

Fevers and Seizures in Infants and Young Children

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Disclosure

- I have no conflicts of interest

Pharmacist Objectives

- Describe the clinical presentation and initial work-up of a febrile infant
- Select an appropriate empiric antibiotic regimen for a febrile infant
- Evaluate the clinical management of febrile seizures in young children
- Explain the risk for febrile seizures following vaccination

Technician Objectives

- List possible causes of fevers in infants
- Identify commonly used antibiotics for the treatment of a febrile infant
- Describe febrile seizures in young children
- State vaccines that have been associated with febrile seizures following vaccination

THE FEBRILE INFANT

Patient Case

- 14 day old female presents to the ED at 3 am with fever and fussiness
- Born at 39 weeks
- Vaccinations are up-to-date
 - Hepatitis B at birth
- Decreased intake by mouth but still making wet diapers
- Vitals
 - Temperature: 38.8° C
 - Heart rate: 180
 - Respiratory rate: 45
 - O₂ Saturation: 99% on room air

Why is it so important?

- Evaluation of fever in infants makes up a significant portion of emergency room visits in this age group
- 2.2% of febrile infants with blood cultures drawn will be diagnosed with bacteremia
- Potential for morbidity and mortality with invasive bacterial infections
- Consequences for both over-treating and undertreating

Greenhow TL et al. *Pediatrics*. 2012; 129(3): e590-596.

Definitions

- Fever: rectal temperature $\geq 38^{\circ}$ C
- Fever of unknown source (FUS, FOU, FWS): etiology not apparent after history and physical exam
- SBI: serious bacterial infection
- IBI: invasive bacterial infection
 - Specifically bacteremia and meningitis
- Neonate: <28 days old
- Young infant: 28 – 60 days old
- Early-onset sepsis: occurs during first week of life
- Late-onset sepsis: occurs from the first week through three months of life

Baraff LJ et al. *Pediatrics*. 1993; 92(1): 1 - 12.
Gomez B et al. *Pediatrics*. 2016; 138(2): e20154381.

Causes of Fever

- Urinary tract infection (UTI)
- Bacteremia
- Meningitis
- Respiratory Syncytial Virus (RSV)
- Herpes Simplex Virus (HSV)
- Others
 - Pneumonia
 - Bone and joint infections
 - Soft tissue abscesses
 - Gastroenteritis

Common Bacterial Pathogens

- *Escherichia coli*
- Group B *Streptococcus*
- *Staphylococcus aureus*
- *Streptococcus pneumoniae*
- *Listeria monocytogenes*

Mischler M et al. *Hosp Pediatr*. 2015; 5(6): 293 - 300.
Biondi E et al. *Pediatrics*. 2013; 132(6): 990 - 996.

Recent Epidemiologic Studies

- Biondi et al performed a retrospective review of positive blood cultures in febrile infants ≤ 90 days
- Collected data from 2006 to 2012 from 6 hospital systems
- Reviewed 181 cases of bacteremia in 177 infants
- Most common pathogens
 - *Escherichia coli* (42%)
 - Group B *Streptococcus* (23%)
 - *Streptococcus pneumoniae* (6%)
 - More likely in older infants ($P = .01$)
 - *Staphylococcus aureus* (5%)
- No cases *Listeria monocytogenes* were identified

Biondi E et al. *Pediatrics*. 2013; 132(6): 990 - 996.

Recent Epidemiologic Studies

- Mischler et al performed a retrospective review of positive blood cultures in febrile infants ≤ 90 days
- Collected data from 2006 to 2013 from 17 hospital systems from across the country
- Reviewed 392 cultures
- Most common pathogens
 - *Escherichia coli* (40%)
 - Group B *Streptococcus* (22%)
 - *Streptococcus viridans* (8%)
 - *Staphylococcus aureus* (6%)
 - *Streptococcus pneumoniae* (5%)
- No cases of *Listeria monocytogenes* were identified

Mischler M et al. *Hosp Pediatr*. 2015; 5(6): 293 - 300.

