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Medical and Surgical Management of PFAPA Syndrome: An Updated Review of Therapeutic Evidence From 2016 Onward

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Abstract

Introduction: Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is the most frequent periodic fever disorder of childhood. Although its long-term prognosis is usually favorable, recurrent attacks can substantially disrupt family life, school attendance, healthcare use, and routine preventive care.

Objective: To reassess therapeutic evidence published from 2016 onward and to describe how newer data modify or extend the treatment framework summarized by Vanoni, Theodoropoulou, and Hofer in 2016.

Material and method: PubMed/MEDLINE was searched using PFAPA and Marshall syndrome terms combined with keywords relating to acute treatment, pharmacological prophylaxis, interleukin-1 inhibition, tonsillotomy, tonsillectomy, and adenotonsillectomy. Original clinical studies reporting treatment or disease-management outcomes were eligible without restrictions on age, sex, or geographical setting. Findings were synthesized narratively.

Results: Corticosteroids continued to provide the most rapid control of individual attacks, although shorter intervals between episodes were reported in a proportion of patients. Colchicine was the most extensively studied preventive agent, but response varied across cohorts; a randomized comparison of prednisolone plus colchicine and prednisolone plus cimetidine showed improvement in both groups without a clear difference between them. Controlled or prospective studies also suggested potential benefit from pidotimod and

ketotifen. Tonsillotomy and tonsillectomy were associated with high short-term remission rates, while long-term observational findings were more heterogeneous. No eligible study of targeted biologic treatment met the review criteria.

Conclusions: The evidence published from 2016 onward favors an individualized treatment sequence based on disease burden and response: corticosteroids for attack termination, selected pharmacological prophylaxis for frequent or disruptive disease, and surgery for appropriately chosen patients. More robust randomized and long-term comparative studies remain necessary.

Keywords: PFAPA syndrome; periodic fever; corticosteroids; colchicine; ketotifen; pidotimod; tonsillectomy; tonsillotomy; treatment.

1. Introduction

PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis) is a recurrent autoinflammatory syndrome and is generally regarded as the most common periodic fever disorder in children. The condition most often begins in early childhood, but persistence into adulthood and genuine adult-onset disease have also been described. Its prevalence and pathogenesis remain incompletely defined, and the absence of a disease-specific laboratory marker means that diagnosis continues to rely mainly on the clinical pattern and the exclusion of alternative causes (Wang et al., 2021).

The typical course consists of highly stereotyped febrile attacks lasting approximately 3-7 days and recurring every 2-8 weeks, with complete or near-complete well-being between episodes. Fever is accompanied by one or more of the characteristic manifestations - pharyngitis, cervical adenitis, and oral aphthae - although abdominal pain, arthralgia or arthritis, headache, rash, diarrhea, and vomiting may also occur. A prodromal period, frequently dominated by fatigue, has been reported in about 60% of patients. In many children,

episodes become less frequent and shorter with age, and spontaneous resolution occurs after several years; however, this trajectory is not universal.

The syndrome is considered benign in terms of long-term organ damage, but its repeated and predictable flares can still generate a considerable practical burden. Children may miss school, caregivers may repeatedly miss work, and families often seek urgent medical assessment because the intensity of each episode resembles infection. The overlap with common childhood infections can lead to repeated antibiotic exposure before the periodic pattern is recognized. Recurrent febrile illness may also interfere with preventive care: a French cohort of children with recurrent autoinflammatory fever syndromes, including PFAPA, demonstrated suboptimal vaccination coverage, particularly among infants experiencing repeated fever episodes (Rollet-Cohen et al., 2021).

Treatment decisions therefore involve more than the rapid termination of fever. The clinician must also consider attack frequency, the child's and family's quality of life, repeated corticosteroid exposure, diagnostic uncertainty, and the risks and benefits of preventive pharmacotherapy or surgery. Vanoni et al. (2016) summarized the earlier evidence and identified single-dose corticosteroids as the principal abortive treatment, colchicine and cimetidine as possible preventive options, tonsillectomy as a strategy for selected patients, and interleukin-1 blockade as a highly selective approach supported mainly by case-level evidence. The present review uses that publication as a reference point and reorganizes the evidence available from 2016 onward around the clinical roles of acute therapy, prophylaxis, and surgery.

2. Materials and Methods

2.1. Search strategy and review scope

A literature review was conducted in PubMed/MEDLINE to identify clinical studies evaluating treatment strategies in patients diagnosed with PFAPA syndrome. Disease-related search terms included "PFAPA," "Marshall syndrome," and combinations of periodic fever, aphthous stomatitis, pharyngitis, and cervical lymphadenitis. These terms were combined with treatment-related keywords covering corticosteroids and other acute therapies; colchicine, cimetidine, pidotimod, and ketotifen; interleukin-1 inhibitors, including anakinra, canakinumab, and rilonacept; and surgical interventions, including tonsillotomy, tonsillectomy, and adenotonsillectomy. Searches were restricted to title and abstract fields to prioritize clinically relevant records.

