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Original article

# Guidelines for the management and treatment of periodic fever syndromes Cryopyrin-associated periodic syndromes (cryopyrinopathies – CAPS)

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ABSTRACT

*Objective:* To establish guidelines based on cientific evidences for the management of cryopyrin associated periodic syndromes.
*Description of the evidence collection method:* The Guideline was prepared from 4 clinical questions that were structured through PICO (Patient, Intervention or indicator, Comparison

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Autoinflammatory syndromes
Guidelines

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:* 1215 articles were retrieved and evaluated by title and abstract; from these, 42 articles were selected to support the recommendations.
*Recommendations:* 1. The diagnosis of CAPS is based on clinical history and clinical manifestations, and later confirmed by genetic study. CAPS may manifest itself in three phenotypes: FCAS (mild form), MWS (intermediate form) and CINCA (severe form). Neurological, ophthalmic, otorhinolaryngological and radiological assessments may be highly valuable in distinguishing between syndromes; 2. The genetic diagnosis with NLRP3 gene analysis must be conducted in suspected cases of CAPS, *i.e.*, individuals presenting before 20 years of age, recurrent episodes of inflammation expressed by a mild fever and urticaria; 3. Laboratory abnormalities include leukocytosis and elevated serum levels of inflammatory proteins; and 4. Targeted therapies directed against interleukin-1 lead to rapid remission of symptoms in most patients. However, there are important limitations on the long-term safety. None of the three anti-IL-1β inhibitors prevents progression of bone lesions.



## Diretrizes de conduta e tratamento de síndromes febris periódicas associadas à criopirina (criopirinopatias – CAPS)

*Palavras-chave:*
Síndrome autoinflamatória familiar associada ao frio
Síndrome de Muckle-Wells
Síndrome neurológica cutânea e articular crônica infantil
Síndromes autoinflamatórias
Diretrizes

RESUMO

*Objetivo:* Estabelecer diretrizes baseadas em evidências científicas para manejo das Síndromes periódicas associadas à criopirina (Criopirinopatias – CAPS).
*Descrição do método de coleta de evidência:* A Diretriz foi elaborada a partir de 4 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.
*Resultado:* Foram recuperados, e avaliados pelo título e resumo, 1215 artigos, tendo sido selecionados 42 trabalhos, para sustentar as recomendações.
*Recomendações:* 1. O diagnóstico de CAPS é baseado na anamnese e manifestações clínicas, sendo posteriormente confirmado por estudo genético. Pode se manifestar sob três fenótipos: FCAS (forma leve), MWS (forma intermediária) e CINCA (forma grave). Avaliações neurológica, oftalmológica, otorrinolaringológica e radiológica podem ser de grande valia na distinção entre as síndromes; 2. O diagnóstico genético com análise do gene NLRP3 deve ser conduzido nos casos suspeitos de CAPS, isto é, indivíduos que apresentam, antes dos 20 anos de idade, episódios recorrentes de inflamação expressa por urticária e febre moderada; 3. As alterações laboratoriais incluem leucocitose e elevação nos níveis séricos de proteínas inflamatórias; 4. Terapias alvo dirigidas contra a interleucina 1 levam a rápida remissão dos sintomas na maioria dos pacientes. Contudo, existem limitações importantes em relação à segurança em longo prazo. Nenhuma das três medicações anti-IL1β evita progressão das lesões ósseas.



## Description of the evidence collection method

This Guideline was prepared from 4 relevant clinical questions related to the management of cryopyrin-associated periodical syndromes (cryopyrinopathies). 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

at 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 cryopyrin-associated periodical syndromes (cryopyrinopathies).

## Introduction

Cryopyrin-associated periodic syndromes (CAPS) comprise a specific, rare group of monogenic autoinflammatory diseases which are included in the group of hereditary periodic fever syndromes caused by a defect in the regulation of inflammatory cytokines, particularly interleukin-1β (IL-1β). These diseases include the familial cold-associated autoinflammatory syndrome (FCAS); Muckle–Wells syndrome (MWS) and chronic infantile neurological, cutaneous, and articular (CINCA) syndrome, also known as neonatal-onset multisystem inflammatory disease (NOMID).