Group B *Streptococcus* (GBS)

- Intrapartum antibiotic prophylaxis guidelines were implemented in the 1990s
 - As a result the incidence of early-onset sepsis from GBS has decreased by 80%
- Prophylaxis indications
 - Previous infant with invasive GBS disease
 - GBS bacteriuria during current pregnancy
 - Positive GBS screening culture
 - Unknown GBS status at time of delivery
- Penicillin is the prophylactic medication of choice

Verani JR et al. CDC. *MMWR Recomm Rep.* 2010; 59(RR-10): 1-36.

Initial Assessment

- Several different methods to classify infants as high risk or low risk for a SBI
 - Boston Criteria
 - Milwaukee Criteria
 - Philadelphia Protocol
 - Rochester Criteria
- New "Step-by-Step" approach was recently compared with the Rochester Criteria
 - Validated by Gomez et al
 - Found to have better sensitivity in identifying low risk patients

Gomez B et al. *Pediatrics.* 2016; 138(2): e20154381.

Criteria for Assessment

	Boston Criteria	Milwaukee Criteria	Philadelphia Protocol	Rochester Criteria
Age Range	28 – 89 days	28 – 56 days	29 – 60 days	≤ 60 days
Temperature	≥ 38.0° C	≥ 38.0° C	≥ 38.2° C	≥ 38.0° C
History	No immunizations or antibiotics in last 48 h Not dehydrated	Not defined	Not defined	Term No perinatal antibiotics No underlying disease Not hospitalized longer than mother
Physical Exam	Well appearing, no sign of focal infection			

Adapted from Table A. Moher D et al. *AHRQ.* 2012; Pub.No. 12-E004-1.

	Boston Criteria	Milwaukee Criteria	Philadelphia Protocol	Rochester Criteria
Lab Parameters	CSF < 10/mm ³ WBC<20,000/mm ³ UA<10 WBC/hpf Chest X-ray: No infiltrate (if obtained)	CSF < 10/mm ³ WBC<15,000/mm ³ UA<5-10 WBC/hpf (no bacteria, negative LE/nitrite) Chest X-ray: No infiltrate (if obtained)	CSF < 8/mm ³ WBC<15,000/mm ³ UA<10 WBC/hpf Urine and CSF gram stain negative Chest X-ray: No infiltrate Stool: no blood, few or no WBCs on smear Band-neutrophil ratio <0.2	CSF: NA (no lumbar puncture indicated) WBC >5,000 and <15,000/mm ³ ABC<1,500 UA<10 WBC/hpf Stool: WBC< 5/hpf smear (if indicated)
Management of low risk	Home/outpatient Empiric antibiotics Follow-up	Reliable caretaker Follow-up IM ceftriaxone with re-evaluation	Home/outpatient No antibiotics Follow-up	Home/outpatient No antibiotics Follow-up
Management of high risk	Hospitalize Empiric antibiotics	Not defined	Hospitalize Empiric antibiotics	Hospitalize Empiric antibiotics

ABC = absolute band count; CSF = cerebrospinal fluid; hpf = high power field; UA = urinalysis; WBC = white blood cells

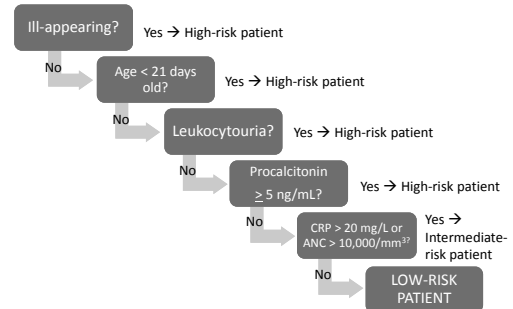
Adapted from Table A. Moher D et al. *AHRQ.* 2012; Pub.No. 12-E004-1.

"Step-by-Step" Approach

- Developed by a group of European pediatric emergency physicians
- Goal of approach
 - To identify low risk infants who can be managed as outpatients without a lumbar puncture or antibiotic treatment
- Lab monitoring required
 - Urine dipstick and urine culture
 - WBC, C-Reactive Protein (CRP), and Procalcitonin (PCT)
 - Blood culture

Gomez B et al. *Pediatrics.* 2016; 138(2): e20154381.

