The Febrile Neonate and Young Infant

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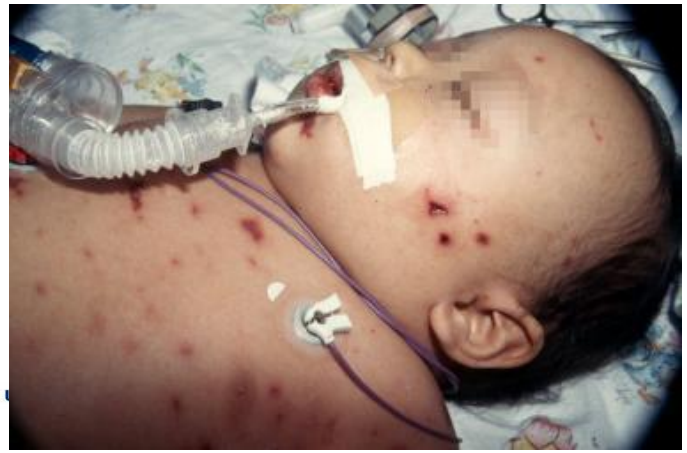
Sick Appearing Infant

- “easy”- know what to do when caring for ill appearing infant
- Don’t panic
- ABC’s
- POC glucose
- Fluids
- Abx
- FSWU
- Admit- floor vs picu vs transfer



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Not so easy….

- Well appearing neonate fever 38.7 at home, no fever in ED
- Well appearing 5 week old that has runny nose and temp 102
- 7 week old with fever 39.4 and no other symptoms

- What do you do????

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Objectives

1. Define fever
2. Discuss variation in care of febrile neonate
3. Review current recommendations for evaluation of the febrile neonate and young infant
4. Discuss role of procalcitonin, other biomarkers in the identification of serious illness in this population

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Introduction

FEVER

Represents ~20% of all encounters in ER setting

Young infants have historically been placed in a different category

Most of these kids do fine

So why the extensive work up?

Osman O et al. Health Bull 2002

Fever

- Fever common presenting symptom in the PED
  15-30% all visits

  - Normal range is 36.5-38.0 C
  - No single value is “normal” temperature
  - Normal temp = range of values for each individual

  - Hyperthermia ≠ fever
    - **Height of fever does not predict serious bacterial illness**

  - Increased risk occult bacteremia > 40 (shook, et al)

  - < 36 months
    - **Rectal temperatures closest to core body temp**
    - **Rectal temp most reliable= standard**
    - Oral – need cooperation
    - TM and TA are very unreliable
    - Axillary – unreliable but OK for screening patients

Get a good temperature

Measuring Fever

- **Rectal - most reliable in infants under 3 mos**
- Oral - only reliable in cooperative children
- Axillary - least invasive; less accurate
- Tympanic - results variable
  Generally 1.0 to 1.8 F lower than rectal temperature
- Pacifier - requires 3 to 4 minutes
  Generally 0.5 F lower than rectal temperature
- **Temperature of 38 C (100.4 F) or greater considered fever**

Key Points: Fever

- Fever reduction does not decrease sequalae of febrile illness
- No decrease in morbidity/ mortality
- Antipyretics don't reduce risk for recurrence febrile sz
- Fever response to antipyretics **does not** differentiate serious bacterial illness from more benign cause
- **Age, appearance, peripheral perfusion better predictors of SBI than height of fever**
- Presence or absence of fever- not specific value- key treatment plan
- Incidence of occult bacteremia < 0.5% overall since universal use pneumococcal vaccination
- **Febrile neonate- < 28 days old- risk SBI 10%**
- **Urinary Tract Infection = most common SBI febrile infants < 2 mths**
- Variety of diagnostic testing/ management strategies for well appearing febrile infants 4-8 weeks of age

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Fever

- **Immunocompromised, SCD, steroid dependent, asplenic, chemo, transplant pt**
- **Ill appearing**
  - **requires prompt, complete evaluation for source**
  - **empiric abx- broad spectrum- gram +/ gram – organisms**
  - **ivf resuscitation**
  - **? Stress steroids**

- **Goal for febrile pt:**

  - **Purely based on patient comfort**
    - the goal is not to keep the patient normothermic
  - Tepid/cool bath- no alcohol baths
  - Oral hydration
  - Antipyretics:
    - Acetaminophen
      - 15 mg/kg q 4-6 hours
      - Hepatotoxicity
    - Ibuprofen
      - 10 mg/kg q 6 hours
      - GI bleeding, nephrotoxicity

Alternating meds not proven to improve outcomes

- Increase risk for dosing errors/ toxicity
- Feeds into “ fever phobia”

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Fever

- **Infants < 2 mths different than older child:**

  risk serious bacterial infection (bacteremia,UTI,meningitis,pneumonia,osteo) relatively high (10%)
  young infants immature immune response
  clinical appearance hard to interpret

  - **<30 days (neonate)**
    - CBC w/diff, Blood Cx, UA, Urine Cx, LP, CSF Cx
    - +/- CXR, +/- Stool studies
    - Cefotaxime/Ampicillin or Gentamicin/Ampicillin
    - Admit
    - Perinatally acquired /maternal organisms: e coli, gbs, staph, listeria
  - **30-60 days (90 days)**
    - CBC w/diff, Blood Cx, UA, Urine Cx
    - +/- LP, +/- CXR, +/- Stool studies
    - WBC – <15,000 and no significant bandemia, extremely unlikely to have occult bacteremia
    - Studies negative – D/C with 24 hour f/u, no antibiotics
    - Studies positive – treat source
    - > 6 weeks- community acquired organisms: pneumococcus, meningococcus, h flu
    - “Low risk criteria” for management well appearing febrile infants-
    - Viral – 30-40%
    - Influenza, RSV, adenovirus, herpes simplex, varicella, enteroviruses

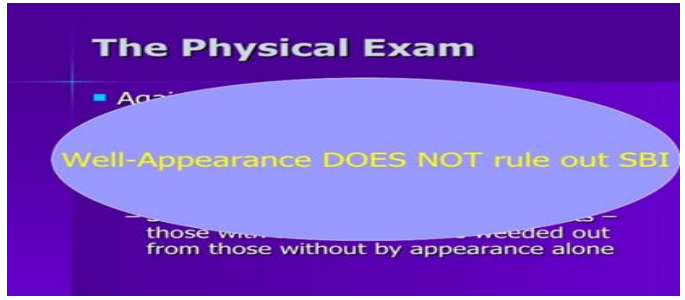
The Neonate

- < 30 days old
- May display limited signs of infection
- Clinically difficult differentiate serious bacterial infection from self limited viral illness
- Can not trust exam!!!!
- SBI: meningitis, pneumonia, UTI, osteo, bacteremia
- **Most common SBI = UTI**
- Organisms: gbs, listeria, e.coli, h flu, strep pneumo
- Incidence SBI:

  < 1 MTH age- 13%
  1-2 mths age- 10%

  0-1 mth > 1-3 mths > 3-36 mths

Younger age = Higher risk



Febrile Infant

- Infant < 90 days
- Context of fever- risk stratification
  - birth- 2 mths
  - 2-3 mths
  - > 3 mths
    - Higher risk for bacterial infections
    - Immature immune systems
    - Unique pathogens

Epidemiology

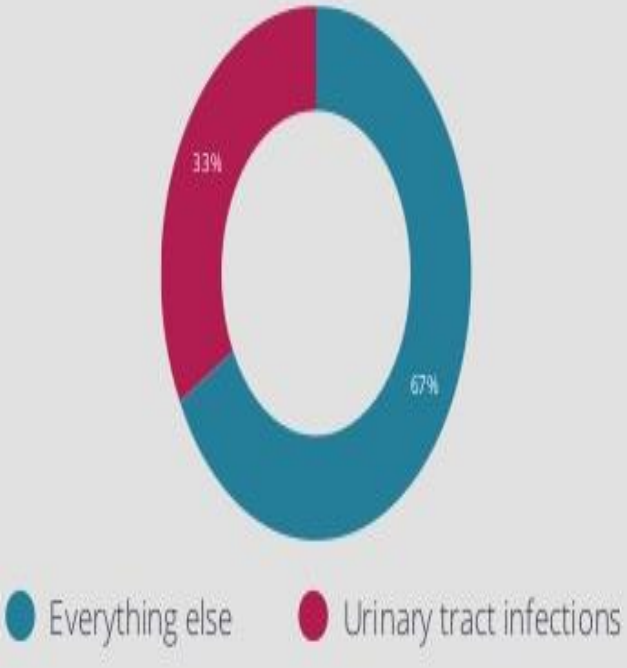
Viruses

UTI

Other bacterial infections (gastro, cellulitis, osteo, pneumonia)

Bacteremia

Bacterial Infections in Infants < 3 months



Brown LA. Crit Decis Emerg Med 2000

“That” Fever Article

Annals of Emergency Medicine
Journal of the American College of Emergency Physicians

PEDIATRICS

Volume 92(1) July 1993 pp 1-12

Practice Guideline for the Management of Infants and Children 0 to 36 Months of Age With Fever Without Source.

Baraff, Larry J.; Bass, James W.; Fleisher, Gary R.; Klein, Jerome O.; McCracken, George H. Jr.; Powell, Keith R.; Schriger, David L.

- Expert consensus panel recommendations
- Meta-analysis of literature
- pre-Hib and prevnar vaccine data
- Rochester criteria selected as screening criteria for high vs low risk
- **Toxic-Appearing Infants and Children**:
  Hospitalize, evaluate and treat for presumed sepsis, meningitis, or SBI
- **Febrile (low risk) Infants < 28 days of age**

  SBI evaluation and hospital admission for all infants with either parenteral therapy or close observation
- **Febrile Low-Risk Infants 28-90 Days of Age**

  Obtain urine culture and provide close follow-up
  - OR -

  Full sepsis evaluation (blood, urine, CSF) and treat with IM ceftriaxone

  All children who receive presumptive therapy should have an LP

Despite published guidelines, no clear standard of care!

