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Persistent and Recurrent Fever Without Focus in Children: A Contemporary Evidence-Based Approach for Pediatricians

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Abstract: Persistent or recurrent fever without a clear source (fever without focus, FWF) in children under 10 years presents a significant diagnostic and therapeutic challenge, especially in high-burden urban settings like Bangalore. This comprehensive review synthesizes current evidence on the epidemiology, evolving infectious etiologies, diagnostic strategies, and management principles. Emphasizing a structured, tiered approach informed by recent advances in molecular diagnostics and prediction models, it advocates for judicious use of resources and antimicrobial stewardship. The article highlights region-specific factors influencing etiologies, including emerging viral infections, tuberculosis, enteric fever, and rickettsial diseases. This evidence-based framework supports clinical decision-making and interdisciplinary collaboration to optimize patient outcomes and reduce unnecessary interventions.

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I. INTRODUCTION

Fever is a leading cause of pediatric consultations and hospital admissions worldwide. Most febrile illnesses in children are self-limited and viral. However, a subset presents as persistent or recurrent high-grade fever without an identifiable clinical focus, posing diagnostic ambiguity that demands systematic evaluation. Persistent fever without focus (FWF) or fever of unknown origin (FUO) is more challenging in settings with high infectious disease burden, varied resource availability, and changing epidemiology post-pandemic.

Children under 10 years are particularly vulnerable due to developmental physiologic characteristics and exposure patterns. The increasing recognition of novel viral strains, antimicrobial resistance, and overlapping infectious and non-infectious causes calls for updated clinical algorithms. This review integrates global and regional evidence, advances in diagnostics such as multiplex PCR, and predictive models for differential diagnosis, aiming to provide pediatricians with a practical, well-rounded approach to prolonged fever in children.

II. DEFINITIONS AND EPIDEMIOLOGY

- Fever Without Focus (FWF): Temperature ≥38°C in a child with no apparent source after comprehensive history and physical examination.
- Prolonged Fever: Fever persisting beyond 7 days warrants reconsideration of differential diagnosis.
- Fever of Unknown Origin (FUO): Traditionally defined as fever ≥38.3°C lasting ≥2–3 weeks with negative initial evaluation.

In urban Indian contexts like Bangalore, studies report infectious causes dominate 65–80% of prolonged fever cases in children, with tuberculosis, enteric fever, and rickettsial illnesses particularly prevalent. Non-infectious causes such as autoimmune diseases and malignancies are increasingly identified due to improvements in diagnostics.

III. CLINICAL APPROACH: STEPWISE EVALUATION

➢ *Detailed Clinical History and Physical Examination*

- Repeated, thorough clinical assessments improve detection of evolving symptoms such as rash, adenopathy, arthritis, or hepatosplenomegaly.
- Key inquiry points include travel, exposure to animals or vectors, vaccination history, familial illness, drug intake, and social determinants.

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- Monitoring clinical trajectory remains essential: changes in general appearance, activity, feeding, or neurological status inform urgency of intervention.

➢ *Initial Laboratory and Imaging Studies (First-Tier)*
- CBC with differential to evaluate leukocytosis, cytopenias, or anemia.
- Acute phase reactants such as C-reactive protein (CRP) and procalcitonin aid in infection/inflammation differentiation.
- Blood and urine cultures to detect bacteremia or urinary infections.
- Liver and renal function panels for systemic involvement.
- Chest radiography if respiratory symptoms or systemic queries suggest pulmonary involvement.
- Regionally pertinent infectious screens include malaria smears, dengue NS1/IgM, enteric fever serologies, and viral panels (e.g., adenovirus, influenza, EBV/CMV).

➢ *Observation and Reassessment*
- Well-appearing children without red flags may be observed with supportive care and serial clinical evaluations to minimize invasive testing.
- Repeat assessments are critical for detecting delayed onset clinical signs.

➢ *Second-Tier Directed Investigations*
- Ultrasonography, CT, or MRI scans help identify occult foci such as abscesses, lymphadenopathy, or masses.
- Autoimmune serologies (ANA, rheumatoid factor, ESR) are indicated for systemic inflammatory suspicion.
- Tuberculosis evaluations (Mantoux test, GeneXpert, gastric aspirate) are fundamental in endemic regions.
- Immunology panels to evaluate for immunodeficiencies in recurrent or suspicious infections.
- Bone marrow aspiration and biopsy for cytopenias or suspicion of hematologic malignancies.

