New insights on multigenic autoinflammatory diseases

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Abstract: Autoinflammatory diseases are disorders of the innate immune system, which can be either monogenic due to a specific genetic mutation or complex multigenic due to the involvement of multiple genes. The aim of this review is to explore and summarize the recent advances in pathogenesis, diagnosis, and management of genetically complex autoinflammatory diseases, such as Schnitzler’s syndrome; adult-onset Still’s disease; synovitis, acne, pustulosis, hyperostosis, osteitis syndrome/chronic recurrent multifocal osteomyelitis/chronic non-bacterial osteomyelitis; Adamantiades-Behçet’s disease; Yao syndrome; and periodic fever with aphthous stomatitis, pharyngitis, and adenitis syndrome. The PubMed database was screened for relevant articles using free text words and specific search strings. The search was limited to English-language articles, reporting the results of studies in humans, published through March 2021. Evidence from literature suggest that these rare multigenic autoinflammatory diseases can present with different clinical features and the diagnosis of these diseases can be challenging due to a combination of nonspecific manifestations that can be seen in a variety of other conditions. Diagnostic delays and disease complications may occur due to low disease awareness and the lack of pathognomonic markers. The pathogeneses of these diseases are complex and in some cases precise pathogenesis is not clearly understood. Conventional treatments are commonly used for the management of these conditions, but biologics have shown promising results. Biologics targeting proinflammatory cytokines including IL-1, IL-6, TNF-α, IL-17A and IL-18 have been shown to ameliorate signs and symptoms of different multigenic autoinflammatory diseases.

Keywords: Adamantiades-Behçet’s disease, adult-onset Still’s disease, autoinflammatory diseases, cytokines, interleukins

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either present in adulthood due to either de novo mutations or presence of mosaicism. Classic examples are cryopyrin-associated autoinflammatory syndromes and tumor necrosis factor receptor associated periodic syndrome.9,10 In addition, the phenotype of certain monogenic ones such as hyperimmunoglobulin D syndrome may be skewed in a growing child to become milder albeit requiring treatment based on persistent clinical symptoms and warranting a high index of suspicion from adult rheumatologists.11 There are a growing number of multigenic autoinflammatory conditions that include Schnitzler’s syndrome; adult-onset Still’s disease (AOSD); synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome/ CRMO/chronic non-bacterial osteomyelitis (CNO); Adamantiades-Behçet’s disease; Yao syndrome (YAO); and PFAPA syndrome.1,2,12,13 Among these conditions, patients with AOSD and Schnitzler’s syndrome share some common features like spiking fever and skin rash.12,14–16 Diagnosis and treatment of multigenic autoinflammatory diseases remain challenging due to their rarity and diverse presentations.

This review focuses on recent advances in genetically complex autoinflammatory diseases, including new insights regarding their pathogenesis, clinical overview, diagnosis, and management.

Methods
The articles included in this narrative review were identified through literature searches of English publications in the PubMed database using the MeSH terms or keywords: ‘Schnitzler’s syndrome’, ‘Still’s disease’, ‘AOSD’, ‘SAPHO syndrome’, ‘CRMO’, ‘Adamantiades-Behçet’s disease’, ‘YAO syndrome’, ‘PFAPA syndrome’, and search strings: ‘Schnitzler’s syndrome and pathogenesis’, ‘Schnitzler’s syndrome and biomarker’, ‘Schnitzler’s syndrome and diagnosis’, ‘Schnitzler’s syndrome and treatment’, ‘Schnitzler’s syndrome and IL-1 inhibitors’, ‘Schnitzler’s syndrome and canakinumab’, ‘AOSD and pathogenesis’, ‘AOSD and biomarker’, ‘AOSD and diagnosis’, ‘AOSD and treatment’, ‘AOSD and IL-1 inhibitors’, ‘AOSD and canakinumab’, ‘SAPHO syndrome and pathogenesis’, ‘SAPHO syndrome and biomarker’, ‘SAPHO syndrome and diagnosis’, ‘SAPHO syndrome and treatment’, ‘SAPHO syndrome and IL-1 inhibitors’, ‘SAPHO syndrome and canakinumab’. ‘CRMO and pathogenesis’, ‘CRMO and biomarker’, ‘CRMO and diagnosis’, ‘CRMO and treatment’, ‘CRMO and IL-1 inhibitors’, ‘CRMO and canakinumab’, ‘Adamantiades-Behçet’s disease and pathogenesis’, ‘Adamantiades-Behçet’s disease and biomarker’, ‘Adamantiades-Behçet’s disease and diagnosis’, ‘Adamantiades-Behçet’s disease and treatment’, ‘Adamantiades-Behçet’s disease and IL-1 inhibitors’, ‘Adamantiades-Behçet’s disease and canakinumab’. ‘YAO syndrome and pathogenesis’, ‘YAO syndrome and biomarker’, ‘YAO syndrome and diagnosis’, ‘YAO syndrome and treatment’, ‘YAO syndrome and IL-1 inhibitors’, ‘YAO syndrome and canakinumab’. ‘PFAPA syndrome and pathogenesis’, ‘PFAPA syndrome and biomarker’, ‘PFAPA syndrome and diagnosis’, ‘PFAPA syndrome and treatment’, ‘PFAPA syndrome and IL-1 inhibitors’, ‘PFAPA syndrome and canakinumab’. In all, 275 relevant articles were identified, reporting the results of studies in humans, published from inception to March 2021. The articles were scrutinized, and the references listed are relevant to the objective of this review.

Schnitzler’s syndrome

Overview
Schnitzler’s syndrome is a rare, acquired autoinflammatory disease, with chronic urticarial rash, lymphadenopathy, bone pain, fatigue, systemic inflammatory response along with monoclonal gammapathy as main features.17 The exact prevalence of the disease is unknown but since 1972, fewer than 300 cases have been reported in the scientific literature.18–20

Pathogenesis
The etiology of Schnitzler’s syndrome is yet to be elucidated. Multiple features indicate that it is an acquired autoinflammatory disorder,21,22 with elevated levels of proinflammatory cytokine IL-1β, playing a central role in the pathophysiology of the disease.23,24 However, a possible link between autoinflammation and the monoclonal component (monoclonal IgM or IgG gammapathy) remains to be determined, because the level of monoclonal component is highly variable in Schnitzler’s syndrome, which can be very low or very high at once.25,26 Lipsker et al. performed immunoblotting on epidermal and dermal skin extracts, and immunoelectron microscopic studies on Lowicryl K4M-embedded skin sections in 3 patients with Schnitzler syndrome. Data showed that two patients had IgM deposits in the epidermis around the keratinocytes and below the
lamina densa region of the anchoring fibrils, which suggest that monoclonal gammopathy plays a part in the pathophysiology of the skin rash and urticarial lesions. Previous reports have shown that the aberrant nod-like receptor protein-3 (NLRP3) inflammasome signaling and cytokine pathway dysregulation play a key role in the pathogenesis of the disease. A study conducted in adult patients with Schnitzler’s syndrome has shown elevated levels of a chemoattractant, C-C motif chemokine ligand 2 (CCL2), in patients with Schnitzler’s syndrome, and there was a correlation between systemic CCL2 levels and the disease activity, suggesting the potential of CCL2 as a biomarker of disease activity and treatment response. In a prospective study, ex vivo cytokine profiles of Peripheral Blood Mononuclear Cells (PBMCs) was evaluated in 36 adult patients with Schnitzler syndrome prior to treatment and after initiation of anti-IL-1 therapy. The spontaneous production of TNFα, IL-6, IL-1β, IL-1α, and IL-1RA by PBMCs was higher in patients with Schnitzler syndrome when compared with controls. In addition, the elevated levels of IL-1β, IL-1α, IL-6, and TNFα may represent an initial aspect of the cytokine signature in Schnitzler syndrome. An additional finding on the T cell cytokine profile was decreased levels of Th1, Th2, and Th17, including reduced IL-10 levels.

Clinical manifestations and diagnosis

The main clinical features of Schnitzler’s syndrome include fever, musculoskeletal pain, lymphadenopathy, with chronic urticarial exanthema and immunoglobulin (Ig) monoclonal gammopathy (IgM or IgG) being the hallmarks of the disease. Patients with Schnitzler’s syndrome may develop lymphoproliferative disease and sustained clinical response and was effective in treating patients with Schnitzler’s syndrome. In a study, an adult patient with Schnitzler’s syndrome received canakinumab treatment every 8 weeks for 6 consecutive months and the clinical response to treatment was fast with sustained remission (Table 1). Krause and colleagues reported the results of a Phase II, randomized controlled study, which evaluated the effects of canakinumab in 20 adult patients with Schnitzler’s syndrome. Data showed that on Day 7, complete clinical response was significantly higher in patients who received canakinumab (n = 7) compared to patients who received placebo (n = 13) (71% vs 0%; p = .001). The long-term extension study of 15 patients with Schnitzler’s syndrome has shown that canakinumab could effectively reduce the clinical signs and symptoms of the disease, decrease the levels of inflammatory markers (CRP and SAA), and sustained the quality of life of the patients over 4 years.

Canakinumab, a fully human monoclonal antibody against IL-1β, was shown to induce a rapid and sustained clinical response and was effective in treating patients with Schnitzler’s syndrome. Data from a case report showed clinical improvement with the disappearance of fever, arthritis, and skin lesions in a patient with Schnitzler’s syndrome after treatment with the IL-1 receptor antagonist anakinra. Rilonacept is an IL-1 trap molecule which can block IL-1α and IL-1β signaling. Data from a prospective study have shown that rilonacept was effective in patients with Schnitzler’s syndrome with significant reductions in health assessment scores and physician’s global assessment scores versus baseline levels. In a retrospective study, out of 42 patients enrolled, 29 received anakinra and responded to the treatment. After a median follow-up of 36 months, the effectiveness of treatment remained unchanged.

Treatment

Treatment with nonsteroidal antiinflammatory drugs (NSAIDs) and immunosuppressive drugs were less effective with inconsistent results. IL-1 blockers have shown to be effective in the management Schnitzler’s syndrome. Data from a case report showed clinical improvement with the disappearance of fever, arthritis, and skin lesions in a patient with Schnitzler’s syndrome after treatment with the IL-1 receptor antagonist anakinra. Rilonacept is an IL-1 trap molecule which can block IL-1α and IL-1β signaling. Data from a prospective study have shown that rilonacept was effective in patients with Schnitzler’s syndrome with significant reductions in health assessment scores and physician’s global assessment scores versus baseline levels. In a retrospective study, out of 42 patients enrolled, 29 received anakinra and responded to the treatment. After a median follow-up of 36 months, the effectiveness of treatment remained unchanged.
Figure 1. Strasbourg criteria for the diagnosis of Schnitzler’s syndrome.
CRP, C-reactive protein; Ig, immunoglobulin.
Adapted from Gellrich and Günther.23

Table 1. Treatment options for the multigenic autoinflammatory diseases.

| Disease           | Conventional treatment/targeted therapy | Design                         | References                                      |
|-------------------|-----------------------------------------|--------------------------------|------------------------------------------------|
| Schnitzler’s syndrome | Anakinra                                | Case report                     | Faggioli et al.36 (n = 1)                        |
|                   | Canakinumab                              | RCT, case report                | Krause et al.39 (n = 20); Vanderschueren and Knockaert38 (n = 1) |
|                   | Rilonacept                               | Prospective study               | Krause et al.37 (n = 8)                          |
| AOSD               | NSAIDs                                   | Observational study             | Iliou et al.40 (n = 30); Gerfaud-Valentin et al.41 (n = 28) |
|                   | DMARDs [methotrexate, cyclosporine]      | Observational study, retrospective study | Iliou et al.40 (n = 19); Gerfaud-Valentin et al.41 (n = 33); Kalyoncu et al.42 (n = 202); Franchini et al.43 (n = 35); Fujii et al.44 (n = 13) |
|                   | Corticosteroids/glucocorticoids [Prednisone] | Observational study, retrospective study, case report | Iliou et al.40 (n = 39); Gerfaud-Valentin et al.41 (n = 51); Kalyoncu et al.42 (n = 199); Franchini et al.43 (n = 45); Antoniou et al.45 (n = 1) |
|                   | Anakinra*                                | Observational study, retrospective study | Iliou et al.40 (n = 10); Gerfaud-Valentin et al.41 (n = 6); Franchini et al.43 (n = 5) |
|                   | Canakinumab**                            | RCT, case report                | Feist et al.46 (n = 301); Kedor, Listing et al.47 (n = 18); Cavalli et al.48 (n = 4); Kontzias and Efthimiou49 (n = 2) |

