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Original article

Guidelines for the management and treatment of periodic fever syndromes: periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome

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ABSTRACT

Objective: To establish guidelines based on scientific evidence for the management of periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome.
Description of the evidence collection method: The Guideline was prepared from 5 clinical questions that were structured through PICO (Patient, Intervention or indicator, Comparison and Outcome), to search in key primary scientific information databases. After defining the potential studies to support the recommendations, these were graduated considering their strength of evidence and grade of recommendation.
Results: 806 articles were retrieved and evaluated by title and abstract; from these, 32 articles were selected to support the recommendations.

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Recommendations: 1. PFAPA is a diagnosis of exclusion established on clinical grounds, and one must suspect of this problem in children with recurrent and periodic febrile episodes of unknown origin, or with recurrent tonsillitis interspersed with asymptomatic periods, especially in children in good general condition and with preservation of weight and height development. 2. Laboratory findings are nonspecific. Additional tests do not reveal pathognomonic changes. 3. The evidence supporting an indication for surgical treatment (tonsillectomy with or without adenoidectomy), is based on two non-blinded randomized clinical trials with small numbers of patients. 4. The use of prednisone at the onset of fever in patients with PFAPA proved to be an effective strategy. There is still need for more qualified evidence to support its use in patients with PFAPA. 5. Despite promising results obtained in studies with IL-1β inhibitors, such studies are limited to a few case reports.

Diretrizes de conduta e tratamento de síndromes febris periódicas: síndrome de febre periódica, estomatite aftosa, faringite e adenite

Palavras-chave:
Síndrome de febre periódica, estomatite aftosa, faringite e adenite cervical
Diretrizes
Infância
Febre
Síndromes autoinflamatórias

RESUMO

Objetivo: Estabelecer diretrizes baseadas em evidências científicas para manejo da Síndrome de febre periódica, estomatite aftosa, faringite e adenite (PFAPA).
Descrição do método de coleta de evidência: A Diretriz foi elaborada a partir de 5 questões clínicas que foram estruturadas por meio do P.I.C.O. (Paciente, Intervenção ou Indicador, Comparação e *Outcome*), com busca nas principais bases primárias de informação científica. Após definir os estudos potenciais para sustento das recomendações, estes foram graduados pela força da evidência e grau de recomendação.
Resultados: Foram recuperados, e avaliados pelo título e resumo, 806 trabalhos, sendo selecionados 32 artigos, para sustentar as recomendações.
Recomendações: 1. O diagnóstico da PFAPA é clínico e de exclusão, devendo a suspeita ser considerada em crianças que apresentam episódios febris de origem indeterminada recorrentes e periódicos ou amidalites de repetição, intercalados com períodos assintomáticos, sobretudo em crianças em bom estado geral e com desenvolvimento pondero-estatural mantido; 2. Os achados laboratoriais são inespecíficos. Não existem alterações patognomônicas nos exames complementares; 3. A evidência que sustenta a indicação do tratamento cirúrgico (tonsilectomia com ou sem adenoidectomia) é baseada em dois ensaios clínicos randomizados não cegos que incluíram pequeno número de pacientes; 4. O uso de prednisona no início do quadro febril em pacientes com PFAPA mostrou ser eficaz. Melhores evidências ainda são necessárias para apoiar seu uso na PFAPA; 5. Apesar dos resultados obtidos de estudos com inibidores de IL-1ß serem promissores, estes são limitados a poucos relatos de casos.

Description of the method of evidence collection

The Guideline was prepared from 5 relevant clinical questions related to the management of periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome. The questions were structured by the use of PICO (Patient, Intervention or indicator, Comparison and Outcome), allowing the generation of strategies for searching evidence (described after each question, with the number of recovered articles), in the main primary databases of scientific information (Medline/Pubmed, Embase, Lilacs/Scielo, Cochrane Library). The recovered evidence has been selected from a critical evaluation using discriminatory instruments (scores): JADAD and GRADE for randomized clinical trials, and New Castle Ottawa scale for observational studies. After defining the potential studies to support the recommendations, these articles were rated based on the strength of evidence and grade of recommendation, according to the classification of Oxford (available in www.cebm.net), including available evidence of greatest strength.

