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Review

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Review

Autoinflammatory manifestations in adult patients

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Summary

Autoinflammatory diseases represent a family of immune-mediated conditions characterized by the unchecked activation of innate immunity. These conditions share common clinical features such as recurrent fever, inflammatory arthritis, and elevation of acute phase reactants, in the absence of an identified infectious etiology, generally without detectable serum autoantibodies, with variable response to glucocorticoids and in some cases colchicine, which represented the mainstay of treatment until cytokine blockade therapies became available. The first autoinflammatory diseases to be described were monogenic disorders caused by missense mutations in inflammasome components and were recognized predominantly during childhood or early adulthood. However, the progress of genetic analyses and a more detailed immunological phenotyping capacity led to the discovery a wide spectrum of diseases, often becoming manifest or being diagnosed in the adult population. The beneficial role of targeting hyperinflammation via interleukin 1 in complex non-immune-mediated diseases is a field of growing clinical interest. We provide an overview of the autoinflammatory diseases of interest to physicians treating adult patients and to analyze the contribution of hyperinflammation in non-immune-mediated diseases; the result is intended to provide a roadmap to orient scientists and clinicians in this broad area.

Keywords: inflammasome; interleukin-1; anakinra; canakinumab; myocarditis; COVID-19

Abbreviations: AID: autoinflammatory disease; NFkB: nuclear factor kappa light chain enhancer of activated B cells; NGS: next generation sequencing; PRR: pattern recognition receptors; IL: interleukin; IFN: interferon; TRAPS: tumor necrosis factor receptor-associated periodic fevers

Introduction

The concept of autoinflammatory disease was introduced in 1999 [1], when tumor necrosis factor receptor-associated periodic fevers (TRAPS) was defined for the first time as 'systemic disorder characterized by apparently unprovoked inflammation in the absence of high-titer autoantibodies or antigen-specific T lymphocytes'. The modern concept of autoinflammatory diseases does not differ much from the original definition while the number of conditions belonging to this spectrum has been constantly increasing over the past decades.

Autoinflammatory diseases (AIDs) are characterized by systemic inflammation caused by deregulated activation of the innate immune system, which occurs in the absence of an identified infectious trigger. In this context, the involvement of the adaptive immune system in the development of systemic inflammation is absent or significantly limited, as opposed to what happens in autoimmune diseases. Historically, the first described autoinflammatory diseases have been regarded as mainly occurring at young age. However, prevalence of AIDs in adult patients, restricted to few cases in the first cohorts, has been increasing over time. In recent years, there has been a better understanding of the clinical spectrum of AIDs, particularly thanks to the advances and refinements of the next generation sequencing (NGS) techniques which have significantly improved the diagnostic capacity in adult patients [2]. Diseases that were diagnosed almost exclusively during infancy or early childhood have acquired an "adult-version" which, in general presents a milder phenotype and a better response to treatment. This mainly applies to monogenic diseases, in which adult onset is significantly mediated by low-penetrance mutations or somatic mosaicism and clinical characteristics may not match those described for children, including some cardinal features. This is reflected by the lower sensitivity of original classification criteria when applied to adult patients, which has led to the formulation of new sets of criteria specifically developed for disease onset in adulthood. Finally, growing research into the complex pathways of innate immunity has led to the recognition or reclassification of a number of diseases with autoinflammation or possessing an autoinflammatory component. Thus, the recognition of clinical manifestations suggestive of systemic AIDs should warrant early referral to specialized centers and to genetic testing,

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which can lead to earlier diagnosis and identification of new pathogenic mutations or new autoinflammatory syndromes.

For these clinically relevant reasons, our review will present the major features of autoinflammatory diseases that may be encountered in the practice of adult rheumatology. We will review and discuss the molecular and genetic bases of autoinflammation, the main autoinflammatory diseases diagnosed in the adults, the contribution of autoinflammation to multifactorial/complex disorders, along with considerations on the relevance of autoinflammation in the clinical manifestations of COVID-19. While falling short of an exhaustive discussion of the vast knowledge on the pathogenesis and mechanisms of these conditions, we are convinced this may be of help to clinical immunologists and rheumatologists involved in routine practice.

The pillars of inflammation

The innate immune system represents a non-specific first line of immunity against external dangerous stimuli. Innate immunity is mainly represented by cells of the myeloid lineage: upon binding of various ligands to specialized receptors, named PRR (pattern recognition receptors), myeloid cells get activated and secrete an array of pro-inflammatory cytokines which induce a myriad of downstream pro-inflammatory signals that mediate the immune response against the noxious stimulus [3]. Deregulated activation of these mechanisms is critical in the pathophysiology of autoinflammatory diseases, resulting in flares of seemingly unprovoked inflammation leading to tissue damage and systemic symptoms. Key players of innate immunity are the inflammasome, the transcription factor NFkB (nuclear factor kappa light chain enhancer of activated B cells) and the pro-inflammatory cytokines interleukin-1 and -6. Other important pathways in the onset of the innate response are the interferon (IFN) pathway and the ubiquitin system which will be briefly discussed.

The inflammasome

First described in 2002 [4], inflammasomes are large multimolecular complexes able to regulate, through Caspase-1, the proteolytic maturation and activation of interleukin-1β and interleukin-18, as well as a rapid inflammatory form of cell death termed pyroptosis [5]. The assembly of inflammasome complexes can triggered directly, upon cytosolic sensing of endogenous danger signals (danger-associated molecular patterns, DAMPs) released from damaged or dying cells [5]. Additionally, infections can trigger inflammasome assembly either directly, upon binding of microbial particles (pathogen-associated molecular patterns, PAMPs) to cytosolic PRRs or, as it is recently emerging as the main mechanism of inflammasome activation, through sensing of alterations in cytoplasmic homeostasis [6,7].

The canonical inflammasome complex consists of a cytosolic sensor, an adaptor protein ASC, and an effector protein, pro-caspase-1 [8]. Pro-caspase-1 is cleaved into its active form, which subsequently leads to the cleavage of pro-IL-1β and pro-IL-18 and the generation of their mature, biologically active form. Several distinct inflammasomes have been identified, each characterized by unique activators, sensors (NLR/ALR family members) and caspase effectors. NLRP3 inflammasome is the best characterized (Fig. 1). As shown in this review, several autoinflammatory diseases are caused by mutations in genes encoding for inflammasome components.