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Case 1

- 17 day old female brought to the ED for fever
- Temp 38.1, HR 152, RR 36, O2 Sat 95% RA, Wt 3.8 kg
- Term, NSVD, No URI Sxs, nl prenatal care and birth hx, MOC GBS- neg
- 2 y.o. sibling at home with URI
- Exam- Alert, non focal, well appearing, NL exam

*WHAT would **you** do?*

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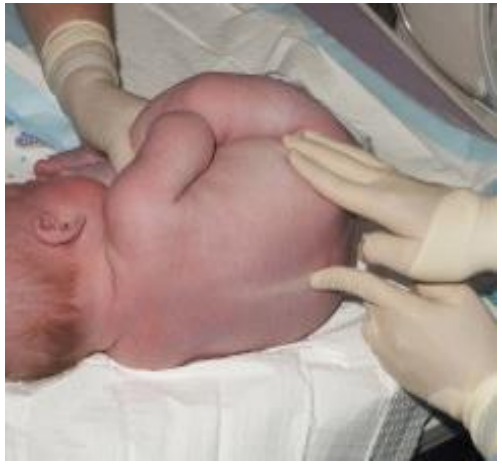
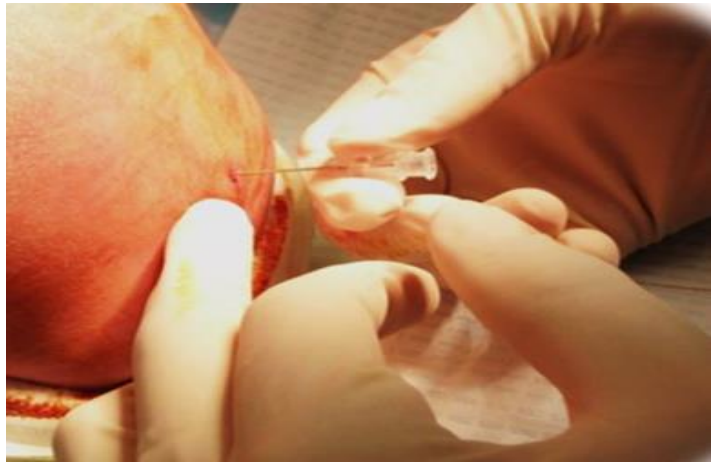
Evaluation

1. CBC/Diff
2. Blood Cx
3. LP/CX
4. UA/CX
5. Viral NP Swab
6. CXR
7. Hospitalize for IV Antibiotics
   - Amp + gent
   - Amp + cefotaxime
   - ? acyclovir





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Predictive Models for FWS To define Low Risk Infants

	Philadelphia	Rochester
Age	29-60 days	<60 days
WBC	<15,000	>5K, <15,000
Bands	Band:Neut <0.2	ABCount <1500
UA	<10 WBC	<= 10 WBC
CSF	< 8 WBC	No LP
CXR	Negative	No CXR
Stool (If indicated)	<= 5 WBC/hpf	<= 5 WBC/hpf

High or Low Risk- LP or Not ?

	Boston	Philadelphia	Rochester
Age	28-89 d	29-60	≤60
Hx	No immunizations in preceding 48 hours No antibiotics within 48 hours		Term No perinatal abx No underlying disease
Exam	Well-appearing No focal infection	Well-appearing No focal infection	Well-appearing No focal infection
Labs	CSF <10 UA <10 WBC/hpf CXR: no infiltrate WBC <20,000	CSF <8 CSF gram stain neg WBC < 15,000 Band-neutrophil ratio <0.2 UA <10 WBC/hpf CXR neg Stool neg	WBC >5000 and <15,000 Absolute band count ≤1500 UA ≤10 WBC/hpf ≤5 WBC/hpf stool smear
High risk	Hospitalize + empiric abx	Hospitalize + empiric abx	Hospitalize + empiric antibiotics
Low risk	Home, Rocephin, F/u within 24 hours	Home, no abx, f/u within 24 hours	Home, no abx, f/u within 24 hours

Criterion	Rochester Criteria (0-60 days of age)	Philadelphia Criteria (29-56 days of age)	Boston Criteria (29-89 days of age)
History and physical examination	Full-term • Normal prenatal and postnatal histories • No postnatal antibiotics • Well appearing • No focal infection	Well appearing • No focal infection	No antibiotics within preceding 48 h No immunizations within preceding 48 h Well appearing No focal infection
Laboratory parameters (defines low risk)	WBC: 5-15,000/mm3 • Band: count < 1500 • UA: < 10 WBC/ HPF • Stool: < 5 wbc /HPF on smear	WBC: < 15,000/mm3 • Band: total neutrophil (I:T) ratio < 0.2 • UA: < 10 WBC/ HPF • Urine: Gram stain negative • CSF: < 8 WBC/mm3 • CSF: Gram stain negative • Chest x-ray: no infiltrate* • Stool: no blood, few or no WBCs on smear*	WBC: < 20,000/mm3 • UA: <10 WBC/ HPF • CSF: < 10 WBC/mm3 • Chest radiograph: no infiltrate*
Treatment for high-risk patients	Hospitalize + empiric antibiotics	Hospitalize + empiric antibiotics	Hospitalize + empiric antibiotics
Treatment for low-risk patients	Home 24-h follow-up required No empiric antibiotics	Home, if patient lives within 30 min of the hospital • 24-h follow-up required • No empiric antibiotics	Home, if caregiver available by telephone • Empiric IM ceftriaxone 50 mg/kg • Return for 24-h follow-up for second dose of IM/IV ceftriaxone
Performance of low-risk criteria	NPV: 98.9% (97.2-99.6)	NPV: 100% (99-100)	NPV: 94.6% (92.2-96.4)

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Application to Infants < 4 Weeks of Age?

- Prospective study of 254 febrile infants < than 1 month
- 5 of 32 (15.6%) who had SBI would have been classified to be at low risk of having bacterial disease according to the Philadelphia criteria
- Would falsely identify as many as 10 per 100 febrile neonates as having low risk of SBI
- Concluded :

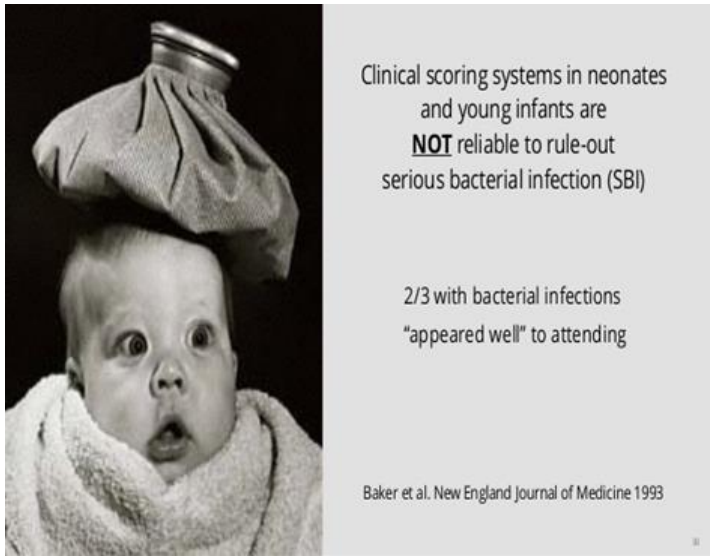
“ febrile infants <1 month of age should include a complete evaluation for bacterial illness and the empiric administration of antibiotics”

*Baker MD, Bell LM, Arch Pediatr Adolesc Med. 1999;153:*508-511.

Screening Tests < 28 Days?

- 225 infants 1-29 days admitted with T >38.0
- SBI in 31
  - 6 missed by Philadelphia criteria (Baker)
  - 8 missed by Boston criteria (Baskin)

Kadish HA, Bolte RG, Tobey J, Loveridge B. Clin Pediatr 2000 Feb;39(2):81-8



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Neonates

Birth to 28 days

Everyone gets blood, urine, csf+ abx + admission

Viral URI sx DO NOT count as a fever source

H&P are UNRELIABLE to rule out SBI

UTI (20%) >>> Bacteremia (3%) >> Meningitis (<1%)

E. Coli, GBS, HSV >> Listeria, Salmonella, Staph. aureus

Neonates

Birth to 28 days

Neonates will have picked up bacteria from the birth canal

Herd immunity doesn't help against what mom can give you

Immune system sucks

Very little shield between blood/brain/urine (membranes are wide open)

Caution

- SBI can present with hypothermia (< 36 c)
- Difficulty with thermoregulation
- Don’t miss low core temp
- Treat same as if fever- fswu

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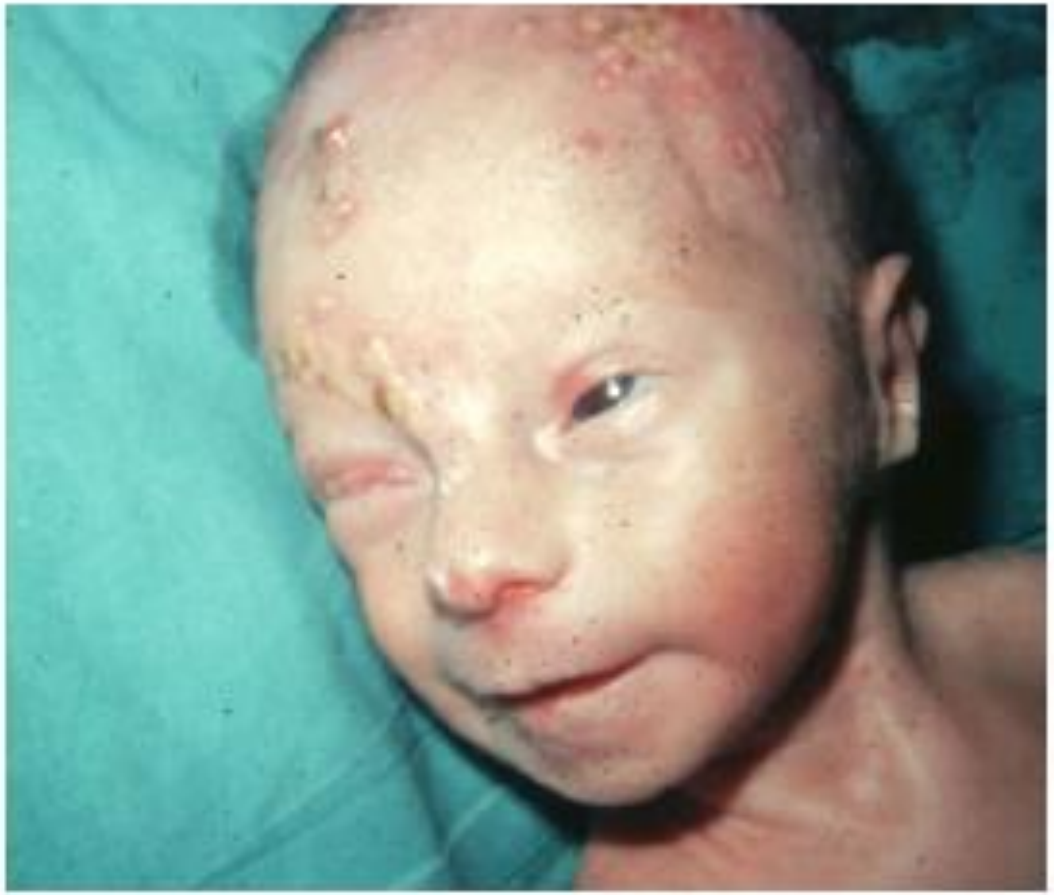
When to consider HSV

- Mucous membranes, CNS or disseminated
- Vesicles, conjunctivitis, seizures, CNS Sx, sepsis
- CSF pleocytosis, elevated LFTs, DIC, acidosis
- Dx with HS PCR from vesicles, CSF or blood



HSV

- Majority of infections transmitted at birth
- If there are risk factors, treat empirically
- Majority present in neonatal period
- Low threshold for acyclovir if you suspect

Herpes Simplex Virus Infection in Infants Undergoing Meningitis Evaluation

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abstract

BACKGROUND: Although neonatal herpes simplex virus (HSV) is a potentially devastating infection requiring prompt evaluation and treatment, large-scale assessments of the frequency in potentially infected infants have not been performed.

