Pediatric Fever of Uncertain Source

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Disclosure:
Reports no financial interests relevant to this presentation

Objectives
• Examine the early evidence influencing the evaluation of febrile infants and children
• Understand the approach to febrile patients in different age groups
  – 0 to 28 days
  – 1 to 2 month olds
  – 2 to 36 month olds = When to Screen for what
• Discuss the impact of heptavalent pneumococcal conjugate vaccine (PCV7) (Prevnar®)
• Keep you awake

Why Do We Care About Fever Anyway?
• Children have lots of fevers
  – Account for 10-20% of Pediatric ED visits
• Vast majority of these illnesses are self limited
• But a small % will have a Serious Bacterial Illness !!
• How can we find those patients with the least amount of invasive testing?
• Are you a Risk Minimizer or a Test Minimizer?

Defining Some Terms
• Fever = 38°C
  – Value 2 standard deviations from 37°C (norm in surveys)
• Fever of Uncertain Source (FUS)
  – Febrile illness w/o clear etiology after history and physical
• Serious Bacterial Illness (SBI)
  – Meningitis - Bone or Joint Infection
  – Cellulitis - Pneumonia
  – UTI - Sepsis/bacteremia
  – Bacterial Enteritis
• Occult Bacteremia (OB)
  – Presence of bacteria in blood without clinical signs
• Neonate: 0-28 days  Young Infant: 28-60/90 days
• Old Infant/Child: 2-24/36 months

How It All Got Started?
Blame It On Boston
• In 1973 evaluated 2K “well” kids with T>38.3 at a walk in clinic
  – 700 blood cultures
  – 4% with + cultures
    • 6% with false positive
• Raised alarm of well, febrile children with bacteremia just waiting to cause badness

So How Do We Do Identify These Patients?
• How about physical exam?
  – Yale Infant Observation Score = 6 Characteristics
    • Cry, Color, Hydration, Arousal, Social Smile, Rxn to Parents
  – Well: <3% chance of SBI  Toxic: 92% chance of SBI
  – Difficulty generalizing to centers outside of Yale
    • Poor sensitivity and specificity in younger infants
• How about labs?
  – Can we identify a group at low risk for illness so that we can limit testing and treatment?
    • Here comes the criteria = Time to Pick a City

Components of Fever Protocols

<table>
<thead>
<tr>
<th></th>
<th>Boston</th>
<th>Philadelphia</th>
<th>Rochester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (days)</td>
<td>28-89</td>
<td>29-56</td>
<td>0-60</td>
</tr>
<tr>
<td>Temp (°C)</td>
<td>≥ 38.0</td>
<td>≥ 38.2</td>
<td>≥ 38.0</td>
</tr>
<tr>
<td>Infant Obs. Score</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Peripheral WBC</td>
<td>&lt; 20,000</td>
<td>&lt; 15,000</td>
<td>5-15,000</td>
</tr>
<tr>
<td>CSF obtained</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Antibiotic given</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>SBI in low risk pts (%)</td>
<td>5.4</td>
<td>0</td>
<td>1.1</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>94.6</td>
<td>100</td>
<td>98.9</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>Not stated</td>
<td>100</td>
<td>92.4</td>
</tr>
</tbody>
</table>

Philly Protocol - 1993

- 747 Well infants = 29-56 do with T > 38.2°C
- All received CBC/UA/LP, CXR and +/- Stool
- Low Risk Criteria
  - WBC 15,000, UA < 10 WBC, CSF < 8, - CXR
  - Yale score < 10 and no skin infection
  - Added band/neutrophil ratio < 0.2 in 3rd yr
- After testing = 460 high risk and 287 low risk
  - High Risk = All admitted and abx started
  - Low Risk = 1/2 admitted w/o abx
  - 1/2 discharged w/o abx
- Had to have phone and ability to return to ED

Philly Protocol

- 8.7% (65) had SBI = 64 of 65 were in High Risk
  - 1 SBI in low risk would have been high risk with modified band/neutrophil ratio
  - 2 outpts were admitted on follow up = cultures negative
  - 2 inpts were started on abx = cultures negative
- Infant Observation Scale alone of limited use
  - 66% with SBI were “Well” only labs made them high risk
- Final criteria 100% sensitive
  - With 95% CI = Sensitive 92%-100% and NPV 100%

And This Helps Us How?

