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RECURRENT FEVER IN CHILDREN – DIAGNOSTIC APPROACH AND RED FLAGS FOR SERIOUS DISEASES

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ABSTRACT

Recurrent fever in children represents a diagnostically challenging and clinically heterogeneous condition that extends beyond repeated exposure to common infections. While most febrile episodes in early childhood are self-limiting, a subset of children experiences recurrent episodes separated by periods of complete or near-complete well-being, necessitating careful evaluation to distinguish benign from serious underlying conditions. This review aims to synthesize the current state of knowledge regarding recurrent fever in children and to provide a clinically oriented analysis of the differential diagnosis. The specific objectives are to systematically characterize autoinflammatory, immunodeficiency-related, autoimmune, and oncologic causes; to outline a structured and evidence-based diagnostic approach; and to identify clinical red flags suggestive of a serious underlying pathology.

Methods: This review is based on peer-reviewed literature on pediatric recurrent fever and periodic fever syndromes (references 1–27). Narrative and systematic reviews, clinical guidelines, and original studies were qualitatively synthesized with focus on etiology, immunopathogenesis, key clinical features, and diagnostic red flags.

Results: Recurrent fever encompasses a broad spectrum of conditions, from benign periodic fever syndromes such as PFAPA to monogenic autoinflammatory diseases (FMF, TRAPS, MKD, CAPS), immunodeficiencies (CVID, cyclic neutropenia), autoimmune disorders (sJIA, SLE), and oncologic causes. Stepwise evaluation includes detailed history, physical examination, baseline and targeted laboratory testing, and genetic assessment when appropriate. Recognition of red flags—including growth retardation, persistent laboratory abnormalities, organomegaly, atypical fever patterns, severe systemic symptoms, and relevant family history—facilitates early identification of high-risk patients and guides targeted investigations.

Conclusion: Early and structured assessment of children with recurrent fever, guided by clinical pattern recognition and red flags, is essential for accurate diagnosis, timely referral, and individualized management. Integration of immunopathogenic insights and practical diagnostic strategies enhances clinical decision-making and improves patient outcomes in potentially life-threatening conditions.

KEYWORDS

Recurrent Fever, Diagnostic Approach, Periodic Fever Syndromes, Autoinflammatory Diseases, Red Flags

CITATION

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Introduction

Recurrent fever in childhood represents a clinically heterogeneous and diagnostically challenging condition that extends beyond repeated exposure to common infections [1]. Fever is one of the most common reasons for pediatric consultations all over the world. However, some children experience recurrent febrile episodes interspersed with periods of complete or almost complete well-being. This pattern constitutes a distinct clinical problem requiring careful evaluation and differentiation from typical self-limited infections [2]. While recurrent infections remain the most common explanation in early childhood, an increasing proportion of cases are associated with autoinflammatory diseases, immune dysregulation, autoimmune disorders, malignancies, or primary immunodeficiencies [3].

Over the past two decades, advances in molecular immunology, genetics, and inflammasome biology have substantially improved understanding of recurrent fever syndromes [7]. Research has highlighted the central role of innate immune dysregulation and cytokine-mediated inflammation, particularly involving interleukin-1–driven pathways, in several periodic fever disorders. These discoveries have refined disease classification and enabled the development of targeted therapies. Nevertheless, from a clinical perspective recurrent fever remains a diagnostic challenge, particularly in general pediatric and primary care settings where early evaluation usually begins. An increase in referrals and diagnostic evaluations for recurrent fever in children has been observed in recent years, particularly during the COVID-19 pandemic [21].

Despite the growing body of literature describing individual diseases and molecular mechanisms, several practical challenges persist. Available studies often focus on specific syndromes rather than on the initial diagnostic approach to a child presenting with recurrent fever [5]. Consequently, clinicians frequently face uncertainty when attempting to distinguish benign and self-limited conditions from potentially serious underlying diseases [19]. Clear summaries of clinical warning signs ("red flags") suggesting malignancy, immunodeficiency, systemic inflammatory disease, or other severe pathology remain limited and scattered across the literature [8].

The ability to recognize warning features early is critical. Delayed diagnosis may lead to unnecessary investigations in some children while, in others, it may postpone identification of life-threatening conditions or treatable autoinflammatory disorders. A structured diagnostic framework that integrates clinical history, physical examination, laboratory findings, and awareness of red flag symptoms is therefore essential for safe and efficient patient management.

