



Adult-Onset Still's Disease

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6.1 Introduction

Adult-onset Still's disease (AoSD) was first described in the early 1970s, by Bywaters, as an inflammatory condition occurring in young adults. The disease was very similar to childhood-onset Still's disease, today called systemic-onset juvenile idiopathic arthritis (SoJIA), described a century ago by Sir Still [1]. Although the exact pathogenic mechanisms of the disease remain unknown, substantial advances have been made first to confirm the homology between AoSD and SoJIA, and then the disease became the archetype of nonfamilial, or sporadic, systemic autoinflammatory disorders (SAID) [2–4].

By definition, AoSD affects people older than 16, either de novo or those with a history of systemic JIA [3, 5, 6]. In the latter, a disease-free interval between the

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childhood episode and the adulthood recurrence differentiates AoSD from persistent SoJIA. In most patients, AoSD is characterized by four cardinal symptoms: spiking fever, an evanescent salmon-pink maculopapular rash, arthritis, and a white blood cell count (WBC) $\geq 10,000/\text{mm}^3$, mainly neutrophilic polymorphonuclear cells (PMNs). Other features are sore throat or pharyngitis, myalgia, lymph node or spleen enlargement, pleuritis or pericarditis, multivisceral involvement, elevated levels of liver enzymes, and other hematologic abnormalities [3, 7, 8]. None of these symptoms is disease specific, so diagnosis of AoSD is difficult, and clinicians must first rule out neoplastic, infectious, or inflammatory conditions.

6.2 Epidemiology

To date, epidemiologic data about AoSD have been scarce and imprecise, because of the heterogeneous clinical presentation of the disease and the complex assessment of diagnosis. The disease occurs worldwide, and no specific familial aggregation has been reported. AoSD satisfies the definition of an orphan disease because historically its prevalence was estimated between one case per million in Europe [9] and ten cases per million in Japan [10]. In the Japanese study, the incidence was estimated at about one case per million in the mid-1990s. However, because of the substantial advances in AoSD diagnosis as well as differential diagnoses during the last two decades, these prevalence and incidence estimates lack robustness, and new studies are clearly needed to update these figures.

Initially, the disease was characterized as affecting exclusively young adults (i.e., 16–35 years of age [1]); however, more recent series identified cases in adults older than 35 and even elderly people [5, 11–14]. The sex ratio is almost balanced, with only a slight female predominance [5, 6, 11, 13–15].

6.3 Clinical Expression

6.3.1 AoSD Clinical Symptoms

AoSD is traditionally characterized by four “cardinal” symptoms (three are clinical, one is biological), with many other manifestations possibly associated [3, 7, 16].

6.3.1.1 Cardinal Symptom 1: Fever

Fever is constant when the disease is active, except in patients with established disease, for whom residual inflammation could remain without it. Typically, fever starts suddenly, and temperature rapidly reaches 39 °C or more, associated with shivers. It evolves with daily evening spikes for more than a week (Fig. 6.1). Patients usually experience rapid deterioration of general health as well as significant weight loss. Of importance, fever may be the only clinical symptom of AoSD as a potential diagnosis in patients with fever of unknown origin [17].

Fig. 6.1 Typical temperature curve during an AoSD flare

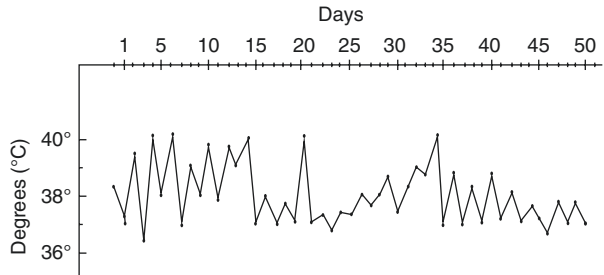


Fig. 6.2 Ankylosing carpal arthritis in adult-onset Still's disease



6.3.1.2 Cardinal Symptom 2: Arthralgia or Arthritis

Joint pain or arthritis is the second most common symptom, with synovitis, usually with concomitant fever spikes, occurring in more than two-thirds of patients. All joints can be involved, including sacroiliac and distal interphalangeal joints. In some patients, the presentation is that of a bilateral symmetrical rheumatoid arthritis (RA)-like polyarthritis [3, 7]. Synovial fluid analysis displays high cellularity, >2000 cells/mm³, which confirms joint inflammation. When performed, synovium biopsy reveals only nonspecific synovitis. During the evolution, arthritis becomes erosive in one-third of patients; in these patients, isolated bilateral carpal ankylosis (i.e., without structural damage of metacarpophalangeal or proximal interphalangeal joints, in contrast to RA) is very suggestive of AoSD (Fig. 6.2) [1, 3, 7].

