

Expert Review

Autoinflammatory Diseases: A Review

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ABSTRACT. Autoinflammatory disease (AID) is a vast spectrum of disorders characterized by recurrent attacks of sterile inflammation. Since the first cloning of the familial Mediterranean fever gene in 1997, there has been a rapid rate of discovery of new AIDs. As of 2022, there have been 485 inborn errors of immunity documented by the International Union of Immunological Societies, for which many display aspects of autoinflammation. The pathophysiology of AIDs is complex. Although many are caused by rare mutations in genes that govern innate immunity, others are polygenic, where disease expression is thought to be triggered by environmental factors in genetically predisposed hosts. AIDs range in prevalence from common entities like gout to ultrarare monogenic diseases. Whereas AIDs were initially studied in pediatric populations, it is now apparent that they can present in adulthood and even in the elderly. AIDs can be clinically challenging given their rarity, as well as the heterogeneity in presentation and underlying etiology. Although the care of AIDs can span medical disciplines, the rheumatologist often plays a central role given the inflammatory nature of these illnesses. In this review, we explore the current understanding of the pathophysiology of these complex conditions and propose a classification system for AIDs. We place an emphasis on AIDs that present to the adult rheumatologist and discuss important AIDs that can mimic more classic rheumatic diseases such as systemic lupus erythematosus and inflammatory arthritis. Finally, we offer an approach to the clinical assessment, diagnosis, and management of AIDs.

Key Indexing Terms: autoinflammation, autoinflammatory diseases, genetics, innate immunity, periodic fevers, recurrent fevers

Introduction

Historically, the term “autoinflammation” was coined at the turn of the century with the identification of the monogenic disorders familial Mediterranean fever (FMF) and tumor necrosis factor (TNF) receptor–associated periodic syndrome (TRAPS).^{1,2} The concept of autoinflammatory diseases (AIDs) has evolved with time and is currently understood as dysregulation of the innate immune system that occurs in predisposed hosts, sometimes with secondary activation of adaptive immunity, resulting in inappropriate inflammation.³

The advent of next-generation sequencing has demonstrated that many AIDs arise from single gene mutations in components of the innate immune system. There has been a rapid pace of discoveries in AIDs, with 17 described in the past 2 years (Table 1). These discoveries have shed light on the complex

immunopathophysiology of rare monogenic AIDs, as well as more common polygenic conditions such as adult-onset Still disease (AOSD) and periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA).

Clinically, AIDs typically present with multifaceted symptoms such as fever, joint pain, abdominal pain, and ocular and skin inflammation. The exact incidence and prevalence of AIDs varies widely depending on the exact condition and population studied. Although AIDs are generally perceived to be rare, the prevalence of some AIDs can be relatively more common, such as FMF being present in up to 1:400 individuals in certain ethnicities.⁴ Although most AIDs were initially described in pediatric cohorts, we are also increasingly recognizing adults presenting with AIDs.^{5–8} Some may have had childhood-onset symptoms and experienced significant delays in diagnosis, whereas others have true adult-onset disease. This review places a focus on AIDs in adults, which can be diagnostically challenging for physicians due to the complex presentations of these diseases.

Pathophysiology

Autoimmune and autoinflammatory conditions are often confused with each other as both result from the inappropriate activation of the immune system. Autoimmune diseases are predominantly driven by T and B lymphocytes that recognize and react to self-antigens,⁹ and usually occur in the setting of several other simultaneous lapses in immune tolerance.

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Table 1. Heat map of autoinflammatory syndromes discussed in the main text.

Category	Autoinflammatory Condition	Gene	Clinical Features																	
			Fever	Joint	Rash	Ulcer	Eye	GI	CNS	Vasculitis	Lung	Bone	HLH	Infection	Lipodys- trophy	Thrombo- cytopenia	DD	Other		
Inflammasomopathies	FMF	<i>MEFV</i>																		
	PAPA	<i>PSTPIP1</i>																		
	CAPS	<i>NLRP3</i>																		
	Majeed syndrome	<i>LPIN2</i>																		Anemia
	<i>NLRP12</i> -related AID	<i>NLRP12</i>																		
	<i>Dpp9</i> deficiency ^r	<i>Dpp9</i>																		Eczema, allergies, fair hair, short stature, dysmorphic lymphoma, elevated IgD
	<i>PMTK</i> -related AID ^a	<i>PMTK</i>																		
	IL-1 pathway DIRA	<i>DIRA</i>																		
	IL-18 pathway AIFEC	<i>AIFEC</i>																		
	FCAS4	<i>FCAS4</i>																		
X-linked proliferative disease 2		<i>NLRCA</i>																		
		<i>NLRCA</i>																		
		<i>NLRCA</i>																		
<i>NLRP1</i> -associated autoinflammation with arthritis and dyskeratosis	IL-18BP deficiency	<i>IL18BP</i>																		Viral hepatitis
		<i>NLRP1</i>																		
Interferonopathies	AGS	<i>TREX1</i> , <i>SAMHD1</i> , <i>RNASEH2A</i> , <i>RNASEH2B</i> , <i>ADAR1</i> , <i>IFIH1</i>																		Dyskeratosis Hepatitis, chilblains
<i>STAT2</i> gain-of-function disease		<i>STAT2</i>																		Brain calcifications
	Pseudo-TORCH	<i>USP18</i>																		Brain calcifications
SMS	SAVI	<i>TMEM173</i>																		
		<i>IFIH1</i> , <i>DDX38</i>																		Dental dysplasia, aortic calcification
PRAAS		<i>PSMB4</i> , <i>PSMB3</i> , <i>POMP</i> , <i>PSMG</i> , <i>PSMB8</i> , <i>PSMB9</i> ^a , <i>PSMB10</i>																		
COPA syndrome		<i>COPA</i>																		Kidney dysfunction
	OPAID ^b	<i>OAS1</i>																		FTT
<i>ATAD3A</i> deficiency ^a		<i>ATAD3A</i>																		Dystonia, thyroiditis, HCM calcifications, HCM
																				Renal disease
<i>ZNFY1</i> deficiency ^a		<i>ZNFY1</i>																		

Table 1. Continued.

Category	Autoinflammatory Condition	Gene	Clinical Features														
			Fever	Joint	Rash	Ulcer	Eye	GI	CNS	Vasculitis	Lung	Bone	HLH	Infection	Lipodys-Thrombotrophy	DD	Other
NF-κB-opathies	Haploinsufficiency of A20	<i>TNFAIP3</i>															
	RAID	<i>RELA</i>															
	<i>RIPK1</i> deficiency	<i>RIPK1</i>															
	<i>RIPK1</i> gain-of-function	<i>RIPK1</i>															
	Orolipemia	<i>FAM105B</i>															
	Blau syndrome	<i>NOD2</i>															
	<i>CARD14</i> -mediated pustular psoriasis	<i>CARD14</i>															
	<i>SYK</i> -associated AID ^a	<i>SYK</i>															
	<i>TBKI</i> deficiency ^r	<i>TBKI</i>															
	DEX ^a	<i>ELF4</i>															
ROSAH ^a	<i>ALPK1</i>																
Cytoskelelopathies	NDAS ^a	<i>IKBKKG</i>															
	NOCARH	<i>CDC42</i>															
	<i>ARPC1B</i> deficiency	<i>ARPC1B</i>															
	<i>NCKA1P1</i> deficiency	<i>NCKA1P1</i>															
	PFIT	<i>WDR1</i>															
Enzymatic deficiencies	MKD	<i>MVK</i>															
	DADA2	<i>CECRI</i>															
	SIFD	<i>TRNT1</i>															
	PLAID	<i>PLCG2</i>															
	APLAID	<i>PLCG2</i>															
Other	TRAPS	<i>TNFRSF1A</i>															
	VEXAS	<i>UBA1</i>															
	<i>C2orf69</i> deficiency ^a	<i>C2orf69</i>															
	<i>HCK</i> -associated AID ^a	<i>HCK</i>															
	IL-33 gain-of-function ^a	<i>IL33</i>															
DPM ^a	<i>STAT6</i> gain-of-function ^a	<i>STAT6</i>															
	DPM ^a	<i>STAT4</i>															
	LAV1 ^a	LYN															

