Case 1

- 8 month old infant
  - Immunizations up to date
  - Sick for 20 hours
  - Temp 102 F (38.8 C)
  - Non-Focal Exam

- If you didn't see this child last shift you will when you get home.

Case 1

- What's the confusion?
  - 1980 ?
  - 2012 ?
Is there really a needle in there?
Or are we just paranoid?

Definitions

• Neonate: <28 days of age
• Septic Work Up
  – Blood Cultures
  – CBC
  – U/A, Urine C&S
  – LP (?)
  – CXR (?)

Definitions

• Occult Bacteremia
  ◦ Non-contaminated + blood culture
• Serious Bacterial Infection (SBI)
  ◦ Meningitis
  ◦ Pneumonia
  ◦ UTI
  ◦ Bacteremia (?)
  ◦ Cellulitis
Definitions

• Fever Without Source
  – Just what it says

• Only 20% of pediatric ED encounters
  – Respiratory symptoms
  – GI symptoms

Definitions

• Likelihood ratio (don’t zone out on me)
  – LR+ > 5.5 (occasionally will see 10)
  – LR- < 0.2 (occasionally will see 0.1)

  – Multiply the LR x’s pre-test odds to determine the post test odds.

  – Take home message: Look at LR as helping you make a decision.

Temperatures

• Fahrenheit
  • 98.6
  • 100.5
  • 102.2
  • 104.0

  • Celsius
  • 37.0
  • 38.0
  • 39.0
  • 40.0

  C = (F-32)*5/9
Three Phases Approach

- Neonates
  - Children < 28 days of age
    - Early Onset (0-4 days)
    - Late Onset (> 4 days)
- Protocol Eligible
  - Children 29 – 56 days
    - (6-8 weeks)
- Older at Risk
  - Children 2 months – 2 years

Febrile Neonate (<28 days)

- Full septic work up
  - CXR
  - LP
- Admission
  - Observation
- Go see another patient

Is a historical fever a fever?

- 399 Febrile Neonates

<table>
<thead>
<tr>
<th>Percent Group</th>
<th>Historical Fever</th>
<th>Measured Fever at Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBI</td>
<td>8.4%</td>
<td>18%</td>
</tr>
<tr>
<td>UTI</td>
<td>12</td>
<td>33</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Yarden, Serious bacterial infections in neonates with fever by history only vs documented fever. Scand J Infect Dis. 2010
Septic Workup?

• 12.85 /1,000 live births
• 50% Group B Streptococcus
  – Most common term
• 29.1% Escherichia coli
  – Most common premature

Etiology

• Pre-term
  ◦ E. coli predominates
• Term
  ◦ GBS (Rapidly decreasing incidence)
• Other gram negative bacilli
• Niesseria species
• Listeria

Lumbar Puncture?

• 5%-11.2% incidence meningitis
  – 1.1% bacterial
  – 10.1% aseptic
Week By Week

• 449 neonates
  – 87 (19.4%) SBI

<table>
<thead>
<tr>
<th>Week</th>
<th>Prevalence SBI</th>
<th>LRC met</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21.6%</td>
<td>15%</td>
</tr>
<tr>
<td>2</td>
<td>26.1%</td>
<td>6.3%</td>
</tr>
<tr>
<td>3</td>
<td>17.9%</td>
<td>3.0%</td>
</tr>
<tr>
<td>4</td>
<td>12.1%</td>
<td>6.7%</td>
</tr>
</tbody>
</table>


Treatment

• Ampicillin
• Gentamicin
• Cefotaxime / Ceftazidime
  ◦ Ceftriaxone
• Anti-viral agents
  ◦ Acyclovir
• Vancomycin (?)

