Season 1, Episode #01

Well-appearing Febrile Infant < 60-days of age

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Background

Fever in young infants < 60 days is a common presentation to pediatric emergency departments. The lack of consensus guidelines has led to variability in clinical practice, especially in infants greater than 1-month-old. Fever is often the only initial sign of a severe illness, but the overwhelming majority of well-appearing febrile infants have self-limited viral infections. Due to the small but significant risk of severe morbidity and mortality, these vulnerable patients are often subjected to routine invasive testing, empiric antibiotics and admission. Clinicians are most familiar with the Boston, Milwaukee, Philadelphia, and Rochester criteria that were designed as to reduce over investigation and healthcare utilization in these infants in the 1980s-1990s. Unfortunately, these clinical decision-making tools do not include many newer labs including viral testing and inflammatory markers like procalcitonin & C-reactive protein that are now available in emergency departments. There have been two recent publications including the Step-by-step protocol and the PECARN clinical prediction rule for febrile infants that include inflammatory markers in their decision-making algorithm that may allow clinicians to more effectively spare low-risk infants invasive testing, antibiotics and admission without missing additional cases of serious bacterial infection.

How prevalent are bacterial infections in febrile infants < 60 days old?

- 8-10% will be diagnosed with a serious bacterial infection (UTI, bacteremia, meningitis).
- UTI is by far the most common site of bacterial infection.
- Invasive bacterial infections (bacteremia and meningitis) are uncommon and present in < 2% of cases.

What bacterial pathogens are most common?

- Previously, the majority of bacterial infections were due to Streptococcus agalactiae (group B strep), Streptococcus pneumoniae, Haemophilus influenzae and Listeria monocytogenes was of relatively greater concern.
- Now after wide spread S. pneumoniae, H. influenzae vaccination and maternal GBS screening, E. coli and other Gram-negative bacteria account for the majority of infections.
- Listeria is now very uncommon due to improved food safety.

Notable viral infections

1) Herpes simplex virus (HSV)
    a) Uncommon viral infection with a high morbidity and mortality if untreated.
    b) Vertically transmitted by maternal shedding at delivery
    c) Most commonly affects neonates in the first month of life; rare after 6-8 weeks of age.
    d) Has 3 distinct presentations:
        i) Skin, eye, mouth (SEM)
        ii) Disseminated disease
        iii) Meningoencephalitis
    e) Risk factors: maternal primary HSV infection or active lesions at time of delivery
    f) Clinical signs: vesicular rash, seizures, conjunctivitis, transaminitis, CSF pleocytosis
    g) Management: empiric acyclovir while awaiting molecular testing of mucous membranes and CSF
2) Enterovirus
    a) Common infection in the summer and fall.
    a) Enterovirus-positive infants have a low rate of concomitant bacterial infections, management of enterovirus-positive infants often consists of supportive care alone.
    b) Testing for enterovirus may safely decrease hospital length of stay and antibiotic exposure for otherwise well-appearing febrile infants
2) Respiratory syncytial virus (RSV)
    a) Most common cause of viral bronchiolitis
    b) Well-appearing febrile RSV-positive infants are at low risk for bacterial meningitis and bacteremia, but still have a notable risk for bacterial UTI.
3) Influenza A & B
    a) Common cause of respiratory infections during winter
    b) The risk of bacterial infection among infants with influenza is also low but this has not been as closely studied as RSV.
4) Rhinovirus
    a) Most common cause of viral respiratory illnesses year-round
    b) Known to have prolonged shedding period after infection for weeks to months.
    c) Positive viral testing for rhinovirus in an otherwise well-appearing without evidence of infection is not reassuring as this test is likely a false positive.