Autoinflammatory syndromes are arranged by pathway with colored boxes representing main clinical features. It is important to note that many conditions may fall into multiple categories and that this heat map is a representation of the predominant mechanism at play. ^a Conditions discovered since 2021. AGS: Aicardi-Goutières syndrome; AID: autoinflammatory disease; AIFEC: autoinflammation with infantile enterocolitis; APLAID: autoinflammation and PLAID; CAPS: cryopyrin-associated periodic syndrome; CNS: central nervous system; COPA: coatomer protein subunit alpha; DADA2: deficiency of adenosine deaminase 2; DD: developmental delay; DEX: deficiency of ELF4, X-linked; DIRA: deficiency of IL-1 receptor antagonist; DPM: disabling pansclerotic morphea; DWS: Dandy-Walker syndrome; FCAS4: familial cold autoinflammatory syndrome 4; FFMF: familial Mediterranean fever; FTT: failure to thrive; GI: gastrointestinal; HCM: hypertrophic cardiomyopathy; HLH: hemophagocytic lymphohistiocytosis; IL: interleukin; LAV1: Lyn kinase-associated autoinflammatory syndrome 4; liver fibrosis; MKD: mevalonate kinase deficiency; NDAS: NEMO deleted exon 5 autoinflammatory syndrome; NF: nuclear factor; NOCARH: neonatal onset of pancytopenia, autoinflammation, rash, and hemophagocytosis; OPAID: *OAS1*-associated polymorphic autoinflammatory immunodeficiency disorder; PAPA: pyogenic arthritis, pyoderma gangrenosum, and acne syndrome; PFIT: periodic fevers, immunodeficiency, thrombocytopenia; PLAID: *PLCG2*-associated antibody deficiency and immune dysregulation; PRAAS: proteasome-associated autoinflammatory syndromes; RAID: *RELA*-associated inflammatory disease; ROSAH: retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis, and migraine headaches; SAVI: stimulator of IFN genes-associated vasculopathy with onset in infancy; SIFD: sideroblastic anemia, immunodeficiency, fevers, and developmental delay; SMS: Singleton-Merton syndrome; STAT: signal transducer and activator of transcription; TORCH: toxoplasmosis, other, rubella, cytomegalovirus, and herpes simplex; TRAPS: tumor necrosis factor receptor-associated periodic syndrome; VEXAS: vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

In contrast, AIDs are driven by innate immune cells of the myeloid lineage such as macrophages, monocytes, neutrophils, and dendritic cells.⁹ Disease often results from defects in germline-encoded elements of innate cells.¹⁰ These include pattern recognition receptors, which recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), signal transduction molecules, or intracellular effector structures (such as inflammasomes) that produce inflammatory cytokines. Gain-of-function (GOF) variants in positive regulators, or loss-of-function (LOF) variants in negative regulators in signal transduction pathways of innate leukocytes, may result in inappropriate immune activation. Autoimmunity and autoinflammation are compared and contrasted in Table 2.

The multifaceted nature of immune dysregulation disease

The components of the immune system are densely intertwined. Depending on the pathways affected, autoinflammation can overlap with other major axes of immunity including autoimmunity, atopy, immune deficiency, or lymphoproliferation.¹¹

Autoimmunity represents a reaction to harmless endogenous self-antigens. Although the effectors are B and T lymphocytes, their activation is often initiated by innate immune cells and components. On the other hand, some AIDs characterized by high levels of type I interferons (IFNs) have concurrent T and B cell activation with autoantibody production.⁹ These include the monogenic diseases stimulator of IFN genes (STING)-associated vasculopathy with onset in infancy (SAVI) and Aicardi-Goutières syndrome (AGS), and polygenic

disorders such as systemic lupus erythematosus (SLE) and juvenile dermatomyositis (JDM).¹²

Atopy represents a reaction to harmless exogenous antigens and can be seen in numerous autoinflammatory disorders. For example, defects in cytoskeleton components and regulators such as *WASP*, *WDR1*, *ARPC1b* can lead to complex immune dysregulation syndromes manifesting in autoimmunity, autoinflammation, immune deficiency, hematologic abnormalities, as well as atopy.^{13,14}

Immune deficiency may be a seemingly paradoxical component of autoinflammatory conditions. The nuclear factor (NF)- κ B pathway is integral to numerous immune processes, and dysfunction can lead to simultaneous inflammation and immune deficiency.⁹ The same genetic variant can also affect leukocytes differently, such as that seen in linear ubiquitin assembly complex (LUBAC) deficiency.¹⁴ The loss of LUBAC in innate monocytes results in enhanced proinflammatory cytokine production, whereas the same mutation in adaptive lymphocytes dampens NF- κ B activation, resulting in immune deficiency.^{15,16}

Immune dysregulation diseases can sometimes exhibit nonmalignant lymphoproliferation. This may be caused by LOF mutations in genes that mediate lymphocyte apoptosis, such as *CASP8/10* or *FAS/EASL*.⁹ GOF mutations in genes that promote lymphoproliferation such as *NRAS* and *KRAS* can also lead to a similar phenotype.¹⁷ Patients with inappropriate lymphoproliferation can display autoimmune manifestations due to autoreactive lymphocytes that have escaped deletion.

Table 2. A comparison of autoimmunity and autoinflammation.

		Autoinflammation	Autoimmunity
Etiology	Genetics	Mutations in germline encoded elements of innate immune system Monogenic > polygenic	Generation of self-reactive lymphocyte receptors by somatic recombination Polygenic > monogenic
	Immunology	Failure of autoinhibitory mechanisms \pm constitutive inflammatory cytokine signaling	Failure of immune tolerance and lymphocyte-driven tissue damage Self-reactive lymphocytes and autoantibodies
Demographics	Age of onset	Pediatric > adult	Adult > pediatric
	Family history	+++	+/-
Clinical features	Triggers	Stress, infections, cold, physical exertion or trauma, vaccination, menses, pregnancy	Stress, infections, pregnancy
	Recurrent fevers	+++	Usually not the presenting complaint
	Ocular	Conjunctivitis, periorbital edema	Episcleritis/scleritis, retinitis, iritis
	Oral/genital ulcers	+++	+
	Gastrointestinal	Colitis in children, peritonitis	IBD in adults
	Bone inflammation	++	-
	Other	Rashes, synovitis, neurologic and renal involvement	
Tests	Elevated inflammatory markers	During attacks	Low grade at baseline
	Autoantibodies	-	+++
	Yield of genetic testing	+++	-
Response to treatment	Colchicine, IL-1 blockers	+++	+
	Antimetabolites ^a , HCQ, CSA, tacrolimus	-	+++
	JAKi/TNFi, steroids		+++

+ and - indicate presence and absence, respectively. ^a Leflunomide, mycophenolate, methotrexate, azathioprine. CSA: cyclosporine A; HCQ: hydroxychloroquine; IBD: inflammatory bowel disease; IL: interleukin; JAKi: Janus kinase inhibitor; TNFi: tumor necrosis factor inhibitor.

Case vignettes

Here we present 3 unique cases that represent the most common classes of autoinflammatory diseases.

