

FEVER IN CHILDREN: REVIEW OF THE LITERATURE AND SUGGESTIONS FOR MANAGEMENT IN 2009

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I. Introduction

Definitions

Fever: rectal temperature of $> 37.9^{\circ}\text{C}$

Bacteremia: Presence of bacteria in the blood stream but without any signs or symptoms of sepsis syndrome.

Serious Bacterial Infection (SBI): Bacterial infection with significant risk of progression and danger to the patient if untreated.

Fever Myths Dispelled

- Fever does not cause brain damage
 - Underlying cause may lead to brain damage
 - Source of the fever is more important than the height of the fever
- Response to fever lowering drugs does not distinguish bacterial from viral source
- White blood cell count does not reliably distinguish viral from bacterial infection
 - Increased WBC associated with increased risk of bacterial infection, but virus still most likely
- Treatment of fever is not necessary

Fever Source in Children?

Vast majority of fevers in children are due to viruses or ear infections: up to 90%

Serious bacterial infections (SBI) account for only a small proportion of all fevers in children, estimated at 2-4% (*Ref)

* McCarthy, Fever in Children. In: Fever. P Mackowiak ed. Lippincott-Raven, Philadelphia, 1997

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FEVER IN INFANTS AND CHILDREN

TABLE 2. Diagnosis of serious illnesses during 1221 episodes of acute infectious illnesses in 369 children followed for the first 33 months of life*

Diagnosis	No.	%
Bacterial meningitis	0	0.00
Aseptic meningitis	1	0.082
Pneumonia	10	0.82
Bacteremia	4	0.33
Focal soft tissue infection	2	0.16
Urinary tract infection	3	0.25
Bacterial diarrhea	5	0.41
Abnormal electrolytes, abnormal blood gases	3	0.25
Total	28	2.29

*Data derived from the study by McCarthy, Ref. 8.

TABLE 1. Diagnosis of serious illness during 995 episodes of acute infectious illness in febrile children less than 36 months of age*

Diagnosis	n	%
Bacterial meningitis	9	0.9
Aseptic meningitis	12	1.2
Pneumonia	30	3.0
Bacteremia	10	1.0
Focal soft tissue infection	10	1.0
Urinary tract infection	8	0.8
Bacterial diarrhea	1	0.1
Abnormal electrolytes, abnormal blood gases	9	0.9
Total	89	8.9

*From McCarthy, Ref. 7, with permission.

Emergency Department Approach to the Febrile Child

- Thorough history, with focus on the patient if verbal or the parent if non-verbal
- Physical examination
 - Gather information to support as specific a diagnosis as possible
 - Look for signs of serious bacterial infection: limp, swollen joint, meningismus, tachypnea, retractions, petechial rash, flank tenderness, tender rash, lethargy, poor perfusion
- Primary objective is to identify SBI

How Are Serious Bacterial Infections (SBI) Diagnosed?

McCarthy et al., *Journal of Pediatrics*, 1987

- Study of 350 children under 36 months age
- Analysis of signs and symptoms indicative of serious illness
- Observation, history, and physical exam had sensitivity of 90% in detecting SBI
 - Pulmonary: tachypnea, nasal flaring, grunting
 - CNS: lethargy, meningismus, irritability

Laboratory/X-ray Data

- Unnecessary in arriving at a diagnosis in most children with fever, **including** most with SBI
 - Viral syndromes diagnosed by typical pattern of signs and symptoms
 - May help to determine severity of SBI
 - May help to guide therapy (e.g. cultures)
- May be helpful in selected cases at the discretion of the physician

Risk of Occult Urinary Tract Infection In Fever Without a Source

- In fever without source:
 - 2-3 % of boys younger than 1 year
 - Circumcised boys: risk greatest under 6 months
 - Uncircumcised boys: significant risk up to 1 year
 - 6-8% of girls younger than 1 year
 - 2% in girls 12 to 24 months (*Ref)

*Baraff, *Annals of Emergency Medicine*, December 2000;36:602-614.