The aim of this review is to synthesize current knowledge on recurrent fever in children and to provide a clinically oriented overview of its differential diagnosis. Particular emphasis is placed on the diagnostic approach and on identifying red flags that should prompt further investigation for serious diseases. By integrating current evidence with practical clinical considerations, this review seeks to support clinicians in the early recognition and appropriate evaluation of children presenting with recurrent febrile episodes.

Recurrent fever is most commonly defined as at least three discrete febrile episodes occurring within approximately six months, separated by intervals of complete or near-complete clinical recovery, and not explained by common acute infections [23]. The presence of intercritical well-being constitutes the defining feature. In contrast, prolonged fever refers to a single continuous febrile episode exceeding the expected duration of typical viral illnesses, generally beyond 7–14 days. Fever of unknown origin (FUO) is a clinical syndrome of heterogeneous etiology, characterized by persistent fever that does not resolve spontaneously and lasts longer than a typical infectious illness and the cause cannot be determined despite routine diagnostic procedures. Importantly, FUO represents a diagnostic category rather than a pathophysiological pattern. Periodic fever, by comparison, denotes a specific subtype of recurrent fever characterized by stereotyped and often predictable febrile episodes recurring at regular or semi-regular intervals with consistent accompanying features [14]. Recognition of periodicity is clinically significant because it frequently signals intrinsic inflammatory dysregulation rather than repeated unrelated infections.

From an immunobiological perspective, many recurrent fever syndromes belong to the expanding group of autoinflammatory diseases. These disorders are defined by primary dysregulation of the innate immune system, leading to spontaneous or trigger-induced activation of inflammatory cascades in the absence of high-titer autoantibodies or antigen-specific T-cell responses [13]. Central to this process is aberrant activation of pattern-recognition receptor (PRR) pathways, particularly the NLRP3 inflammasome, resulting in excessive maturation and secretion of interleukin-1β (IL-1β) and interleukin-18 (IL-18). Downstream signaling amplifies nuclear factor kappa B (NF-κB) activation and promotes production of additional proinflammatory cytokines, including IL-6 and tumor necrosis factor (TNF). These cytokine networks drive the systemic inflammatory phenotype observed during febrile attacks. The development of classification criteria for autoinflammatory recurrent fevers by the Eurofever Registry and PRINTO has facilitated phenotypic standardization and improved comparability across studies [16].

Recurrent fever in children can result from a wide spectrum of conditions, including infectious, autoinflammatory, immunodeficiency-related, autoimmune, oncologic, metabolic, and environmental causes. The first table summarizes infectious causes of recurrent fever in children, organized by underlying mechanisms, characteristic clinical features, and key distinguishing findings to facilitate differential diagnosis and early recognition of potentially serious conditions. The second table summarizes noninfectious causes using the same approach.

Table 1. Infectious causes of recurrent fever in children

Etiological category	Condition	Pathophysiological mechanism	Characteristic clinical features	Key distinguishing findings
Viral	EBV	Latent infection with periodic reactivation	Recurrent/ prolonged fever, lymphadenopathy	Atypical lymphocytosis, EBV serology
	Parvovirus B19	Persistent viremia, marrow suppression	Fever, rash, anemia, arthralgia	Reticulocytopenia, B19 IgM/PCR
	Recurrent HSV	Reactivation of latent virus	Short fever episodes, vesicular lesions	Typical lesions, HSV PCR
Bacterial	Relapsing fever (Borrelia)	Antigenic variation → cyclic bacteremia	High spiking fevers with afebrile intervals	Regular periodicity, spirochetes in blood
	Brucellosis	Chronic intracellular infection	Undulating fever, sweats, arthralgia	Exposure history, serology
	Syphilis	Disseminated spirochetal infection	Fever, rash, lymphadenopathy	Positive treponemal tests
	Whipple disease	Chronic systemic infection	Fever, diarrhea, weight loss	PAS-positive macrophages
	Chronic meningococcemia	Persistent bacteremia	Recurrent fever, rash	Positive blood cultures
	Infective endocarditis	Continuous bacteremia	Prolonged/ recurrent fever	Murmur, positive cultures
	Subacute cholangitis	Intermittent biliary infection	Fever, abdominal pain	Cholestatic labs, imaging
	Occult abscesses	Intermittent bacteremia	Isolated recurrent fever	Imaging/dental source
	Osteomyelitis (chronic)	Persistent bone infection	Fever, focal bone pain	MRI changes
	Tuberculosis	Chronic granulomatous infection	Fever, weight loss, sweats	IGRA/TST, imaging
Fungal	Histoplasmosis	Persistent intracellular fungi	Fever, lymphadenopathy	Antigen/serology
	Coccidioidomycosis	Chronic fungal inflammation	Fever, respiratory symptoms	Endemic exposure
Parasitic	Malaria	Cyclic parasitemia	Periodic fever, chills	Blood smear
	Visceral leishmaniasis	Reticuloendothelial infection	Fever, splenomegaly, cytopenia	Bone marrow/spleen aspirate