28 days to 8 weeks

• Full Septic Workup (kinda)
  – Philadelphia criteria
  – Rochester criteria
  – Boston criteria
  ◦ NPPV > 97%
Common Criteria

- Age 29 days to 60 days
- History
  - Term infant
  - No recent immunizations
  - No prior antibiotics
- Physical Exam
  - Prestine

Common Criteria

- CBC
  - 5,000 < WBC < 15,000
  - Band-neutrophil ratio <0.2
- UA
  - < 10 WBC on cath specimen
- CXR
  - Mandatory only for Philadelphia
- Stool
  - No WBC

Common Criteria

- Sensitivity SBI 92%-98%
- Specificity SBI 42%-50%

- High Risk Patients:
  - Admit
  - Antibiotics
Current Performance

• 2005
  – 449 febrile infants < 8 weeks
• NPV
  – Philadelphia 97.1%
    • Original paper 99.7%
  – Rochester 97.3%
    • Original paper 98.8%

Garra: Reappraisal of criteria used to predict serious bacterial illness in febrile infants less than 8 weeks of age. Acad Emerg Med. 2009

Now for the rest of the febrile little squirts.

Workup or No Workup

What is the risk?

• Prevalence Occult Bacteremia
  – 1.5%-2%
    • SBI
      – 2% of Occult Bacteremia patients
        » Sepsis or Meningitis
        » 0.03% of all children
• 10,000 Febrile Children
  • 3 with Sepsis or Meningitis
What is the risk?

• Serious bacterial infections
  – 985 children
  • 79% vaccinated
  – 132 cases SBI
    • Pneumonia 82
    • UTI 45
    • Bacteremia 5
    • Meningitis 0

What is the risk?

• Invasive Bacterial Infection
• Louisville, KY
  – 115 cases Pneumococcal SBI
    • 1999-2002
  • 10 cases Pneumococcal SBI
    – 2001-2002
  • 13 cases meningitis
    – 1999-2002

What is the risk?

• Northern California Kaiser Health Plan
• Post Vaccination Era (2000)
  – 3 cases SBI
  – 15.3 cases / 100,000 pt yrs
What is the risk?

- Pneumococcal Bacteremia
- Pre Heptavalent Vaccine
  - 2.4%
- Post Heptavalent Vaccine
  - 0.0%


What is risk?

- In United States 2011
  - 40 cases of invasive s. pneumonia
  - Children < 2 years of age

  • ACEP News 8/8/2012

Is there really a needle in there?

There is a needle but the haystack is pretty big.
Workup or No Workup

- History
- Physical examination
- Laboratory Studies
- Radiographs
- Social Circumstances

History

- Age of child
  - 8 weeks to 2 years
- Siblings / Contacts
- Immediate local ID activity
  - Viral infection de jour

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Finding</th>
<th>Sensi</th>
<th>Speci</th>
<th>L.R</th>
<th>L.R</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBI*</td>
<td>Something is wrong</td>
<td>96.8%</td>
<td>88.5%</td>
<td>8.4</td>
<td>0.04</td>
</tr>
<tr>
<td>SBI*</td>
<td>Different illness</td>
<td>93.6%</td>
<td>85.5%</td>
<td>7.8</td>
<td>0.04</td>
</tr>
<tr>
<td>Sepsis / Men</td>
<td>Something is wrong</td>
<td>88.9%</td>
<td>97.1%</td>
<td>30.7</td>
<td>0.11</td>
</tr>
<tr>
<td>Sepsis/ Men</td>
<td>Different illness</td>
<td>77.8%</td>
<td>95.3%</td>
<td>16.4</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Van den Bruel: Signs and symptoms for diagnosis of serious …… British Journal of General Practice 2007
Duration of Fever

• No real consensus
  – Prior to immunizations early = sicker
  – Most recent data longer duration greater SBI

  • UTI
    – Bresman: Predicting severe bacterial infections... Pediatric Infect Dis J 2010
    – Goh, Predictors of serious bacterial infection ... Singapore Med J. 2006
    – Gijs. Duration of fever and serious bacterial ....
    – BMC Family Practice 2011

Immunizations

• Antibodies
  – Maternal
  – Vaccination induced

• Herd Immunity
• Mass Media Stupidity

Immunizations

• Haemophilus Influenzae type B (1987)
  ◦ HIB Infection decreased 99%
• Strep. Pneumoniae (2000)
  ◦ S. Pneumo decreased 94% worldwide

