KEY ADVANCES
CLINICAL POLICY ALERT

Febrile Infants


Changing bacteriology, advances in technology, opportunities for improvement in care, and cost concerns have prompted the American Academy of Pediatrics to publish a clinical practice guideline for the well-appearing, full-term, previously healthy, febrile ($\geq 38^\circ C$) infant. Evaluation is based on age, history, physical examination, and inflammatory markers (IMs) (if obtained): elevated temperature $>38.5^\circ C$ (older age groups); procalcitonin (PCT) $>0.5$ mg/mL; C-reactive protein (CRP) $>20$ mg/L; absolute neutrophil count (ANC) $>4000$ per mm$^3$; or ANC $>5200$ per mm$^3$ when PCT is unavailable.

All infants under 28 days
- Obtain urinalysis, urine culture, and blood culture
  Grade: A; Strong Recommendation

For infants 8-21 days (no change from standard practice)
- Perform lumbar puncture (LP) on all
  Grade: A; Strong Recommendation
- Evaluate for risk of herpes simplex virus (HSV)
  Grade: A; Strong Recommendation
- Administer appropriate parenteral antimicrobials
  Grade: A; Strong Recommendation
- Admit
  Grade: A; Strong Recommendation

For infants 22-28 days (may treat as above category)
- Obtain IMs
  Grade: B; Moderate Recommendation
- Any abnormal IM prompts LP  
  \textit{Grade: C; Moderate Recommendation}
- Any positive infectious source requires admission  
  \textit{Grade: A; Strong Recommendation}
- If LP is not successful or not attempted, admit. If IM is abnormal, give antibiotics; if negative, may hold antibiotics  
  \textit{Grade: B; Weak Recommendation}
- In rare cases, if all workup is negative and caregivers are amenable and able: there is an option to give intravenous antimicrobials, send home with cultures pending, and follow-up next day  
  \textit{Grade: B; Moderate Recommendation}

\textbf{Infants 29-60 days} (selective workup and treatment)
- Obtain urinalysis, urine culture, and blood culture  
  \textit{Grade: B; Moderate Recommendation}
- IMs guide further workup  
  \textit{Grade: B; Moderate Recommendation}
- Depending on laboratory results and situational factors, options vary in terms of LP, antimicrobials, and disposition

\textbf{Algorithm for 8- to 21-day-old infants}
\begin{enumerate}
\item Laboratory values of inflammation are considered elevated at the following levels: (1) PCT >0.5 ng/mL, (2) CRP >20 mg/L, and (3) ANC >4000 per mm$^3$, >5200 per mm$^3$. Although we recommend all infants in this age group have a complete sepsis workup, receive parenteral antimicrobial agents, and be monitored in a hospital, knowing IM results can potentially guide ongoing clinical decisions.
\item Send cerebrospinal fluid (CSF) for cell count, Gram stain, glucose, protein, bacterial culture, and enterovirus polymerase chain reaction (PCR) (if available) if pleocytosis is present and during periods of increased local enterovirus prevalence.
\item HSV should be considered if the mother has genital HSV lesions or fever from 48 hours before to 48 hours after delivery and in 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. Recommended HSV studies are CSF PCR; HSV surface swabs of the mouth, nasopharynx, conjunctivae, and anus for an HSV culture (if available) or PCR assay; alanine aminotransferase; and blood PCR.
\end{enumerate}
Algorithm for 22- to 28-day-old infants

(1) If available, PCT should be obtained along with ANC. If PCT is unavailable, ANC and CRP should be obtained, and a temperature >38.5°C is considered abnormal. PCT is considered abnormal at >0.5 mg/mL; CRP is considered abnormal at >20 mg/L; ANC is considered abnormal at >4000 per mm$^3$ when used in conjunction with PCT or >5200 per mm$^3$ when PCT is unavailable.

(2) LP is recommended before administration of antimicrobial agents because interpreting CSF after the administration of antimicrobial agents is difficult. However, the risk of meningitis in 22- to 28-day-old infants was lower than that in infants <22 days old in several studies. Therefore, in some circumstances, clinicians may elect to defer an LP and initiate antimicrobial agents, recognizing the potential risk of partially treated meningitis. Send CSF for cell count, Gram stain, glucose, protein, bacterial culture, and enterovirus PCR (if available) if pleocytosis is present and during periods of increased enterovirus prevalence. HSV can occur in this age group.