(Continued)
Table 1. (Continued)

| Disease                        | Conventional treatment/targeted therapy | Design                                      | References                                      |
|--------------------------------|----------------------------------------|---------------------------------------------|------------------------------------------------|
|                                |                                        |                                             |                                                |
| Infliximab, etanercept,        | Observational study; retrospective study| Gerfaud-Valentin et al.\(^{61}\) \(n = 17\); Franchini et al.\(^{61}\) \(n = 2\) |                                                |
| adalimumab                     |                                        |                                             |                                                |
|                                |                                        |                                             |                                                |
| Tocilizumab                    | RCT, case series, case report          | Kaneko et al.\(^{50}\) \(n = 27\); Reihl Crnogaj et al.\(^{51}\) \(n = 8\); Bannai et al.\(^{52}\) \(n = 7\) |                                                |
|                                |                                        |                                             |                                                |
| Sarilumab                      | Case report                            | Simeni Njonnou et al.\(^{53}\) \(n = 1\) |                                                |
|                                |                                        |                                             |                                                |
| SAPHO/CRMO/CNO                 | Infliximab, etanercept, adalimumab     | Observational study; retrospective study    | Ben Abdelghani et al.\(^{54}\) \(n = 6\); Deutschmann et al.\(^{55}\) \(n = 1\) |
|                                |                                        |                                             |                                                |
|                                | Tocilizumab                            | Case report                                | Sato et al.\(^{56}\) \(n = 2\)                |
|                                |                                        |                                             |                                                |
|                                | Anakinra                               | Case report                                | Wendling et al.\(^{57}\) \(n = 6\); Colina et al.\(^{58}\) \(n = 1\); Eleftheriou et al.\(^{59}\) \(n = 1\) |
|                                |                                        |                                             |                                                |
|                                | Canakinumab                            | Case report                                | Sun et al.\(^{61}\) \(n = 1\)                |
|                                |                                        |                                             |                                                |
|                                | Secukinumab                            | Case report                                | Sun et al.\(^{61}\) \(n = 1\)                |
|                                |                                        |                                             |                                                |
| Adamantiades-Behçet’s disease  | NSAIDs, DMARDs, glucocorticoids or     | RCT, retrospective study, case report       | Yazici et al.\(^{62}\) \(n = 37\); Simsek et al.\(^{63}\) \(n = 30\); Mat et al.\(^{64}\) \(n = 42\); Emmi, Vitale et al.\(^{65}\) \(n = 35\); Kashiwado et al.\(^{66}\) \(n = 1\) |
|                                | corticosteroids                         |                                             |                                                |
|                                | Infliximab, etanercept, adalimumab     | Prospective study, case report              | Hibi et al.\(^{67}\) \(n = 18\); Saulsbury et al.\(^{68}\) \(n = 1\); Watanabe et al.\(^{69}\) \(n = 1\); Inoue et al.\(^{70}\) \(n = 20\) |
|                                |                                        |                                             |                                                |
|                                | Anakinra                               | Case report                                | Botsios et al.\(^{71}\) \(n = 1\); Caso et al.\(^{72}\) \(n = 1\); Cantarini et al.\(^{73}\) \(n = 9\) |
|                                |                                        |                                             |                                                |
|                                | Canakinumab                            | Case report                                | Vitale et al.\(^{74}\) \(n = 3\); Cantarini et al.\(^{75}\) \(n = 1\) |
|                                |                                        |                                             |                                                |
|                                | Rituximab                              | Case report                                | Sadreddini et al.\(^{76}\) \(n = 1\)          |
|                                |                                        |                                             |                                                |
|                                | Ustekinumab                            | Case report                                | Baerveldt et al.\(^{77}\) \(n = 1\)          |
|                                |                                        |                                             |                                                |
|                                | Alemtuzumab                            | Retrospective study                        | Mohammad et al.\(^{78}\) \(n = 32\)          |
|                                |                                        |                                             |                                                |
| Yao syndrome                   | Glucocorticoid (prednisone)            | Retrospective study                        | Yao and Shen\(^{79}\) \(n = 19\)             |
|                                |                                        |                                             |                                                |
|                                | Sulfasalazine                          | Retrospective study                        | Yao and Shen\(^{79}\) \(n = 22\)             |
|                                |                                        |                                             |                                                |
|                                | Tocilizumab                            | Retrospective study                        | Yao and Shen\(^{79}\) \(n = 1\)             |
|                                |                                        |                                             |                                                |
|                                | Canakinumab                            | Retrospective study                        | Yao\(^{80}\) \(n = 7\); Yao and Shen\(^{79}\) \(n = 2\) |
|                                |                                        |                                             |                                                |
|                                | Anakinra                               | Retrospective study                        | Yao and Shen\(^{79}\) \(n = 2\)             |
|                                |                                        |                                             |                                                |
| PFAPA syndrome                 | Corticosteroids                        | Case report, registry study, prospective    | Więsiak-Szewczyk et al.\(^{81}\) \(n = 1\); Ter Haar et al.\(^{81}\) \(n = 81\); Król et al.\(^{83}\) \(n = 77\) |
|                                |                                        | study                                       |                                                |
|                                | Colchicine                              | Case report, registry study, RCT            | Więsiak-Szewczyk et al.\(^{81}\) \(n = 1\); Ter Haar et al.\(^{81}\) \(n = 3\); Butbul Aviel et al.\(^{84}\) \(n = 8\) |
|                                |                                        |                                             |                                                |
|                                | Anakinra                               | Prospective study, case report             | Stojanov et al.\(^{85}\) \(n = 5\); Cantarini et al.\(^{86}\) \(n = 1\) |
|                                |                                        |                                             |                                                |
|                                | Canakinumab                            | Case report, case review                   | Lopalco et al.\(^{87}\) \(n = 1\); Soylu et al.\(^{88}\) \(n = 1\) |

*Approved by US FDA; #Approved by European Medicines Agency.

n, number of patients received the respective therapy.

Anakinra, canakinumab and rilonacept are IL-1 inhibitors; infliximab, etanercept and adalimumab are anti-TNF-α agents; tocilizumab and sarilumab are IL-6 inhibitors; secukinumab is an IL-17A inhibitor; NSAIDs, DMARDs, corticosteroids and glucocorticoids are conventional treatment.
Adult onset Still’s disease

Overview
AOSD is a rare, systemic autoinflammatory disorder characterized by a classic triad of high spiking fever, arthralgia/arthritis, skin rash, being commonly accompanied by hyperferritinemia, lymphadenopathy, and leukocytosis. The estimated incidence of AOSD is approximately 0.16 cases in 100,000 people in Western France,89,90 the annual incidence of AOSD is approximately 0.4 per 100,000 people in Northern Norway91 and the estimated prevalence of AOSD is 3.9 per 100,000 people in Japan.92 A study in patients with AOSD in Turkey reported an annual incidence of 0.62 and overall prevalence of 6.77 per 100,000 population.93 Globally, the estimated annual incidence of AOSD is between 0.16 and 0.62 (per 100,000 persons) and its approximate prevalence 1–24 per million.90,91,94,95 Data from US nationwide inpatient sample (NIS) database have shown that 5,820 AOSD patients were hospitalized between 2009 and 2013.96 AOSD is associated with significant morbidity-mortality and life-threatening manifestations, with a negative impact on the health-related quality of life of patients.96 Macrophage activation syndrome is a severe, life-threatening complication of both sJIA and AOSD.97–100

Pathogenesis
The pathogenesis of AOSD is complex and not clearly understood. Studies have shown that activation of the innate immune system and dysregulation of proinflammatory cytokines together mediate the pathogenesis of AOSD.101 Increased levels of NLRP3 inflammasome and its correlation with disease activity suggest the involvement of NLRP3 in the pathogenesis of AOSD.102 The activation of inflammasome NLRP3 can lead to overproduction of cytokines IL-1β and IL-18.102–105 These cytokines can trigger the dysregulation of downstream inflammatory cytokines, such as IL-6, IL-8, IL-17, and TNF-α, which are involved in the pathogenesis of AOSD.15,105–110 Levels of the serological marker serum ferritin are often elevated in patients with AOSD, with ferritin elevations correlating with disease activity. Serum ferritin levels > 5 times the normal upper limit in fever of unknown origin suggest AOSD with a sensitivity of up to 80%, which can increase to 93% if combined with glycosylated ferritin of less than 20%.89 In addition, there is increasing evidence of uncontrolled T-cell and macrophage activation – inducing proinflammatory cytokines, such as IL-1, IL-6, IL-18, TNF-α, and interferon (IFN)-γ overproduction – playing a crucial role in the pathogenesis of AOSD.15,51,106,111 A study has shown higher levels of serum IL-33 and its soluble ST2 receptor in patients with active AOSD.112 With reduction of disease activity, there is a decrease in serum IL-33 levels. Therefore, the IL-33/ST2 signaling pathway might play a key role in the pathogenesis that causes inflammation and skin manifestations in AOSD.112 Another study which evaluated SDF-1/CXCL12 and soluble CXCR4 (sCXCR4) levels and their clinical relevance observed higher levels of serum CXCL12 and serum sCXCR4 in patients with AOSD versus healthy volunteers. The results from this study showed that sCXCR4 is a potential clinical biomarker for AOSD and higher levels of CXCR4/CXCL12 may trigger the inflammatory conditions and skin manifestations associated with AOSD.113 Higher levels of IL-18 have been identified in AOSD patients.97,111,114,115

Clinical manifestations and diagnosis
Patients with AOSD usually present with high spiking quotidian fever, arthralgia and/or arthritis, a characteristic salmon-colored skin rash (usually concomitant with episodes of fever), lymphadenopathy, leukocytosis, and hyperferritinemia.12,14–16 A study investigated 66 patients with AOSD over an 18-year period and most prominent symptoms observed in patients were high fever (91%), arthralgia (89%) and cutaneous rash (56%).116 Joint involvement is common in patients with AOSD; arthritis, usually mild and localized at the beginning, can aggravate through the course of the disease, becoming more severe and polyarticular. The most commonly involved joints are the knees, wrists, ankles, elbows, and proximal interphalangeal joints. AOSD often spares the distal interphalangeal joints of the hand and shoulders. Narrowing of the intercarpal or carpometacarpal joint spaces has been observed in up to 75% of patients with chronic articular AOSD.43,116–121 The characteristic rash in Still’s disease is transient, nonpruritic, salmon-colored, with macular or maculopapular lesions, which are often observed during febrile episodes, predominantly in the late afternoon or evening. The typical rash appears mainly on the trunk and proximal extremities, in some occasions being misdiagnosed as an adverse reaction to medicines.116,122 In rare cases, neurological and vascular manifestations are present,
and the diagnosis may become more challenging due to a less frequent clinical presentation. A rapid and efficient, non-invasive diagnosis method is needed for a better management of AOSD.

The diagnosis of AOSD depends on the disease presentation upon exclusion of differential diagnoses including infection, malignancy, and other rheumatic inflammatory diseases. Although AOSD has been regarded as being part of the same disease spectrum of systemic juvenile idiopathic arthritis (sJIA), the patterns of disease course, their clinical and laboratory features may differ between adults and children, possibly because children – with a more naïve immune system – may react differently on first exposure to antigens. The current ILAR classification criteria for sJIA are based on clinical and analytical manifestations in the first 6 months of illness and the presence of arthritis at presentation is mandatory. On the other hand, the Yamaguchi criteria for AOSD diagnosis, only require the presence of arthralgia for more than 2 weeks. Comparison of clinical characteristics of AOSD and sJIA have shown significant female predominance among patients with AOSD (p < 0.05). Significantly increased serum ferritin levels, hepatomegaly, and splenomegaly were observed more frequently with AOSD (p < 0.05). Arthritis was more common among sJIA patients than among AOSD patients (p < 0.05). More AOSD patients versus sJIA patients presented with a sore throat (81% vs 46%; p = 0.03). AOSD patients had a significantly higher serum ferritin concentration than sJIA patients during the active disease phase (p < 0.01).

To identify AOSD patients, the Yamaguchi’s criteria are widely used being a sensitive tool (sensitivity 96.2% and specificity 92.1%) for diagnosis and classification of AOSD and ACR70 and remission, compared with placebo. It was difficult to complete the recruitment of this trial due to the rarity and severity of the disease as well as the conditional approval of canakinumab for AOSD by the EMA; therefore, the study was terminated prematurely.47 A retrospective real-life study in a cohort of 50 adult patients with refractory Still’s disease have shown high rates of sustained remission in patients treated with canakinumab. A complete response was observed in 78% of patients. Of 50 patients, 37 had a follow-up longer than 1 year and 27 more than 2 years and canakinumab had a long-term efficacy in the majority of patients with a significant steroid sparing effect.

Canakinumab has shown rapid and sustained improvement of both articular and systemic features in AOSD.49 Canakinumab was approved by the US Food and Drug Administration and the European Medicines Agency for Still’s disease, which is supported by the concept of a disease continuum that includes both SJIA and AOSD. Feist et al. have shown that treatment with canakinumab in a subgroup of patients with sJIA ≥ 16 years of age, who are representative of AOSD patients, led to an improvement in the systemic and arthritic components of the disease in older adolescents and young adults. The available data indicate that canakinumab is effective and well tolerated for treating AOSD.

A study has shown that treatment of adult patients with AOSD and active joint involvement with canakinumab led to a clinically significant improvement of outcome measures including DAS28-ESR, DAS28-CRP, ACR30, ACR50 and ACR70 and remission, compared with placebo. Response to treatment mainly depended on disease phenotype, such as arthritis and a chronic articular phenotype was associated with response to tocilizumab therapy, whereas the systemic form and the absence of arthritis were associated with response to anakinra therapy. This study has shown the therapeutic implications of the phenotypic dichotomy of AOSD. This suggests that AOSD treatment can be tailored, at least in some patients, based on the clinical presentation. There are limited data on the effectiveness of rilonacept in AOSD, but available reports have shown that rilonacept is effective in reducing the symptoms related to arthritis and other systemic symptoms, in patients with AOSD.

Treatment

NSAIDs, disease-modifying anti-rheumatic drugs (DMARDs), glucocorticoids or corticosteroids have been used as conventional treatments for AOSD. Tocilizumab, an IL-6 inhibitor, has shown efficacy in the treatment of patients with refractory AOSD. Data from a multicenter retrospective study involving 27 patients ≥ 16 years of age with AOSD showed that the remission was achieved in all patients, except one, with either anakinra or tocilizumab treatment.

Response to treatment mainly depended on disease phenotype, such as arthritis and a chronic articular phenotype was associated with response to tocilizumab therapy, whereas the systemic form and the absence of arthritis were associated with response to anakinra therapy. This study has shown the therapeutic implications of the phenotypic dichotomy of AOSD. This suggests that AOSD treatment can be tailored, at least in some patients, based on the clinical presentation. There are limited data on the effectiveness of rilonacept in AOSD, but available reports have shown that rilonacept is effective in reducing the symptoms related to arthritis and other systemic symptoms, in patients with AOSD.
SAPHO/CRMsO/CNO

Overview
SAPHO syndrome is a rare disease with chronic osteoarticular and dermatological disorders. SAPHO generally occurs in adults. SAPHO affects the skeletal system including the anterior chest wall, long bones and spine, and may involve polyostotic lesions, as seen in bone scintigraphy the characteristic “bull’s head”, which is a sign of increase tracer uptake in the regions of sternocostoclavicular and manubriosternal joints. The

Table 2. Criteria for diagnosis of AOSD.