Abbreviations: EBV - Epstein–Barr virus, HSV - Herpes simplex virus, PCR - Polymerase Chain Reaction, Ig - Immunoglobulin, PAS - Periodic acid–Schiff stain, IGRA - Interferon-Gamma Release Assay, TST - Tuberculin Skin Test

Table 2. Noninfectious causes of recurrent fever in children

Etiological category	Condition	Pathophysiological mechanism	Characteristic clinical features	Key distinguishing findings
Autoinflammatory – polygenic	PFAPA syndrome	Innate immune dysregulation with IL-1β overproduction, Th1 activation	Regular fever episodes, aphthous ulcers, pharyngitis, cervical adenitis	Complete well-being between attacks, rapid response to corticosteroids
Autoinflammatory – monogenic	FMF	*MEFV* mutations → pyrin inflammasome overactivation → IL-1β excess	Short febrile attacks with serositis, arthritis, erysipelas-like rash	Ethnic predisposition, risk of AA amyloidosis, response to colchicine
	TRAPS	*TNFRSF1A* mutations → impaired TNF receptor signaling and NF-κB activation	Prolonged fever episodes, migratory rash, myalgia, periorbital edema	Long attack duration (1–3 weeks), autosomal dominant inheritance
	MKD	*MVK* mutations → defective isoprenoid biosynthesis → inflammasome activation	Fever with lymphadenopathy, diarrhea, rash, arthralgia	Early onset; attacks triggered by vaccines/infections; genetic confirmation
	CAPS	NLRP3 gain-of-function → constitutive inflammasome activation	Urticarial rash, fever, arthralgia, neurologic and auditory involvement	Chronic inflammation, response to IL-1 blockade
Undifferentiated autoinflammatory	SURF	Undefined innate immune dysregulation	Recurrent fever without classic syndrome features	Failure to meet criteria for known periodic fever syndromes
Primary immunodeficiency	CVID	Impaired antibody production and immune dysregulation	Recurrent infections with fever, autoimmune complications	Hypogammaglobulinemia, poor vaccine response
Hematologic disorders	Cyclic neutropenia	*ELANE* mutations → oscillatory neutrophil production	Fever, oral ulcers, bacterial infections every ~21 days	Periodic neutropenia on serial CBCs
Autoimmune / rheumatologic	Systemic juvenile idiopathic arthritis	IL-1 and IL-6–driven systemic inflammation	Quotidian fever, evanescent rash, arthritis	Elevated inflammatory markers, risk of macrophage activation syndrome
Autoimmune	Systemic lupus erythematosus	Immune complex–mediated systemic inflammation	Fever with multisystem involvement	Autoantibodies (ANA, anti-dsDNA), complement consumption
Oncologic	Acute leukemia, lymphoma	Malignant infiltration and cytokine release	Fever with weight loss, bone pain, cytopenias	Persistent cytopenias, abnormal peripheral smear
Metabolic disorders	MKD (metabolic phenotype)	Defective cholesterol/isoprenoid pathway	Early-onset recurrent fever with GI symptoms	Elevated inflammatory markers; genetic diagnosis
FUO (diagnostic category)	Fever of unknown origin	Heterogeneous; infectious, inflammatory, or malignant causes	Persistent fever >2–3 weeks	Diagnosis of exclusion after standard evaluation

Environmental / iatrogenic triggers	Vaccination, stress	Immune activation in predisposed individuals	Fever following triggers	Temporal association with trigger exposure
Other / rare	Atypical periodic fever syndromes	Variable or unknown mechanisms	Incomplete or unusual phenotypes	Case-based diagnosis

