

## Distinguishing Among Prolonged, Recurrent, and Periodic Fever Syndromes: Approach of a Pediatric Infectious Diseases Subspecialist

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Approaching the differential diagnosis of a child with a prolonged, recurrent, or periodic fever requires an extensive interview with disciplined dissection of the history. Diagnoses are considered and supported or excluded. Review of systems is used to understand the totality of the condition and to seek certain occurrences specific to diagnoses considered. A careful and complete physical examination is systems based, beginning with growth and ending with a thorough neurologic examination. Laboratory tests rarely establish an unexpected diagnosis. They are used to support or confirm a diagnosis, or to establish “wellness” of major organ systems as predicted by history and physical examination. This article discusses three objectives for the clinician: (1) to categorize patterns of fever illnesses and prioritize differential diagnoses; (2) to diagnose and manage the most frequently encountered prolonged fever syndrome, deconditioning; and (3) to expand knowledge and approach to diagnosing periodic fever syndromes. The approach described in this article represents the honed, 30-year experience of a pediatric infectious diseases subspecialist. Definitions of fever syndromes are shown in **Box 1**. **Figs. 1 and 2** are algorithms to help the pediatrician manage confidently

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### Box 1. Defining fever patterns\*

**Prolonged fever:** A single illness in which duration of fever exceeds that expected for the clinical diagnosis (eg, > 10 days for viral upper respiratory tract infections; > 3 weeks for mononucleosis)

or

A single illness in which fever was an initial major symptom and subsequently is low grade or only a perceived problem

**Fever of unknown origin:** A single illness of at least 3 weeks' duration in which fever > 38.3°C is present on most days, and diagnosis is uncertain after 1 week of intense evaluation

**Recurrent fever:** A single illness in which fever and other signs and symptoms wane and wax (sometimes in relationship to discontinuation of antimicrobial therapy)

or

Repeated unrelated febrile infections of the same organ system (eg, sinopulmonary, urinary tract)

or

Multiple illnesses occurring at irregular intervals, involving different organ systems in which fever is one, variable component.

**Periodic fever:** Recurring episodes of illness for which fever is the cardinal feature, and other associated symptoms are similar and predictable, and duration is days to weeks, with intervening intervals of weeks to months of complete well-being. Episodes can have either "clockwork" or irregular periodicity.

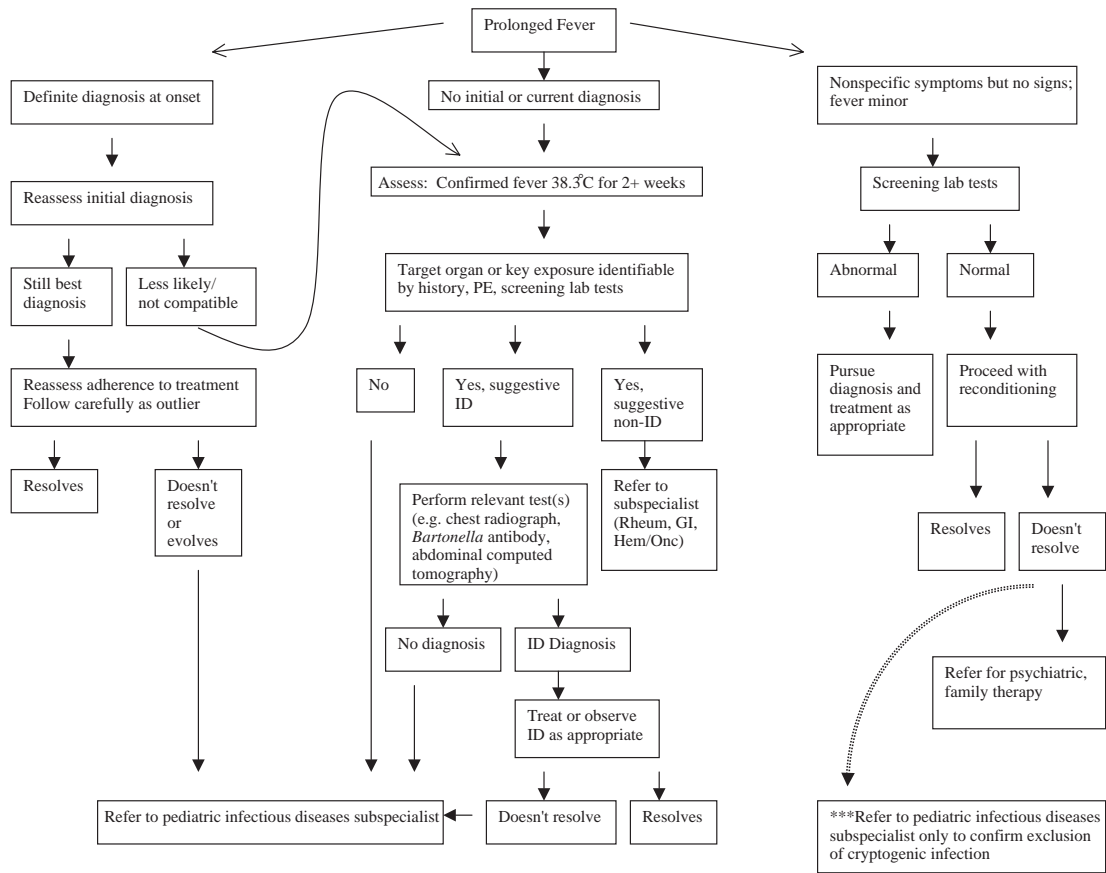
\* Categories are not diagnoses. Definitions are useful only as they help weight a differential diagnosis (see [Figs. 1 and 2](#)) and prioritize investigation and referral.