Interleukin-1

IL-1 comprises IL-1α and IL-1β with the IL-1α precursor constitutively expressed in a wide variety of cells, hematopoietic and non-hematopoietic, and being released in the extracellular space upon cell death by necrosis [9]. Unlike the IL-1β precursor, IL-1α precursor already possesses full biological activity and can function as an "alarmin" by rapidly inducing a cascade of inflammatory cytokines and chemokines, thus accounting for the early phases of sterile inflammation [10]. Interleukin 1β is mainly produced by inflammatory cells of the myeloid lineage. It is synthesized as an inactive precursor (termed pro-IL-1β), which requires proteolytic cleavage by Caspase 1 in order to acquire biological activity [11]. Despite being the best characterized, Caspase 1 cleavage is not the exclusive mechanism of IL-1β activation. Indeed, there is evidence of proteinase 3-dependent IL-1β processing in Caspase1-KO murine models of inflammatory arthritis [12]. The biologic effects of IL-1α and IL-1β are mediated by binding to the membrane receptor named interleukin 1 receptor 1 (IL-1R1). This binding induces multiple cellular signaling pathways culminating in the activation of NFkB and the induction of other pro-inflammatory cytokines such as IL-6, TNFα, and IFNy [9]. Importantly, IL-1α and β induce themselves, a key mechanism in sustained autoinflammation [11]. Interleukin-1-mediated inflammation results in a broad variety of organ specific damage, such as arthritis, inflammatory rash, uveitis, serositis, and systemic involvement with fever and elevation of acute phase reactants [13]. Of note, IL-1, together with interleukin 6 (IL-6) and tumor necrosis factor α (TNFα), acts as a transcriptional stimulus on the hepatocytes to induce the synthesis of serum amyloid A (SAA) [13]. Sustained elevated levels of SAA may result in development of systemic amyloidosis, a frequent and potentially severe complication of autoinflammatory diseases [14]. Along with production of IL-1, myeloid cells secrete IL-1 receptor antagonist (IL-1Ra), a soluble molecule which binds to IL-1R1 and prevents its activation. The recombinant form IL-1Ra, named anakinra, has been employed successfully in treatment of several autoinflammatory diseases as well as other inflammatory conditions. In the attempt of quenching deregulated IL-1-driven inflammation several other inhibitors have been designed: from the best characterized canakinumab (monoclonal antibody against IL-1β) and rilonacept (a soluble receptor-Fc fusion protein acting as decoy receptor), to the newly developed gevokizumab (a monoclonal antibody against IL-1β) and belnacasan (a caspase-1 inhibitor).

Finally, IL-1 family extends beyond IL-1α and β, including other proinflammatory and anti-inflammatory cytokines. Of note, the role of IL-18, activated by the inflammasome together with IL-1β, has been clearly established in the pathogenesis of autoinflammatory diseases, especially in mediating macrophage activation syndrome (MAS), a severe complication of AIDs [15].

Interleukin-6

IL-6 is a pro-inflammatory cytokine with pleotropic functions that modulates host defense acting through a number of immune stimulating mechanisms: control of monocytes and their differentiation into macrophages, production of acute phase reactants, modulation of antigen-dependent B cell differentiation, increased IgG production by B cells, promotion of Th2 response by inhibiting Th1 polarization [16].

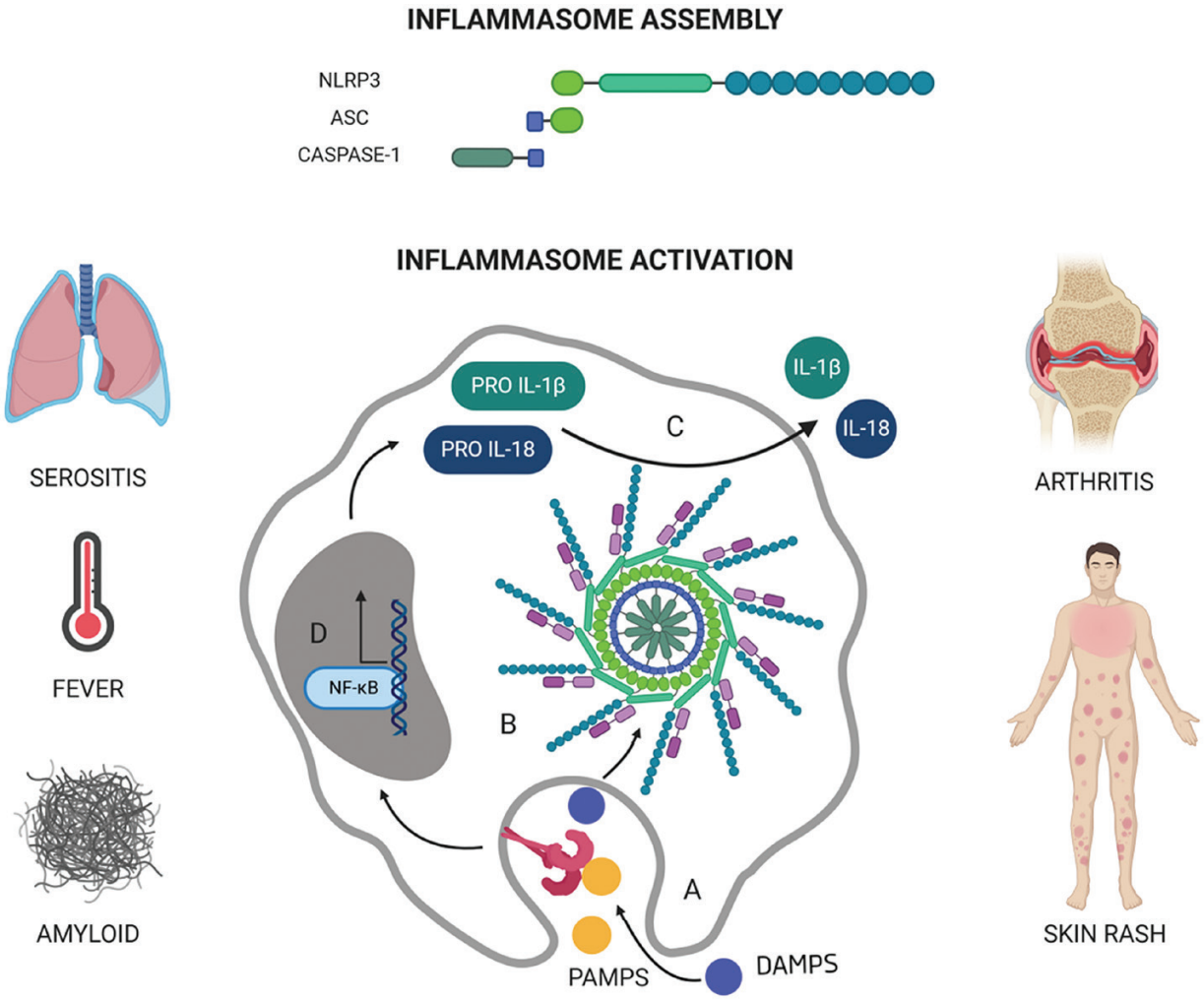

Figure 1: inflammasome assembly and activation. (A) PAMPs and DAMPs phagocytosis directly and, mainly, indirectly induces the intracellular assembly of the inflammasome (B), which catalyzes the proteolytic cleavage of pro-interleukin-1 and pro-interleukin18 (C). In the meantime, TLR binding activates intracellular pathways that culminate in the nuclear synthesis of NFkB, which in turn induces increased synthesis of inflammasome components, and pro-IL1 and pro-IL18 (D). Activated proinflammatory cytokines mediate multiorgan inflammation with characteristic clinical features.

