Fever in Well-Appearing Infants 3-60 Days Old

Scope and Definitions:
This guideline applies to previously healthy, term (≥37 weeks), well-appearing infants aged 3–60 days presenting with fever ≥38.0°C (100.4°F), without an obvious source of infection. It does not apply to ill-appearing infants, preterm infants, or those with significant comorbidities, who require immediate full sepsis evaluation and empiric treatment regardless of age.

For infants <3 days old, please refer to NICU Early onset sepsis/Late onset sepsis or NEC guidelines.

Epidemiology and Risk:
- More than 2% of all US full-term infants are evaluated for fever in the first months of life.
- Approximately 8–13% of febrile young infants have a bacterial infection, predominantly urinary tract infections (UTIs).
- Approximately 1–4% of febrile infants ≤28 days old harbor invasive bacterial infections (bacteremia and/or bacterial meningitis).
- Infants ≤21 days old carry the highest risk of serious bacterial infection (SBI).
- Most febrile young infants with invasive bacterial infections are well-appearing and cannot be reliably identified by history and physical examination alone.

Common Pathogens:
- Group B Streptococcus (GBS): Most common Gram-positive pathogen; responsible for >20% of bacteremia after the first week of life and the most common cause of bacterial meningitis.
- Escherichia coli: Most common overall pathogen; accounts for 70–90% of UTIs, 30–60% of bacteremia, and 15–30% of bacterial meningitis.
- Other: Listeria monocytogenes (rare), Enterococcus, Staphylococcus aureus, Streptococcus pneumoniae, Klebsiella species.
- Herpes simplex virus (HSV): Population-based rates of 2–5 per 100,000 neonates; 15% present with fever as the only symptom.

Exclusion Criteria:
- <37 weeks gestation at birth
- Infants <2 weeks old with perinatal course complicated by fever/infection/antimicrobial use
- High suspicion for HSV infection (see specific HSV page 5)
- Focal bacterial findings
- Documented or suspected immune compromise
- Complicated neonatal course (surgery or infection)
- Congenital anomalies
- Medically fragile/technology dependent infants

Fever After Immunizations:
Fever is a common and expected adverse event following routine immunizations. In infants younger than 60 days of age, fever occurring within 24 to 48 hours after vaccination may be vaccine-related; however, a serious bacterial infection cannot be excluded based on recent immunization alone. Clinical evaluation should consider the infant's age, appearance, timing of vaccination, temperature, and other risk factors. Recent immunization does not eliminate the need for medical assessment of a febrile infant when clinically indicated.

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ANMC Fever in Well Appearing Infant 3-21 Days Guideline

Temperature **≥ 100.4°F (38°C)**
from any source, including home thermometer
OR
Temperature **≤ 96.8°F (36°C)** that does not quickly resolve
with environmental measures

Laboratory Work Up

Blood	Urine	CSF*	HSV Eval – if increased risk¶	Other
• Blood Culture • CBC • CRP • ALT • AST	• Urine culture (cath specimen) • Urinalysis	• CSF culture • Gram stain • Cell count • Glucose • Protein • Multiplex PCR	• Serum HSV PCR • CSF HSV PCR (included in multiplex PCR) • Surface Swab HSV PCR (conjunctivae, nasopharynx, mouth, anus) • CMP	• RSV/Flu/Covid swab if clinically appropriate • Consider stool studies if diarrhea • Consider CXR if indicated

*If unable to obtain LP: re-attempt in 12-24h, treat with meningitic dosing/antibiotics while awaiting re-attempt.
¶ Maternal history of genital HSV lesions or fevers from 48 hours before to 48 hours after delivery. Infants with vesicles, seizures, hypothermia, mucous membrane ulcers, CSF pleocytosis in the absence of a positive Gram stain result, leukopenia, thrombocytopenia, or elevated alanine aminotransferase levels.

Laboratory Interpretation

Urine: Negative UA does not rule out UTI. Diagnose UTI with urine culture >10,000 cfu/mL of single uropathogen
CSF: Normal CSF WBC <20, Absence of neutrophils (polys) makes bacterial meningitis unlikely; CSF neutrophils (polys) >75% increases likelihood of bacterial meningitis . If LP difficult to interpret/bloody: Do not use correction formulas for WBC.

Suspicion for meningitis?