The principal evidence window began in 2016, corresponding to the year of the review by Vanoni et al. (2016), and extended to the date of the final literature search. Studies published before this window were retained only when they provided contextual long-term comparison relevant to interpretation of newer evidence, as in the observational report by Vigo et al. (2014).

2.2. Eligibility criteria and evidence synthesis

Eligible publications reported original clinical outcomes related to treatment efficacy, attack control, prophylaxis, surgical management, adverse events, quality of life, or the course of PFAPA. Randomized controlled trials, controlled or pragmatic clinical trials, comparative studies, prospective and retrospective observational studies, multicenter cohorts, and clinical evaluation studies were considered. No restrictions were applied according to patient age, sex, or geographical location.

Titles and abstracts were screened for relevance, followed by full-text assessment of potentially eligible reports. Publications without original treatment or disease-management outcomes were excluded. Because the identified studies differed substantially in design, treatment selection, follow-up, and outcome definitions, the results were summarized qualitatively rather than pooled statistically.

2.3. Use of generative AI

During the preparation of this manuscript, the authors used ChatGPT as a supportive tool for selected editorial tasks, including the summarization of scientific articles, assistance in sentence construction, and improvement of the overall standard of academic English. The use of this tool was limited to linguistic and organizational support and did not substitute for the authors' own critical appraisal of the literature, data interpretation, or formulation of conclusions. All content generated or refined with the assistance of ChatGPT was subsequently reviewed, edited, and validated by the authors. The authors remain fully responsible for the scientific integrity, accuracy, and substantive content of the final manuscript.

3. Therapeutic Evidence

3.1. Control of acute attacks

Corticosteroids remain the most consistently effective intervention for terminating an individual PFAPA flare. In the multicenter cohort reported by Özaslan et al. (2024), 659 of 806 patients received corticosteroids during attacks. Fever resolved within 6 hours in 602 of those treated (91.3%). The same cohort, however, documented an increase in attack frequency in 214 corticosteroid-treated patients (32.4%), reinforcing the distinction between rapid symptomatic control and modification of the underlying disease course.

Similar short-term effectiveness was observed in the multicenter cohort of Ibáñez Alcalde et al. (2019), in which 80.8% of patients achieved symptom remission within 24 hours after oral corticosteroid administration during febrile episodes. Collectively, these findings support corticosteroids as the preferred abortive treatment while also indicating that repeated use may be followed by shorter inter-attack intervals in a clinically relevant subgroup.

3.2. Pharmacological prophylaxis

Preventive pharmacotherapy is generally considered when attacks are frequent, when acute treatment is required repeatedly, or when PFAPA substantially affects the child and family. Evidence published from 2016 onward has focused mainly on colchicine, with additional studies evaluating pidotimod and ketotifen. Across these interventions, treatment response was variable and no agent was uniformly effective.

3.2.1. Colchicine and cimetidine

The largest study addressing colchicine was the retrospective multicenter cohort of 806 patients described by Özaslan et al. (2024). Colchicine was prescribed to 519 patients, and 419 were classified as having a favorable response. This corresponds to 80.7% of patients who received colchicine and 52.0% of the entire cohort. Pharyngitis, arthralgia, and a higher baseline attack frequency were associated with colchicine non-response, whereas carriage of the M694V variant was identified as a predictor of responsiveness.

Randomized evidence did not establish a clear advantage of colchicine over cimetidine. In a trial of 67 patients, the frequency of febrile episodes decreased significantly in both the prednisolone-plus-colchicine and prednisolone-plus-cimetidine groups ($P \leq 0.001$), with no significant between-group difference in the reported outcomes. Colchicine response also did not differ between MEFV-positive and MEFV-negative subgroups ($P = 1$) (Raeeskarami et al., 2022).

In the smaller retrospective cohort reported by Dusser et al. (2016), 9 of 20 patients fulfilled the predefined criteria for response to colchicine. MEFV heterozygosity was more common among responders, but the association was not statistically significant. These data indicate that colchicine can reduce disease activity in a subset of patients, although reliable clinical or genetic selection criteria have not yet been established.