Excessive synthesis of IL-6 and dysregulation of IL-6 receptor signaling is involved in the pathophysiology of several autoimmune and autoinflammatory diseases. Two IL-6 inhibitors are currently approved by FDA: tocilizumab and sarilumab, both monoclonal antibodies against interleukin-6 receptor (IL-6R), while several other agents are currently being evaluated in clinical trials.

Ubiquitination

Ubiquitination is a post-translational modification process involved in the regulation of several intracellular processes, from protein transcription to degradation, DNA-repair and endocytosis [17]. It is a dynamic process, in which ubiquitin chains can be added by ubiquitinases or removed by deubiquitinases. Ubiquitin chains have been proven essential in the stabilization of the signal downstream to TLR, NLR, IL1R, and TNFR activation, ultimately promoting NFkB activation. Deubiquitination *vice versa* serves as a negative regulator of innate inflammation, quenching NFkB activation [18]. Moreover, recent findings have suggested a role for ubiquitination in the regulation of inflammasome activity [19] and can also influence the NLRP3 inflammasome activation. Based on these mechanisms, alterations at any level in the ubiquitination machinery have been linked to the development of a type of AIDs termed ubiquitinopathies [20].

Type I IFN

The type I IFN family includes inflammatory polypeptides expressed in immune and non-immune cells which represent another pathway of innate immunity, simultaneous to the inflammasome pathway, which gets activated in response to viral infections and some bacterial antigens [21]. Viral nucleic acids are sensed in the cytoplasm or endosomes by various receptors, which induce, directly or through activation of stimulator of interferon genes (STING), the translocation of IFNs regulatory factors (IRF) 3 and 7 to the nucleus; there, IRFs stimulate transcription of type I interferon genes. STING can also directly stimulate NFkB transcription. Paracrine and autocrine binding of type I IFNs to IFN receptor activates downstream signal through janus kinase/signal transducers and activators of transcription (JAK-STAT), resulting in apoptosis of the infected cell and immune response against the microbial antigen [22]. Dysregulation at any level in these pathways can lead to overactivation of the interferon system,

resulting in the development of type I interferonopathies, a recently described group of inherited monogenic AIDs. Presently, 13 diseases have been classified in this group [23], and, despite clinical heterogeneity, they share some common clinical features such as recurrent fever, cutaneous involvement with early-onset skin vasculopathy and panniculitis, interstitial lung disease or encephalopathy [24]. This group of diseases typically occurs early in life, with anecdotal cases in the adult population and will thus not be discussed extensively in this review.

Monogenic autoinflammatory diseases

Monogenic autoinflammatory diseases constitute a group of hereditary disorders caused by mutations in genes involved in inflammasome assembly, NFkB activation, cytokine secretion, ubiquitination, and type I interferon signaling. In this paragraph, the most common and best characterized monogenic autoinflammatory diseases will be presented, with special consideration regarding their presentation in adult patients (Table 1).

Familial Mediterranean fever

Familial Mediterranean fever (FMF) is the most common hereditary systemic autoinflammatory disease. It is caused by autosomal recessive gain-of-function mutations of the Mediterranean fever (MEFV) gene, which encodes for pyrin, a cytosolic sensor capable of inducing inflammasome assembly (thus called the pyrin inflammasome) [25]. Approximately 90% of patients with FMF develop symptoms before the third decade of life; however, the presence of low-penetrance or *de novo* mutations may result in later disease onset [26]. The disease typically presents with sporadic and recurrent episodes of fever, lasting from few hours to few days, associated with serositis as manifested by acute abdominal or chest pain. Other manifestations include arthritis or arthralgia of large joints which in general is unilateral and development of erysipelas-like erythema of the lower limbs [26]. Adult-onset FMF seems to bear a milder clinical presentation, with lower occurrence of arthritis and erysipelas-like erythema [27]. Diagnosis of FMF can be formulated using the clinical criteria published by Livneh *et al.* [28], illustrated in Table 2. Nevertheless, genetic analyses demonstrating mutations in *MEFV* gene is mandatory for a definitive diagnosis [29]. Amyloidosis is the most severe complication and the major cause of mortality in patients with FMF, occurring in a high proportion of untreated patients [30]. Colchicine represents the cornerstone of treatment for FMF, although some patients are refractory to standard treatment. Anakinra proved to be very effective in treatment of refractory cases and represents a suitable therapy to prevent development of systemic amyloidosis [28]. Adult-onset FMF is associated to a better treatment outcome, with favorable response to low-dose colchicine [27].

Tumor necrosis factor receptor-associated periodic syndrome

TRAPS represents the second most common hereditary autoinflammatory disease and is caused by autosomal dominant mutations in the TNFRSF1A gene, which encodes the p55 TNF receptor type 1 [1]. Mutations produce a misfolded receptor that accumulates in the cell cytoplasm, leading to enhanced NFκB activation, reactive oxygen species (ROS) production and impaired autophagy, ultimately resulting in inflammasome assembly and IL-1 proteolytic activation [31].