Case 1. A 40-year-old female individual born to nonconsanguineous Turkish parents presented with a lifelong history of episodic fevers > 38 °C, concurrent knee and ankle arthritis, and peritonitis. The frequency of episodes varied from weekly to monthly. The fevers lasted 2 to 3 days, but the pain and fatigue would resolve over a week. She had multiple emergency room visits for this over the years and received an appendectomy at the age of 18, which did not resolve her symptoms. Nonsteroidal antiinflammatory drugs (NSAIDs) did not help and occasionally she was treated with opioids. She had an uncle who died of unexplained renal failure at age 40. She was eventually evaluated at a specialist pediatric center at 19 years old. Her physical examination was unremarkable. Investigations revealed normal complete blood count (CBC), liver and renal function tests, abdominal radiograph, and ultrasound. She exhibited elevated inflammatory markers including a maximal erythrocyte sedimentation rate (ESR) of 102 mm/h and C-reactive protein (CRP) of 127 mg/L during flares. Single gene testing for *MEFV* revealed homozygous variants c.2080A>G (p.Met694Val), which led to her diagnosis of FMF. Subsequent urine albumin-creatinine ratio was elevated at 58.3 and renal biopsy revealed amyloidosis. She could not tolerate colchicine due to diarrhea and was started on anakinra 100 mg subcutaneously (SC) daily, which significantly reduced the frequency and severity of flares. She remained clinically well at 1-year follow-up, with stable proteinuria.

Case 2. An 18-year-old male individual was referred to an adult rheumatologist for ongoing management. He was initially seen at the age of 7 for possible vasculitis.¹⁸ At the age of 1, he developed intermittent conjunctivitis and painful chilblains over the extremities and helices of the ears (Figure 1C). He had developmental delay in gross and fine motor activities, speech, and learning. His Amish parents were nonconsanguineous and of Swiss-German background. There were no similar symptoms in family members. On examination, height and weight were below the third percentile. Scattered erythematous macules and plaques were present on the dorsum of his hands. The helices of both ears were crusted and ulcerated. There was bilateral swelling of the toes. Over the next decade, his chilblains worsened and he developed symmetrical small joint nonerosive polyarthritis. Magnetic resonance imaging (MRI) of the brain was performed due to his developmental delay and was unremarkable. Laboratory testing showed negative antinuclear antibodies (ANAs), antineutrophil cytoplasmic antibodies (ANCA), and rheumatoid factor. He had intermittent mild neutropenia, persistent elevation of ESR ranging from 13 to 55 mm/h and a consistently normal CRP. He had elevations in IgG (maximum 18.7 g/L) and IgA (maximum 4.2 g/L). Panel testing for AGS in 2014 did not reveal any variants in *TREX1* or *RNASEH2A/B/C*. Years later, exome sequencing revealed a homozygous variant in *SAMHD1* (c.1411-2 A>C) consistent with type 5 AGS. Both parents were heterozygous for this variant. His polyarthritis did not respond to NSAIDs, intraarticular corticosteroids, or methotrexate. Etanercept was eventually started, with improvement of arthritis.

Case 3. A 29-year-old White female individual presented with monthly oral ulcers since early childhood and vaginal ulceration at the age of 20.¹⁹ At age 25, she developed recurrent facial rashes, arthralgias, myalgias, and subjective fevers (< 38 °C) occurring every 2 months and lasting 2 weeks. Her physical examination was unremarkable. Investigations revealed elevated CRP ranging from 57 to 231 mg/L during flares. Her CBC, creatinine, urinalysis, ANAs, and liver enzymes were normal or negative. Workup for infection was negative. She was diagnosed previously with Behçet disease (BD) and despite methotrexate 20 mg SC weekly, she continued to have flares of severe oral ulcerations leading to hospitalizations requiring intravenous corticosteroids. A targeted gene panel revealed a heterozygous variant of uncertain significance in *NLRP3* (p.Thr954Met) associated with cryopyrin-associated periodic fever syndrome (CAPS), which was inconsistent with the patient's phenotype. Further genetic sequencing as part of a research program revealed a heterozygous variant in *RELA* (c.1153C>T, p.Gln385*). On a closer review of her family history, several other family members across 4 generations were identified who shared similar symptoms, as well as the same variant on segregation analysis. They were diagnosed with *RELA*-associated inflammatory disease (RAID). The patient was switched to colchicine and etanercept, which resolved her oral ulcers.

Classification

There are currently different classification schemes that categorize AIDs by manifestations as well as by pathophysiology.²⁰ Multifactorial disorders are driven by multiple genes exerting small individual effects, combined with environmental factors such as infection or trauma.¹⁴ In contrast, monogenic disorders are driven by single highly penetrant and usually rare gene variants. Monogenic disorders may result from a pathogenic variant carried by all cells (germline) or by only some (somatic), in which the variant arises following the earliest zygotic divisions in embryogenesis.²¹ Somatic and germline disorders can then be further classified according to the predominant signaling pathway or immune components that are dysregulated, such as the inflammasome, IFN, or NF- κ B pathways.²⁰

Major classes of monogenic AIDs. We describe the main classes of germline monogenic AIDs below according to the mechanism of innate immune pathway activation. Note that these are generalized classifications, whereas in reality, AIDs can fall into multiple different categories due to crosstalk between immune pathways. For example, mevalonate kinase deficiency (MKD) may fall under inflammasomopathies as well as enzyme deficiencies. The regulation of inflammasomes, IFN, and NF- κ B are depicted in Figure 2.

- **Inflammasomopathies.** The inflammasome is a cellular structure that senses danger signals reflective of pathogen infiltration or tissue damage.²² Inflammation is induced through the aggregation of inflammasome subunits and activation of caspase-1, which converts prointerleukin (IL)-1 β and pro-IL-18 into their active forms for release. Different inflammasomes exist, which are distinguished and named according to their sensor subunit.

Case 1 above exemplifies a typical inflammasomopathy that



Figure 1. Clinical images of select AIDs. Patient consent was obtained to publish these images. (A) A 68-year-old man with Sweet syndrome related to VEXAS. (B) A 21-month-old girl with urticaria-like lesions characteristic of Muckle-Wells syndrome. (C) A 10-year-old boy with Aicardi-Goutières syndrome (compound heterozygous variants in *SAMHD1*) showing chilblain lesions of the hands and pinna. (D) Severe psoriatic rash in a 2-year-old boy with DIRA. (E) Extensor tenosynovitis in a 3-year-old girl with Blau syndrome. (F) A glomerulus with segmental mesangial amyloid deposition; salmon pink staining of amyloid with Congo red in a 10-year-old boy with TRAPS. (G) Purpuric subcutaneous nodules in a 15-month-old boy with DADA2. AID: autoinflammatory disease; DADA2: deficiency of adenosine deaminase 2; DIRA: deficiency of IL-1 receptor antagonist; TRAPS: tumor necrosis factor receptor-associated periodic syndrome; VEXAS: vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

arises from pathogenic variants in genes encoding inflammasome components or proteins that directly or indirectly interact with inflammasomes. Typical clinical features include recurrent fevers, neutrophilic rashes, arthritis, and serositis.²³ Some inflammasomopathies are predominantly IL-1-mediated, and so they respond to IL-1 inhibition. These include FMF, CAPS, Majeed syndrome, and *NLRP12*-related AID. Some conditions involve the IL-1 pathway but are not technically inflammasomopathies given the absence of mutations affecting the inflammasome itself. Examples include deficiency of IL-1 receptor antagonist (DIRA; Figure 1D) caused by loss of endogenous IL-1 inhibitor, and X-linked inhibitor of apoptosis protein (XIAP) deficiency, whereby loss of XIAP results in disinhibited *NLRP3* inflammasome signaling.^{24,25}

Some inflammasomopathies can also present with hemophagocytic lymphohistiocytosis and are characterized by elevated IL-18²⁶ such as *NLRC4* GOF disease.²⁶⁻²⁸