METHODS: We performed a retrospective cross-sectional study of infants ≤60 days old who had cerebrospinal fluid culture testing performed in 1 of 23 participating North American emergency departments. HSV infection was defined by a positive HSV polymerase chain reaction or viral culture. The primary outcome was the proportion of encounters in which HSV infection was identified. Secondary outcomes included frequency of central nervous system (CNS) and disseminated HSV, and HSV testing and treatment patterns.

RESULTS: Of 26 533 eligible encounters, 112 infants had HSV identified (0.42%, 95% confidence interval [CI]: 0.35%–0.51%). Of these, 90 (80.4%) occurred in weeks 1 to 4, 10 (8.9%) in weeks 5 to 6, and 12 (10.7%) in weeks 7 to 9. The median age of HSV-infected infants was 14 days (interquartile range: 9–24 days). HSV infection was more common in 0 to 28-day-old infants compared with 29- to 60-day-old infants (odds ratio 3.9; 95% CI: 2.4–6.2). Sixty-eight (0.26%, 95% CI: 0.21%–0.33%) had CNS or disseminated HSV. The proportion of infants tested for HSV (35%; range 14%–72%) and to whom acyclovir was administered (23%; range 4%–53%) varied widely across sites.

CONCLUSIONS: An HSV infection was uncommon in young infants evaluated for CNS infection, particularly in the second month of life. Evidence-based approaches to the evaluation for HSV in young infants are needed.

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WHAT'S KNOWN ON THIS SUBJECT: Herpes simplex virus (HSV) can present subtly yet have devastating outcomes. Fortunately, it is a relatively uncommon infection, yet empirical acyclovir therapy is commonly provided to at-risk infants. Accurate frequency data are needed to guide decision-making.

WHAT THIS STUDY ADDS: Of 26 533 infants 0 to 60 days old who underwent lumbar puncture at 1 of 23 emergency departments, 0.42% (95% confidence interval: 0.35%–0.51%) had HSV infection. For every 1 infant with HSV infection, 237 infants needed to be treated. This knowledge could guide empiric acyclovir use.

To cite: Cruz AT, Freedman SB, Kulik DM, et al. Herpes Simplex Virus Infection in Infants Undergoing Meningitis Evaluation. *Pediatrics*. 2018;141(2):e20171688

Case 2

- 51 day old female brought to the ED for fever
- Temp 38.5, HR 152, RR 36, O2 Sat 95% RA Wt 4.3 kg
- Term, NSVD, No URI Sxs, nl prenatal care and birth hx, Mom GBS- neg
- 2 y.o. sibling at home with URI
- Exam- Alert, non focal, well appearing, NL exam

*WHAT would **you** do?*

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Evaluation

CBC/Diff
Blood Cx
LP/CX- ?????
UA/CX
Viral NP Swab
CXR
Empiric Antibiotics????

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Evaluation

	Boston, ’92 (Baskin)	Philly, ’93 (Baker)	Rochester, ’94 (Jaskiewicz)
# of pts	503	747	931
Age	28-89 d	29-56	0-60
Temp	>38	>38.2	>38
WBC	<20	<15	5-15
CSF for all	Yes	Yes	No
Abx	Yes	No	No
% in low risk		38.4%	41.3%
SBI in low risk	5.4 %	0.3 %	1.1 %
NPV	94.6%	100%	98.9%
Sensitivity	?	100%	92.4%

Viral sx MAY count as a fever source

UTI (15%) >>> bacteremia (1%) >>> meningitis (0.2-0.4%)

Invasive bacterial infection (IBI) rate 1/100 to 1/1000

E. coli, GBS, S.pneumo >>>N.meningitides, H. flu, Staph. aureus

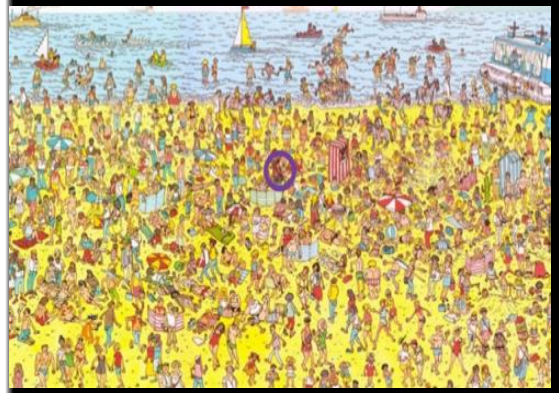
Classically: Blood, urine, CSF, +/- antibiotics, +/-admission

Variation in Care

There's still debate regarding who gets a full septic work up

Respect the worst case scenario

How comfortable are you sending this kid home without a full workup?



Variability Common Still

ARTICLE

Management of Febrile Neonates in US Pediatric Emergency Departments

Among pediatric emergency departments across the US, does the management of febrile infants <28 days old vary from recommended clinical guidelines?

Retrospective cohort study; 36 different children's hospitals

Records reviewed for compliance with recommended testing (blood, urine CSF), treatment (Amp + Gent/3rd gen ceph), management (labs, treatment, admission)

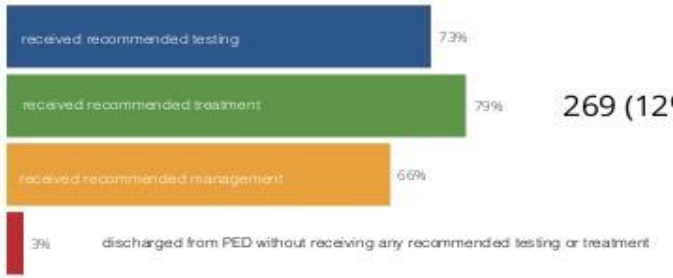
41,890 neonates evaluated; 2253 had fever

Jain S et al. Pediatrics 2014

ARTICLE

Management of Febrile Neonates in US Pediatric Emergency Departments

Percentage of febrile neonates receiving recommended testing, management,



269 (12%) diagnosed with SBI

Jain S et al. Pediatrics 2014

TABLE 3 Details of Evaluation of Febrile Neonates Across 36 US PEDs

	Overall ($n = 2253$)		Discharged From ED ($n = 369$)		Admitted to Hospital ($n = 1884$)		P
	%	95% CI	%	95% CI	%	95% CI	
Blood + urine + CSF culture[a]	72.9	71.1–74.7	8.4	6.0–11.7	85.6	83.9–87.1	<.0001
Blood + urine culture	7.3	6.2–8.4	15.2	11.9–19.2	5.7	4.7–7.8	<.0001
Blood culture only	1.1	0.7–1.6	3.0	1.7–5.3	0.7	0.4–1.2	.0005
Urine culture only	0.9	0.6–1.4	4.1	2.5–6.6	0.3	0.2–0.7	<.0001
CSF culture only	1.7	1.3–2.4	0.3	0.05–1.5	2.0	1.5–2.8	.0145
Other cultures or combinations	3.6	2.9–4.5	4.6	2.9–7.3	3.5	2.7–4.4	.2868
No cultures	12.5	11.2–13.9	64.5	59.5–69.2	2.3	1.7–3.1	<.0001
Chest radiograph	32.8	30.9–34.7	10	7.4–13.5	37.3	35.1–39.4	<.0001

[a] Recommended testing for neonatal fever.

Jain S et al. Pediatrics 2014

Decisions, decisions……

ARTICLE

Variation in Care of the Febrile Young Infant <90 Days in US Pediatric Emergency Departments

Retrospective cohort study of febrile infants < 90 days old

37 Pediatric EDs

Assessed variation in testing, treatment, and disposition for kids in 3 distinct age groups: ≤28 days, 29-56, and 57-89 days

35,070 ED visits met inclusion criteria

Aronson PL et al. Pediatrics 2014

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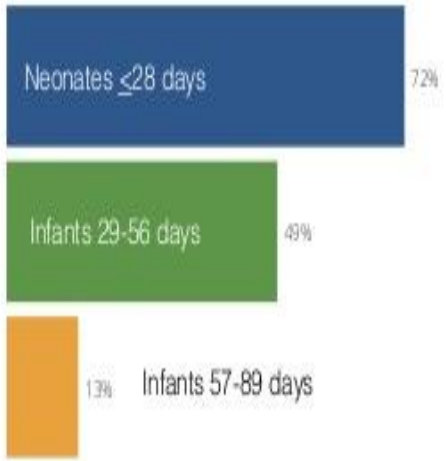
ARTICLE

Variation in Care of the Febrile Young Infant <90 Days in US Pediatric Emergency Departments

Percentage of febrile neonates/young infants receiving **full septic workup**



Aronson PL et al. Pediatrics 2014

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Peds ED Adherence

- TCH Denver 2004-06
- 167 patients total
  - 79 29-59d
  - 88 60-90d
- 19 ‘SBI’ (11%)
  - OB 4
  - UTI 11
  - Pneumonia 4
  - BM 0
- **Complete SBI W/U as by ‘guideline’**
  - Age 29-59 day old 49%
  - Age 60-90 day old 8%

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Study Conclusions

- Pediatric emergency medicine physicians in our institution **do not follow existing practice guidelines** for the workup of fever in young infants

- Whether this reflects a lack of awareness of the guidelines or more likely, a culture that favors test minimization over risk minimization, could not be determined from this study.

- These physicians obtained fewer CBCs, blood cultures, urine cultures, CSF cultures, and viral studies in the infants aged 60 to 90 days than in those infants aged 28-59 days.