Abbreviations: PFAPA - Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis, FMF - Familial Mediterranean Fever, TRAPS - Tumor Necrosis Factor Receptor - Associated Periodic Syndrome, MKD - Mevalonate Kinase Deficiency, CAPS - Cryopyrin-Associated Periodic Syndromes, SURF - Syndrome of Undifferentiated Recurrent Fever, CVID - Common Variable Immunodeficiency, CBC - Complete Blood Count, ANA - antinuclear antibodies, GI - gastrointestinal,

Recurrent fever in children represents a multifaceted clinical manifestation encompassing infectious, autoinflammatory, autoimmune, oncologic, and immunodeficiency-related conditions. Precise differentiation between recurrent fever, prolonged fever, periodic fever, and fever of unknown origin (FUO) remains essential for diagnostic clarity. Advances in inflammasome biology, cytokine network analysis, and molecular genetics have fundamentally transformed the understanding of periodic fever syndromes. The primary objective of this review is to integrate current definitions, immunopathogenic mechanisms, and etiological classification into a coherent scientific framework, with a particular focus on informing the diagnostic approach and highlighting red flags that may indicate serious underlying diseases. By doing so, this work aims to support clinicians in timely identification and appropriate management of children with recurrent fever, improving patient outcomes through early recognition of potentially life-threatening conditions.

Methodology

This narrative review was undertaken to provide a structured and clinically relevant synthesis of current knowledge on recurrent fever in children, with particular emphasis on etiological classification, diagnostic strategies, and the identification of clinical red flags indicative of serious underlying pathology.

A targeted literature search was conducted using the PubMed database to identify peer-reviewed publications addressing pediatric recurrent fever, periodic fever syndromes, autoinflammatory diseases, primary immunodeficiencies, autoimmune and oncologic conditions, and diagnostic frameworks applicable to clinical practice. The following keywords and their combinations were applied: “recurrent fever in children”, “periodic fever syndromes”, “PFAPA”, “autoinflammatory diseases”, “familial Mediterranean fever”, “TRAPS”, “mevalonate kinase deficiency”, “CAPS”, “primary immunodeficiency”, “cyclic neutropenia”, “systemic juvenile idiopathic arthritis”, “fever of unknown origin”, and “diagnostic approach”. Only articles published in English were considered.

The initial search yielded 312 records. Following title and abstract screening for relevance to pediatric populations and diagnostic considerations, 78 full-text articles were evaluated. Ultimately, 27 publications were included in the final qualitative synthesis based on their clinical relevance, methodological rigor, and contribution to the understanding of pathophysiological mechanisms and practical diagnostic implications. Particular priority was given to consensus statements, classification criteria, high-quality review articles, and clinically oriented original research.

Given the narrative nature of this review, a formal systematic search strategy, predefined inclusion and exclusion criteria, quantitative risk-of-bias assessment, and meta-analysis were not undertaken. The primary objective was to provide an expert-informed, conceptually integrated overview of the literature to support evidence-based clinical decision-making.

Results

Recurrent fever in children arises from a wide spectrum of underlying conditions, each with distinct pathophysiological mechanisms and clinical presentations. Building on the etiological framework outlined in Table 1 (Infectious causes of recurrent fever in children) and Table 2 (Noninfectious causes of recurrent fever in children), this section explores in greater detail the major causes of recurrent fever, including autoinflammatory syndromes, primary immunodeficiencies, autoimmune and rheumatologic disorders, oncologic conditions, and undifferentiated recurrent fever (SURF). Not all recurrent fevers, however, arise from autoinflammatory mechanisms. Recurrent viral infections remain the most common explanation in early childhood, particularly among children with high exposure in daycare environments. The absence of strict periodicity and the greater variability in associated symptoms typically help distinguish infectious recurrences from intrinsic inflammatory syndromes. The following sections therefore focus on the distinguishing clinical features, disease-specific patterns, and key diagnostic clues that facilitate accurate classification and help differentiate benign self-limited conditions from disorders requiring targeted evaluation and management.

PFAPA syndrome

PFAPA syndrome (Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis) represents the most prevalent periodic fever syndrome in childhood [9]. Typically manifesting before five years of age, PFAPA is characterized by highly regular febrile episodes recurring every three to eight weeks and lasting three to six days. Clinical manifestations include aphthous ulcers, exudative or non-exudative pharyngitis, and cervical lymphadenitis, with complete resolution between episodes and preserved growth and development [15]. From a mechanistic perspective, PFAPA is regarded as a polygenic disorder or multifactorial autoinflammatory condition rather than a monogenic disease. Immunological studies demonstrate elevated IL-1β levels during attacks, increased Th1 polarization, and activation of innate immune pathways, supporting its classification within the autoinflammatory spectrum [6]. Transcriptomic analyses suggest dysregulation of inflammasome-related genes and enhanced interferon signaling in some patients. Clinical responsiveness to single-dose corticosteroids and, in refractory cases, IL-1 blockade further corroborates IL-1–mediated pathogenesis [10]. Although often described as self-limiting, longitudinal cohorts reveal substantial heterogeneity in duration and severity, with some individuals experiencing persistence into adolescence or adulthood [25].