• **Interferonopathies.** The type 1 IFNs include IFN- α and IFN- β , and signal through the IFN receptor. Interferonopathies arise from mutations in genes that regulate the sensing and processing of nucleic acid, resulting in the inappropriate and excessive production of type 1 IFN.^{12,29} These include AGS (*TREX1*, *SAMHD1*, *RNA5EH2A*, *RNA5EH2B* and *ADAR1*), *STAT2* GOF, *USP18*-related pseudo-toxoplasmosis, other, rubella, cytomegalovirus, and herpes simplex (TORCH), SAVI (*TMEM173*), Singleton-Merton syndrome (*IFIH1* and *DDX38*), and coatmer protein subunit alpha (COPA) syndrome.^{12,30} Further, mutations in genes (such as *PSMB8*, *PSMB10*, *PSMC5*, *POMP*) that impair proteasome function can lead to the accumulation of aberrant proteins and the unfolded protein response, which drives IFN signaling.³¹⁻³³

Case 2 discussed above exemplifies a typical interferonopathy. Although clinical manifestations vary, classic features of interferonopathies include panniculitis, lipodystrophy, leukocytoclastic vasculitis, interstitial lung disease, and intracranial calcifications.¹² Acute-phase reactants (eg, CRP) may not be

elevated. The IFN gene expression score is available at some research centers and can be diagnostically helpful by quantifying the expression level of genes induced by type 1 IFN.³⁴ Treatment with Janus kinase (JAK) inhibitors has been effective in these AIDs.^{35,36}

• **NF- κ B-opathies.** The NF- κ B pathway is central to many inflammatory processes. It consists of upstream receptors, intermediary signaling complexes, and transcription factors that translocate into the nucleus to drive proinflammatory gene expression. Some NF- κ B-opathies, such as haploinsufficiency of A20 (*HA20*), arise from LOF mutations in enzymes that normally inhibit NF- κ B activation.³⁷ Other examples of AIDs driven by NF- κ B dysregulation include RAID, *RNF31* deficiency, *RIPK1* deficiency or GOF, otulipenia (*FAM105B*), Blau syndrome (*NOD2*), and *CARD14*-mediated pustular psoriasis (PsO).^{19,38}

Case 3 above exemplifies a typical NF- κ B-opathy. Due to the ubiquitous nature of the NF- κ B pathway, the spectrum of clinical manifestations is broad but typically includes rashes, mucocutaneous ulceration, and arthritis.³⁹ More serious features can also occur such as uveitis, inflammatory bowel disease, and immune deficiency. In addition to corticosteroids, TNF inhibitors (TNFi) can be effective.³⁹

• **Cytoskelopathies.** Beyond the orchestration of leukocyte mobility and phagocytosis, the actin cytoskeleton is also critical in forming immune synapses and thus in regulating inflammatory responses.⁴⁰ Mutations in genes that regulate the actin cytoskeleton hence lead to cytoskelopathies (sometimes referred to as actinopathies) marked by frank immune dysregulation. Autoinflammatory conditions under this category include neonatal onset of pancytopenia, autoinflammation, rash, and hemophagocytosis (NOCARH), as well as deficiencies of *ARPC1B*, *NCKAP1*, and *WDR1*. Overlapping with some inflammasomopathies, pyogenic arthritis, pyoderma gangrenosum, and acne syndrome (PAPA) and cytoskelopathies mediated by *WDR1* and *CDC42* mutations can also exhibit increased IL-18.⁴¹⁻⁴³

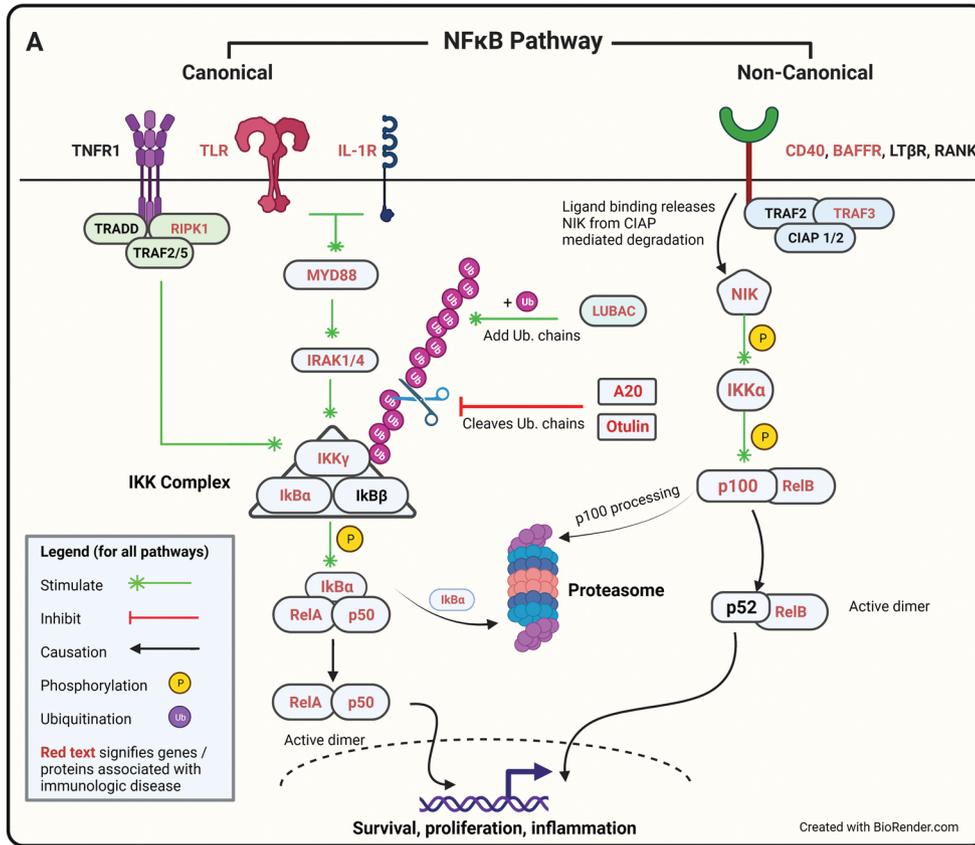


Figure 2A: The NFκB pathway is important in regulating immunity and inflammation, but also cell survival, growth and development. It is mediated by five major components: RelA (p65), RelB, c-Rel, NFκB1 (p105/50), and NFκB (p100/52).

The **canonical** pathway is activated by diverse stimuli such as TNF receptor superfamily members, pattern recognition and cytokine receptors, and B and T cell receptors (not shown). Signaling converges onto the IKK complex which phosphorylates IκBα leading to ubiquitin mediated destruction in the proteasome. This releases the active RelA/p50 dimer to translocate into the nucleus and bind the κB enhancer, driving inflammatory gene expression.

Throughout, receptor signaling complexes (such as IKK) are stabilized by long chains of Met-1 linked ubiquitin generated by LUBAC. This is countered by deubiquitinases such as A20 and Otulin, which cleave ubiquitin chains, destabilizing receptor signaling complexes and dampening pathway activation.

The **non-canonical** pathway differs in that signalling does not converge on the IKK complex. It is activated in response to a more selective set of stimuli namely CD40, BAFFR, LTβR, and RANK. Without stimulation, the central component NIK is tagged for ubiquitin mediated destruction by the TRAF2-3/CIAP1-2 complex. Upon stimulation, this complex is recruited to the membrane, releasing NIK to phosphorylate and activate downstream components leading to the translocation of RelB/p52 active dimers into the nucleus to drive gene expression.