6.3.1.3 Cardinal Symptom 3: Skin Rashes

Skin rash is typically salmon pink-colored macular or maculopapular (Figs. 6.3 and 6.4). The rash is transient, mainly visible during fever spikes on the proximal limbs or trunk, and rarely involves the face, palms, or soles of the feet [3, 7, 18]. No specific histological feature has been described. Misdiagnosis with drug allergy is frequent and usually attributed to nonsteroidal anti-inflammatory drugs (NSAIDs) prescribed for joint symptoms or fever. Complete regression without scars is the rule.

Fig. 6.3 Typical rash of the arm in adult-onset Still's disease



Fig. 6.4 Transient erythema of the elbow in adult-onset Still's disease



Atypical patterns also reported are urticarial or pruritic with dermographism [3, 7, 18]. Presence of purpuric lesions should lead to urgent coagulation workup because these lesions are suggestive of the AoSD hematologic complications of hemophagocytic syndrome or reactive hemophagocytic lymphoproliferation (RHL), disseminated intravascular coagulation (DIC), or thrombotic microangiopathy (TMA), also called thrombocytic thrombocytopenic purpura or Moschcowitz syndrome [3, 7].

6.3.1.4 Other Clinical Symptoms

Sore throat (odynophagia) and sometimes pharyngitis are classical symptoms, concomitant with fever (and not just a few weeks previous, e.g., in post-streptococcal arthritis) [3]. All microbiological test results are negative. The presence of this symptom in such a systemic context seems to exclude lymphoma or another neoplastic disease [19].

Diffuse and symmetrical lymphadenopathy is possible, eventually associated with splenomegaly or even hepatomegaly. However, large and nonsymmetrical lymphadenopathy should lead to the exclusion of malignant lymphoma by biopsy: reactive polyclonal lymphoid hyperplasia is the usual pattern in AoSD [3, 7]. Kikuchi necrotizing lymphadenitis has been described in a few cases [20].

Myalgia is frequent, but myositis or polymyositis is exceptional [3, 7, 21, 22].

Finally, as in many other inflammatory disorders, nonspecific manifestations have been reported: abdominal pain related to deep lymphadenitis, aseptic peritonitis or rarely acute pancreatitis, pleural effusion or pericarditis, or interstitial lung infiltrates [3, 7].

6.3.2 AoSD Biological Abnormalities

6.3.2.1 Cardinal Symptom 4: Increased Leukocyte and Neutrophil Counts

A major increase in leukocyte and neutrophil counts is observed (i.e., leukocyte count $>10,000\text{--}15,000/\text{mm}^3$, with neutrophils $>80\%$). Greatly increased counts, up to $50,000/\text{mm}^3$, can be observed, associated with myeloma. Leucopenia has also been described, in isolation or with anemia and/or thrombopenia; it often reveals RHL or TMA [3, 7].

6.3.2.2 Acute-Phase Reactants

Besides increased leukocyte and neutrophil counts, a substantial increase in acute-phase reactants—ESR and levels of CRP, fibrinogen, and serum immunoglobulins—is always present during AoSD flares.

6.3.2.3 Liver Function Tests

Elevated serum liver enzyme levels, rarely fulminant hepatitis, are often present, related to systemic inflammation or the use of drugs, such as antibiotics or NSAIDs, as symptomatic treatment before diagnosis.

6.3.2.4 Serum Ferritin and Glycosylated Ferritin

High serum ferritin level, an indicator of macrophage activation, has been frequently reported [5, 12, 23–26]. Although hyperferritinemia was first considered suggestive of AoSD, several studies showed that hyperferritinemia, whatever the threshold used, has poor positive predictive value in isolation without a suggestive context [27, 28].