• Vaccinated Population
  ◦ Incidence of Bacteremia in Vaccinated Population
    • 0% - 0.7%
  ◦ Rudinsky, Serious bacterial infections in febrile infants in post-pneumococcal vaccine era. Acad Emerg Med 2009
Immunizations

- Recently vaccinated fevers
  - 6-12 weeks
  - Immunization < 72 hrs
- Serious Bacterial Infection
  - NRI 7.0%
  - RI 2.8%
  - 100% UTI
  - Immunization < 24 hrs 0.6%
  - Wolff: Serious Bacterial Infections in recently immunized young febrile infants. Acad Emerg Med 2009

Physical Examination

- Height of Fever
  - < 104 F (40 C)
  - No relationship
  - > 104 F (40 C)
    - Higher incidence SBI in neonates
      - Rudinsky, Serious bacterial infections in febrile infants in post-pneumococcal vaccine era. Acad Emerg Med 2009

Physical Examination

- Height of Fever

<table>
<thead>
<tr>
<th>Fever</th>
<th>LR +</th>
<th>LR -</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;38 C</td>
<td>3.5</td>
<td>0.38</td>
</tr>
<tr>
<td>&gt;39</td>
<td>2.3</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Thompson: Systemic review and validation of prediction rules for identifying children with serious illness. High Technology Assessment 2012
Physical Examination

- Height of Fever
- Hyperpyrexia
  - $> 106\,\text{F}$
  - Equal incidence of viral and bacterial infections
- Rhinorrhea
  - Viral
- Diarrhea
  - Bacterial

*Trautner: Prospective Evaluation of the Risk of Serious... Pediatrics 2006*

Physical Examination

- Obvious Bacterial Source
  - Treat appropriately

- Skin Infections in Era of MRSA
  - Check under the diaper!

Physical Exam

- Obvious Viral Infection
  - Croup
  - Varicella
    - Secondary skin infections
  - Stomatitis
  - Influenza
    - 2.4%
      - Krief; Influenza virus infection and risk of serious bacterial infection... Pediatrics, 2009
Obvious Viral Infection

- Bronchiolitis
- 330 patients < 2 years age
  - 11.9% pneumonia
  - 3.4% UTI
  - 1.1% meningitis (28 day old)
  - Muniz, AE: Research Forum 2009

Confirmed Viral Infection

- Viral Direct Fluorescent Antibody
  - 413 Febrile Infants
    - 163 (39.5% positive)
  - Positive FDA
    - 4.9% SBI
  - Negative FDA
    - 13.5% SBI

  • Hsiao: Incidence and Predictors of Serious Bacterial Infection .. Pediatrics 2006

Physical Examination

- Global Assessment
  - Child behavior

- Circulatory
- Respiratory
- Neurological Exam
Physical Examination

<table>
<thead>
<tr>
<th>Finding</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental Concern</td>
<td>14</td>
<td>0.55</td>
</tr>
<tr>
<td>Clinician Gut Feeling</td>
<td>23</td>
<td>0.38</td>
</tr>
<tr>
<td>Child Behavior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crying</td>
<td>10.5</td>
<td>0.67</td>
</tr>
<tr>
<td>Drowsy</td>
<td>6.6</td>
<td>0.85</td>
</tr>
<tr>
<td>Moaning</td>
<td>5.9</td>
<td>0.92</td>
</tr>
<tr>
<td>Inconsolable</td>
<td>5.5</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Thompson: Systemic review and validation of prediction rules for identifying children with serious .... High Technology Assessment 2012

Physical Examination

<table>
<thead>
<tr>
<th>Finding</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyanosis</td>
<td>50-52</td>
<td>0.88-0.93</td>
</tr>
<tr>
<td>Poor Peripheral Circulation</td>
<td>2.39-3.88</td>
<td>0.4-0.83</td>
</tr>
<tr>
<td>SOB</td>
<td>9.3</td>
<td>0.82</td>
</tr>
<tr>
<td>Rapid Breathing</td>
<td>9.78</td>
<td>0.7</td>
</tr>
<tr>
<td>Meningeal Irritation</td>
<td>2.7-275</td>
<td>0.03-0.97</td>
</tr>
</tbody>
</table>