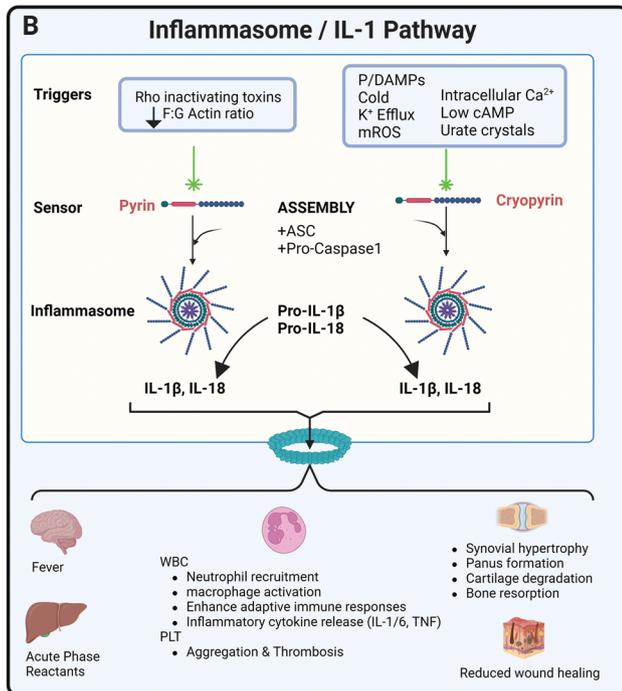


Figure 2B: The priming phase (not shown) occurs when the canonical NFκB pathway is activated, leading to expression and generation of inflammasome components and pro-IL-1β. Upon further stimulation, the activation phase is triggered (above). ASC and pro-caspase 1 are assembled with the sensor molecule into the mature inflammasome which then processes pro-IL-1β and pro-IL-18 into its active cytokine forms. There are many inflammasomes beyond pyrin and cryopyrin such as NLRP1, NLRP2, NLRP4, AIM2, IFI-16, and RIG-1 (not shown). Mutations in inflammasome sensors can lead to autoinflammatory disease.

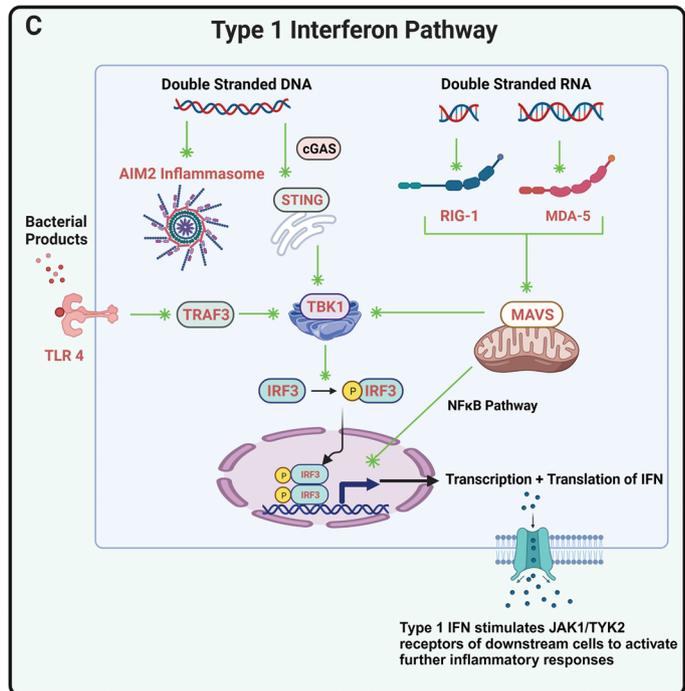


Figure 2C: The interferon pathway is activated by the accumulation of nucleic acid in the cytosol. Double stranded DNA is sensed by cGAS which generates cGAMP and stimulates downstream STING (endoplasmic reticulum). STING activates TBK1 (golgi) which phosphorylates IRF3 leading to its nuclear translocation to drive expression and release of type 1 interferon. This subsequently stimulates JAK1/TYK2 receptors of downstream cells to signal through the JAK/STAT pathway (not shown) to promote further inflammatory gene expression. In addition to RIG-1, MDA-5, AIM2, and cGAS, there are numerous other sensors of nucleic acid such as endosomal TLRs, IFI-16, ZBP1 (not shown).

Figure 2. The regulation of NF-κB, IL-1, and type 1 IFN pathways and associated pathologies. AIM2: absent in melanoma 2; ASC: adaptor molecule apoptosis-associated speck-like protein containing a CARD; BAFFR: B cell-activating factor receptor; cAMP: cyclic adenosine 3,5-monophosphate; cGAMP: cyclic

guanosine monophosphate–adenosine monophosphate; cGAS: cyclic GMP-AMP synthase; CIAP: cellular inhibitor of apoptosis; IFI: interferon γ -inducible protein; IFN: interferon; IKK: I κ B kinase; IL: interleukin; IRF: interferon regulatory factor; JAK: Janus kinase; LTBR: lymphotoxin- β receptor; LUBAC: linear ubiquitin assembly complex; MDA: melanoma differentiation–associated protein 5; mROS: mitochondrial reactive oxygen species; NF: nuclear factor; NIK: NF- κ B-inducing kinase; P/DAMP: pathogen/damage associated molecular patterns; PLT: platelet; RANK: receptor activator of NF- κ B; RIG: retinoic acid-inducible gene; STING: stimulator of IFN genes; TBK: TANK-binding kinase 1; TLR: Toll-like receptor; TNF: tumor necrosis factor; TNFR: tumor necrosis factor receptor; TRADD: tumor necrosis factor receptor–1 associated death domain; TRAF: tumor necrosis factor receptor–associated factor; TYK: tyrosine kinase; WBC: white blood cell; ZBP: Z-DNA-binding protein.

• *Enzymatic deficiencies and intersection with metabolism.* LOF variants in genes that encode enzymes can lead to AID. These include MKD, deficiency of adenosine deaminase 2 (DADA2), sideroblastic anemia, immunodeficiency, fevers and developmental delay (SIFD), purine nucleoside phosphorylase (PNP) deficiency, *PLCG2*-associated antibody deficiency and immune dysregulation (PLAID), and the related autoinflammation and PLAID (APLAID) syndrome, which has a prominent auto-inflammatory component. The mechanism by which enzyme deficiencies lead to autoinflammation varies depending on the enzyme involved, but it generally remains an area under active investigation.

Somatic monogenic AID

Mosaic diagnoses are important to consider in adults as they present later in life, sometimes with attenuated or atypical symptoms. Somatic mosaicism in *NLRP3* could account for up to 35% of patients with CAPS.^{44,45} Mosaicism in *NLRCA* causes a late-onset autoinflammatory disease characterized by arthritis, recurrent fever, and skin rashes.⁴⁶ Mosaicism has also been reported in Blau syndrome, TRAPS, and SAVI.⁴⁷⁻⁴⁹

Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome, a new multisystem inflammatory condition first reported in 2020, is caused by somatic variants in *UBA1*.⁵⁰ Typical autoinflammatory symptoms including fever, chondritis, eye inflammation, myocarditis, colitis, and arthritis are observed, in addition to neutrophilic dermatosis and vasculitis. Hematologic abnormalities are also common, including cytopenias, myelodysplastic syndrome, multiple myeloma, and vacuoles in myeloid cells on bone marrow aspirates. VEXAS should be suspected in elderly male individuals with autoinflammation and macrocytic anemia. Morbidity and mortality with this condition is high, as the only definitive therapy is bone marrow transplant. Treatment otherwise consists of corticosteroids and immunosuppression as used in more common rheumatic diseases. Hypomethylating agents such as azacytidine has shown efficacy in some cases of VEXAS.⁵¹ We anticipate many more somatic monogenic autoinflammatory diseases will be discovered in the future.

