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REVIEW ARTICLE

# Treatment options for periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome in children and adults: a narrative review

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## Abstract

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is the most frequent non-hereditary autoinflammatory disorder in childhood: Its onset is usually observed before 5 years, though reports regarding adulthood are increasing. The pathogenesis of the syndrome is not completely understood, but a multifactorial origin, probably based on a polygenic pattern of susceptibility, is the most probable rational pathogenetic hypothesis. Treatment of PFAPA syndrome relies on the administration of low-dose corticosteroids, which promptly abort flares but cannot prevent subsequent disease episodes over time. Tonsillectomy with or without adenoidectomy has proved to be successful in some pediatric patients, as proven by different studies. On the other hand, colchicine, cimetidine, nonsteroidal anti-inflammatory drugs, and interleukin-1 inhibitors have shown efficacy, which require further definite confirmations. This review is aimed at summarizing all the recent evidence about treatment options available for PFAPA syndrome both in pediatric and adult patients.

**Keywords** Aphthous stomatitis · Autoinflammation · Cimetidine · Colchicine · Corticosteroids · Familial Mediterranean fever · Innovative biotechnologies · Interleukin-1 · *MEFV* · Nonsteroidal anti-inflammatory drugs · Periodic fever · Personalized medicine · Pharyngitis and cervical adenitis (PFAPA) syndrome · Tonsillectomy

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is considered the most common non-hereditary autoinflammatory disease in childhood. The syndrome, initially described in 1987 [1], presents with fever attacks accompanied by nonspecific but quite homogeneous symptoms which name the disease: aphthous stomatitis, pharyngitis, and cervical adenitis. Flares usually last 3–7 days and recur at intervals of 2–8 weeks, resulting highly predictable in most pediatric cases [2]. Initially, it was believed that PFAPA syndrome was a disorder limited to childhood, but an increasing number of reports has clearly proven that it can also affect non-pediatric patients at different ages [3]. The currently available diagnostic criteria of PFAPA syndrome in pediatric and adult patients are reported in Tables 1 and 2.

In most children, the disease has a spontaneous resolution within a few years, mostly before puberty, but in 20% of cases, the initial recovery is followed by new occurrence of febrile flares in adulthood [4]. The overall prognosis for PFAPA patients is excellent as regards pediatric growth and development, since the syndrome does not induce long-term sequelae and is not associated with comorbidities [5, 6].

Its pathogenesis is not completely clarified, though a large evidence supports a possible multifactorial background [7]. A comprehensive assessment of potential mechanisms of inheritance for PFAPA syndrome was recently published, revealing a familial clustering with a presumed autosomal-dominant inheritance pattern of susceptibility [8, 9]. Inflammasome/interleukin-1 (IL-1) β pathway genes and numerous other genes involved in

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**Table 1** Diagnostic criteria of PFAPA syndrome currently used in children

1. Regularly recurring fevers with early age of onset (<5 years of age), occurring in the absence of upper respiratory tract infections
2. One at least among the following symptoms:
   A. aphthous stomatitis
   B. cervical lymphadenitis
   C. pharyngitis
3. Exclusion of cyclic neutropenia
4. Asymptomatic interval between episodes
5. Normal growth and development

From Thomas et al. [36]

different periodic fever syndromes have been implicated in the pathogenesis of the disease [10–14]. Nevertheless, environmental influences are supposed to play a significant role in the phenotypical expression of the syndrome [7], whereas the efficacy of tonsillectomy and analysis of tonsil specimens arouse interest in the putative immunological and microbiological role that tonsils might play [5, 6].

This review is aimed at summarizing the most recent evidence about treatment of PFAPA syndrome both in pediatric and adult patients. A systematic literature search in the MEDLINE database has been performed up to August 2018. We searched for studies through the following words: "PFAPA," "Periodic Fever, Aphthous stomatitis, Pharyngitis and cervical Adenitis," and "Marshall syndrome." All observational studies, clinical trials, case series, and reviews published in English language over the last 5 years were screened for eligibility, based on title, abstract, and keywords. Papers were included if they reported the outcome of any treatment in children and adults diagnosed with PFAPA syndrome, according to the diagnostic criteria widely adopted in international studies. References in the relevant papers were also reviewed. Main reports published before the aforementioned period of time were included as well.