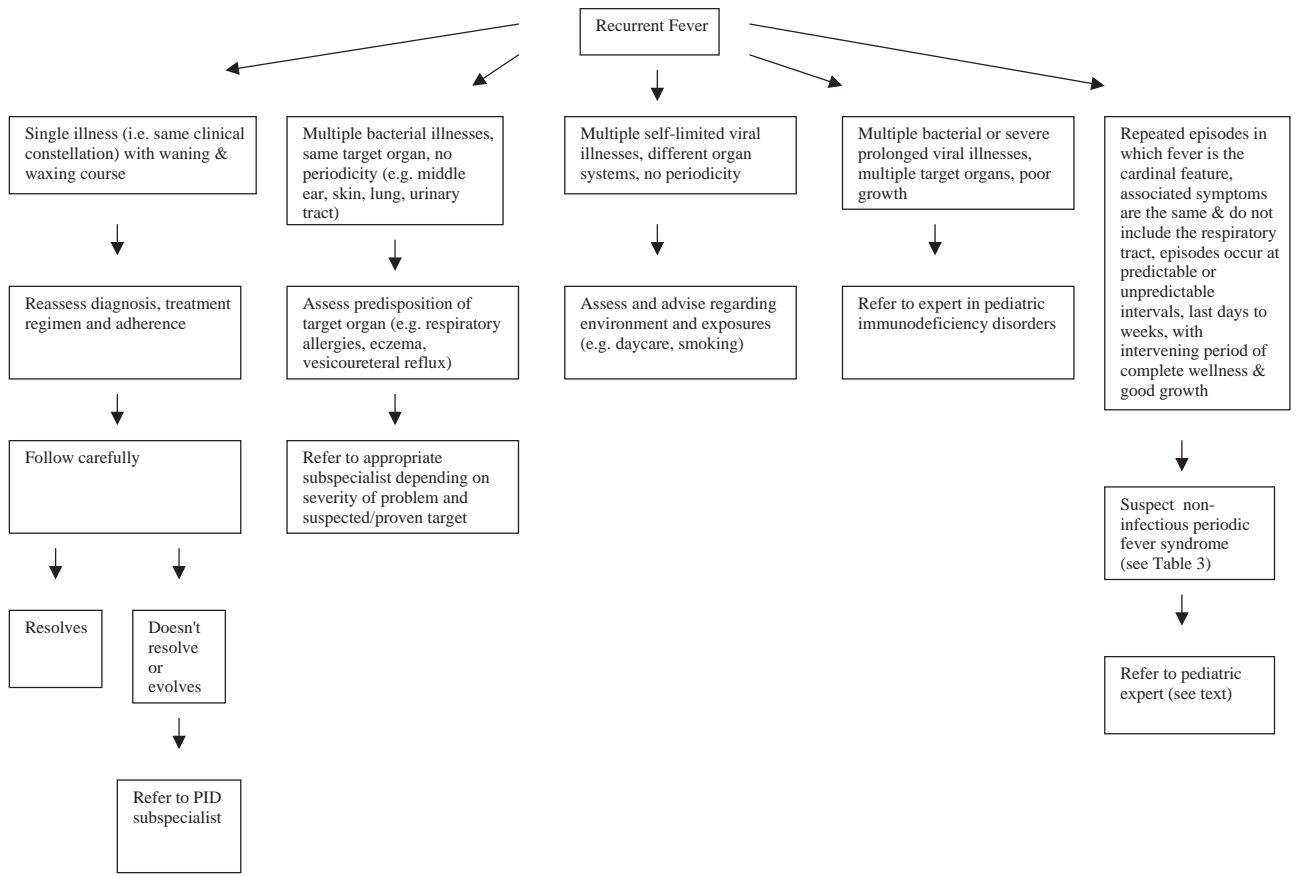
most patients with prolonged or recurrent fever and recognize patients who require subspecialty consultation.

## History

The most frequent outpatient consultation performed by this subspecialist is to evaluate children with the predominant complaint of fever or of a prolonged illness that includes fever. The first step is to categorize the illness according to the pattern and duration of the elevated temperature. The accompanying features

Fig. 1. Primary practitioner's decision tree for a child or adolescent with prolonged fever. GI, gastrointestinal; Hem/Onc, hematology/oncology; ID, infectious disease; PE, physical examination; Rheum, rheumatology.





of the illness, environmental exposures, and genetic background often are important clues to the diagnosis.

### *Fever of unknown origin*

By convention, fever of unknown origin (FUO) is defined as a single illness that has lasted for 3 or more weeks, with temperature greater than 38.3°C on most days and with uncertain diagnosis after 1 week of intense evaluation (formerly to include hospitalization; now to include CT of the abdomen). Attention to uncovering exposures, symptoms, signs, or laboratory findings that target an organ or multiple organs is the most fruitful approach to making the correct diagnosis. Excellent reviews of FUO are published [1–3]. A thoughtful differential diagnosis and performance of the crucial laboratory test is a more successful approach than is “running a list.” General principles of diagnosis of infectious diseases pertain to FUO—that is, the patient is more likely to have an uncommon presentation (ie, prolonged fever) of a common disease than an uncommon disease [4]. The frequent diagnosis of visceral cat-scratch disease as a cause of FUO is an example, and a history of exposure to kittens is the clue [3,5]. Table 1 provides examples in which the obvious findings of conditions may be absent, but subtle findings can lead to a simple test to confirm the diagnosis, the best working diagnosis, or the site for biopsy.

There are a few infectious diseases for which fever and nonspecific symptoms and signs may be the only findings, such as endocarditis, tuberculosis, and chronic meningococcemia. Blood cultures for routine bacteriology and isolation of mycobacteria should be performed in patients with FUO. There are numerous cases of FUO that are not infectious diseases. Inflammatory diseases and neoplasms are prominent among the noninfectious etiologies. Follow-up for development of specific organ or laboratory abnormalities may be the only way to diagnose some malignancies. Removing exposures to “medicinal” products can be diagnostic and therapeutic.

### *Prolonged illness with fever*

One of the most frequent referrals to pediatric infectious disease subspecialists for “prolonged fever” is an adolescent with low-grade or falsely perceived fever who generally feels unwell and is unable to attend school and social activities – the adolescent has the so called “dwindles”. Such patients require the same disciplined performance of history and examination as those with true FUO. Referral to a pelvic inflammatory disease subspecialist frequently is one of many. For the subspecialist to offer a definitive opinion, the family must perceive that a thorough and thoughtful consultation has occurred. All laboratory test results, actual imaging studies, and biopsy slides should be reviewed. The