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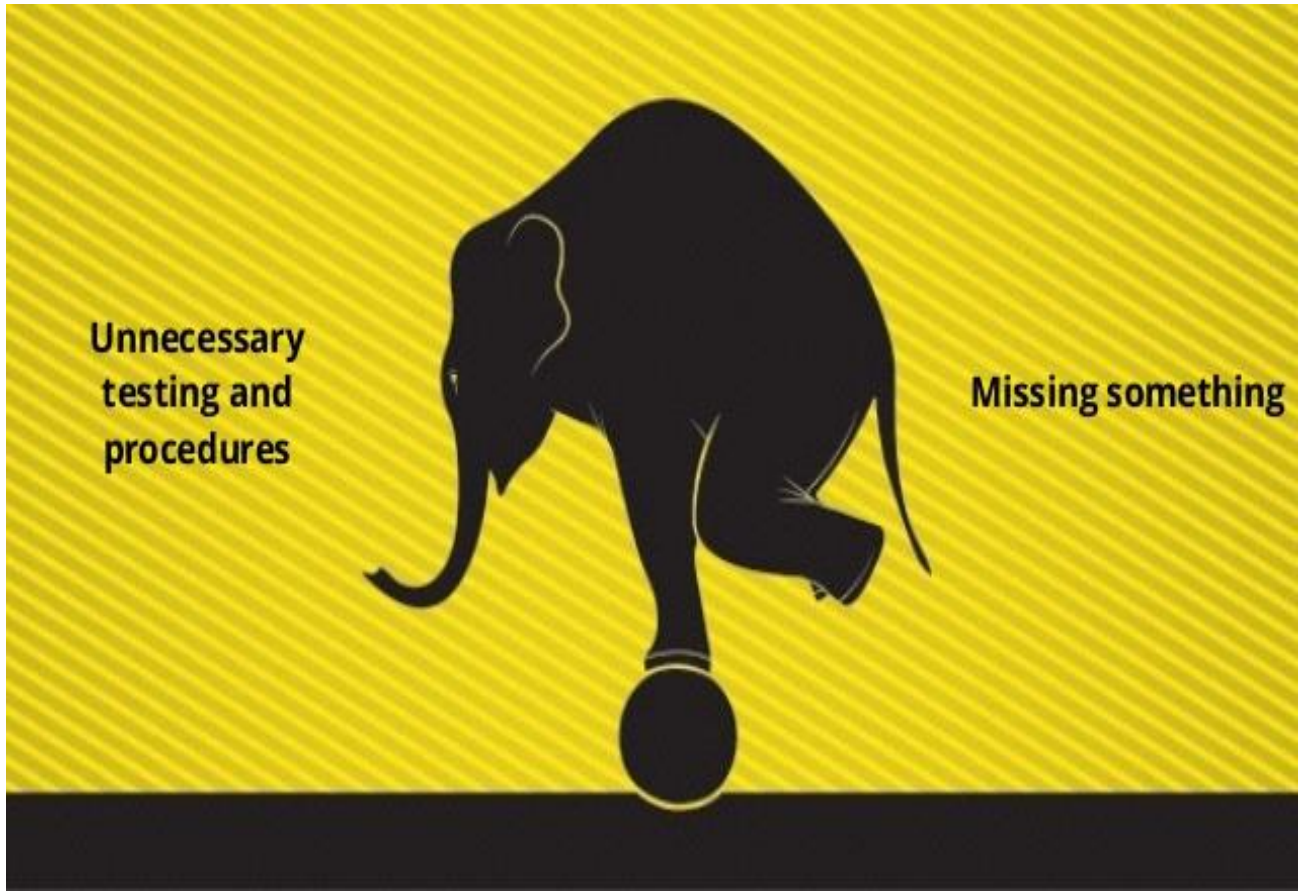
CY MEDICINE

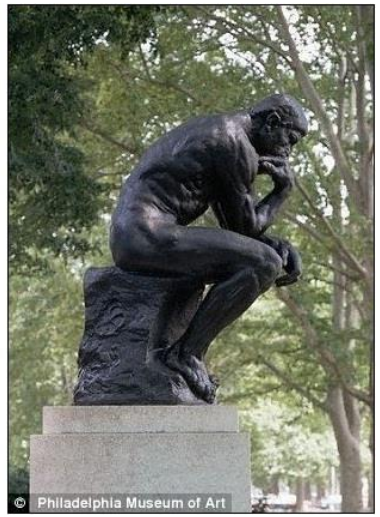
Do the Right Thing



What Should I Do?

- Are you a **risk minimizer** or a **test minimizer**?
- Editorial article by Green and Rothrock
  - suggests that controversy lies not in the data itself, but rather in how it is interpreted by the individual physician

Green SM, Rothrock SG: Evaluation styles for well-appearing febrile children: Are you a “risk-minimizer” or a “test-minimizer”? *Ann Emerg Med* Feb 1999;33:211-214.



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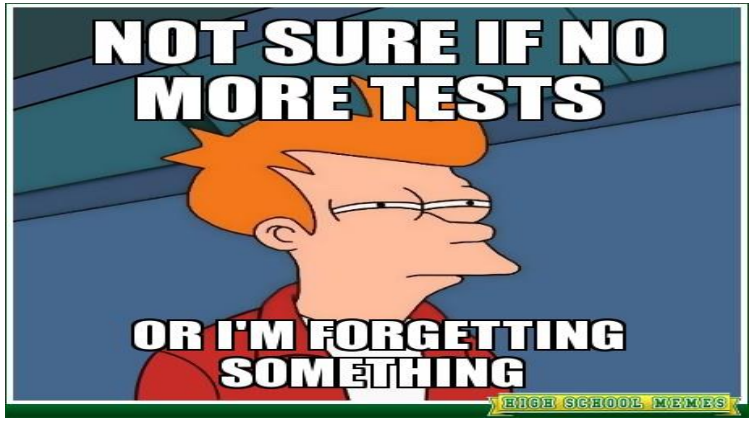
Risk Minimizers

- Desire to lower risk of adverse sequelae from occult infections
- Use risk stratification to target higher-risk patient subsets for intervention
- Believe that structured, methodical, and laboratory-intensive strategy minimizes adverse sequelae from occult infections
- Believe when consistently implemented will save lives
- Many perceive this strategy as lowest possible liability risk

Test Minimizers

- Believe majority of rare children whose condition progresses to serious bacterial illness identified through close follow-up and return ED visits
- Believe parents prefer less testing and treatment- even if it means a greater risk of an adverse outcome
- Argue liberal ordering of blood cultures necessitates frequent unnecessary reevaluations and hospitalizations for children with false+ culture results or OB
- Even if undetected, would most likely clear without intervention



So, Are You a Risk-Minimizer ?

Green SM, Rothrock SG: Ann Emerg Med 1999; 33:211

- Desire to lower risk of adverse sequelae from occult infections
- Do not believe that clinical evaluation is sufficient to reliably identify ill children
- Use risk stratification to target higher risk patient groups for intervention
- Believe potential benefit of reducing adverse sequelae justifies empiric diagnostic testing and treatment

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If Not, Perhaps a Test-Minimizer ?

Green SM, Rothrock SG: Ann Emerg Med 1999; 33:211

- Believe occurrence of adverse outcomes is so low as to not justify time, expense and invasiveness of risk stratification
- Believe clinical evaluation and follow up will serve to identify nearly all ill children
- Believe parents prefer less testing and treatment
- Willing to accept a greater chance of being wrong

No right or wrong answer
Both defendable
Do what you feel is best for baby and family

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More Evidence

Performance of Low-Risk Criteria in the Evaluation of Young Infants With Fever: Review of the Literature

Meta-analysis of 21 studies looking at low-risk criteria for febrile infants <90 days old

Rate of SBI in low-risk patients in all studies was **2.23%**

The rate of low-risk patients in prospective studies without empiric antibiotics (variations of Rochester criteria) was significantly different: **0.67%**

Huppler et al. Pediatrics 2010

Low risk criteria decision rules

- Perform very well in infants > 28d old
- Huppler et al.
- Systematic review
- 0.67% had an SBI

WHAT'S KNOWN ON THIS SUBJECT: Fever in neonates is common. The rate of SBIs in young infants may be as high as 12%. Low-risk criteria have been developed to aid in management decisions for well-appearing, febrile young infants.

WHAT THIS STUDY ADDS: Although the total risk of SBI in febrile young infants in this review was 10.9%, low-risk criteria allowed 30% of these patients to be treated safely without empiric antibiotic therapy.

Low-risk clinical criteria (infants 29-60 days old)	
• well-appearing • previously healthy • no focal source of infection	
Low-risk laboratory criteria	
Urinalysis	• ≤10 WBC/hpf • No bacteria on Gram's stain
CBC	• WBC 5,000 to 15,000/mm^3 • ≤1,500 band cells/mm^3
Chest radiograph (if obtained)	• No evidence of discrete infiltrate
Stool smear (when diarrhea is present)	• Negative for blood • ≤5 WBC/hpf

Cincinnati Children's Evidence-Based Care Guideline 2010

Fever > 40- is this a problem?

Hyperpyrexia Among Infants Younger Than 3 Months

Rachel Stanley, MD, MHSA, Zrinka Pagon, MD,† and Richard Bachur, MD‡*

Over 5000 infants younger than 3 months with fever were retrospectively reviewed

98 patients (1.7%) had temp ≥40 C (104F)
Prevalence of SBI among febrile infants ≥40 C was **38%** compared with those with fever ≤40 C **8.8%**

TABLE 2. Organisms Causing Serious Bacterial Illness in Infants Younger than 3 Months with Temperatures ≥40°C

23 Urinary tract infections	*E. coli*
1 Urinary tract infection	*Pseudomonas aeruginosa*
1 Urinary tract infection	*Klebsiella*
2 Meningitis	Group B alpha hemolytic streptococcus
1 Bacteremia	*Streptococcus pneumonia*
1 Bacteremia	Group B alpha hemolytic streptococcus
2 Bacterial enteritis	*Salmonella*

Stanley R et al. Pediatric Emergency Care 2005

Concomitant Viral Illness- Friend or Foe?

RAPID INFLUENZA TEST IN YOUNG FEBRILE INFANTS FOR THE IDENTIFICATION OF LOW-RISK PATIENTS

Santiago Mintegi, MD, Juan José Garcia-Garcia, MD,†*

844 febrile infants ≤60 days of age who were tested for influenza,

A significantly lower rate of serious bacterial illness (SBI) was noted in the 123 infants who were influenza-positive compared with the 721 infants who were influenza-negative:
2.5 percent versus 11.7 percent

If the CBC and urinalysis do not suggest bacterial infection, lumbar puncture can be omitted in well-appearing febrile infants who are older than 28 days of age, have a positive rapid influenza test, and no evidence of bacterial infection on physical examination.

Mintegi S et al. Pediatric Infectious Disease Journal 2009

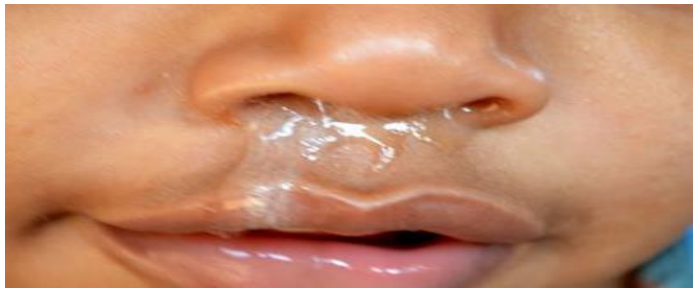
A PROSPECTIVE STUDY OF THE RISK FOR SERIOUS BACTERIAL INFECTIONS IN HOSPITALIZED FEBRILE INFANTS WITH OR WITHOUT BRONCHIOLITIS

Efraim Bilavsky, MD, Dror S. Shouval, MD,* Havatzelet Yarden-Bilavsky, MD,† Naama Fisch, MD,† Shai Ashkenazi, MD,†‡ and Jacob Amir, MD*‡*

Prospectively looked at 448 febrile infants <3months with and without bronchiolitis

SBI in 30/312 (**9.6%**) infants without bronchiolitis and 3/136 (**2.2%**) with bronchiolitis

Bilavsky E et al. Pediatr Infect Dis 2008)



WBC and SBI- Is this the Answer ?