"Step-by-Step" Approach



Adapted from Figure 1. Gomez B et al. *Pediatrics.* 2016; 138(2): e20154381.

Validation of “Step-by-Step”

- Gomez et al performed a multicenter, prospective study from 2012 to 2014
- Tested the accuracy of the Step-by-Step approach, the Rochester Criteria, and the Lab-score
- Included 2185 infants \leq 90 days old with FWS
 - 504 patients diagnosed with a bacterial infection (23.1%)
 - IBI – 87 patients (3.9%)
 - Non-IBI – 417 patients (19.1%)

Sensitivity and negative predictive value for ruling out IBI	Step-by-Step	Rochester	Lab-score
	92.0% and 99.3%	81.6% and 98.3%	59.8% and 98.1%

Gomez B et al. *Pediatrics*. 2016; 138(2): e20154381.

HSV Evaluation

- HSV infection is rare but can lead to significant morbidity and mortality in neonates
- Occurs in 0.2 – 0.5% of neonates undergoing evaluation for SBI
- Recommended criteria for HSV evaluation
 - Test and treat if \leq 42 days and:
 - Vesicular skin lesions
 - Abnormal CSF
 - Seizures
 - Consider testing and treating if:
 - Septic appearance

Caviness AC et al. *Clin Ped Emerg Med*. 2013; 14(2): 135-145.

Summary of High Risk Criteria

- Infant < 21 or < 28 days
- Concerns about appearance
- Prematurity
- Underlying conditions
- Abnormal infectious markers
- Abnormal CSF
- Suspicion of HSV

Workup Based on Risk

High-Risk

- Urine
 - UA dipstick
 - Urine culture
- Blood
 - CBC with differential
 - Blood culture
- CSF with culture
- Chest X-ray
- Viral studies
 - HSV evaluation
 - Respiratory panel
- Broad spectrum antibiotic therapy

Low-Risk

- Urine
 - UA dipstick
 - Urine culture
- Blood
 - CBC with differential
 - Blood culture
- Consider viral studies
- No treatment or... antibiotics ?

Baraff LJ et al. *Pediatrics*. 1993; 92(1): 1-12.
Byington CL et al. *Pediatrics*. 2004; 113(6): 1662-1666.

Empiric Therapy

	1 – 28 Days	29 – 90 Days
Suspected UTI or no focus of infection	Ampicillin (50 mg/kg/dose every 6 hrs) + Cefotaxime (50 mg/kg/dose every 6-8 hrs)	Ceftriaxone (100 mg/kg/day) Alternative: Cefotaxime
Suspected meningitis or abnormal CSF	Ampicillin (75-100 mg/kg/dose every 6-8 hrs) + Cefotaxime (50 mg/kg/dose every 6 hrs) +/- Gentamicin (5 mg/kg/dose every 24 hrs)	Ampicillin (75-100 mg/kg/dose every 6-8 hrs) + Ceftriaxone (100 mg/kg/day) +/- Gentamicin (5 mg/kg/dose every 24 hrs) Alternatives: Cefotaxime + Vancomycin
Suspected HSV	Acyclovir (20 mg/kg/dose every 8 hrs)	

Pediatric & Neonatal Infectious Diseases, 1st ed. Churchill, 2016.

The Future of Empiric Therapy?

- Will the recent epidemiologic studies change practice?
- Other changes in the last few decades
 - Vaccines
 - Improved food safety guidelines
 - Prophylactic antibiotics at time of delivery
- Empiric regimens with ampicillin and gentamicin or third generation cephalosporins have remained the same

Patient Case

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Patient Case

- High-risk or Low-risk?
 - 14 days old → High-risk
- Workup?
 - Blood culture
 - Urine analysis and urine culture
 - CBC with differential
 - Lumbar puncture
- Empiric therapy?
 - Ampicillin + Cefotaxime
 - Concern for HSV → Acyclovir

FEBRILE SEIZURES

Febrile Seizures

- Affect 2 – 5% of children
- Occur between the ages of 6 months and 5 years
- Do not include patients with:
 - Intracranial infection
 - Metabolic disturbance
 - History of afebrile seizures

American Academy of Pediatrics. *Pediatrics*. 2008; 121(6): 1281-1286.