IV. DIFFERENTIAL DIAGNOSIS

Infectious Causes Relevant to Bangalore and Similar Settings
- Adenovirus: Post-pandemic changes see an unusual increase in prolonged adenoviral febrile illnesses lasting up to two weeks with respiratory and systemic symptoms.
- Influenza viruses (H3N2 and others): Associated with febrile episodes extending beyond typical durations, sometimes complicated by pneumonia.
- Varicella (Chickenpox) and Enteroviruses (HFMD): These viral infections can cause prolonged fevers especially if complicated by pneumonia, encephalitis, or secondary bacterial infections.
- Tuberculosis (TB): Still a leading cause of prolonged fever, often extrapulmonary in children without classic symptoms, necessitating high index of suspicion.
- Enteric Fever (Typhoid/Paratyphoid): A classic cause of protracted fever continued to be endemic, often lasting beyond seven days.
- Rickettsial Diseases (Scrub Typhus, Indian tick typhus): Increasing diagnosis frequency due to heightened awareness and better access to IgM ELISA and PCR diagnostics.
- Atypical Dengue and Other Viral Illnesses: Reports of biphasic or prolonged febrile illnesses not always confirmed by rapid tests.
- Bacterial Deep-Seated Infections: Abscesses, endocarditis, UTIs, and osteomyelitis, especially when initial workup is negative.

➢ *Non-Infectious Causes*
- Autoimmune/Inflammatory Diseases: Juvenile idiopathic arthritis (systemic subtype), Kawasaki disease, systemic lupus erythematosus (SLE), vasculitis.
- Malignancies: Leukemia, lymphoma, neuroblastoma.
- Drug Fever and Hereditary Periodic Fever Syndromes.

➢ *Red Flags Necessitating Immediate Attention*
- Hemodynamic instability or shock.
- Petechial or purpuric rash.
- Neurologic impairment or altered sensorium.
- Rapidly evolving or extensive rash.
- Persistent vomiting, jaundice or abdominal distension.
- Pallor, bruising, hepatosplenomegaly.
- Failure to thrive or weight loss.
- Oxygen desaturation or respiratory distress.

➢ *Recent Advances and Diagnostic Innovations*
- Multiplex PCR Panels: Allow rapid identification of viral pathogens in blood and respiratory samples, enabling targeted diagnosis and reducing empirical antibiotic use.
- Biomarker Usage: Procalcitonin and CRP can help discriminate bacterial from viral etiologies.
- Prediction Models: Clinical decision tools incorporating features such as arthritis, cytopenias, hepatosplenomegaly, and lymphadenopathy aid stratification between infectious, autoimmune, and malignant causes.
- Stepwise Algorithms: Guidelines advocate tiered escalation of diagnostic effort based on evolving clinical features and initial test results, optimizing resource use.

➢ *Management Principles*
- Supportive care for well-appearing children with close outpatient follow-up.
- Empirical antimicrobial therapy restricted to children with clinical or laboratory evidence suggestive of bacterial infection.
- Paracetamol as first-line antipyretic; avoid polypharmacy.
- Immunomodulatory therapy (e.g., corticosteroids) only after infectious causes ruled out and clear autoimmune diagnosis established.
- Multidisciplinary approach in indeterminate cases including infectious diseases, rheumatology, and hematology consultation.
- Emphasis on antimicrobial stewardship amid increasing resistance patterns.

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➢ *Region-Specific Considerations for Bangalore*

- High prevalence and atypical presentations of tuberculosis, necessitating repeated and sensitive diagnostic evaluation.
- Increased recognition of rickettsial infections following enhanced diagnostics.
- Post-pandemic immunity gaps contributing to prolonged viral infections such as adenovirus and influenza.
- Local antimicrobial resistance trends require regional surveillance to guide empirical therapy.
- Public health interventions targeting hygiene, vector control, and vaccination coverage remain critical.

Table 1 Suggested Clinical Algorithm

Step	Action	Rationale
1	Initial detailed history and physical	Identify exposures, guiding first tests
2	First-tier labs and imaging	Quick exclusion of common infections and complications
3	Observation with serial clinical reviews	Prevent premature invasive testing or antibiotics
4	Second-tier tests based on suspicion	Target occult or less common etiologies
5	Specialist referral if no diagnosis or red flags	Early intervention for severe/non-infectious causes

V. CONCLUSION

Persistent and recurrent fever without focus in children requires a disciplined, evidence-based, and context-aware approach that prioritizes careful clinical evaluation, judicious investigations, and thoughtful management. Advances in molecular diagnostics and clinical prediction tools enhance differentiation between infectious, autoimmune, and malignant etiologies. Recognition of emerging infectious agents and regional epidemiology is essential, especially in high-burden settings like Bangalore. Multidisciplinary collaboration and antimicrobial stewardship underpin optimal outcomes for these complex presentations.

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