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CURRENT THERAPEUTIC STRATEGIES IN PEDIATRIC PFAPA SYNDROME: EFFICACY, SAFETY, AND QUALITY-OF-LIFE CONSIDERATIONS – A NARRATIVE REVIEW

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ABSTRACT

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is a common periodic fever disorder of childhood. Although it usually has a favorable long-term course, recurrent attacks may substantially disrupt school attendance, family life, and quality of life. This narrative review summarizes current therapeutic strategies for pediatric PFAPA, focusing on efficacy, safety, and patient-centered outcomes. A structured PubMed/MEDLINE search, supplemented by the Cochrane Library and reference screening, was used to identify relevant evidence on corticosteroids, colchicine, cimetidine, non-standard preventive therapies, interleukin-1 inhibition, and tonsil surgery. Corticosteroids are highly effective for rapid termination of acute attacks but do not prevent recurrence and may shorten attack-free intervals in some patients. Colchicine has the strongest evidence among pharmacological preventive options and can reduce attack frequency and corticosteroid use. Evidence for cimetidine, ketotifen, probiotics, and vitamin D is more limited. Tonsillectomy may lead to sustained remission and can improve quality of life and school functioning, but spontaneous remission, surgical risk, incomplete response, and recurrence must be considered. Evidence for interleukin-1 inhibition remains insufficient for routine use. Current data do not support one universally superior treatment. Management should be individualized according to attack burden, response to previous therapy, safety, quality of life, and family preferences. Better prospective comparative studies with standardized outcomes are needed.

KEYWORDS

PFAPA Syndrome, Periodic Fever, Pediatric Autoinflammatory Diseases, Colchicine, Tonsillectomy, Quality of Life

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1. Introduction

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is a recurrent autoinflammatory disorder characterized by stereotyped febrile episodes accompanied by aphthous stomatitis, pharyngitis, and/or cervical adenitis. It usually begins in early childhood, and children are generally well between attacks [1,2]. The exact pathogenesis is not fully understood, but dysregulation of innate immunity and interleukin-1-related inflammatory pathways appears to be important [3].

PFAPA is often described as benign and self-limiting because it usually does not cause progressive organ damage and many children improve over time [1,3]. Nevertheless, frequent attacks can create a considerable practical and emotional burden. Studies using pediatric quality-of-life measures have shown impairment in physical and psychosocial functioning, fatigue, school attendance, and family functioning [4–6]. For this reason, the burden of PFAPA should not be judged by fever frequency alone.

Treatment options differ in purpose. Corticosteroids are mainly used to terminate acute attacks, whereas colchicine and cimetidine aim to prevent recurrent episodes. Tonsillectomy may provide prolonged remission, while interleukin-1 inhibitors remain experimental for selected refractory cases [7,8]. Recent systematic reviews and comparative analyses have expanded the evidence for colchicine and surgery but still do not support a simple universal treatment hierarchy [9–11].

In clinical practice, treatment decisions depend not only on the diagnosis itself but also on how strongly recurrent attacks affect the child and family. Some children experience only several manageable episodes each year, whereas others have frequent attacks that repeatedly interrupt school and family routines. This variability explains why the same intervention may be appropriate for one patient but unnecessarily intensive for another and supports an approach based on treatment goals and patient-centered outcomes.

Several reviews have described the clinical presentation, pathogenesis, and general management of PFAPA. However, treatment studies remain difficult to compare because the available interventions address different therapeutic goals and use different definitions of response. Patient-centered outcomes are also measured less consistently than fever resolution or attack frequency. This creates an important gap between

evidence of clinical efficacy and the everyday outcomes that matter to children and families. A focused synthesis integrating efficacy, safety, quality of life, school functioning, and family burden may therefore provide a more practical basis for individualized treatment decisions.

The aim of this narrative review is to summarize current therapeutic strategies for pediatric PFAPA, with emphasis on efficacy, safety, quality of life, and factors that may help individualize treatment. It also considers the limitations of the available evidence and priorities for future research.

2. Methodology

2.1. Review design and scope

This article was prepared as a narrative review with a structured literature-search approach. The aim was to summarize clinically relevant evidence on the treatment of PFAPA in children and adolescents rather than to perform a formal systematic review or meta-analysis. The review focused on the main therapeutic questions encountered in practice: rapid control of acute attacks, prevention of recurrent episodes, the role of tonsil surgery, treatment safety, and the effect of disease and treatment on quality of life. Publications from January 2000 to September 2026 were considered, with particular attention to studies published from 2020 onward. Older landmark randomized trials and mechanistic studies were retained when they remained important for understanding current treatment options.