1. When should we suspect that an individual is a carrier of cryopyrin-associated periodical syndromes (cryopyrinopathies)?

### *Strategy*

(Cryopyrin-Associated Periodic Syndromes OR Urticarias, Familial Cold OR Familial Cold Autoinflammatory Syndrome 1 OR Muckle–Wells Syndrome OR Chronic Neurologic Cutaneous and Articular Syndrome OR NOMID OR Prieur–Griscelli Syndromes OR Cryopyrinopathy OR UDA Syndromes OR Chronic Infantile Neurological, Cutaneous, and Articular Syndrome OR Neonatal Onset Multisystem Inflammatory Disease) AND Signs and Symptoms. $n = 543$.

The cryopyrin-associated periodic syndromes (CAPS) are autoinflammatory diseases characterized by recurrent episodes of systemic inflammation, involving multiple tissues, including joints, skin, central nervous system (CNS), eyes and ears. Contrary to what happens with autoimmune diseases, CAPS are not associated with immune response through autoantibodies or antigen-specific T cells, but with the dysfunction of the innate immune system, which is not specific, not requiring initial sensitization by antigen.[1] (D)

Familial cold-associated autoinflammatory syndrome, Muckle–Wells syndrome and chronic infantile neurological, cutaneous and articular syndrome were originally described as distinct clinical entities, despite the overlapping of symptoms and signs.[2] (D) Patients often are seen with recurrent episodes of fever and pseudourticariform rash, as well as with inflammation of tissues such as joints, brain, ears and eyes. Indeed, these three syndromes exist in a progression of severity, with familial cold-associated autoinflammatory syndrome being the least severe condition and CINCA the most severe of them; MWS has an intermediate phenotype of severity. Skin rash, a signal present in all three diseases, is usually the first manifestation to develop after birth or in early childhood. This condition has a migratory, maculopapular, urticariform rash, and usually is associated with pruritus.[2,3] (D)

Familial cold-associated autoinflammatory syndrome (FCAS), or cold-induced urticaria, is the mildest form of CAPS and has an autosomal dominant trait. FCAS is characterized by recurrent and self-limited episodes of mild fever, skin rash and arthralgia, precipitated by exposure to environmental changes characterized by low temperatures (*e.g.*, wind exposure, refrigerator door opening). FCAS differs from cold-induced hives, where contact with cold surfaces is the triggering factor. Other related symptoms include conjunctivitis, myalgia, sweating, somnolence, headache, and nausea.[4] (C) Symptoms usually begin a few hours after exposure to low temperatures, usually with a short duration of episodes.[5] (C) Although late cases of renal amyloidosis have been reported in family members affected by FCAS, deafness and amyloidosis are not usually observed in this syndrome, as opposed to what occurs in MWS and CINCA patients.[6] (C)

Muckle–Wells Syndrome (MWS), is characterized by episodes of urticaria and deafness, and renal amyloidosis.[7] (C) Recurrent episodes of fever and skin rash associated with joint and ocular manifestations were described, although not always with fever.[8] (C) The course of the disease varies, from recurrent attacks to permanent symptoms.[9] (C) As in FCAS, conjunctivitis is often present. Neurological impairment is often not described, although in some cases headache and papilledema have been reported. Amyloidosis is the most severe complication, developing into adulthood in approximately 30% of the cases.[8] (C) Sensorineural hearing loss is observed in 70% of cases.[10] (D)

Chronic infantile neurological, cutaneous and articular (CINCA) syndrome, also known as neonatal-onset multisystem inflammatory disease (NOMID), is associated with the most severe phenotype of this spectrum of diseases.[11] (C) The first symptoms of CINCA occur already in the first weeks of life or in early childhood.[12] (C) Fever can be an intermittent and mild finding; in some cases this sign is even absent. Skin rash is variable among individuals, depending from disease activity. Involvement of bones and joints also varies in severity: in approximately two thirds of these patients, joint manifestations, mainly in large joints, are limited to transient arthralgia and edema. However, in one third of patients a crippling arthropathy can be seen.[12] (C) Patients with CINCA/NOMID can also exhibit an excessive growth of epimetaphysary cartilage, particularly of long bones, which eventually causes deformations leading to a discrepancy in the length of limbs, joint contractures and degenerative arthropathy.[13,14] (C) CNS abnormalities are present in almost all patients and are caused by chronic aseptic meningitis through leukocyte infiltration.[12]

