

KEY ADVANCES CLINICAL POLICY ALERT

Febrile Infants

June 2023

Pantell RH, Roberts KB, Adams WG, Dreyer BP, Kuppermann N, O'Leary ST, Okechukwu K, Woods CR Jr; Subcommittee on Febrile Infants. Clinical practice guideline: evaluation and management of well-appearing febrile infants 8 to 60 days old. Pediatrics 2021;148(2):e2021052228. doi:10.1542/peds.2021-052228

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 ($\geq 38^{\circ}\text{C}$) infant. Evaluation is based on age, history, physical examination, and inflammatory markers (IMs) (if obtained): elevated temperature $>38.5^{\circ}\text{C}$ (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

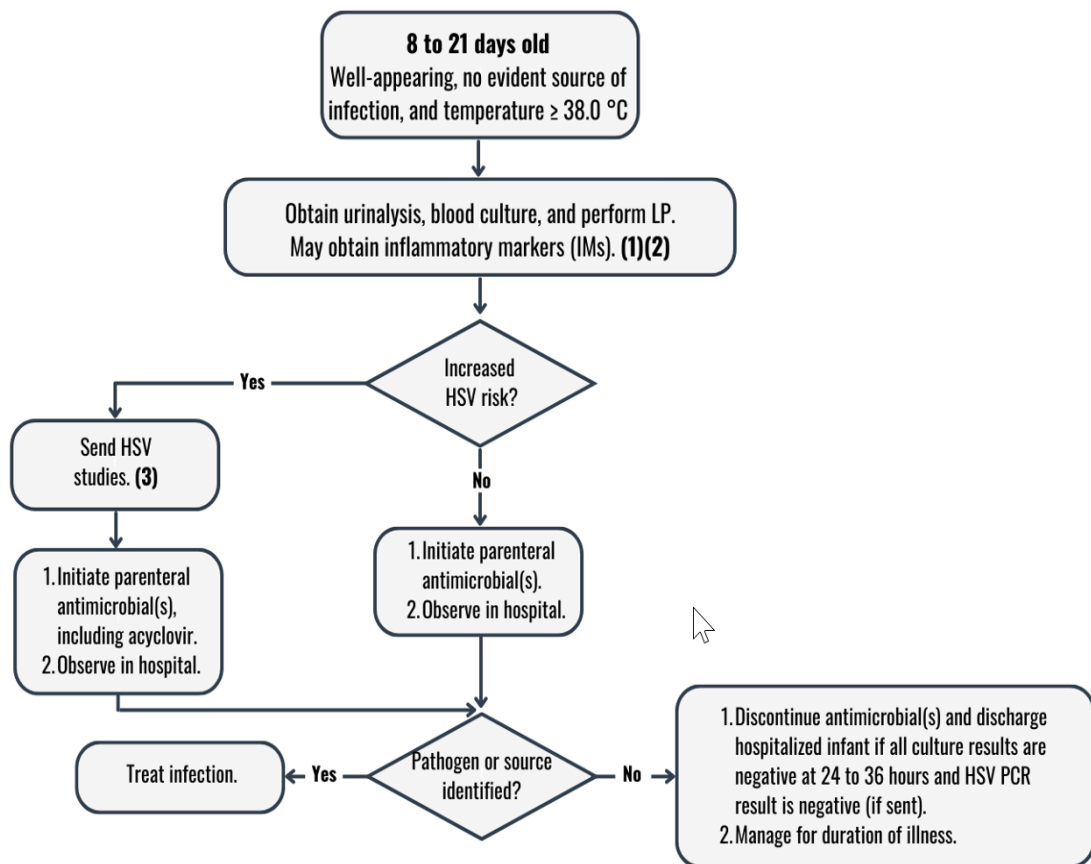
For infants 22-28 days (may treat as above category)

- Obtain IMs
Grade: B; Moderate Recommendation
- Any abnormal IM prompts LP
Grade: C; Moderate Recommendation
- Any positive infectious source requires admission
Grade: A; Strong Recommendation
- If LP is not successful or not attempted, admit. If IM is abnormal, give antibiotics; if negative, may hold antibiotics
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, follow-up next day
Grade: B; Moderate Recommendation

Infants 29-60 days (selective workup and treatment)