Summary of grades of recommendation and strength of evidence

A. Experimental or observational studies of higher consistency.
B. Experimental or observational studies of lower consistency.

C. Case reports (non-controlled studies).
D. Expert opinion without explicit critical appraisal, or based on physiology or bench research.

Objective

To establish guidelines based on scientific evidence for the management of periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome.

When should we suspect that an individual is a carrier of periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome?

Strategy
(Pharyngitis OR Pharyngitides OR Sore Throat OR Lymphadenitis OR Adenitis OR Stomatitis, Aphthous OR Fever OR PFAPA) AND Periodicity* $n = 336$.

Described by Marshall for the first time in 1987, periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome – PFAPA is the autoinflammatory syndrome belonging to the group of the most common recurrent febrile syndromes in childhood, although its exact prevalence is not known[1] (C). This is a recurrent, febrile, self-limiting disease, well characterized from a clinical point of view based on case reports and case series descriptions[2] (C). The onset of PFAPA almost always occurs before the age of five, and in most patients the clinical picture resolves spontaneously before 10–12 years of age. Rare cases have been reported in adulthood[3,4] (C). PFAPA displays a yet unknown etiology, however, increased expression of genes related to IL-1β, interferon and chemokines have been found during febrile periods[5] (D). A significant number of patients with PFAPA syndrome have a positive family history of recurrence of febrile episodes suggesting a possible genetic origin; however, no mutation has never been identified[6] (C).

PFAPA syndrome is characterized by the presence of sudden recurrent episodes of high fever, lasting from 2 to 8 days and which are repeated every 2–12 weeks, accompanied by aphthous ulcers, pharyngitis, sometimes with exudate, or cervical lymphadenopathy (upper cervical region), with mobile and painless lymph nodes in the absence of upper respiratory tract infection[3] (C). Patients usually complain of malaise hours before the onset of an attack. Pharyngitis and cervical adenitis are present in 80–100% of these patients, and aphthous stomatitis can be seen in 60–70%. Other associated symptoms are abdominal pain, arthralgia, headache, nausea or vomiting[7] (C). For the diagnosis of this syndrome, there is no need of the presence of the whole group of symptoms, and one should rule out the possibility of an episode of upper respiratory tract infection; the patient must present asymptomatic periods between attacks and maintain normal psychomotor growth and development[8] (D).

Recommendation
PFAPA is a diagnosis of exclusion established on clinical grounds, and one must suspect of this problem in children with recurrent and periodic febrile episodes of unknown origin, or with recurrent tonsillitis, interspersed with asymptomatic periods, especially in children with a good general condition and with preservation of weight and height development. Other monogenic auto-inflammatory diseases such as a periodic syndrome associated with tumor necrosis factor receptor (TRAPS) and mevalonate kinase deficiency, should be taken in consideration in the differential diagnosis.

What tests should be required for the evaluation of patients with periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome?

Strategy
(Pharyngitis OR Pharyngitides OR Sore Throat OR Lymphadenitis OR Adenitis OR Stomatitis, Aphthous OR Fever OR PFAPA) AND Periodicity* AND (Diagnosis/Broad [filter]) $n = 150$.

Laboratory findings are nonspecific and the diagnosis of PFAPA syndrome is established on clinical grounds.[9] (C). Although not producing pathognomonic changes, complementary tests should be requested to support the exclusion of other diagnoses. Crises are often associated with leukocytosis and moderate neutrophilia and high erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), which normalize in the intervals between episodes[10] (C). Hemoglobin levels are normal, and platelet levels may be normal or slightly elevated. A tonsil secretion culture may be performed to exclude diseases that may exhibit similar symptoms, especially streptococcal infection[11] (D).

Recommendation
Laboratory findings are nonspecific and PFAPA is a diagnosis of exclusion established on clinical grounds. No pathognomonic changes are found with additional tests.

What is the role of surgical approach (tonsillectomy with or without adenoidectomy) in the treatment of periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome?

Strategy
(Pharyngitis OR Pharyngitides OR Sore Throat OR Lymphadenitis OR Adenitis OR Stomatitis, Aphthous OR Fever OR PFAPA) AND Periodicity* AND (Therapy/Broad [filter]) $n = 93$.