- Findings resulted in 1993 guidelines published in both Pediatrics and Annals of EM
  - A step in the right direction but lots of options
  - Established data that still influences current practices
- But a lot has changed since 1993
  - Vaccine against H flu
  - Technology has improved
    - Continuous culture monitoring
    - Rapid Viral Testing
  - What about PCV7 vaccine (Prevnar®) against Strep pneumonia?

So - Now For The Specifics

- 0-28 Day, Well, Febrile
  - Less immuno-competent
  - Different infectious agents
    - Group B Strep, E. Coli, Listeria, Enterococcus
  - Lack social interaction = tough exam
  - Are these facts enough to separate them from the older cohort?
0-28 Day, Well, Febrile

- Multiple studies = Rate of SBIs 8.8–13.7%
- 1999: 254 3-28 days T>38°C well
  - 42.9%(109) low risk = 4.5%(5) with SBI
  - Total SBI in all was 12.6%
- Yes - they are different
- No - you can’t risk stratify
- Just do it
  - CBC and Culture  Cath UA and Culture
  - LP and Culture  +/- viral studies

0-28 Day, Well, Febrile

- Full admission
  - No standard for outpatient observation
- Treatment
  - Gentamicin 2.5mg/kg IV vs Cefotaxime 50 to 100mg/kg
  - Ampicillin 50mg/kg for Listeria
    - Need to treat 138 patients to prevent one Listeria illness
    - How about Acyclovir? 20mg/kg
      - 7-14% present with fever - Only 27% with seizure
      - 95-98% are younger than 22 days
      - PCR has made decision easier

How About 28-60 Days?

- Still some debate about 60 vs 90 day old
  - Arises due to the age difference of Boston/Philly
- Multiple studies = Rate of SBIs 5% - 9%
  - Majority are UTI’s but still some OB
- Still use Well, T38º and no source on exam
- All get Cath UA with micro and Culture
- All CBC and Culture
  - Starting to see some variation on CBC
  - We will talk about if they have a virus

What About The Tap?

- Study tested utility of WBC as screen for LP in infants 3 – 89 day olds
- Retrospective 1992-1999 5K with T ≥38.0°C
  - 0.4% (22) had Meningitis
    - E coli 11; Group B Strep 9; S pneumo 1; Citrobacter 1
    - 40% with meningitis had WBC between 5K-15K
- Concluded peripheral WBC poorly predictive for meningitis

Can WBC Predict The Need For LP?

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So every infant less than 2 months with a fever needs to be tapped???
How come my kid’s pediatrician just observed him???
Incidence Of SBI In Outpatient Febrile Infants

<table>
<thead>
<tr>
<th>Age (Mo.)</th>
<th>Total # Patients</th>
<th>Cases of Bacteremia</th>
<th>Cases of Meningitis</th>
<th>Total Cases of SBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>775</td>
<td>23 (2.9)</td>
<td>9 (1.2)</td>
<td>32 (4.1)</td>
</tr>
<tr>
<td>&gt;1-2</td>
<td>1220</td>
<td>18 (1.5)</td>
<td>5 (0.4)</td>
<td>23 (1.9)</td>
</tr>
<tr>
<td>&gt;2-3</td>
<td>1071</td>
<td>8 (0.7)</td>
<td>0</td>
<td>8 (0.7)</td>
</tr>
<tr>
<td>Totals</td>
<td>3066</td>
<td>49 (1.6)</td>
<td>14 (0.5)</td>
<td>63 (2.1)</td>
</tr>
</tbody>
</table>

So - There may be difference between 29 and 59 day olds... BUT still need the LP to classify infants as HIGH or LOW risk

How About RSV?
- 0-24mo well appearing with fever and clinical bronchiolitis
  - 156 Bronchiolitis = 0 OB, 1.9% UTI
  - 269 No Bronchiolitis = 2.7% OB, 13.6% UTI
- 1248 <60d, T>38º during 3yrs RSV season
  - 269 RSV+= 7% SBI rate vs 12.5% in those RSV-
    - RSV+ 0-28do = 10% with SBI (3% Bacteremia)
    - RSV+ 28-60do = 5.5% SBI ALL UTI
    - Not sufficient power for Bacteremia/UTI but 0 cases

How About The Flu?
- 844 pts <60 days old, T>38, Well and Not Well
  - 99% had blood/urine cx, 96% LP
  - 11.7% had SBI = 9.6% UTI
- 123 Flu+
  - 2.4%(3) UTI, 0 Bact/UTI
  - CI for Bact and BM still large = 0-2.4%
- 721 Flu-
  - 10.8% UTI / 2.2% Bact / 0.9% BM

- Possible role for UA and Flu and wait for Blood?