Besides total ferritin level, the diagnostic performance of glycosylated ferritin (GF) level has been investigated [29]. The GF level normally represents more than half of the total ferritin level. In inflammatory conditions, the concentration of GF decreases and usually ranges from 20% to 50%; this decrease has been related to the saturation of glycosylation mechanisms due to hyperferritinemia. However, in AoSD, GF level is typically markedly decreased (below 20%), which suggests a more specific phenomenon. More extensive data revealed a sensitivity and specificity of GF $\leq 20\%$ for AoSD diagnosis of 78% and 64%, respectively [27]. The combination of both hyperferritinemia and GF level $\leq 20\%$ yielded a sensitivity and specificity of 67% and 84%, respectively. Of note, although serum ferritin level fluctuates according to systemic inflammation, GF level remains low several weeks to several months after disease remission [30]. However, as mentioned previously, low GF level is not completely specific to AoSD and is observed in other inflammatory processes, such as severe systemic infections [27]. Moreover, the GF level is usually low, $\leq 20\%$, in hemophagocytic syndromes, regardless of the cause, such as infection, neoplasm, or inflammation [31–33].

6.3.2.5 Immunological Findings

Results of immunological workups performed to exclude other connective tissue diseases or inflammatory joint diseases must be negative.

6.4 Pathogenesis

6.4.1 A Systemic Autoinflammatory Disorder as Opposed to a Systemic Autoimmune Disease

Approximately ten years ago, McGonagle and McDermott formulated the hypothesis of two main pathogenic mechanisms underlying immune-mediated inflammation against the self and proposed a new classification for immunological diseases contrasting autoimmunity and autoinflammation [2, 34]. Autoimmunity referred to adaptive immunity and was defined as aberrant dendritic, B- and T-cell responses in primary and secondary lymphoid organs leading to tolerance break and development of immune reactivity toward native antigens (with autoantibodies in most cases), whereas autoinflammation referred to innate immunity and was defined as dysregulated activation of macrophages and neutrophils in response to a danger signal leading to tissue damage. These categories represent a continuum, which allowed for a new classification of immune-mediated inflammatory disorders that was refined in the following years [2, 4].

Although autoimmune diseases were rather easily diagnosed based on autoantibody or autoantigen-specific T and B cells, no specific biomarker exists for SAID. The definition mainly relies on similarities with monogenic, hereditary periodic fever syndromes, which were at the origin of the concept. They include several key features: intense inflammation with periodic fever, tissue inflammation depending on the disease, increased leukocyte and neutrophil count, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level, and, more recently, a pathogenic role of inflammasome and response to interleukin-1 (IL-1) blockade [35]. Besides monogenic familial syndromes, Crohn's disease was the first nonfamilial polygenic AID, mainly tissue specific, with predominant gut involvement [36, 37]. A few years later, Still's disease was described as another nonfamilial AID, becoming one of the most characteristic polygenic systemic SAID [3].

6.4.2 A Pro-inflammatory Cascade

The mechanisms underlying AoSD pathogenesis are largely hypothetical, but, from the evident pathogenic pathway seen in SoJIA patients and the growing understanding of SAID, a pro-inflammatory cascade can be proposed (Fig. 6.5) [3, 7, 16, 38, 39].

