The Febrile Infant

SJRH ED Rounds
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Objectives

- Discuss the risk of serious bacterial infection (SBI) in the neonate or young infant (<90d) with fever

- Review current suggestions for the work up, management, disposition, and follow up in the care of neonates and young infants with fever

- Discuss the role of decision tools (ex: Rochester, Boston, Philadelphia) to aid in decision making for the well-appearing infant with fever
Introduction

- The febrile neonate (<28d) and young infant (<90d) are commonly encountered in the emergency dept.

- Many will have a self limited, viral illness

- A small but significant proportion (up to 15% in some series) will have a serious bacterial infection (SBI)

- How to best assess and manage such infants has long been a matter of debate.
Local context

- No SJRH EM Guideline exists for the management of neonatal fever

- Local variation in practice regarding:
  - Work up
  - Empiric management
  - Disposition
  - Follow up

- Recent clinical cases have highlighted this issue

- Forthcoming SJRH EM Guideline
Burning questions…

• What IS the full septic work up?
• Which kids >30 days need blood work?
• Which kids >30 days need the LP?
• Can I avoid antibiotics in any of these kids?
• Which kids can I send home?
• Are there any harms to over-investigating and over-treating?
Definitions

- Neonate: 0 to 28d
- Young Infant <90d

- Fever = rectal temp \( \geq 38.0^\circ\text{C} \)

- Serious bacterial infections (SBI) include\(^2\):
  - Bacterial meningitis, bacteremia, UTI, pneumonia
  - Some series: enteritis, cellulitis, abscess, osteomyelitis, septic joint

- Invasive Bacterial Infect (IBI)\(^2\)
  - Bacterial meningitis and bacteremia
Rates of SBI

• Many infants with fever have a self-limited viral illness

• Rates of serious bacterial infection\(^3\):
  • 3 to 28d: 13%
  • 29 – 56d: 9%
  • 90 days and younger: 7%
  • *in pre-pneumococcal vaccine era

• Prevalence is highest <2wk (25%)
• UTI most common SBI, with prevalence 3 to 11%

• 1 – 2 % will have IBI\(^4\)
Common pathogens

In neonates < 28d, most common pathogens are:

- **E. coli**
- **Group B streptococcus**
- **S. pneumoniae**
- **S. aureus**
- **L. monocytogenes**

Also:

- Herpes simplex virus
- Respiratory syncytial virus
- Enterovirus
Work up of the toxic infant

- Good consensus on management

- For infants ill appearing / toxic appearing, including:
  - Lethargy
  - Poor perfusion
  - Cyanosis
  - Hypo or hyperventilation
  - Significant abnormalities in vital signs

→ Full septic work up
Work up of toxic infant

“Full septic work up” always includes:

- CBC
- Metabolic panel (routines)
- Blood culture
- Urinalysis with report of HPF (catheter specimen)
- Urine culture
- CSF cell count, glucose, protein
- CSF fluid culture
Work up of toxic infant

- CXR 2-view
  - only if respiratory symptoms present (tachypnea, hypoxemia, focal findings on exam)$^6$

- Respiratory panel for RSV if cough, rhinorrhea
- Stool cultures if diarrhea
- ALT / AST if considering HSV

- HSV testing if at risk:
  - < 21d, maternal hx, seizure, vesicles
  - Elevated AST, ALT, thrombocytopenia, CSF pleocytosis

- CRP?
- Procalcitonin?
Does every kid need the kitchen sink?

- In the 1970s and 1980s, guidelines recommended a full septic work up for all infants <90d⁴,⁷

- In 1980’s various groups derived Low-Risk Criteria for Management of Febrile Young Infants:
  - Rochester Criteria
  - Philadelphia Criteria
  - Boston Criteria
Rochester Criteria

- Includes 0 to 60 days of age

- Inclusion:
  - Full term
  - Normal prenatal and post natal history
  - No post natal antibiotics
  - Well appearing
  - No focal infection

- Laboratory parameters defining low risk:
  - WBC 5000 to 15000
  - Bands < 1500
  - UA: <10 WBC/HPF
  - Stool < 5 WBC/HPF on smear (of obtained based on sx)

- Modified Rochester includes normal CRP
Rochester Criteria\textsuperscript{8}

- Treatment for high risk:
  - Hospitalize
  - Empiric antibiotics

- Treatment if low risk:
  - Home
  - 24h follow up required
  - No empiric antibiotics

- **NPV: 98.9\% (97.2 – 99.6)**
  - Did not perform as well on series including infants > 60 days
Philadelphia Criteria