2.2. Information sources and search strategy

The literature search was last updated on 10 September 2026. PubMed/MEDLINE was the main bibliographic database. The search was supplemented by relevant systematic reviews identified through the Cochrane Library and by manual screening of reference lists from key reviews, randomized trials, and recent comparative studies. This approach was selected to provide a transparent but practical search process appropriate for a narrative review.

Searches combined the term “PFAPA” and the full syndrome name (“periodic fever, aphthous stomatitis, pharyngitis, and adenitis” or “periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis”) with treatment-related terms. These included “treatment”, “therapy”, “corticosteroid”, “prednisone”, “prednisolone”, “colchicine”, “cimetidine”, “tonsillectomy”, “adenotonsillectomy”, “tonsillotomy”, “anakinra”, “canakinumab”, “interleukin-1”, “IL-1”, “probiotic”, “ketotifen”, and “vitamin D”. Additional searches used outcome terms such as “attack frequency”, “attack-free interval”, “remission”, “recurrence”, “safety”, “adverse effects”, “quality of life”, “HRQoL”, “school absence”, and “family burden”. Boolean operators AND and OR were used to combine PFAPA terms with intervention and outcome terms.

The search was intentionally broad because the evidence base includes different study designs and because several therapies, especially biologic and non-standard preventive approaches, have been evaluated only in small cohorts or case-based publications. Within the predefined 2000–2026 period, older studies were retained when they represented landmark randomized trials or provided information that remained clinically relevant. No attempt was made to restrict the review only to statistically significant findings; negative, uncertain, and conflicting results were also considered when they were important for interpreting therapeutic choices.

2.3. Eligibility criteria

Peer-reviewed English-language publications were considered when they included children or adolescents with PFAPA and reported information relevant to treatment. Eligible outcomes included rapid resolution of acute attacks, attack frequency or duration, length of symptom-free intervals, corticosteroid requirements, partial or complete remission, recurrence, adverse effects, tolerability, school functioning, family burden, and health-related quality of life. Randomized controlled trials, prospective and retrospective cohort studies, comparative studies, systematic reviews, meta-analyses, and consensus documents were prioritized. Case reports and small case series were used mainly for experimental therapies, particularly IL-1 inhibition, where higher-level PFAPA-specific evidence remains limited.

Studies were excluded when they focused exclusively on adults, did not provide separable data for PFAPA, addressed diagnosis or pathogenesis without clear relevance to treatment, or evaluated other autoinflammatory diseases without PFAPA-specific outcomes. Conference abstracts without a full peer-reviewed publication, editorials, opinion articles, duplicate reports, and publications that did not provide

enough information to interpret the treatment outcome were also excluded. When several publications addressed the same therapeutic question, greater attention was given to more recent, larger, comparative, or methodologically stronger studies while older landmark trials were retained where appropriate.

2.4. Study selection and evidence synthesis

Potentially relevant publications were assessed for their direct relevance to the objectives of the review. Titles and abstracts were used to identify studies addressing therapeutic strategies or patient-centered outcomes, and full reports or detailed publication records were examined when more information was required. Reference lists of key articles were screened to identify additional relevant publications. Study selection was performed for the purpose of a clinically focused narrative synthesis rather than a formal systematic-review flow process. The final narrative synthesis drew on 49 publications cited in the manuscript.

Evidence was organized thematically according to treatment strategy: corticosteroids, colchicine, cimetidine and other preventive approaches, interleukin-1 (IL-1) inhibition, and tonsil surgery. Separate attention was given to comparative effectiveness, safety, quality of life, school functioning, family burden, and possible predictors of treatment response. When interpreting the findings, greater weight was given to randomized trials, systematic reviews and meta-analyses, larger comparative cohorts, and studies with longer follow-up. Observational results were interpreted cautiously because spontaneous improvement, differences in disease severity, and treatment selection may influence apparent effectiveness.