No

Empiric Antibiotics – No Suspicion for Meningitis

Goal: administer within 60 minutes of presentation

Ampicillin
50mg/kg/dose IV q8hrs

AND

Gentamicin	
≤7 days	4mg/kg/dose IV q24hrs
8-28 days	5mg/kg/dose IV q24hrs

ADD IF APPROPRIATE

Acyclovir
20mg/kg/dose IV q8hrs

Yes

Empiric Antibiotics – Suspicion for Meningitis

Goal: administer within 60 minutes of presentation
Consider ID Consultation

Ampicillin – Meningitis Dosing	
≤7days	100mg/kg/dose IV q8hrs
8-28 days	75mg/kg/dose IV q6hrs

AND

Cefepime
50mg/kg/dose IV q12hrs

ADD IF APPROPRIATE

Acyclovir
20mg/kg/dose IV q8hrs

Admit to the hospital

Pathogen or source identified at 24-36 hours?

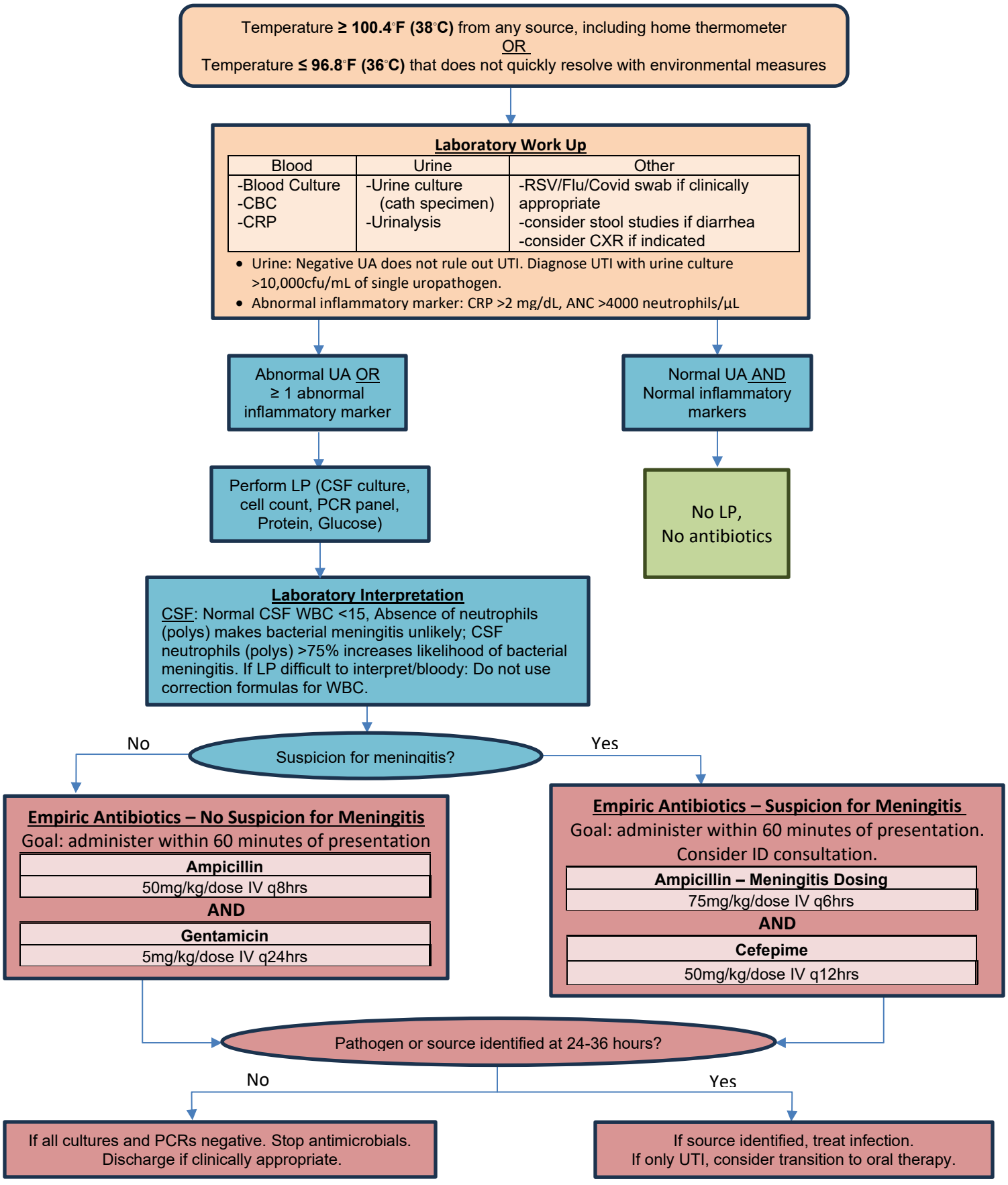
No

If all cultures and PCRs negative. Stop antimicrobials.
Discharge if clinically appropriate.