Table 1  
Clues to diagnosis in enigmatic cases of fever of unknown origin\*

Disorder	History	Examination	Abnormal screening laboratory test
Inflammatory bowel disease	Vague intermittent abdominal discomfort or loose stools	Mild abdominal tenderness or guarding; perianal skin tag; erythema nodosum; decreased velocity of growth	Hypochromic, microcytic anemia; elevated ESR or CRP; occult blood test on stool; pANCA test
Bacterial endocarditis	Fatigue	Cardiac murmur, splenomegaly, splinter hemorrhages	Anemia, thrombocytopenia; urinalysis with RBCs; elevated ESR; decreased complement
Visceral cat-scratch disease	Kitten exposure	Papular skin lesion; abdominal tenderness; hepatomegaly, splenomegaly	Elevated ESR
EBV infection	Fatigue, periorbital edema	Splenomegaly	Reactive lymphocytes; elevated serum hepatic enzymes; elevated direct bilirubin
HIV infection	Mononucleosis-like (rash, sore throat, myalgia, arthralgia), night sweats	Lymphadenopathy, pharyngitis	Reactive lymphocytes, leukopenia, thrombocytopenia

<i>Salmonella, Yersinia</i> infection	Exposure; no appetite → rapid weight loss	Mild lower or right upper quadrant abdominal tenderness or guarding	Left shift neutrophils; mildly elevated serum hepatic enzymes; ESR > 60 mm/h
sJIA Malignancy	Fatigue; broad daily fever swings Fatigue, excessive weight loss unrelated to appetite	Truncal rash during fever Unusual node enlargement (eg, supraclavicular, post-cervical, asymmetric tonsillar enlargement)	ESR > 60 mm/h, frequently ≥100 mm/h Neutropenia or all blood cell lines decreased; elevated serum uric acid
Nephrogenic diabetes insipidus	Morning fever; “excess” fluid intake	Normal	Normal CBC and ESR; hypernatremia, elevated BUN
Drug hypersensitivity	History of use of nonprescription, prescription or alternative medicine product	Normal	Mild eosinophilia
Chronic inflammatory pseudotumor	Mild, persistent abdominal discomfort; poor appetite	Mild abdominal tenderness or guarding	Anemia of chronic inflammation; elevated ESR (< 60 mm/h)

*Abbreviations:* CRP, C-reactive protein; EBV, Epstein-Barr virus; ESR, estimated sedimentation rate; pANCA, perinuclear antineutrophil cytoplasmic antibody; RBCs, red blood cells; sJIA, systemic-onset juvenile idiopathic arthritis.

\* Clues on history, examination, or a laboratory test result that frequently are subtle or have been overlooked. Usually present singly; notation can lead to a narrow differential diagnosis or focused confirmatory test.

findings listed in [Box 2](#) taken together suggest that no cryptogenic infection or serious medical condition is present. Deconditioning (ie, diminution of physical strength, stamina, and vitality), loss of self-esteem, fear of failure to perform at previous expectation, and secondary gain all may play into the clinical state of affairs.

Before the illness, the patient usually was a super-energetic athlete or super-achieving student. Self and family expectations are high. Self-esteem or place in the family rests on achievement. An acute illness occurred, with clear date of onset and objective findings—frequently fever, headache, congestion, muscle aches, poor appetite, and excessive sleeping—which precluded usual activities and which attracted concern of parents, extended family, schoolmates, coaches, or teachers. The acute illness is self-limited, but the adolescent does not feel “100%” well and does not return to school or activities. All interested parties become more concerned. The primary practitioner recommends rest.

A family *modus operandi* ensues that centers around the patient despite lack of objective abnormalities. Over the next 4 to 6 weeks, the patient becomes increasingly sedentary. Temperature infrequently exceeds 38°C after the first week. Review of systems usually elicits multiple subjective positive responses. Weight that was lost in the first 2 weeks has been regained; sometimes there is excessive weight gain. Prodded recitation of a typical 24-hour period of activity reveals late morning awakening, snacking, lounging, hours of television and computer activity, performance of home-delivered or e-mail-delivered schoolwork, and no or little daytime sleep despite constant feeling of tiredness. Evening activity is talking with family or friends (by telephone or computer) and early retirement to room but difficulty (and often late) falling asleep, which is then uninterrupted. There is no physical exertion or exercise. Forays into social events or school frequently are avoided or aborted for fear of or for feeling of tiredness

### **Box 2. Typical findings in patients with deconditioning**

- Age >12 years
- Preillness achievement high
- Family expectations high
- Acute febrile illness with onset easily dated
- Family and outside attention high
- Lengthy list, but vague complaints
- Odd complaints (eg, “shooting” pains; 30-second “blindness”; stereotypic sporadic, brief unilateral tremors, jerks, or “paralysis”)
- No daytime sleep
- Preserved weight
- Extreme cooperation with examination
- Normal physical and neurologic examination
- Normal results of screening laboratory tests (see text and [Box 4](#))

or faintness. When the adolescent is asked what physical problem precluded attending school the day before, there is no concrete answer. There may be a family model of chronic illness, mental illness, or recent loss of a person important to the patient. The patient is dispassionate at least or is highly animated while enumerating symptoms and expresses hopes and plans for the future when queried. (If this is not the observed affect, depression is a possible diagnosis.) The patient and parent should be interviewed alone to inquire about disruptive family events or possible abuse.

Physical and neurologic examinations and growth are normal. Laxity of joints has been a finding in some patients with prolonged fatigue [6]. Screening laboratory tests (complete blood count; serum chemistry tests of electrolytes, blood urea nitrogen and creatinine, hepatic enzymes, uric acid, calcium and glucose; erythrocyte sedimentation rate and C-reactive protein; urinalysis) are normal; when extensive laboratory testing has been performed, an unimportant finding out of the normal range may be present. Sometimes Epstein-Barr virus, cytomegalovirus, or Lyme serologic testing has been interpreted incorrectly.

It is a disservice to diagnose “chronic fatigue syndrome” in such a patient or to infer a need for or to refer to another subspecialist for targeted symptoms when they are minor, such as congestion or headache. Two precise conclusions of the consultation should be addressed with the parents and patient: what the diagnosis is not and what it is. After oral summation of the history, it is concluded that maintenance of weight, abnormal pattern but not excessive sleeping, normal physical examination (naming the organ systems evaluated), and normal screening laboratory tests (naming the organ systems evaluated) so many weeks after onset of illness virtually exclude cryptogenic infection and serious medical conditions. Pointing out the discordance of the lengthy list of symptoms versus the normal matching physical and test findings of critical organ function helps segue to the assessment of the problem as deconditioning rather than ongoing disease. Treatment includes forced, incremental return to school and other activities (with any day’s decision to stay home requiring examination by the pediatrician) and promises from family members to levy no expectation of productivity and to focus on health rather than illness. Finally, the thoughtful physician needs to validate that the patient truly feels ill and will have to work through increased feeling of fatigue during the reconditioning process. The pediatrician needs to assume the leadership role in setting the pace of activity and determining the need for professional family therapy or psychiatric care.

