respiratory viruses


Risk of SBI in RSV

- Only 1 multicenter trial
- Prospective, cross-sectional study performed in 8 EDs from 1998-2001
- Febrile (T ≥38.0°C) infants ≤60 days
- 1248 patients enrolled
  - ~22% (269) were RSV+

Risk of SBI with RSV

- Conclusions: Compared to RSV- infants
  - RSV+ infants <28 d have **similar** risk of SBI
  - RSV infection in this age group may **not** obviate need for complete evaluation
  - Consider disposition in medical decision making (i.e., if admission, LP may be deferred in non-severely ill infant)
  - RSV+ infants 29-60 d have lower risk of SBI
  - RSV+ infants have clinically important rate of UTIs
  - Issue of LP remains controversial
- Risk of SBI in influenza + infants is substantially lower


Current Controversies #2

- Does UTI obviate need for LP?

UTI

- Two studies with similar approach
  - Royal Children’s Hospital, Melbourne, Australia, 2001-2010
  - 23 U.S. emergency departments, 2005-2013
- Inclusion: Positive urine culture and CSF sample obtained within 24 h (U.S.) or 48 h (Australia) of urine sample

Teb ruegge M. PLoS One 2011; Thomson J. PIDJ 2017

UTI

<table>
<thead>
<tr>
<th>Age</th>
<th>Episodes</th>
<th>Co-existing Meningitis</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 month</td>
<td>163</td>
<td>2 (1.2%)</td>
<td>0.2 – 4.4%</td>
</tr>
<tr>
<td>1-2 months</td>
<td>304</td>
<td>0</td>
<td>0 – 1.3%</td>
</tr>
<tr>
<td>3-5 months</td>
<td>129</td>
<td>0</td>
<td>0 – 2.8%</td>
</tr>
<tr>
<td>Thomson et al*</td>
<td>803</td>
<td>7 (0.9%)</td>
<td>0.4-1.8%</td>
</tr>
<tr>
<td>29-60 days</td>
<td>934</td>
<td>2 (0.2%)</td>
<td>0-0.7%</td>
</tr>
</tbody>
</table>

*All 9 cases had positive blood cultures
Teb ruegge M. PLoS One 2011; Thomson J. PIDJ 2017

UTI

- Routine LP may not be necessary for infants with UTI, especially if age >28 days
- Consider possibility of bacterial meningitis in infants with UTI + bacteremia, especially if age <28 days

Current Controversies #3

- Office management
Office-Based Strategies

- Many strategies developed from infants cared for in inner-city emergency departments
- A large proportion of office-based pediatricians do not routinely follow any of these strategies

PROS Study: Setting

- Pediatric research in office settings (PROS) network of the AAP
  - 219 practices, 573 practitioners (91% MDs)
  - 44 states, Washington DC & Puerto Rico
  - 7% practice in urban areas (compared to 12% of all AAP members)

PROS Study: Patients

- Age <3 months
- T >38.0°C
- No comorbid conditions

PROS Study: Study Design

- Prospective observational cohort study
- February 1995 to April 1998
- Data collection
  - Clinical appearance (similar questions to YOS)
  - Management determined by individual clinician

PROS Study: Results (1)

- 3066 of 3131 evaluated infants were eligible
- LP/hospitalization/antibiotics
  - 45.7% of infants ≤30 days
  - 35.8% of infants 31-90 days

PROS Study: Results (2)

<table>
<thead>
<tr>
<th>Age</th>
<th>No.</th>
<th>BSI</th>
<th>Meningitis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-30 d</td>
<td>775</td>
<td>23</td>
<td>9</td>
<td>32 (4.1)</td>
</tr>
<tr>
<td>31-60 d</td>
<td>1220</td>
<td>28</td>
<td>5</td>
<td>23 (1.9)</td>
</tr>
<tr>
<td>61-90 d</td>
<td>1071</td>
<td>8</td>
<td>0</td>
<td>8 (0.7)</td>
</tr>
<tr>
<td>Total</td>
<td>3066</td>
<td>49</td>
<td>14</td>
<td>63 (2.1)</td>
</tr>
</tbody>
</table>