(C) Headache, seizures, mental retardation, spasticity of the lower limbs and papilledema are often observed as a consequence of an increased intracranial pressure. Eye involvement with identification of uveitis occurs in approximately 50% of patients, with posterior uveitis in around 20%. Optic atrophy may also develop, and ocular manifestations can progress to blindness.[15,16] (C) Sensorineural hearing loss can also be noted.

### *Recommendation*

The diagnosis of CAPS is based on clinical history and clinical manifestations, being later confirmed by genetic studies. CAPS may manifest itself in three phenotypes, with no fixed demarcation among them: FCAS (mild form), MWS (intermediate form) and CINCA (severe form).[17] (C) The distinction between these cryopyrinopathies may be a difficult task, since they have symptoms in common. Neurological, ophthalmic, otorhinolaryngological and radiological assessments can be critical in distinguishing among the syndromes.

2. How the genetic diagnosis of cryopyrin-associated periodical syndrome is established?

### *Strategy*

(Cryopyrin-Associated Periodic Syndromes OR Urticarias, Familial Cold OR Familial Cold Autoinflammatory Syndrome 1 OR Muckle–Wells Syndrome OR Chronic Neurologic Cutaneous and Articular Syndrome OR IOMID OR Prieur–Griscelli Syndromes OR Cryopyrinopathy OR UDA Syndromes OR Chronic Infantile Neurological, Cutaneous, and Articular Syndrome OR Neonatal Onset Multisystem Inflammatory Disease) AND (Medical Genetics[filter]). *n* = 270.

Periodic syndromes associated with cryopyrin are caused by mutations (with an autosomal dominant pattern, or *de novo* mutations) in CIAS1 gene – cold-induced autoinflammatory syndrome 1, also known as NLRP3 or NALP3 (NACHT, nucleotide binding oligomerization domain, leucine rich-repeat family, pyrin domains containing protein 3), located on chromosome 1q44. The mechanism by which mutations in the gene CIAS1 cause inflammatory diseases is not fully understood, however *in vitro* studies suggest that these mutations present a function gain effect, probably through loss of regulatory mechanisms associated with activation.[18] (D) So far, the online database known as *Infevers*, dedicated to autoinflammatory hereditary diseases, describes more than 170 mutations related to CAPS.[19] (D)

This gene encodes the protein cryopyrin, which belongs to a family of proteins called nucleotide binding domain and leucine-rich repeats (NLR), predominantly expressed in peripheral blood leukocytes.[10,20] (D) Cryopyrin is related to the regulation of caspase-1, and changes in its concentration cause overexpression of IL-1β, and this increased production triggers recurrent episodes of systemic inflammation. Cryopyrin is also involved in the regulation of the apoptosis pathway and in the activation of nuclear factor kappa B, despite conflicting evidence on the activation of this factor.[21,22] (D) Different mutations in CIAS1 gene have been linked to CAPS, and some of these mutations are exclusively related to one of these syndromes (FCAS, MWS and/or CINCA/NOMID).[23] (D) It is further recognized that in about 50% of patients with a diagnosis of CINCA/NOMID and in around 25–33% of patients with MWS, NLRP3 mutations are not identified.[24] (C)

Because this is a genetic disease that follows an autosomal dominant pattern, individuals with CAPS usually have one of their parents affected by the disease, with a 50% probability of having their offspring affected.[25] (D) Patients with CINCA/NOMID are usually affected by mutations *de novo*, with no family history of CAPS.