### *Recurrent fever*

Children normally have 10 or fewer self-limited viral illnesses per year for the first 2 to 3 years of life. Children attending daycare have more. Many of these illnesses are associated with fever, especially when complicated by otitis media (or especially in the “otitis-prone child”). A child with multiple, self-limited illnesses, no serious or unusual infections, and good growth and development should not be pursued for a defect in host immune response or cryptogenic

Table 2  
Differentiating features in the history that help to categorize the problem in children with recurrent fever

	Self-limited infections in healthy child	Compromised host*	Child with a periodic fever syndrome
Periodicity of episodes	Irregular	Relapse/recurrence of bacterial infection quickly after discontinuation of antibiotics	Clockwork periodicity or irregularly frequent or occasional
Characteristics of episodes	Waning and waxing course of a single illness (eg, EBV); multiple simple illnesses (ie, different symptoms, exanthems, diagnoses)	Slow response to treatment of bacterial infections (eg, sinopulmonary); some episodes require hospitalization/parenteral antibiotic therapy	Abrupt onset and cessation; fever dominant; no respiratory tract symptoms
Clustering of episodes	Concurrent illness in contacts (home, daycare, school); few-to-no episodes in summer	Ill during all seasons, when others are and are not	Episodes during all seasons; contacts are not ill before or after
Course of episodes	Each as expected for infectious agent	Even simple infections (eg, AOM, skin and soft tissue infections) are protracted; skin infections heal with scarring	Identical, symptoms predictable course
History of identifiable childhood illnesses	Expected course (eg, chickenpox, HSV stomatitis, gastroenteritis)	Severe and protracted course; hospitalization	Expected course (often notably less ill, less frequently than peers)
Interval between episodes	Completely well (or frequently atopic symptoms)	Never well generally; lingering specific symptoms	Completely well
Catch-up growth and energy	Excellent	Poor	Excellent

*Abbreviations:* AOM, acute otitis media; EBV, Epstein-Barr virus; HSV, herpes simplex virus.

\* Conditions such as acquired (HIV-associated) or congenital immunodeficiency, cystic fibrosis, or ciliary dyskinesia.

**Box 3. Targeted questions in history of episodes for children with suspected periodic fever syndrome**

- Prodrome and first symptoms of episode
- Cadence of appearance of other symptoms
- Peak of fever
- Duration of fever
- Associated symptoms and signs (eg, exanthem; mouth ulcers; pain in abdomen, chest, or joints; mood change)
- Duration of associated symptoms and signs
- Similarity of symptoms and course for each episode

infection. Although most children with recurrent fevers have had a series of self-limited infections, other infectious disease considerations include recurrent urinary tract infection, sinopulmonary infection, and occult dental infection. With history of certain exposures, brucellosis, borreliosis, and malaria are considered. Autoimmune diseases (eg, systemic lupus erythematosus) and especially auto-inflammatory diseases (eg, inflammatory bowel disease and systemic-onset juvenile idiopathic arthritis) also can manifest as recurrent fever [7,8]. Additional targeted questions help to sort through common recurring, self-limited viral illnesses in healthy children to uncover the unusual child with a periodic fever syndrome or the rare child with a congenital or acquired defect in immune function (Table 2). Most importantly, the exact features of the episodes, the rapidity of return to health at the conclusion of episodes, time interval between episodes, and family history should be determined. Key elements of periodic fever syndromes are that fever is the cardinal feature of the illness, episodes recur after symptom-free intervals, and episodes have a predictable course (ie, the same constellation of symptoms) and lack respiratory tract symptoms. Specific features of episodes are identified (Box 3). Family history includes genetic background and history in family members or siblings of similar problems, autoimmune or autoinflammatory illness, or amyloidosis. It is important to query whether immunizations elicit a highly febrile response or trigger a typical episode.

**Physical examination**

The physical examination and laboratory evaluation are important components of the evaluation of children with prolonged, recurrent, or periodic fever (Box 4). A great deal of reassurance can be obtained if evaluation of the growth chart reveals recovery of weight between episodes of fever and steady velocity of height and weight increments over time. Inflammatory bowel disease can present with recurring fevers (that typically are “low grade” and of variable periodicity). Examination is aimed at excluding abnormalities in target organs that might be affected if infection is the cause of prolonged fever and to ascertain the presence

**Box 4. Physical examination and laboratory testing in children with prolonged, recurrent, or periodic fever***Physical examination*

- Growth chart
- Thorough general examination
- Careful organ-specific examination
- Notation of mouth ulcers, exanthem, joint abnormalities, lymph nodes

*Tests*

- Simple (during episode and interval, if periodic fever)
- Complete blood count with manual differential count of white blood cells
- Erythrocyte sedimentation rate and C-reactive protein
- Screening serum chemistry tests (and uric acid level if prolonged fever)
- Serum quantitative immunoglobulin levels
- Urinalysis
- Urine culture
- Chest plain radiograph (if prolonged or recurrent fever)
- Other imaging only as directed by examination
- Blood culture (if prolonged fever)

of signs consistent with noninfectious diseases, such as malignancies and autoimmune, endocrine, and metabolic disorders. Special attention should be given to the presence of mouth ulcers, gingivitis, or rashes; abnormalities of joints or lymph nodes; or findings on abdominal examination in patients being assessed for a periodic fever syndrome.

**Laboratory evaluations and imaging studies**

Laboratory testing for patients with prolonged or recurrent fever are simple and should be targeted to specific organs (see **Box 4**) [1,2,4]. The main goal of performing laboratory tests in children with periodic fever is to lead the clinician toward a specific disorder (eg, recurrent urinary tract infection) or to support the diagnosis of a noninfectious periodic fever syndrome. Simple tests rarely *confirm* a specific noninfectious periodic fever syndrome. Tests for unusual infectious causes of recurrent fever rarely are diagnostic in the absence of a specific exposure history.