- Meningitis in 0.5% overall
- Blood culture obtained in 80% of infants; bacteremia in 2.4% of these infants
- UTI in 5.4% overall
PROS Study: Results (3)

• Performance of clinical prediction model to diagnose bacteremia/meningitis
• Initial antibiotics started in 97% of patients with bacteremia/meningitis; all but 1 received IV

<table>
<thead>
<tr>
<th>Clinical Model</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>58%</td>
<td>68%</td>
</tr>
<tr>
<td>Appearance + abnl WBC</td>
<td>83%</td>
<td>54%</td>
</tr>
<tr>
<td>Appearance + abnl WBC &amp; UA</td>
<td>87%</td>
<td>51%</td>
</tr>
<tr>
<td>Initial antibiotics</td>
<td>97%</td>
<td>36%</td>
</tr>
</tbody>
</table>

PROS Study: Results (4)

• Summary of findings
  • If close follow-up care attained, management of selected cases by experienced clinicians using clinical judgment may be more appropriate than strict adherence to published hospital-based protocols
  • Do current guidelines really optimize care?

PROS Study: Results (5)

• Follow-up study compared those with and without bronchiolitis (age <3 months, T ≥38°C)

<table>
<thead>
<tr>
<th>Infection</th>
<th>No./No. With Cultures (%)</th>
<th>P</th>
<th>Upper Limit of 1-Sided 95% CI for Those With Cultures in Bronchiolitis Group a,b</th>
</tr>
</thead>
<tbody>
<tr>
<td>UUT</td>
<td>Q/11</td>
<td>.003</td>
<td>4.2</td>
</tr>
<tr>
<td>Bacteremia only</td>
<td>Q/114</td>
<td>.001</td>
<td>2.6</td>
</tr>
<tr>
<td>Meningitis</td>
<td>Q/0</td>
<td>.000</td>
<td>7.5</td>
</tr>
<tr>
<td>Bacteremia or bacterial meningitis</td>
<td>Q/119</td>
<td>.031</td>
<td>2.5</td>
</tr>
<tr>
<td>Any of the above</td>
<td>Q/25</td>
<td>&lt;.000</td>
<td>2.4</td>
</tr>
</tbody>
</table>

* The upper limit of all of the 95% CIs for the whole bronchiolitis group (N = 208) was 1.4%.
* Five of the 14 infants with meningitis also had bacteremia.


PROS Study: Limitations (1)

• 1 infant with bacterial meningitis excluded
  • No data on initial appearance
• 2 infants did not receive initial antibiotics
  • One with WBC 15,300/mm³ returned following day with GBS bacteremia
  • One with pneumococcal meningitis returned following day with clinical worsening
• Infants taken directly to the ED for evaluation were not included (unclear how many infants)

PROS Study: Limitations (2)

• Only 7% of PROS MDs in urban setting
  • Data from this study cannot be generalized to ED or to urban settings
• Follow-up, Follow-up, Follow-up
  • Most infants had >1 office visit and multiple phone contacts
  • Many offices/centers cannot achieve this level of follow-up

Variation in Inpatient Management

• Variation in evaluation of neonates & young infants at 37 U.S. pediatric ED’s

<table>
<thead>
<tr>
<th>Setting</th>
<th>Overall Median [IQR]</th>
<th>≤3 mo Medical [IQR]</th>
<th>&gt;3 mo Medical [IQR]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine + Blood + CSF</td>
<td>40.6 (35.6-46.6)</td>
<td>67.2 (50.3-77.4)</td>
<td>40.6 (35.6-46.6)</td>
</tr>
<tr>
<td>Urine + Blood</td>
<td>26.4 (21.9-31.6)</td>
<td>32.3 (25.9-38.5)</td>
<td>26.4 (21.9-31.6)</td>
</tr>
<tr>
<td>Urine only</td>
<td>5.4 (4.3-6.5)</td>
<td>5.0 (2.7-2.9)</td>
<td>5.4 (4.3-6.5)</td>
</tr>
<tr>
<td>Other combinations of Urine, Blood, CSF</td>
<td>5.8 (4.8-6.9)</td>
<td>5.8 (4.8-6.9)</td>
<td>5.8 (4.8-6.9)</td>
</tr>
<tr>
<td>None</td>
<td>15.2 (10.7-21.9)</td>
<td>15.2 (10.7-21.9)</td>
<td>15.2 (10.7-21.9)</td>
</tr>
<tr>
<td>Radiographs</td>
<td>14.0 (10.1-18.1)</td>
<td>14.0 (10.1-18.1)</td>
<td>14.0 (10.1-18.1)</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>27.8 (19.4-34.1)</td>
<td>27.8 (19.4-34.1)</td>
<td>27.8 (19.4-34.1)</td>
</tr>
</tbody>
</table>