Polygenic diseases

AOSD is a systemic inflammatory disorder and the adult counterpart of systemic juvenile idiopathic arthritis (JIA). The presentation and diagnosis are usually familiar to adult rheumatologists and are discussed elsewhere.⁵² The pathophysiology is multifactorial and is thought to involve the activation of Toll-like receptors (TLRs) and inflammasomes in monocytes. This can lead to the release of IL-1 and IL-18, which can result in

macrophage activation syndrome, an important complication to monitor for, given its high morbidity and mortality.^{53,54} Systemic JIA is similar in presentation and pathophysiology, but occurs in children.⁵⁵ Systemic JIA differs from the other subtypes of JIA in that its epidemiology, clinical features, and pathogenesis resemble a systemic AID more than a classic autoimmune arthritis. Studies have shown that the genetic architecture of systemic JIA is unique and differs from other subtypes of JIA, further supporting a shift in how it may be classified and conceptualized in the future.⁵⁶

PFAPA syndrome occurs primarily in young children, although it is being increasingly recognized as an important cause of fever of unknown origin in adults as well.⁵⁷⁻⁵⁹ Although family clustering of periodic fevers can occur in PFAPA, a monogenic etiology has not been found.¹⁴ Diagnosis is ultimately clinical but can be guided by the Marshall or Eurofever criteria. These specify the clockwork periodicity of fevers and cardinal features specified in the syndrome name, duration of 3 to 6 days, exclusion of other conditions, elevated inflammatory markers during flares, and normalization of clinical and laboratory abnormalities between flares.^{60,61} Diagnosis is based on the clockwork periodicity of fevers and cardinal features specified in the syndrome name, duration of 3 to 6 days, exclusion of other conditions, elevated inflammatory markers during flares, and normalization of clinical and laboratory abnormalities in between. Prednisone is helpful in aborting attacks, and colchicine may reduce the frequency and severity of attacks. Tonsillectomy can be curative in some cases.

Some patients with systemic inflammation do not have an identifiable monogenic cause and do not fit the criteria for AOSD or PFAPA.^{62,63} There are various diagnostic labels for this patient population in the literature, such as the syndrome of undifferentiated recurrent fever (SURF), which are applicable when recurrent fevers are the predominant feature.⁶² Otherwise, these patients are also described as having unclassified systemic autoinflammatory disease (USAID). Age of onset is variable, and adult-onset disease is common. These patients often present with flares of inflammation in various organ systems and may have milder ongoing symptoms between attacks. In our cohort (An, unpublished data, June 2024), most patients report a trigger that preceded disease onset or clinical worsening. Some, but not all, have elevated inflammatory markers. Common variants in autoinflammatory genes (eg, *MEFV*, *NOD2*, *NLRP3*) are sometimes uncovered, of which their pathogenic contribution remains unclear.⁶³ Some studies suggest that these variants of uncertain significance may be risk factors that predispose an individual to developing autoinflammation.⁶⁴ Depending on the phenotypic manifestations, trials of colchicine, disease-modifying antirheu-

matic drugs, corticosteroids (short courses), IL-1 inhibitors, or TNFi may be beneficial.^{62,65}

Gout is an inflammatory malady well known to adult rheumatologists that spans the domains of metabolism and autoinflammation. It is a polygenic condition, and polymorphisms have been identified in genes that regulate urate production, excretion, and innate immunity. Specifically, these include variants in genes encoding TLRs, *CARD8*, *IL1 β* , *PPARGC1B*, and components of the NLRP3 inflammasome.⁶⁶ Its pathogenesis involves monosodium urate (MSU) crystals acting as DAMPs, and activating leukocytes through TLR2 and TLR4 leading to endocytosis and subsequent activation of the NLRP3 inflammasome and release of active IL-1 and IL-18.^{67,68} Like many other AIDs, gout flares are self-limited. This process of self-resolution has been linked to the production of neutrophil extracellular traps that sequester MSU crystals and cytokines, as well as promote neutrophil death.⁶⁹ Although the metabolic aspects are addressed by urate-lowering agents, the autoinflammatory component responds well to colchicine. This may act through disrupting the cytoskeletal machinery that traffics crystals to the inflammasome and the ASC subunit to the NLRP3 sensor during inflammasome formation.^{67,70} IL-1 inhibitors have also been shown to be effective.⁷¹

Chronic recurrent multifocal osteomyelitis (CRMO)/chronic nonbacterial osteomyelitis (CNO) is an inflammatory disease of bone characterized by recurrent attacks of bone pain with or without swelling.⁷² The usual age of onset is 8-12 years and female individuals are slightly more commonly affected than male individuals. Typical sites of involvement include metaphyses of long bones, medial clavicle, mandible, and vertebral bodies. Extraosseous manifestations are common and include PsO, palmoplantar pustulosis, acne, and inflammatory bowel disease. Adults have similar bony lesions as part of synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome.⁷³ IL-1 appears to be central to the pathogenesis of CRMO, as similar bony lesions also occur in certain IL-1-mediated monogenic diseases such as PAPA syndrome, DIRA, and Majeed syndrome.^{24,74,75} Recently, classification criteria have been proposed for CRMO/CNO.⁷⁶

Pericarditis is a frequent manifestation of classic autoinflammatory diseases such as FMF and TRAPS. However, it most frequently occurs in an isolated fashion and the vast majority of patients do not have a detectable underlying etiology. Pericarditis can be recurrent in 20% to 40% of cases. When common etiologies such as infection, malignancy, trauma (including post surgery), and autoimmune diseases have been excluded, a diagnosis of idiopathic recurrent pericarditis can be made.⁷⁷ This is defined as a relapse of disease after a documented first acute episode followed by a symptom-free interval of at least 4 weeks.⁷⁸ Idiopathic recurrent pericarditis is considered an AID mediated by IL-1, supported by the excellent clinical response to treatment with colchicine and IL-1 blocking agents.⁷⁹⁻⁸¹

Mimics of classic rheumatic disease

Inflammatory arthritis (IA) can be a nonspecific manifestation of monogenic inflammasomopathies, interferonopathies, and

disorders affecting the NF- κ B pathway.¹³ For example, Blau syndrome is characterized by tenosynovitis (Figure 1E), arthritis, and uveitis, among other features, and thus is often mistaken for JIA.⁸² Monogenic autoimmune lymphoproliferative syndrome (ALPS) and complex immune dysregulation diseases such as CTLA4 and lipopolysaccharide-responsive and beige-like anchor protein (LRBA) haploinsufficiency may also cause IA.¹³ Paradoxically, IA can be seen in immune deficiency disorders such as chronic granulomatous disease.⁸³

BD can be mimicked by mutations in genes involved in the NF- κ B pathway such as *NFKB1*, *TNEAIP3*, *OTULIN*, and *RELA*.^{19,84} These disorders may present with mucosal ulcerations, ocular lesions, pathergy, and vasculitis. Interestingly, BD has also been associated with myelodysplastic syndrome in patients with acquired trisomy 8.⁸⁵

SLE is another highly variable phenotype for which over 30 monogenic causes have been documented.⁸⁶ These involve genes that encode early complement proteins, or those that repair and remove damaged DNA such as *DNASE1L3* and *DNASE2*.⁸⁷ Mutations in nucleic acid sensing genes such as *TREX1* and type 1 IFN responsive genes such as *IFIH1* can also drive SLE development.