Thompson: Systemic review and validation of prediction rules for identifying children with serious .... High Technology Assessment 2012

Physical Examination

- Limited Help in Ruling In or Our Serious Infections (LR+ <5.5 or LR- >0.2)

<table>
<thead>
<tr>
<th>Physical Finding</th>
<th>Mixed</th>
<th>URI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Finding</td>
<td>DIARRHEA</td>
<td>URINAL</td>
</tr>
<tr>
<td>Physical Finding</td>
<td>SMILE</td>
<td>VOMITING</td>
</tr>
<tr>
<td>Physical Finding</td>
<td>COUGH</td>
<td>HEADACHE</td>
</tr>
</tbody>
</table>

Thompson: Systemic review and validation of prediction rules for identifying children with serious .... High Technology Assessment 2012
Physical Examination

- Retractions
  - Independent risk factor SBI
    - Vomiting
    - Chest wall retractions
    - Poor peripheral circulation
  - Bleeker: Validating and updating a prediction rule for serious bacterial infections ... Acta Paediatr 2007

Physical Examination

- Petechiae
  - 411 Patients
    - 6 SBI
    - Clinically ill
      - Sensitivity 100%

Physical Exam

- Benign Petechiae
  - Distribution SVC
  - Well appearing
- Significant Petechiae
  - Diffuse
  - Toxic appearing
    - Klinkhammer MD Pediatric myth: fever and petechiae. CJEM. 2008: 10(5)
Laboratory Studies

- Acute Phase Reactants (APR)
  - Inflammatory Markers
    - White Blood Cell Count (WBC)
    - Absolute Neutrophil Count (ANC)
    - C-Reactive Protein (CRP)
    - Procalcitonin (PCT)
    - To Be Announced (TBA)
  - None are of any value < 24 hrs.

CBC

- Using the white blood cell count in the assessment of a febrile child is like going out for just one drink.

  - It will rarely help you but will frequently lead you astray.

WBC

- What organism
  - H. Influenzae type B
    - WBC insensitive
  - S. Pneumoniae
    - Sensitive
  - N. meningitidis
    - Useless
WBC

- Never has been of any predictive value
- Never will be of any predictive value
- Will continue to be ordered because the first question from any consultant pediatrician is:
  - “What’s the CBC show?”

Inflammatory Markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>LR + (Cut Off)</th>
<th>LR - (Cut Off)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT (0.5 ng/ml)</td>
<td>1.75-2.96</td>
<td>0.08-0.35</td>
</tr>
<tr>
<td>PCT (2 ng/ml)</td>
<td>&gt;4</td>
<td></td>
</tr>
<tr>
<td>CRP (1.8-50 mg/l)</td>
<td>2.5-3.8</td>
<td>0.25-0.6</td>
</tr>
<tr>
<td>PCT, CRP &amp; WBC</td>
<td>10.6</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Thompson: Systemic review and validation of prediction rules for identifying children with serious ...
High Technology Assessment 2012

Inflammatory Markers

- Change the cut offs

<table>
<thead>
<tr>
<th>Test</th>
<th>Cut Off</th>
<th>Purpose</th>
<th>LR +</th>
<th>90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT</td>
<td>2 ng/ml</td>
<td>Rule In</td>
<td>3.6</td>
<td>90%</td>
</tr>
<tr>
<td>CRP</td>
<td>80 mg/ml</td>
<td>Rule In</td>
<td>8.4</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LR -</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCT</td>
<td>0.5 ng/ml</td>
<td>Rule Out</td>
<td>0.08</td>
<td>80%</td>
</tr>
<tr>
<td>CRP</td>
<td>20 mg/ml</td>
<td>Rule Out</td>
<td>0.19</td>
<td>80%</td>
</tr>
</tbody>
</table>