The initial tests to consider in the workup of patients with prolonged or recurrent fever include complete blood count with manual examination of white blood cells; erythrocyte sedimentation rate and C-reactive protein; screening serum chemistry tests, including hepatic enzymes and albumin; quantitative immunoglobulins, including IgA, IgD, and IgE. Bacterial cultures of blood and urine should be performed during at least two febrile episodes, and culture of a throat specimen for *Streptococcus pyogenes* should be obtained if pharyngitis symptoms or signs have been present.

### Differential diagnosis of periodic fever

Periodic fever is defined as recurrent episodes of illness in which fever is the cardinal feature and is associated with a predictable and similar set of symptoms that last days to weeks. Each episode is separated by symptom-free intervals ranging from weeks to months. In some instances, the episodes have *consistent, clockwork periodicity*, whereas in others, they do not. Patients with auto-inflammatory disorders in which recurrent urticaria, arthritis, and multiorgan dysfunction are the prominent feature of the febrile episodes are not likely to be referred to infectious diseases consultants [9,10]. These disorders include Muckle-Wells syndrome, familial cold autoinflammatory syndrome, neonatal-onset multisystem disease, and chronic infantile neurologic cutaneous and articular syndrome. These disorders are not discussed further. Disorders that are discussed all have the cardinal feature of periodic fever; they are considered in order of their frequency (Table 3).

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenopathy (PFAPA) is the most common disorder with periodic fever, it has no defined etiology, and no confirmatory laboratory tests are available. Other syndromes are uncommon, and each syndrome is associated with a specific genetic mutation that can be diagnosed. Only cyclic neutropenia has a simple confirming laboratory test finding (neutropenia) and confirming genetic mutation. Several excellent reviews of the hereditary periodic fever syndromes are published [11–14]. With genetic testing becoming available (<http://www.genedx.com>), disorders previ-

Table 3  
Periodic fever syndromes\*

Syndrome	Cause
PFAPA syndrome	Unknown
Cyclic neutropenia	Enzyme defect
Familial Mediterranean fever	Protein defect
HIDS	Enzyme defect
TRAPS	Protein defect

*Abbreviations:* HIDS, hyperImmunoglobulinemia D; TRAPS, tumor necrosis factor receptor-associated syndrome.

\* Conditions for which the patient is likely to be referred to an infectious diseases subspecialist.

Table 4  
Differentiating features of periodic fever syndromes

	PFAPA	Cyclic neutropenia	Familial Mediterranean fever	HIDS	TRAPS
Onset <5 y	Expected	Usual; often <1 year old	Common; peak onset middle of first decade	Expected; often <1 year old	Variable
Length fever episode	4 d	5–7 d	2 d	4 d	Weeks; sometimes days
Periodicity of episodes	q3–6 wk (28 d)	q21 d in >90%	Irregular intervals: weekly, q3–4 mo or less often	q4–8 wk or irregular	Irregular intervals; varies weeks to years
Associated symptoms/signs	Pharyngitis 65–70%; aphthous stomatitis 65–70%; cervical adenopathy 75–85%	Ulcers, gingivitis, periodontitis; otitis media and sinusitis; rare peritonitis; rare gram-negative bacillary or clostridial septicemia	Polyserositis; erysipelas-like rash; scrotal pain and swelling	Abdominal pain, diarrhea in young; arthralgia; rashes; splenomegaly; mood swings; immunizations trigger	Migratory myalgia; pseudocellulitis; conjunctivitis, periorbital edema; other
Ethnic/geographic	None; rare in siblings	No ethnic	Jewish, Armenian, Arab, Turkish	Dutch, French, others	Irish and Scottish but variable including Mediterranean descent

Inheritance	None; parent may have history of excessive high fevers as child	Autosomal dominant	Autosomal recessive	Autosomal recessive	Autosomal dominant
Laboratory findings	Mild neutrophilia; ESR elevated <60 mm/h during episode only	Absolute neutrophil count <200 cells/mm <sup>3</sup> for 3–5 d	Elevated acute-phase reactants	Elevated acute-phase reactants; variable ↓ serum cholesterol; variable ↑ IgA and IgD	Elevated acute-phase reactants
Etiology/diagnosis	Unknown; clinical diagnosis	Chromosome 19; <i>ELA2</i> mutations leading to mutant neutrophil elastase; apoptosis marrow myeloid cells	Chromosome 16; <i>MEFV</i> missense mutations leading to ↓ pyrin	Chromosome 12; <i>MVK</i> mutations leading to ↓ mevalonate kinase and isoprenoids	Chromosome 12; <i>TNFRSF1A</i> mutations leading to ↓ soluble TNF receptor superfamily type 1A
Treatment	None established (see text)	Recombinant G-CSF; aggressive periodontal care; aggressive treatment suspected septicemia	Colchicine	Simvastatin (preliminary) Etanercept (preliminary)	Corticosteroid Etanercept (preliminary)

*Abbreviations:* ESR, erythrocyte sedimentation rate; G-CSF, granulocyte colony stimulating factor.

*Modified from* Long S. Periodic fever. In: Pollard AJ, Finn A, editors. Hot topics in infection and immunity in children. New York: Kluwer Academic/Plenum Publishers; 2005. p. 101–15.

ously believed to be rare are being diagnosed increasingly, and spectra of clinical findings are being broadened. Differentiating features of periodic fever syndromes are shown in [Table 4](#) [15].

### *Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenopathy*

PFAPA is a nonhereditary, autoinflammatory disorder first described in 12 children from Tennessee and Alabama in 1987 [16]. Now more than 200 cases have been described or anecdotally reported representing all racial backgrounds and continents except South America and Africa. Europe, and the Middle East account for most cases outside the United States. No case definition or diagnostic test has been universally agreed on. Population-based incidence figures do not exist. There may be underrepresentation in the United States of African American and Hispanic children; referral bias cannot be excluded as a reason. In the United States, the diagnosis of PFAPA is much more common than the diagnoses of cyclic neutropenia and other genetically determined periodic fever syndromes. In 1992, Feder [17] reported a beneficial effect of cimetidine on the manifestations of individual episodes and frequency of recurrent disease. In 1989, Abramson et al [18] reported unexpected resolution of PFAPA after tonsillectomy in three cases. Except for two anecdotal cases, in which Epstein-Barr virus infection with aberrant antibody response was reported [19] and disseminated *Mycobacterium chelonae* infection was proved in a normal child [20], no infectious or autoimmune cause of this disorder has been established. Marshall et al [16] noted dramatic resolution of individual episodes of illness after a single-dose corticosteroid; subsequent reports supported this observation [21–23].

