# Autoinflammatory Diseases in Pediatrics

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**KEYWORDS**

• Autoinflammatory diseases • Periodic fever • Pediatrics • Familial Mediterranean fever • PFAPA • HIDS • TRAPS • CAPS

**KEY POINTS**

- Viral infections are the most common cause of recurrent fevers in children.
- Autoinflammatory diseases (AIDs) should be considered in a child with recurrent or persistent fever, when infectious and malignant causes have been excluded.
- AIDs are characterized by recurrent episodes of systemic and organ-specific inflammation, and are caused by defects in the innate immune system.
- Periodic fevers with aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) is the most common AID in children and occurs at regular intervals.
- Familial Mediterranean fever (FMF) is the most common monogenic AID and presents with recurrent attacks of fever, abdominal pain, arthritis, and rash that last for 1 to 3 days.

## INTRODUCTION

Repeated febrile illnesses are common in young children, especially in those attending daycare and school. Most often, these febrile episodes are caused by repeated viral infections. However, if there is continued recurrence of fever and other associated symptoms, it is important to maintain a broad differential that includes primary immunodeficiencies, anatomic and metabolic abnormalities, malignancies, and autoinflammatory diseases (AIDs). The diagnosis of an AID may be challenging, because there are numerous diseases, overlapping signs and symptoms, and lack of specific laboratory testing.

AIDs are characterized by recurrent episodes of systemic and organ-specific inflammation. Unlike patients with autoimmune disorders such as systemic lupus erythematosus, patients with AIDs do not have autoantibodies or antigen-specific T cells. Instead, AIDs result from inborn errors of the innate immune system.[1] They involve disorders of neutrophils, macrophages, and molecules of innate immunity that evolved to protect against external pathogens. These innate immune cells are activated by endogenous or exogenous stimuli, so-called pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), which lead to inflammation.

In contrast with most autoimmune diseases, AIDs usually present during childhood. Many are characterized by recurrent or persistent fever, and they are an important part of the differential diagnosis of the febrile child. It is essential for physicians who care for children to recognize these disorders, and to refer these children to specialists who can initiate treatment, improve quality of life, and avoid long-term complications.

Researchers over the last 10 years has identified many of the genes that cause AIDs. Most of these diseases are monogenic and inherited in an

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autosomal dominant or recessive pattern. However, our understanding of these diseases continues to evolve. Most children with periodic fevers (greater than 80% in some studies) do not have mutations in known periodic fever syndrome genes.[2] This article presents the differential diagnosis of recurrent fever in children. It discusses periodic fevers with aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA), the most common AID in children. It then focuses on the clinical presentation of monogenic AIDs that present with fevers in children, including familial Mediterranean fever (FMF), Hyper-IgD syndrome (HIDS), tumor necrosis factor (TNF) receptor–associated periodic syndrome (TRAPS), cryopyrin-associated periodic syndromes (CAPS), deficiency of interleukin-36 receptor antagonist (DITRA), Majeed syndrome, chronic atypical neutrophilic dermatosis with lipodystrophy and increased temperature syndrome (CANDLE), and deficiency of the interleukin-1 receptor antagonist (DIRA). Two granulomatous disorders, pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome and Blau syndrome, are also discussed.

## RECURRENT FEVERS

Fever is one of the most common reasons for a child to visit his or her pediatrician.[3] Some children present with recurrent or periodic fevers, defined as 3 or more episodes of fever in a 6-month period without a known illness to explain the fevers, and with at least 7 days between febrile episodes.[4] The approach to children with recurrent fevers should be different than that for children presenting with fever of unknown origin, because their etiologies differ.

To better create a differential diagnosis, the pattern of the fevers should be characterized precisely, especially whether there is a regularity to the intervals of fever. Episodes of fever occurring at regular intervals suggest a diagnosis of PFAPA or cyclic neutropenia. Other characteristics that should be noted include the age of fever onset, height of the fever, and pattern during the day. It is important to monitor for associated symptoms during an episode, including rashes, and involvement of the mucosa, joints, eyes, lung, or abdomen.

Viral infections are the most common causes of fevers occurring at irregular intervals in children.[4] Although most viral infections cause obvious symptoms, such as those of upper or lower respiratory tract infections, many viruses can also cause fevers without any other defining signs or symptoms.

Most children with occult bacterial infections present with prolonged rather than recurrent fevers. However, children with repeated bacterial infections should be evaluated for immunodeficiencies, cystic fibrosis, or anatomic abnormalities. Parasitic infections with *Plasmodium* may occur in children who have traveled to endemic areas.

Inflammatory bowel disease is a common cause of recurrent fevers, and the fevers may precede other signs of inflammatory bowel disease, such as abdominal pain, bloody stools, poor growth, and anemia, by weeks or months.

In Behçet disease, febrile children also present with recurrent oral and genital ulcers, uveitis, or skin rashes such as erythema nodosum. Systemic juvenile idiopathic arthritis presents with at least 2 weeks of daily fevers, along with a rash, lymphadenopathy, hepatosplenomegaly, or serositis. These two syndromes share many of the features of AIDs but no clear genetic causes have been identified.

After the diagnoses mentioned earlier have been excluded, AIDs should be considered, especially if there is a family history of recurrent fevers or if the child is of certain ethnic groups. One of the characteristics of AIDs is that the fever pattern and associated features are similar with each episodes. In most of these diseases, children are well between episodes, although some of AIDs follow a more chronic course and cause significant morbidity and mortality unless treated. Fever is not a part of all of the AIDs, although this article focuses on the ones in which fever is present, and briefly touch on several without fevers.

Clinical scoring systems have been created to determine the likelihood that a child will have an AID with a known genetic cause, and may help guide genetic testing (http://www.printo.it/periodicfever), although this needs to be validated in a diverse patient population.

## PERIODIC FEVERS WITH APHTHOUS STOMATITIS, PHARYNGITIS, AND CERVICAL ADENITIS

The syndrome of PFAPA is the most common cause of periodic fevers in childhood. First described in 1987,[5] it is characterized by recurrent febrile episodes lasting 3 to 6 days, occurring every 3 to 6 weeks, in addition to the presence of the features that make up the name of this syndrome. Regular intervals (with almost clockwork regularity) between episodes are the cardinal feature of PFAPA, whereas the presence of associated symptoms is more varied. The disease is common in most ethnic groups.[6]