### *Recommendation*

The genetic diagnosis with an analysis of NLRP3 gene must be obtained in suspected cases of CAPS, *i.e.*, individuals presenting, recurrent episodes of inflammation expressed by mild fever and urticaria before the age of 20. It should be left clear, however, that in fact a significant number of individuals clinically diagnosed as carriers of cryopyrinopathy have no mutations associated with the disease.

3. Besides genetic studies, what tests should be required for the evaluation of patients with cryopyrin-associated periodical syndrome?

### *Strategy*

(Cryopyrin-Associated Periodic Syndromes OR Urticarias, Familial Cold OR Familial Cold Autoinflammatory Syndrome 1 OR Muckle–Wells Syndrome OR Chronic Neurologic Cutaneous and Articular Syndrome OR IOMID OR Prieur–Griscelli Syndromes OR Cryopyrinopathy OR UDA Syndromes OR Chronic Infantile Neurological, Cutaneous, and Articular Syndrome OR Neonatal Onset Multisystem Inflammatory Disease) AND (Diagnosis/Broad[filter]). *n* = 203.

Usually, acute-phase proteins, such as C reactive protein (CRP) and serum amyloid A protein (SAA), exhibit increased serum levels, despite the absence of cutaneous signs; thus, these indicators should be monitored.[26,27] (D) Neutrophilia may also occur. Proteinuria and renal function tests should be performed, since progression to nephrotic syndrome and renal failure reflects a late complication of systemic amyloidosis.

Cerebrospinal fluid examination can be conducted in suspected cases of CINCA/NOMID and MWS. High polymorphonuclear cell counts, high concentration of protein and an increase in intracranial pressure can be found.[27,28] (D,C) Imaging studies such as CT scan or brain MRI should be obtained, confirming the diagnosis. These studies can identify ventricular dilatation with a prominent sulcus and central atrophy.[29] (C) Plain radiographs can identify bone and joint involvement through the demonstration of metaphyseal osteopathy and impairment of growth plates.[30] (C) Audiometry is an important test for the establishment of an early diagnosis and monitoring of sensorineural hearing loss; also important is an ophthalmic evaluation.

### *Recommendation*

Laboratory changes are the same observed in other autoinflammatory diseases, including leukocytosis and higher

serum levels of inflammatory proteins; these should be monitored. Imaging studies may be critical in distinguishing among syndromes, as well as for the ophthalmologist and otolaryngologist evaluation.

The scarcity of periodic syndromes associated with cryopyrin and the presence of overlapping symptoms with other conditions often result in a delay in the establishment of a diagnosis. Because of the different phenotypes related to CAPS, a review of clinical symptoms is in order, as well as a combination of diagnostic procedures.

4. What is the role of biological agents in the management of cryopyrin-associated periodical syndrome?

### *Strategy*

(Cryopyrin-Associated Periodic Syndromes OR Urticarias, Familial Cold OR Familial Cold Autoinflammatory Syndrome 1 OR Muckle–Wells Syndrome OR Chronic Neurologic Cutaneous and Articular Syndrome OR IOMID OR Prieur–Griscelli Syndromes OR Cryopyrinopathy OR UDA Syndromes OR Chronic Infantile Neurological, Cutaneous, and Articular Syndrome OR Neonatal Onset Multisystem Inflammatory Disease) AND (Interleukin 1 Receptor Antagonist Protein OR Anakinra OR Urine-Derived IL1 Inhibitor OR IL1 Inhibitor, Urine-Derived OR Urine Derived IL1 Inhibitor OR IL1 Febrile Inhibitor OR Febrile Inhibitor, IL1 OR infliximab OR etanercept OR adalimumab OR golimumab OR certolizumab OR Tumor Necrosis Factor alpha OR Cachectin-Tumor Necrosis Factor OR Cachectin Tumor Necrosis Factor OR TNFalpha OR TNF-alpha OR Tumor Necrosis Factor OR Tumor Necrosis Factor Ligand Superfamily Member 2). $n = 199$.