- Includes **29 – 56 days** of age

- Inclusion:
  - Well-appearing
  - No focal infection

- Lab parameters defining low risk:
  - WBC < 15 000
  - Band: total neutrophil (I:T) ratio < 0.2
  - UA < 10 WBC / HPF
  - **CSF: gram stain neg**
  - CXR: no infiltrate (if obtained)
  - Stool: no blood, few or no WBC on smear (if obtained)
Philadelphia Criteria\textsuperscript{9}

- Treatment for high risk:
  - Hospitalize
  - Empiric antibiotics

- Treatment for low risk:
  - Home, if patient lives within 30 min of hospital
  - 24h follow up required
  - No empiric antibiotics

- NPV: 99\% (99 – 100)
Boston Criteria

- Includes 28 – 89 days of age

Inclusion:
- No antibiotics within preceding 48h
- No immunizations within preceding 48h
- Well appearing
- No focal infection

Laboratory parameters defining low risk:
- WBC < 20 000
- UA: < 10 WBC / HPF
- CSF: < 10 WBC/mm³
- CXR: no infiltrate (if performed)
Boston Criteria\textsuperscript{10}

- Treatment for high risk patients:
  - Hospitalize
  - Empiric antibiotics

- Treatment for low risk patients
  - Home if caregiver available by telephone
  - \textbf{Empiric IM ceftriaxone 50mg/kg}
  - Return for 24h follow up for second dose of IM/IV ceftriaxone

- \textbf{NPV: 94.6\% (92.2 – 96.4)}
Comparing the criteria

- All have high NPVs
- All have high sensitivity (92 to 97 %)
- All have low specificity (40 to 55%)

- Low Risk Criteria allow approximately 30% of patients to be treated safely without empiric antibiotic therapy

- Rochester less invasive but not validated > 60 days
Don’t forget HSV!

- Most acquired in peripartum period, 90% < 21d\(^1\)
  - mean age of 14d

- Three types
  - Skin / Eye Mouth (SEM)
  - Central Nervous System
  - Disseminated

- Risk factors:
  - Maternal history
  - Seizure at presentation
  - Vesicles
  - CSF with pleocytosis
  - For disseminated disease: transaminitis, DIC, acidosis

- Treatment: high dose acyclovir (20mg/kg/dose q8h)
What about suspected viral infections?

- Enterovirus positive infants have low rates of co-contaminant bacterial infection\(^7\)
  - Management may consist of supportive care alone

- Well-appearing, febrile, RSV positive infants are at decreased risk of SBI (7% vs 12.5\%)\(^12\)
  - Notable risk for UTI (5.5%)
  - Low risk bacteremia (1.5%)
  - No cases meningitis
  - \(\rightarrow\) Do perform urinalysis and culture, ?may avoid Abx and CSF

- …how this applies to suspected viral infections before viral panel results is lest clear...
Procalcitonin (PCT)

- Protein prohormone of calcitonin released by liver and mononuclear cells 4h after tissue injury, peaks 6h after tissue injury, with sustained peak for 8 to 24 h

- In studies < 90d, favorable test characteristics compared to WBC and CRP

- Biggest challenge is threshold to define positivity
  - 0.13ng/mL – high sensitivity, low specificity
  - 0.5ng/mL – high specificity, inadequate sensitivity for SBI detection
    - Most consistent cut off value reported
    - Sensitivity of 60% for SBI and 85% for IBI, specificity 85% for both

- Up and coming “Step-By-Step” approach?\(^\text{17}\)
Step By Step

- Validation of “Step by Step” Approach in Management of of Young Febrile Infants\(^\text{17}\) (Pediatrics Aug 2016)

- Superior sensitivity to Rochester (92% vs 81%)
- Up to age 90 days

- Considered low risk if:
  - not ill appearing
  - age > 21d
  - no WBC in urine
  - Procalcitonin <0.5
  - CRP <20
  - ANC <10 000

- If meeting low risk criteria, infants are admitted x 24h without antibiotics and then discharged if still well-appearing.
Antibiotic treatment:

If infant toxic or decision to treat:

**Less than 28d:\(^1\):**

- Consider common pathogens:
  - *E. coli*, *Group B streptococcus*, *S. pneumoniae*, *S. aureus*, *L. monocytogenes*

- Cefotaxime 50 mg/kg IV OR Gentamicin 4mg/kg IV
- AND Ampicillin 50mg/kg IV (for *L. monocytogenes*)
- Add vancomycin if CSF pleocytosis
- Add acyclovir 20mg/kg/dose q8h if <21d, toxic or high risk for HSV
Antibiotic treatment

29 to 60 days\(^1\)