### *Clinical features*

Based on numerous case series, a constellation of signs and symptoms has emerged that distinguish PFAPA as a syndrome, separate from others (see [Table 4](#)). Slight male predominance and onset before 3 years old (almost always before 5 years old) are typical. The child has a brief prodrome of clinginess and “glassy eyes,” then suddenly temperature increases to 39°C to 40.5°C followed by poor appetite, low energy, and chills but no rigors. Fever typically is poorly responsive to acetaminophen or ibuprofen and lasts 3 to 4 days. During the episode, a few shallow, mildly painful ulcers may appear in the mouth. All symptoms and signs cease after 4 to 5 days. Episodes occur at intervals of 21 to 36 days (typically 28 days). The only laboratory abnormalities are mildly elevated white blood cells during episodes (typically approximately 13,000/mm<sup>3</sup>) with neutrophilia and sometimes a modest left shift. Platelets are normal or modestly elevated (<400,000/mm<sup>3</sup>); erythrocyte sedimentation rate is elevated (usually <60 mm/h). Hemoglobin characteristically is unaffected; urinalysis is normal; serum hepatic enzymes, albumin, and immunoglobulins are normal.

Between episodes, children have no lingering symptoms, seem uncommonly energetic, and have good appetite. They do not have recurrent, unusual, or severe

infections. Parents report fewer “regular colds” than siblings or peers. Any laboratory abnormality reverts to normal between episodes.

In most cases, the syndrome is typical, and the working diagnosis is made with confidence. PFAPA should not be the working diagnosis if age of onset is older than 5 years, the child is not completely healthy outside of episodes, “extra symptoms” exist (eg, repeated or severe gastrointestinal or neurobehavioral symptoms) during episodes, or when a sibling also has a periodic fever syndrome.

PFAPA is considered to be an autoinflammatory syndrome. It has no known cause, and there is no confirming diagnostic test. Sometimes a single dose of prednisone at the onset of an episode may be useful as a “test.” Although rapid resolution is expected in PFAPA, the specificity of this response is unknown.

#### *Treatment and outcome*

In 1999, Thomas et al [21] reported a follow-up study of 94 children cared for in Tennessee and Connecticut over a 10-year period. Mean age at follow-up was 8.9 years. Mean duration of PFAPA was 4.5 years; only 41% of children had resolution over the mean follow-up of 3.3 years, and episodes retained characteristics as on diagnosis. Cimetidine, which was used in less than one third of the children for either treatment or prophylaxis, was judged to be “somewhat-to-very effective” in 43%. Prednisone (most often given as one or two doses of 1–2 mg/kg/d) was judged to be somewhat-to-very effective in 90%. Inexplicably, but consistent with the experience of most experts, prednisone often was associated with more frequent episodes of illness. Tonsillectomy and adenoidectomy was performed in 47 of the 94 children and was judged to be somewhat-to-very effective in 86%. Characteristics of febrile episodes do not change in PFAPA, although wellness interval may lengthen as a harbinger of resolution. The working diagnosis should be revisited over time because other periodic fever syndromes evolve over years, and sometimes initial features could mimic PFAPA.

#### *Cyclic neutropenia*

Cyclic neutropenia is a rare hematologic disorder characterized by regular cycling of the peripheral neutrophil count (to nadir of  $<200$  cells/mm<sup>3</sup>), and a symptom complex manifesting during the neutropenic nadirs. Because blood monocytes, reticulocytes, platelets, and lymphocytes can have similar periodic oscillations as neutrophils, the disorder sometimes is called *cyclic hematopoiesis*.

Cyclic neutropenia was first recognized almost a century ago. The autosomal dominant pattern of inheritance, natural history, and clinical associations of mucosal ulcerations and skin infections were described half a century ago. In 1989, Hammond et al [24] reported the favorable response to granulocyte colony-stimulating factor, and 10 years later mutations of the gene for neutrophil elastase (*ELA2*) were identified [25]. All cases of cyclic neutropenia and most cases of severe congenital neutropenia are due to mutations of *ELA2*. In 2001, Aprikyan

et al [26] hypothesized that accelerated cellular apoptosis was the cause for cyclic neutropenia.

### *Clinical features*

Diagnosis of cyclic neutropenia usually is established early in childhood. Cardinal features include recurrent fever with clockwork periodicity, pharyngitis, mouth ulcers, and lymphadenopathy. Some cases are diagnosed because of recurrent cellulitis or furunculosis. Compared with the mild oral manifestations of PFAPA syndrome, children with cyclic neutropenia complain of deep and painful mouth ulcers that often last more than 1 week. In contrast to PFAPA, gingivitis and periodontitis are common in patients with cyclic neutropenia. Recurrent bacterial otitis media, sinusitis, and pharyngitis are frequent. Recurrent cellulitis and furunculosis after insect bites, minor cuts, or abrasions distinguish cyclic neutropenia from other periodic fever syndromes. Some patients have few and relatively minor associated bacterial infections, but acute bacterial peritonitis and septic shock and overwhelming gram-negative bacillary or clostridial septicemia resulting from colonic ulcers during the period of neutropenia have been described. Bacterial complications occur only during the periods of neutropenia. Although ulcers, gingivitis, and periodontal disease linger, the child usually is well before the onset of the next episode.

### *Etiology and diagnostic tests*

During the neutropenic period, peripheral neutrophils are reduced to less than 200 cells/mm<sup>3</sup> for 3 to 5 days. The count then usually increases to about 2000 cells/mm<sup>3</sup>, where it remains until the next neutropenic period. If bone marrow is examined at the onset of neutropenia, early myeloid precursors are present, but postmitotic neutrophils are absent. Recovery is rapid, with cells from promyelocytic to band neutrophilic forms. Because neutropenia appearing in the peripheral blood may be resolving by the time the clinical features of fever, stomatitis, and tender lymphadenopathy appear, children with a history compatible with cyclic neutropenia should have twice-weekly complete blood counts performed beginning during the interval of wellness and continuing through the next febrile episode.

Cyclic neutropenia is inherited as an autosomal dominant disorder with full penetrance but varying severity of clinical manifestations. Commonly an affected parent of a child with cyclic neutropenia has not been recognized because of milder clinical and laboratory manifestations. The genetic abnormality is localized to chromosome 19p13.3, resulting in mutation of *ELA2* and its neutrophil elastase protein product. Diagnosis is confirmed by genetic testing.