## Corticosteroids

Low-dose corticosteroid is the most commonly used first-line treatment in children with PFAPA syndrome. In a survey performed by Manthiram et al., it has been shown that many specialists prescribed prednisolone or prednisone at the dose of 1 mg/kg of body weight (64%), 2 mg/kg (29%), 0.5 mg/kg (6%) per episode, and 95% of them perceived corticosteroids as "effective" or "very effective" in the control of PFAPA symptoms [15]. Clinical remission of fever was observed within 24 h after an oral dose of prednisone in 80.8% of pediatric patients evaluated via a retrospective multicenter study [16]. Moreover, in a prospective cohort study, prednisone was administered to 77 pediatric patients, showing to be successful in 94% of them [17]. Betamethasone at the daily dose of 0.1–0.2 mg/kg is also considered effective [6]. A case series of 268 children published by Cattalini et al. showed a complete response to prednisone (1–2 mg/kg/day) or betamethasone (0.1–0.2 mg/kg/day) in 226, and a partial response in two cases [18]. A cross-sectional study conducted by Mehregan et al. reported efficacy for prednisolone and dexamethasone in 84.61% of 21 PFAPA pediatric patients [19]. In addition, corticosteroids given at the onset of attacks aborted fever in 73 cases (90%) out of 81 children with PFAPA syndrome recruited from the Eurofever Registry and induced partial improvement in 6 [20]. According to Federici et al., corticosteroids can reliably abort a PFAPA flare to the point that a failure to respond within a few hours should bring a doubt to the diagnosis of PFAPA syndrome [21].

A multicenter study conducted by Rigante et al. on pediatric ($n = 85$) and adult ($n = 30$) populations with PFAPA syndrome showed that a single corticosteroid administration (up to 25 mg of prednisone or equivalent) was followed by complete resolution of symptoms in 82% of adults, a lower response if compared to pediatric studies (99%), probably due to the lower prednisone dosage used in adults [4]. Furthermore, Cattalini et al. reviewed a number of case reports available in the medical literature about adult patients with PFAPA syndrome, pointing out a complete response to corticosteroids in 28/33 treated; they also found that 9/33 adults experienced a free-interval shortening after corticosteroid administration [18].

Celiksoy et al. studied a cohort of 64 patients with PFAPA syndrome, highlighting differences between those carrying *MEFV* gene pathogenetic variants (66%) and those who were not (34%). In all patients who received prednisolone during flares (47/64), fever decreased within hours and did not recur: Among them, 32 were carriers of *MEFV* variants and 15 patients not [22]. Feder and Salazar showed also that fever attacks subsided within 24 h after administration of the single corticosteroid dose [23]. Conversely, other symptoms related to the oral cavity tended to disappear in a slower way than fever [24]. Anyway, prednisone administration could not prevent the subsequent PFAPA episodes of fever [25], and it is quite accepted that, for unknown reasons, a significant proportion of PFAPA patients experience shortening of the interfebrile periods after starting treatment with corticosteroids [4, 5, 15, 16, 20].

**Table 2** Diagnostic criteria for adult-onset (over 16 years old) PFAPA syndrome

| | |
|---|---|
| 1. | Recurrent fever accompanied by:<br>A. erythematous pharyngitis *and/or*<br>B. cervical lymphadenitis |
| 2. | Increased inflammatory markers during febrile attacks |
| 3. | Presence of symptom-free intervals |

The exclusion of infections, autoimmune and neoplastic diseases, and monogenic and polygenic autoinflammatory disorders should be also considered mandatory. From Cantarini et al. [71]

## Nonsteroidal anti-inflammatory drugs

Indomethacin or ibuprofen have been used at full dosage per os with some beneficial effects on adult patients and, less significantly, on children [4]. According to Ter Haar et al., NSAIDs were beneficial in 21 out of 28 patients inserted in the Eurofever registry, but only completely effective in 1 patient using these drugs as monotherapy, and an additional 1 in combination with corticosteroids [20]. In a long-term follow-up study, Wurster et al. noted that NSAIDs were more effective than acetaminophen in controlling PFAPA symptoms, and indeed, when asked to rate the efficacy of acetaminophen and NSAIDs, patients answered "moderately effective" or very effective in 25.4% and 57.7% of cases, respectively [26].

## Colchicine

Colchicine, an alkaloid with inhibitory effects on multiple cellular functions, including microtubule assembly, cell adhesion, and inflammasome activation, has been the first medication approved for treatment of familial Mediterranean fever (FMF) [27] but is not routinely used in PFAPA patients because of the need of a continuous daily administration. However, colchicine prophylaxis has been adopted by different clinicians with overall good control on PFAPA symptoms, although complete responses have been rarely observed [28]. A randomized controlled trial on 18 children diagnosed with PFAPA syndrome revealed that the colchicine-treatment group (0.5 mg/day if < 5 years of age, 1 mg/day if 5–10 years, and 1.5 mg/day if > 10 years) had significantly less febrile attacks than controls ($p \leq 0.01$) [29]. Gunes et al. followed 400 patients on colchicine prophylaxis for 12 months, highlighting an extension of interfebrile periods in 85% of them. Moreover, the effectiveness was found to be significantly higher in children with *MEFV* pathogenetic variants (96%) than in those without (80%) [30]. This result had been previously reported by Dusser et al. in a retrospective study on 20 pediatric patients with PFAPA syndrome [31]: In the group of patients who had a favorable response to colchicine, 71% were found to carry heterozygous *MEFV* mutations, while *MEFV* variants were detected in 43% of nonresponders. In the same study, nonresponders had more frequently chronic fatigue and oral aphthosis than responders, while colchicine appeared more effective in the incomplete PFAPA phenotype, but without achieving statistical significance [31]. Another paper reported a favorable response to colchicine prophylaxis in 50% of a small cohort of patients ($n = 18$) carrying *MEFV* variants, with episodes of fever decreasing within months [22]. Wekell suggests using colchicine in children with atypical PFAPA syndrome, in children who did not improve following tonsillectomy, and in children with a predominance of aphthous stomatitis, though further evidence is needed to reinforce this statement [32].

