Fever in young infants

Rural Rounds

December 7th, 2023

Nothing to declare

Objectives

- Age-based management of young febrile infant
  - < 28 days old
  - 29-60 day old
  - 61-90 day old
- Special considerations:
  - Fever and intercurrent viral illness
  - Reported fever
  - Fever in an ex-prem
  - Post-immunization fever
- Choice of antimicrobials

Definitions

- **Fever** among infants aged ≤90 days is any rectal temperature ≥38.0°C, measured at home or in a clinical setting.
- **Invasive bacterial infections (IBIs)** include bacteremia and bacterial meningitis.
- **Serious bacterial infections (SBIs)** include urinary tract infections (UTIs), bacteremia, and bacterial meningitis.
- **Full Septic Work Up (FSWU)** includes examination of CSF, blood, urine.
- **Partial Septic Work Up (PSWU)** includes examination of blood, urine.

Epidemiology

- Management of young febrile infants is an area of significant practice variation.
- 2% of healthy term patients < 90 days are brought to medical attention for fever.
- 10-13% harbour an SBI.
- IBI incidence is highest in the 1st month of life and decreases with age.

lower threshold for investigations

- underdeveloped immunity
- partial vaccination
- viral illness associated with higher risk of intercurrent bacterial infection
- poor sensitivity of physical examination

need risk stratification tools

Risk stratification Rules

- Old rules of identifying low risk young febrile infants (Boston, Philadelphia, Rochester) relied on CSF, WBC, UA; not biomarkers.

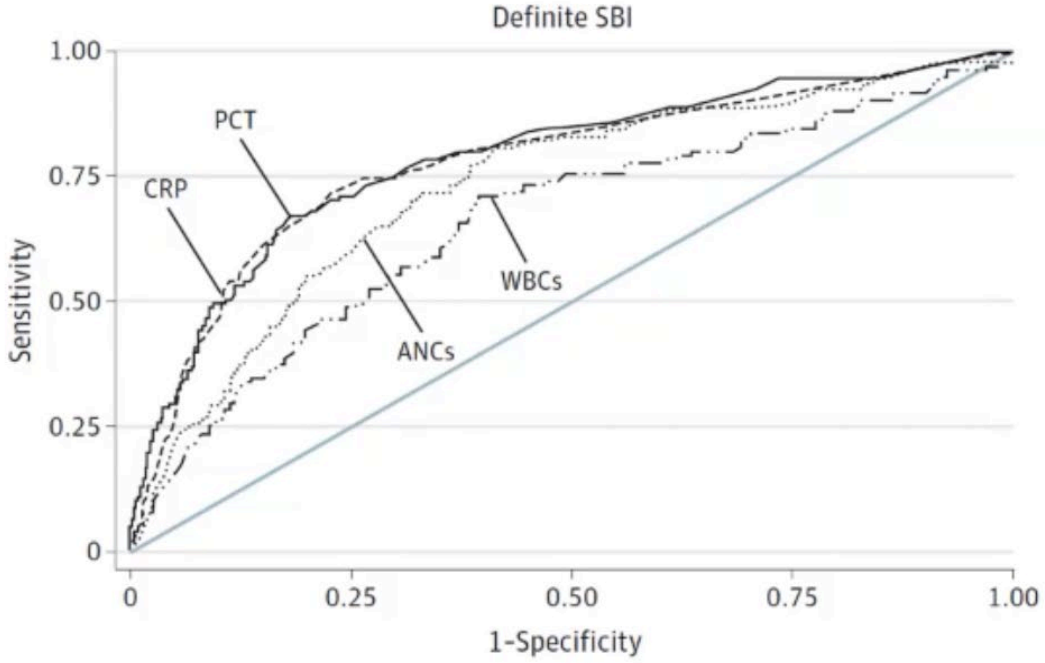
- Bacteriology landscape is different now due to enhanced immunization, better prenatal care, and improved food standards.