- **No !!!!!!**
- PPV for more serious infections (meningitis, osteomyelitis, septic arthritis) is much lower
- Majority of children with bacterial meningitis have a WBC < 15,000
- **NEVER** use CBC results to determine the need for an LP

Utility of the peripheral blood white blood cell count for identifying sick young infants who need lumbar puncture

Bema K. Bonsu, Marvin B. Harper. Ann Emerg Med. 2003;41:206-214

We assess the utility of the peripheral blood WBC count as a screen for lumbar puncture among young infants evaluated for serious bacterial infections. Twenty-two of 5,353 (4.1 per 1,000) infants had acute bacterial meningitis.

For diagnosing acute bacterial meningitis, the peripheral blood WBC count was poorly discriminating and significantly inferior to the cerebrospinal fluid WBC count.

Decisions to perform or withhold lumbar puncture should not be based on prevailing interpretations of the total peripheral blood WBC counts to maximize detection of bacterial meningitis in young infants.

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When Thinking About Predictive Value of a Test...

Imagine you are the patient receiving test results of a screening test

If the test is POSITIVE,
How likely is it that you really have the disease?
How worried should you be?

If the test is NEGATIVE,
How likely is it that you really don't have the disease?
How reassured should you be?

UTI and the Young Infant

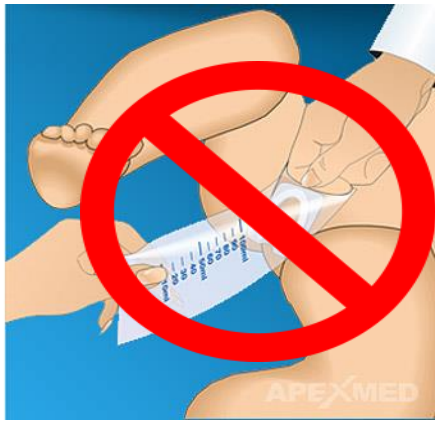
- Equal gender incidence under 3 months
- Over 3 months, more common in females
- Positive urine cultures - FWS
  - male infants < 6 mo: 7%
  - female infants < 2 years: 8%
- Incidence as high as 17.5% of white girls under 24 months T ≥39c
- **Check the urine!!!!!**

  boys < 1yr – uncircumcised, < 6 mths circumcised
  girls < 2yrs

Urine Specimens Acceptable for Culture

- Suprapubic aspiration
- Cathetererized specimen
- Clean mid-stream void
- **Bagged specimens of any type at any time = Not Acceptable**

- **Negative UA does not rule out UTI!**
- Urine culture is still gold standard



What is positive:

Clean Catch >100,000 cfu/ml
Straight catheterization > 10,000 cfu/mL
SPA > 1,000 cfu/mL

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The Future is Now - PECARN

- Project is to incorporate a RNA-based diagnostic technology
  (transcriptional signatures)
- Goal: distinguish between bacterial and non-bacterial infections in otherwise well-appearing febrile infants presenting to ED
- Patient enrollment 2008 through 2013

Application of Transcriptional Signatures for Diagnosis of Febrile Infants within the PECARN Network:

The ultimate goal of this project is to incorporate a RNA-based diagnostic technology (called transcriptional signatures) to distinguish between bacterial and non-bacterial infections in otherwise well-appearing febrile infants who present to the EDs. The project aims to create a PECARN wide infrastructure for conducting translational genomic research and demonstrate feasibility of screening, consenting, collecting, and processing of small volumes of blood samples to abstract high quality RNA from febrile infants. After initially defining bacterial and non-bacterial biosignatures, we will conduct a limited validation of these diagnostic biosignatures on an independent group of febrile infants. Patient enrollment began in 2008 and continued through May 2013. **Analysis is in progress.** This project is co-funded by NICHD.

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PECARN

Conducting High Priority, High-Quality Research in Pediatric Emergency Care

What About Procalcitonin?

ARTICLE

Procalcitonin in Young Febrile Infants for the Detection of Serious Bacterial Infections

Vincenzo Maniaci, MD[a,b], Andrew Dauber, MD[b], Scott Weiss, MD[b], Eric Nylen, MD[c,d], Kenneth L. Becker, MD, PhD[c,d], Richard Bachur, MD[a,b]

234 infants

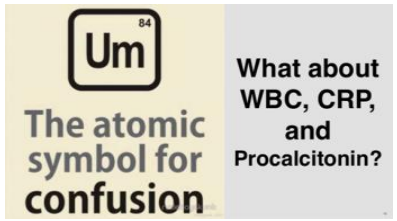
30 had SBI (12.8%)

LR- 0.5-1 USELESS
LR- 0.1-0.5 MOD
LR- <0.1 **STRONG**

For identifying definite and possible serious bacterial infections, a cutoff value of **0.12** ng/mL had a sensitivity of 95.2%, specificity of 25.5%, negative predictive value of 96.1%, and a **negative likelihood ratio of 0.19**

All cases of bacteremia were identified accurately with this cutoff value

Maniaci V et al. Pediatrics 2008



ARTICLE

Diagnostic Value of Procalcitonin in Well-Appearing Young Febrile Infants

TABLE 5 Positive and Negative LRs for Ruling Out or Confirming SBIs and IBIs

	Definite SBI		IBI	
	+LR	−LR	+LR	−LR
Rule out				
PCT (<0.5 ng/mL)	5.70 (4.28–7.62)	0.68 (0.59–0.75)	5.68 (4.57–7.38)	0.25 (0.12–0.55)
CRP (≤20 mg/L)	4.20 (3.46–5.09)	0.47 (0.40–0.54)	2.74 (2.06–3.66)	0.41 (0.22–0.76)
Confirm				
PCT (≥2 ng/mL)	7.12 (4.52–11.21)	0.82 (0.76–0.88)	11.14 (7.81–15.89)	0.32 (0.17–0.60)
CRP (>40 mg/mL)	7.38 (5.39–10.14)	0.85 (0.57–0.70)	5.45 (2.21–5.42)	0.61 (0.41–0.80)

LR+ 1-2 USELESS
LR+ 2-10 MOD
LR+ >10 **STRONG**

LR- 0.5-1 USELESS
LR- 0.1-0.5 MOD
LR- <0.1 **STRONG**

1112 infants <3 months old fever without a source

23 cases of SBI (2.1%)

PCT better than CRP in identifying kids with SBI

Gomez B et al. Pediatrics 2012

Original Investigation

Use of Procalcitonin Assays to Predict Serious Bacterial Infection in Young Febrile Infants

Karen Milcent, MD, MSc; Sabine Faesch, MD; Christèle Gras-Le Guen, MD, PhD; François Dubos, MD, PhD; Claire Poulalhon, MD; Isabelle Badier, MD; Elisabeth Marc, MD; Christine Laguille, MD; Loïc de Pontual, MD, PhD; Alexis Mosca, MD; Gisèle Nissack, MD; Sandra Biscardi, MD; Hélène Le Hors, MD, PhD; Ferielle Louillet, MD; Andreea Madalina Dumitrescu, MD; Philippe Babe, MD; Christelle Vauloup-Fellous, PharmD, PhD; Jean Bouyer, PhD; Vincent Gajdos, MD, PhD

IMPORTANCE The procalcitonin (PCT) assay is an accurate screening test for identifying invasive bacterial infection (IBI); however, data on the PCT assay in very young infants are insufficient.

OBJECTIVE To assess the diagnostic characteristics of the PCT assay for detecting serious bacterial infection (SBI) and IBI in febrile infants aged 7 to 91 days.

DESIGN, SETTING, AND PARTICIPANTS A prospective cohort study that included infants aged 7 to 91 days admitted for fever to 15 French pediatric emergency departments was conducted for a period of 30 months (October 1, 2008, through March 31, 2011). The data management and analysis were performed from October 1, 2011, through October 31, 2014.

MAIN OUTCOMES AND MEASURES The diagnostic characteristics of the PCT assay, C-reactive protein (CRP) concentration, white blood cell (WBC) count, and absolute neutrophil cell (ANC) count for detecting SBI and IBI were described and compared for the overall population and subgroups of infants according to the age and the duration of fever. Laboratory test cutoff values were calculated based on receiver operating characteristic (ROC) curve analysis. The SBIs were defined as a pathogenic bacteria in positive culture of blood, cerebrospinal fluid, urine, or stool samples, including bacteremia and bacterial meningitis classified as IBIs.

RESULTS Among the 2047 infants included, 139 (6.8%) were diagnosed as having an SBI and 21 (1.0%) as having an IBI (11.0% and 1.7% of those with blood culture (n = 1258), respectively). The PCT assay offered an area under the curve (AUC) of ROC curve similar to that for CRP concentration for the detection of SBI (AUC, 0.81; 95% CI, 0.75-0.86; vs AUC, 0.80; 95% CI, 0.75-0.85; $P = .70$). The AUC ROC curve for the detection of IBI for the PCT assay was significantly higher than that for the CRP concentration (AUC, 0.91; 95% CI, 0.83-0.99; vs AUC, 0.77; 95% CI, 0.65-0.89; $P = .002$). Using a cutoff value of 0.3 ng/mL for PCT and 20 mg/L for CRP, negative likelihood ratios were 0.3 (95% CI, 0.2-0.5) for identifying SBI and 0.1 (95% CI, 0.03-0.4) and 0.3 (95% CI, 0.2-0.7) for identifying IBI, respectively. Similar results were obtained for the subgroup of infants younger than 1 month and for those with fever lasting less than 6 hours.

CONCLUSIONS AND RELEVANCE The PCT assay has better diagnostic accuracy than CRP measurement for detecting IBI; the 2 tests perform similarly for identifying SBI in febrile infants aged 7 to 91 days.

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Journal Club Slides and Supplemental content at jamapediatrics.com

CME Quiz at jamanetworkcme.com and CME Questions page 95

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Published online November 23, 2015.

Validation of the "Step-by-Step" Approach in the Management of Young Febrile Infants

Borja Gomez, MD,[a,b] Santiago Mintegi, MD, PhD,[a,b] Silvia Bressan, MD, PhD,[c] Liviana Da Dalt, MD,[d] Alain Gervaix, MD,[e] Laurence Lacroix, MD,[e] on behalf of the European Group for Validation of the Step-by-Step Approach

abstract

BACKGROUND: A sequential approach to young febrile infants on the basis of clinical and laboratory parameters, including procalcitonin, was recently described as an accurate tool in identifying patients at risk for invasive bacterial infection (IBI). Our aim was to prospectively validate the Step-by-Step approach and compare it with the Rochester criteria and the Lab-score.

METHODS: Prospective study including infants ≤90 days with fever without source presenting in 11 European pediatric emergency departments between September 2012 and August 2014. The accuracy of the Step-by-Step approach, the Rochester criteria, and the Lab-score in identifying patients at low risk of IBI (isolation of a bacterial pathogen in a blood or cerebrospinal fluid culture) was compared.

RESULTS: Eighty-seven of 2185 infants (4.0%) were diagnosed with an IBI. The prevalence of IBI was significantly higher in infants classified as high risk or intermediate risk according to the Step by Step than in low risk patients. Sensitivity and negative predictive value for ruling out an IBI were 92.0% and 99.3% for the Step by Step, 81.6% and 98.3% for the Rochester criteria, and 59.8% and 98.1% for the Lab-score. Seven infants with an IBI were misclassified by the Step by Step, 16 by Rochester criteria, and 35 by the Lab-score.