TRAPS displays a wide variability in terms of age of onset, clinical presentation, and disease severity, depending on the mutation hitting the TNFRSF1A gene. Until now, more than 160 mutations in TNFRSF1A gene have been reported. Low-penetrance variants have been associated to a later, more subtle and mild clinical presentation and lower tendency to become chronic; high-penetrance variants (especially when involving cysteine residues) have been associated to an early-onset disease with a severe and potentially disabling clinical course [32]. Furthermore, some of the most frequent

Table 1: The most common monogenic autoinflammatory disorders with a focus on differences in presentation in adults

Monogenic autoinflammatory disease	Gene	Mode of inheritance	Cardinal features	In adults
Familial Mediterranean fever (FMF)	MEFV	AR	Recurrent self-limiting attacks of fever, abdominal pain, thoracic pain, arthritis	Lower occurrence of erythema and arthritis. Better response to treatment
Tumor Necrosis Factor Receptor- Associated Periodic Syndrome (TRAPS)	TNFRSF1A	AD	Arthromyalgia, fasciitis, rash, conjunctivitis and periorbital edema, splenomegaly	Milder clinical presentation and lower tendency to chronicity
NLRP3-AID	NLRP3	AD	Fever, urticarial rash, sensorineural hearing loss, lymphadenopathy, splenomegaly, myalgia, arthropathy	No major differences
A20 haploinsufficiency (HA20)	TNFRSF1A	AD	Fever, recurrent oral and genital ulcers, abdominal pain, skin rash, arthritis	No major differences
Mevalonate kinase deficiency (MVK)	MVK	AR	Abdominal pain, diarrhea, hepatosplenomegaly, lymphadenopathy	Cases mainly due to diagnostic delay
VEXAS syndrome	UBA1	n.a.	fever, cutaneous vasculitis, neutrophilic dermatosis, ear and nose chondritis, pulmonary infiltrates, bronchial vasculitis, criteria of myelodysplastic syndrome	n.a.

AR, autosomal recessive; AD, autosomal dominant.

Table 2: Livneh 1997 classification criteria for Familial Mediterranean Fever

Major criteria	Minor criteria
Recurrent febrile episodes with serositis (peritonitis, synovitis, or pleuritic)	Recurrent febrile episodes
Favourable response to regular colchicine treatment	Erysipelas-like erythema
AA-type amyloidosis without a predisposing disease	FMF diagnosis in a first-degree relative

Diagnosis requires the presence of MEFV mutation and: 2 major or 1 major + 2 minor criteria.

low-penetrance variants, such as R92Q and P46L, bear an uncertain pathogenic role, since many carriers are completely asymptomatic, while others develop a mild–moderate disease [33].

Disease onset is typically around 3 years of age, but adult onset is not infrequent (up to 45% in some case series) [32]. Clinical presentation is characterized by recurrent febrile episodes (lasting >1 week), serositis, periorbital edema, and myalgia with overlying migratory rash. Patients may also refer arthralgia or develop inflammatory arthritis [34]. Recurrent pericarditis is frequent in the presence of low-penetrance variants, and may sometimes be the only symptom of the disease [35]. Reactive amyloidosis, which represents the most severe complication of TRAPS, is significantly more frequent in patients with high-penetrance mutations [36]. Diagnosis of TRAPS is made upon detection of a mutation in TNFRSF1A gene [1]. Disease flares are usually responsive to corticosteroids; however, increasing doses of steroids and repeated courses of treatment are sometimes necessary. Nowadays treatment mainly relies on selective IL-1 blockers, which have been proven successful in controlling disease manifestations and preventing recurrent flares, even in refractory cases [37].

NLRP3-AID/cryopyrin-associated periodic syndromes

NLRP3 autoinflammatory diseases, formerly called cryopyrin-associated periodic syndromes (CAPS), encompass a clinical continuum of three diseases, which are listed in order of increased severity as familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID).

NLRP3-AIDs are autosomal dominant diseases caused by gain-of-function mutations in NLRP3 inflammasome. The inheritance pattern is usually familial, although NOMID cases caused by sporadic *de novo* mutations have been described [38].

All three disease variants present most frequently at birth or in early childhood, but cases of adult-onset NLPR3-AID, in patients with a negative family history have been recently described. A somatic NLPR3 mosaicism has been identified as the etiology of adult-onset NLRP3-AID; the timing of when the mutation occurs and the subsequent selection can vary, along with the age at presentation. In a recent case series of 8 Caucasian patients the median age at diagnosis was 50 years (range 31–71) and all patients had typical NLRP3-AID features, with high fever, urticarial rash, and bilateral sensorineural hearing loss [39]. Of note, this series represented the 8% of NLRP3-AID diagnosis in a single center, suggesting that acquired NLRP3 mutations may not be an infrequent cause of the syndrome.

FCAS is the mildest of the cryopirin-associated disorders and is characterized by flares of fever, urticarial rash and conjunctival injection, typically occurring after prolonged exposure to cold temperature. MWS is characterized by seemingly unprovoked flares of fever, arthritis/arthralgia, and urticarial rash together with a progressive severe sensorineural hearing loss probably caused by chronic inflammation of the cochlea or leptomeninges [40]. NOMID is the most severe autoinflammatory cryopyrinopathy. Symptoms usually appear at birth or in the first weeks of life and include fever, urticarial-like migratory rash features, chronic meningitis, chronic arthritis with bone deformity and growth impairment with characteristic facial features [41]. Nearly 25% of patients with NLRP3-AID develop amyloidosis, which is the leading cause of death [41].

IL-1 blocking agents are extremely effective in treating the clinical manifestations of NLRP3-AID and preventing the occurrence of amyloidosis [42].

A20 haploinsufficiency

A20 haploinsufficiency (HA20) is a rare autoinflammatory disease caused by the autosomal dominant loss-of-function mutation of TNFα-induced protein 3 gene (TNFAIP3) on chromosome 6. A20 is a negative regulator of the NFkB activation, via its deubiquitinating activity, thereby its loss-of-function results in unchecked NFkB signaling and increased secretion of proinflammatory cytokines [43]. Most patients have a positive family history, while the remaining cases are caused by *de novo* mutations. The mean age at diagnosis is 14 years; however, age of onset in early adulthood is not infrequent [44,45] with typical symptoms including recurrent fever, oral, and genital ulcers. Gastrointestinal symptoms with abdominal pain, vomit, or diarrhea are frequent. Cutaneous involvement including folliculitis, pustules, or nonspecific rash has been reported in 50% of cases. Other manifestations include arthritis, ocular involvement with anterior uveitis or retinal vasculitis, myopericarditis, vasculitis, and recurrent infections [44]. HA20 frequently mimics Behçet disease (discussed later in this article) and is sometimes referred to as the monogenic version of Behçet. An important difference is represented by ocular involvement, which is significantly less frequent in HA20 [44]. Treatment mainly relies on corticosteroids and colchicine; refractory cases have been managed with synthetic DMARDs or targeted drugs against IL-1, IL-6R, or JAK [44,46].