3.2.2. Pidotimod

A prospective controlled open-label crossover study included 22 children and compared a phase of pidotimod plus betamethasone with a phase of betamethasone alone. Combination treatment was associated with lower fever frequency ($P = 0.002$), fewer episodes of pharyngitis ($P = 0.049$) and aphthous stomatitis ($P = 0.036$), and reduced use of on-demand

betamethasone ($P = 0.007$). Overall clinical benefit was reported in 19 of 22 patients (86.4%), and no serious adverse events were described in the available safety summary (Manti et al., 2020). The findings suggest a possible corticosteroid-sparing role, but the small open-label design limits certainty.

3.2.3. Ketotifen

Ketotifen was evaluated in a prospective clinical study including 142 patients, of whom 111 were evaluable for the reported response analysis. A positive treatment effect was observed in 86 of 111 patients (77.5%). The reported attack-free interval increased from 4.4 $\pm$ 1.9 days before treatment to 14.7 $\pm$ 8.9 days during therapy ($P < 0.001$). Mild adverse effects occurred in four patients and consisted of restlessness, irritability, agitation, or constipation (Kapustova et al., 2023). Although these results are encouraging, confirmation in placebo-controlled studies is required.

3.3. Surgical management

Evidence for surgery includes randomized data as well as several observational cohorts. In a randomized multicenter sequential-design trial of 16 patients, 7 of 8 children assigned to tonsillotomy (87.5%) were symptom free at 3 months, compared with 2 of 8 children managed by observation alone (25%). The mean number of PFAPA-compatible fever days was also lower after tonsillotomy (0.8, SD 1.4) than in the observation group (6.5, SD 6.0; 95% CI -10 to -1; $P = 0.007$). Every participant initially assigned to observation subsequently underwent rescue tonsillectomy, whereas no rescue procedure was required in the tonsillotomy group (Lantto et al., 2024).

Observational comparisons have produced less uniform results. Erdogan et al. (2016) evaluated 105 patients and reported better outcomes after tonsillectomy, with or without adenoidectomy, than after medical treatment based on single intramuscular methylprednisolone injections. Surgically treated patients had fewer episodes (1.8 vs 5.8), shorter attacks (1.1 vs 2.2 days), fewer hospitalizations (0.1 vs 1.1), and a higher remission rate (98.6% vs 56.6%). In contrast, a long-term retrospective study of 275 patients found an overall complete remission rate of 59.6% and no statistically significant difference between tonsillectomy and standard medical management (65.9% vs 59.1%; $P = 0.51$). Remission was less frequent among patients with a positive family history (Vigo et al., 2014).

The multicenter cohort of Ibáñez Alcalde et al. (2019) included 32 patients managed with different strategies. Among 14 patients who underwent tonsillectomy, 11 (78.6%) achieved complete remission and the other three had fewer episodes. Postoperative bleeding occurred in two cases (14.3%). Disease duration did not differ significantly between tonsillectomized

and non-tonsillectomized children (37.7 vs 24.4 months; $P = 0.683$), although the longer course in the surgical group was interpreted as a probable consequence of selection bias.

Surgical benefit has also been reported across different PFAPA phenotypes. Lantto et al. (2016) observed symptom resolution in 56 of 58 patients (97%) who met classic Thomas criteria and in all 50 patients with an incomplete PFAPA presentation. In the multicenter case series by Aktas et al. (2019), 21 of 23 patients (91%) experienced immediate complete resolution after tonsillectomy with or without adenoidectomy.

The extent of tonsillar surgery may influence the balance between efficacy and complications. In a retrospective cohort of 36 patients, partial tonsillectomy reduced the annual number of episodes by approximately 10 (range 5-21; $P < 0.005$), corresponding to about a 50% reduction. Total tonsillectomy produced a 93% reduction, although this within-group result narrowly missed conventional statistical significance ($P = 0.056$). The difference in reduction between partial and total procedures was statistically significant ($P = 0.028$). Complications were reported in 0% of partial and 10% of total tonsillectomy cases. Two patients required completion surgery and subsequently achieved remission (Banh Chong et al., 2025).

Beyond attack counts, surgery may improve everyday functioning. In a pre-post study of 56 patients, tonsillectomy with or without adenoidectomy reduced episode frequency from 3.0 to 0.6, school absence from 10.28 to 2.85 days, and hospital presentations from 3.8 to 1.1. Quality-of-life and emotional or behavioral scores also improved significantly (all $P < 0.001$) (Karayağmurlu and Aytaç, 2020). In the large cohort of Özaslan et al. (2024), surgery was recommended for 134 patients and performed in 90; complete cessation of episodes was reported by 74 of those operated on (82.2%).