CONCLUSIONS: We validated the Step by Step as a valuable tool for the management of infants with fever without source in the emergency department and confirmed its superior accuracy in identifying patients at low risk of IBI, compared with the Rochester criteria and the Lab-score.

Fever– the old infant and toddler

- **3-36 months of age**
- **Majority viral**
- **Occult Bacterial Infections:**
  - Pneumonia – 20%, Temp >39, WBC >20,000
  - UTI
  - Bacteremia
    - Prior to vaccines – 5%
    - After vaccines <1%
    - Fully immunized – 3 PCV, 2 Hib

- **Evaluation:**
  - UA with culture
    - Females <2 years
    - All males < 6months, uncircumcised <12months

Highest risk – Caucasian females with temp >39, and uncircumcised males <6 months

Other ancillary testing based on exam, history, appearance of child
CXR- tachypnea, hypoxia, clinical suspicion
CBC suggests occult pneumonia
CBC, Blood Cx- not routine , ill appearing, not " fully immunized"
LP- not routine, ill appearing

No role for routine CBC, blood culture, and empiric antibiotic use

Higher threshold to prompt a work up ≥39 C (102.2 F)

Females ≤24 mo: UA/UCx

Uncircumcized Males ≤6 mo: UA/UCx; consider in ≤12 mo

Circumcized males: consider UA/UCx in ≤6mo

Odds are in your favor: physiology + vaccinations

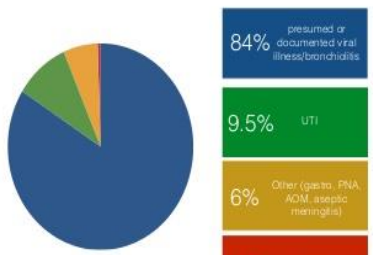
Occult bacteremia rates becoming very very low (<0.5%)

False positive blood culture rate is higher than rate of occult bacteremia

Physical exam is useful

Incidence and Predictors of Serious Bacterial Infections Among 57- to 180-Day-Old Infants

Allen L. Hsiao, MD, Lei Chen, MD, M. Douglas Baker, MD



Evaluation of 429 febrile infants 57-180 days old

SBI rate 10.3%

Most of which were UTI and no bacterial meningitis was diagnosed

No infants, aged 2-3 months had a positive blood culture

This suggests that infants 2-3 months of age perhaps can be managed less conservatively and be grouped with their older counterparts

Hsiao AL et al. Pediatrics 2006

Prevalence of Occult Bacteremia in Children Aged 3 to 36 Months Presenting to the Emergency Department with Fever in the Postpneumococcal Conjugate Vaccine Era

Matthew Wilkinson, MD, Blake Bulloch, MD, and Matthew Smith, MD

Looked at rate of occult bacteremia in 8408 well appearing febrile children aged 3 to 36 months:

0.25%

Wilkinson M et al. Acad Emerg Med 2009

Management of Low-risk Pediatric Fever with No Source

- **0-28 days**
  - CBC, UA C&S, blood culture, LP, ?CXR
  - Admit for IV Abx, possible Acyclovir

- **29-90 days**
  - UA, Urine Culture
  - Consider CBC/diff, blood culture, CXR
  - Strongly consider LP if planning on outpatient antibiotics

Baby Fever

- Ill appearing
  - –Admit
  - –Abx
- Less than 29d
  - –Full septic work up
  - –Abx
  - –Admit

Baby Fever

- 29 to 60d
  - –Cbc, BC, UA, urine culture
  - –Bronchiolitis
    - UA/urine culture
    - Can skip LP
  - –Normal: D/C with close f/u 12-24 hrs
  - –Abnormal: CSF, abx, admit

Conclusion- What Do We Know?

- Fever extremely common presenting complaint- much concern (phobia?) regarding fever
- Fairly effective strategies to identify low risk infants
- **These <u>do</u> <u>not</u> apply to neonates**
- #1 bad actor (H. flu) effectively erradicated
- Meningitis/ meningococcemia - “pediatrician’s nightmare” - still out there
- Risk of OB now under 2%
- 93-96% spontaneous resolution of occult bacteremia
- Keep abreast of the literature
- Discuss this with colleagues & mentors
- Be aware :
  - local practice variations
  - institutional practice guidelines
  - antimicrobial resistance rates
- Both approaches (RM & TM) are defensible
- **Choose the best strategy for you**
- Be consistent

Always treat the ill appearing child with fever

Questions ?????

Summary of various criteria for determiningbacterial infection in infants.

	Rochester	Philadelphia	Cincinnati	Intermountain
Age	< 60 d	29-60 d	29- 60 d	29-90
Rectal temp	≥ 38.0	≥ 38.2	≥ 38.0	≥ 38.0
Appearance	Well, no ear, soft tissue or bone infxn	Well	Well, no focal source	Well, no focal source/resp distress
History	≥ 37 wks gestation, previously healthy	n/a	≥ 37 wks gestation, previously healthy, no previous or current abx	≥ 37 wks, no underlying medical condition
WBC	5,000 – 15,000, band <1,500	<15,000, band-neutrophil ratio <0.2	5,000-15,000, band <1,500	5,000-15,000, band <1,500
UA	<10 wbc/hpf, no bacteria	<10 wbc/hpf, neg urine gram stain	≤ 10 wbc/hpf, no bacteria	≤ 10 wbc/hpf, neg LE
CSF		<8 wbc/microL and neg CSF gram stain		Defer LP in low risk infants
Stool	< 5 wbc/hpf if obtained	w/o blood, few or no wbc if diarrhea	No blood, ≤ 5 wbc/hpf if diarrhea is present	
CXR	n/a	No infiltrate	No infiltrate if obtained	
Stats	NPV 98.9%, 931 infants	NPV 99.7%, 747 infants	LR of ruling out SBI 0.8	8044 infants, no missed SBI
Other				VIRAL studies, AST/ALT if <42 d

References:

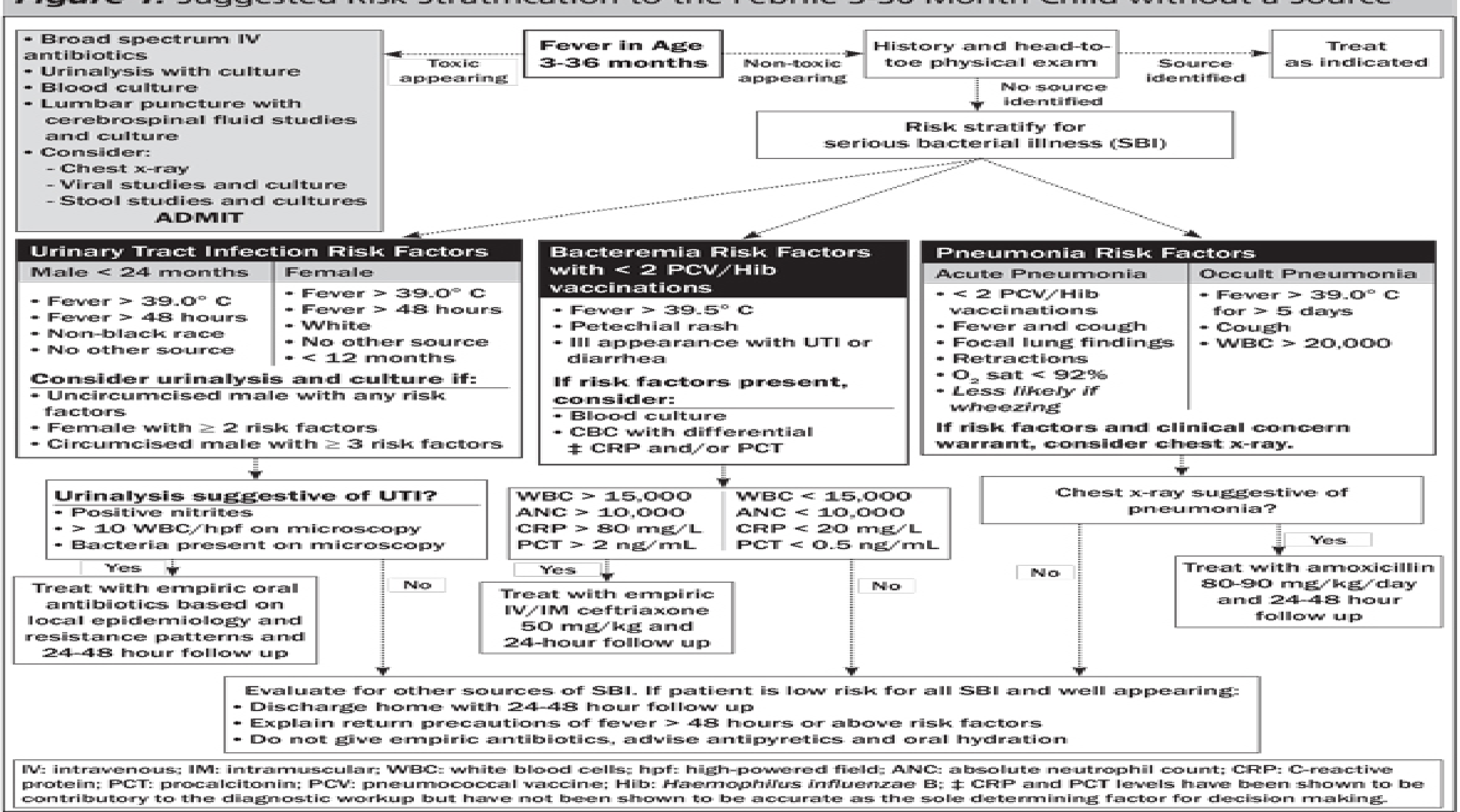
1. Rochester Criteria: McCarthy CA, Powell KR, Jaskiewicz JA, Carbrey CL, Hylton JW, Monroe DJ, Meyer HSO. Outpatient management of selected infants younger than two months of age evaluated for possible sepsis. Pediatr Infect Dis J. 1990;9(6):385.

2. Philadelphia Protocol: Baker MD, Bell LM, and Avner JR. Outpatient management without antibiotics of fever in selected infants. N Engl J Med. 1993; 329(20): 1437

2. Cincinnati Guidelines: available at http://www.cincinnatichildrens.org/svc/alpha/h/health-policy/ev=based/default.htm Guideline 02, pages 1-14, October 2010.

4. Intermountain Protocol: Byington CL, Reynolds CC, Korgenski K, et al. Costs and infant outcomes after implementation of a care process model for febrile infants. *Pediatrics.* 2012; 130: e16-e24.

Figure 1. Suggested Risk Stratification to the Febrile 3-36 Month Child without a Source



IV: intravenous; IM: intramuscular; WBC: white blood cells; hpf: high-powered field; ANC: absolute neutrophil count; CRP: C-reactive protein; PCT: procalcitonin; PCV: pneumococcal vaccine; Hib: *Haemophilus influenzae* B; ‡ CRP and PCT levels have been shown to be contributory to the diagnostic workup but have not been shown to be accurate as the sole determining factor for decision making.