(A) Yamaguchi criteria*

| Major criteria | Minor criteria | Exclusion criteria |
|----------------|----------------|-------------------|
| Arthralgia or arthritis (≥2 weeks) | Lymphadenopathy | Infection |
| Fever > 39°C (≥1 week) | Sore throat | Rheumatic diseases |
| Typical rash (“salmon-pink”) | Hepatomegaly or splenomegaly | Malignant diseases |
| Leucocytosis > 10,000/mm³ (>80% PMN cells) | Elevated AST, ALT, and LDH | - |
| Negative RF (IgM) and ANA | | |

(B) Fautrel's criteria**

| Major criteria | Minor criteria |
|----------------|----------------|
| Arthralgia | Maculopapular rash |
| Spiking fever ≥ 39°C | Leucocytosis ≥ 10,000/mm³ |
| Transient erythema | |
| Pharyngitis | |
| PMN cells ≥ 80% | |
| Glycosylated ferritin ≤ 20% | |

(C) Crispín's clinical scale for diagnosis#

| Findings | Description | Score |
|----------|-------------|-------|
| Arthritis | Presence of synovitis | 10 |
| Pharyngitis | Present during the onset of the disease | 7 |
| Still rash | Macular or maculopapular, pink-salmon, non-pruriginous rash that accompanies the fever | 5 |
| Splenomegaly | Detected clinically or by imaging technique (>11 cm) | 5 |
| Neutrophilia | PMN cells ≥ 9.500/mm³ | 18 |
| Total | | 45 |

*Five or more criteria are required, with two or more being major criteria for diagnosis of AOSD.
**Four or more major criteria are required, or three major and two minor criteria.
#At least 30 points in patients with fever of unknown origin allows for the diagnosis of AOSD without further studies [specificity ~98%].

ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; PMN, polymorphonuclear; RF, rheumatoid factor

[Source: Seco et al.89].
annual prevalence of SAPHO syndrome varies from 0.00144 in 100,000 people in Japan to less than 1 in 10,000 in the White population. In another report, the annual prevalence of SAPHO is estimated to be less than 1/10,000. In a cross-sectional study on a cohort of SAPHO patients, prevalence of fibromyalgia in SAPHO syndrome was approximately 18%.

CNO/CRMO are rare diseases with disorders of chronic osteoarticular inflammation and skin manifestations. CRMO/CNO predominantly affects children. CRMO/CNO affect the skeletal system including the anterior chest wall, long bones and spine, and may involve polyostotic lesions. The estimated prevalence of CRMO/CNO is 1–2 per million population, mostly affecting children. Incidence rate of CNO was estimated at 0.4 per 100,000 children/year in Germany. A chart review from a retrospective single-center analysis reported incidences of CNO increased from approximately 2.5 cases per year (1998–2007) to 4.7 CNO cases per year, which suggest that the suspected lower incidence rate of CNO may be an underestimation.

Pathogenesis
The precise pathogenesis of SAPHO syndrome remains unclear. However, it is believed to be related to genetic factors, infections, and immune dysregulation. As in Schnitzler’s syndrome and AOSD, overproduction of IL-1β was also reported in SAPHO syndrome. Studies have shown dysregulation of cytokines, including IL-1β, IL-8, IL-17, IL-18, and TNF-α, to be potentially involved in the pathogenesis of SAPHO. A study that measured the expression of receptor activator nuclear factor κ-B ligand (RANKL)/osteoprotegerin (OPG) in patients with SAPHO syndrome reported higher levels of RANKL in patients with active disease. Another study, comparing patients with SAPHO with healthy controls, found that the proportion of natural killer (NK) cells was significantly lower in SAPHO patients and the ratio of T-helper cell 17 (Th17) and regulatory T-cells (Treg) was higher. A depletion of NK cells and an imbalance of Th17 and Treg cells in SAPHO patients could be related to immune inflammation-mediated pathogenesis.

JAK/STAT signaling pathway may play a role in the pathogenesis of SAPHO syndrome. A retrospective review of data from a cohort of SAPHO patients has shown benefits with the use of tofacitinib, a Janus kinase (JAK) 1/3 inhibitor. A decrease in systemic inflammation, reduction in pain and rash, improvement in quality of life and remission on MRI was observed with tofacitinib treatment. Although tofacitinib is not approved for use for SAPHO, these findings provide evidence that tofacitinib could be a potential therapeutic option for the treatment of SAPHO syndrome.

Clinical manifestations and diagnosis
Patients with SAPHO syndrome present with sterile joint inflammation (synovitis), skin manifestations, such as severe acne and palmoplantar pustulosis, hyperostosis and non-infectious osteitis. In CRMO/CNO, symptoms are heterogeneous, such as swelling of the affected area, severe bone pain, fever, malaise, and weight loss. The symptoms related to bone inflammation and pain can often get worse at night. In patients with CRMO/CNO, sporadic inflammatory bone pain occurs as recurrent flares due to osteomyelitis, which presents as multiple aseptic foci. Diagnosis of SAPHO/CRMO/CNO is based on clinical and radiological findings. The diagnosis of CRMO/CNO is mainly achieved by exclusion of differential diagnoses, such as bacterial osteomyelitis and malignancy. For diagnosis of patients with CNO, clinical score from Jansson et al., blood test, bone biopsy, microbiological investigations, radiological findings on MRI are generally used. The Jansson score includes white blood cell counts, symmetric bone lesions, marginal sclerosis, normal body temperature, vertebral, clavicular, or sternal lesions, greater than two lesions in radiological imaging, and CRP ≥ 10 mg/l. Scores of 39 or higher indicate CNO. The clinical presentation of CNO range from self-limited unifocal to chronic recurrent multifocal bone inflammation. In most SAPHO/CRMO/CNO patients, polyostotic involvement is observed. Bone scintigraphy has shown a characteristic ‘bull’s head’ sign in the sternocostoclavicular and manubriosternal joints,
which is considered as a characteristic of SAPHO syndrome.\(^{146,174,175}\) The most widely applied diagnostic criteria for SAPHO syndrome were developed by Benhamou and colleagues\(^ {176–178}\) (Table 3).

### Table 3. Diagnostic criteria for SAPHO syndrome.

| Benhamou and colleagues | Kahn and Khan | Kahn |
|-------------------------|---------------|------|
| At least 1 of the following 4 conditions: (1) Osteoarticular manifestation of PPP | At least 1 of the following 3 conditions: (1) Acute, subacute, or chronic arthritis associated with PPP, pustular psoriasis, or SA | At least 1 of the following 5 conditions: (1) Bone–joint involvement associated with SA |
| (2) Osteoarticular manifestations of acne conglobate, acne fulminans, or hidradenitis suppurativa | (2) Chronic recurrent multifocal sterile and axial osteomyelitis, with or without dermatosis | (2) Bone–joint involvement associated with PPP and psoriasis vulgaris |
| (3) Hyperostosis of the ACW, limbs or spine with or without dermatosis | (3) Any sterile osteitis associated with PPP, pustular psoriasis, or SA | (3) Isolated sterile hyperostosis/osteitis |
| (4) CRMO involving the axial or peripheral skeleton with or without dermatosis | | (4) CRMO (children) |
| | | (5) Bone–joint involvement associated with chronic bowel diseases |

Exclusion: Infectious osteitis, tumoral conditions of bone, non-inflammatory condensing lesions of bone.

ACW, anterior chest wall; CRMO, chronic recurrent multifocal osteomyelitis; PPP, palmoplantar pustulosis; SA, severe acne; SAPHO, synovitis, acne, pustulosis, hyperostosis, and osteitis.

[Source: Liu et al.\(^ {150}\)].

### Treatment

Conventional treatments for SAPHO include NSAIDs, DMARDs, glucocorticoids or corticosteroids, bisphosphonates and antibiotics.\(^ {157,167,179}\) NSAIDs, DMARDs, glucocorticoids or corticosteroid, bisphosphonates and antibiotics have also been used as conventional treatments for CRMO/ CNO.\(^ {180–182}\) Pamidronate, a bisphosphonate, has shown efficacy on osteoarticular manifestations of SAPHO, but did not improve cutaneous lesions.\(^ {157,183}\) Gil et al.\(^ {184}\) described a case in which an adult patient with SAPHO syndrome who developed palmoplantar pustulosis and sternoclavicular osteitis received treatment with bisphosphonate, systemic corticosteroid, and cyclosporine which resulted in complete resolution of the articular and dermatologic manifestations without any side effects. Bisphosphonate has shown a favorable treatment response in pediatric SAPHO syndrome.\(^ {185}\) In an observational study, clinical data of 24 adult patients with SAPHO syndrome were analyzed. Out of 17 patients who received the combination treatments of NSAIDs and DMARDs, 15 experienced an improvement in their symptoms. In total, 18 patients with SAPHO syndrome received bisphosphonates, and 4 patients received TNF blockers. Among the patients who received TNF blockers, adalimumab was ineffective in one patient; however, the disease activity was controlled in that patient by add-on treatment with DMARDs. Patients with SAPHO syndrome responded to NSAIDs, DMARDs, and bisphosphonates combination therapy. TNF blockers were shown to be effective in patient with SAPHO syndrome refractory to NSAIDs and DMARDs.\(^ {186}\) The CNO/CRMO subgroup of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) held meetings to develop standardized treatment regimens for CNO/CRMO and enable comparative effectiveness treatment strategies, which resulted in 3 consensus treatment plans for pediatric patients with CNO/CRMO refractory to NSAIDs. The 3 consensus treatment plans are sulfasalazine or methotrexate, TNF inhibitors with optional methotrexate, and bisphosphonates.\(^ {187}\) TNF-\(\alpha\) antagonists have shown a favorable treatment response in pediatric SAPHO syndrome.\(^ {188}\) TNF inhibitors, such as etanercept, adalimumab, infliximab are generally used in SAPHO syndrome after methotrexate failure.\(^ {54}\) Anti-TNF-\(\alpha\) agents
have shown promising results in SAPHO syndrome\textsuperscript{167,179,185,188} and in CRMO/CNO.\textsuperscript{55,172,182,189}
In a case study, tocilizumab was shown to be effective in controlling symptoms and inflammatory markers in adult patients with CRMO/CNO.\textsuperscript{56}

IL-1 inhibitors also seem to be effective in the treatment of patients with SAPHO and CRMO/CNO. As per available data related to IL-1 inhibition, most patients with SAPHO show a significant improvement in musculoskeletal manifestations.\textsuperscript{188} IL-1 inhibition with anakinra has shown efficacy in the treatment of SAPHO syndrome. In a case study, anakinra treatment in a patient with SAPHO syndrome resulted in resolution of systemic and osteoarticular symptoms.\textsuperscript{58,159} In a study, treatment with canakinumab, an IL-17A inhibitor, successfully treated refractory mandibular lesions in an adult patient with SAPHO syndrome.\textsuperscript{61}

**Adamantiades-Behçet’s disease**

**Overview**

Adamantiades-Behçet’s disease is a multisystem, autoinflammatory disease of unknown etiology characterized by recurrent painful mucocutaneous ulcerations, and idiopathic systemic vasculitis that affects both large and small blood vessels. It can also present with arthralgia/arthritis, other skin lesions, uveitis and neurological manifestations.\textsuperscript{190–198} The incidence of Adamantiades-Behçet’s disease varies according to geographic location, with the highest prevalence of 20–420 (per 100,000 people) in Turkey, followed by 80 in Iran, 20 in Saudi Arabia, and 17 in Iraq.\textsuperscript{190} In the United Kingdom, the prevalence of Adamantiades-Behçet’s disease is 0.64 cases per 100,000 population.\textsuperscript{199,200} A study in United States reported an overall incidence of 0.38 per 100,000 population and prevalence rate of 5.2 per 100,000 population.\textsuperscript{201}

**Pathogenesis**

The pathogenesis of Adamantiades-Behçet’s disease is still unclear. IL-1 seems to play a crucial role in the pathogenesis of Adamantiades-Behçet’s disease, as IL-1 levels were shown to be significantly higher in patients with Adamantiades-Behçet’s disease versus healthy controls.\textsuperscript{202–204} Elevated levels of serum IL-6 were also seen in patients with active Adamantiades-Behçet’s disease, which may correlate with disease activity.\textsuperscript{205–207} Functional abnormalities of Toll-like receptors in monocytes have been noted in patients with Adamantiades-Behçet’s disease, and may be correlated with disease activity. One of the most consistent findings in the pathogenesis of Adamantiades-Behçet’s disease is hyperactive state of neutrophils. The antigen presenting cells (macrophages) stimulate immune cells by Toll-like receptors activation and the innate and adaptive immune pathways together with neutrophil activation play a crucial role in the pathogenesis of Adamantiades-Behçet’s disease.\textsuperscript{195,208}

Histocompatibility leucocyte antigen (HLA)-B51, a class I MHC antigen, represents the strongest genetic risk factor associated with Adamantiades-Behçet’s disease. Other HLA-independent loci, such as IL23R/IL12RB2 and IL10 (allele rs1518111 A) have also been associated with Adamantiades-Behçet’s disease.\textsuperscript{195,209} Data from a gene expression study, which identified genes that might be related to pathogenesis of Adamantiades-Behçet’s disease, have shown that 1103 genes and 652 genes were differentially expressed in the CD8$^+$CD27−CD28− and CD8$^+$CD27+CD28+ T-cell subsets, respectively, of patients with Adamantiades-Behçet’s disease.\textsuperscript{210} A case-control study found that the gene expression of TNF-α increased in patients with Adamantiades-Behçet’s disease, suggesting that TNF-α has a role in the pathogenesis of the Adamantiades-Behçet’s disease.\textsuperscript{211}

**Clinical manifestations and diagnosis**

The notable clinical manifestations in patients with Adamantiades-Behçet’s disease are recurrent oral and genital ulcerations, and ocular inflammation. Articular, neurological, and gastrointestinal involvement are also reported.\textsuperscript{190–193} Cardiopulmonary signs and symptoms may be the first manifestation.\textsuperscript{197} The diagnosis of Adamantiades-Behçet’s disease is challenging, because it is mainly based on clinical manifestations, which are frequent manifestations (oral aphthosis, genital aphthosis, pseudofolliculitis, erythema nodosum) also seen in other diseases.\textsuperscript{199} The International Criteria for Behçet Disease (ICBD) was developed in collaboration with the experts from 27 countries to address the diagnostic dilemma of Adamantiades-Behçet’s disease. ICBD is a point score system, a scoring $\geq$ 4 is classified as Adamantiades-Behçet’s disease. As per ICBD, ocular lesions, genital aphthosis and oral aphthosis are assigned 2 points each, while skin lesions, vascular manifestations and neurological
manifestations are assigned 1 point each. If pathergy test is done, an additional 1 point is assigned.\textsuperscript{212} The diagnostic criteria for Adamantiades-Behçet’s disease are presented in Table 4.\textsuperscript{212}