Several case series have shown good results, with reports of complete resolution of symptoms in patients with PFAPA who underwent surgery (tonsillectomy)[12–16] (C). However, there is controversy regarding this approach[17] (C). A systematic review analyzing evidence on the role of tonsillectomy or adenoidectomy in treating children with PFAPA syndrome found that the success of the surgical approach is widely variable, with studies demonstrating complete resolution of symptoms, and others which did not identify any clinical improvement[18] (A). A meta-analysis published in 2010 noted that, when comparing the clinical treatment with corticosteroids *versus* tonsillectomy, both therapies were equally effective in treating PFAPA. However, surgical intervention was considered the best choice in the long run[19] (A). Taking into account the possibility of surgical risk related to tonsillectomy, surgery should be considered in those patients in whom the symptoms of

PFAPA clearly affect their quality of life or in those with poor response to medical treatment.

A randomized clinical trial carried out in order to assess the effectiveness of tonsillectomy in children with a mean age of 4.1 years ($n = 26$) and who had suffered at least five episodes related to PFAPA syndrome found that all children who had undergone tonsillectomy ($n = 14$) were free of symptoms after a 6-month follow-up, with disappearance of fever episodes. On the other hand, in the group under clinical surveillance only in half of these patients the symptoms subsided (6/12)[20] (**B**). Four of the 14 children who underwent surgical treatment showed a febrile episode compatible with periodic fever within six months after surgery *versus* 34 episodes reported by all children in the control group (0.05 episodes per child/month in the surgical group *versus* 0.47 episodes per child/month in the control group, based on a 6-month period of follow-up). After a 6-month follow-up, 42% of the children ascribed to the control group were submitted to surgical treatment due to persistence of symptoms. In this study, no complications related to surgery were identified[20] (**B**).

In another non-blinded, randomized, clinical trial, which also analyzed the role of tonsillectomy (with adenoidectomy), children diagnosed with PFAPA syndrome ($n = 39$) were allocated for surgical treatment ($n = 19$) or clinical follow-up only (control group $n = 20$), and both groups received treatment with corticosteroids[21] (**B**). In this study, at the end of an 18-month period of follow-up the authors identified a complete resolution of symptoms in 13 patients; 12 of these patients (12/19) had been randomized for surgical treatment. Overall, 12 episodes of PFAPA syndrome were identified in the group undergoing surgery *versus* 179 episodes recorded in the control group during the 18-month follow-up (0.04 episodes per child/month in the surgical group *versus* 0.5 episodes per child/month in the control group; RR = 0.07; 95% CI: 0.04–0.13). The proportion of patients who experienced resolution of symptoms with surgery *versus* clinical follow-up was 63% *versus* 5% respectively[21] (**B**).

Recommendation

The evidence supporting the indication for surgical treatment (tonsillectomy with or without adenoidectomy) of patients with PFAPA syndrome is based on two non-blinded, randomized clinical trials that included small numbers of patients[22,23] (A). Although these studies demonstrate effectiveness of surgical treatment with immediate and long-term resolution of symptoms related to this syndrome, each case must be assessed individually, and further studies should be conducted. Taking into account the possibility of a surgical risk related to tonsillectomy, some authors suggest that surgery should be considered in those patients in whom the symptoms of PFAPA clearly affect their quality of life or in those with poor response to medical treatment.[22]

What is the role of corticosteroids in the treatment of periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome?

Strategy

(Pharyngitis OR Pharyngitides OR Lymphadenitis OR Adenitis OR Stomatitis, Aphthous) AND (Fever, Periodic OR Periodicity OR Syndrome OR PFAPA) AND (Steroids OR Glucocorticoid* OR Prednisone OR Dexamethasone) = 208.

Series and case reports have demonstrated the occurrence of fever resolution in less than 6 h, and of the other symptoms in less than 48 h after an initial dose of prednisone 1–2 mg/kg, with a second dose of 0.5–1 mg/kg that may be repeated if the disease has not been controlled within 48–72 h[3,7,24–27] (**C**).