Because this was a narrative review, no formal risk-of-bias tool, certainty-of-evidence framework, preregistered protocol, or author-performed quantitative meta-analysis was used. Numerical results from published meta-analyses were reported when they helped illustrate the strength or uncertainty of the available evidence. Differences in study populations, treatment doses, surgical techniques, follow-up periods, and definitions of response were considered when drawing conclusions. The purpose of the synthesis was therefore to provide a balanced clinical overview rather than a formal ranking of treatments.

2.5. Outcomes considered in the review

For each publication, the information of interest depended on the therapeutic question being addressed. For acute treatment, the main outcome was rapid resolution of fever and associated symptoms. For preventive treatment, greater attention was given to changes in attack frequency, attack duration, symptom-free intervals, and the need for corticosteroids. Surgical studies were assessed mainly for complete or partial remission, recurrence, follow-up duration, and postoperative complications. Safety findings were considered together with practical treatment burden, such as repeated medication use or the need for an invasive procedure.

Quality-of-life evidence was considered separately because clinical response does not always reflect the everyday effect of PFAPA. Studies reporting validated pediatric quality-of-life measures, school absence, parental work absence, or family impact were therefore included when available. Results were not combined into a new numerical estimate. Instead, findings were compared according to the aim of each treatment and the strength of the available study design. This was important because rapid termination of one attack, prevention of future attacks, and long-term remission are different outcomes and should not be treated as equivalent measures of success.

3. Results

3.1. Therapeutic Goals and General Principles of PFAPA Management

The main goals of PFAPA treatment are to terminate acute attacks, reduce the frequency of future episodes, limit treatment burden, and improve daily functioning. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) consensus treatment plans group management into supportive care, abortive corticosteroids, prophylactic treatment with colchicine or cimetidine, and surgery [7]. These plans are a framework for comparative research rather than a mandatory stepwise guideline.

The best strategy depends on the clinical problem. Corticosteroids are highly effective for individual attacks but do not prevent recurrence [12]. Colchicine may reduce future attacks [9], while tonsil surgery may provide sustained remission in many children [10,11]. Because PFAPA often resolves spontaneously, treatment intensity should be matched to attack severity, frequency, response to previous therapy, school and family disruption, and patient or family preferences [4–7].

3.2. Corticosteroids as Abortive Treatment

Prednisone or prednisolone is the best-supported treatment for rapid termination of a PFAPA attack. CARRA treatment plans include a single dose of 1 mg/kg, with higher dosing up to 2 mg/kg (maximum 60 mg) when response is incomplete [7]. A 2025 review covering 46 publications and 4,564 patients reported an overall corticosteroid response of about 94% [12], and a recent Polish cohort reported prednisone efficacy of 97.6% [13]. A small randomized study also suggested that lower-dose prednisolone may be effective in many children, although the sample was too small to establish the optimal minimum dose [14].

The main limitation is that corticosteroids do not prevent future attacks. Shortening of the interval between episodes has been reported in observational studies [12,15,16]. This does not prove a causal effect, but it becomes clinically important when repeated treatment is needed every few weeks. Short-term adverse effects are usually mild and transient, while PFAPA-specific data on cumulative long-term exposure are limited [12]. Thus, intermittent corticosteroids are particularly useful when attacks are relatively infrequent and rapidly responsive; frequent recurrence may justify consideration of prophylaxis or surgery.

An additional practical advantage of corticosteroids is the simplicity of treatment: families can administer medication at the beginning of a typical attack without requiring continuous daily therapy. At the same time, repeated use can become inconvenient when attacks are frequent. In this situation, the number of successful steroid-treated episodes should not be viewed as evidence that long-term management is satisfactory. A child who responds within several hours but requires treatment every two or three weeks may still experience considerable cumulative disease burden. This distinction between acute response and overall control is important when deciding whether to continue an abortive strategy or consider prevention [7,12].

3.3. Colchicine as Preventive Therapy

Colchicine is the most studied pharmacological preventive therapy for PFAPA. A 2026 systematic review found that prophylaxis generally reduces attack frequency, prolongs symptom-free intervals, and decreases corticosteroid requirements, although much of the evidence remains observational [9]. In a multicenter study of 806 children, 519 received colchicine and 80.7% had a favorable response [17]. Other cohorts have shown reductions in attack frequency, duration, and disease activity, with improvement often becoming evident during the first month [18,19].