Risk of Occult Pneumonia in Fever Without a Source

- Studies have consistently shown that screening chest films in the absence of specific symptoms of pneumonia are unwarranted
- Occult pneumonia may occur in 3% of children without tachypnea, respiratory distress, rales, or decreased breath sounds (*Ref)
 - Up to 80% of pneumonia is viral in origin, no treatment necessary (antibiotics)

*Baraff et al., *Practice Guidelines, Pediatrics* 1993;92:1-12

Occult Pneumonia (Continued)

- Bachur et al, *Annals of Emerg Med* 1999
- Studied FWS and leukocytosis
 - Children under 5, temp over 39, no source, WBC greater than 20,000
 - 26% had occult pneumonia
 - In children *with* respiratory symptoms who had CXR, 40% had pneumonia

What Is The Risk of Meningitis With Any Fever?

- Consider children 1 month to 5 yrs
- 3.5 million children/birth cohort in US
- Therefore 17.5 million children
- Assume 1 fever per year
- 1,250 cases bacterial meningitis/year (*ref)
 - 1.25×10^3 : 1.75×10^7
 - Equals 1 case : 14,000 children with fever

*Schuchat, New England Journal of Medicine, Oct 2 1997, p 970-976

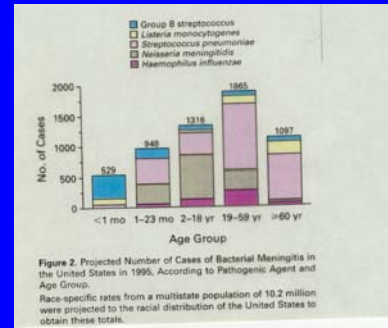


Figure 2. Projected Number of Cases of Bacterial Meningitis in the United States in 1995, According to Pathogenic Agent and Age Group. Race-specific rates from a multistate population of 10.2 million were projected to the racial distribution of the United States to obtain these totals.

Risk of Meningococcal Infection With Any Fever

- Approximately 2,500 cases per year in the US in all age groups
- Approximately half are in children
 - peak in children 3 and under
- **If** following assumptions:
 - All meningococcus in children in those under 3
 - All children < 3 have at least one fever/year
 - **THEN** risk in febrile child < 3y 1:8,400

How Helpful is White Blood Cell Count (WBC) in Evaluation of Fever?

- In most cases not helpful at all, including for the diagnosis of most SBI
 - Clinical signs and symptoms of much greater value: what is the pattern?
 - Pneumonia, pyelonephritis, meningitis, cellulitis
- **In most cases, the reason a physician sends a WBC is to use it as a screen for clinically inapparent SBI**

II. Occult Bacteremia

Background

Teele et al., Journal of Pediatrics, 1975

- Pediatric “Walk in” clinic
- 600 consecutive febrile (> 101) children
- Ages 4 weeks to 2 years
- Blood cultures done in all

Results, Teele et al.

- 19 were bacteremic (3.2%)
- All those with bacteremia had rectal temperatures over 38.9
- 15/19 had WBC > 15,000

McCarthy et al., Pediatrics, 1976

- ED based study
- 1,783 febrile children under age 16 years
- 117 positive blood cultures (6.5%)
- 75% of those with bacteremia had WBC counts over 15,000

Frequency of Fever, FUO

Soman et al., J Family Practice, 1985

Followed 311 children for 2 years:

- 65% had outpatient visits for fever
 - 75% had temperatures under 39
 - 14% had fever without source

Outcome of Bacteremia: H flu

Marshall et al., J Pediatrics, 1979

- febrile children managed as outpatients
- 42 later found to have H flu B bacteremia
- 70% under 36 months

H. flu bacteremia, continued

Of those not initially treated with oral antibiotics:

- 15/20 with persistent fever
- 11/20 with focal infection on follow up
- 10/20 with persistently positive culture

2/3 of those with bacteremia had WBC over 15,000

Outcome of Bacteremia: Strep pneumoniae

Bratton et al., J Pediatrics, 1977

- Febrile children managed as outpatients
- 97 later found to have Pneumococcal bacteremia
- 72% of the 97 aged 7-24 months

Pneumococcal bacteremia, continued

Of those not treated with oral antibiotics:

- 16/51 improved clinically
- 13/51 had persistently positive blood cultures

73% of those with bacteremia had WBC over 15,000

89% of those with bacteremia had temperature over 39.3

Outcome in Pneumococcal Bacteremia in an ED Setting

Alpern et al., *Pediatrics* 2000

- Study done from 1993 to 1996
- Children 2 to 24 months, fever 39.0 or above
 - Overall rate occult bacteremia 1.9%
 - Strep pneumoniae accounted for 82.9% of OB,
 - 96% of S pneumoniae OB resolved without the use of parenteral antibiotics

Predictors of Bacteremia

1. WBC

Jaffe and Fleisher, *Pediatrics*, May 1991

- Generated receiver-operator curves (ROC) for WBC and fever
- 955 children 3-36 months, temp over 39
- ED based study
- 27/955 bacteremic

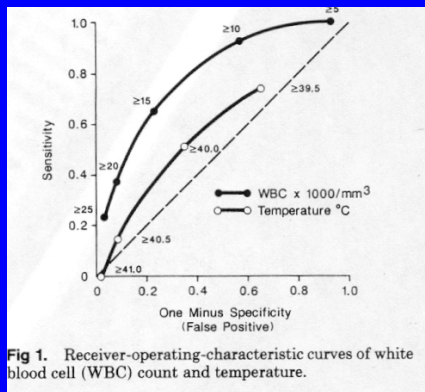


Fig 1. Receiver-operating-characteristic curves of white blood cell (WBC) count and temperature.

ROC Curve, cont.

Best combination sensitivity and specificity at WBC 15,000 and temperature 39 C

This combination still only identifies 2/3 of those with bacteremia; 1/3 escape detection

ROC Curve, cont.

Positive Predictive Value (definition): The ability of a test to correctly identify someone with the disease

<u>WBC</u>	<u>PPV Bacteremia</u>
>10,000	4.6%
>15,000	7.8%
>20,000	12.5%
>25,000	18.8%

Shah et al., *Peds ID Journal* 2005

- Examined extreme leukocytosis (EL) as marker for SBI: WBC greater than 25,000
- Compared with modest leukocytosis (LK): WBC 15,000 to 25,000
- Rates of SBI similar in both groups

Trautner et al., *Pediatrics* July 2006

- Examined risk for SBI in children who present with hyperpyrexia: temp over 106
 - Children under 18 years of age, ED setting
 - Rate one case hyperpyrexia per 1270 patient visits
 - 20/103 had SBI; most were clinically apparent (UTI, pneumonia)
 - WBC was NOT predictive for SBI

Kupperman et al., *Pediatrics* 1999;103:e20

- Study of children with occult bacteremia due to *Neisseria meningitidis*
 - Only 12% (45/381) of all cases meningococcal disease over 11 year period, four med centers
 - Temperature, WBC not significantly different from children with viral infections
- Concluded WBC not helpful screen

WBC as a Screen

- Limited utility in detecting occult pneumonia
- Limited utility in detecting occult pneumococcal bacteremia
 - Quite controversial: Fever guidelines
 - Predictive value quite low
- Little utility in detecting occult meningococcal bacteremia

What Is The Risk of Developing Meningitis With Fever Over 39°C and No Source in 2009?

- Assume rate of occult bacteremia 1% (10/1000)
- 10% fail to clear spontaneously (1/1000)
- 5% go on to develop meningitis as a complication of untreated pneumococcal bacteremia (1/2,000)
- 30% suffer death or major sequelae as a result of meningitis (3/20,000)
- 2/3 detected by WBC cutoff 15,000 (2/20,000)

Implications of Routine Use of WBC for Detection of Pneumococcal Bacteremia

- 10,000 febrile children must be screened to prevent death or serious sequelae due to meningitis in one child
- False positive rate for blood cultures in an ED setting approx 4%
 - 400 children must return for further workup, possible admission

(Predictors Bacteremia, cont.)