**Treatment**

NSAIDs, DMARDs, glucocorticoids or corticosteroids have been used as conventional treatments for Adamantiades-Behçet’s disease.\textsuperscript{62–66,213} Higher doses of corticosteroids are effective for treatment of acute exacerbations of Adamantiades-Behçet’s disease with vascular involvement, NBD and refractory or severe gastrointestinal involvement.\textsuperscript{198,214} The treatment goal is to prevent irreversible organ damage by suppressing inflammatory exacerbations.\textsuperscript{198} A combination of immunosuppressants, such as azathioprine, cyclosporine-A or cyclophosphamide is recommended for the management of acute deep vein thrombosis in Adamantiades-Behçet’s disease.\textsuperscript{198,214}

Emerging evidence supports the use of biologics in patients with refractory, severe Adamantiades-Behçet’s disease, and especially for those with ocular,\textsuperscript{220,221} central nervous system,\textsuperscript{221} and gastrointestinal\textsuperscript{70,221,222} involvements, anti-TNF-\(\alpha\) therapy has been shown to have benefits.\textsuperscript{68,69,198} Infliximab and adalimumab can be useful in managing patients with intestinal Adamantiades-Behçet’s disease, especially in severe or refractory cases.\textsuperscript{223} In a case study, tocilizumab has been
shown to be effective in the treatment of intestinal Adamantiades-Behçet’s disease. Anakinra and canakinumab have shown some benefit in Adamantiades-Behçet’s disease including in patients with mucocutaneous manifestations and in intestinal Adamantiades-Behçet’s disease. Data from studies have shown that IL-1 inhibitors could effectively control mucocutaneous and ocular manifestations in patients with Adamantiades-Behçet’s disease. In a retrospective study, 36 patients with Adamantiades-Behçet’s disease treated with anakinra or canakinumab were enrolled and divided into two groups. Patients showing a treatment duration of at least 52 weeks and no secondary inefficacy during the first follow-up year were included in group 1 and patients showing primary or secondary inefficacy within the first 52 weeks of treatment were included in group 2. Anakinra was administered in 13/18 patients and canakinumab in 5/18 patients, in both the groups. Data from this study showed that within the 3-month follow-up, clinical response (complete resolution of all active Adamantiades-Behçet’s disease-related clinical manifestations) was obtained in 100% (18/18) of patients in group 1 and 38.9% (7/18) of patients in group 2 ($p < 0.0001$), which demonstrated that anakinra and canakinumab were effective in Adamantiades-Behçet’s disease. In another retrospective study, 19 patients with Adamantiades-Behçet’s disease-uveitis received treatment with IL-1 inhibitors (anakinra $[n = 13]$ and canakinumab $[n = 6]$) and followed-up for 12 months. The number of patients presenting with ocular flares (ocular inflammatory manifestations that occurred after a period of remission) and the number of reported ocular flares decreased during the 12-month follow-up period. Anakinra and canakinumab were shown to be effective in managing Adamantiades-Behçet’s disease-related uveitis with a significant reduction of ocular inflammatory flares.

Yao syndrome

Overview

YAOS, formerly called nucleotide-binding oligomerization domain 2 (NOD2)-associated autoinflammatory disease, is characterized by fever, polyarthritis, dermatitis, distal extremity swelling, gastrointestinal and sicca-like symptoms associated with specific variants of NOD2 sequence. YAOS is predominantly observed in white adults at an estimated disease prevalence of 1–10 per 100,000 population. It might be the most common form of sporadic autoinflammatory disease occurring in adults.

Pathogenesis

The molecular mechanisms and underlying pathogenesis of YAOS are unclear, but there is a genetic association with certain NOD2 variants. A study that examined NOD2 expression and activation of signaling pathway reported that NOD2 transcript level and basal p38 mitogen-activated protein kinase activity was elevated in peripheral blood mononuclear cells from IVS8 + 158 YAOS patients. Also, the cells of the patients had high basal IL-6 levels which were increased by muramyl dipeptide stimulation, indicating that NOD2 expression and pathway activation are aberrant in YAOS. In a case series, genetic testing in three YAOS patients detected presence of the following heterozygous NOD2 variants:

- Q902 K/rs201035873 (c.2704 C > A) in exon 7
A recent study\(^2\) reported that the following NOD2 variants are linked to YAOS:

- **R541 P/rs753857915 (c.1622G > C)** in exon 4
- **Y514 H/rs540122692 (c.1540 T > C)** in exon 4

Data from a retrospective study have shown that canakinumab was effective and well tolerated in adult patients with YAOS and may be considered as a therapeutic option.\(^3\)

**PFAPA syndrome**

**Overview**

PFAPA syndrome is the most common autoinflammatory disease in children, but its hereditary basis remains uncharacterized and specific genetic causes are yet to be identified.\(^2\)\(^4\)\(^5\) Although, PFAPA is the most common periodic fever disease in children, some studies have reported it in adults.\(^3\)\(^4\) PFAPA syndrome has a delayed onset during adulthood. Clinical features of PFAPA in adults which are mainly overlapping with those of children are fever, oral aphthous, pharyngitis, cervical lymphadenopathy, abdominal pain, headache, and nausea.\(^2\)\(^4\) Among the key signs and symptoms of PFAPA syndrome, the occurrence of recurrent fever with erythematous pharyngitis represent the most strongly associated diagnosis of PFAPA syndrome in adulthood.\(^2\)\(^4\) The estimated incidence of PFAPA is 2.3 per 1000 children up to 5 years of age in Norway.\(^1\)\(^2\)\(^4\)\(^9\)

**Pathogenesis**

PFAPA is a genetically complex autoinflammatory disease with disorders of innate and adaptive immunity.\(^2\)\(^5\) PFAPA syndrome indicates a heterogenous, polygenic, or complex inheritance. In several PFAPA cohorts, two types of mutations with a functional effect on the inflammasomes (MEFV E148Q and NLRP3 Q703 K) were seen. Therefore, inflammasome-related genes may play a role in PFAPA pathogenesis.\(^2\)\(^5\) The exact pathogenetic processes underlying the symptoms of PFAPA syndrome are still unknown. An analysis of the upstream regulator of immune pathways indicated that activation of toll-like receptors (TLRs), production of IFN-\(\gamma\), and decrease in 1,25-dihydroxyvitamin D may be associated with the immune pathways involved in the pathogenesis of PFAPA.\(^2\)\(^5\)\(^2\) The elevated serum IL-1\(\beta\) concentrations and elevated proinflammatory cytokine production by monocytes of PFAPA
patients upon stimulation of lipopolysaccharide indicate that dysregulation of the immune responses could be associated with PFAPA flares.252–254 Previous reports have shown that a variant upstream of IL-12A (rs17753641) is associated with PFAPA syndrome. The monocytes from patients heterozygous or homozygous for the rs17753641 risk allele secreted higher levels of IL-12p70 upon stimulation with IFN-γ and lipopolysaccharide. Data also suggest that abnormal antigen-presenting cell function, and T-cell activity and polarization, are associated with the pathogenesis of PFAPA.255 An analysis in patients with PFAPA showed that B-cell adapter protein (PIK3AP1) and spondin-2 (SPON2) gene regions are differentially methylated, which suggests that PIK3AP1 and SPON2 could play a role in PFAPA syndrome.246 There are few studies which have surveyed familial clustering in PFAPA syndrome, and some reports from those studies are in favor of positive family history, which have shown that siblings and parents of PFAPA patients are similarly affected.245,256–258 In a study, comprehensive genetic analysis of families with PFAPA syndrome has shown the absence of a common gene harboring exonic mutations in the affected patients, which indicates that PFAPA syndrome is either inherited as a Mendelian disease with high genetic heterogeneity, or transmitted as an oligogenic or complex trait.259 One study reported 27% of variants in MEFV and NLRP3 genes in a cohort of 62 patients with PFAPA.260 In another study two mutations were observed, one in NLRP3 and one in MEFV, both known to be associated with PFAPA and found in one family.259 In a study by Padeh et al., 28 patients of Arab and Jewish origin with PFAPA syndrome were analyzed of which six patients (21%) were found heterozygotes for M694 V and were carriers of FMF gene. The authors indicated that the reported frequency of FMF genes might be similar to that of a normal population.261

Clinical manifestations and diagnosis
PFAPA syndrome is characterized by recurrent fever, as in AOSD and YAOS, which last for approximately 3–6 days and occurring once every 3–8 weeks. Other characteristics – which include pharyngitis, stomatitis, cervical adenitis, and leukocytosis – are variable in their appearance.264,265 As per recent reports, there are genetic similarities between PFAPA and Behçet’s syndrome. PFAPA shares risk loci at IL12A, STAT4, IL10, and CCR1-CCR3 with Behçet’s syndrome and recurrent aphthous stomatitis.264,265 Based on some common genetic and clinical similarities, it has been suggested that PFAPA together with recurrent aphthous stomatitis and Behçet’s syndrome form a construct which Manthiram et al. proposed to name Behcet Spectrum of Disorders.264,265

PFAPA syndrome is diagnosed based on clinical criteria and by exclusion of other etiologies. Elevated white blood cell counts and C-reactive protein levels may be seen during episodes.266 Differential diagnoses include infectious

| Clinical criteria | Comments |
|-------------------|----------|
| Major             | 1. Periodic occurrence ≥ twice  
|                   | 2. Recurrent fever or dermatitis or both |
| Minor             | 1. Oligo- or polyarticular/inflammatory arthritis, or distal extremity swelling  
|                   | 2. Abdominal pain or diarrhea or both  
|                   | 3. Sicca-like symptoms  
|                   | 4. Pericarditis or pleuritis or both |
| Molecular criterion* | NOD2 IVS8 + 158 or R702 W or both, or other rare variants |
| Exclusion criteria | High titer antinuclear antibodies, inflammatory bowel disease, Blau syndrome, adult sarcoidosis, primary Sjögren syndrome and monogenic autoinflammatory diseases |

Yao syndrome is diagnosed if two major criteria, at least one minor criterion, the molecular criterion, and exclusion criteria are fulfilled.

*The genetic testing was performed at the Center for Genetic Testing at Saint Francis, Tulsa, Oklahoma.

[Source: Yao and Shen79]
pharyngitis and cyclic neutropenia. The absence of symptoms related to seasonal flares, upper respiratory tract infection, and negative pharyngeal swabs can facilitate diagnosis. The main differential diagnosis depends on the age of patients. Compared with children, the clinical picture is more heterogeneous in nature in adults; hence, PFAPA can be a diagnostic challenge for treating physicians. For PFAPA, as per Eurofever/PRINTO clinical classification, at least 7 criteria need to be met out of 8 proposed criteria, which are presence of pharyngotonsillitis, cervical lymphadenitis, periodicity and duration of episodes 3–6 days, and absence of diarrhea, chest pain, skin rash, and arthritis. PFAPA diagnostic criteria according to Marshal, Pedeh and Cantarini are presented in Table 6.

**Treatment**

The pharmacological management of PFAPA includes colchicine for prophylaxis of attacks. Data from two randomized controlled trials which compared tonsillectomy against non-surgical interventions have shown the effectiveness of tonsillectomy in children with PFAPA syndrome. Tonsillectomy with or without adenoidectomy can be useful in some pediatric patients, whereas available data suggest that tonsillectomy is not so effective in adults. At the onset of fever in patients, prednisone can be effective in the resolution of fever episodes in pediatric and adult patients. Corticosteroids are effective for the resolution of flares in pediatric and adult patients with PFAPA. Steroids can be used during each episode. The use of prednisolone at the time of fever onset has been shown to be useful in a randomized clinical trial because fever was decreased in pediatric patients with PFAPA syndrome. Studies have shown that colchicine might be an effective preventive therapy in pediatric patients with PFAPA. Pediatric and adult patients with PFAPA have shown a prompt clinical response to the IL-1 inhibitors, anakinra and canakinumab.

**Table 6.** Diagnostic criteria for PFAPA according to Marshal, Pedeh and Cantarini.

| Criteria | Details |
|----------|---------|
| (a) Diagnostic criteria of PFAPA based on Marshall et al. |
| 1. | Regularly recurring fevers with early age of onset (patients < 5 years of age) |
| 2. | Constitutional symptoms in the absence of upper respiratory infection with at least 1 of the following clinical signs: |
| | • aphthous stomatitis |
| | • pharyngitis |
| | • cervical lymphadenitis |
| 3. | Exclusion of cyclic neutropenia |
| 4. | Completely asymptomatic interval between episodes (resolve spontaneously within 4–5 days) |
| 5. | Normal growth and development without long-term sequelae of the disease |
| (b) Diagnostic criteria of PFAPA according to Padeh et al. |
| 1. | Monthly fevers – cyclic fever at any age group |
| 2. | Exudative tonsillitis + negative throat culture |
| 3. | Cervical lymphadenitis |
| 4. | Possibly aphthous stomatitis |
| 5. | Completely asymptomatic interval between episodes |
| 6. | Rapid response to a single dose of corticosteroids (60 mg prednisone) |
| (c) Proposed diagnostic criteria for adult-onset PFAPA according to Cantarini et al. |
| 1. | Age = 16 |
| 2. | Recurrent fever accompanied by erythematous pharyngitis and/or cervical lymphadenitis |
| 3. | Increased inflammatory markers during attacks |
| 4. | Intervals between disease flare without any symptoms |
| Exclusions: | |
| | • infections, autoimmune and neoplastic diseases as well as monogenic autoinflammatory diseases and febrile polygenic autoinflammatory diseases |
| | • throat swab performed during fever has to be negative and antibiotic therapy considered ineffective |

[Source: Więsiak-Szewczyk et al.].
Conclusion
Schnitzler’s syndrome, AOSD, SAPHO syndrome/ CRMO/CNO, Adamantiades-Behçet’s disease, YAOS, and PFAPA syndrome are a group of rare multigenic autoinflammatory diseases that can present varied clinical features. Diagnosis of these diseases can be challenging due to a combination of nonspecific manifestations that can also be seen in a variety of other conditions. Diagnostic delays and disease complications may occur as a consequence of low disease awareness and the lack of pathognomonic markers.