- Obtain urinalysis, urine culture, and blood culture
Grade: B; Moderate Recommendation
- IMs guide further workup
Grade: B; Moderate Recommendation
- Depending on laboratory results and situational factors, options vary in terms of LP, antimicrobials, and disposition

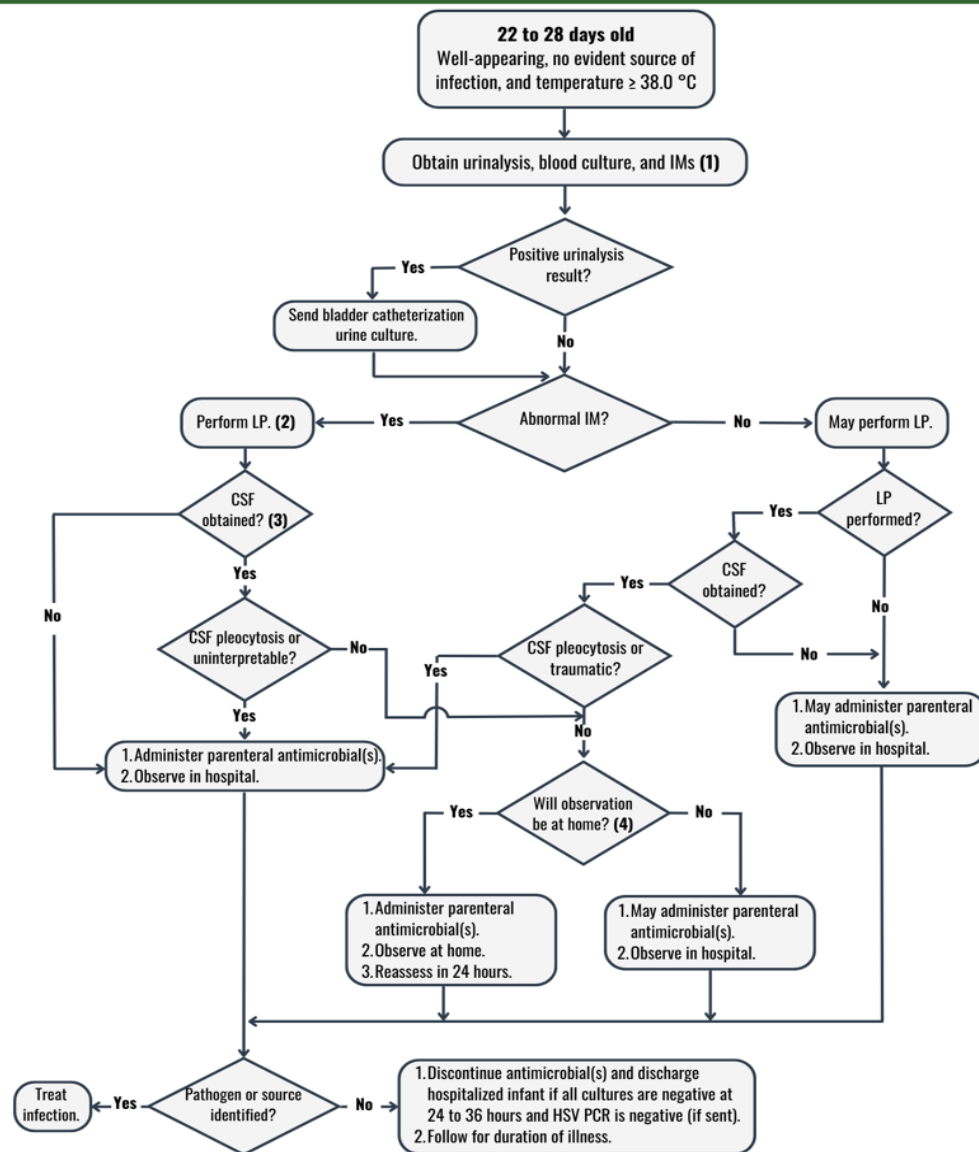
Febrile Infants Recommendation Algorithm



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Algorithm for 8- to 21-day-old infants

- (1) 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 mm³, >5200 per mm³. 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.
- (2) 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.
- (3) 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.