How About A CXR?
- Included as part of Philly criteria
  - 5 of 36 1-2m T>38 had +CXR but no symptoms
- 1993 <3mo with T>38 but no resp sympts
  - 0/361 positive studies
- 1999 study <5yo, T>39 and WBC >20K
  - 26% without clinical suspicion had radiographic findings c/w pneumonia
  - Not Routine but consider if symptoms or elevated WBC

How About The Flu?
- 705 0-36mo presenting with Fever w/o source and blood work done
- 163 Influenza+
  - 0.6%(1/163) Bacteremia
    - 3mo ill, admitted, grew Strep pyogenes
  - 1.8% (2/110) UTI
    - 3mo female and 9mo male T40 ?circ?
    - 0/40 BM
- 542 Flu- = 4.2% Bact, 9.9%UTI, 2.2%BM
  - 18 Strep pneumo / 2 E coli / 3 Other

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- Possible role for UA and Flu and wait for Blood?
And This Helps How?

- There is no recent study with large enough numbers to clearly establish the Risk of Bacterial Meningitis and Occult Bacteremia
  - But the numbers hint that in well appearing infants the risk of SBI/OB is very low and even lower if they have a viral illness
- But still have to worry about UTI
- Simple answer is to do everything

Recommendations For 28-60 Day Olds

- Remember this is for WELL infants only
- Philly protocol is still the standard
  - All get cath UA/Culture, CBC/Culture, LP
  - Some are incorporating the PROS data and not performing LP after 4 or 6 weeks
  - Some are using viral testing and if + not tapping
- Disposition = Lots of options
  - Can D/C with or w/o Abx BUT most will Admit and Tx
  - Ceftriaxone 50mg/kg vs Ampicillin and Cefotaxime 50mg/kg
- NO TREATMENT WITHOUT TAP !!!

How About 3-36 Months?

- Take a deep breath
  - “Better” Physical exam
  - Still WELL only but Temp cut off is higher
  - “Easier” to find source if there is one
  - Vaccinations on Board – Don’t forget to ASK
- So what do we have to worry about
  - Occult UTI = By and far the most common
  - Occult Bacteremia
  - Already touched on Occult pneumonia

What Is The Risk Of Occult UTI?

- 2400 kids  T>38.5º <1y(Boy) and <2y(Girl)
  - Overall prevalence UTI = 3.3%
  - Male <6mth = 2.7%, >6m = 1.8%
    - All age Circ = 1.2%, Uncirc = 8.0%
  - Female <12m = 6.0%, >12m = 2.1%
    - White = 10%, AA = 2.1%, Other = 5.7%
  - Temp<39 = 2.2%, T>39 = 3.9%
- Other studies put the risk 2-5%
- Maybe we can find a High Risk Group?

High Risk For UTI In Febrile Children

- Developed a clinical decision rule for Females
  - Temp > 39 Fever > 2 Days
  - White Age < 1yr
  - All with UTI had at least one risk factor
  - 2 Risk Factors = Sens 95% Spec 31%
  - Eliminated 30% of unneeded cultures
- Males
  - Most will screen all < 6m and Uncircumcised <12m
  - Obtain by Cath not Bag
  - UA is less sensitive in less than 3 months
  - Send Culture for increased sensitivity and ID

What About Occult Bacteremia?

It is all about trying to prevent BADNESS

SO – how much Badness is out there?
### Philly 2000
- 3 yr retrospective 5900 kids T>39º
  - Excluded focal infection but not OM
  - All positives were re-evaluated in the ED
- **Occult Bacteremia rate = 1.9%**
  - 83% grew Strep pneumo
  - Focal infections on re-eval 0.3% (17)
    - 8 Pneumo, 4 Cellulitis, 2 Osteo, 3 other (UTI, SSTI, Joint)
  - Serious Infection on re-eval 0.03% (2)
    - 1 BM = 10 mo Initially Dx OM
    - 1 Sepsis = 5 mo Dx OM with 9K WBC – congenital asplenia
- **95.7% of OPB had resolved by time of re-eval**
  - 50% of these received oral abx but NO ceftriaxone

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### A Word About Ceftriaxone
**Does It Really Help?**
- No great study exists
- 3-36 month T>39 well or OM and culture
  - ½ received IM and ½ PO Amox
    - 2.9% SBI - 84% Strep Pneumo
  - Of those with repeat evaluation
    - Definite infections = 0 with IM vs 5 with PO
    - Probable inf = 3 with IM vs 6 with PO
    - “Less febrile and less definite infections in IM”
- Meta Analysis
  - Abx decreased risk of localizing to SBI slightly
  - Need to treat 414 to prevent one SBI
  - Concluded minimal benefit