The pathogenesis of the multigenic autoinflammatory diseases are complex and, in some cases, precise pathogenesis is not clearly understood. Therefore, further research is warranted to understand the pathogenesis of these diseases.

Although conventional treatments are commonly used, biologics have shown promising results in the management of multigenic autoinflammatory diseases. Biologics targeting proinflammatory cytokines including IL-1, IL-6, TNF-α, IL-17A and IL-18 have been shown to ameliorate signs and symptoms of different multigenic autoinflammatory diseases.

Declarations

Ethics approval and consent to participate
As this work is a review, therefore did not require an ethical board approval.

Consent for publication
Not applicable

Author contributions
Petros Efthimiou: Conceptualization; Writing – review & editing.
Olga Petryna: Conceptualization; Writing – review & editing.
Priscila Nakasato: Conceptualization; Writing – review & editing.
Apostolos Kontzias: Conceptualization; Writing – review & editing.

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Not applicable

References
1. Wekell P, Karlsson A, Berg S, et al. Review of autoinflammatory diseases, with a special focus on periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome. Acta Paediatrica 2016; 105: 1140–1151.

2. Navallas M, Inarejos Clemente EJ, Iglesias E, et al. Autoinflammatory diseases in childhood, part 2: polygenic syndromes. Pediatric Radiol 2020; 50: 431–444.

3. Cavuoto M and Bonagura VR. Adult-onset periodic fever, aphthous stomatitis, pharyngitis, and adenitis. Ann Aller Asthma Immunol 2008; 100: 170.

4. Padeh S, Stoffman N and Berkun Y. Periodic fever accompanied by aphthous stomatitis, pharyngitis, and adenitis. Israel Med Assoc J 2008; 10: 358–360.

5. Colotto M, Maranghi M, Durante C, et al. PFAPA syndrome in a young adult with a history of tonsillectomy. Intern Med 2011; 50: 223–225.
to a cohort of 17 adults with unexplained recurrent fevers. Clin Exp Rheumatol 2012; 30: 269–271.

7. Cazzato M, Neri R, Possemato N, et al. A case of adult periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome associated with endocardial proliferative glomerulonephritis. Clin Rheumatol 2013; 32(Suppl. 1): S33–S36.

8. Cantarini L, Lucherini OM and Rigante D. Caution should be used in the recognition of adult-onset autoinflammatory disorders: facts or fiction? Front Immunol 2013; 4: 96.

9. Rowczenio DM, Gomes SM, Aróstegui JJ, et al. Late-onset cryopyrin-associated periodic syndromes caused by somatic NLRP3 mosaicism-UK Single Center Experience. Front Immunol 2017; 8: 1410.

10. Kontzias A, Zarabi SK, Calabrese C, et al. Somatic mosaicism in adult-onset TNF receptor-associated periodic syndrome (TRAPS). Mol Genet Genomic Med 2019; 7: e791.

11. van der Hilst JCH, Bodar EJ, Barron KS, et al. Long-term follow-up, clinical features, and quality of life in a series of 103 patients with hyperimmunoglobulinemia D syndrome. Medicine 2008; 87: 301–310.

12. Ruscitti P and Giacomelli R. Pathogenesis of adult onset still’s disease: current understanding and new insights. Expert Rev Clin Immunol 2018; 14: 965–976.

13. Demir S, Sag E, Dedegolu F, et al. Vasculitis in systemic autoinflammatory diseases. Front Pediatr 2018; 6: 377.

14. Feist E, Mitrovic S and Fautrel B. Mechanisms, biomarkers and targets for adult-onset Still’s disease. Nat Rev Rheumatol 2018; 14: 603–618.

15. Li S, Zheng S, Tang S, et al. Autoinflammatory pathogenesis and targeted therapy for adult-onset Still’s disease. Clin Rev Allergy Immunol 2020; 58: 71–81.

16. Kim HA, Kim YH, Jeon YK, et al. Histopathology and expression of the chemokines CXCL10, CXCL13, and CXCR3 and the endogenous TLR-4 ligand S100A8/A9 in lymph nodes of patients with adult-onset Still’s disease. Sci Rep 2019; 9: 7517.

17. Gameiro A, Gouveia M, Pereira M, et al. Clinical characterization and long-term follow-up of Schnitzler syndrome. Clin Exp Dermatol 2016; 41: 461–467.

18. Simon A, Aši B, Braun-Falco M, et al. Schnitzler’s syndrome: diagnosis, treatment, and follow-up. Allergy 2013; 68: 562–568.

19. de Koning HD. Schnitzler’s syndrome: lessons from 281 cases. Clin Transl Allergy 2014; 4: 41.

20. Gorodetskiy VR, Salugina SO and Fedorov ES. Increasing the interval of canakinumab administration effectively supports the remission of Schnitzler’s syndrome. Case Rep Rheumatol 2018; 2018: 5416907.

21. Lipsker D. The Schnitzler syndrome. Orphanet J Rare Dis 2010; 5: 38.

22. Efthimiou P (ed.). Auto-inflammatory syndromes. Cham: Springer, pp. 159–166.

23. Gellrich FF and Günther C. Schnitzler syndrome. Hautarzt. Epub ahead of print 5 June 2019. DOI: 10.1007/s00105-019-4434-4.

24. de Koning HD, Schalkwijk J, Stoffels M, et al. The role of interleukin-1 beta in the pathophysiology of Schnitzler’s syndrome. Arthritis Res Ther 2013; 17: 187.

25. Pizzirani C, Falzoni S, Govoni M, et al. Dysfunctional inflammasome in Schnitzler’s syndrome. Rheumatology (Oxford, England) 2009; 48: 1304–1308.

26. Gusdorf L and Lipsker D. Schnitzler syndrome: a review. Curr Rheumatol Rep 2017; 19: 46.

27. Lipsker D, Spehner D, Drillien R, et al. Schnitzler syndrome: heterogeneous immunopathological findings involving IgM-skin interactions. Br J Dermatol 2009; 162: 954–959.

28. Krause K, Bonneko H, Ellrich A, et al. Long-term efficacy of canakinumab in the treatment of Schnitzler syndrome. J Allergy Clin Immunol 2020; 145: 1681–1686.

29. Krause K, Sabat R, Witte-Händel E, et al. Association of CCL2 with systemic inflammation in Schnitzler syndrome. Br J Dermatol 2019; 180: 859–868.

30. Masson Regnault M, Frouin E, Jéru I, et al. Cytokine signature in Schnitzler syndrome: proinflammatory cytokine production associated to th suppression. Front Immunol 2020; 11: 588322.

31. Krause K, Grattan CE, Bindseil-Jensen C, et al. How not to miss autoinflammatory diseases masquerading as urticaria. Allergy 2012; 67: 1465–1474.

32. Lipsker D, Veran Y, Grunenberger F, et al. The Schnitzler syndrome. Four new cases and review of the literature. Medicine 2001; 80: 37–44.

33. Bonneko H, Scheffel J, Kambe N, et al. The role of mast cells in autoinflammation. Immunol Rev 2018; 282: 265–275.

34. de Koning HD, Bodar EJ, van der Meer JW, et al. Schnitzler syndrome: beyond the case
reports: review and follow-up of 94 patients with an emphasis on prognosis and treatment. Semin Arthritis Rheum 2007; 37: 137–148.

35. Néel A, Henry B, Barbarot S, et al. Long-term effectiveness and safety of interleukin-1 receptor antagonist (anakinra) in Schnitzler’s syndrome: a French multicenter study. Autoimmun Rev 2014; 13: 1035–1041.

36. Faggioli P, Tamburello A, Roncoroni L, et al. Schnitzler syndrome, a rare autoinflammatory disease. Complete response to IL-1 blockade. Clin Practice 2017; 7: 1018.

37. Krause K, Weller K, Stefaniak R, et al. Efficacy and safety of the interleukin-1 receptor rilonacept in Schnitzler syndrome: an open-label study. Allergy 2012; 67: 943–950.

38. Vanderschueren S and Knockaert D. Canakinumab in Schnitzler syndrome. Semin Arthritis Rheum 2013; 42: 413–416.

39. Krause K, Tsianakas A, Wagner N, et al. Efficacy and safety of canakinumab in Schnitzler syndrome: a multicenter randomized placebo-controlled study. J Allergy Clin Immunol 2017; 139: 1311–1320.

40. Iliou C, Papagoras C, Tsifetaki N, et al. Adult-onset Still’s disease: clinical, serological and therapeutic considerations. Clin Exp Rheumatol 2013; 31: 47–52.

41. Gerfaud-Valentin M, Maucort-Boulch D, Hot A, et al. Adult-onset still disease: manifestations, treatment, outcome, and prognostic factors in 57 patients. Medicine (Baltimore) 2014; 93: 91–99.

42. Kalyoncu U, Solmaz D, Emmungil H, et al. Response rate of initial conventional treatments, disease course, and related factors of patients with adult-onset Still’s disease: data from a large multicenter cohort. J Autoimmun 2016; 69: 59–63.

43. Franchini S, Dagna L, Salvo F, et al. Efficacy of traditional and biologic agents in different clinical phenotypes of adult-onset Still’s disease. Arthritis Rheum 2010; 62: 2530–2535.

44. Fujii T, Akizuki M, Kameda H, et al. Methotrexate treatment in patients with adult onset Still’s disease–retrospective study of 13 Japanese cases. Ann Rheum Dis 1997; 56: 144–148.

45. Antoniou KM, Margaritopoulos GA, Giannarakis I, et al. Adult onset Still’s disease: a case report with a rare clinical manifestation and pathophysiological correlations. Case Rep Med 2013; 2013: 981232.

46. Feist E, Quartier P, Faivre B, et al. Efficacy and safety of canakinumab in patients with Still’s disease: exposure-response analysis of pooled systemic juvenile idiopathic arthritis data by age groups. Clin Exp Rheumatol 2018; 36: 668–675.

47. Kedor C, Listing J, Zernicke J, et al. Canakinumab for treatment of adult-onset Still’s disease to achieve reduction of arthritis manifestation (CONSIDER): phase II, randomised, double-blind, placebo-controlled, multicentre, investigator-initiated trial. Ann Rheum Dis 2020; 79: 1090–1097.

48. Cavalli G, Tomelleri A, De Luca G, et al. Efficacy of canakinumab as first-line biologic agent in adult-onset Still’s disease. Arthritis Res Therapy 2019; 21: 54.

49. Kontzias A and Efthimiou P. The use of Canakinumab, a novel IL-1β long-acting inhibitor, in refractory adult-onset Still’s disease. Semin Arthritis Rheum 2012; 42: 201–205.

50. Kaneko Y, Kameda H, Ikeda K, et al. Tocilizumab in patients with adult-onset still’s disease refractory to glucocorticoid treatment: a randomised, double-blind, placebo-controlled phase III trial. Ann Rheum Dis 2018; 77: 1720–1729.

51. Reihl C, Ogorevc M, Ćubelić D, Babić A, et al. Treatment of refractory adult onset Still’s disease with tocilizumab–a single centre experience and literature review. Rheumatol Int 2020; 40: 1317–1325.

52. Bannai E, Yamashita H, Kaneko S, et al. Successful tocilizumab therapy in seven patients with refractory adult-onset Still’s disease. Mod Rheumatol 2016; 26: 297–301.

53. Simeni Njonou SR, Soyfoo MS and Vangergheynst FA. Efficacy of sarilumab in adult-onset Still’s disease: data from a phase IIb, multicentre, investigator-initiated trial. Clin Exp Rheumatol 2018; 36: 668–675.

54. Ben Abdelghani K, Dran DG, Gottenberg JE, et al. Tumor necrosis factor-alpha blockers in SAPHO syndrome. J Rheumatol 2010; 37: 1699–1704.

55. Deutschmann A, Mache CJ, Bodo K, et al. Successful treatment of chronic recurrent multifocal osteomyelitis with tumor necrosis factor-alpha blockade. Pediatrics 2005; 116: 1231–1233.

56. Sato H, Wada Y, Hasegawa E, et al. Adult-onset chronic recurrent multifocal osteomyelitis with high intensity of muscles detected by magnetic resonance imaging, successfully controlled with tocilizumab. Intern Med (Tokyo, Japan) 2017; 56: 2353–2360.
57. Wendling D, Prati C and Aubin F. Anakinra treatment of SAPHO syndrome: short-term results of an open study. *Ann Rheum Dis* 2012; 71: 1098–1100.

58. Colina M, Pizzirani C, Khodeir M, *et al.* Dysregulation of P2X7 receptor-inflammasome axis in SAPHO syndrome: successful treatment with anakinra. *Rheumatology (Oxford)* 2010; 49: 1416–1418.

59. Eleftheriou D, Gerschman T, Sebire N, *et al.* Biologic therapy in refractory chronic non-bacterial osteomyelitis of childhood. *Rheumatology (Oxford)* 2010; 49: 1505–1512.

60. Moussa T, Bhat V, Kini V, *et al.* Clinical and genetic association, radiological findings and response to biological therapy in seven children from Qatar with non-bacterial osteomyelitis. *Int J Rheum Dis* 2017; 20: 1286–1296.

61. Sun B, Cao Y, Wang L, *et al.* Successful treatment of refractory mandibular lesions in SAPHO syndrome with secukinumab. *Rheumatology (Oxford, England)* 2020; 60: 473–474.

62. Yazici H, Pazarli H, Barnes CG, *et al.* A controlled trial of azathioprine in Behçet’s syndrome. *N Engl J Med* 1990; 322: 281–285.

63. Simsek H, Dundar S and Telatar H. Treatment of Behçet disease with indomethacin. *Int J Dermatol* 1991; 30: 54–57.

64. Mat C, Yurdakul S, Uysal S, *et al.* A double-blind trial of depot corticosteroids in Behçet’s syndrome. *Rheumatology (Oxford)* 2006; 45: 348–352.

65. Emmi G, Vitale A, Silvestri E, *et al.* Adalimumab-based treatment versus disease-modifying antirheumatic drugs for venous thrombosis in Behçet’s syndrome: a retrospective study of seventy patients with vascular involvement. *Arthritis Rheumatol* 2018; 70: 1500–1507.