### *Treatment and outcome*

Adverse effects of cyclic neutropenia include pain and discomfort, periodontal disease frequently resulting in deciduous tooth extractions in childhood, recurrent common bacterial infections, and serious or life-threatening bacterial infections. Increased rates of spontaneous abortion in women with cyclic neutropenia have

been reported. No tendency toward malignancy has been noted in children with cyclic neutropenia.

Most children with cyclic neutropenia should be treated with recombinant granulocyte colony-stimulating factor daily or on alternate days ( $\leq 5 \mu\text{g/kg/d}$ ) [27]. More than 90% of children respond to this therapy with a reduced frequency of episodes of neutropenia and associated complications.

### *Familial Mediterranean fever*

Familial Mediterranean fever (FMF) is an inherited autoinflammatory syndrome in which seemingly unprovoked or minor stress or trauma causes fever and inflammatory serositis/synovitis without autoantibodies or autoreactive T lymphocytes. FMF is an autosomal recessive disease and the most prevalent inherited periodic fever syndrome, affecting more than 10,000 individuals worldwide. FMF is almost completely restricted to non-Ashkenazi Jews, Armenians, Arabs, and Turks [28]. More than 90% of Jewish FMF patients are of Sephardic or Middle Eastern origin. The high heterozygous carrier frequency ( $>1$  in 10 North African Jews and Armenians) is speculated to have conferred survival advantage, probably against an infectious pathogen [29]. In 1997, the International Familial Mediterranean Fever Consortium and the French Familial Mediterranean Fever Consortium independently cloned the mutant *MEFV* gene, the former group naming the protein product *pyrin* (indicating relationship to fever) and the latter group calling it *marenostrin* (meaning “our sea,” indicating relationship to the Mediterranean Sea). Pyrin protein is a member of the death-domain-fold superfamily, which provides critical biochemical pathways of apoptosis and innate immunity [30,31].

*MEFV* mutations are more varied and complex than originally described. Single genotype-phenotype correlations are not solid, and multiple genotypes exist. Description of manifestations as if FMF were a single disease are valuable only as generalities.

### *Clinical features*

Symptoms of FMF begin before age 2 years in 20% of patients; two thirds of affected individuals have manifestations before 10 years of age. Less than 10% have onset after age 30. Episodes do not have predictable periodicity. A typical attack is heralded by abdominal pain, then an increase in temperature to  $40^{\circ}\text{C}$  followed by chills. Fever lasts 12 hours to 3 days and is rarely the only manifestation. Abdominal pain, which is sometimes accompanied by diarrhea, is present in greater than 90% of patients, begins suddenly a few hours before fever, and persists 1 to 2 days after defervescence. This presentation can simulate other causes of “acute abdomen,” and attacks can follow surgical trauma to the peritoneal serosa. Pleuritic chest pain occurs in 25% to 80% of patients; it is the presenting manifestation in less than 10% of patients. Pericarditis is less common ( $<1\%$  of cases). Small fluid collections can be detected by various imaging techniques when serosal involvement occurs. Arthritis is common and varies in

nature by ethnic origin. Acute pain and effusion in the wrists, ankles, or knees, occurring asymmetrically and resolving completely over days, is typical. An erysipelas-like exanthem reported in 7% to 40% of patients almost invariably affects the extensor surface of the lower leg and dorsum of the foot. It usually is unilateral and fades spontaneously within 2 to 3 days. Splenomegaly occurs in 30% to 50% of patients.

#### *Etiology and diagnostic tests*

There is no specific laboratory marker for FMF. During febrile attacks, nonspecific elevations in inflammatory mediators, fibrinogen, C-reactive protein, neutrophils, and erythrocyte sedimentation rate occur. If sampled, serosal or synovial fluid shows neutrophilic pleocytosis. Proteinuria (>0.5 g protein/24 h) in patients with FMF suggests amyloidosis. At least 28 mutations in the *MEFV*, most clustered in one exon, have been described on the short arm of chromosome 16. Genetic testing is the confirmatory test for FMF, with some limitations. Genetics laboratories usually screen for the five most frequent mutations (accounting for 85% of FMF). Also, single mutant-allele disease and double mutant-allele nondisease are described.

#### *Treatment and outcome*

Colchicine is the treatment of choice. The drug is concentrated in neutrophils, where it acts on microtubules, possibly by up-regulating *MEFV* gene expression. Colchicine prevents attacks in 60% of individuals with FMF and significantly reduces the number of attacks in an additional 20% to 30%. Adherence to therapy is important because attacks can follow within days of discontinuance. Regardless of efficacy in prevention of attacks, colchicine therapy arrests or prevents amyloidosis, the life-threatening complication of FMF.

#### *Hyperimmunoglobulinemia D and periodic fever syndrome*

Hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) was first described in several Dutch patients by van der Meer et al in 1984 [32]. Most patients with HIDS are white and from western European countries; 60% are Dutch or French. The HIDS registry in the Netherlands currently has data on more than 200 patients worldwide. In 1999, the defect in HIDS patients was mapped to mutations in the *MVK* gene on the long arm of chromosome 12 that encodes mevalonate kinase [33,34]. HIDS is inherited as an autosomal recessive trait; most affected patients are compound heterozygotes for missense mutations in the *MVK* gene. In most patients with HIDS, the activity of mevalonate kinase is 5% to 15% of normal. Less than 1% of patients have complete deficiency of the enzyme, which is associated with mevalonic aciduria. Mevalonic aciduria is characterized by dysmorphic features, failure to thrive, mental retardation, ataxia, recurrent fever attacks, and death in early childhood. Five adults with neurologic signs and symptoms and mevalonate kinase deficiency have been

described, suggesting that there may be overlap syndromes and a continuum of disease [35].

### *Clinical features*

Recurrent attacks of fever usually begin in the first year of life [36]. Periodicity can vary, but recurrence every 4 to 6 weeks is typical. Characteristically, some attacks are triggered by immunization, injury, or stress and heralded by chills followed by a rapid increase of temperature to 39°C or greater. Fever usually lasts 4 to 6 days. Headache, abdominal pain, vomiting, and diarrhea may accompany attacks. Some children with HIDS display irritable or aggressive behavior during febrile attacks.