2. C-Reactive Protein

- Sanders et al., *J Pediatr* 2008
 - Review of CRP studies to detect SBI
 - Pooled estimates from 6 studies:
 - Sensitivity 77%
 - Specificity 79%
 - Positive predictive value 3.5% (1% rate SBI)
 - Negative predictive value 99.7%

(Predictors Bacteremia, cont.)

3. Band Count

- Generally not found to differentiate viral from bacterial infection reliably
 - Yilmaz, Ann Acad Med Singapore 2008
 - 377 children, 4% rate bacteremia
 - Positive Pred Value bands 15% if rate SBI 1%
 - Lacour, Pediatrics 2003
 - 99 children, 29% with SBI
 - Positive Pred Value bands 9% if rate SBI 1%

Predictors, continued

4. Yale Observation Scale: McCarthy et al., *Pediatrics* 1982

Developed a scale based solely on clinical findings

- Quality of cry
- Reaction to parent stimulation
- State variation
- Color
- Hydration
- Response (talk, smile) to social overtures

(YOS, continued)

- Sensitivity for SBI 77%
- Specificity for SBI 88%
- Only 2.7% with score under 10 had SBI
- 92% with score over 16 had SBI

Observation scales have not proven very helpful in assessing for occult bacteremia, particularly in young infants.

Observation scales may have some utility in assessing for SBI in older children.

Predictors, continued

ROCHESTER CRITERIA

McCarthy et al., *Pediatric ID Journal*, 1990
Combination clinical, lab data
Children under 2 months

Rochester Criteria, cont.

Low risk criteria:

- Previously healthy (37 wks EGA, no antibiotics)
- No OM/focal infection
- WBC 5-15K, less than 1500 bands
- UA less than 10 WBC/HPF
- Stool less than 5 WBC/HPF (if diarrhea)
- All children underwent LP

Rochester Criteria, cont.

If all low risk criteria met:

- Home
- Ceftriaxone 50 mg/Kg
- Follow up next day

Only one serious bacterial infection/86 enrollees

Philadelphia Criteria

- Baker et al, NEJM 1993
- Used low risk criteria in children 29-56 days old, similar to Rochester Criteria
- Designed to limit use of Ceftriaxone
- All children underwent LP
- Conclusions
 - Low risk infants do not need antibiotics
 - Prospective studies have confirmed conclusions

Summary: Occult Bacteremia Prior to 1991

- Occurs in 3-5% of children 3-36 months who have temperatures > 39 , no source
- Lower incidence in children with otitis
- Most common cause is *S. pneumo*
- 65-95% resolve spontaneously
- 2/3 have WBC $> 15,000$
- 5% risk meningitis if untreated *S pneumo*
- 26% risk meningitis if untreated H flu

III. Practice Guidelines: “The Fever Guidelines”

- Published July 1993
- Simultaneously in *Pediatrics*, *Annals of EM*
- Consensus statement from panel of experts
- Written for fever without source

Toxic (definition): Clinical picture consistent with sepsis syndrome

- lethargy
- poor perfusion
- hypoventilation
- hyperventilation
- cyanosis

All toxic appearing children should be hospitalized, evaluated, and treated for possible sepsis or meningitis

Practice guidelines are not intended for use in toxic children

Practice Guidelines, cont.

In evaluation of non-toxic febrile children, three age groups defined:

- 0-28 days
- 29-90 days
- 3 months to 36 months

Infants 0-28 days, fever without source
Temperature > 38 C

Full sepsis workup

blood/urine/CSF

Hospitalization

Parenteral antibiotics

May hold antibiotics if low risk criteria met and negative laboratory screening

Infants 29-90 days, fever without source
Temperature > 38 C

Low risk criteria not met: full sepsis workup, parenteral antibiotics, admission

If low risk criteria met:

- Discharge home
- IM Ceftriaxone optional
- LP recommended if antibiotics to be administered

Children 3-36 months

- Temp < 39
 - No diagnostic testing warranted
- Temp > 39
 - Viral syndrome evident: No diagnostic testing
 - Benign clinical appearance and obvious viral syndrome in family or close contacts: No testing warranted