Van den Bruel: Diagnostic value of laboratory tests in identifying serious...
BMJ 2011
APR Testing

• Receive Operator Curve
  – Sensitivity vs 1-Specificity
  • 328 children
  • 1084 children

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>AUC</td>
<td></td>
</tr>
<tr>
<td>PCT</td>
<td>0.82</td>
<td>0.77</td>
</tr>
<tr>
<td>CRP</td>
<td>0.88</td>
<td>0.75</td>
</tr>
<tr>
<td>WBC</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>Clinical Impression</td>
<td>0.77</td>
<td></td>
</tr>
</tbody>
</table>


Yet Another APR

Soluble triggering receptor expressed on myeloid cells

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>45%</td>
<td>82%</td>
</tr>
<tr>
<td>PCT</td>
<td>55%</td>
<td>75%</td>
</tr>
<tr>
<td>s-TREM-1</td>
<td>82%</td>
<td>48%</td>
</tr>
</tbody>
</table>

Stein: Clin Pediatr, 2014

Laboratory Testing

• The holy grail of a single ideal SBI indicator remains elusive.

Blood Cultures

- Retrospective Cohort FWS
- Post PCV era
- 8,408 children 3-36 months
  - 21 true positives (0.25%)
  - 14 s. pneumo (0.17%)
  - 159 contaminants (1.9%)
  » Wilkinson: Prevalence of occult bacteremia ...in the postpneumococal conjugate vaccine era. Acad Emerg Med. 2009:16(3)

Laboratory Studies

- Urinalysis
- UTI
  - 7.0% Fever without source
- Variability
  - Age
  - Gender
  - Race

UTI Risk Factors

- Fever > 39.0C (102.2 F)
- Temp > 24 hours
- Non-black race
- Female
- Uncircumcised male
  » Sahsi R: Does this child have a urinary tract infection? Ann EM 2008
Collection Methods

- Bag vs Catheter
  - Dipstick testing only
  - Sensitivity (85% vs 71%)
  - Specificity (62% vs 97%)
- Microscopy (> 5 WBC / hpf)
  - Sensitivity (95% vs 83%)
  - Specificity (45% vs 95%)

  McGillivray D: A head to head comparison: Clean Void Bag versus Catheter Urinalysis....; J Peds 2005; 41

Radiographs

- 188 children < 3 years
  - Temp > 39.0 C
  - WBC > 20,000
  - CRP
  - No chest findings
- CXR: 13% infiltrate
  - Increased with age > 12 months
    - ANC > 20,000

  Mintego: Occult Pneumonia in Infants....; Ped Emerg Care, 2010

Radiographs

- 308 febrile children
  - No clinical evidence pneumonia
  - 21 (6.8%) pneumonia
- 0 patients fever < 1 day
  - No cough
- Don’t X-ray

  Shah: Detection of Occult Pneumonia ....; Ped Emerg Care, 2010
Social Circumstances

- Access to care
- ED as follow up resource
  - Closed loop discharge
- “Follow up if no better.”
  - Prescription for disaster

Putting All Together

- 8 month female
- Temp 39.0 C (102.2 F)
- 18 Hours
- Fully Vaccinated
- Normal Exam

Management

- Fever Without Source
  - Duration greater than 24 hrs
- Non-toxic exam
- Urine Evaluation
  - High Risk Population
- CXR
  - Respiratory symptoms
  - SaO2 < 95%
Management

• Best management well appearing FWS observation and re-evaluation.
• No single published algorithm in the evaluation of FWS can be recommended.

Conclusions

• You will forget all the percentages, LR and other statistics.

• Full Septic Work Up <28 days

• Criteria Based W/U 29 days-6 wks

Conclusions

• 8 Weeks to 2 months Vaccinated
  – Clinical evaluation
  – Consider UTI in high risk
    • Leave their blood in their vessels
  – Closed loop discharge instructions

• 8 Weeks to 2 months Non-Vaccinated
  – Screening CBC
  – BC
Questions

Comments

Complaints