66. Kashiwado Y, Uchino A, Ota T, *et al.* Intestinal Behçet’s disease with pyoderma gangrenosum successfully treated with the combination therapy of adalimumab and glucocorticoids. *Mod Rheumatol* 2018; 28: 901–905.

67. Hibi T, Hirohata S, Kikuchi H, *et al.* Infliximab therapy for intestinal, neurological, and vascular involvement in Behçet disease: efficacy, safety, and pharmacokinetics in a multicenter, prospective, open-label, single-arm phase 3 study. *Medicine (Baltimore)* 2016; 95: e3863.

68. Saulsbury FT and Mann JA. Treatment with infliximab for a child with Behçet’s disease. *Arthritis and Rheumatism* 2003; 49: 599–600.

69. Watanabe S, Aizawa-Yashiro T, Tsuruga K, *et al.* A young girl with refractory intestinal Behçet’s disease: a case report and review of literatures on pediatric cases who received an anti-tumor necrosis factor agent. *Rheumatol Int* 2013; 33: 3105–3108.

70. Inoue N, Kobyashi K, Naganuma M, *et al.* Long-term safety and efficacy of adalimumab for intestinal Behçet’s disease in the open label study following a phase 3 clinical trial. *Intest Res* 2017; 15: 395–401.

71. Botsios C, Sfriso P, Furlan A, *et al.* Resistant Behçet disease responsive to anakinra. *Ann Int Med* 2008; 149: 284–286.

72. Caso F, Rigante D, Vitale A, *et al.* Efficacy of anakinra in refractory Behçet’s disease sacroiliitis. *Clin Exp Rheumatol* 2014; 32(4 Suppl. 84): S171.

73. Cantarini L, Vitale A, Scalini P, *et al.* Anakinra treatment in drug-resistant Behçet’s disease: a case series. *Clin Rheumatol* 2015; 34: 1293–1301.

74. Vitale A, Rigante D, Caso F, *et al.* Inhibition of interleukin-1 by canakinumab as a successful mono-drug strategy for the treatment of refractory Behçet’s disease: a case series. *Dermatology* 2014; 228: 211–214.

75. Cantarini L, Vitale A, Borri M, *et al.* Successful use of canakinumab in a patient with resistant Behçet’s disease. *Clin Exper Rheumatol* 2012; 30: S115.

76. Sadreddini S, Noshad H, Molaeefard M, *et al.* Treatment of retinal vasculitis in Behçet’s disease with rituximab. *Mod Rheumatol* 2008; 18: 306–308.

77. Baerveldt EM, Kappen JH, Thio HB, *et al.* Successful long-term triple disease control by ustekinumab in a patient with Behcet’s disease, psoriasis and hidradenitis suppurativa. *Ann Rheum Dis* 2013; 72: 626–627.

78. Mohammad AJ, Smith RM, Chow YW, *et al.* Alemtuzumab as remission induction therapy of refractory Behçet’s disease with rituximab. *J Rheum Dis* 2013; 72: S115.

79. Yao Q. Research letter: effectiveness of canakinumab for the treatment of Yao syndrome patients. *J Am Acad Dermatol*. Epub ahead of print 18 September 2019. DOI: 10.1016/j.jaad.2019.09.020.
81. Więsik-Szewczyk E, Wolska-Kuśnier B and Jawñź-Różyk K. Periodic fever, aphtous stomatitis, pharyngitis and cervical adenitis syndrome persisting to adulthood – an example of a diagnostic and therapeutic challenge. Reumatologia 2019; 57: 292–296.

82. Ter Haar N, Lachmann H, Özên S, et al. Treatment of autoinflammatory diseases: results from the Eurofever Registry and a literature review. Ann Rheum Dis 2013; 72: 678–685.

83. Krol P, Bohm M, Sula V, et al. PFAPA syndrome: clinical characteristics and treatment outcomes in a large single-centre cohort. Clin Exp Rheumatol 2013; 31: 980–987.

84. Butbul Aviel Y, Tatour S, Gershoni Baruch R, et al. Colchicine as a therapeutic option in periodic fever, aphtous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome. Semin Arthritis Rheum 2016; 45: 471–474.

85. Stoianov S, Lapidus S, Chitkara P, et al. Periodic fever, aphtous stomatitis, pharyngitis, and adenitis (PFAPA) is a disorder of innate immunity and Th1 activation responsive to IL-1 blockade. Proc Nat Acad Sci USA 2011; 108: 7148–7153.

86. Cantarini L, Vitale A, Galeazzi M, et al. A case of resistant adult-onset periodic fever, aphtous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome responsive to anakinra. Clin Exp Rheumatol 2012; 30: 593.

87. Lopalco G, Rigante D, Vitale A, et al. Canakinumab efficacy in refractory adult-onset PFAPA syndrome. Int J Rheum Dis 2017; 20: 1050–1051.

88. Soylu A, Yildiz G, Torun Bayram M, et al. IL-1β blockade in periodic fever, aphtous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome: case-based review. Rheumatol Int 2021; 41: 183–188.

89. Seco T, Cerqueira A, Costa A, et al. Adult-onset Still’s disease: typical presentation, delayed diagnosis. Careus 2020; 12: e8510.

90. Magadur-Joly G, Billaud E, Barrier JH, et al. Epidemiology of adult Still’s disease: estimate of the incidence by a retrospective study in west France. Ann Rheum Dis 1995; 54: 587–590.

91. Evensen KJ and Nossent HC. Epidemiology and outcome of adult-onset Still’s disease in Northern Norway. Scand J Rheumatol 2006; 35: 48–51.

92. Asanuma YF, Mimura T, Tsuboi H, et al. Nationwide epidemiological survey of 169 patients with adult Still’s disease in Japan. Mod Rheumatol 2015; 25: 393–400.

93. Balci MA, Pamuk ÖN, Pamuk GE, et al. Epidemiology and outcome of adult-onset Still’s disease in Northwestern Thrace region in Turkey. Clin Exp Rheumatol 2015; 33: 818–823.

94. Vercruysse F, Barnette T, Lazaro E, et al. Adult-onset Still’s disease biological treatment strategy may depend on the phenotypic dichotomy. Arthritis Res Ther 2019; 21: 53.

95. Wakai K, Ohta A, Tamakoshi A, et al. Estimated prevalence and incidence of adult Still’s disease: findings by a nationwide epidemiological survey in Japan. Semin Arthritis Rheum 1997; 7: 221–225.

96. Mehta BY, Ibrahim S, Briggs W, et al. Racial/Ethnic variations in morbidity and mortality in adult onset Still’s disease: an analysis of national dataset. Semin Arthritis Rheum 2019; 49: 469–473.

97. Inoue N, Shimizu M, Tsunoda S, et al. Cytokine profile in adult-onset Still’s disease: comparison with systemic juvenile idiopathic arthritis. Clin Immunol 2016; 169: 8–13.

98. Ravelli A, Grom AA, Behrens EM, et al. Macrophage activation syndrome as part of systemic juvenile idiopathic arthritis: diagnosis, genetics, pathophysiology and treatment. Genes Immun 2012; 13: 289–298.

99. Di Cola I, Ruscitti P, Giacomelli R, et al. The pathogenic role of interferons in the hyperinflammatory response on adult-onset Still’s disease and macrophage activation syndrome: paving the way towards new therapeutic targets. J Clin Med 2021; 10: 1164.

100. Gao Q, Yuan Y, Wang Y, et al. Clinical characteristics of macrophage activation syndrome in adult-onset Still’s disease. Clin Exp Rheumatol 2021; 39(Suppl. 132): 59–66.

101. Gerfaud-Valentin M, Jamilloux Y, Iwaz J, et al. Adult-onset Still’s disease. Autoimmun Rev 2014; 13: 708–722.

102. Hsieh CW, Chen YM, Lin CC, et al. Elevated expression of the NLRP3 inflammasome and its correlation with disease activity in adult-onset Still disease. J Rheumatol 2017; 44: 1142–1150.

103. Rau M, Schiller M, Krienke S, et al. Clinical manifestations but not cytokine profiles differentiate adult-onset Still’s disease and sepsis. J Rheumatol 2010; 37: 2369–2376.

104. Choi JH, Suh CH, Lee YM, et al. Serum cytokine profiles in patients with adult onset Still’s disease. J Rheumatol 2003; 30: 2422–2427.

105. Chen DY, Lan JL, Lin FJ, et al. Proinflammatory cytokine profiles in sera and
pathological tissues of patients with active untreated adult onset Still's disease. J Rheumatol 2004; 31: 2189–2198.

106. Fuji T, Nojima T, Yasuoka H, et al. Cytokine and immunogenetic profiles in Japanese patients with adult Still's disease. Rheumatology (Oxford) 2001; 40: 1398–1404.

107. Mitrovic S and Fautrel B. New markers for adult-onset Still's disease. Joint Bone Spine 2018; 85: 285–293.

108. Maria AT, Le Quellec A, Jorgensen C, et al. Adult-onset Still's disease (AOSD) in the era of biologic therapies: dichotomous view for cytokine and clinical expressions. Autoimmun Rev 2014; 13: 1149–1159.

109. Kim HA, Choi B, Suh CH, et al. Highly expression of CD11b and CD32 on peripheral blood mononuclear cells from patients with adult-onset Still's disease. Int J Mol Sci 2017; 18: 202.

110. Sfriso P, Bindoli S and Galozzi P. Adult-onset Still's disease: molecular pathophysiology and therapeutic advances. Drugs 2018; 78: 1187–1193.

111. Naniwa T, Uehara K, Yamabe T, et al. Reintroduction of tocilizumab elicited macrophage activation syndrome in a patient with adult-onset Still’s disease with a previous successful tocilizumab treatment. Modern Rheumatol Case Rep 2020; 2020: 1–10.

112. Han JH, Suh CH, Jung JY, et al. Serum levels of interleukin 33 and soluble ST2 are associated with the extent of disease activity and cutaneous manifestations in patients with active adult-onset Still’s disease. J Rheumatol 2017; 44: 740–747.

113. Han JH, Ahn MH, Jung JY, et al. The levels of CXCL12 and its receptor, CXCR4, as a biomarker of disease activity and cutaneous manifestation in adult-onset Still’s disease. Clin Exp Rheumatol 2019; 37(Suppl. 121): 67–73.

114. Weiss ES, Girard-Guyonvarch C, Holzinger D, et al. Interleukin-18 diagnostically distinguishes and pathogenically promotes human and murine macrophage activation syndrome. Blood 2018; 131: 1442–1455.

115. Kaplanski G. Interleukin-18: biological properties and role in disease pathogenesis. Immunol Rev 2018; 281: 138–153.

116. Franchini S, Dagna L, Salvo F, et al. Adult onset Still's disease: clinical presentation in a large cohort of Italian patients. Clin Exp Rheumatol 2010; 28: 41–48.

117. Chen DY, Lan JL, Hsieh TY, et al. Clinical manifestations, disease course, and complications of adult-onset Still's disease in Taiwan. J Formos Med Assoc 2004; 103: 844–852.

118. Zeng T, Zou YQ, Wu MF, et al. Clinical features and prognosis of adult-onset Still's disease: 61 cases from China. J Rheumatol 2009; 36: 1026–1031.

119. Riera E, Olivé A, Narváez J, et al. Adult onset Still's disease: review of 41 cases. Clin Exp Rheumatol 2011; 29: 331–336.

120. Liu Z, Lv X and Tang G. Clinical features and prognosis of adult-onset Still's disease: 75 cases from China. Int J Clin Exp Med 2015; 8: 16634–16639.

121. Hu QY, Zeng T, Sun CY, et al. Clinical features and current treatments of adult-onset Still's disease: a multicentre survey of 517 patients in China. Clin Exp Rheumatol 2019; 37(Suppl. 121): 52–57.

122. Chen PD, Yu SL, Chen S, et al. Retrospective study of 61 patients with adult-onset Still’s disease admitted with fever of unknown origin in China. Clin Rheumatol 2012; 31: 175–181.

123. Santos M, Rodrigues D, Santos H, et al. Neurological manifestations of adult-onset Still's disease-case-based review. Clin Rheumatol 2021; 40: 407–411.

124. Sun Y, Wang F, Zhou Z, et al. Urinary proteomics identifying novel biomarkers for the diagnosis of adult-onset Still's disease. Front Immunol 2020; 11: 2112.

125. Piriou PG, Plessis J, Letocart V, et al. Adult-onset Still’s disease revealed by a complete atrioventricular block, totally regressive under corticosteroid therapy. J Cardiol Cases 2020; 11: 110–113.

126. Silva JR and Brito I. Systemic juvenile idiopathic arthritis versus adult-onset Still’s disease: the pertinence of changing the current classification criteria. Acta Reumatol Port 2020; 46: 150–151.

127. Efthimiou P, Kontzias A, Hur P, et al. Adult-onset Still’s disease in focus: clinical manifestations, diagnosis, treatment, and unmet needs in the era of targeted therapies. Semin Arthritis Rheum 2021; 51: 858–874.

128. Lin SJ, Chao HC and Yan DC. Different articul manifestations of Still’s disease in Chinese children and adults. Clin Rheumatol 2000; 19: 127–130.

129. Yamaguchi M, Ohta A, Tsunematsu T, et al. Preliminary criteria for classification of adult Still’s disease. J Rheumatol 1992; 19: 424–430.
130. Cush JJ, Medsger TA Jr, Christy WC, et al. Adult-onset Still’s disease. Clinical course and outcome. *Arthritis Rheum* 1987; 30: 186–194.

131. Nassereddine H, Fite C, Kottler D, et al. An atypical persistent eruption of adult-onset Still’s disease with neutrophilic urticarial dermatosis-like dermal features: a case report and review of the literature. *J Cutan Pathol* 2018; 45: 793–799.

132. Mahroum N, Mahagna H and Amital H. Diagnosis and classification of adult Still’s disease. *J Autoimmun* 2014; 48–49: 34–37.

133. Fautrel B, Zing E, Golmard JL, et al. Proposal for a new set of classification criteria for adult-onset still disease. *Medicine (Baltimore)* 2002; 81: 194–200.

134. Fautrel B, Le Moël G, Saint-Marcoux B, et al. Diagnostic value of ferritin and glycylated ferritin in adult onset Still’s disease. *J Rheumatol* 2001; 28: 322–329.