Children 3-36 months, temp > 39 C, no evidence viral infection

- UA/urine culture
 - males < 6 months, females < 2 years
- WBC count
 - Blood culture, Ceftriaxone if WBC over 15,000
- LP not mandatory

Ancillary testing

Stool exam for leukocytes
Stool culture
Chest X-ray

Recommended only if clinical situation suggests utility

Outpatient follow up: Blood culture positive

If still febrile:

- Complete sepsis workup
- Admit
- Parenteral antibiotics

Outpatient follow up: Blood culture positive

If afebrile:

- Full workup/admission for pathogens other than Strep pneumoniae
- Repeat blood culture, oral antibiotics for Strep pneumoniae

Criticism of Fever Guidelines

- Guidelines have been controversial since the day they were published
- Guidelines were never meant to represent the standard of care
- Guidelines have never been endorsed by the American Academy of Pediatrics
- Studies have consistently shown that private practitioners and ED based physicians have largely ignored them

Criticism (cont)

- Guidelines can easily be misused
 - Never intended for children > 36 months
 - Ceftriaxone used as an antipyretic
- Guidelines based on flawed data
- Reliance on a very imperfect screen (WBC)
- Potential for litigation for physicians who do not do screening tests in febrile children

Are The Fever Guidelines Relevant in 2009?

- Two major advances since their publication have altered the playing field dramatically
 - H flu B conjugate vaccine (HiB): 1991
 - H flu B has been all but eliminated in children
 - Pneumococcal conjugate vaccine
 - Approved for use in children Feb 2000
 - Studies show up to 90% effectiveness in reducing invasive disease
- Bulk of data on FWS is from the era before these vaccines

Occult Bacteremia in the 21st Century

- Rate in 2000 probably around 1.5%
- 90% due to Strep pneumoniae
- Lee et al., *Pediatrics* Oct 2001
 - Cost/benefit analysis for following guidelines
 - Guidelines cost effective at current rate occult bacteremia
 - Clinical judgement “useful” at OB rate 1%
 - If rate OB drops to 0.5%, guidelines should be abandoned

Kupperman, *Arch Ped Adol Med* Sept 2003

- Nice discussion about the approach to fever in children
- Suggests a reevaluation of the fever guidelines
- Suggests that routine laboratory screens and selective empiric antibiotic therapy for non-toxic children is now difficult to justify

IV. A Reasonable Approach To Healthy Febrile Children In The ED

1. Take a thorough history
 2. Do a careful physical exam.
 3. Document findings.
- A. If patient is toxic, assume SBI; full sepsis workup, admission, and antibiotics
- B. If patient has focal signs or symptoms consistent with SBI, order labs/X-Rays as appropriate, (admit), begin appropriate antibiotics

Reasonable Approach (cont)

C. If H&P reveal evidence for a viral infection and vital signs other than temperature are within expected range, discharge with careful follow-up instructions. No labs are indicated.

D. If child is non-toxic, > 24-36 months of age, has acute FWS, and vital signs are within expected range, discharge with careful follow-up instructions. No labs are indicated.

Reasonable Approach (cont)

E. If child is non-toxic, < 24-36 months of age, has acute FWS, and vital signs are within expected range, two reasonable options:

1. Follow the fever guidelines, or
2. Amend the fever guidelines as appropriate

**Caution: know the pediatric fever literature, be able to defend your actions

F. If child has underlying health problems, use clinical judgement but be more conservative

Section of Pediatric EM at the Medical College of Georgia: Our approach

- Full sepsis workup, admission, and empiric parenteral atbx for febrile children under 1 month
- General adherence to the "fever guidelines" for children under 6 months
- Screening urines for non-verbal children up to 2 years depending on the sex
- Very few WBCs ordered on children over 4 months of age: guidelines largely abandoned
- CXR if specific clinical signs and symptoms are present (fever PLUS tachypnea or retractions)

V. Conclusions

- Most fevers in children are not due to serious bacterial infections, so...
- Most febrile illnesses require no specific treatment (antibiotics)
- Screening WBC is of limited value and does not reliably predict bacterial infection
- Most febrile children require no laboratory tests
- Most fevers can be managed by history, physical exam, careful follow-up instructions