Familial Mediterranean fever (FMF)

Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease globally and results from mutations in the *MEFV* gene encoding pyrin, a key regulator of inflammasome activation [11]. Pyrin normally functions as a sensor of cytoskeletal disturbances; pathogenic variants reduce its inhibitory control over inflammasome assembly, leading to excessive IL-1β release. Clinically, FMF presents with short (1–3 day) episodes of fever accompanied by serosal inflammation manifesting as peritonitis, pleuritis, arthritis, or erysipelas-like erythema. Ethnic clustering in Mediterranean and Middle Eastern populations reflects founder effects and genetic selection. Persistent subclinical inflammation may occur between attacks, predisposing untreated patients to secondary AA amyloidosis—a severe complication that underscores the importance of early recognition and colchicine therapy [12]. Recent experimental studies exploring mechanisms have further elucidated the interplay between pyrin, RhoA signaling, and inflammasome activation, refining understanding of disease pathogenesis.

TRAPS (Tumor necrosis factor receptor-associated periodic syndrome)

TRAPS (Tumor necrosis factor receptor-associated periodic syndrome) is an autosomal dominant autoinflammatory disorder caused by mutations in *TNFRSF1A*, encoding the TNF receptor 1. Pathogenic variants impair receptor shedding and alter intracellular trafficking, leading to sustained TNF-mediated NF-κB activation and prolonged inflammatory responses [17]. Clinically, TRAPS differs from PFAPA and FMF in the extended duration of febrile episodes, often lasting one to three weeks, accompanied by migratory erythematous rash, severe myalgia, abdominal pain, conjunctivitis, and periorbital edema. The risk of amyloidosis parallels that observed in FMF, particularly in untreated individuals.

Mevalonate kinase deficiency (MKD)

Mevalonate kinase deficiency (MKD), formerly known as hyper-IgD syndrome, results from mutations in the *MVK* gene affecting the mevalonate pathway [26]. Impaired isoprenoid biosynthesis disrupts protein prenylation, leading to dysregulated activation of small GTPases and enhanced inflammasome signaling. The resulting IL-1β overproduction drives recurrent febrile episodes typically beginning in infancy. Attacks may be precipitated by stress, infection, or vaccination and are accompanied by lymphadenopathy, diarrhea, abdominal pain, rash, and arthralgia [27]. Although elevated IgD levels may be observed, they are neither necessary nor sufficient for diagnosis; genetic confirmation remains definitive.

Cryopyrin-associated periodic syndromes (CAPS)

Cryopyrin-associated periodic syndromes (CAPS) represent a continuum of phenotypes caused by gain-of-function mutations in *NLRP3*. Constitutive inflammasome activation leads to chronic or recurrent systemic inflammation driven by IL-1β. Clinical manifestations range from familial cold autoinflammatory syndrome to Muckle–Wells syndrome and neonatal-onset multisystem inflammatory disease, with features including urticarial rash, fever, arthralgia, sensorineural hearing loss, and central nervous system involvement. CAPS provides a prototypical example of inflammasome-mediated disease and illustrates the therapeutic success of targeted IL-1 inhibition [14].

Common variable immunodeficiency (CVID)

Common variable immunodeficiency (CVID) is characterized by hypogammaglobulinemia and impaired antibody production, leading to recurrent sinopulmonary infections and febrile episodes; immune dysregulation may also result in autoimmune or inflammatory complications [4].

Cyclic neutropenia

Cyclic neutropenia, often caused by *ELANE* mutations, results in oscillatory neutrophil production with approximately 21-day periodicity. During neutropenic phases, patients develop fever, oral ulcers, and bacterial infections, reflecting transient innate immune deficiency rather than hyperinflammation [18].