Prominent cervical lymphadenopathy is common. Arthralgias or arthritis of medium joints (knees, ankles, wrists) and an erythematous macular, popular, or petechial rash predominantly on extremities are less common. Painful aphthous ulcers in the mouth or vagina occur in some patients. Orchitis has been described. Patients are well between attacks, and growth is unimpaired. With increasing age, frequency and severity of febrile episodes tend to decrease.

### *Etiology and diagnostic tests*

HIDS should be suspected when periodic fever begins in infancy. Elevated serum levels of IgD (>100 IU/dL) and IgA (>5 times upper limit of normal) are characteristic but not universally present, especially in children younger than 3 years old [36,37]. Screening for *MVK* mutations is confirmatory. More than 20 mutations have been identified, but one mutation, *V377I*, is present in more than 80% of patients. Screening for this mutation is an important first step. If the mutation is not found, and suspicion remains high, sequencing of the gene to detect other mutations is indicated. Measurement of mevalonate kinase activity in leukocytes or urine has intrinsic limitations and is not recommended as a diagnostic test.

### *Treatment and outcome*

There is no established treatment for HIDS. Beneficial effect of simvastatin, which acts by inhibiting hydroxymethylglutaryl-coA reductase in the isoprenoid pathway, has been reported [38]. Although abnormalities of tumor necrosis factor (TNF)- $\alpha$  are not the primary cause of HIDS, plasma TNF- $\alpha$  levels are elevated in HIDS patients during attacks. Treatment with etanercept has been reported [39]. Although HIDS previously was not thought to be associated with increased mortality or amyloidosis, the first case of amyloidosis in a patient with HIDS was reported in 2004 [40].

### *Tumor necrosis factor receptor-associated periodic syndrome*

The TNF receptor-associated periodic syndrome (TRAPS) was first described in 1982 in a large Irish family. It was called familial Hibernian fever [41]. Although most of the reported families with TRAPS are of Irish and Scottish

descent, a wide range of ethnic origins have been reported [42]. Although inheritance is autosomal dominant, there is variable penetrance, and sporadic cases appear occasionally. The susceptibility gene for this familial periodic fever syndrome had been mapped to the short arm of chromosome 12. It results from a missense mutation in the *TNFRSF1A* gene, from which the name *TRAPS* arises [43,44]. The hypothesized pathogenesis of TRAPS is that missense mutations lead to structural abnormalities that cause failure of shedding of TNF- $\alpha$  receptor from its intracellular site to the extracellular circulation, where binding to TNF- $\alpha$  would prevent ongoing induction of inflammation.

### *Clinical features*

The prototypic clinical syndrome described in familial Hibernian fever is only one manifestation of the ever-growing group of genotypes and phenotypes of TRAPS. Some cases are FMF-like, some are HIDS-like, and kindreds have been described with combined defects. Age of onset varies from a few weeks to older than 40 years. Siblings may be affected. Most often, symptoms first occur in school-age children. Attacks of fever are heralded by severe localized pain and tightness of one muscle group, which is migratory, in most patients. Skin rashes—tender, raised erythematous plaques simulating cellulitis—occur most frequently on the extremities and migrate distally. Painful conjunctivitis and periorbital edema also distinguish TRAPS from the other periodic fever syndromes. Less specific but frequent symptoms include abdominal pain, arthralgia, testicular pain, and pleuritic chest pain. Duration of fever and other symptoms usually is greater than 1 week, but shorter and milder, nonspecific symptoms or fever alone are described.

The case report of genetic diagnosis of TRAPS in a man who had been diagnosed with PFAPA (with atypical features) at age 8 years highlights situations in which gene analysis would be invaluable [45,46]. MR imaging has suggested involvement of subcutaneous tissue, fascia, and muscles; biopsy specimens have shown mononuclear cell infiltration of fascia without myositis in one [47] and panniculitis with small vessel vasculitis in another [48]. Attacks occur at irregular intervals weeks to years apart and can be triggered by minor infections, physical stress, or emotional stress. Neutrophilia and elevated C-reactive protein and erythrocyte sedimentation rate are typical findings during attacks. Elevated serum immunoglobulins, including IgA and IgD, can be present.

### *Etiology and diagnostic tests*

In patients with symptoms suggesting TRAPS, identification of mutations in the *TNFRSF1A* gene is the definitive diagnostic test. More than 28 described mutations lead to qualitative or quantitative abnormalities in TNF receptor-family type 1A proteins. Most are in exons 2 to 4 in the extracellular domains. In 2003, Aganna et al [49] showed heterogeneous gene defects in patients with familial TRAPS-like syndromes, but found that *TNFRSF1A* mutations were not commonly associated with sporadic (nonfamilial) TRAPS-like cases. In “classic” TRAPS, soluble *TNFRSF1A* is low (<1 mg/mL). During attacks, serum levels

may increase to within normal limits. If gene analysis is not available, measurement of serum soluble *TNFSF1A* level between attacks can be used as a screening test.

#### *Treatment and outcome*

Attacks of TRAPS respond dramatically to high-dose oral prednisone (>20 mg in adults), but response wanes over time. Colchicine has no effect. Etanercept is highly effective; it was reported to result in long-term remissions in some patients after a single course [50]. Prognosis is related mainly to presence or absence of amyloidosis, which is reported to occur in 10% to 25% of affected families. Certain mutations in *TNFSF1A* and other modifier genes may influence occurrence of amyloidosis.

## Summary

Most children with the perceived problem of prolonged, recurrent, or periodic fever are healthy and have self-limited, common illnesses. With careful delineation of specific features of the illness, confirmation of maintenance of growth and sense of well-being, and reassurance of normal findings on physical examination, the primary care practitioner usually can reassure families and continue to reassess the patient as circumstances dictate. For a child with true fever of unknown origin, a pediatric infectious diseases subspecialist should be consulted. For the unusual child with a course compatible with a noninfectious periodic fever syndrome, referral to a subspecialist is important because condition-specific diagnostic tests and interventions are available or are under study, genetic counseling may be important, and follow-up for evolution of disease or sequelae is crucial. The consultant might be a pediatric immunologist, rheumatologist, infectious diseases consultant, or hematologist depending on findings and expertise of available consultants. For the rare child with a suspected immunologic defect, referral to an immunologist (or infectious diseases subspecialist in some geographic areas) is necessary to begin complex evaluations, which often lead to lifesaving therapies.

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