Randomized evidence is limited. In a trial of 67 children, both prophylactic regimens were associated with a reduction in attack frequency, with no statistically significant difference between groups [20]. A 2026 comparative cohort also supported longer attack-free intervals with colchicine compared with standard care [21]. Whether variants in the Mediterranean Fever (MEFV) gene predict response to colchicine remains uncertain: some studies suggest a better response with the M694V variant of the MEFV gene, whereas others do not show a consistent genetic effect [9,17,18,20,21].

Dosing varies across studies, commonly beginning with low daily doses and increasing according to weight, response, and tolerability [20,22]. Gastrointestinal symptoms such as abdominal pain, diarrhea, nausea, and vomiting are the most frequently reported adverse effects; discontinuation is uncommon [9,22]. Overall, colchicine is a reasonable preventive option for children with frequent attacks or repeated corticosteroid use, but response is not universal and validated predictors are lacking.

Colchicine is especially relevant when the main treatment goal is to increase the interval between attacks rather than to achieve immediate symptom relief. Its effect is usually assessed over weeks or months, and families should therefore understand that prophylaxis is not intended to stop a febrile episode as quickly as corticosteroids. Because published studies use different definitions of response, a clinically useful improvement may range from fewer attacks to a clearly longer symptom-free interval rather than complete disappearance of the syndrome [9,17–21].

Another practical issue is duration of therapy. Existing studies do not establish one standard period of prophylaxis for all children. In clinical practice, continued treatment is generally judged according to attack pattern, tolerability, and whether benefit persists over time. This makes regular reassessment important, particularly because PFAPA may improve spontaneously with age. The available evidence supports colchicine as a useful preventive option, but not as a treatment that every child with PFAPA necessarily needs [9].

3.4. Cimetidine and Other Non-standard Preventive Approaches

Cimetidine is included with colchicine in the CARRA prophylactic framework [7], but its evidence base is smaller. In the randomized study by Raeeskarami et al., both prophylactic regimens were associated with fewer attacks, with no statistically significant difference between groups [20]. A Japanese retrospective cohort also reported clinical improvement in many cimetidine-treated children [23]. These findings support possible benefit, but they are insufficient to establish equivalence with colchicine.

Other preventive approaches remain less established. Ketotifen was associated with clinical improvement in an uncontrolled prospective pediatric study, with only a few mild adverse effects [24]. Two studies of Streptococcus salivarius K12 reported fewer and shorter PFAPA attacks [25,26], while a 2026 retrospective comparison found improvement with both a probiotic preparation and colchicine, but the time to the first subsequent attack was longer with colchicine [27]. Vitamin D supplementation has been studied mainly in small heterogeneous cohorts; correction of deficiency may be appropriate, but vitamin D cannot currently be considered a specific PFAPA therapy [28]. These approaches require controlled prospective studies before routine use can be recommended.

The limited evidence for cimetidine and other non-standard therapies is clinically relevant because these interventions may appear attractive when families prefer to avoid surgery or long-term colchicine. However, encouraging results from uncontrolled cohorts should be interpreted carefully. PFAPA naturally changes over time, and reductions in attack frequency may occur even without treatment. For this reason, these strategies should not be placed on the same evidence level as corticosteroids, colchicine, or tonsil surgery. They may be considered in selected cases, but stronger comparative data are required before their routine role can be defined [20,23–28].

3.5. IL-1 Inhibition and Experimental Therapeutic Approaches

The biological rationale for IL-1 inhibition is strong because PFAPA is associated with innate immune activation and IL-1-related pathways [29]. However, PFAPA-specific clinical evidence is extremely limited. In a small proof-of-concept study, anakinra produced rapid improvement in five children, but some had early recurrence and no control group was included [29]. Published canakinumab experience is limited to case-based evidence [30].

There are no adequately powered randomized trials supporting routine IL-1 blockade in PFAPA [3,7]. Broader pediatric rheumatology data suggest that injection-site reactions and minor infections are common and that infections are an important serious adverse event, but these data are indirect and should not be fully extrapolated to PFAPA [31]. IL-1 inhibition should therefore remain an experimental option for rare, highly selected refractory cases.

3.6. Tonsillectomy, Adenotonsillectomy and Tonsillotomy

Tonsil surgery differs from pharmacological treatment because it may result in prolonged or complete remission. In an early randomized trial, all 14 children allocated to tonsillectomy were symptom-free after six months, although spontaneous resolution also occurred in 6 of 12 controls [32]. Another randomized trial found complete resolution in 63% after adenotonsillectomy compared with 5% with expectant management [33]. A Cochrane review concluded that surgery probably increases the chance of symptom resolution and reduces episode frequency, while emphasizing that the evidence was based on small trials and that spontaneous remission must be considered [34].