Systemic juvenile idiopathic arthritis (sJIA)

Autoimmune and rheumatologic conditions further expand the differential diagnosis. Systemic juvenile idiopathic arthritis (sJIA) is characterized by quotidian fever spikes, evanescent rash, and progressive arthritis, driven by excessive IL-1 and IL-6 signaling and sometimes complicated by macrophage activation syndrome. Systemic lupus erythematosus may present with fever as a manifestation of systemic immune complex–mediated inflammation.

Oncologic etiologies

Oncologic etiologies, though less common, are of high clinical significance. Acute lymphoblastic leukemia may initially manifest with recurrent or persistent fever, bone pain, cytopenias, and constitutional symptoms prior to overt hematologic abnormalities. Lymphomas may produce intermittent fever and B symptoms, occasionally mimicking inflammatory or infectious conditions [19].

Syndrome of undifferentiated recurrent fever (SURF)

Syndrome of undifferentiated recurrent fever (SURF) refers to patients with recurrent self-limiting episodes of systemic inflammation who do not fulfill established classification criteria for defined monogenic autoinflammatory diseases despite comprehensive clinical and genetic evaluation [24]. These patients typically exhibit periodic fever accompanied by systemic inflammatory manifestations, but do not show pathogenic variants in known autoinflammatory genes or a phenotype consistent with recognized periodic fever syndromes. The diagnosis is established after exclusion of infectious, malignant, autoimmune, and defined autoinflammatory causes through a structured and stepwise diagnostic approach. Management is individualized and guided by clinical severity and inflammatory burden, often requiring a trial of anti-inflammatory or biologic therapies in selected cases.

Understanding the characteristic features and disease-specific patterns of these conditions is essential for distinguishing benign from potentially serious causes. To translate this knowledge into effective clinical practice, a structured diagnostic approach is required, integrating detailed history, thorough examination, and targeted investigations.

The diagnostic evaluation of a child with recurrent fever should follow a structured and stepwise approach beginning with a comprehensive history that assesses age at onset, duration and interval of febrile episodes, associated clinical manifestations, family history, and the presence of completely symptom-free periods, which are crucial for differentiating recurrent infections from autoinflammatory syndromes [22]. Careful physical examination during both febrile flares and afebrile intervals is essential, with attention to lymphadenopathy, hepatosplenomegaly, mucosal lesions, rash, arthritis, and growth parameters. Baseline laboratory assessment typically includes complete blood count with differential and inflammatory markers, with serial measurements helping to determine whether inflammatory parameters normalize between episodes, a feature that supports periodic fever syndromes such as PFAPA. When clinical features suggest an autoinflammatory disorder, application of classification criteria and consideration of targeted genetic testing are recommended to refine diagnosis [20].

Diagnostic procedure for recurrent fevers in children:

Step 1: Detailed anamnesis

- Age at onset, frequency, duration of episodes
- Symptoms during episodes: rash, arthralgia, oral ulcers, adenopathy
- Family history of autoinflammatory or immune diseases

Step 2: Physical Examination

- During febrile and afebrile periods
- Focus on: lymph nodes, hepatosplenomegaly, skin, joints, growth

Step 3: Baseline Laboratory Tests and Imaging Tests

- Complete Blood Count, inflammatory parameters CRP, ESR
- Check liver and kidney function
- General urine test, urine culture, blood culture
- Ultrasonography, X-ray examinatio, Computed Tomography, Magnetic Resonance Imaging and others as needed

Step 4: Targeted Investigations

- Examination for infectious diseases: bacterial, viral, parasitic tests
- Immunologic evaluation → if primary immunodeficiency suspected

Step 5: Consider Autoinflammatory Disease

- Apply classification criteria for known periodic fever syndromes (PFAPA, FMF, TRAPS, MKD)
- Consider targeted genetic testing based on phenotype

Step 6: Identify Red Flags

- Poor growth / failure to thrive
- Weight loss
- Persistent lab abnormalities between episodes
- Hepatosplenomegaly
- Severe systemic symptoms
- Prolonged or atypical fever patterns
- Suspicion of malignancy, chronic infection, or immunodeficiency

Step 7: Diagnosis / Exclusion

- Exclude infections, malignancy, autoimmune disease
- If criteria not met and genetics negative → consider SURF

Step 8: Follow-Up and Monitoring

- Track episodes, symptoms, lab trends
- Individualized treatment and monitoring plan

In the evaluation of children with recurrent fever, it is essential to distinguish between benign periodic fever syndromes, such as PFAPA, and serious underlying conditions that require urgent investigation. Certain clinical features, laboratory abnormalities, and historical findings—referred to as red flags—serve as indicators of potentially severe disease, including primary immunodeficiencies, systemic autoinflammatory disorders, chronic infections, or malignancies. The following table summarizes the key red flags identified in the literature, categorizing them by clinical presentation, laboratory findings, and family history, along with their diagnostic significance and supporting references. This structured overview can assist clinicians in early recognition of high-risk patients and guide prompt, targeted diagnostic workup.