Algorithm for Managing Fever of Unknown Source in Neonates (0-28 days)

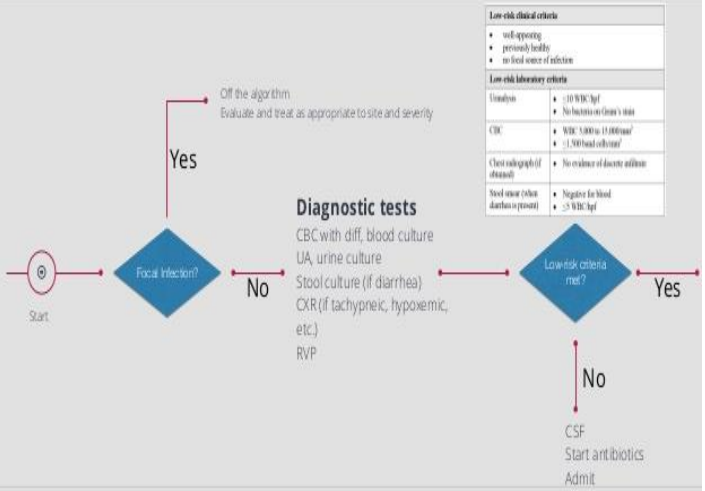
Evidence-Based Care Guideline for Fever of Unknown Source. Cincinnati Children's Hospital Medical Center 2010

It is recommended that CSF HSV polymerase chain reaction (PCR) testing **not** be routinely performed in neonates who present with FUS and no other evidence of an HSV infection *(Cavness 2008c [1a], Shah 2010 [4b], Local Consensus [5b])*.

It is recommended that CSF HSV PCR be considered in neonates with CSF pleocytosis and a negative Gram stain *(Cavness 2008c [1a], Cavness 2008b [4b], Local Consensus [5b])*.

Algorithm for Managing Fever of Unknown Source in Young Infants (29-60 days)

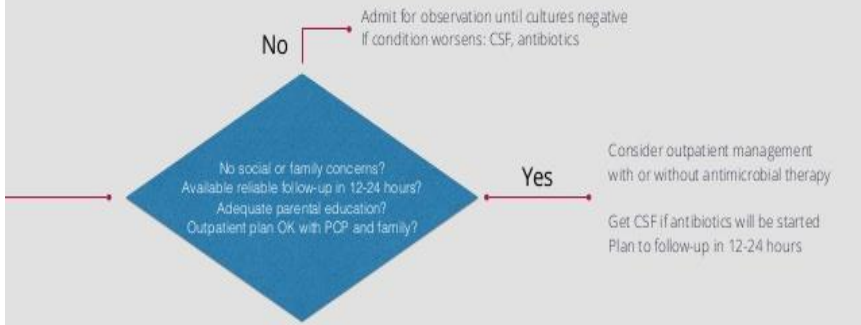
Evidence-Based Care Guideline for Fever of Unknown Source. Cincinnati Children's Hospital Medical Center 2010



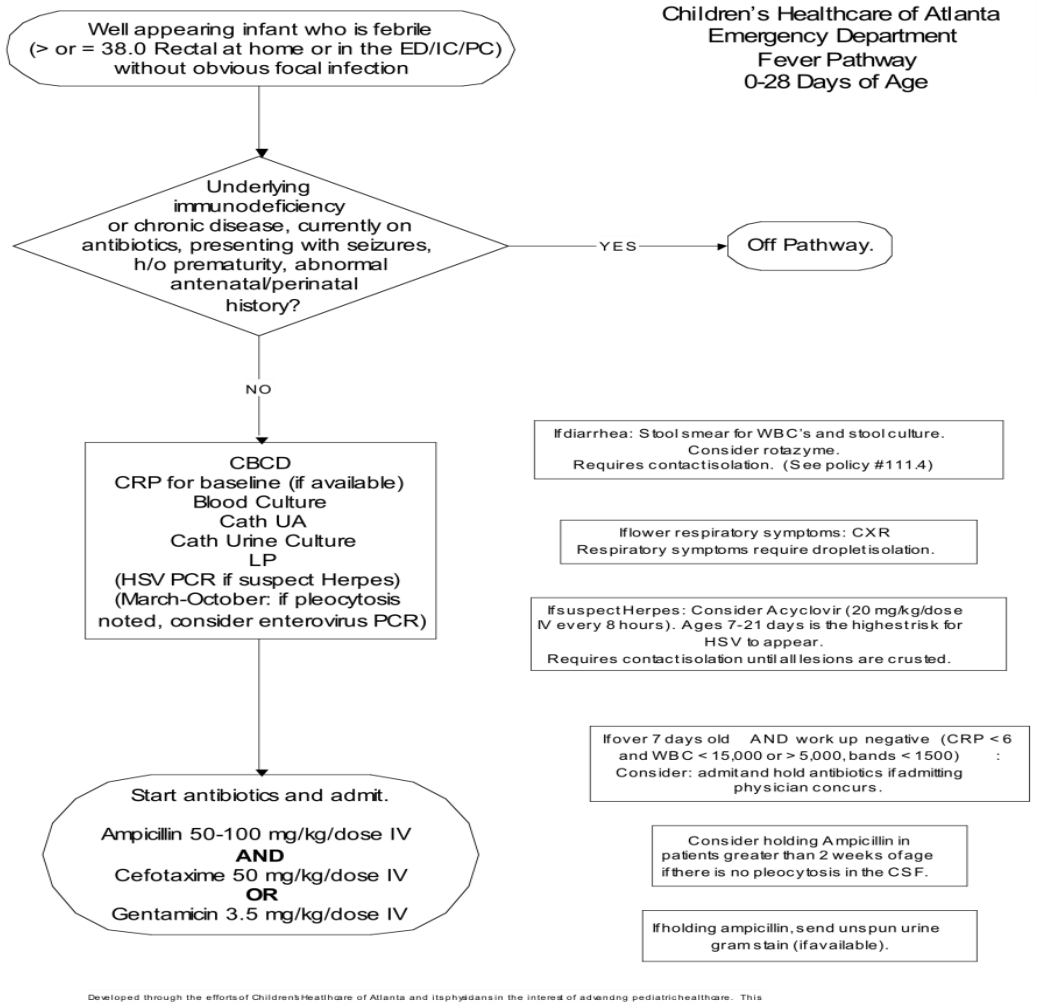
Low-risk clinical criteria	
• well-appearing • previously healthy • no focal source of infection	
Low-risk laboratory criteria	
Urinalysis	• <10 WBC/hpf • No bacteria on Gram's stain
CBC	• WBC 5,000 to 15,000/mm³ • ≤1,500 band cells/mm³
Chest radiograph (if obtained)	• No evidence of discrete infiltrate
Stool smear (when diarrhea is present)	• Negative for blood • ≤5 WBC/hpf

Algorithm for Managing Fever of Unknown Source in Young Infants (29-60 days)

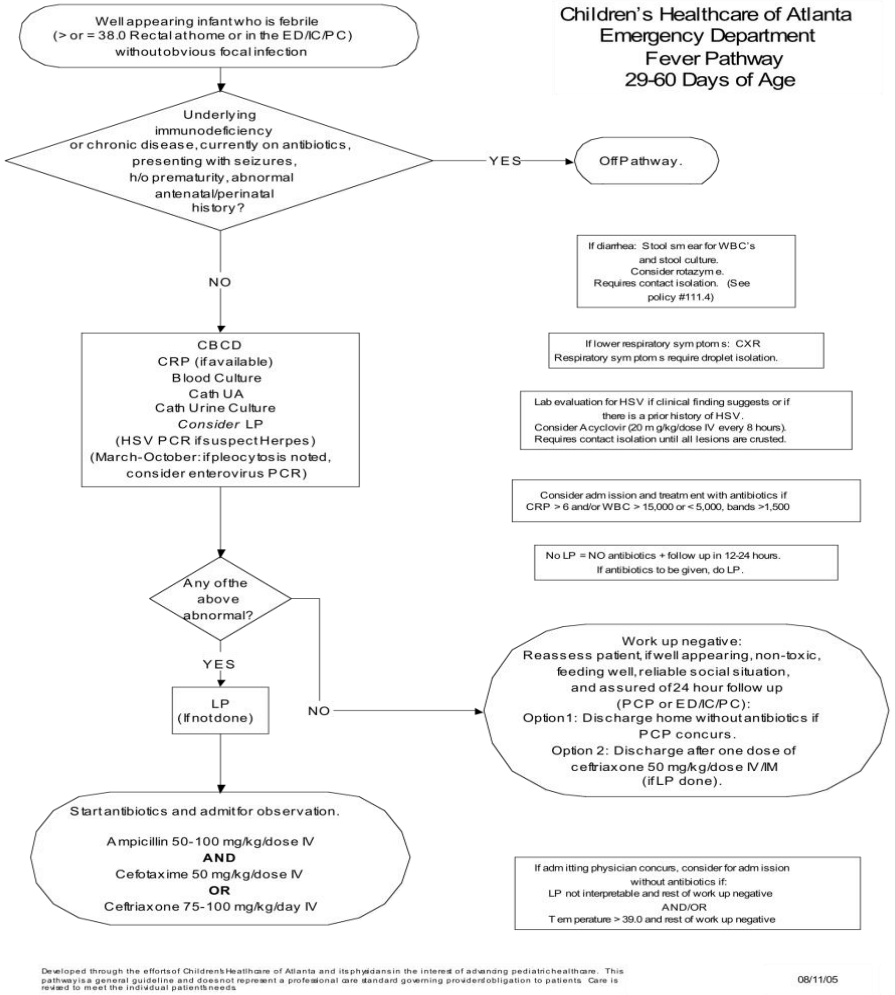
Evidence-Based Care Guideline for Fever of Unknown Source. Cincinnati Children's Hospital Medical Center 2010