Risk-stratifying Tools:

	Boston	Milwaukee	Philadelphia	Rochester
Age range	28–89 days	28–56 days	29–60 days	≤60 days
History	No immunizations or antimicrobials in prior 48 h	Not defined	Not defined	Term infant; no prior antibiotics; no underlying disease; no hospitalization longer than mother
Physical exam	Well appearing; no signs of focal infection	Well appearing; no signs of focal infection	Well appearing; no signs of focal infection	Well appearing; no signs of focal infection
Laboratory parameters	CSF < 10 WBC/mm^3 WBC < 20,000 mm^3 UA < 10 WBC/hpf CXR without infiltrate (if obtained)	CSF < 10/mm^3 WBC < 15,000/mm^3 UA < 5–10 WBC/hpf; UA no bacteria, negative leukocyte esterase, negative nitrites CXR without infiltrate	CSF < 8 WBC/mm^3 WBC < 15,000/mm^3 UA < 10 WBC/hpf CXR without infiltrate (if obtained)	WBC > 5000 and < 15,000/mm^3 ABC < 1500/mm^3 UA ≤ 10 WBC/hpf CXR without infiltrate (if obtained) Stool: WBC ≤ 5/hpf smear (if indicated)
Management strategies for high risk	Hospitalize, empiric antibiotics	Not defined	Hospitalize, empiric antibiotics	Hospitalize, empiric antibiotics
Management strategy for low risk	Home/outpatient ok Empiric antibiotics, outpatient follow up required	Home/outpatient ok i.m. ceftriaxone 50 mg/kg followed by outpatient follow up within 24 h Must have reliable caretaker	Home/outpatient ok No antibiotics, but outpatient follow up is required	Home/outpatient ok No antibiotics, but outpatient follow up is required

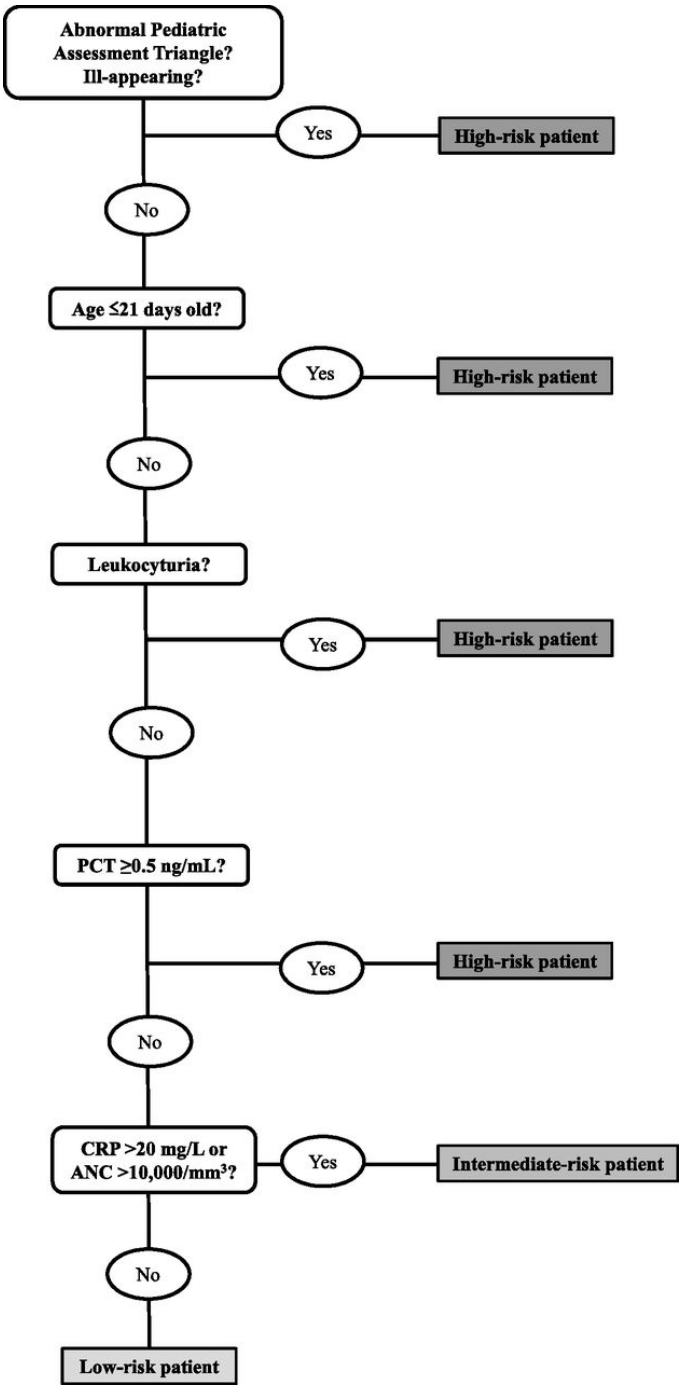
CXR chest X–ray, *UA* urinalysis, *CSF* cerebrospinal fluid, *WBC* white blood cells, *ABC* absolute band count, *hpf* high power field, *i.m.* intramuscular