3.4. Targeted biologic therapy

Cytokine-directed treatment, particularly interleukin-1 inhibition, remains biologically plausible for severe or refractory PFAPA. Vanoni et al. (2016) described anakinra as a promising but highly selective option supported primarily by limited case-based evidence. The present search did not identify an eligible original clinical study of anakinra, canakinumab, rilonacept, or another targeted biologic agent that fulfilled the inclusion criteria. The available evidence is therefore insufficient to support a general recommendation or to define patient-selection criteria.

4. Discussion

This updated synthesis shows that the therapeutic landscape of PFAPA has expanded since 2016 without producing a single universally preferred strategy. The evidence continues to support three distinct clinical objectives: rapid termination of an individual flare, reduction of future attack burden, and sustained remission through surgery. The optimal choice depends on the frequency and severity of episodes, response to previous treatment, family preferences, and tolerance of uncertainty in a disorder that may resolve spontaneously.

For acute attacks, corticosteroids remain the intervention with the clearest and most immediate effect. Resolution within hours is common, as demonstrated both in earlier reports and in the large cohort of Özaslan et al. (2024). Their limitation is equally important: corticosteroids do not appear to alter the underlying course of PFAPA and may shorten the interval to the next episode in some patients. They should therefore be viewed as highly effective abortive therapy rather than as preventive or disease-modifying treatment (Vanoni et al., 2016; Özaslan et al., 2024).

Among preventive medications, colchicine has the largest evidence base, but interpretation depends on how response is defined and which denominator is used. The multicenter cohort by Özaslan et al. (2024) documented 419 responders among 519 treated patients, while smaller studies demonstrated more modest response rates. Associations between MEFV variants and treatment effect have not been consistent across studies: the M694V variant predicted response in one large cohort, whereas the randomized comparison by Raeeskarami et al. (2022) found no difference according to MEFV status. Colchicine is therefore a reasonable option for selected patients, but genetic findings alone should not currently determine treatment.

Pidotimod and ketotifen broaden the range of possible preventive therapies. Both were associated with lower attack burden in prospective studies, and pidotimod also reduced the need for on-demand betamethasone (Manti et al., 2020; Kapustova et al., 2023). These observations are clinically relevant for patients who experience frequent attacks or repeated corticosteroid exposure. Nevertheless, the small sample size, open-label design, lack of placebo control, and limited independent replication prevent firm comparative conclusions.

Surgical studies consistently report substantial short-term improvement in many selected patients. The randomized tonsillotomy study strengthens the evidence that removal of tonsillar tissue can suppress PFAPA activity over the short term (Lantto et al., 2024). At the same time, the contrast between high remission rates in selected surgical cohorts and the absence of a long-term advantage over medical treatment in the study by Vigo et al. (2014) highlights two major interpretive problems: spontaneous resolution and selection bias.

Children referred for surgery often have more persistent or burdensome disease, while children with milder courses may improve before surgery is considered. The choice between partial and total tonsillectomy also requires balancing the possibility of greater episode reduction against a potentially higher complication rate (Banh Chong et al., 2025).

Taken together, the data support a stepwise and preference-sensitive approach. Corticosteroids are appropriate when the principal goal is reliable termination of a flare. Preventive medication can be discussed when attacks are frequent, disruptive, or followed by repeated steroid use. Surgery may be offered to carefully selected patients and families after discussion of spontaneous remission, perioperative risk, the possibility of incomplete response, and the limited certainty of long-term comparative benefit. Targeted biologic treatment remains investigational because adequately designed clinical studies are lacking.

4.1. Limitations of the evidence

The evidence base has several important limitations. Only a small number of randomized studies were identified, while most reports were retrospective, uncontrolled, or open label. Diagnostic criteria, baseline attack burden, definitions of response and remission, follow-up duration, and indications for surgery varied considerably. These differences precluded meaningful quantitative pooling and make indirect comparisons between treatments uncertain.

The review itself was limited to PubMed/MEDLINE and was conducted as a qualitative update rather than a formal systematic review with meta-analysis. The inclusion of an earlier observational study for long-term context also means that not every cited report falls within the primary evidence window. These limitations should be considered when applying the findings to individual patients.

5. Conclusions

Current evidence supports individualized management of PFAPA rather than a single standard treatment pathway. Corticosteroids remain the most effective option for rapid termination of acute episodes, but they do not prevent recurrence and may shorten inter-attack intervals in some patients. Colchicine is the best studied prophylactic drug, while pidotimod and ketotifen represent emerging alternatives supported by more limited evidence. Tonsillotomy and tonsillectomy can produce high short-term remission rates in selected patients, although long-term benefit over medical management is less certain in unselected populations. Well-designed randomized studies with standardized outcomes and longer

follow-up are needed to clarify comparative effectiveness, patient selection, and durable disease-modifying strategies.

Disclosure Section

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