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### So – Any Predictors After The H Flu Vaccine But Before PVC7 (Prevnar®)?
- Retrospective review of 6500 3-36mo
  - 2.5% had Occult bacteremia with Strep pneumo
  - 3 Variable associated with OPB
    - ANC = Odds ratio increased by 1.15 for each 1K
    - ANC>10,000 = OPB rate 8.2%
    - Temp = Odds ratio of 1.77 for each increase of 1º
    - Age < 2 odds ratio of 2 vs age 2-3 years
- Combo of several studies
  - OPB in 3-26m with T>39.5 = 1% with WBC<15K vs. 10% with WBC>15K

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### Anything Other Than CBC To Help Predict SBI?
- **C Reactive Protein**
  - Acute phase protein increased in face of infection/inflammation/trauma
    - Formed 4-6 hours after trigger
- **ProCalcitonin**
  - Prohormone of calcitonin
    - Minimal response in viral compared to bacterial infections in multiple studies
    - Limited available at this time - FDA approval in 2008

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### Heptavalent Pneumococcal Conjugate Vaccine (PCV7) (Prevnar®)
- Introduced in 2000
  - Delivered as primary series (2/4/6 months) and then booster at 12 months
  - Covers 7 of the now 91 serotypes of strep pneumo
    - These strains were responsible for about 80-90% of the cases of invasive disease
  - By 2006 87% of 2-3yo in Cleveland had received at least 3 doses
    - 80-90% coverage nationally
Impact of PCV7 (Prevnar®) on Invasive Pneumococcal Disease

- CDC Surveillance data 1998/99 vs 2001
  - Rates of IPD in 7 regions = 1 Million kids <5yrs
- IPD deceased 68% in kids <2 years old
  - # cases requiring hospitalization decreased 63%
    - Vx Type = Decreased 78% / Vx Related = Decreased 50%
    - NonVx Type = Increased but not significant
- IPD decreased 44% in 2-3yo = Herd Immunity
  - Stopped here due to replacement with nonVx strains

So What Does This Mean Clinically?

- Reviewed All Blood Cultures obtained in 3-36mo from clinic/ED between 1998-2003
  - Kaiser system approx 92K kids/yr
  - Included all pts - not just "well" or certain temp
- 37K blood cx = 352 positive
  - Overall rate/yr decreased by 76% during study
    - 136 in 1999 vs 45 in 2003
    - 2003 bacteremia rate = 0.7% (1 in 135)
  - S pneumo rate decreased by 90% during study

Kaiser Post-PCV7 (Prevnar®) Blood Cultures

- 13,229 Cx from 02/03 = 0.6%+ (78)
  - 45% had a focus of infection/tx
    - An additional 22% admitted due to ill appearance
  - 0.25% (26/78) had true Occult Bacteremia
  - All E coli bacteremia pts were diagnosed with a UTI or Pyelo at time of initial visit
  - 15% of S pneumo and 40% E coli bacteremia had a "normal" WBC = 5K-15K
    - WBC in post-PCV7 (Prevnar®) yrs = Sens 74%/Spec 54%

Rates of Pneumococcal Meningitis

- CDC surveillance data from 1998-05
  - 1379 cases of Pneumococcal meningitis
    - 8% fatal in children / 20% in adults
  - Rate in kids <2yo decreased 64%
    - 10.1 per 100K = 3.6 per 100K
    - Vx Type = 93% decrease / Vx Related = 83% decease
    - Non-Vx Type = 275% INCREASE
      - 0.7 to 2.8 per 100K
    - Rate for whole population decreased by 30%

Proportion Of Bacteremia Cases Caused By Specific Bacteria

- POST-PCV7

How About Occult Bacteremia In 2-36 Month Olds?

- Reviewed ED visits of 2-36mo with T>39 but not hospitalized 2001-2003
  - Included OM but excluded UTI/cellulitis
  - 329 cultures = 0.91%+ (3)
    - All strep pneumo
      - 1 non-vx type in a 9mo
      - 2 cases in a single un-immunized pt at 20/21mo
        - Lost to follow up before immuno work up

Another Occult Bacteremia Study

- Post-PCV7 (Prevnar®) looked at all patients 3-36mo T>39 w/ blood cx obtained in the ED
  - Excluded ill or with source on exam (OM)
  - 275 total patients = Rate 0.4%
    - 1 Positive Blood Cx vs 13 Contaminants
      - 1 w/ Enterococcus
    - 7.6% with +Urine Cultures
    - 57% received Antibiotics

What if They Have Spots?