Critique of the single-center criteria (Boston, Milwaukee, Philadelphia, Rochester): They do not include procalcitonin that is more sensitive for bacterial infection than WBC or absolute band count. Procalcitonin is included in both the Step-by-step and PECARN rules that follow.

The **Step-by-step protocol** was validated in over 2000 patients and guides the provider through a stepwise approach evaluating young febrile infants. Goal is to identify which patients are low risk and may be spared lumbar puncture and empiric antibiotics. If the patient is determined to be high risk then they likely need a full work up (blood, urine, CSF culture +/- viral testing) and empiric antibiotics.

- This first step is to carefully exam the infant and ensure they are well-appearing. If this is not the case then this protocol does not apply.
- Infants less than 21-days-old are at such high risk for bacterial infections that they were not included in this protocol.
- The first lab test recommended is a urinalysis to evaluate for WBC in the urine.
- If serum procalcitonin is < 0.5 ng/mL then the patient can move on to the final step.
- Finally, if the CRP is < 20 mg/L (2 mg/dL) or the absolute neutrophil count (ANC) < 10,000 the infant is low risk according to this protocol.

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



How did this protocol compare to the Rochester criteria?

TABLE 4 Sensitivity, Specificity, PPVs, NPVs and Positive and Negative LR, with 95% CI, of Each Approach for Identifying IBIs

	Sensitivity, %	Specificity, %	PPV	NPV	Positive LR	Negative LR
Rochester criteria	81.6 (72.2–88.4)	44.5 (42.4–46.6)	5.7 (4.6–7.2)	98.3 (97.3–99.0)	1.47 (1.32–1.64)	0.41 (0.26–0.65)
Lab-score	59.8 (49.3–69.4)	84.0 (82.4–85.5)	13.4 (10.4–17.2)	98.1 (97.3–98.6)	3.74 (3.07–4.56)	0.48 (0.37–0.62)
Step by Step	92.0 (84.3–96.0)	46.9 (44.8–49.0)	6.7 (5.4–8.3)	99.3% (98.5–99.7)	1.73 (1.61–1.85)	0.17 (0.08–0.35)

Step-by-step out-performed the Rochester criteria and Lab-score criteria (not discussed).