(3) HSV should be considered in 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. Recommended HSV studies: CSF PCR; HSV surface swabs of mouth, nasopharynx, conjunctivae, and anus for HSV culture (if available) or PCR assay; alanine aminotransferase; and blood PCR.
(4) Infant may be managed at home if parent and clinician agree that the following are present: reliable phone and transportation, parent willingness to observe and communicate changes in condition, and agreement to the infant being reevaluated in 24 hours. If CSF is positive for enterovirus, clinicians may withhold or discontinue antimicrobial agents and discharge at 24 hours, provided they meet other criteria for observation at home.

Algorithm for 29- to 60-day-old infants

(1) If available, PCT should be obtained along with ANC. If PCT is unavailable, ANC and CRP should be obtained, and a temperature >38.5°C is considered abnormal. PCT is considered abnormal at >0.5 mg/mL; CRP is considered abnormal at >20 mg/L; ANC is considered abnormal at >4000 per mm$^3$ when used in conjunction with PCT or >5200 per mm$^3$ when PCT is unavailable.
Send CSF for cell count, Gram stain, glucose, protein, bacterial culture, and enterovirus PCR (if available) if CSF pleocytosis is present and during periods of increased local enterovirus prevalence. Although uncommon in this age group, HSV should be considered when there is a maternal history of genital HSV lesions and in 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. Recommended HSV studies are CSF PCR; HSV surface swabs of mouth, nasopharynx, conjunctivae, and anus for HSV culture (if available) or PCR assay; alanine aminotransferase; and blood PCR.

If CSF is unobtainable or uninterpretable, there are insufficient data to make a specific recommendation. Options include the following: observe without treatment for a period of time and, depending on infant clinical condition, repeat LP and/or laboratory markers; begin empirical antimicrobial agents and reassess in 24 hours on the basis of infant response and results of blood culture; if CSF is bloody or antimicrobial agents have been started previously, analysis by multiplex PCR can add additional information; consult with a local pediatric infectious disease specialist.

Most 29- to 60-day-old infants with negative IMs and urinalysis results may be observed at home. However, hospital observation is an option for infants when there are barriers to follow-up.

### Febrile Infants Recommendation Algorithm

**29 to 60 days old**
Well appearing, no evident source of infection, and temperature ≥ 38.0 °C

**Obtain urinalysis, blood culture, and IMs (1)**

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**Increased IMs?**

- **Yes**
  - 1. Send bladder catheterization urine culture if positive urinalysis.
  - 2. May perform LP.
  - 3. If CSF result is positive: (2) a. Administer oral antimicrobial(s).
  - b. Observe closely in hospital.
  - 4. If CSF result is negative and either urinalysis negative or positive:
    - a. May administer parenteral or oral antimicrobial(s).
    - b. May observe closely in hospital or at home. (4)
  - 5. If CSF not available or uninterpretable: (3) a. Administer parenteral antimicrobial(s).
    - b. May observe closely in hospital or at home. (4)

- **No** positive urinalysis result?
  - **Yes**
    - 1. Send bladder catheterization urine culture.
    - 2. Need not perform LP.
    - 3. Administer oral antimicrobial(s).
    - 4. May observe closely at home. (4)
    - 5. Follow-up in 12 to 24 hours.
  - **No**
    - 1. Need not perform LP.
    - 2. Need not administer antimicrobial(s).
    - 3. Observe closely at home. (4)
    - 4. Follow-up within 24-36 hours.

**Pathogen or source identified at 24 to 36 hours?**

- **Yes**
  - 1. Discontinue antimicrobial(s) if administered.
  - 2. Discharge hospitalized infants.
  - 3. Manage for duration of illness.
- **No**
  - 1. Complete treatment with oral antimicrobial(s).
  - 2. Discharge hospitalized infants.
  - 3. Manage for duration of illness.
Editor’s notes:

This new policy guideline increases the specificity of detecting bacteremia and/or meningitis while maintaining acceptable sensitivity. Clinicians will differ in thresholds for testing and intervention.

A full sepsis workup, LP, antimicrobials, and admission are required in infants 8-21 days old. A tailored approach begins with the 22- to 28-day-old group and includes the incorporation of IMs. There are more options for investigation, treatment, and disposition in the 29- to 60-day-old group.

These guidelines should not deter the thoughtful physician from a more conservative approach as needed; as an option, they allow for a full sepsis workup, LP, antibiotics, and admission for all age categories, 8-60 days.

The spirit of this policy is to empower the physician to choose the best plan of care for the individual infant—consistent with available evidence—in the context of resources, expectations, risk tolerance, and harm reduction.

Resources for additional learning:


Pediatric EM Morsels: Febrile Infants 29 to 60 Days: https://pedemmorsels.com/pediatric-fever-update-febrile-infants-29-to-60-day-old/

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