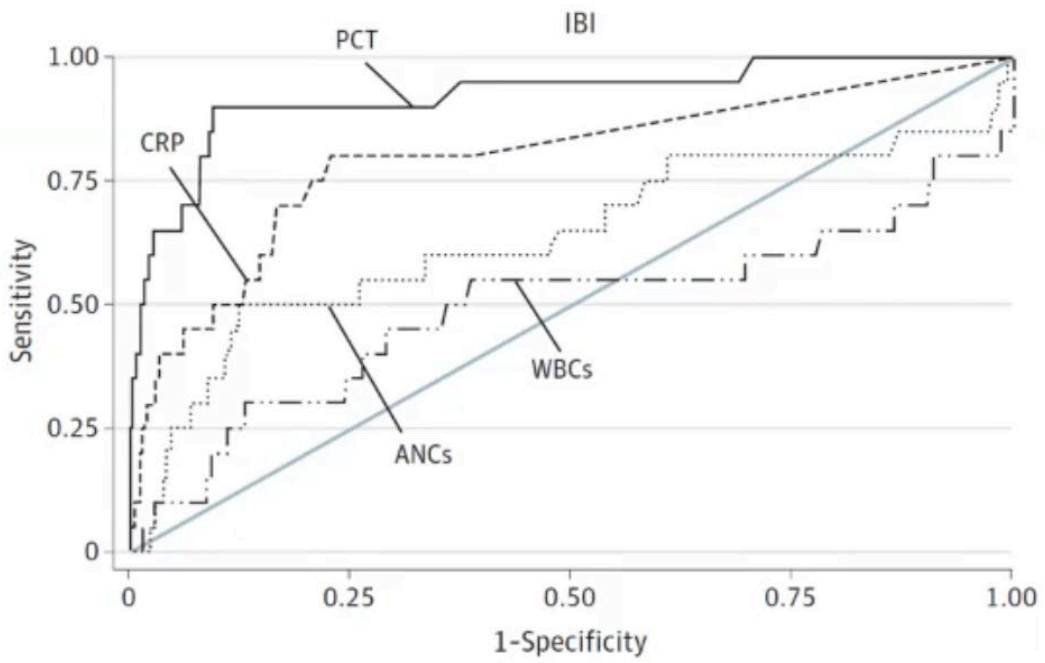
- Pathogenic causes of SBI shifted from Gram-positives to Gram-negatives.

We now have biomarkers!

Advent of Biomarkers

Figure. Area Under the Curve (AUC) for the Receiver Operating Characteristic Curves for Biomarkers to Detect Definite Serious Bacterial Infections (SBIs) and Invasive Bacterial Infections (IBIs)





SBI:

CRP and PCT performed equally but better than ANC and WBC in detection of SBI

IBI:

PCT performed better than CRP, both out-performing ANC and WBC in detection of IBI

Recent Risk Stratification Rules for Young Febrile Infants

Risk Stratification Rule	Year	Patient Age	Gestation Criteria	Low risk markers
Step-by-Step	2016	0-90		ANC < 10,000 CRP < 20 - Procalcitonin < 0.5 No Leukocyturia No CSF required for risk stratification
PECARN	2019	0-60	> 36 weeks at birth	ANC < 4090 Procalcitonin < 1.71 UA < 5 WBC/HPF & NEG L.E. & NEG NITRITES No CSF required for risk stratification
TREKK	2019	0-60	> 37 weeks at birth	CRP and Procalcitonin are superior to WBC and ANC
AAP	2021	8-21 21-28 28-60	> 37 weeks at birth	ANC < 4000 CRP < 20 - Procalcitonin < 0.5 No Leukocyturia No CSF required for risk stratification
CPS (Aronson rule used if PCT unavailable)	2023 (Oct 27)	0-28 29-60 61-90	>37 weeks at birth	Low risk if < or equal to 1 point: 1) Age < 21 days (1 point) 2) Highest temp in the ED: 38.0-38.4 (2 pts); > 38.4 (4 pts) 3) ANC > 5185/uL 4) UA + (leuk est, nitrite, or >5 WBC/hpf) (3 pts)

Latest Fever Concepts

- Risk of IBI declines with age.