- **Negative predictive value 99.3% (Rochester criteria 98.3%)**

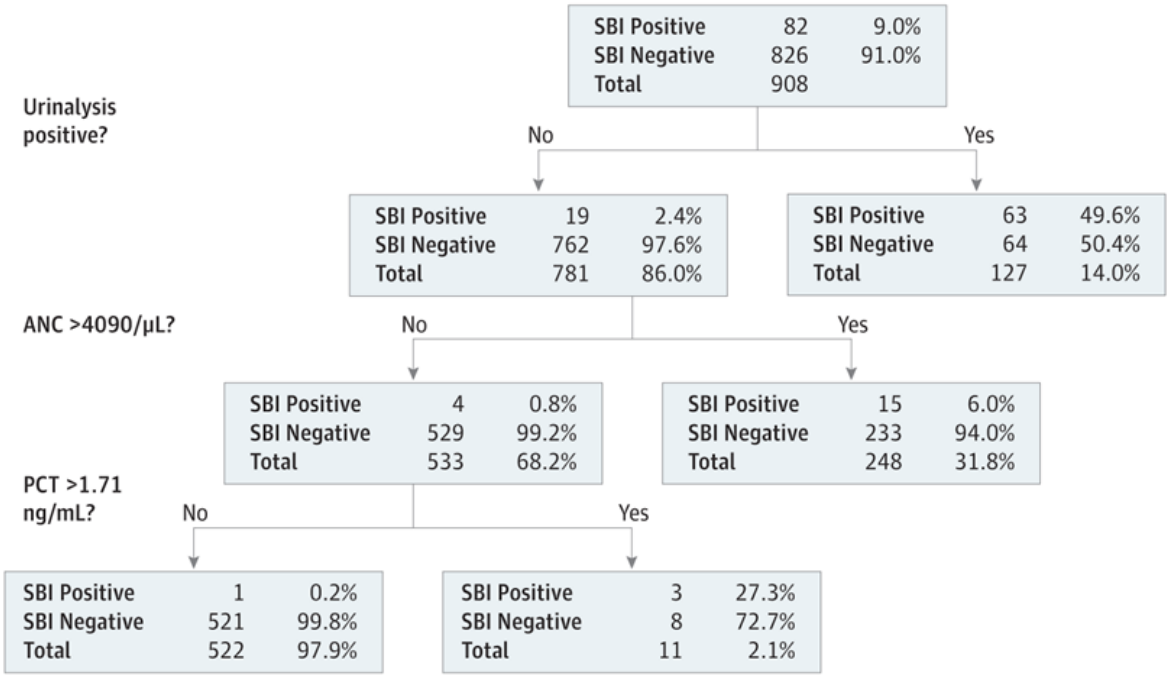
Limitations of Step-by-step:

- There were 7 cases of invasive bacterial infections missed (bacteremia & meningitis)
- 3/7 patients had a history of fever for < 1 hour or fever was discovered in the ED.
- Protocols that include inflammatory markers (procalcitonin, CRP, WBC) are likely not reliable in patients with a very short history of fever.

JAMA Pediatrics | Original Investigation

A Clinical Prediction Rule to Identify Febrile Infants 60 Days and Younger at Low Risk for Serious Bacterial Infections

PECARN prospectively studies about 900 well appearing febrile infants less than 60 days old. Their protocol included urinalysis, absolute neutrophil count and procalcitonin.



Well-appearing infants who had a negative urinalysis, ANC < 4090 and procalcitonin < 1.71 ng/mL had their risk for serious bacterial infection (urinalysis, bacteremia and meningitis) dropped to a minimal 0.2%.

PECARN offered a simplified criteria including negative urinalysis, ANC < 4000 and procalcitonin < 0.5 and this did not worsen the negative predictive value of the clinical decision rule.

There were 3 missed serious bacterial infections (1 positive blood culture and 2 positive urine cultures)

Table 3. Misclassified Patients With SBIs[a]

Age, d	Qualifying Temperature, °C	YOS	Clinician Suspicion, %	Disposition of Infant After ED Visit	Urinalysis	WBC, /µL	ANC, /µL	Bands, %	PCT, ng/mL	CSF	SBI
30	38.1	6	6-10	Admitted	Negative	6700	2700	0 (B:N 0)	0.14	Negative	*Enterobacter cloacae* bacteremia
55	38.4	8	1-5	Discharged	Negative	3800	2200	3 (B:N 0.05)	0.20	Negative	*Escherichia coli* UTI
36	38.5	6	1-5	Admitted	Negative	2300	900	12 (B:N 0.3)	0.16	Negative	*Pseudomonas aeruginosa* UTI

The patient with enterobacter bacteremia had a repeat blood culture obtained prior to starting antibiotics that was negative (possible contaminant). The two patients with negative urinalysis but positive urine cultures may have been due to asymptomatic bacteriuria.

Limitations for the PECARN clinical prediction rule:

- Not appropriate for use in patients less than 1-month-old

Take home points

1. Young febrile infants are at high risk for serious bacterial infections.

2. Well-appearing infants older than 1-month may be risk stratified after a careful history, exam and laboratory assessment.

3. The well-accepted Boston, Milwaukee, Philadelphia, and Rochester criteria may be displaced by Step-by-step and PECARN clinical prediction rule that use procalcitonin and CRP that are now available in some emergency departments.

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