- Cefotaxime 50mg/kg OR Ceftriaxone 100mg/kg
- May defer ampicillin (very low risk of L monocytogenes)
- Add vanco if CSF Pleocytosis
- Add acyclovir if high risk for HSV
Antibiotic treatment

61 to 90 days

- Cefotaxime 50mg/kg OR Ceftriaxone 100mg/kg
- May defer ampicillin (very low risk of L monocytogenes)
- Add vanco if CSF Pleocytosis
Current controversies

• Many studies done in 1980’s and early 1990s
  • Before HiB (1987) and Pneumococcal vaccine (2000)
  • Before routine GBS prophylaxis in labour
  • Before CRP and procalcitonin available
  • Higher rates of circumcision compared to today
Current controversies

- Significant variation in literature recommendations regarding work up of well-appearing neonate older than > 28d

  - Is CSF > 28 days really necessary?
  - What about suspected viral infections?
Current controversies

- Iatrogenic harms of over testing and over treatment are not well studied\(^7\)
  - Traumatic lumbar puncture
  - Antibiotic pre-treated CSF culture
  - Unnecessary antibiotic exposure
  - Radiation from x-rays
  - Phlebitis due to venipuncture injury
  - Hospitalization during a critical period of family bonding
  - Vulnerable child syndrome
Some suggested management

• Less than 28 days\textsuperscript{1}:

  • All get full septic work up regardless of appearance \textsuperscript{1,5,14,15,16}:
    • CBC
    • Metabolic panel (routines)
    • Blood culture
    • Urinalysis with report of HPF (catheter specimen)
    • Urine culture
    • CSF cell count, glucose, protein
    • CSF fluid culture

  • + HSV testing (vesicles, serum, CSF) if <21d or high risk
  • +/- CXR, RSV panel, stool culture only if indicated per sx
Some suggested management

• **Less than 28 days**:  
  
  • ALL get empiric antibiotics:  
    • Ceftaxime or Gentamicin  
    • AND Ampicillin  
    • AND Acyclovir if < 21d or high risk for HSV  
    • AND Vancomycin if CSF pleocytosis or suspect meningitis  
  
  • Admit for IV antibiotics x 48 - 72h pending culture results
Some suggested management

- **28 to 60 days:**
  - Full septic work up if toxic appearing
  - Use corrected age for premature infants\(^\text{14}\)

- May use Rochester Criteria
  - If high risk per criteria → Full septic work up (add CSF)
    - Admit on IV Cefotaxime or Ceftriaxone pending culture results
  - If low risk per criteria:
    - May discharge home without Abx + Follow up in 24h

- If decision to tx with antibiotics, consensus\(^1,3,5\) to also do LP
- If well appearing and suspect bronchiolitis, may consider UA only, but many guidelines recommend\(^5,14,15,16\) or “strongly consider”\(^1\) CBC, routines, blood cultures, +/- CRP
Rochester Criteria

- Includes 0 to 60 days of age

Inclusion:
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Laboratory parameters defining low risk:
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Modified Rochester includes normal CRP
Some suggested management

- **61 to 90 days:**
  - Full septic work up if toxic appearing
  - Use corrected age for premature infants\(^{14}\)

- Rochester Criteria not well validated
  - Many existing guidelines do not include CSF (ex: NICE)

- Per NICE\(^{13}\), perform for all infants < 90d:
  - CBC, CRP, blood culture, urinalysis + culture
  - CXR only if resp sx present
  - Stool culture only if diarrhea

- Add CSF if high WBC
- ??Step-By-Step
Some suggested management

- **61 to 90 days:**
  - If sx suggestive of bronchiolitis, some guidelines\(^1,14\) suggest deferring bloods and still do UA
    - Original study endorsed this strategy only for confirmed RSV\(^12\)
  - Admit if work up positive, ex:
    - WBC > 15000
    - UA with >10 WBC / HPF
    - CRP > 20 mg/L (2mg/dL)
  - Start Abx pending neg cultures (Cefotaxime or Ceftriaxone)
  - If starting Abx, most guidelines recommend lumbar puncture
Conclusions

- Many febrile infants have a viral infection
  - Significant minority (up to 15%) have serious bacterial infection

- Cannot determine risk for SBI and IBI with Hx & P alone

- All toxic appearing infants need full septic work up, empiric antibiotics, and admission

- Several Low Risk Criteria exist to aid in decision making
  - Low specificity, often include recommendation for invasive testing
  - Much variation in existing guidelines for management

- In absence of an accepting national or society guideline, best approach is a thoughtful departmental guideline for the management of neonatal fever
Questions?
Resources

Resources