Age in days	bacteremia	meningitis
0-28	3%	1%
29-61	1.6%	0.4%
61-90	<1.5%	<0.25%

- Risk of SBI decrease after 1st week of life:
  - So may be able to treat infants 21-28 days like those >28 days

Week	SBI
Week 2	5.3%
Week 3	3.3%
Week 4/5/6	1.6%

- New biomarkers are more sensitive:
  - procalcitonin > 0.5
  - CRP ≥ 20
  - ANC > 4,000
  - rectal temp ≥ 38.5
  - **Total WBC is no longer used an an inflammatory marker**

- CSF is necessary for babies less than 21 days and should be considered for > 21 days up to 60 days.

- CSF not necessary in children > 28 days with UTI and normal biomarkers.

CPS. 2023

Case 1

- A well-looking 17-day old boy
- Axillary temperature of 38.2^{o}C at home
- Rectal temperature 38.0^{o}C in the ER

(a) FSWU, IV Abx, and admit

(b) FSWU, IV Abx and admit if biomarkers elevated

(c) PSWU, IV Abx and admit if biomarkers elevated

(d) UA and Urine Culture only

(e) Diagnose patient with viral infection, reassure and discharge home

Case 2

- A well-appearing 56-day old girl
- Axillary temperature of 38.5°C at home
- In ED, her temperature is 38.7°C rectal.
- PSWU done.

(a) LP, IV Abx, and hospitalization
(b) IV Abx and hospitalization
(c) IM Abx and FU next day
(d) UA only
(e) Reassure and discharge home

- UA (CATH): negative
- cbc:
  - wbc 14.4
  - ANC 7.0
  - Hgb 142
  - PLT 552
- CRP 27

Case 3

- A well-appearing immunized 67-day old girl
- Temperature 38.4^{o}C rectal
- PSWU done

(a) LP, IV Abx, and admit
(b) IV Abx and admit
(c) IV Abx and discharge, FU 24-48 hrs
(d) PO Abx and FU 24-48 hrs
(e) Reassure and discharge home

- UA (CATH):
  - + leuk est
  - - nitrite
  - 5-10 WBC/hpf

- cbc:
  - wbc 13.7
  - ANC 3.6
  - Hgb 112
  - PLT 430

- CRP 14

Age-based Recommendations

- 0-28 days: binary decision – FSWU, admission, and antibiotics

- 29-60 days: less binary -PSWU
  - If abnormal biomarkers: FSWU
  - If biomarkers normal
    - UA NEG: home, close FU
    - UA POS: could omit LP, give IV or PO Abx, close FU

- 61-90 days: not binary
  - At least a UA and Urine C/S required
  - May opt to carry out PSWU
    - If abnormal biomarkers: FSWU
    - If biomarkers normal
      - UA NEG: home, close FU
      - UA POS: could omit LP, give IV or PO Abx, close FU

AAP 2021 & CPS. 2023

Case 4

- A 2-week-old baby
- Axillary temperature of 38.2°C at home
- Rectal temperature of 37.6°C in the ED

(a) FSWU, IV Abx, and admit

(b) PSWU, Rectal Temperature q1h x 4 hours, LP , IV Abx and admit if temperature ≥38.0°C

(c) Rectal Temperature q1h x 4 hours, FSWU, IV Abx and admit if temperature ≥38.0°C

(d) PSWU, IV Abx, and admit if biomarkers elevated

(e) UA and Urine Culture only

Reported Fever

- Reported fever at home does not necessarily carry a lower risk of IBI compared with those who are febrile in the ED.
- Therefore, reported fever from a reliable parent should prompt investigations without delay.
- Axillary, oral, tympanic, temporal, or tactile measurements are inaccurate measurements of core temperature in infants.
- Infants with hypothermia (i.e., temperature <36.0°C) should be managed in the same way as infants with pyrexia.