A small randomized trial also evaluated tonsillotomy as a less extensive surgical approach. Seven of eight children undergoing tonsillotomy were free of PFAPA symptoms after three months compared with two of eight children managed by observation [35]. The sample was very small and follow-up was short, so these findings should be interpreted cautiously.

More recent analyses support substantial surgical efficacy. A 2025 meta-analysis reported a lower risk of persistent PFAPA after surgery [36], and a 2026 randomized-trial meta-analysis also found a marked increase in complete remission, although only 81 patients were included [37]. A network meta-analysis favored surgical approaches over conservative management [10], but a broader 2026 network analysis found no reliable overall difference between pooled surgical and medical strategies because heterogeneity was very high and certainty of evidence was very low [11]. These results indicate uncertainty in comparative ranking rather than lack of surgical efficacy.

Long-term outcomes also show that surgery is not a guaranteed cure. In an 86-patient cohort with a median follow-up of 8.8 years, some children had persistent symptoms or later recurrence after initial remission

[38]. A multicenter cohort of 97 children similarly described complete, partial, and recurrent responses after tonsillectomy [39]. Potential predictors of better response have included typical pharyngeal features, strong corticosteroid response, absence of some musculoskeletal symptoms, later onset, and headache, but these findings require validation [39,40]. Coexisting familial Mediterranean fever may be associated with lower surgical remission rates [41].

Evidence for partial tonsil surgery remains limited. A retrospective comparison suggested improvement after both partial and total procedures, while some children treated with partial surgery experienced persistent or recurrent symptoms or later required complete tonsillectomy [42]. Limited data suggest that partial procedures may reduce perioperative morbidity, but it remains uncertain whether this benefit is accompanied by a higher risk of persistent or recurrent PFAPA [10,42]. It also remains uncertain whether adenoidectomy provides additional benefit beyond tonsillectomy in PFAPA [34].

Surgery also has patient-centered benefits. Prospective and retrospective studies have reported improvements in pediatric health-related quality of life (HRQoL), family impact, and school attendance following successful tonsillectomy [5,43]. However, perioperative risks and spontaneous disease resolution must remain part of the decision. Tonsil surgery is therefore best considered for children with substantial recurrent disease burden rather than as a universal first choice.

The decision about surgery should also include the child's age and current course of disease. Because many children eventually improve without invasive treatment, an operation may be less attractive when attacks are already becoming less frequent. In contrast, surgery may be more reasonable when episodes remain frequent over a prolonged period and cause repeated school absence despite effective acute treatment. Importantly, the goal is not simply to choose the intervention with the highest remission percentage, but to balance the chance of long-term benefit against procedural risk and the possibility that the syndrome could resolve naturally [11,32,34,38].

The distinction between total and partial tonsil surgery also remains clinically relevant. Partial techniques may offer a less burdensome postoperative course, but the evidence is still too limited to determine whether this advantage is accompanied by a higher chance of later recurrence [10,35,42]. Until larger comparative studies are available, the choice of surgical technique should therefore depend on local surgical practice, individual risk assessment, and discussion with the family rather than on a PFAPA-specific evidence-based preference.

3.7. Comparative Effectiveness of Medical and Surgical Treatment

Direct comparison is difficult because PFAPA therapies have different goals. Corticosteroids offer the most reliable acute control [12], colchicine aims to reduce future attacks [9], and tonsil surgery may provide sustained remission without the need for continuous prophylactic treatment [10]. Response percentages therefore should not be interpreted as if they measured the same outcome.

For children with occasional attacks, rapid corticosteroid response may provide adequate control. When frequent recurrences cause repeated drug use or disruption of school and family life, preventive therapy becomes more attractive. Colchicine has a broader evidence base than cimetidine and generally favorable tolerability [9,20,23]. Surgery may be appropriate when disease burden is high or medical treatment is unsatisfactory, but it is invasive and does not guarantee permanent remission [10,38,39].

The most recent network meta-analysis did not establish a statistically reliable overall advantage of surgery over medical management and rated comparative certainty as very low [11]. This does not mean that therapies are equivalent; it shows that available studies are too heterogeneous to create a dependable universal ranking. Treatment effectiveness should therefore be interpreted according to the goal of therapy and the burden experienced by the individual child.