- Prior studies suggest a high risk for bacteremia in children with petechiae
  - 7 to 11% incidence of meningococcemia
- Enrolled 411 kids w/ petechiae (58% 3-36 mo)
  - 1.9% (8) with bacteremia or clinical sepsis
    - 6 with serious invasive bacteremia
    - None of 357 well-appearing children had OB
    - Toxic appearance had sensitivity of 100%
    - WBC > 15 K or < 5K had sensitivity of 100%
    - All children with meningococcemia had purpura

What If They Don’t Have Spots YET?

- Very challenging to detect children with unsuspected meningococcal disease
  - Retrospective, four center study (1985-1996)
  - 381 children with meningococcal disease
  - 12% (45) were d/c home from ED
  - Compared to 6400 culture negative children
    - No difference in temperature, WBC, ANC
    - Significantly higher band counts in UMD
    - Predictive value of band count was low (PPV 0.06%)
- Sorry – No easy answer

Risk Of SBI In 60-180 Day Olds Post-pcv7 (Prevnar®)

- 429 infants T > 37.9 °C 57-180 days old
  - All received Full Septic Work up
- SBI diagnosed in 10.3% (44)
  - 9.6% (41) with UTI
  - 0.9% (4) with bacteremia (False + 5.4%)
    - 1 each E coli, Group B Strep, S pneumo and EnteroC
  - 0 with meningitis
- Predictors for SBI
  - WBC was elevated in infants with SBI (17K vs 12,400)
  - CRP was elevated in those with SBI (2.6 vs 0.9)

Now - How About Those Recommendations?

- PCV7 (Prevnar®) has decreased occult pneumococcal bacteremia by about 60-70%
- Total Occult bacteremia rate now below 1%
  - May be as low as .25%
  - Still waiting for a PROSPECTIVE STUDY
- Much more likely to have UTI
  - Viral illness decreases risk of concurrent UTI/OB
- Utility of “screening” for OB is greatly reduced
  - WBC less helpful post-PCV7 world
    - Maybe falsely reassuring????
  - Future role for CRP/PCT to replace WBC??
**Core Content In Urgent Care Medicine**

**Food For Thought**
- Post-PCV7 (Prevnar®) risk of OB: 0.25 to 1%
  - Contamination rate for Blood Culture 3-5%
- Risk for OPB progressing to BM 1-4%
  - Risk of localizing infection 10-20%
  - Don’t know about MRSA/E coli/Salmonella etc
  - Maybe higher or lower
- Would need to culture and treat 3333 pts to prevent one case of Bacterial meningitis
  - Would have to deal with 99-165 False Positives
- But it could be the 1st pt you see or the 3333rd

**Even Boston is Changing**

**Well appearing infant**

Age 3 to 36 months
Q: Fever > 39°C

- Q > 6 months of age with both lab and PCV7 (3 doses each)
  - UA & urine culture for Uncirc males 1yr and female <2yr
  - No routine blood work
  - UA and urine culture CBC & blood culture
  - Chest x-ray if WBC > 20,000
  - Antibiotics if WBC > 15,000

**No**

Antipyretics

No routine Lab work

**Final Thoughts**
- All this applies only to the WELL INFANT!!
- Need to continue to monitor new strains of Strep Pneumo while awaiting new vaccines
- Awaiting PROSPECTIVE studies
- Need more info on what WBC does in non Strep pneumo bacteremia
- Waiting for large prospective studies to define exact role for CRP/PCT
- “Antibiotics aren’t Antipyretics”

Dr Steven Krug

**Reading List**

**Now – About Those Recs**
- 2 to 36 month old – Most use 39° for WELL kids
  - UA/Cult if high risk
  - Circ boys < 6m, Uncirc <12m, Girls <2yrs
  - CBC/Culture – starting to see lots of variation
    - Predictive value of CBC may be eliminated by PCV7 (Prevnar®)
    - Balance test where false+ are more frequent than true+
  - Most will stop checking if >6month and Vaccinated
  - Viral source = Consider Urine only
  - LP only if meningitis on exam or sick
  - But think about it every time you give antibiotics
  - Trust you feelings = OK to treat if CBC is normal but something doesn’t feel right


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