Mevalonate kinase deficiency

Mevalonate kinase deficiency (MKD) is an autoinflammatory disorder characterized by recurrent episodes of systemic hyperinflammation and by increased serum levels of polyclonal immunoglobulin D (IgD). The classical variant, accounting for 75% of cases, is caused by autosomal recessive loss of function mutations in the gene encoding for mevalonate kinase (MVK), an enzyme downstream of hydroxymethylglutaryl coenzyme A (HMG-CoA). MVK deficiency leads to increased production of mevalonic acid and reduced levels of isoprenoid products, due to interference with the regulation of the mevalonate pathway of cholesterol synthesis [47]. The pathogenesis has not been clearly defined but lack of isoprenoid products has been directly linked with the

increased production of IL-1β from peripheral blood mononuclear cells of patients with MKD [48]. Moreover elevated levels of immunoglobulin D (IgD) might directly contribute to the increased secretion of proinflammatory cytokines as demonstrated in vitro [49].

MVK is predominantly a disease of pediatric rheumatology, but some cases diagnosed in adult patients have been reported: recently Durel *et al.* reported a series of 23 adults diagnosed with MVK, with a median age at diagnosis of 37 years and highly concordant genetic and clinical features compared to pediatric MVK. The appearance in adulthood was likely secondary to a delay in the diagnosis linked to medical misunderstanding, as most patients recalled the onset of recurrent fever in early childhood [50].

A partial deficiency in MVK causes the milder form, hyperimmunoglobulinemia D, and periodic fever syndrome (HIDS); on the other hand, an absent enzymatic activity causes the more severe mevalonic aciduria (MA) [51]. HIDS is characterized by cyclical flares of fever, painful lymphadenopathy (usually cervical), severe abdominal pain, diarrhea, arthralgias, splenomegaly, mucocutaneous ulcerations, skin rash, and an elevated serum polyclonal IgD level. MA represents instead the most severe end of the MKD spectrum and characteristically presents in the first few months of life. Patients with MA classically have developmental delay, psychomotor retardation, physical dysmorphisms, hepatosplenomegaly, ocular abnormalities, ataxia, seizures, and myopathies [51].

Before the advent of biological therapy, the mainstay of treatment was represented by NSAIDs and glucocorticoids. Based on the evidence of critical IL-1β role in the pathogenesis of MKD selective IL-1 blockade has been exploited in treatment of cases refractory to standard therapy. Specifically, anakinra and canakinumab have been demonstrated to effectively reduce the frequency and severity of attacks, especially in HIDS [52,53].

VEXAS syndrome

The presence of vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) characterizes a recently described monogenic autoinflammatory disorder of the adult. VEXAS syndrome is caused by somatic mutations in UBA1 gene, which encodes for ubiquitin activating enzyme, necessary for the initiation of ubiquitylation [54]. The mutation (at the locus p.Met41) is present with mosaicism, with the mutant variant detected in hematopoietic progenitor cells and myeloid cells. Loss of ubiquitylation causes activation of the unfolded protein response and autophagy pathways, ultimately resulting in abundant production and secretion of proinflammatory cytokines (IL-6, IFNγ, TNFα). Being X-linked, the disease occurs almost exclusively in males, with a median age of onset of 60 years [54]. However some cases of VEXAS in females have been described, mainly due to X monosomy [55,56]. The most common clinical manifestations are fever, cutaneous involvement (cutaneous vasculitis and neutrophilic dermatosis), ear and nose chondritis, and pulmonary involvement (pulmonary infiltrates, pleural effusion, medium-sized bronchial vessel vasculitis or alveolitis). It frequently features hematopoietic dyspoiesis meeting criteria of myelodysplastic syndrome (MDS). Bone marrow aspirate shows characteristic vacuolization of myeloid and erythroid precursor cells [54].

Of note, several patients met the diagnostic or classification criteria of other inflammatory disorders, especially relapsing polychondritis [54].

Treatment of VEXAS syndrome is presently not codified and data are based on case series. High-dose glucocorticoids are often employed as a first-line therapy, frequently followed by the introduction of a DMARD as a steroid-sparing agent or due to inadequate response. Importantly, cytotoxic agents should be used with caution since most patients present features of myelodysplastic syndromes and may experience worsening of cytopenia. Janus kinase inhibitors have shown efficacy especially in the treatment of cutaneous manifestations [57] while anti-cytokine agents such as tocilizumab, anakinra, and TNFα inhibitors have been employed with variable efficacy [58,59]. The hypomethylating agent azacytidine has provided clinical response in 5 of 11 patients with VEXAS and MDS. Three patients from this cohort underwent allogeneic hematopoietic stem cell transplant, with complete resolution of the disease [60].

Overall, VEXAS syndrome frequently becomes refractory to treatment and has a mortality rate as high as 50% [59].

Multifactorial autoinflammatory diseases

Beyond monogenic autoinflammatory diseases, there is a spectrum of disorders that unambiguously feature a deregulated activation of the myeloid compartment and autoinflammation, though lacking a specific driver mutation to their pathogenesis. They are considered complex autoinflammatory diseases, in which environmental stimuli in genetically predisposed individuals result in unchecked activation of the innate immune compartment. These diseases are typically diagnosed in adulthood and should be considered in the differential diagnosis of adult patients with unexplained recurrent fever.

Adult onset still disease

Adult onset still disease (AOSD) is a rare, systemic inflammatory syndrome characterized by seemingly unprovoked flares of fever, arthritis, sore throat, evanescent skin rash, multiorgan inflammation, together with striking elevation of inflammatory markers, especially non-glycosylated ferritin [61]. Median age at diagnosis is around 36 years, though clinical onsets were described up to 83 years [61]. Two clinical phenotypes can be identified in AOSD: one characterized by recurrent flares of sterile multiorgan inflammation, and another characterized by predominant joint involvement, with a lower degree of systemic inflammation [61], probably subtending different pathophysiological backgrounds. In some cases AOSD may evolve into macrophage activation syndrome, a life-threatening complication characterized by high fever, liver dysfunction, pancytopenia, and coagulopathy [61]. The standard treatment of AOSD is represented by high-dose steroids and DMARDs (disease modifying anti-rheumatic drugs). However, up to 20-30% of patients are refractory to the conventional treatment and progress toward chronic disease [61]. These patients benefit from therapy with biologic agents against IL-1 (especially those exhibiting the "systemic" variant), and IL-6 [62] (effective in both disease variants). In particular, consistent with observations that the NLRP3 inflammasome is highly expressed and activated in AOSD [63], IL-1β blockade, with anakinra or canakinumab, even in monotherapy, represents the mainstay of biologic treatment and effectively controls disease manifestations [64,65].