Yes

If source identified, treat infection.
If only UTI, consider transition to oral therapy.

ANMC Fever in Well Appearing Infant 22-28 Days Guideline



ANMC Fever in Well Appearing Infant 29-60 Days Guideline

Temperature **≥ 100.4°F (38°C)** from any source, including home thermometer
OR
Temperature **≤ 96.8°F (36°C)** that does not quickly resolve with environmental measures

Clinical suspicion of bronchiolitis?

Yes

Laboratory Work Up

Urine	Other
-Urine culture (cath specimen) -Urinalysis	-RSV/Flu/Covid PCR (+/- Pertussis if circulating) -consider blood culture and CBC -consider CXR if indicated

No

Laboratory Work Up

Blood	Urine	Other
-Blood Culture -CBC -CRP	-Urine culture (cath specimen) -Urinalysis	-consider stool studies if diarrhea -consider CXR if indicated

- Urine: Negative UA does not rule out UTI. Diagnose UTI with urine culture >10,000cfu/mL of single uropathogen.
- Abnormal inflammatory marker: CRP >2 mg/dL, ANC >4000 neutrophils/µL

Laboratory Interpretation

CSF: Normal CSF WBC <9, Absence of neutrophils (polys) makes bacterial meningitis unlikely; CSF neutrophils (polys) >75% increases likelihood of bacterial meningitis. If LP difficult to interpret/bloody: Do not use correction formulas for WBC.

Normal UA, Abnormal inflammatory markers

Perform LP (CSF culture, cell count, PCR panel, Protein, Glucose)

Abnormal UA, Abnormal inflammatory markers

LP is a "weak recommendation" if any inflammatory marker is abnormal

Abnormal UA, Normal inflammatory markers

No LP

Cephalexin
17mg/kg/dose PO TID x7-10 days

Normal UA AND Normal inflammatory markers

No LP, No antibiotics

No — Suspicion for meningitis? — Yes

Empiric Antibiotics – No Suspicion for Meningitis

Goal: administer within 60 minutes of presentation

Ceftriaxone
50mg/kg/dose IV q24hrs

Empiric Antibiotics – Suspicion for Meningitis

Goal: administer within 60 minutes of presentation.
Consider ID Consultation.

Ceftriaxone – Meningitis Dosing
50mg/kg/dose IV q12hrs

AND

Vancomycin
15mg/kg/dose IV q6-8hrs (depending on post-menstrual age), Pharmacy to dose

Pathogen or source identified at 24-36 hours?

No

If all cultures and PCRs negative. Stop antimicrobials. Discharge if clinically appropriate.

Yes

If source identified, treat infection.
If only UTI, consider transition to oral therapy.

ANMC Fever in Well Appearing Infant HSV

Age	HSV Risk Factors	HSV Studies	HSV Treatment
<6 weeks old	• Toxic or critically Ill appearance (not included in this guideline) • Prematurity: <37 weeks EGA - off guideline • Known or suspected HSV exposure • Vesicles or mucous membrane ulcers • Seizure • Persistent hypothermia: <36°C • Thrombocytopenia: <150/mm^3 • Elevated alanine aminotransferase (if obtained) >1.5x ULN	• HSV blood PCR • HSV CSF PCR • HSV cutaneous lesions PCR – unroof one or more vesicular lesions and obtain vesicular fluid on an appropriate swab • HSV surface swabs PCR – swab conjunctivae, nasopharynx, mouth, anus; may be obtained as a single swab starting with the conjunctivae and moving caudally • Liver function tests (AST, ALT)	**Acyclovir 20mg/kg/dose IV q8h**
>6 weeks old	• Vesicles or mucous membrane ulcers • Risk of Neonatal HSV is highest in the first four weeks, and is rare at and beyond 6 weeks of life.	• HSV cutaneous lesions PCR – unroof one or more vesicular lesions and obtain vesicular fluid on an appropriate swab	

References

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