Risk Factors

- Severity of the fever
- Family history in first-degree relatives
- Male gender
- Underlying cause of fever
- Antenatal complications
- Iron deficiency

Leung AK et al. *J Pediatr Health Care*. 2007;21(4):250–255. Fetveit A. *Eur J Pediatr*. 2008;167(1):17-27. Hartfield DS et al. *Clin Pediatr (Phila)*. 2009; 48(4): 420-426. Sharawat IK et al. *J Clin Diagn Res*. 2016; 10(5):SC10-13.

Two Categories

- | | |
|---|--|
| <ul style="list-style-type: none"> • Simple Febrile Seizure <ul style="list-style-type: none"> • 65-91% of febrile seizures • Duration < 15 minutes • Generalized • Once in a 24 hour period | <ul style="list-style-type: none"> • Complex Febrile Seizure <ul style="list-style-type: none"> • Duration > 15 minutes • Focal • Multiple times in a 24 hour period |
|---|--|

American Academy of Pediatrics. *Pediatrics*. 2008; 121(6): 1281-1286.
Nelson KB et al. *Pediatrics*. 1978; 61(5): 720-727. Waruiru C et al. *Arch Dis Child*. 2004;89:751-756.

Clinical Implications of Simple Febrile Seizures

- No decline in IQ has been found
- High rate of recurrence
 - Age < 12 months have a 50% probability
 - Age >12 months have a 30% probability
 - With the 2nd febrile seizure the probability increases to 50%
- Risk of developing epilepsy
 - Only increased in children with multiple febrile seizures starting before 12 months of age and a family history
- Potential complications from the seizure

American Academy of Pediatrics. *Pediatrics*. 2008; 121(6): 1281-1286. Chang YC et al. *Epilepsia*. 2000; 41(4): 412-420. Nelson KB et al. *N Engl J Med*. 1976; 295(19): 1029-1033. Annegers JF et al. *N Engl J Med*. 1987; 316(9): 493-498. Rapp RT et al. *Arch Pediatr Adolesc Med*. 1997; 151(10): 1371-1376.

Clinical Management

- Although there is a high risk of recurrence, no long term adverse effects have been seen
- Benefit of anticonvulsant therapy
 - Prevent recurrent febrile seizures
- Harm of anticonvulsant therapy
 - Numerous adverse effects
- Per the American Academy of Pediatrics Clinical Practice Guidelines on Febrile Seizures:
 - It is recommended that no anticonvulsant therapy be used in children with one or more simple febrile seizures

American Academy of Pediatrics. *Pediatrics*. 2008; 121(6): 1281-1286.

Antipyretic Therapy

- Acetaminophen and ibuprofen
- Have not been shown to have a benefit in preventing febrile seizures
- Should only be used for comfort

American Academy of Pediatrics. *Pediatrics*. 2008; 121(6): 1281-1286.

VACCINATIONS AND FEBRILE SEIZURES

Vaccines Associated with Risk

- Diphtheria, tetanus toxoids, and whole cell pertussis (DTP)
- Measles, mumps, and rubella (MMR)
- Measles, mumps, rubella, and varicella (MMRV)
- Trivalent inactivated influenza vaccine (IIV3)
- Pneumococcal conjugate vaccine (PCV7 and PCV13)
- Diphtheria, tetanus, and acellular pertussis vaccine (DTaP)

DTP and MMR Vaccines

- Barlow et al examined the risk of seizures following administration DTP and MMR
- Included 679,942 children < 7 years of age
 - 340,386 received DTP
 - 137,457 received MMR
- Risk with DTP was increased on day of administration
 - Relative risk (RR): 5.7; 95% confidence interval (CI): 1.98 – 16.42
 - 6 to 9 per 100,000 children
- Risk with MMR was increased on days 8 to 14 after administration
 - RR: 2.83; 95% CI: 1.44 – 5.55
 - 24 to 34 per 100,000 children

Barlow WE et al. *N Engl J Med*. 2001; 345:656-661.