A case series with 12 children showed immediate fever improvement in nine patients after the dose of prednisone, and the interval between attacks was extended from 21 days (mean interval prior to treatment) to 133 days post treatment ($p = 0.007$)[2] (**C**). And a decrease of 50% in the time between attacks was already assigned to corticosteroids.[4]

In adults with PFAPA, prednisone at a dose of 60 mg/day administered at the onset of symptoms, improved fever; and a significant improvement of other symptoms, particularly with respect to a decrease of tonsillar exudate and oral ulcers, was also observed. During follow-up, eight of the 15 patients evaluated exhibited an increased incidence of crisis episodes, with recurrence at 3-week intervals after the beginning of treatment with corticosteroids[4] (**C**).

In a randomized clinical trial[28] (**B**) with 41 children, treatment with low doses of prednisone was compared with higher doses of this drug. The children were divided into two groups to receive 0.5 mg/kg/day or 2 mg/kg/day. In the first group, the fever ceased in 8–12 h, and in the second group in 6–8 h. The other symptoms disappeared after 24 h in both groups. There was no increase in the interval between crises with prednisone in these two doses. The adverse effects observed were restlessness and sleep disturbance, which can be minimized by administering the dose of the corticosteroid at least 4–6 h before bedtime.

Recommendation

The use of prednisone at a dose of 1–2 mg/kg body weight at the onset of fever in patients with PFAPA has proved effective in a number of series and case reports and in a randomized study. Despite the small samples in these trials, and also taking into account that these were non placebo-controlled studies, the use of prednisone on demand probably is a valid therapeutic strategy for crises of this syndrome, with a low risk of adverse events.[29] The best evidence is still needed to support its use in PFAPA patients.

What is the role of IL-1 inhibitors in the treatment of periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome?

Strategy

(Pharyngitis OR Pharyngitides OR Lymphadenitis OR Adenitis OR Stomatitis, Aphthous) AND (Fever, Periodic OR Periodicity OR Syndrome OR PFAPA) AND (Interleukin 1 Receptor Antagonist Protein OR Anakinra OR Kineret OR Antril OR Receptors, Interleukin) $n = 19$.

Inflammatory mechanisms adjacent to PFAPA are still unknown. One study showed increased serum cytokines IL-1β and IL-6, when compared to the control group; and a decrease in serum levels of anti-inflammatory cytokines, particularly IL-4 and IL-10[30] (**C**).

One study looked at the blood profile, inflammatory markers and cytokine levels in 15 children with PFAPA in and off-febrile episodes. The ability of monocytes to secrete IL-1β was assessed by ELISA; and active secretion of IL-1β was visualized by Western blotting. During febrile periods, stimulated monocytes secreted significantly more IL-1β *versus* off-febrile episodes. The authors concluded that an IL-1β release dysregulation by monocytes occurs in patients with PFAPA syndrome, and approximately 20% had NLRP3 variants, suggesting that inflammasome-related genes may be involved in this auto-inflammatory syndrome[31] (**C**). In one case report, a 27-year old adult patient who exhibited resistance against conventional treatment with prednisone and tonsillectomy and featuring more than 10 attacks/year was treated with the IL-1β inhibitor, anakinra, at a dose of 100 mg/day. After a 6-month follow-up, the patient remained asymptomatic, with no signal of recurrence[32] (**C**).

In a randomized clinical trial with 21 children, blood samples of children with PFAPA, of children with other hereditary periodic fever, and of healthy children were analyzed. In those patients with PFAPA a significant elevation of C3, IL-18 and IL-1β in febrile periods was noted. In the same study, five patients with PFAPA were treated with a recombinant IL-1 receptor antagonist; in all patients, a quick clinical response was observed[5] (**B**).

Recommendation

While the results obtained with IL-1β inhibitors are promising, the studies are limited to a few case reports, requiring randomized clinical trials to define the role of IL-1β inhibitors in the management of PFAPA.

Conflict of interests

Maria Teresa R.A. Terreri and Flavio Roberto Sztajnbok serve as speakers for Novartis. Clovis Artur Almeida da Silva has a conflict of interests with *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq 302724/2011-7), Federico Foundation and *Núcleo de Apoio à Pesquisa "Saúde da Criança e do Adolescente"*, USP (NAP-CriAd). The other authors declare no conflict of interests.

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