Use of biologic agents as a first-line therapy is under evaluation in AOSD and SOJIA (considered the juvenile form of AOSD). Anti-TNFα agents can be employed in case of failure of anti-IL-1 and anti-IL-6 biologics [66] while a recombinant IL-18 binding protein, which acts as a decoy receptor for IL-18, represents a novel therapeutic opportunity for AOSD. In a recent small phase II study the use of tadekinig alfa led to clinical improvement in 50% of patients with AOSD refractory to steroid e conventional DMARDs therapy. Of note, the majority of patients had arthritis and did not have fever at enrolment [67]. Another option to be considered in refractory AOSD is represented by JAK inhibitors, which were associated with complete or partial response in 5 over 9 patients in a recent retrospective study [68].

Schnitzler syndrome

Schnitzler syndrome (ShS) is a rare, acquired systemic autoinflammatory disease characterized by recurrent fever, urticaria, and monoclonal gammopathy. Around 15-20% develop overt lymphoproliferative disease, typically Waldenstrom's macroglobulinaemia [69]. Patients usually present in the fifth decade, without a positive family history [70]. Diagnosis of ShS requires the fulfillment of Strasbourg diagnostic criteria (illustrated in Table 3), which allow to formulate a probable or definite diagnosis [71]. The efficacy of anakinra or canakinumab in ShS patients is so distinctive that treatment failure should bring to reconsider the diagnosis [72].

Behçet disease

Behçet disease (BD) is a complex systemic disease, at the bridge between autoimmunity and autoinflammation. It his strongly associated with the presence of HLA-B*51 allele, although GWAS analyses identified an association with a common variant in IL-10 locus, associated with decreased IL-10 production [73].

It typically affects young adults with a median age of onset around 30 years, even though juvenile onset (i.e. <16 years) is possible [74,75]. BD is characterized by recurrent oral aphthous ulcers, genital sores, and ocular lesions. Inflammation is typically self-limiting in time, in fact BD is characterized by episodes of relapses and remissions with sequelae. Clinical manifestations may include vascular, articular, gastrointestinal, neurologic, urogenital, pulmonary, and cardiac involvement [76]. Current treatment mainly relies on glucocorticoids and DMARDs (especially azathioprine). TNFα inhibitors have been widely employed in patients refractory to conventional therapy with excellent results, especially in patients with uveitis [77]. However, some patients relapse or show no response to TNFα-blockers. Selective IL-1 inhibition proved effective in dampening inflammation and achieving a sustained clinical response in several case series and reports, leading to interesting results and intriguing new pathogenic implication [78]. Convincing evidence for a role of IL-1β in BD also derives from the positive results reported in a trial of gevokizumab in patients with multi-resistant uveitis [79].

Table 3: Strasbourg criteria for ShS diagnosis

Obligate criteria	Minor criteria
Chronic urticarial rash	Unexplained recurrent fever (>38°C)
Monoclonal IgM or IgG	Objective findings of abnormal bone remodeling with or without cone pain
	Neutrophilic dermal infiltrate
	Leukocyte count >10 000/mm^3 or CRP >30 mg/L

Definite diagnosis if 2 obligate criteria and 2 minor criteria if IgM+ or 3 minor criteria if IgG+. Probable diagnosis if 2 obligate criteria and 1 minor criteria if IgM+ or 2 minor criteria if IgG+. * As assessed by bone scintigraphy, MRI or elevation in alkaline phosphatase.

PFAPA syndrome

Periodic fever with Apthous Stomatitis, Pharyngitis, and Adenitis (PFAPA) is the most common cause of periodic fever in childhood. It is a complex disorder with a genetic component, as documented by the different reports of familial cases [80]. The proposed pathogenesis of PFAPA involves inflammasome activation during disease flares, with IL-1β, IL-6, and IL-18 production and subsequent T-cell activation with polarization towards a Th1 phenotype [81].

PFAPA is characterized by recurrent episodes of fever associated with oral aphthous lesions, cervical adenitis, and erythematous or exudative pharyngitis. Usually, PFAPA syndrome wanes during adolescence; however, there is increasing evidence that it may persist into adulthood; additionally, multiple studies have reported PFAPA cases in adults [82]. Clinical presentation in adults is more subtle, the classic triad is present only in approximately half of the cases, and flares follow less clockwork regularity [82]. Diagnosis was traditionally based on the modified Marshall's criteria developed in 1999, which considered an early age of onset (<5 years) as a criterion [83]. More recently, Cantarini *et al.* proposed a new set of criteria to be applied for late-onset PFAPA, removing the age threshold and being less stringent on coexistence of cardinal symptoms [84]. A comparison of the 2 sets of criteria is presented in Table 4. Treatment is based on glucocorticoids: a single administration at flare onset is usually sufficient interrupt the attack, but often resulting in earlier relapse of the attack. For these patients, colchicine has been shown to decrease the frequency of the flares [83]. Interleukin 1 inhibition is an extremely effective therapeutic options and is employed in selected cases, such as patients resistant to conventional therapy or with frequent disease flares [85].

SAPHO syndrome

The SAPHO acronym stands for Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis. As described by the name, it is a syndrome characterized by a variety of osteoarticular disorders frequently accompanied by neutrophilic dermatosis. The proposed pathophysiological mechanism involves enhanced NLRP3-mediated IL-1β secretion in genetically predisposed individuals, with a role for chronic infection by Propionibacterium acnes [86,87].

SAPHO syndrome typically ensues in early adulthood, with a median age at diagnosis around 40 years [88,89]. The disease can have a chronic course or proceed in a relapsing remitting way; disease flares can be mono- or multifocal. Osteoarticular involvement can occur in the form of inflammatory arthritis, hyperostosis, osteitis and axial spondyloarthritis [90]. The most common form of cutaneous involvement is palmoplantar pustulosis (PPP), which occurs in up to 60% of patients. Severe acne is frequent and usually subsides with residual scarring. Rarer cutaneous manifestations include Sweet's syndrome and pyoderma gangrenosus

Table 4: Comparison of 1999 modified Marshall's criteria for PFAPA and 2018 Cantarini's criteria for adult PFAPA

Criteria set	Modified Marshall's criteria	Cantarini's criteria
Age at onset	<5 years	>16 years
Fever pattern	Regularly recurring	Recurrent
Symptoms and signs	At least one between: • Aphtous stomatitis • Cervical lymphoadenitis • Pharyngitis	Erythematous pharyngitis and/or cervical adenitis. Increased inflammatory markers during attacks
Inter-attack periods	Completely asymptomatic and normal growth	Symptom-free
Exclusion	Upper respiratory tract infections Cyclic neutropenia	Infections Malignancy Autoimmune diseases Other AIDs

[90]. Fever is not commonly reported. The clinical spectrum SAPHO syndrome is highly reminiscent of chronic recurrent multifocal osteomyelitis (CRMO), indeed considered by many experts the pediatric form of SAPHO syndrome. First line of treatment is usually represented by NSAIDs or glucocorticoids for osteoarticular manifestations. DMARDs, especially methotrexate, are employed in patients with predominant peripheral arthritis or as steroid-sparing agents. Several reports documented promising results for TNF inhibitors in patient resistant to first-line treatments [91]. Owing to the central pathophysiological role of IL-1, anakinra has been employed in the treatment of SAPHO syndrome, with reported efficacy both as first-line biologic and in cases resistant to TNFα inhibition [92].