Table 3. Red flags in recurrent fever in children

Red Flag	**Clinical Significance**
Growth retardation	Suggests chronic systemic disease, malignancy, or immune deficiency rather than benign periodic fever
Unintentional weight loss	Raises concern for chronic infection, malignancy, or systemic inflammatory disease
Persistent laboratory abnormalities between febrile episodes	Anemia, neutropenia, or thrombocytopenia may indicate immune dysfunction, bone marrow pathology, or systemic disease
Hepatosplenomegaly	May indicate malignancy, chronic infection, or systemic inflammatory disorder
Severe systemic manifestations (e.g., marked malaise, organ involvement)	Suggests more aggressive autoinflammatory or systemic disease
Prolonged, irregular, or progressively worsening fever pattern	Atypical for classic periodic fever syndromes and warrants extended evaluation
Poor general condition between episodes	Inconsistent with benign periodic fever syndromes such as PFAPA
Positive family history of hereditary or autoinflammatory disease	Increases suspicion for monogenic periodic fever syndromes
Clinical features suggestive of malignancy, chronic infection	"B symptoms" in lymphoma: - fever - drenching night sweats - unexplained weight loss more than 10% of body weight within the previous 6 months.
Clinical features suggestive of primary immunodeficiency	- Frequent, severe, or unusual infections (e.g., recurrent pneumonia, pyoderma, opportunistic infections) - Abnormal response to vaccinations – lack of antibody production after vaccinations - Bacterial infections requiring long-term treatment or hospitalization - Family history of immunodeficiency

Discussion

In the diagnosis of recurrent fever in children, several pitfalls frequently occur, which can lead to unnecessary interventions or delayed recognition of serious conditions. One of the most common issues is the overuse of antibiotics. Many children receive repeated antibiotic courses for each febrile episode, even though most episodes are caused by viral infections or autoinflammatory disorders that do not require antibacterial therapy. Excessive pharmacological treatment not only increases the risk of adverse effects but may also mask symptoms of chronic conditions and delay accurate diagnosis.

Another critical aspect is the importance of longitudinal observation. Clinicians often attempt to make a diagnosis based on a single fever episode, leading to misinterpretation of laboratory results or misclassification as "frequent infectious child". Careful documentation of the frequency, duration, and associated symptoms of fever episodes allows better recognition of patterns characteristic of autoinflammatory syndromes such as PFAPA, FMF, or MKD, and helps distinguish them from self-limiting febrile illnesses.

The role of the primary care physician is essential in the initial evaluation of children with recurrent fever. PCPs should systematically monitor patients, identify potential red flags, and educate families on proper

documentation of fever episodes. Early risk stratification minimizes unnecessary invasive tests and prevents complications.

Equally important is the role of specialist consultation, particularly when fever persists, systemic symptoms appear, or autoinflammatory disease is suspected. Collaboration with pediatric rheumatologists, immunologists, or infectious disease specialists allows targeted genetic testing, proper classification of autoinflammatory syndromes, and individualized management planning. Early specialist involvement is especially critical in PFAPA, SURF, and other rare syndromes that require tailored therapeutic approaches.

In summary, avoiding unnecessary antibiotic use, systematic longitudinal observation, active involvement of the primary care physician, and timely specialist consultation constitute the foundation of effective management of children with recurrent fever. These steps reduce the risk of complications and facilitate timely and accurate diagnosis.

Conclusions

Timely recognition and evaluation of recurrent fever in children are crucial not only for establishing an accurate diagnosis but also for preventing potential complications associated with delayed or missed identification of serious conditions. Incorporating awareness of red flags into clinical practice allows healthcare providers to prioritize patients at higher risk, streamline further investigations, and tailor management strategies to individual needs. Beyond immediate diagnostic implications, early and structured assessment promotes longitudinal monitoring and informed decision-making, ultimately enhancing patient outcomes and supporting families through a complex and often anxiety-provoking clinical course.

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