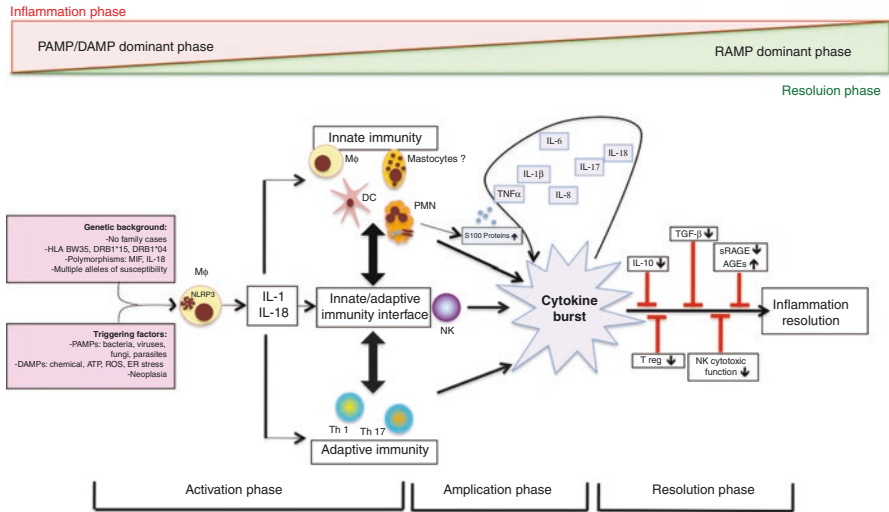


Fig. 6.5 Pathogenic pathways involved in AoSD (adapted from [16]). *AGE* advanced glycosylated end products, *ATP* adenosine triphosphate, *ER* endoplasmic reticulum, *DAMP* damage-associated molecular pattern, *DC* dendritic cells, *HLA* human leukocyte antigen, *IL* interleukin, *MΦ* macrophages, *MIF* macrophage inhibitory factor, *NK* natural killer, *PAMP* pathogen-associated molecular pattern, *PMN* polymorphonuclear neutrophil, *RAMP* resolution-associated molecular pattern, *ROS* reactive oxygen species, *sRAGE* soluble receptors of AGE products, *TGF* transforming growth factor, *Th1* T-helper 1 cells, *Treg* T-regulatory cells

6.4.2.1 A Cytokine Storm

The starting point is likely specific danger signals, such as pathogen- or damage-associated molecular patterns (i.e., PAMPs or DAMPs). Danger signals are transmitted to macrophages and neutrophils via specific Toll-like receptors that activate specific inflammasomes, likely NOD-like receptor family pyrin domain containing 3 (NLRP3), leading to caspase activation and overproduction of active IL-1 [39–42]. This step seems to be central to the AoSD pathogenesis and leads to intense innate immune cell activation and overproduction of several pro-inflammatory cytokines including IL-6, IL-18, tumor necrosis factor (TNF), as well as IL-8 and IL-17. Several factors actively contribute to an amplified inflammatory response, often referred to as the cytokine “burst” or “storm” [3, 42]. In addition to IL-1 itself, conferring retrograde activation of macrophages and neutrophils; different alarmins, such as the S100 protein—S100A12 protein seeming to be more specific to Still’s disease in children—and advanced glycosylated end (AGE) products are involved in these processes [39, 42–46]. Besides amplification mechanisms, SAID pathogenesis has been suggested to involve deficiency or failure in regulatory or anti-inflammatory mechanisms: deficiency in T regulator or natural killer cells, insufficient IL-10 production, and deficiency in resolution lipid mediators, soluble receptors of AGEs (RAGEs), or other resolution-associated molecular patterns [47–50].

6.4.2.2 A Role for Infections as a Trigger

Bacteria or viruses are the usual suspects for the danger signals. Numerous case reports describe the occurrence of AoSD after viral infection (rubella; measles; mumps; Epstein-Barr virus; hepatitis A, B, or C virus; HIV; cytomegalovirus; parvovirus B19; adenovirus; echovirus; human herpes virus 6; influenza and parainfluenza viruses; Coxsackie virus) or bacterial infection (*Yersinia enterocolitica*, *Campylobacter jejuni*, *Chlamydia trachomatis* or *pneumoniae*, *Mycoplasma pneumoniae*, *Borrelia burgdorferi*) [3, 7, 39]. In addition, patients often experience odynophagia or pharyngitis just before the start of the disease or the relapse, which could correspond to the infectious danger signal that will trigger Toll-like receptors and start the intense inflammatory process.

6.4.2.3 A Role for a Genetic Background

In contrast to monogenic, hereditary, periodic fever syndromes, the underlying genetic background of AoSD is largely unknown. The disease is present in different geographic regions and different ethnic groups [3, 4, 7, 39, 51]. Association studies have suggested a potential predisposing genetic background. HLA-Bw35 was the first identified as a susceptibility antigen and associated with a mild self-limiting pattern of the disease [52]. HLA-DR4 was found more prevalent in AoSD cases versus healthy controls, and HLA-DRw6 was associated with the occurrence of proximal arthralgia [53]. However, no functional analysis has confirmed these hypotheses [3, 39, 53].

Recently, two major findings have been reported in SoJIA patients. Firstly, a homoallelic missense mutation in the enzyme laccase (multicopper oxidoreductase) domain-containing 1—*LACCI*—has been identified in 13 SoJIA patients from five Saudi consanguineous families [54]. Although familial SoJIA is not the rule, this study raises the potential role of this laccase in the pathogenesis of SoJIA. Secondly, a large association study performed in 982 SoJIA children and 8010 healthy controls identified a strong association between SoJIA and different HLA-DRB1*11 haplotypes which all contain glutamate 58 [55]. This finding is more challenging since it would involve adaptive immunity in the AoSD pathogenesis which was not expected [56].