MMRV and MMR + Varicella

- Klein et al reviewed data in the Vaccine Safety Datalink (VSD) from 2000 – 2008
- Assessed seizures and fever visits among children 12 – 23 months following MMRV and MMR + varicella
 - 83,107 children received MMRV
 - 376,354 children received MMR + varicella
- Found an increased risk of febrile seizure with MMRV compared with MMR + varicella
 - RR: 1.98; 95% CI: 1.43 – 2.73
 - 1 additional febrile seizure for every 2300 doses

Klein NP et al. *Pediatrics*. 2010; 126(1): e1-8.

Influenza Vaccine

- Increased risk for febrile seizure with the trivalent inactivated influenza vaccine (IIV3) was first seen in Australia in 2010
- Tse et al reviewed the VSD for febrile seizures during the 2010 – 2011 influenza season in the United States
- Included 206,174 children, ages 6 months to < 5 years
- Identified febrile seizures in days 0 - 1 following the first dose of IIV3

Tse A et al. *Vaccine*. 2012; 30(11): 2024-2031.

Influenza Vaccine (cont.)

- Found an increased risk of febrile seizure with IIV3
 - Incidence rate ratio (IRR): 4.0; 95% CI: 2.1 – 6.2
- Risk was elevated with concomitant administration of pneumococcal vaccine (PCV13)
 - IRR: 5.9; 95% CI: 3.1 – 11.3
- The highest risk occurred at 16 months of age
 - 12.5 per 100,000 doses with IIV3 alone
 - 44.9 per 100,000 doses with IIV3 and PCV13 concomitantly

Tse A et al. *Vaccine*. 2012; 30(11): 2024-2031.

Recent Literature

- Duffy et al reviewed the VSD from 2006 – 2011 for febrile seizure risk following IIV3 administration with other vaccines
- Focused on children 6 to 23 months
- Examined risk of febrile seizure on day 0 to 1 post vaccination
- 348 chart confirmed febrile seizures out of 1,915,108 vaccination events

Duffy J et al. *Pediatrics*. 2016; 138(1): e20160320.

Recent Literature (cont.)

- Only PCV7 had an independent risk
 - IRR: 1.98; 95% CI: 1 – 3.91
- IIV3 had no independent risk
 - IRR: 0.46; 95% CI: 0.21 – 1.02
- Increased risk found with:
 - IIV3 in combination with either PCV, IRR: 3.5; 95% CI: 1.13 – 10.85
 - IIV3 in combination with DTaP, IRR: 3.5; 95% CI: 1.52 – 8.07
- Maximum absolute risk of concomitant administration was 30 febrile seizures in 100,000 persons vaccinated

Duffy J et al. *Pediatrics*. 2016; 138(1): e20160320.

How does the risk for febrile seizures impact our patients?

Clinical Implications

- An increased risk of febrile seizures has been shown with certain combinations of immunizations
- The absolute risk is low
- Must consider the benefits of timely vaccination compared with the risks of febrile seizures

Conclusion

- Infants ≤ 90 days presenting with a fever require evaluation and often empiric antibiotic therapy
- Antibiotic therapy is based on the common pathogens and can vary by patient age
- Medication therapy is not recommended for children presenting with simple febrile seizures
- Certain vaccinations have been associated with increased risk of febrile seizures, however the risk versus benefit must be considered when making recommendations on immunization

Test Your Knowledge

Which empiric antibiotic regimen would be appropriate for an ill-appearing 10 day old with a fever of 38.6°C?

- Clindamycin + acyclovir
- Ampicillin + cefotaxime + acyclovir
- Ceftriaxone + vancomycin
- Gentamicin + acyclovir

Test Your Knowledge

True or False: Children who experienced a simple febrile seizure should be discharged home on anti-epileptic medications.

False

Test Your Knowledge

A mother tells you she is nervous about her 1 year old and 3 year old getting a seizure from the flu shot. She asks you if she should avoid the flu shot while they are young. What could you tell her?

- She can prevent febrile seizures by giving acetaminophen before the shot.
- 75% of children get a febrile seizure after the flu shot so she may want to avoid it.
- A recent study showed no increased risk with the flu shot alone. Certain vaccinations have been shown to increase risk for seizures, but the risk is minimal.

Thank you!

QUESTIONS?