JAMA Network Clinical Guideline Synopsis

Clinical Guideline Synopsis of Evaluation and Management of Well-Appearing Febrile Infants Aged 8 to 60 Days

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GUIDELINE TITLE: Evaluation and Management of Well-Appearing Febrile Infants 8 to 60 Days Old

DEVELOPER: American Academy of Pediatrics

RELEASE DATE: August 2021

PRIOR VERSION: None

FUNDING SOURCE: None

TARGET POPULATION: Previously healthy, well-appearing term infants, aged 8 to 60 days, with tempreature ≥38.0 °C

MAJOR RECOMMENDATIONS AND QUALITY/EVIDENCE RATINGS:

Infants aged 8 to 21 days
- All infants in the age group should have a complete sepsis workup (grade A, strong), receive parenteral antimicrobials (A, strong), and be hospitalized (B, moderate)
- Inflammatory marker (IM) results can guide ongoing clinical decisions (B, weak)

Infants aged 22 to 28 days
- Should obtain urinalysis and blood culture; if urinalysis result is positive, send urine culture (A, strong)
- Should assess IMs (B, strong)
- Should obtain cerebrospinal fluid (CSF) if any IM is abnormal (B, moderate); may obtain CSF if urinalysis results and IMs are normal (B, moderate)
- Should hospitalize and administer parenteral antimicrobials if CSF suggests bacterial meningitis or urinalysis is positive (A, strong); may hospitalize and administer parenteral antimicrobials if CSF and urinalysis results are normal but any IM is abnormal (B, moderate)
- Infants may be treated at home if urinalysis results are negative and all IMs are normal, CSF is normal or enterovirus positive, home care and return instructions are provided, and follow-up within 24 hours is arranged (B, moderate); may administer parenteral antimicrobial therapy to infants who will be treated at home even if urinalysis results, CSF, and all IMs are normal (C, moderate)

Infants aged 29 to 60 days
- Should obtain urinalysis; if positive, obtain culture (A, strong)
- Should obtain blood culture and assess IMs (B, moderate)
- Need not obtain CSF if all IMs are normal (B, moderate); may obtain if any IM is abnormal (C, weak)
- Should use parenteral antimicrobials if CSF suggests bacterial meningitis (A, strong)
- May use parenteral antimicrobials if CSF is normal but any IM is abnormal (B, moderate)
- Should initiate oral antimicrobials if urinalysis result is positive but all IMs and CSF (if obtained) are normal (B, strong)
- Need not start antimicrobials if CSF (if obtained) normal or enterovirus positive, urinalysis results are negative, and no IM abnormal (B, moderate)
- Should hospitalize if CSF is abnormal (A, strong); may hospitalize if any IM abnormal (B, moderate)
- Should treat at home without antimicrobials if urinalysis results and CSF are normal, no IM abnormality, and 24-hour follow up is available (B, moderate)
- May treat at home without antimicrobials if no CSF is obtained if urinalysis results and IMs are normal and 24-hour follow up is available (B, moderate)

Summary of the Clinical Problem

Efforts to develop an evidence-based approach to the evaluation and management of young febrile infants have spanned decades. Nonadherence to previous clinical prediction models[1] as well as changing bacteriology,[2] cost of unnecessary care, advances in testing, and evolving research provided the impetus for this guideline.[3,4]

Characteristics of the Guideline Source

This guideline was developed by the American Academy of Pediatrics subcommittee on febrile infants and was based on an Agency for Healthcare Research and Quality evidence review.[5] Supplemental reviews by epidemiologists were incorporated, and unpublished data were solicited and analyzed. Recommendations were further evaluated by American Academy of Pediatrics Sections and Committees, external organizations, and physician and parent reviewers (**Table**).