135. Crispín JC, Martinez-Baños D and Alcocer-Varela J. Adult-onset Still disease as the cause of fever of unknown origin. *Medicine* 2005; 84: 331–337.

136. Yoo DH. Treatment of adult-onset still’s disease: up to date. *Expert Rev Clin Immunol* 2017; 13: 849–866.

137. de Boysson H, Février J, Nicolle A, et al. Tocilizumab in the treatment of the adult-onset Still’s disease: current clinical evidence. *Clin Rheumatol* 2013; 32: 141–147.

138. Puéchal X, DeBandt M, Berthelot JM, et al. Tocilizumab in refractory adult Still’s disease. *Arthritis Care Res* 2011; 63: 155–159.

139. Junge G, Mason J and Feist E. Adult onset Still’s disease-The evidence that anti-interleukin-1 treatment is effective and well-tolerated (a comprehensive literature review). *Semin Arthritis Rheum* 2017; 47: 295–302.

140. Petryna O, Cush JJ and Efthimiou P. IL-1 Trap rilonacept in refractory adult onset Still’s disease. *Ann Rheum Dis* 2012; 71: 2056–2057.

141. Nirmala N, Brachat A, Feist E, et al. Gene-expression analysis of adult-onset Still’s disease and systemic juvenile idiopathic arthritis is consistent with a continuum of a single disease entity. *Pediatric Rheumatol Online* 2015; 13: 50.

142. Sfirsio P, Bindoli S, Doria A, et al. Canakinumab for the treatment of adult-onset Still’s disease. *Exp Rev Clin Immunol* 2020; 16: 129–138.

143. Gallozi P, Baggio C, Bindoli S, et al. Development and role in therapy of canakinumab in adult-onset Still’s disease. *Front Pharmacol* 2018; 9: 1074.

144. Laskari K, Tektonidou MG, Katsiari C, et al. Outcome of refractory to conventional and/or biologic treatment adult Still’s disease following canakinumab treatment: countrywide data in 50 patients. *Semin Arthritis Rheum* 2021; 51: 137–143.

145. Xu W, Li C and Zhang W. The coexistence of SAPHO syndrome and rheumatoid arthritis: a case report. *Medicine (Baltimore)* 2017; 96: e5724.

146. Himuro H, Kurata S, Nagata S, et al. Imaging features in patients with SAPHO/CRMO: a pictorial review. *Jpn J Radiol* 2020; 38: 622–629.

147. Zhang X, Wu X and Li C. Successful treatment of synovitis, acne, pustulosis, hyperostosis, and osteitis and paradoxical skin lesions by Tripterygium Wilfordii Hook F: a case report. *J Int Med Res* 2020; 48: 300060520949100.

148. Cao Y, Li C, Xu W, et al. Spinal and sacroiliac involvement in SAPHO syndrome: a single center study of a cohort of 354 patients. *Semin Arthritis Rheum* 2019; 48: 990–996.

149. Nguyen MT, Borchers A, Selmi C, et al. The SAPHO syndrome. *Semin Arthritis Rheum* 2012; 42: 254–265.

150. Liu S, Tang M, Cao Y, et al. Synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome: review and update. *Ther Adv Musculoskelet Dis* 2020; 12: 17597.

151. Xiang Y, Jiao R, Cao Y, et al. Fibromyalgia in patients with synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome: prevalence and screening. *Clin Rheumatol* 2021; 40: 1559–1565.

152. Hayem G. Valuable lessons from SAPHO syndrome. *Joint Bone Spine* 2007; 74: 123–126.

153. Rech J, Manger B, Lang B, et al. Adult-onset Still’s disease and chronic recurrent multifocal osteomyelitis: a hitherto undescribed manifestation of autoinflammation. *Rheumatol Int* 2012; 32: 1827–1829.

154. Chen Z, Cheng L and Feng G. Bone inflammation and chronic recurrent multifocal osteomyelitis. *Eur Rev Med Pharmacol Sci* 2018; 22: 1380–1386.

155. Schnabel A, Range U, Hahn G, et al. Unexpectedly high incidences of chronic nonbacterial as compared to bacterial osteomyelitis in children. *Rheumatol Int* 2016; 36: 1737–1745.

156. Jansson AF, Grote V and Group ES. Nonbacterial osteitis in children: data of a
German Incidence Surveillance Study. Acta Paediatr 2011; 100: 1150–1157.

157. Hussain A, Gondal M, Abdallah N, et al. Synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO): an interesting clinical syndrome. Cureus 2020; 12: e10184.

158. Berthelot JM, Corvec S and Hayem G. SAPHO, autophagy, IL-1, FoxO1, and Propionibacterium (Cutibacterium) acnes. Joint Bone Spine 2018; 85: 171–176.

159. Firinu D, Garcia-Larsen V, Manconi PE, et al. SAPHO syndrome: current developments and approaches to clinical treatment. Curr Rheumatol Rep 2016; 18: 35.

160. Firinu D, Barca MP, Lorrai MM, et al. TH17 cells are increased in the peripheral blood of patients with SAPHO syndrome. Autoimmunity 2014; 47: 389–394.

161. Zhang S, Li C, Zhang S, et al. Serum levels of proinflammatory, anti-inflammatory cytokines, and RANKL/OPG in synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome. Mod Rheumatol 2019; 29: 523–530.

162. Xu D, Liu X, Lu C, et al. Reduction of peripheral natural killer cells in patients with SAPHO syndrome. Clin Exp Rheumatol 2019; 37: 12–18.

163. Li Y, Huo J, Cao Y, et al. Efficacy of tofacitinib in synovitis, acne, pustulosis, hyperostosis and osteitis syndrome: a pilot study with clinical and MRI evaluation. Ann Rheum Dis 2020; 79: 1255–1257.

164. Xie W, Huang H and Zhang Z. Off-label use of tofacitinib: a potential treatment option for SAPHO syndrome. Ann Rheum Dis 2022; 81: e91.

165. Hofmann SR, Kubasch AS, Ioannidis C, et al. Altered expression of IL-10 family cytokines in monocytes from CRMO patients result in enhanced IL-1β expression and release. Clin Immunol 2015; 161: 300–307.

166. Scianaro R, Insalaco A, Bracci Laudiore L, et al. Deregulation of the IL-1β axis in chronic recurrent multifocal osteomyelitis. Pediatr Rheumatol Online J 2014; 12: 30.

167. Luzzati M, Simonini G, Filippeschi C, et al. SAPHO syndrome: the supposed trigger by isotretinoin, the efficacy of adalimumab and the specter of depressive disorder: a case report. Italian J Pediatr 2020; 46: 169.

168. Wang M, Li Y, Cao Y, et al. Mandibular involvement in SAPHO syndrome: a retrospective study. Orphanet J Rare Dis 2020; 15: 312.

169. Mahady S and Ladani A. Clinical and diagnostic considerations for atypical, adult onset presentation of chronic recurrent multifocal osteomyelitis (CRMO). Case Rep Rheumatol 2019; 2019: 8206892.

170. Buch K, Thuesen ACB, Brens C, et al. Chronic non-bacterial osteomyelitis: a review. Calc Tissue Int 2019; 104: 544–553.

171. Jansson AF, Muller TH, Gliera L, et al. Clinical score for nonbacterial osteitis in children and adults. Arthritis Rheum 2009; 60: 1152–1159.

172. Hedrich CM, Hahn G, Girschick HJ, et al. A clinical and pathomechanistic profile of chronic nonbacterial osteomyelitis/chronic recurrent multifocal osteomyelitis and challenges facing the field. Expert Rev Clin Immunol 2013; 9: 845–854.

173. Hedrich CM, Hofmann SR, Pablík J, et al. Autoinflammatory bone disorders with special focus on chronic recurrent multifocal osteomyelitis (CRMO). Pediatric Rheumatol Online J 2013; 11: 47.

174. Rukavina I. SAPHO syndrome: a review. J Children Orthopaed 2015; 9: 19–27.

175. Sallés M, Olivé A, Perez-Andres R, et al. The SAPHO syndrome: a clinical and imaging study. Clin Rheumatol 2011; 30: 245–249.

176. Benhamou CL, Chamot AM and Kahn MF. Synovitis-acne-pustulosis hyperostosis-osteitis syndrome (SAPHO). A new syndrome among the spondyloarthropathies? Clin Exp Rheumatol 1988; 6: 109–112.

177. Kahn MF and Khan MA. The SAPHO syndrome. Bailliere’s Clin Rheumatol 1994; 8: 333–362.

178. Kahn MF. Abstracts of the American College of Rheumatology 67th annual meeting and the Association of Rheumatology Health Professionals 38th annual meeting. Arthritis Rheum 2003; 48(9 Suppl.): S53–S750.

179. Furer V, Kishimoto M, Tsuji S, et al. The diagnosis and treatment of adult patients with SAPHO syndrome: controversies revealed in a multidisciplinary international survey of physicians. Rheumatol Ther 2020; 7: 883–891.

180. Girschick HJ, Krauspe R, Tschammler A, et al. Chronic recurrent osteomyelitis with clavicular involvement in children: diagnostic value of different imaging techniques and therapy with non-steroidal anti-inflammatory drugs. Eur J Pediatr 1998; 157: 28–33.

181. Job-Deslandre C, Krebs S and Kahan A. Chronic recurrent multifocal osteomyelitis: five-year outcomes in 14 pediatric cases. Joint Bone Spine 2001; 68: 245–251.
Hofmann SR, Schnabel A, Rösen-Wolff A, et al. Chronic nonbacterial osteomyelitis: pathophysiological concepts and current treatment strategies. *J Rheumatol* 2016; 43: 1956–1964.

Alijuhani F, Tournadre A, Tatar Z, et al. The SAPHO syndrome: a single-center study of 41 adult patients. *J Rheumatol* 2015; 42: 329–334.

Gil F, Mariano P, Silva S, et al. SAPHO syndrome: the value of classic drugs in the era of biologics. *Dermatol Online J* 2020; 26: 13030/ qt28x3f2g6.

Wu N, Shao Y, Huo J, et al. Clinical characteristics of pediatric synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome: the first Chinese case series from a single center. *Clin Rheumatol* 2021; 40: 1487–1495.

Huang H, Zhang Z, Zhao J, et al. The effectiveness of treatments for patients with SAPHO syndrome: a follow-up study of 24 cases from a single center and review of literature. *Clin Rheumatol* 2021; 40: 1131–1139.

Zhao Y, Wu EY, Oliver MS, et al. Consensus treatment plans for chronic nonbacterial osteomyelitis refractory to nonsteroidal antiinflammatory drugs and/or with active spinal lesions. *Arthritis Care Res* 2018; 70: 1228–1237.

Dauossis D, Konstantopoulou G, Kraniotis P, et al. Biologics in SAPHO syndrome: a systematic review. *Semin Arthritis Rheum* 2019; 48: 618–625.

Hofmann SR, Roesen-Wolff A, Hahn G, et al. Update: cytokine dysregulation in chronic nonbacterial osteomyelitis (CNO). *Int J Rheumatol* 2012; 2012: 310206.

Costagliola G, Cappelli S and Consolini R. Behçet’s disease in children: diagnostic and current management challenges. *Ther Clin Risk Manag* 2020; 16: 495–507.

Yıldız M, Köker O, Adrovic A, et al. Pediatric Behçet’s disease – clinical aspects and current concepts. *European Journal of Rheumatology* 2019; 7: 1–10.

Tong B, Liu X, Xiao J, et al. Immunopathogenesis of Behçet’s disease. *Front Immunol* 2019; 10: 665.

Greco A, De Virgiliis A, Ralli M, et al. Behçet’s disease: new insights into pathophysiology, clinical features and treatment options. *Autoimmun Rev* 2018; 17: 567–575.

van der Houwen T and van Laar J. Behçet’s Disease, and the Role of TNF-α and TNF-α Blockers. *Int J Mol Sci* 2020; 21: 3072.

Perazzo SF, Andrade LEC and de Souza AWS. Understanding Behçet’s disease in the context of innate immunity activation. *Front Immunol* 2020; 11: 586558.

Tsalta-Mladenov ME, Georgieva DK and Andonova SP. Neuro–Behçet’s disease – case report and review. *Acta Reumatol Port* 2020; 45: 137–142.

Ben-David Y, Gur M, Ilivitzki A, et al. Atypical cardiopulmonary manifestations in pediatric Behçet’s disease. *Pediatr Pulmonol* 2020; 55: 3407–3413.

Hu YC, Chiang BL and Yang YH. Clinical manifestations and management of pediatric Behçet’s disease. *Clin Rev Aller Immunol* 2020; 61: 171–180.

Davatchi F, Chams-Davatchi C, Shams H, et al. Behçet’s disease: epidemiology, clinical manifestations, and diagnosis. *Expert Rev Clin Immunol* 2017; 13: 57–65.

Lee NH, Bae M, Jin M, et al. Characterization of venous involvement in vasculo-Behçet disease. *Korean J Thoracic Cardiovasc Surg* 2020; 53: 381–386.

Calamia KT, Wilson FC, Icen M, et al. Epidemiology and clinical characteristics of Behçet’s disease in the US: a population-based study. *Arthr Rheum* 2009; 61: 600–604.

Vitale A, Rigante D, Lopalco G, et al. Interleukin-1 Inhibition in Behçet’s disease. *Israel Med Assoc J* 2016; 18: 171–176.

Mege JL, Dilsen N, Sanguedolce V, et al. Overproduction of monocyte derived tumor necrosis factor alpha, interleukin (IL) 6, IL-8 and increased neutrophil superoxide generation in Behçet’s disease. *J Rheumatol* 1993; 20: 1544–1549.

Castrichini M, Lazzerini PE, Gamberucci A, et al. The purinergic P2×7 receptor is expressed on monocytes in Behçet’s disease and is modulated by TNF-α. *Eur J Immunol* 2014; 44: 227–238.

Akiyama M, Kaneko Y and Takeuchi T. Effectiveness of tocilizumab in Behçet’s disease: a systematic literature review. *Semin Arthritis Rheum* 2020; 50: 797–804.