When comparing approaches, the amount of treatment required over time should also be considered. A single successful dose of corticosteroid may create less overall burden than daily prophylaxis in a child with only a few attacks per year. The balance may reverse when attacks occur very frequently and each episode requires medication, time away from school, and parental absence from work. Similarly, tonsillectomy has greater short-term burden but may reduce repeated disease-related disruption if sustained remission is achieved. Therefore, the most meaningful comparison is not simply medical versus surgical treatment, but the total burden produced by disease and therapy over time [5,7,11].

3.8. Safety and Treatment-Related Adverse Effects

Safety is especially important in PFAPA because the disease usually has a favorable prognosis. Intermittent corticosteroids are generally well tolerated, although transient behavioral, sleep, appetite, or metabolic effects may occur and repeated long-term PFAPA-specific exposure has not been well studied [12]. A shorter interval between attacks may also increase cumulative treatment burden [12,15,16].

Colchicine is usually well tolerated, with gastrointestinal symptoms being the main adverse effects and occasional need for dose reduction or discontinuation [9,22]. Safety data for cimetidine, ketotifen, probiotics, and vitamin D are less systematic [20,23–28]. The absence of reported adverse events in small studies should not be interpreted as proof of long-term safety.

Tonsil surgery shifts much of the treatment burden from repeated medication use toward perioperative risk and postoperative recovery. Small PFAPA trials report few complications, but broader surgical evidence confirms that postoperative morbidity occurs [10,37,42]. Limited data suggest that partial tonsil procedures may reduce perioperative burden, although a possible higher risk of persistent or recurrent symptoms remains uncertain [10,42]. For IL-1 inhibitors, PFAPA-specific safety evidence is insufficient; indirect pediatric data identify injection-site reactions and infections as relevant concerns [29–31]. Overall, safety assessment should include conventional adverse events as well as treatment burden, invasiveness, cumulative exposure, and recurrence risk.

Long-term safety information is particularly difficult to interpret because most PFAPA studies were designed primarily to measure efficacy. Mild adverse effects may be incompletely recorded in retrospective cohorts, whereas rare complications cannot be reliably estimated from small trials. This limitation is important when counseling families: a statement that a treatment was “well tolerated” in a small study is weaker than evidence from a large study specifically designed to evaluate safety. Treatment decisions should therefore use the best available evidence while acknowledging these uncertainties [9–12,20,31].

3.9. Quality of Life, School Functioning and Family Burden

PFAPA can substantially affect quality of life even though children are usually healthy between attacks. In a Pediatric Quality of Life Inventory (PedsQL) study, children with PFAPA had lower overall quality-of-life scores than children with familial Mediterranean fever, with the largest differences observed in preschool-aged children; greater fatigue was reported across age groups [4]. More recent studies confirm effects on physical and emotional functioning, school participation, and family concern [6,44].

School absence is one of the clearest practical consequences. In a study of 56 children undergoing tonsil surgery, mean school absence fell from about 10.3 to 2.9 days after treatment, together with fewer febrile episodes and improved quality-of-life measures [43]. A prospective cohort using PedsQL and the Family Impact Module also demonstrated substantial burden before surgery and significant improvement in both child and family outcomes afterward [5]. A small 2026 parental survey additionally described missed school, parental work absence, and negative effects on family well-being, although its sample of ten families limits generalization [45].

An important evidence gap is that validated quality-of-life (QoL) outcomes have been studied more often in surgical cohorts than in pharmacological studies. Most corticosteroid and colchicine studies focus on fever resolution or attack frequency [9,12,17–21]. Therefore, better QoL evidence after tonsillectomy should not automatically be interpreted as proof of superiority; it may partly reflect what investigators chose to measure. Future studies should include standardized HRQoL, school absence, parental work absence, and family impact as routine outcomes.

Quality-of-life assessment can also help explain why two children with a similar number of attacks may require different management. Attack frequency and duration, school absence, parental work absence, and the wider impact on family functioning may all influence the practical burden of PFAPA [4–6,43–45]. These consequences are difficult to capture with attack counts alone. A patient-centered assessment therefore adds information that is directly relevant to treatment decisions, especially when considering long-term prophylaxis or surgery.