### *IL-1 receptor antagonist*

The proposed use of drugs targeting the blockage of the inflammatory cytokine activation pathway is based on the identification of defects in the regulation of these cytokines, where significantly elevated serum levels are observed. Three different types of IL-1 receptor antagonists are available: human recombinant non-glycosylated analog of IL-1 receptor antagonist (rhIL-1Ra) (anakinra); fusion protein comprising type I receptor of IL-1; and accessory protein of IL-1 receptor and the Fc portion of human IgG1 (rilonacept) and human monoclonal antibody against IL-1β (canakinumab).[31] (D)

*1. Anakinra (human recombinant non-glycosylated analog of IL-1 receptor antagonist)*

The mechanism of action of anakinra is a competitive inhibition of binding of IL-1α and IL-1β to their receptors.[32] (D) The first study on the use of anakinra in patients with CAPS was a case report of two patients diagnosed with MWS presenting, as clinical features, fever, skin rash, conjunctivitis and increased serum levels of serum amyloid A.[33] (C) In this study, treatment with anakinra (100 mg/day) provided improvement of inflammatory symptoms hours after administration of the drug, and both patients showed a reduction in serum levels of amyloid A. This response was found to be maintained throughout a six-month follow-up period in both patients, with a substantial reduction in inflammatory protein levels.[33] (C)

In a prospective study, an analysis was conducted on 18 patients (age range, 4–32 years) diagnosed with CINCA, where all of them should have at least two of the following symptoms: skin rash, central nervous system impairment (expressed by hearing loss and papilledema), and osteopathy identified by patella or epiphysis overgrowth. In this study, it was found that the treatment with anakinra (1.0 mg/kg) was associated with skin rash and conjunctivitis resolution three days after administration of the drug.[34] (C) One month after the initiation of treatment, a decrease in inflammatory proteins (amyloid A and C-reactive protein), as well as in erythrocyte sedimentation rate, was noted; and these reduced levels were maintained through the six-month evaluation.[34] (C) Overall, eight patients had remission of inflammatory symptoms in the 3rd month of follow-up, while the remainder ($n = 10$) showed remission at 6 months. With regard to adverse events, the most commonly reported ones were reactions at the site of application, and upper respiratory tract infection.[34] (C)

A retrospective study analyzing patients with CAPS found that 15 patients treated with anakinra showed complete remission in disease activity within 12 h after administration of the drug.[35] (C) In this study it was also observed that serum levels of C-reactive protein and of amyloid A returned to normal one week after the initiation of treatment.[35] (C) Another study on quality of life of children diagnosed with CAPS showed that the use of anakinra for a mean period of 37.5 months produced significant improvement in overall quality of life, analyzed by CHQ (Child Health Questionnaire)-PF50.[36] (C)

*2. Rilonacept (fusion protein comprising type I IL-1 receptor, IL-1 receptor accessory protein, and the Fc portion of human IgG1)*

Rilonacept is a dimeric fusion protein consisting of the extracellular domain of interleukin-1 receptor and of human IgG1 Fc domain that binds and neutralizes IL-1. This was the first drug approved by the FDA (Food and Drug Administration) for the treatment of CAPS, specifically focused on FCAS and MWS. In 2008, an analysis of results of 47 patients with FCAS and MWS enrolled in two consecutive phase III studies was conducted. The first of these, a double-blind, randomized study with a six-week follow-up, compared the administration of weekly subcutaneous injections of rilonacept 160 mg/week *versus* placebo. The second study consisted of two parts: Part A – nine weeks of an open-phase treatment with rilonacept; and Part B – Nine-week of a double-blind, randomized, placebo-controlled study of drug discontinuation. In this study, it was shown that rilonacept administration was associated with improvement in disease activity within a few days of the onset of therapy (an improvement of 84% in the symptom score in the treated group *versus* 13% in placebo group).[37] (A) A decrease in serum levels of C-reactive protein and serum amyloid A *versus* baseline values was also found.[37] (A) An extension of this analysis with a 96-week follow-up period showed continued improvement in signs and symptoms, as well as maintenance of low serum levels of inflammatory proteins.[38] (B) With regard to adverse events, reaction at the site of drug application, upper respiratory tract infection, headache, and diarrhea were the most frequently reported.[37,38] (A,B)

*3. Canakinumab (monoclonal antibody against human IL-1β)*

Canakinumab, approved in 2009 by the FDA, is directed to the treatment of children over four years and adults with a diagnosis of FCAS and MWS. This is a human monoclonal antibody against IL-1β with high affinity to binding human IL-1β, blocking its interaction with receptors and therefore neutralizing its activity.