Talaat RM, Sibaii H, Bassyouni IH, et al. IL-17, IL-10, IL-6, and IFN-γ in Egyptian Behçet’s disease: correlation with clinical manifestations. *Eur Cytokine Netw* 2019; 30: 15–22.

Gholijani N, Ataollahi MR, Samiei A, et al. An elevated pro-inflammatory cytokines profile in Behçet’s disease: a multiplex analysis. *Immunol Lett* 2017; 186: 46–51.
208. Gur M, Golcuk M, Gul A, et al. Molecular dynamics simulations provide molecular insights into the role of HLA-B51 in Behçet’s disease pathogenesis. *Chem Biol Drug Des* 2020; 96: 644–658.

209. Remmers EF, Cosan F, Kirino Y, et al. Genome-wide association study identifies variants in the MHC class I, IL10, and IL23R-IL12RB2 regions associated with Behçet’s disease. *Nat Genet* 2010; 42: 698–702.

210. Kim SM, Park MJ, Park S, et al. Anti-TNF-α therapy in patients with refractory, et al. controlled crossover trial. *Mod Rheumatol* 2019; 38(Suppl. 127): 17–25.

211. Aziz SG, Aziz SG, Khabbazi A, et al. The methylation status of TNF-α and SOCS3 promoters and the regulation of these gene expressions in patients with Behçet’s disease. *Biomarkers* 2020; 25: 384–390.

212. Davatchi F, Assaad-Khalil S and Calamia KT. The International Criteria for Behçet’s Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. *J Eur Acad Dermatol Venereol* 2014; 28: 338–347.

213. Saleh Z and Arayssi T. Update on the therapy of Behçet disease. *Ther Adv Chronic Dis* 2014; 5: 112–134.

214. Hatemi G, Christensen R, Bang D, et al. 2018 update of the EULAR recommendations for the management of Behçet’s syndrome. *Ann Rheum Dis* 2018; 77: 808–818.

215. Takeno M. Positioning of apremilast in treatment of Behçet’s disease. *Mod Rheumatol* 2020; 30: 219–224.

216. Hatemi G, Melikoglu M, Tunc R, et al. Apremilast for Behçet’s syndrome—a phase 2, placebo-controlled study. *N Eng J Med* 2015; 372: 1510–1518.

217. Hatemi G, Mahr A, Ishigatubo Y, et al. Trial of apremilast for oral ulcers in Behçet’s syndrome. *N Eng J Med* 2019; 381: 1918–1928.

218. Yurdakul S, Mat C, Tüzün Y, et al. A double-blind trial of colchicine in Behçet’s syndrome. *Arthritis Rheum* 2001; 44: 2686–2692.

219. Davatchi F, Sadeghi Abdollahi B, Tehrani Banhishemi A, et al. Colchicine versus placebo in Behçet’s disease: randomized, double-blind, controlled crossover trial. *Mod Rheumatol* 2009; 19: 542–549.

220. Calvo-RÁ-o V, Blanco R, Beltrán E, et al. Anti-TNF-α therapy in patients with refractory uveitis due to Behçet’s disease: a 1-year follow-up study of 124 patients. *Rheumatology (Oxford)* 2014; 53: 2223–2231.

221. Vallet H, Riviere S, Sanna A, et al. Efficacy of anti-TNF alpha in severe and/or refractory Behçet’s disease: multicenter study of 124 patients. *J Autoimmun* 2015; 62: 67–74.

222. Tanida S, Inoue N, Kobayashi K, et al. Adalimumab for the treatment of Japanese patients with intestinal Behçet’s disease. *Clin Gastroenterol Hepatol* 2015; 13: 940–948.

223. Park Y and Cheon JH. Update on the treatment of Behçet’s disease of the small bowel with biologic agents. *Current Gastroenterology Reports* 2020; 22: 24.

224. Chen J, Chen S and He J. A case of refractory intestinal Behçet’s disease treated with tocilizumab, a humanised anti-interleukin-6 receptor antibody. *Clin Exp Rheumatol* 2017; 35(Suppl. 108): 116–118.

225. Emmi G, Talarico R, Lopalco G, et al. Efficacy and safety profile of anti-interleukin-1 treatment in Behçet’s disease: a multicenter retrospective study. *Clin Rheumatol* 2016; 35: 1281–1286.

226. Cantarini L, Lopalco G, Vitale A, et al. Paradoxical mucocutaneous flare in a case of Behçet’s disease treated with tocilizumab. *Clin Rheumatol* 2015; 34: 1141–1143.

227. Grayson PC, Yazici Y, Merideth M, et al. Treatment of mucocutaneous manifestations in Behçet’s disease with anakinra: a pilot open-label study. *Arth Res Therapy* 2017; 19: 69.

228. Caso F, Costa L, Rigante D, et al. Biological treatments in Behçet’s disease: beyond anti-TNF therapy. *Mediators Inflamm* 2014; 2014: 107421.

229. Hatemi G, Seyahi E, Fresko I, et al. One year in review 2020: Behçet’s syndrome. *Clin Exp Rheumatol* 2020; 38(Suppl. 127): 3–10.

230. Bettiol A, Silvestri E, Di Scala G, et al. The right place of interleukin-1 inhibitors in the treatment of Behçet’s syndrome: a systematic review. *Rheumatol Int* 2019; 39: 971–990.

231. Hatemi G, Seyahi E, Fresko I, et al. One year in review 2019: Behçet’s syndrome. *Clin Exp Rheumatol* 2019; 37(Suppl. 121): 3–17.

232. Fabiani C, Vitale A, Rigante D, et al. The presence of uveitis is associated with a sustained response to the interleukin (IL)-1 inhibitors anakinra and canakinumab in Behçet’s disease. *Ocul Immunol Inflamm* 2020; 28: 298–304.

233. Fabiani C, Vitale A, Emmi G, et al. Interleukin (IL)-1 inhibition with anakinra and canakinumab in Behçet’s disease-related uveitis:
a multicenter retrospective observational study. *Clin Rheumatol* 2017; 36: 191–197.

234. Messina MJ, Rodegher M, Scotti R, et al. Treatment of myelitis in Behçet’s disease with rituximab. *BMJ Case Rep* 2014; 2014: bcr2014204366.

235. Zhao BH and Oswald AE. Improved clinical control of a challenging case of Behçet’s disease with rituximab therapy. *Clin Rheumatol* 2014; 33: 149–150.

236. Vitale A, Rigante D, Lopalco G, et al. New therapeutic solutions for Behçet’s syndrome. *Expert Opin Investig Drugs* 2016; 25: 827–840.

237. Mirouse A, Barete S, Monfort JB, et al. Ustekinumab for Behçet’s disease. *Journal of Autoimmunity* 2017; 82: 41–46.

238. Mirouse A, Barete S, Desbois AC, et al. Long-term outcome of Ustekinumab therapy for Behçet’s disease. *Arthritis Rheumatol* 2019; 71: 1727–1732.

239. Yao Q, Shen M, McDonald C, et al. NOD2-associated autoinflammatory disease: a large cohort study. *Rheumatology (Oxford)* 2015; 54: 1904–1912.

240. Yao Q, Li E and Shen B. Autoinflammatory disease with focus on NOD2-associated disease in the era of genomic medicine. *Autoimmunity* 2019; 52: 48–56.

241. Yang X, Wu D, Li J, et al. A Chinese case series of Yao syndrome and literature review. *Clin Rheumatol* 2018; 37: 3449–3454.

242. McDonald C, Shen M, Johnson EE, et al. Alterations in nucleotide-binding oligomerization domain-2 expression, pathway activation, and cytokine production in Yao syndrome. *Autoimmunity* 2018; 51: 53–61.

243. Yao Q and Kontzias A. Expansion of phenotypic and genotypic spectrum in Yao syndrome: a case series. *J Clin Rheumatol* 2022; 28: e156–e160.

244. Yao Q, Lacbawan F and Li J. Adult autoinflammatory disease frequency and our diagnostic experience in an adult autoinflammatory clinic. *Semin Arthritis Rheum* 2016; 45: 633–637.

245. Amariyo G, Harel L, Abu Ahmad S, et al. Periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome – is it related to ethnicity? An Israeli multicenter cohort study. *J Pediatr* 2020; 227: 268–273.

246. Lovšin E, Kovač J, Tesovnik T, et al. PIK3AP1 and SPON2 genes are differentially methylated in patients with periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome. *Front Immunol* 2020; 11: 1322.

247. Cattalini M, Soliani M, Rigante D, et al. Basic characteristics of adults with periodic fever, aphthous stomatitis, pharyngitis, and adenopathy syndrome in comparison with the typical pediatric expression of disease. *Mediators Inflamm* 2015; 2015: 570418.

248. Cantarini L, Vitale A, Sicignano LL, et al. Diagnostic criteria for adult-onset periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome. *Front Immunol* 2017; 8: 1018.

249. Førsvoll J, Kristoffersen EK and Øymar K. Incidence, clinical characteristics and outcome in Norwegian children with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome; a population-based study. *Acta Paediatrica* 2013; 102: 187–192.

250. Ombrello MJ. Advances in the genetically complex autoinflammatory diseases. *Semin Immunopathol* 2015; 37: 403–406.

251. Kraszewska-Glomba B, Matkowska-Kocjan A and Szenborn L. The pathogenesis of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome: a review of current research. *Mediators Inflamm* 2015; 2015: 563876.

252. Hara M, Morimoto N, Suzuki N, et al. Transcriptome analysis reveals two distinct endotypes and putative immune pathways in tonsils from children with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome. *Allergy* 2020; 76: 359–363.

253. Kolly L, Busso N, von Scheven-Gete A, et al. Periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis syndrome is linked to dysregulated monocyte IL-1β production. *J Allergy Clin Immunol* 2013; 131: 1635–1643.

254. Stojanov S, Hoffmann F, Kéry A, et al. Cytokine profile in PFAPA syndrome suggests continuous inflammation and reduced anti-inflammatory response. *Eur Cytokine Netw* 2006; 17: 90–97.

255. Manthiram K, Preite S, Dedegolu F, et al. Common genetic susceptibility loci link PFAPA syndrome, Behçet’s disease, and recurrent aphthous stomatitis. *Proc Nat Acad Sci USA* 2020; 117: 14405–14411.

256. Asna Ashari K and Rezaei N. PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and adenitis) syndrome: an overview of genetic background. *Clin Rheumatol* 2021; 40: 4437–4444.
257. Sampaio IC, Rodrigo MJ and Monteiro Marques JG. Two siblings with periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome. *Pediatr Infect Dis J* 2009; 28: 254–255.

258. Valenzuela PM, Majerson D, Tapia JL, *et al.* Syndrome of periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) in siblings. *Clin Rheumatol* 2009; 28: 1235–1237.

259. Di Gioia SA, Bedoni N, von Scheven-Gete A, *et al.* Analysis of the genetic basis of periodic fever with aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome. *Sci Rep* 2015; 5: 10200.

260. Perko D, Debeljak M, Toplak N, *et al.* Clinical features and genetic background of the periodic Fever syndrome with aphthous stomatitis, pharyngitis, and adenitis: a single center longitudinal study of 81 patients. *Mediators Inflamm* 2015; 2015: 293417.

261. Padeh S, Brezniak N, Zemer D, *et al.* Periodic fever, aphthous stomatitis, pharyngitis, and adenopathy syndrome: clinical characteristics and outcome. *J Pediatr* 1999; 135: 98–101.

262. Gunes M, Cekic S and Kilic SS. Is colchicine more effective to prevent periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis episodes in Mediterranean fever gene variants. *Pediatr Int* 2017; 59: 655–660.

263. Luu I, Sharma A, Guaderrama M, *et al.* Immune dysregulation in the tonsillar microenvironment of periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome. *J Clin Immunol* 2020; 40: 179–190.

264. Ben-Chetrit E and Yazici H. How to classify PFAPA? No hard evidence for associated CAPS or CARD variants and not any for links with Behcet’s syndrome. *Clin Exp Rheumatol* 2021; 39(Suppl. 132): 14–17.

265. Manthiram K, Preite S, Dedeoglu F, *et al.* Common genetic susceptibility loci link PFAPA syndrome, Behcet’s disease, and recurrent aphthous stomatitis. *Proc Nat Acad Sci USA* 2020; 117: 14405–14411.

266. Statler VA and Marshall GS. Evaluation of prolonged and recurrent unexplained fevers. *Pediatric Annals* 2018; 47: e347–e353.

267. Gattorno M, Hofer M, Federici S, *et al.* Classification criteria for autoinflammatory recurrent fevers. *Ann Rheum Dis* 2019; 78: 1025–1032.

268. Marshall GS, Edwards KM, Butler J, *et al.* Syndrome of periodic fever, pharyngitis, and aphthous stomatitis. *The Journal of Pediatrics* 1987; 110: 43–46.

269. Burton MJ, Pollard AJ, Ramsden JD, *et al.* Tonsillectomy for periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome (PFAPA). *Cochrane Database Syst Rev* 2019; 12: CD008669.

270. Rigante D, Vitale A, Natale MF, *et al.* A comprehensive comparison between pediatric and adult patients with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenopathy (PFAPA) syndrome. *Clin Rheumatol* 2017; 36: 463–468.

271. Della Corte C, Ranucci G, Tufano M, *et al.* Autoimmune hepatitis type 2 arising in PFAPA syndrome: coincidences or possible correlations? *Pediatrics* 2010; 125: e683–e686.

272. Gaggiano C, Rigante D, Sota J, *et al.* Treatment options for periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome in children and adults: a narrative review. *Clin Rheumatol* 2019; 38: 11–17.

273. Yazgan H, Gültekin E, Yazıcılar O, *et al.* Comparison of conventional and low dose steroid in the treatment of PFAPA syndrome: preliminary study. *Int J Pediatr Otorhinolaryngol* 2012; 76: 1588–1590.

274. Tasher D, Stein M, Dalal I, *et al.* Colchicine prophylaxis for frequent periodic fever, aphthous stomatitis, pharyngitis and adenitis episodes. *Acta Paediatrica* 2008; 97: 1090–1092.

275. Soriano A, Soriano M, Espinosa G, *et al.* Current therapeutic options for the main monogenic autoinflammatory diseases and PFAPA syndrome: evidence-based approach and proposal of a practical guide. *Front Immunol* 2020; 11: 865.