Finally, substantial advances have been made in exploring the human genome, which will facilitate the identification of potential mutations in genes involved in autoinflammatory pathways, including de novo germinal mutations or somatic mutations occurring during fetus development or after birth [57, 58].

6.5 Atypical Forms and Life-Threatening Complications

Several severe manifestations have been described in AoSD, which explains the potentially pejorative prognosis of the disease [3, 59]. The disease can be life-threatening because of the predominant involvement of one organ or of systemic complications with multiple organ failure from the outset, while the diagnosis isn't

clearly confirmed. The articular signs may often fall by the wayside because of the gravity of the complications of such clinical forms, which can contribute to misdirect the clinicians who are not familiar with AoSD.

These complications are given in Table 6.1, and the most frequent and relevant ones are discussed in more detail.

6.5.1 Reactive Hemophagocytic Lymphohistiocytosis (RHL)

This is a common complication of AoSD at the time of diagnosis, right after treatment introduction or during the course of the disease. In systemic-onset JIA, it is also called macrophage activation syndrome. This serious complication should be suspected in a patient with persisting fever (in contrast to evening spiking fever) and decrease in initially elevated leukocyte and neutrophil counts [3, 32, 59]. Several other manifestations can be associated.

The key issue with RHL is to determine whether its occurrence is related to AoSD intense inflammation or to concomitant infection, potentially favored by immunomodulators introduced because of AoSD. The list of possible infections is quite long, with viral reactivation at first place.

6.5.2 Coagulation Disorders

AoSD can be complicated by two serious coagulation disorders, mainly at the acute phase of the disease.

The first disorder, disseminated intravascular coagulation (DIC), is not rare and may occur at a frequency of 1–5% [8, 53, 59–67]. This diagnosis should be suspected with the combination of thrombotic events and cutaneous or mucosal bleeding and sometimes specific organ involvements, such as fulminant hepatitis, cardiac or respiratory failure, or stroke. Hemostasis workups reveal platelet and coagulation factor consumption, increased thromboplastin time, and high D-dimer levels.

The other rare but quite severe coagulation disorder is thrombotic microangiopathy (TMA). It must be suspected with unexplained multiorgan failure or stroke, related to multiple small thrombi leading to tissue ischemia and mechanical hemolytic anemia [60, 74, 75]. Acute vision impairment, such as blurred vision related to Purtscher-like retinopathy, is frequently the first symptom [74]. Key diagnostic tests display thrombocytopenia by platelet consumption, anemia, and schistocytes (fragmented red blood cells), which are specific to this diagnosis. Organ imaging may reveal multiple infarctions. In addition, ADAMTS13 enzymatic activity needs to be tested because acquired deficiency has been found to predispose to TMA [59, 96–98]. TMA has been mainly described during AoSD flare, related to intense inflammation or to concomitant infection with Shiga toxin-producing microorganisms [74].

Table 6.1 Main life-threatening complications of AoSD

Complications	Signs and symptoms	Diagnosis	Treatment	References
Reactive hemophagocytic lymphohistiocytosis (RHL)	<ul style="list-style-type: none"> • High (>38.5 °C), persistent fever^a • Peripherical lymphadenopathy, hepatomegaly, splenomegaly • Polymorphous skin rashes^b; rashes, edema, petechiae, urticaria, or purpura • Multiple organ involvement: pulmonary, neurological, gastrointestinal, or renal involvement, bleeding • Rapid change on hemogram: resolution of high leukocyte and neutrophil counts, occurrence of anemia and thrombocytopenia 	<ul style="list-style-type: none"> • Cytopenia: anemia, thrombocytopenia, and/or leukopenia • Decreased ESR^d • Increased liver function tests: transaminases and alkaline phosphatases • Elevated LDH level • Hypertriglyceridemia • Hyperferritinemia^e • High soluble CD25 or CD163 level • Hemophagocytosis in bone marrow smear (or reticuloendothelial organs) • Increased CD163 staining in bone marrow <p>Or</p> <ul style="list-style-type: none"> • HScore^f 	<ul style="list-style-type: none"> • Supportive care in ICU • Exclusion of an additional trigger: mainly infections^g • Immunomodulatory agents: <ul style="list-style-type: none"> – High-dose corticosteroids – \pmIL-1 or IL-6 inhibitors after a few days – If refractory, etoposide or cyclosporine A 	[3, 32, 59]
Disseminated intravascular coagulopathy (DIC)	<ul style="list-style-type: none"> • Hematoma, bleeding • Thrombotic event • Multi-organ involvement or failure: ARDS, pleural effusion, myocarditis, pulmonary embolism, gastrointestinal bleeding, CNS involvement 	<ul style="list-style-type: none"> • Thrombocytopenia • Prolongation of prothrombin time and activated thromboplastin time • Decreased fibrinogen • Increased levels of fibrin degradation products 	<ul style="list-style-type: none"> • Supportive measures in ICU • Immunomodulatory agents: <ul style="list-style-type: none"> – High-dose corticosteroids – \pmIL-1 or IL-6 inhibitors – If refractory, cyclosporine A 	[8, 53, 59–73]