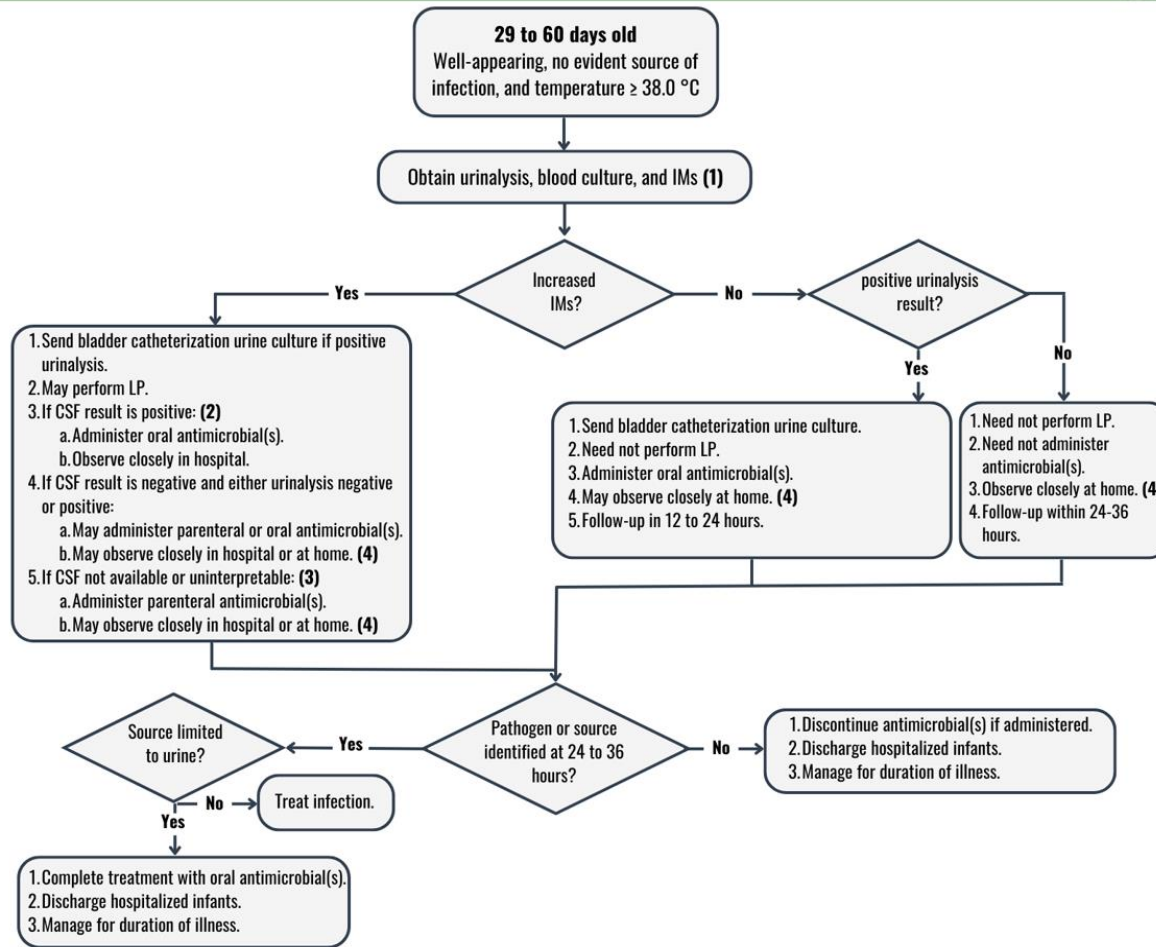


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Algorithm for 22- to 28-day-old infants

- (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 mm³ when used in conjunction with PCT or >5200 per mm³ 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 is 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.

Febrile Infants Recommendation Algorithm



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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 $>38.5^{\circ}\text{C}$ is considered abnormal. PCT is considered abnormal at $>0.5\text{ mg/mL}$; CRP is considered abnormal at $>20\text{ mg/L}$; ANC is considered abnormal at $>4000\text{ per mm}^3$ when used in conjunction with PCT or $>5200\text{ per mm}^3$ when PCT is unavailable.
- (2) 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.
- (3) 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.
- (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. 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.

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. 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 Emergency Playbook: The Febrile Infant: <https://pemplaybook.org/podcast/the-febrile-infant>