Vasculitis can be caused by monogenic AIDs such as DADA2 (Figure 1G), COPA syndrome, hemopoietic cell kinase (HCK) AID, and SAVI.^{29,30,88,89} For example, DADA2 can present as vasculopathy resembling polyarteritis nodosa as its major manifestation, and may also be associated with cytopenias and immune deficiency.⁸⁹ SAVI is also a classic autoinflammatory cause of vasculitis and has been reported to exhibit positive ANCA titers in some patients.⁹⁰

As discussed earlier, VEXAS is an important mimic of relapsing polychondritis, IA, and Sweet syndrome (Figure 1A). More rarely, it can also present with polyarteritis nodosa and giant cell arteritis.⁵⁰

Rheumatologic disorders mimicked by monogenic immunologic diseases are summarized in Table 3.

Clinical approach

Clinical suspicion. Given the potentially severe effect on quality of life and threat of organ damage, it is important to maintain a high index of suspicion for AID in appropriate patients. AID should be considered in patients with recurrent documented fevers where more common causes such as infection, malignancy, and autoimmune diseases have been excluded. However, it is important to note that absence of fevers does not rule out autoinflammation. Features such as ethnicity, consanguinity, or close family members having similar symptoms may raise suspicion, as well as early age of disease onset. AID should be considered in the presence of stereotyped flares of inflammatory manifestations including rash, arthritis, pleuritis, peritonitis, lymphadenopathy, pharyngitis, or ocular inflammation. Initial symptom-free intervals may coalesce into more chronic features later in the disease course if left untreated.⁹¹

Patients with monogenic AID may exhibit syndromic features (eg, developmental delay, dysmorphic facies), or other aspects of dysregulated immunity, such as immune deficiency, atopy, auto-

Table 3. Autoinflammatory mimics of classic rheumatic diseases.

	Autoinflammatory Mimics	Notes
Inflammatory arthritis	ALPS, Blau, AOSD, FMF, Majeed syndrome, TRAPS, MWS, VEXAS, PAPA, COPA, <i>LACCI</i>	IA can be seen in virtually any autoinflammatory condition
Juvenile dermatomyositis	CANDLE, SAVI, PAAND, DADA2	–
Behçet disease	HA20, RAID, <i>NFKB1</i> , otulipenia, trisomy 8, PFIT, veoIBD, PAPA, PFAPA, MKD, <i>NLRP12</i> , DITRA, cryopyrinopathies, VEXAS, CAPS	There are many monogenic causes of very early-onset IBD
Systemic lupus erythematosus	<i>C1q/r/s</i> , <i>C4</i> , <i>C2</i> , <i>DNASE1L3</i> , <i>DNASE2</i> , <i>IKZF2</i> , <i>SOCS1</i> , AGS, HA20, RAID, ALPS, Castleman disease, SPENCD, <i>DNASE1</i> , <i>UNC93B</i>	List is not exhaustive; there are many other monogenic causes of SLE
Vasculitis	DADA2, <i>COPA</i> , SAVI, VEXAS, PAAND, AGS5, SPENCD, otulipenia, <i>HCK</i> , <i>ARPC1B</i> , FMF	–
Relapsing polychondritis	VEXAS	VEXAS can also cause Sweet syndrome, vasculitis, and arthritis
Spondyloarthritis	FMF, CRMO	FMF is associated with many inflammatory conditions, for which the most common is SpA
Polymyalgia rheumatica	Protracted FMF, TRAPS	–

Italicized terms represent genes (eg, *DNASE1L3*) where pathogenic variants cause diseases that do not have names or acronyms (eg, FMF, TRAPS). Specific details and full names of diseases under column “autoinflammatory mimics” can be found in Table 1. AGS: Aicardi-Goutières syndrome; ALPS: autoimmune lymphoproliferative syndrome; AOSD: adult-onset Still disease; CANDLE: chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; CAPS: cryopyrin-associated periodic fever syndrome; COPA: coatamer protein subunit alpha; CRMO: chronic recurrent multifocal osteomyelitis; DADA2: deficiency of adenosine deaminase 2; DITRA: deficiency of the IL-36 receptor antagonist; FMF: familial Mediterranean fever; HA20: haploinsufficiency of A20; IBD: inflammatory bowel disease; MKD: mevalonate kinase deficiency; MWS: Muckle-Wells syndrome; PAAND: pyrin-associated autoinflammation with neutrophilic dermatosis; PAPA: pyogenic arthritis, pyoderma gangrenosum, and acne syndrome; PFAPA: periodic fever, aphthous stomatitis, pharyngitis, and adenitis; PFIT: periodic fever, immunodeficiency, and thrombocytopenia syndrome; RAID: *RELA*-associated inflammatory disease; SAVI: stimulator of interferon genes–associated vasculopathy with onset in infancy; SPENCD: spondyloenchondrodysplasia; TRAPS: tumor necrosis factor receptor–associated periodic syndrome; VEXAS: vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

immunity, lymphoproliferation, or cell line dyscrasias. Typical rheumatic diseases with unusual manifestations should also raise suspicion for AID (eg, a man with relapsing polychondritis but also skin nodules and macrocytic anemia should raise suspicion for VEXAS). Laboratory features that should prompt suspicion of AID include markers of inflammation such as elevated CRP, ESR, or ferritin.¹¹ Similarly, normocytic anemia and hypoalbuminemia may indicate inflammation. Proteinuria may be a sign of amyloidosis (Figure 1F) and reduced hearing thresholds may reflect sensorineural hearing loss in longstanding untreated AID. AID should be considered in patients exhibiting a response to colchicine, which can be seen in AIDs driven by IL-1, or who are unusually refractory to standard medications.⁹²

Investigation and diagnosis. The first step in the investigation of autoinflammation is the exclusion of noninflammatory disorders such as infection and malignancy. The physician should then consider the features discussed earlier that raise clinical suspicion for AID.

If there is clinical suspicion for AID, the second step is to carry out deep phenotyping. A detailed personal and family history should be conducted, including the construction of a comprehensive pedigree to delineate inheritance patterns and identify additional affected family members. A thorough physical examination should be performed, followed by laboratory testing to establish objective evidence of inflammation, such as with acute-phase markers and serum amyloid A. Laboratory testing may also provide clues to the category of AID. For

example, CRP may be significantly elevated in inflammasomopathies but normal in interferonopathies. Serum amyloid A can be used to detect and monitor inflammation in AIDs such as FMF. Metabolite testing can be helpful in some disorders, such as urine mevalonate acid in MKD, and enzyme activity levels in others, such as adenosine deaminase 2 in DADA2. Imaging with positron emission tomography or enhanced MRI can help uncover hidden foci of inflammation and guide potential tissue sampling, which can shed light into the underlying etiologies driving inflammation. For example, biopsy showing neutrophilic infiltration in an atypical urticarial lesion (Figure 1B) favors an autoinflammatory rather than an atopic process.

The third step involves genetic testing, often with panels, which include some AID-associated genes as outlined above. If panel testing is nondiagnostic, clinicians can consider exome or genome sequencing, which is becoming increasingly available as a clinical test. A genetic diagnosis is confirmed when the phenotype matches the genotype, and a correlation is made by the clinician. Such a precise diagnosis allows for personalized therapy and familial testing to inform recurrence risk where appropriate. If genetic testing is nondiagnostic, more advanced cytokine profiling can be obtained in some tertiary centers to reveal the immune pathways affected and, in turn, help guide treatment.

Treatment. The treatment of AIDs hinges on establishing a molecular diagnosis, which can guide the selection of therapies to block the aberrant immune component itself, or other

elements of the relevant pathway to modulate the inflammatory response.