Evidence Base

The guideline provides recommendations for evaluating and treating well-appearing term infants aged 8 to 60 days with fever of 38.0 °C or higher. The committee addressed several challenges, including (1) age-based risk stratification[6]; (2) serious vs invasive bacterial infection; (3) prevalence of bacterial meningitis; (4) changing epidemiology of bacterial pathogens; (5) subjectivity in defining well appearing; (6) variable care delivery settings; (7) variable availability of diagnostic testing; and (8) the importance of shared decision-making between clinicians and parents.[7]

Excluded from the guideline are infants in the first week of life and infants born before 37 weeks' or after 42 weeks' gestation. Infants with evidence of focal bacterial infection, clinical bronchiolitis, immune system compromise, congenital or chromosomal abnormalities, medical fragility, and those given immunizations in the

previous 24 hours are excluded. Pooled reanalysis of bacteremia risk by week of life was performed to identify 3 distinct age strata: 8 to 21, 22 to 28, and 29 to 60 days.[2,8]

The committee recommends assessment of inflammatory markers (IMs) to guide initial management for all infants older than 22 days. A procalcitonin value less than 0.5 ng/mL indicates low risk. Absent timely procalcitonin results, a combination of temperature less than 38.5 °C, a C-reactive protein level less than 2 mg/dL (to convert to milligrams per liter, multiply by 10), or an absolute neutrophil count below 1 of 2 suggested cutoffs, derived from separate studies (<4000 or <5200 /mm^3), are recommended to define low risk.[4,8]

Benefits and Harms

Physicians caring for febrile infants are confronted with the challenge of when to perform invasive testing and potentially harmful interventions to identify uncommon diagnoses with severe outcomes for missed or delayed identification. This guideline explicitly addresses assessment of risks, harms, and costs with a summary metric for each key action statement. However, the authors suggest reasonable, well-informed clinicians and families may have very different risk tolerances. Key risk-benefit discussions include refinement of previously defined age-based risk strata and the need for invasive testing, the use of IMs to assess risk, indications for parenteral antimicrobials, and hospitalization.

Discussion

This guideline is thorough, applicable to varied practice settings, and in accordance with Institute of Medicine standards regarding development. However, recommendations for individualized care and shared decision-making may increase practice variation and make implementation difficult. There are multiple weaknesses that limit the potential impact of this guideline, particularly the overwhelming complexity of the 21 key action statements. Although the authors summarize these in 3 visual algorithms, there are unanswered questions, including the impact of viral testing, how to safely incorporate shared decision-making, and the interpretation of traumatic lumbar punctures. Additionally, the authors propose using previously untested combinations of IMs when procalcitonin results are not readily available. The authors of this synopsis are unaware of any data to support this recommendation.

Table. Guideline Rating

Standard	Rating
Establishing transparency	Good
Management of conflict of interest in the guideline development group	Good
Guideline development group composition	Good
Clinical practice guideline-systematic review intersection	Fair
Establishing evidence foundation and rating strength for each of the guideline recommendations	Good
Articulation of recommendations	Fair
External review	Good
Updating	Good
Implementation issues	Poor

Articulation of recommendations was judged to be fair owing to reliance on individualized decisions based on risk tolerance, available testing, and caregiver preference. Implementation issues were judged to be poor due to complexity of the recommendations, the emphasis on shared decision-making and individualized care, and the inclusion of unvalidated combinations of IMs. The authors do not provide any guidance on how to perform shared decision-making or address variable risk tolerance and there are no available tools, such as electronic health record risk calculators, which could assist with implementation.

Areas in Need of Future Study or Ongoing Research

The authors comment extensively regarding the need for additional research in this area, particularly on clarifying the diagnostic accuracy of IMs for risk strata and individualizing care using patient factors. The focus of this guideline on shared decision-making and individualized care require extensive research to understand how to perform these in the clinical setting and to facilitate the development of platforms to support decision-making especially across diverse populations and practice settings.

ARTICLE INFORMATION

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Published Online: March 14, 2022. doi:10.1001/jamapediatrics.2022.0066

Conflict of Interest Disclosures: None reported.

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