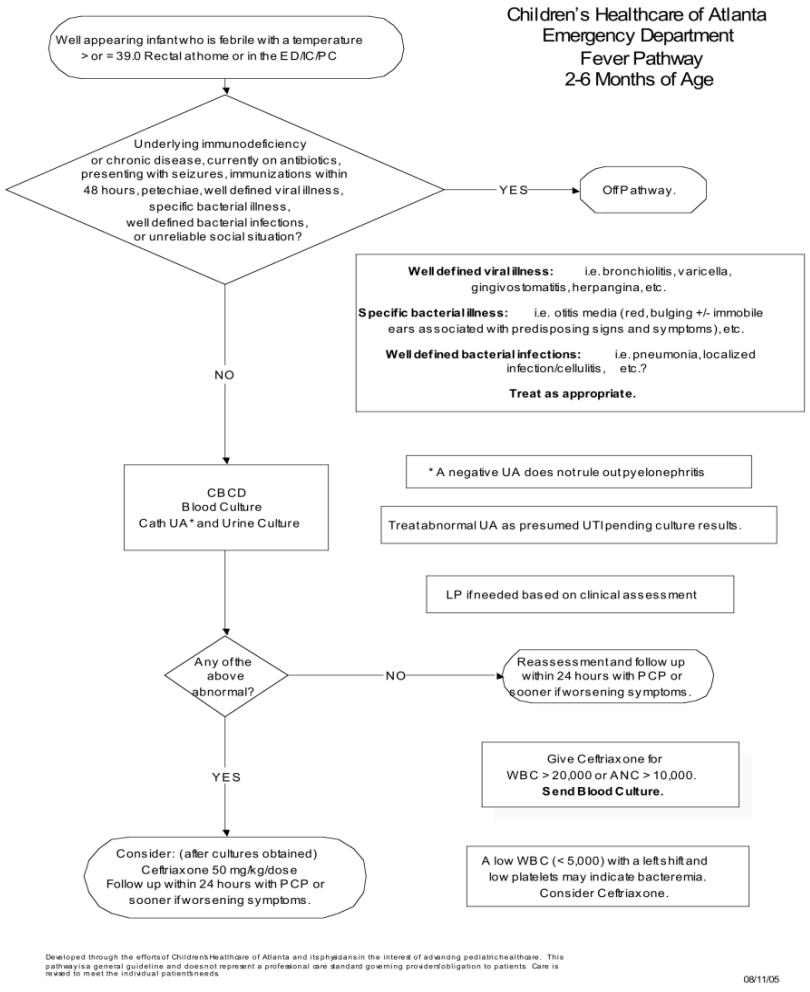
Children's Healthcare of Atlanta Guidelines < 29 days

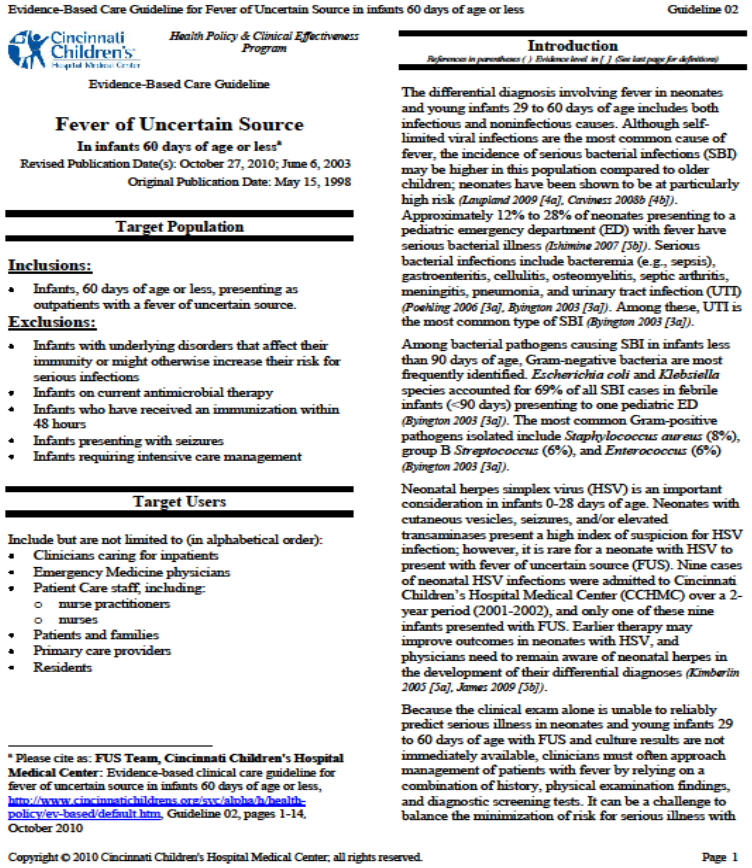


CHOA Guidelines 29 – 60 days



CHOA Guidelines 2-6 months





Evidence-Based Care Guideline for Fever of Uncertain Source in infants 60 days of age or less — Guideline 02

Cincinnati Children's Hospital Medical Center — *Health Policy & Clinical Effectiveness Program*

Evidence-Based Care Guideline

Fever of Uncertain Source

In infants 60 days of age or less*

Revised Publication Date(s): October 27, 2010; June 6, 2003

Original Publication Date: May 15, 1998

Target Population

Inclusions:

- Infants, 60 days of age or less, presenting as outpatients with a fever of uncertain source.

Exclusions:

- Infants with underlying disorders that affect their immunity or might otherwise increase their risk for serious infections
- Infants on current antimicrobial therapy
- Infants who have received an immunization within 48 hours
- Infants presenting with seizures
- Infants requiring intensive care management

Target Users

Include but are not limited to (in alphabetical order):

- Clinicians caring for inpatients
- Emergency Medicine physicians
- Patient Care staff, including:
  - nurse practitioners
  - nurses
- Patients and families
- Primary care providers
- Residents

* Please cite as: **FUS Team, Cincinnati Children's Hospital Medical Center**: Evidence-based clinical care guideline for fever of uncertain source in infants 60 days of age or less, http://www.cincinnatichildrens.org/svc/alpha/h/health-policy/ev-based/default.htm, Guideline 02, pages 1-14, October 2010

Introduction

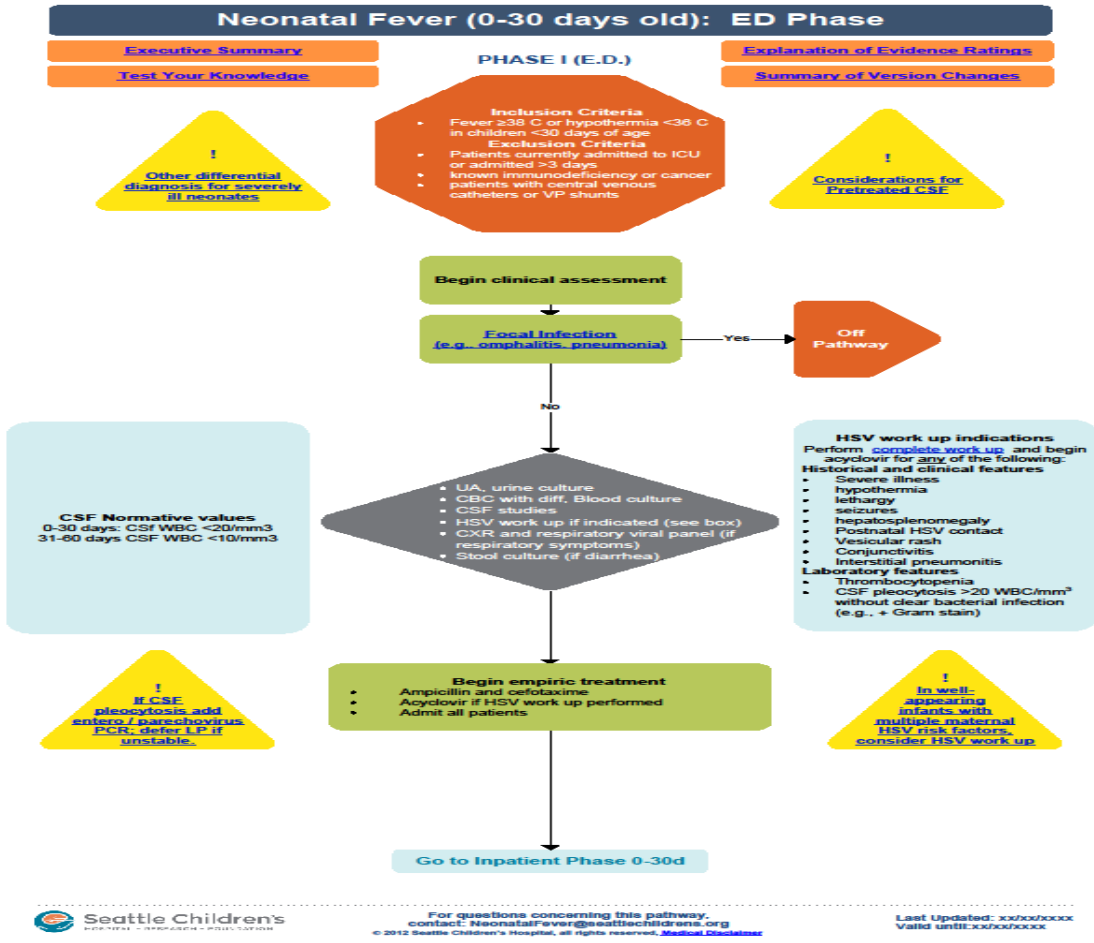
References in parentheses ( ) Evidence level in [ ] (See last page for definitions)

The differential diagnosis involving fever in neonates and young infants 29 to 60 days of age includes both infectious and noninfectious causes. Although self-limited viral infections are the most common cause of fever, the incidence of serious bacterial infections (SBI) may be higher in this population compared to older children; neonates have been shown to be at particularly high risk *(Laupland 2009 [4a], Civinoss 2008b [4b])*. Approximately 12% to 28% of neonates presenting to a pediatric emergency department (ED) with fever have serious bacterial illness *(Ishimine 2007 [5b])*. Serious bacterial infections include bacteremia (e.g., sepsis), gastroenteritis, cellulitis, osteomyelitis, septic arthritis, meningitis, pneumonia, and urinary tract infection (UTI) *(Poehling 2006 [3a], Byington 2003 [3a])*. Among these, UTI is the most common type of SBI *(Byington 2003 [3a])*.

Among bacterial pathogens causing SBI in infants less than 90 days of age, Gram-negative bacteria are most frequently identified. *Escherichia coli* and *Klebsiella* species accounted for 69% of all SBI cases in febrile infants (<90 days) presenting to one pediatric ED *(Byington 2003 [3a])*. The most common Gram-positive pathogens isolated include *Staphylococcus aureus* (8%), group B *Streptococcus* (6%), and *Enterococcus* (6%) *(Byington 2003 [3a])*.

Neonatal herpes simplex virus (HSV) is an important consideration in infants 0-28 days of age. Neonates with cutaneous vesicles, seizures, and/or elevated transaminases present a high index of suspicion for HSV infection; however, it is rare for a neonate with HSV to present with fever of uncertain source (FUS). Nine cases of neonatal HSV infections were admitted to Cincinnati Children's Hospital Medical Center (CCHMC) over a 2-year period (2001-2002), and only one of these nine infants presented with FUS. Earlier therapy may improve outcomes in neonates with HSV, and physicians need to remain aware of neonatal herpes in the development of their differential diagnoses *(Kimberlin 2005 [5a], James 2009 [5b])*.

Because the clinical exam alone is unable to reliably predict serious illness in neonates and young infants 29 to 60 days of age with FUS and culture results are not immediately available, clinicians must often approach management of patients with fever by relying on a combination of history, physical examination findings, and diagnostic screening tests. It can be a challenge to balance the minimization of risk for serious illness with



Evaluation and management of the febrile young infant (7 to 90 days of age).html

Febrile Infant - Clinical Pathway_ Emergency _ The Children's Hospital of Philadelphia.html