Colchicine is a well-established treatment for FMF, BD, gout, idiopathic recurrent pericarditis, and PFAPA. In FMF, it has been shown to reduce frequency and severity of flares, as well as in preventing amyloidosis. Response to colchicine thus supports an autoinflammatory etiology and can also be helpful diagnostically in patients with SURF who lack a genetic diagnosis.⁹³

Inhibiting the action of ILs can be helpful for AIDs. IL-1 blockers are effective for inflammasomopathies such as FMF, CAPS, and gout.⁹² They are also used to treat MKD and DIRA. For patients who have infrequent attacks, on-demand anakinra can be a helpful strategy to minimize chronic medication burden. Anakinra, rilonacept, and canakinumab have also shown benefit in other conditions with a complex pathophysiology that may not be directly or solely driven by IL-1, such as TRAPS,

AOSD, idiopathic recurrent pericarditis, and USAID.⁶⁵ Work is underway to develop oral agents, such as NLRP3 blockers in CAPS, that can more selectively target the defective immune component.⁹⁴

IL-6 blockers can be useful in a variety of AIDs including AOSD, VEXAS, multicentric Castleman disease, cytokine storm secondary to coronavirus disease 2019 (COVID-19), and some immune dysregulatory conditions such as signal transducer and activator of transcription 3 (STAT3) GOF disease.^{51,52,95-97}

Anti-IL-17 or anti-IL-12/IL-23 inhibition is useful in the treatment of generalized pustular PsO (deficiency of IL-36 receptor antagonist [DITRA], *CARD14*). IL-18 inhibitors (eg, recombinant IL-18BP) may be helpful in NLRC4 GOF and XIAP deficiency.²⁷

TNFi can be helpful in conditions of dysregulated NF-κB signaling such as HA20, RAID, and Blau syndrome.⁹³ TNFi are

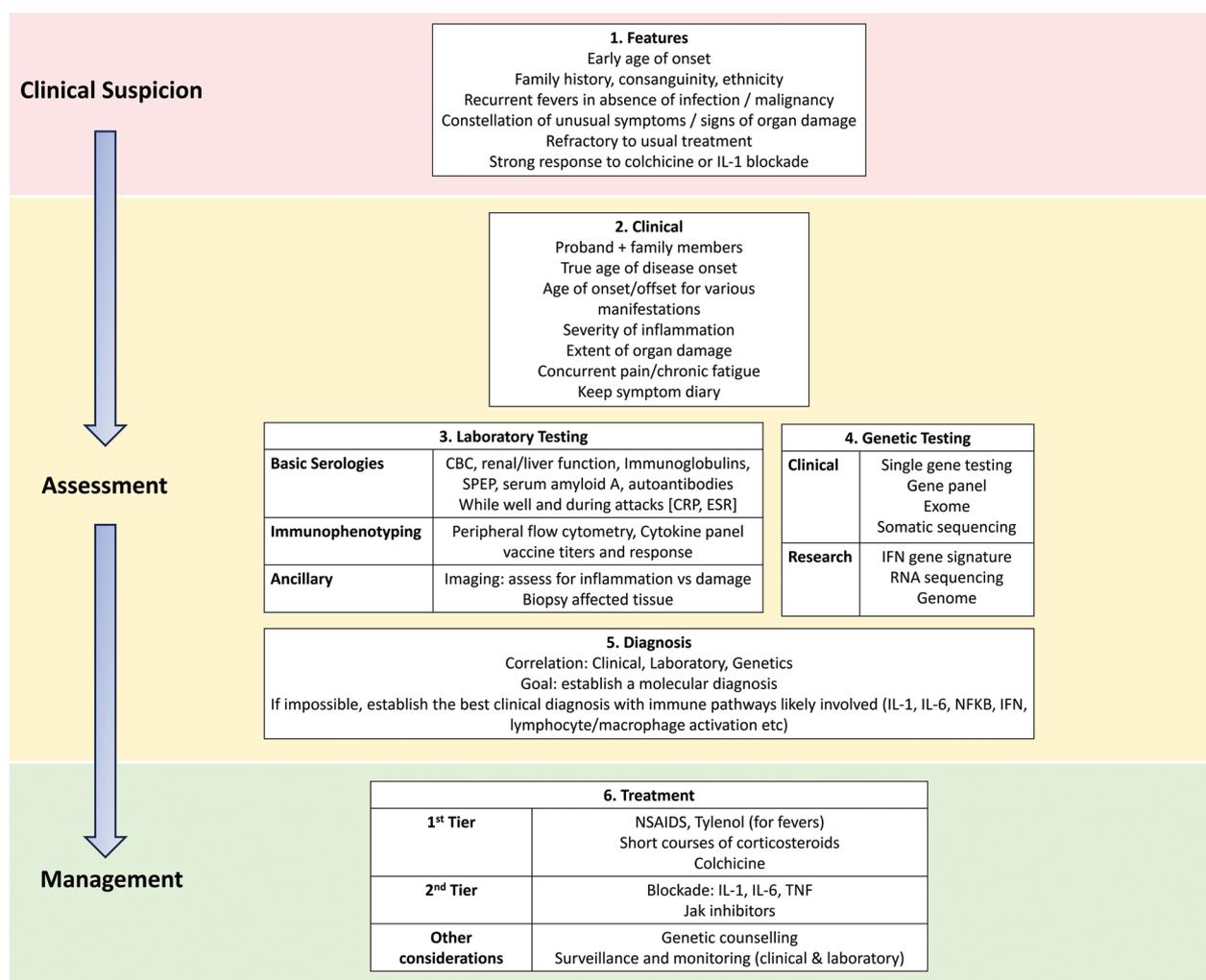


Figure 3. Algorithm in the management of AID from clinical and laboratory evaluation to treatment. Clinical features to raise suspicion of AID are detailed in box 1. Clinical assessment should include those outlined in box 2. Laboratory testing can be ordered as detailed in box 3. Genetic testing can be ordered according to what is available clinically or via research as outlined in box 4. Diagnosis is optimally made by molecular testing, but if genetic testing is not definitive then other variables can be used to help classify the type of AID as outlined in box 5. Treatment may be targeted to a molecular diagnosis, but otherwise, first- and second-line empiric therapy may be initiated as outlined in box 6. AID: autoinflammatory disease; CBC: complete blood count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IFN: interferon; IL: interleukin; JAK: Janus kinase; NF: nuclear factor; NSAID: nonsteroidal antiinflammatory drug; SPEP: serum protein electrophoresis; TNF: tumor necrosis factor.

also the first-line treatment in patients with DADA2 and have been shown to reduce inflammatory manifestations as well as recurrence of strokes.⁹⁸

JAK inhibition is effective in the treatment of interferonopathies such as SAVI, AGS, and proteasome disorders.⁹³ Higher doses are often required to treat patients with interferonopathies compared to patients with rheumatoid arthritis.³⁶ This class of medications is also effective in VEXAS and certain immune dysregulatory disorders.^{51,95} Potential adverse effects include BK viremia and viruria, herpes virus, as well as upper respiratory and gastrointestinal infections.²⁹

The clinical approach from suspicion to investigation and treatment is summarized in Figure 3.

As research reveals further insights into the pathophysiology of immune dysregulatory disorders, novel therapeutics can be developed to target aberrant immune pathways. For example, elevated levels of granulocyte-colony stimulating factor (G-CSF) were recently found in serum of patients and mouse models with APLAID.⁹⁹ Treatment with anti-G-CSF reversed autoinflammation as well as immune deficiency, highlighting its potential to be a disease-altering therapy.

State of current genetic services and future directions

A common barrier for patients with systemic AIDs includes restriction of higher-tier genetic testing (ie, beyond panels) to clinical geneticists, coupled with long wait times for genetics consultations. Although panel testing can usually be ordered by any physician, it is limited by the number of included genes, which may not always reflect the newest discoveries. One possible solution is enrollment into research studies for exome or genome sequencing, as well as transcriptomic profiling to evaluate gene expression. As technology continues to improve and costs for genetic services further decrease, we hope that widened accessibility to clinical genetic tests will ultimately reduce diagnostic delay and improve diagnostic yield along with patient outcomes.

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