## Cimetidine

The medical literature provides some PFAPA reports supporting the usefulness of cimetidine prophylaxis [33–35], though evidence of efficacy in both pediatric (300 mg/day or 20 mg/kg) and adult patients (400–800 mg/day) is weak [26, 28]. Feder and Salazar reported 7 children diagnosed with PFAPA syndrome out of 26 (27% of the total), who responded to cimetidine with permanent resolution of febrile episodes [23]. It was previously reported by Thomas et al. in a 10-year-follow-up that 8 out of 28 children using cimetidine reported a complete response [36]. A partial efficacy of cimetidine was noted in a few number of patients by Pignataro et al. [37], while a long-term follow-up by Wurster et al. found that 6 patients (24%) out of 25 had very effective results, with febrile episodes terminating while on therapy [26].

## Surgery

Since the first reports of PFAPA patients successfully treated via tonsillectomy with (ATE) or without (TE) adenoidectomy were published in 1999 [36, 38, 39], several case series published so far have shown good results, with reports of complete resolution of symptoms [23, 40–43], but there has been also some controversy regarding this approach [44, 45]. A meta-analysis performed in 2010 by Peridis et al. demonstrated that surgery is a valid treatment for PFAPA syndrome ($p < 0.001$), significantly more effective than cimetidine and antibiotics, while a comparison of treatment with corticosteroids or surgery did not show a statistically significant difference [46]. Analogue results were achieved by Vigo et al. [47], while Erdogan study group proved the superiority of surgery to medical treatment for PFAPA syndrome, in terms of increased remission rates, decrease in the number and duration of flares, and reduction of the need of hospitalization in a cohort of 105 pediatric patients [48].

As regards randomized controlled trials, the efficacy of ATE relies on two small studies. The first RCT was conducted by Renko et al. in 2007: It included 26 children with PFAPA syndrome and showed a significant difference in the resolution of fever between the TE group ($n = 14$) and control group ($n = 12$) within 6 months after inclusion in the study ($p < 0.001$) [49]. This paper was criticized by Spalding et al. since accepted diagnostic criteria for PFAPA syndrome were not used [50]. Additionally, Lantto et al. demonstrated the efficacy of TE in a retrospective analysis of 108 PFAPA patients diagnosed with complete ($n = 58$) or incomplete ($n = 50$) PFAPA syndrome, suggesting that the disease should be

suspected and TE considered in children with a later onset of symptoms (> 5 years of age), also with fever occurring as the only symptom during episodes [51].

A second randomized controlled trial was performed by Garavello et al., who reported a prompt resolution of febrile episodes in 12 out of 19 children of the ATE group (63%) and in 1 out of 20 patients of the pharmacologically managed group (5%) during an 18 months follow-up ($p < 0.001$). Also, the mean number of episodes recorded during the follow-up period and their severity was lower in the ATE group [52]. According to the last Cochrane systematic review, it is uncertain whether adenoidectomy combined with tonsillectomy adds any additional benefit to the tonsillectomy alone [53].

Despite the low level of evidence provided by case series, Førsvoll et al. found a positive result after TE or ATE in 523 out of 555 children reported in the literature until 2016 [54]. More recently, in two cohort studies conducted by Ibáñez Alcalde et al. ($n = 14$) [16] and Aktas et al. ($n = 23$) [55], febrile episodes stopped in 78.6% and 91.3% of patients who underwent TE or ATE, respectively. A similar duration of the disease was reported in patients who were tonsillectomized and those not [37]. A retrospective study performed by Pehlivan et al. on 359 patients with PFAPA syndrome found that complete clinical remission was achieved in 127 (80.3%) out of 158 patients after surgical treatment. The difference in persistence of PFAPA symptoms between those undergoing tonsillectomy from those who did not was significant ($p < 0.05$). Another interesting result reported by the same group was the presence of heterozygous *MEFV* mutations in 52.4% of PFAPA children who responded partially or did not show any response to tonsillectomy, finding a significant difference in the response to surgical treatment between patients with and without coexistence of FMF clinical features ($p < 0.05$). Such results should need further confirmation, since this study had the bias of being based on interviews with patients; furthermore, *MEFV* mutations were only assessed in patients who fulfilled the Turkish criteria for diagnosis of FMF and had a family history of FMF [56].