Case 5

- A well-looking 36-day old boy
- Cough and congestion
- Axillary temperature 38.1^{o}C at home

(a) FSWU, IV Abx, and hospitalization
(b) FSWU, IV Abx + admit if biomarkers elevated
(c) PSWU, IV Abx + admit if biomarkers elevated
(d) UA and Urine Culture only
(e) Diagnose patient with viral illness, reassure, and discharge home

Risk of concurrent SBI's

- Even with confirmed viral infection, there remains a non-negligible risk of bacteremia and meningitis.

- Infants with lab-confirmed viral infections are at lower risk of SBI's.

- Co-infection rate is pathogen-dependent:
  - UTI in febrile RSV+ infants: 13.4%
  - SBI in febrile COVID+ infant in < 90 days: 8% (mostly UTI)
  - SBI rate high in febrile Rhinovirus+ infants

- Thus even in presence of viral symptoms, the initial diagnostic evaluations should follow age-based recommendations.

Case 6

- A 66-day old girl
- Axillary temperature 38.9^{o}C at home
- She was immunized yesterday am.

(a) FSWU, IV Abx, and hospitalization
(b) FSWU, IV Abx, and admit if biomarkers elevated
(c) PSWU, IV Abx, and admit if biomarkers elevated
(d) UA and Urine Culture only
(e) Reassure, and discharge home

Post-immunization fever

- Approximately half experience fever.
- Those with fever within 24 hrs are at low risk for SBI.
- Risk increases when fever persists beyond 24 hrs.
- Biomarkers can be elevated post-immunization and therefore not as helpful.
- Two studies of recently immunized febrile infants found that all SBI's detected were UTI's; not a single case of IBI was found.
- Urine testing is recommended for infants with fever persisting >24 h post-immunization.

Case 7

- A 6 wk-old boy born at 34 wks gestation
- Rectal temperature in the ED of 38.3^{o}C

(a) FSWU, IV Abx, and admit
(b) FSWU, IV Abx and admit if biomarkers elevated
(c) PSWU, IV Abx and admit if biomarkers elevated
(d) UA and Urine Culture only
(e) Diagnose patient with viral illness, reassure, and discharge home

Fever in an ex-prem

- approach adopted by AAP is to correct gestation to 37 weeks

- e.g. a 34 wker at 6 wks chronological age is actually considered a 3 wk old and requires risk factor stratification based on a 21 day old baby with fever

AAP 2021

Case 8

- A 2-week-old with fever and raised inflammatory markers has had a FSWU. What antimicrobial would you start?

(a) Ceftriaxone IM

(b) Cefotaxime/Vancomycin IV

(c) Cefotaxime/Ampicillin/Acyclovir IV

(d) Cefixime PO

(e) Cefotaxime/Vancomycin/Acyclovir IV

Antimicrobial therapy for suspected sepsis

- First 28 days:

  ampicillin: 75 mg/kg/dose IV/IM/IO q6h

  cefotaxime: 50 mg/kg/dose IV/IM/IO q6h

  acyclovir: 20 mg/kg/dose IV/IO q8h

ceftriaxone competes with bilirubin for binding to serum albumin and can increase free bilirubin thus increasing the risk of bilirubin encephalopathy. Therefore, it is contraindicated in neonates.

- Day 29-60:

  cefTRIAXone : 100 mg/kg/dose IV/IM/IO q24h (Maximum: 2000 mg/dose)

  or **cefotaxime:** 75 mg/kg/dose IV/IM/IV q6h (Maximum: 2000 mg/dose)

  vancomycin: 15 mg/kg/dose IV/IO q6h (Maximum: 1500 mg/dose)

  If risk factors for HSV: acyclovir: acyclovir 20 mg/kg/dose IV/IO q8h

If UTI is suspected and the infant is low risk, may treat with PO cefixime 8 mg/kg/dose every 24 h

- Day 61-90:

  cefTRIAXone : 100 mg/kg/dose IV/IM/IO q24h (Maximum: 2000 mg/dose)

  or **cefotaxime:** 75 mg/kg/dose IV/IM/IV q6h (Maximum: 2000 mg/dose)

  vancomycin: 15 mg/kg/dose IV/IO q6h (Maximum: 1500 mg/dose)

If UTI is suspected and the infant is low risk, may treat with PO cefixime 8 mg/kg/dose every 24 h

CPS. 2023

Case 9

- A 16-day-old ex-35 weeker
- rectal temperature of 38.7^{o}C
- Attempts at vascular access and LP fail. How would you manage this child?