Aronson PL. Pediatrics 2014
Current Controversies #4

• Role of HSV testing

Neonatal HSV Infection is Uncommon

• 1 per 3,500 live births
• 0.3% of all neonates requiring hospitalization
• 1.6% of all neonates with fever and elevated CSF WBC count

Kimberlin DW. Pediatrics 2001;108:230-238

Frequency of Neonatal HSV

<table>
<thead>
<tr>
<th>HSV culture (15,923 women)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV positive n=52 (0.33%)</td>
</tr>
<tr>
<td>Primary Infection n=18/52 (35%)</td>
</tr>
<tr>
<td>Reactivation n=34/52 (65%)</td>
</tr>
<tr>
<td>Neonatal infection n=6/18 (33%)</td>
</tr>
<tr>
<td>Neonatal infection n=1/34 (3%)</td>
</tr>
</tbody>
</table>


Frequency of Neonatal HSV

• High attack rate in primary infection versus recurrence
  • higher viral load during primary infection
  • longer duration of viral excretion during primary infection
  • lack of transplacentally-acquired protective antibody early in maternal infection

Features of Neonatal HSV

• 3 clinical manifestations
  • Skin, eye, mouth (SEM) disease (34%)
  • CNS disease with or without skin vesicles (34%)
  • Disseminated infection (may include CNS) (32%)

Features of Neonatal HSV

• Time of disease onset
  • 9% at <24 hours of life
  • 30% at 1-5 days of life
  • 60% at >5 days of life
  • Typical onset occurs at 11-17 days of life
    • Disseminated usually <10 days
    • SEM usually 7-14 days
    • CNS usually 14-21 days

Features of Neonatal HSV

<table>
<thead>
<tr>
<th>Finding</th>
<th>CNS</th>
<th>Disseminated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin vesicles</td>
<td>63%</td>
<td>58%</td>
</tr>
<tr>
<td>Lethargy</td>
<td>49%</td>
<td>47%</td>
</tr>
<tr>
<td>Seizures</td>
<td>57%</td>
<td>22%</td>
</tr>
<tr>
<td>DIC</td>
<td>0%</td>
<td>34%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>-</td>
<td>37%</td>
</tr>
</tbody>
</table>


Neonatal HSV infection is Serious

- Isolated CNS infection
  - 5% mortality
  - 60% of survivors have neurologic disability

- Disseminated infection
  - 30% mortality
  - 20% of survivors have neurologic disability

Kimberlin DW. Pediatrics 2001;108:230-238

Neonatal HSV infection

Photo removed per AAP guidelines

Neonatal HSV infection

Photo removed per AAP guidelines

Timing of Acyclovir & Odds of Death

- 24% of 1086 neonates with HSV had delayed acyclovir started > day 1
- 7.3% overall mortality
  - 9.5% delayed
  - 6.6% early


Bottom Line

- Undertesting has importance consequences
HSV PCR Testing

- Consequences of “missing” the diagnosis leads to overtesting
  - Tests positive in 2% of infants undergoing CSF HSV PCR testing
  - Many low-risk infants undergo testing (i.e., age > 28 days, normal CSF WBC count)
  - Are there consequences of overtesting?