4. Discussion

4.1. Selecting the Optimal Therapeutic Strategy

Current evidence supports a goal-oriented rather than hierarchical approach to PFAPA treatment. For a child with relatively infrequent attacks, rapid response to corticosteroids, and little disruption between episodes, intermittent abortive therapy may be sufficient [7,12]. In contrast, frequent attacks, shortening symptom-free intervals, repeated corticosteroid use, or substantial school and family disruption may justify preventive treatment [4–7,12].

Colchicine is the best-supported pharmacological preventive option and is particularly useful when families wish to avoid surgery [9,17–21]. Cimetidine represents another preventive option, although its evidence base is substantially smaller than that for colchicine [20,23]. Tonsillectomy may provide sustained remission and measurable improvement in quality of life, making it reasonable for selected children with high disease burden or unsatisfactory medical control [5,32–39,43]. Nevertheless, spontaneous remission, perioperative burden, and possible recurrence mean that surgery should not automatically be preferred for all patients [11,32,38,39].

The choice should therefore combine attack frequency and severity, response and tolerability of previous treatment, cumulative treatment burden, disease duration, quality of life, and family preferences. Shared decision-making is particularly appropriate because current comparative evidence does not identify one treatment as universally superior [7,11]. Treatment should also be reassessed over time, since an approach that is appropriate during one phase of the disease may become unnecessary or insufficient as attack patterns change.

A useful practical way to interpret the evidence is to begin with the problem that requires treatment. If the main difficulty is a prolonged febrile attack, abortive corticosteroids directly address that problem. If repeated attacks are the main source of burden, preventive therapy becomes more relevant. If recurrent disease continues to cause major disruption despite acceptable medical options, surgery may be considered. This approach avoids presenting PFAPA management as a rigid ladder in which every child must move through the same sequence of therapies [7,11].

Treatment goals should also be discussed with families before changing therapy. Complete remission may be the preferred goal for some families, while others may consider a reduction in attack frequency sufficient if it avoids surgery or daily medication. Because PFAPA generally does not cause progressive organ damage and may resolve spontaneously, shared decision-making is particularly important [1,3,7].

4.2. Individualized Treatment and Potential Predictors of Response

Attempts to predict treatment response are promising but not yet ready for routine clinical decision-making. MEFV variants have received the most attention in relation to colchicine. One large cohort associated M694V with a favorable response [17], whereas other studies found no significant relationship between MEFV status and response [18,20,21,46]. Genetic results should therefore not be used alone to decide whether colchicine should be prescribed.

Several clinical features have also been associated with response to tonsillectomy. A multicenter study linked better surgical outcomes with good glucocorticoid response, exudative pharyngitis, and absence of rash or arthralgia/myalgia [39]. Another smaller study found associations with headache and later disease onset [40]. Children with coexisting PFAPA and familial Mediterranean fever may have a lower probability of complete surgical remission [41]. These findings suggest that clinically meaningful PFAPA subgroups may exist, but none of the proposed predictors has been prospectively validated.

Prediction of spontaneous remission may also influence treatment intensity. Later onset, family history, and absence of headache have been associated with earlier disease resolution in one cohort [47], while other studies show that PFAPA can persist into adolescence or recur after symptom-free periods [48]. A 2026 study proposed several early-life factors associated with persistence, but these findings remain exploratory [49]. At present, personalization should therefore rely mainly on repeated clinical assessment rather than a fixed genetic or clinical prediction score.

The search for predictors is clinically attractive because it could reduce trial-and-error treatment. Nevertheless, the present findings are not consistent enough to support simple rules such as “MEFV-positive patients should receive colchicine” or “children with a particular symptom should undergo tonsillectomy.” Associations found in retrospective cohorts may reflect population differences or chance, and a predictor that performs well in one center may not work in another. Prospective validation in independent groups is therefore necessary before these factors can be used as reliable decision tools [17,39,40,46].

4.3. Limitations of Current Evidence

The main limitation of PFAPA treatment literature is methodological heterogeneity. Many studies are retrospective, single-center, or small, and randomized evidence remains limited [11,32–37]. Definitions of success differ widely and include rapid fever resolution, fewer attacks, longer symptom-free intervals, partial improvement, or complete remission. These outcomes measure different therapeutic goals and cannot be directly compared [9–12].