A few studies about efficacy of ATE in adult patients with PFAPA syndrome are available. Current data seem to indicate a lower response to surgery in adults compared to children. Anyway, some authors suggested that, since PFAPA syndrome does not show a self-limited course in adults, tonsillectomy would represent an option to try [3].

## Other therapies

Recently, it has been hypothesized that IL-1 inhibition might be beneficial in PFAPA syndrome given the overexpression of inflammasome-related genes and IL-1β dysregulation with induction of Th1 chemokines in PFAPA febrile flares [8]. Stojanov et al. treated five PFAPA children with anakinra (1 mg/kg, administered subcutaneously on the second day of fever), obtaining both a clinical response within hours of the injection and a decline of white blood cell count and C-reactive protein 48 h after injection [11]. Anakinra (100 mg subcutaneously daily) and canakinumab (150 mg every 8 weeks) were both proved to be effective in one adult patient with frequent PFAPA flares, after failure of corticosteroids, colchicine, and tonsillectomy [57]. In the authors' opinion, since PFAPA syndrome is a self-limited disease in children, IL-1 blockers should be reserved to strictly selected patients (especially adults) in whom the cost-effectiveness of treatment is justified.

Thalidomide, a glutamic acid derivative, initially used as a hypnosedative and antiemetic drug, has reemerged as a treatment for autoimmune and inflammatory disorders following its anti-inflammatory, immunomodulatory, and anti-angiogenic potential. Some evidences support thalidomide use for treatment of recurrent aphthous stomatitis [58] and prophylaxis of PFAPA flare ups [18, 59, 60], but its unfavorable safety profile remains a significant restriction.

There is also evidence supporting the role of vitamin D as an immune-regulatory factor in PFAPA syndrome, and some authors found a significant correlation between PFAPA symptoms and vitamin D deficiency [61]. According to this premise, some children with PFAPA syndrome and 25-OH-vitamin D deficiency have been supplemented with cholecalciferol (400 IU/day), showing a significant reduction in the number of febrile episodes and shortening of mean duration of febrile episodes [62, 63]. Finally, anecdotal positive results have been noted in children supplemented with immunomodulatory molecules like pidotimod in association with bacterial lysates [64] or with oral cavity probiotics such as *Streptococcus salivarius* K12 [65], though the overall evidence of efficacy for these treatments in PFAPA syndrome remains feeble.

## Conclusive remarks

Although PFAPA syndrome is considered a self-limited condition in childhood, its impact on families and social lives of children can be remarkable in many cases [66]. Moreover, this syndrome appears less benign in adults, in whom the control of febrile flares is challenging, and no spontaneous resolution is usually expected. To date, the pathogenesis of PFAPA syndrome remains obscure, though many studies aimed at assessing immunological mechanisms behind this condition are changing its opportunities of treatment, highlighting an abnormal IL-1 release in response to many environmental triggers and associating this condition to other hereditary periodic fever disorders [67–69]. However, unlike other autoinflammatory disorders mainly characterized by recurrent

fever attacks, no genetic mutations have been associated pathogenetically with PFAPA syndrome.

Studies supporting the efficacy of different therapeutic strategies in PFAPA patients are based mostly on small cohorts of patients and provide moderate-to-low quality of evidence. Actually, corticosteroids can be recommended as the first-line treatment in children. Tonsillectomy with or without adenoidectomy has proved to be effective in stopping disease flares or at least reducing their frequency in selected children, though clinicians as well as parents and caregivers should weigh the risks and consequences of surgery against the alternative of simply using medications.

Some evidences suggest a possible role of *MEFV* genotype as a risk factor in PFAPA syndrome, underscoring differences in the phenotypical expression and in response to therapies, according to the presence or absence of *MEFV* heterozygote variants. This hypothesis might acquire more relevance in geographical areas where the prevalence of *MEFV* variant carriage is relatively high. On the other hand, there are studies which report no statistical significance between *MEFV*+ and *MEFV*− groups, as concerning clinical, therapeutic, and prognostic issues [70]. Anyway, if any causative *MEFV* mutation is found, a colchicine test should be reasonably tried to exclude the diagnosis of FMF.

Future research advances aimed at understanding inflammation and the role of its biologic actors in the pathogenesis of autoinflammatory disorders will probably suggest more specific therapeutic strategies in PFAPA syndrome. Among these, IL-1 blockers seem to be promising tools in adult patients who are resistant to conventional therapies, though more studies in larger cohorts of patients are needed to assess their overall efficacy in the long-term.

## Compliance with ethical standards

**Disclosures** None.

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