NOD2-associated autoinflammatory disease

Nucleotide binding oligomerization domain containing 2 (NOD2)-associated autoinflammatory disease (NAID) is an AID characterized by recurrent fever, dermatitis, inflammatory arthritis, and gastrointestinal symptoms [93]. It has a strong genetic association with variants of NOD2, a gene encoding for an intracellular protein with N-terminal caspase recruitment domain. NAID is an adult-onset AID, with mean age at diagnosis around 45 years. Most cases are sporadic, but some familial cases have also been described [94]. The diagnosis of NAID is based on the presence of typical symptoms and NOD2 variants, most commonly IVS8^{+158} or compound IVS8^{+158} and R702W variants [94]. The main differential diagnosis is with Blau syndrome, an autosomal dominant pediatric disease characterized by recurrent fever, inflammatory rash, arthritis and granulomatous panuveitis [95]. The two diseases can be distinguished by the age of onset (early childhood for Blau syndrome), and absence of uveitis. Treatment of NAID is empirical, based on non-steroidal anti-inflammatory drugs and oral glucocorticoids. Case reports documented modest response to infliximab, canakinumab, and tocilizumab [94].

Autoinflammatory component in complex diseases

Deregulated inflammasome activation and secretion of proinflammatory cytokines appears to be part of the pathophysiological background of a variety of immune and non-immune-mediated diseases, ranging from sepsis to heart disease [13]. In the following paragraphs, we move from the field of rare diseases to that of common complex diseases, frequently encountered in adult clinics, in which therapeutic strategies targeting autoinflammation may, or do, represent a major clinical turning point.

Myocarditis

Myocarditis is defined by the WHO as an inflammatory disease affecting the myocardium, diagnosed through endomyocardial biopsy (EMB) using established histological, immunological, and immunohistochemical criteria [96]. If no infectious agents are identified on EMB and other known causes are excluded, myocarditis is defined as autoimmune [97]. Autoimmune myocarditis can occur as isolated cardiac involvement or in the context of systemic autoimmune or autoinflammatory disorders.

NLRP3 inflammasome was found upregulated in cardiomyocytes and infiltrating macrophages in a mouse model of viral myocarditis [98]. Moreover, intracellular aggregates of ASC and/or caspase-1, indirect proof of inflammasome formation, have been observed in EMB samples from patients with acute lymphocytic myocarditis [99]. Of note, the number of inflammasome-containing leukocytes per-field correlated with the degree of systolic dysfunction [99]. Moreover, experimental animal models of acute myocarditis demonstrated elevated expression of IL-1β [100] and dramatic response in terms of decreased myocardial inflammation and decreased mortality upon recombinant IL-1Ra administration [101].

These evidences strongly suggest that IL-1 inhibition has the potential to curb the heart inflammatory response and simultaneously ameliorate contractile dysfunction, as suggested by emerging evidence on the effectiveness of anakinra [102] and canakinumab [103], both of which dampened cardiac inflammation and improved contractility on some patients. Currently, a double-blind, randomized, phase IIb placebo-controlled clinical trial of anakinra in acute myocarditis is ongoing (ARAMIS-trial, https://clinicaltrials.gov/ct2/show/NCT03018834).

Idiopathic recurrent pericarditis

Pericarditis is a clinical manifestation often encountered as part of the clinical spectrum of inherited and complex autoinflammatory disorders. However, inflammation of pericardium can occur as an isolated, recurrent manifestation, with no clear genetic predisposition or identified infectious etiology. Idiopathic pericarditis represents almost 90% of the cases of acute pericarditis in developed countries and recurs

in up to 30% of patients [104]. Standard treatment with nonsteroidal anti-inflammatory drugs and colchicine is not always able to neutralize pericardial inflammation and prevent recurrences.

Inflammasome activation, long hypothesized to be the key driver of inflammation in acute pericarditis, has been recently demonstrated in human specimens of patient with acute pericarditis [105], reinforcing the biological basis of the striking response to selective IL-1 inhibition therapies frequently reported. Anakinra is highly effective in suppressing the inflammatory response and prevent recrudescence of the disease, as demonstrated in several case series and in one randomized clinical trial [106,107]. Rilonacept recently showed striking results both in resolving the acute attack of pericarditis and in preventing relapses in a phase III trial for idiopathic recurrent pericarditis [108]. Data on the efficacy of canakinumab are more limited but it is safe to expect analogous results. Hence, the role of interleukin-1 inhibition as a second-line treatment has been well established and is recommended in the 2015 ESC guidelines [109], while the potential use of selective IL-1 blockade as a first-line therapy needs yet to be thoroughly investigated.

Crystal arthropathies

Gout is the most prevalent inflammatory arthritis in the world. It is a chronic disease characterized by flares of mono/oligoarthritis due deposition of monosodium urate crystals in joints, in the presence of increased urate concentrations. Monosodium urate crystals directly activate the NLRP3 inflammasome and trigger the release of active IL-1β, with a contribution of free fatty acids, which likely account for the diet-related flares of gout [110]. Given the prominent neutrophil infiltrates detected during an acute flare, extracellular processing by neutrophil proteases likely contributes to the activation of IL-1β precursor in gouty joints, in a proteinase3-dependent, caspase-1-independent fashion [12]. Traditional options for managing acute gouty flares include colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), and steroids. However, a percentage of patients is refractory to standard treatment. Off-label use of anti-IL-1 agents is dramatically effective at dampening articular inflammation [111], while also resulting in reduced frequency of disease flares.

Characteristic response to IL-1 inhibition strategies is also encountered in pyrophosphate crystal arthritis. Calcium pyrophosphate deposition disease (CPPD), previously referred to as pseudogout, is characterized by long-lasting mono-/oligoarticular arthritis flares, resembling acute gouty attacks, due to calcium pyrophosphate crystals deposition in joints [112]. Once CPP crystals are generated, they induce tissue damage by activating components of the NLRP3 inflammasome [113] and by creating neutrophil extracellular traps [114]. Standard treatment of acute flares is represented by intra-articular glucocorticoids, NSAIDs or colchicine. The efficacy of anakinra has been reported in some treatment-refractory cases, resulting in both resolution of the acute attack and in increased inter-critical periods [115].