Follow-up duration and spontaneous remission are additional problems. Short studies may overestimate lasting benefit, particularly after surgery, while uncontrolled studies cannot reliably separate treatment effects from the natural improvement of PFAPA [32,38,39]. Treatment regimens also vary in corticosteroid dose, colchicine dose and duration, and surgical technique [7,9,10,12,14,17–22,32–42].

Safety and quality-of-life outcomes are reported inconsistently. Small studies may miss uncommon adverse events, and validated HRQoL measures are used far more often in surgical studies than in pharmacological research [5,9,12,20,23–31,43]. Proposed genetic and clinical predictors also vary between populations [9,17,18,20,21,39,40,46]. These limitations explain why the expanding literature has not yet produced a universally accepted treatment hierarchy.

Another limitation is that many publications come from specialized referral centers. Children managed in these settings may have more frequent, atypical, or treatment-resistant disease than those seen in general pediatric practice. Reported response rates may therefore not apply equally to all children with PFAPA. Geographic differences are also important, particularly for MEFV variants and the availability or preference for surgical treatment. These factors reduce the generalizability of some single-center studies and support the need for multicenter research [17,20,41,46].

This review also has limitations. As a narrative review, it did not include a formal risk-of-bias assessment, a preregistered protocol, or an independent quantitative synthesis. The structured search was based primarily on PubMed/MEDLINE, supplemented by the Cochrane Library and reference screening, and only English-language publications were considered. Relevant studies indexed only in other databases may therefore have been missed. In addition, study selection was guided by clinical relevance to the review objectives rather than by a formal systematic-review process. The conclusions should therefore be interpreted as a critical narrative synthesis rather than as a quantitative estimate of comparative treatment effects.

4.4. Future Research Directions

Future research should prioritize prospective multicenter studies using standardized diagnostic criteria, treatment protocols, definitions of response, and follow-up. Direct comparisons between commonly used strategies—especially colchicine and tonsil surgery—would be particularly useful in children with frequent attacks [11,20,32–37]. Studies should distinguish clearly between termination of an acute attack, reduction in attack frequency, partial control, sustained remission, and long-term complete remission.

Patient-centered outcomes should become standard. In addition to fever and attack frequency, trials should measure validated pediatric HRQoL, school absence, parental work absence, family impact, treatment burden, and adverse effects [4–6,43–45]. Longer follow-up is necessary because spontaneous remission and late recurrence can both occur [32,38,39]. Prospective evaluation of clinical phenotype, MEFV variants, and inflammatory biomarkers may eventually support prediction of response, but multivariable models require external validation [17,29,39,40,46].

Further controlled research is also needed for partial tonsil surgery, cimetidine, ketotifen, probiotics, vitamin D, and IL-1 inhibition [20,24–31,35,42]. The main goal of future PFAPA research should move from showing that a therapy can work to identifying which treatment offers the best balance of efficacy, safety, and quality of life for a particular child.

A practical future study design would compare clearly defined treatment strategies in children grouped by disease burden. For example, children with frequent corticosteroid-treated attacks could be followed after starting colchicine, after choosing surgery, or after continued episodic treatment, using the same definitions of response and the same follow-up period. Such a design would make results easier to interpret than the current literature, in which different studies often measure different outcomes. Including simple patient-reported measures would also help determine whether a statistically significant reduction in attacks produces a meaningful improvement in everyday life.

5. Conclusions

PFAPA is a recurrent childhood autoinflammatory disorder with several effective management options but no universally optimal treatment. Corticosteroids remain highly effective for rapid termination of attacks but do not prevent recurrence. Colchicine has the strongest evidence among pharmacological preventive strategies and can reduce attack frequency and corticosteroid use. Evidence for cimetidine and other non-standard approaches is less robust. Tonsillectomy may provide sustained remission and improve quality of life and school functioning in selected children, but spontaneous remission, surgical burden, incomplete response, and recurrence must be considered.

Treatment should therefore be individualized according to the main therapeutic goal, attack burden, previous response, safety, treatment burden, disease course, quality of life, and family preferences. Current evidence does not justify a universal ranking of medical and surgical options. Future prospective comparative studies should use standardized outcomes, longer follow-up, systematic safety assessment, and validated patient- and family-reported measures. Until stronger evidence is available, shared decision-making remains the most appropriate approach to balancing efficacy, safety, invasiveness, and quality-of-life considerations in children with PFAPA.

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