(a) Ceftriaxone IM or IO and attempt LP next day

(b) Cefotaxime IM or IO and attempt LP next day

(c) Cefixime PO and attempt LP next day

(d) Keep attempting LP prior to commencing Abx

(e) Keep attempting vascular access then commence Abx

Recent Advances in CSF testing - BioFire

- Rapid Multiplex PCR technology
- High sensitivity & specificity
- Maintains accuracy after Abx institution
- Obviates the need to obtain CSF sample prior to Abx institution
- Limitation
  - E. coli K1 isolate only (85% of cases)
  - Encapsulated *N. meningitidis (majority)*
  - False negatives with HSV if done early
- Both C/S and BioFire done

To take home…

- Clinical assessment and vital signs alone may not be sufficient in risk stratification of young febrile infants for IBI. Adjunctive investigations i.e. biomarkers and cultures are most definitely required.

- The biomarkers that assist in risk stratification include PCT, CRP, ANC, and rectal temperature. Total WBC is not helpful.

- In the 29-60 day old well-looking febrile infant with negative biomarkers, LP may safely be omitted. Children with UTI do not necessarily require an LP.

- Assessment of reported fever at home requires the same evaluation as infants who are febrile in the ED.

- Assess patients presenting with fever or reported fever without delay and consider early septic workup, referral, and antibiotic administration. Aim to provide antibiotics within one hour of presentation. Don't delay antibiotics for IV or LP in the febrile unwell neonate.

- Urine testing is recommended for infants with fever persisting >24 hr post-immunization.

- Premature babies are at higher risk for bacterial infections, especially *E. coli.* Correct the age to 37 weeks when determining risk of SBI in the ex-prem babies.

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Q & A

Original Risk Stratification Rules for Young Febrile Infants

Risk Stratification Rule	Year	Patient Age	Gestation Criteria	Low risk markers
Boston	1992	28-90		WBC < 20,000 UA < 10 WBC/HPF CSF < 10 WBC/mcL CXR normal
Philadelphia	1993	29-56		WBC 5000-15000; Band: total neut < 0.2 UA < 10 WBC/HPF; gm stain NEG CSF < 10 WBC/mcL; gm stain NEG CXR normal
Rochester	1994	0-60	FULLTERM -Normal prenatal and postnatal histories -No postnatal ABx	WBC 5000-15000 Absolute band count < 1500 UA < 10 WBC/HPF Stool < 10 WBC/HPF No CSF required for risk stratification

Recent Advances in CSF testing

- **BioFire** MeningoEncephalitis Panel
  - Rapid multiplex PCR technology
  - Tests for 14 pathogens including common bacterial pathogens
  - Requires 0.5 ml CSF
  - Takes 60-90 minutes
  - Sensitivity 94.2% & Specificity 99.8% (?better than C/S)

- Advantages:
  - Maintains accuracy after antibiotic institution
  - Shorter time to diagnosis
  - Reduction in antibiotic/antiviral duration
  - Shorter length of stay

- Limitations:
  - Only detects *E. coli* K1 isolate (85% of cases)
  - Only encapsulated *N. meningitidis* detected (majority of cases)
  - False negatives reported with HSV if sample sent early in disease course

- Both C/S and BioFire panel performed for now

BACTERIA:

- *Escherichia coli* K1
- *Haemophilus influenzae*
- *Listeria monocytogenes*
- *Neisseria meningitidis*
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae*

VIRUSES:

- Cytomegalovirus (CMV)
- Enterovirus (EV)
- Herpes simplex virus 1 (HSV-1)
- Herpes simplex virus 2 (HSV-2)
- Human herpesvirus 6 (HHV-6)
- Human parechovirus (HPeV)
- Varicella zoster virus (VZV)

YEAST:

- *Cryptococcus neoformans/gattii*

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