Philadelphia Experience*

- In setting without standardized approach...
  - Among infants <28 days, HSV PCR testing associated with
    - 28% increase in LOS
    - 41% increase in hospital charges
  - Among infants 29-56 days, HSV PCR testing associated with
    - 39% increase in LOS
    - 41% increase in hospital charges

*Models adjusted for age, mode of delivery, prematurity, hypoxia, lethargy, seizures, serious bacterial infection, HSV infection, peripheral WBC count, mechanical ventilation, & transported from another institution

LOS and HSV PCR Turnaround Time

LOS increases by 22% for each 12 hour increase in turnaround time

Strategies to Streamline Testing

- Caviness et al
  - HSV testing cost-effective if
    - Testing limited to neonates with CSF pleocytosis
    - Test results available by 3rd day of hospitalization
  - Potential impact
    - Would reduce testing in the CHOP cohort
      - 52% to 25% in those <28 days
      - Eliminated testing in those 29-56 days
      - No patients missed

Complications of Therapy

- Short course acyclovir
  - IV infiltrates (5%)
  - Acute kidney injury?
  - Other iatrogenic injury?

- Long term course
  - Neutropenia (21% with ANC <1000/mm³)
  - Renal insufficiency (6%)
  - CVC related complications


Bottom Line

- Overtesting has importance consequences
  - Testing may change physician perceptions of tested infants
  - Rapid test turnaround not cost-effective unless physicians react to negative tests

Therapy for HSV Meningitis

- NIAID Collaborative Antiviral Study Group
- 88 infants with HSV
- Randomized to high- (60 mg/kg/d), intermediate- (45), or standard- (30) dose acyclovir
  - Lower mortality with HD vs. SD
    - OR=3.3; 95% CI: 1.5-7.3
  - Improved neurodevelopmental outcome for HD group not statistically significant
    - OR=6.6; 95% CI: 0.8-113.6

Effect of Treatment on PCR

<table>
<thead>
<tr>
<th>Days Post-therapy</th>
<th>% Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td>100%</td>
</tr>
<tr>
<td>Day 5</td>
<td>98%</td>
</tr>
<tr>
<td>Day 8-14</td>
<td>47%</td>
</tr>
<tr>
<td>Day &gt;15</td>
<td>21%</td>
</tr>
</tbody>
</table>

HSV CSF PCR is very reliable up to 7 days after initiation of acyclovir

Prognosis

- SEM infection
  - no mortality if treated
  - neurologic impairment with recurrent lesions
- CNS infection
  - low risk of death (5% for those treated)
  - >60% of survivors with neurologic impairment
- Disseminated Infection
  - high risk of death (30%) despite treatment
  - <20% of survivors have neurologic impairment

Prior CCHMC Guidelines:

“...CSF HSV PCR testing not be routinely performed ...considered in neonates with CSF pleocytosis and a negative Gram stain...treatment ... considered with FUS, CSF pleocytosis, and a negative Gram stain until an alternative diagnosis is established or CSF PCR is negative...”

The Team

- Hospital Medicine
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  - Amanda Schondelmeyer
  - Samir S. Shah
- Infectious Diseases
  - Josh Courter (ASP Pharmacist)
  - David Haslam
  - Samir S. Shah
- Emergency Medicine
  - Eileen Murtagh-Kurowski
  - Paria Wilson
- Pathology
  - David Witte
- Neonatology
  - Neera Goyal
- Anderson Center
  - Wendy Gerhardt
Case

- 8 day old infant who appears well
- Fever
- No maternal STI history
- Would you test this infant for HSV?

Case

- 8 day old infant who appears well
- Fever
- No maternal STI history
- Would you test this infant for HSV?
- If no, what features would prompt HSV testing?

Survey of HM and EM Providers

For an 8 day old well appearing infant with fever and negative maternal STI history

<table>
<thead>
<tr>
<th></th>
<th>Hospital Medicine</th>
<th>Emergency Medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empiric HSV Testing</td>
<td>&lt;40%</td>
<td>58%</td>
</tr>
<tr>
<td>Top 3 Factors prompting evaluation</td>
<td>Vesicles, maternal hx genital herpes, seizures</td>
<td>Vesicles, maternal hx genital herpes, seizures</td>
</tr>
<tr>
<td>Only perform CSF HSV PCR</td>
<td>37%</td>
<td>53%</td>
</tr>
<tr>
<td>Raises concern for CNS HSV disease</td>
<td>70% any pleocytosis vs 19% monocyte predominance concerning for CNS HSV disease</td>
<td>41% any pleocytosis vs 64% RBC predominance vs. 11% monocyte predominance</td>
</tr>
</tbody>
</table>

So What’s the Problem?