Ankylosing spondylitis

Ankylosing spondylitis (AS) is part of the spectrum of spondyloarthropathies, a group of diseases characterized by various degrees of inflammation of spina, peripheral joints, and entheses. The proposed pathophysiological mechanism behind AS involves interaction between gut microbiota and resident intestinal immune cells, which mediate recruitment of myeloid and lymphoid cells and their migration toward peripheral tissues, including joints, entheses, and lymph nodes, where they exert their proinflammatory action via IL-23, IL-17, and IL-22 secretion [116]. Historically, AS has been considered a disease primarily mediated by adaptive immune response, since autoreactive Th17 cells were identified as the primary source of IL-17 secretion in ankylosing spondylitis and in seronegative spondyloarthropathies in general [117]. However, more recent data are highlighting the pivotal role of the innate immune compartment in mediating disease onset and perpetrating the inflammatory process. First, recently a Turkish study detected a significant association between MEFV gene SNPs and the risk of AS. Moreover, patients harboring the variant of interest also had higher levels of IL-1β and IL-23 [118]. Second, a putative role for dysfunctional inflammasome activation can be inferred as several genes encoding for inflammasome components have been associated with an increased risk of AS [119]. Inflammasome activation may be involved in mediating gut inflammation and dysbiosis in AS, as supported by the increased expression of inflammasome components in the gut of HLA-B27 transgenic rats [120]. Third, genome-wide association studies documented a significant association between single nuclear polymorphisms in IL1 and IL1-related genes, particularly IL1A, and AS [121]. Interleukin-1 blockade with anakinra has been attempted in the treatment of AS: in a 3-month open label trial anakinra was administered to 9 patients with active AS not responsive to NSAIDs, with significant improvement documented in several clinical AS scores, accompanied by an improvement of enthesitis/osteitis measured with MRI [122]. However, these findings were not reproduced in a subsequent trial [123]. Taken together these data suggest that a subset of patients might benefit from IL-1 inhibition, specifically those with higher inflammatory indexes or carrying genetic variants involved in IL-1 production and activation.

The unique scenario of pregnancy

Pregnancy represents a unique challenge in the management of AIDs as numerous conventional DMARDs employed in AIDs therapy are not safe during pregnancy and should be avoided or withdrawn. Synthetic DMARDs such as methotrexate, mycophenolate mofetil, and cyclophosphamide are teratogenic and should be avoided months before conception and their use in childbearing age requires a specific consultation about procreational needs. On the other hand, colchicine and glucocorticoids are safe and well tolerated during pregnancy. Use of NSAIDs instead should be suspended at 20th weeks while biologic agents against TNFα, namely etanercept and certolizumab pegol may be continued throughout pregnancy due to the low transplacental active transfer. Other TNF inhibitors, IL-1 inhibitors and IL-6 inhibitors have limited data on safety during pregnancy and should be used only in cases refractory to all other treatments or when safer molecules are not indicated [124].

Autoinflammation in COVID-19

While vaccination campaigns are continuously demonstrating to be the best strategy to cope with Coronavirus disease 19 (COVID-19) burden, treatment of clinically overt COVID-19 remains a relevant challenge. To date, most recent advances in pharmacologic therapy against COVID-19 are

represented by monoclonal antibodies directed against SARS CoV2 (Severe Acute Respiratory Syndrome Coronavirus 2) "Spike" protein, able to significantly prevent progression towards symptomatic or severe COVID in selected patients in the early phases of infection. However, treatment with monoclonal antibodies is of little effect in hospitalized patients [125], who still represent a major clinical and public health challenge. It is becoming increasingly clear that the innate immune system is a critical player in host's response to SARS CoV2 infection. Severe patients display significantly increased levels of acute phase reactants (e.g. CRP, ferritin, fibrinogen) and pro-inflammatory cytokines [126]. Severe acute respiratory syndrome-related coronavirus (SARS-CoV) shows high homology with SARS-CoV2 and has been proven to activate the NLRP3 inflammasome through interaction with different viral proteins [127,128]. Increased levels of IL-1β, produced by inflammasome activation, as well as its response gene product, IL-1RA, are found to be elevated in the sera of COVID-19 patients [129]. Moreover, increased levels of IL-6, downstream IL-1β, have been demonstrated in acutely ill COVID19 patients, and correlated with SARS-CoV2 viraemia [130].

Targeting inflammation represents the mainstay of specific treatment in severe COVID-19. Indeed, the role of glucocorticoids in preventing adverse outcome in COVID patients requiring oxygen therapy has been thoroughly ascertained and is part of the standard of care [131]. Moreover, treatment with IL-6 inhibitors, especially tocilizumab, has provided an additional benefit in preventing all-cause mortality and need of mechanical ventilation [132]. Promising results have been reported for selective IL-1 inhibition as well. A meta-analysis of 6 studies (mostly observational) analyzing the effect of intravenous anakinra added to standard treatment in patients requiring oxygen supplementation documented a 50% reduction in 28-day mortality [133]. The only available double-blind, randomized placebo-controlled trial reported a statistically significant reduction in 28-day mortality and increased likelihood of clinical recovery [134]. As for other immunosuppressive strategies, careful patient selection is decisive to maximize the effect of anti-IL1 treatment. Indeed, most studies included patients with elevated inflammatory markers and requiring oxygen support, thus analyzing the subset of patients with a likely ongoing hyperinflammation. Overall, data on the efficacy of anti-IL-1 agents are promising but more robust evidence is warranted, especially to demonstrate superiority against anti-IL-6 biologics.

Finally, tranilast, a tryptophan analogue with a direct inhibitory action against NLRP3 [135], is currently undergoing randomized control trials in COVID-19 patients in China (registration number: ChiCTR2000030002 on the Chinese Clinical Trial Registry) and Iran (IRCT20200419047128N1 on the Iranian Registry of Clinical Trials).

Conclusions

Autoinflammatory disorders are ultimately caused by unchecked activation of the innate immune system. They represent a challenging clinical entity, especially in the adult population, due to the pleiotropy of their clinical phenotypes and the high rate of misdiagnosis. This review presents an overview of the clinical features, diagnosis, and treatment of the most important to-be-known AIDs. Dampening the inflammatory response represents the mainstay of treatment of AIDs. The clinical benefits of targeting hyperinflammation extends way beyond the treatment of autoinflammatory diseases: growing clinical evidence suggests a future critical role for therapies blocking the inflammasome and its products in non-immune-mediated diseases.

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Data availability

This article does not present new data.

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