The first randomized controlled trial examining the use of canakinumab in patients with CAPS was completed in 2008 and consisted of three parts. In phase 1, 35 patients received canakinumab 150 mg. Those with complete response to treatment entered part 2 of the study and were randomly assigned to treatment with canakinumab every eight weeks for up to 24 weeks *versus* non-treatment. After the completion of phase 2 or in face of the occurrence of relapse, phase 3 was initiated, in which the participants received at least two more doses of canakinumab.[39] (A) In Phase 1, this study showed (open-label) complete response with respect to improvement of disease symptoms in 97% of patients (34/35). During phase 2 (double-blind), all 15 patients randomized to treatment with canakinumab remained in remission of the disease, in contrast to 81% (15/16) of patients randomized to placebo, who showed active disease (including high serum levels of C-reactive protein and serum amyloid A). At the end of this phase, 52% of patients treated with canakinumab reported remission of symptoms, compared to zero patients in placebo group. This study also identified that 75% of untreated patients remained with symptoms of mild to moderate intensity, compared to zero patients treated with canakinumab.[39] (A) In this study, the use of canakinumab was well tolerated, with only two patients reporting serious adverse events, including a vertigo episode followed by closed-angle glaucoma related to complications of CAPS, and lower urinary tract infection and sepsis. The most commonly reported adverse events among those receiving the drug were pharyngitis, rhinitis, nausea, diarrhea and vertigo. Most patients reported no reactions at the injection site.[39] (A)

In agreement with the findings described above, one multicenter phase III study (open-label) also associated the use of canakinumab to improvement of symptoms and suppression of systemic inflammation, with normalization of serum C-reactive protein and amyloid A.[40] (B) This study aimed to examine the effects, in the long run, of the use of canakinumab (150 mg or 2.0 mg/kg every eight weeks, over more than two years) in patients with previously untreated CAPS, or who had already been treated in previous studies.[40] (B) A complete response was achieved (according to evaluation scores of disease activity) by 78% (85/109) of those treatment-naive patients. The adverse events noted were considered to be of mild to moderate intensity; most patients (92%) reported having suffered no reaction at the injection site.[40] (B)

### *Recommendation*

Targeted therapies directed against cytokines (interleukin-1 in this case) are associated with a rapid remission of symptoms in most patients diagnosed with CAPS. The use of rilonacept for patients with FCAS and MWS demonstrated improvement in disease activity in a follow-up period of 6–96 weeks, with reduced serum levels of inflammatory proteins (C-reactive protein and amyloid A). The use of canakinumab also promoted reduction of clinical manifestations. However, there are significant limitations on the use of these drugs, especially in relation to short follow-ups, small number of patients evaluated, intrinsic bias when evaluating rare diseases, and in comparing the efficacy of treatment with placebo, parameters that prevent a more robust assessment of the effectiveness of these drugs, as well as in relation to their safety, taking into account their potential long-term risks. In the literature, two studies demonstrating ongoing efficacy using anakinra were found.[41,42] It is not yet clear whether rilonacept or canakinumab offer a therapeutic option for treatment of aseptic meningitis, ocular impairment or hearing loss. None of the three anti-IL-1β medications prevent the progression of bone lesions.[41] Worldwide, the high cost of these biologicals, which are drugs of chronic use in all patients, is still the main limitation to its use in clinical practice of pediatric rheumatologists. Usually an increase of the dose, or even a change of immunobiological agent during the follow-up, is needed. Importantly, we do not count on direct comparisons of the three different types of IL-1 receptor antagonists currently available. Consequently, it becomes impossible to suggest preferentially one or other of these drugs based on evidence.

## Conflicts of interest

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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