1. No standardized practices for workup and management of neonates at risk for HSV infection
2. No constellation of lab, history, or physical exam findings that can reliably predict neonatal HSV disease

Other Centers

- St Christopher’s: Empiric testing and treatment for all infants <21 days admitted on antibiotics for SBI evaluation
- CHOP: Empiric acyclovir for infants <21 days or 22-40 days with high risk clinical features
- Children’s Mercy: Selective HSV evaluation and treatment based on clinical appearance and history

CCHMC Algorithm

- Test everyone within a certain, higher-risk age range and empirically treat only those with high risk features pending results.
Workup

- CSF PCR
- Serum PCR
- Surface PCR (swab eye, mouth, rectum in order with one swab)
- Vesicle PCR (if any present)
- Hepatic Panel
- Basic Metabolic Panel

AND

Treatment

- Acyclovir 20mg/kg q8hours

In addition to SBI evaluation per CCHMC guidelines

High Risk

Non-High Risk

Preventing Complications

- Historically up to 50% of those with neonatal HSV had recurrent skin lesions in first year of life
- Direct correlation between frequency of recurrent skin lesions and neurologic outcome

Preventing Complications

- In those with SEM disease
  - 0% with neurologic abnormalities if <3 recurrences
  - 21% with neurologic abnormalities if ≥3 recurrences

Preventing Complications

- Daily acyclovir (suppressive therapy) prevents recurrent skin lesions
  - 18 patients with HSV SEM disease
  - Comparison with historical controls
  - Acyclovir given at 30 mg/kg/day
  - Recurrence in 19% with acyclovir compared to 46% in controls

Kimberlin DW. Pediatr Infect Dis J 1996

- 2 parallel, placebo controlled, multicenter trial of acyclovir suppression, 1997-2008
- Randomization after 14- (SEM) or 21- (CNS) days of IV acyclovir
  - Oral placebo vs acyclovir (300 mg per square meter BSA given 3 times/day x 6 months)
  - CASG 103: 45 infants with CNS HSV
  - CASG 104: 29 infants with SEM HSV
  - Infants switched to open label acyclovir suppression after 2nd recurrence


Preventing Complications

- Neutropenia (Kimberlin)
  - CNS
    - Acyclovir: 25%
    - Placebo: 5%
  - SEM
    - Acyclovir: 20%
    - Placebo: 7%
- Other complications (n=89) (Ericson)
  - Thrombocytopenia (25%)
  - Elevated creatinine (2%)
  - Many adverse events likely related to HSV rather than acyclovir though often difficult to distinguish

Kimberlin DW. N Engl J Med 2011; Ericson JE. PIDJ 2017

Event (2 recurrences) Free Survival

No. at Risk
Acyclovir 39 38 30 25 21 7 0
Placebo 35 35 35 35 35 35 35

P=0.068 by log rank test

25% moderate or severe neurologic impairment
58% moderate or severe neurologic impairment


What Do We Actually Know? (1)

- Forthcoming national guidelines will provide additional guidance

What Do We Actually Know? (2)

- Office-based practitioners in some settings can successfully use clinical and laboratory findings to exclude meningitis with sufficient confidence without LP
  - Balance risk minimization & test minimization
  - Close follow-up essential
What Do We Actually Know? (3)

- Subsets of febrile infants evaluated in the ED may not require LP
  - Admission is still prudent for neonates
  - Management styles should acknowledge consequences of delayed therapy
- HSV testing/treatment algorithms should
  - Acknowledge & attempt to balance risks/benefits
  - Evolve as knowledge advances

What Strategy Should You Use?

- No single correct answer
- Keep abreast of the literature
  - Discussions with colleagues & mentors
- Choose the best strategy for your setting and practice style
  - Institutional practice guidelines
  - Regional practice variations
- Be consistent in your approach

Thank You!
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