Complications	Signs and symptoms	Diagnosis	Treatment	References
Thrombotic microangiopathy (TMA) or Moschowitz syndrome	<ul style="list-style-type: none"> • Acute vision impairment (early sign) • Weakness • Confusion, seizures, or coma • Abdominal pain, nausea, vomiting, diarrhea • Cutaneous gangrene • Arrhythmias caused by myocardial damage • Multi-organ failure 	<ul style="list-style-type: none"> • Mechanical hemolytic anemia (schistocytes on the peripheral blood smear with a negative Coomb's test) • Thrombocytopenia • Multiple organ failure of varying severity (mainly the kidneys and the CNS) 	<ul style="list-style-type: none"> • Supportive measures in ICU • Specific treatment: <ul style="list-style-type: none"> – High-dose corticosteroids and plasma exchange – \pmHemodialysis – If insufficient, multidisciplinary round \pmIL-1 or IL-6 inhibitors or cyclosporine or IVIG 	[60, 74–76]
Fulminant hepatitis	<ul style="list-style-type: none"> • Physical status deterioration: appetite loss, fatigue • Jaundice • Hepatomegaly • Right abdominal pain • Rarely, bleeding • Elevated liver function test findings 	<ul style="list-style-type: none"> • Abnormal and rapidly increasing liver function test findings • High activity on multi-biomarker FibroTest • Liver biopsy (if performed): nonspecific portal infiltrates of lymphocytes, plasma cells, and neutrophils, hepatocytic lesions or massive necrosis 	<ul style="list-style-type: none"> • Supportive measures in ICU • Discontinuation of all potentially hepatotoxic drugs^h; mainly acetaminophen, aspirin, NSAIDs, or methotrexate • Rule out RHL, DIC, and/or TMA • Rule out viral reactivation • Specific treatment: <ul style="list-style-type: none"> – High-dose corticosteroids – \pmIL-1 or IL-6 inhibitorsⁱ or cyclosporine • Liver transplantation in extreme cases 	[42, 60]
Cardiac complications	<ul style="list-style-type: none"> • Pericarditis, sometimes recurrent • Tamponade • Myocarditis • Endocarditis (exceptional cases) 	<ul style="list-style-type: none"> • Electrocardiography • Echocardiography • Troponin and creatinine kinase level increase if myocarditis 	<ul style="list-style-type: none"> • Supportive measures in ICU • Specific treatment: <ul style="list-style-type: none"> – High-dose corticosteroids usually – \pmIL-1 or IL-6 inhibitors 	[42, 60]

(continued)

Complications	Signs and symptoms	Diagnosis	Treatment	References
Pulmonary arterial hypertension	<ul style="list-style-type: none"> • Dyspnea (key symptom) • Fatigue, dizziness • Syncope • ARDS 	<ul style="list-style-type: none"> • Electrocardiography: right atrium hypertrophy • Echocardiography: systolic PAP >35 mmHg • Right heart catheterization (gold standard): <ul style="list-style-type: none"> – Mean PAP ≥ 25 mmHg at rest – End-expiratory PAWP ≤ 15 mmHg – Pulmonary vascular resistance >3 wood units 	<ul style="list-style-type: none"> • Close monitoring and refer to a pulmonary hypertension reference center (multidisciplinary rounds) • Vasodilatation therapy: calcium channel blockers, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and/or prostacyclin analogues • Immunosuppressive therapy: <ul style="list-style-type: none"> – High-dose steroids – \pmIL-1 or IL-6 inhibitors or cyclosporine 	[77–88]
Pulmonary complications	<ul style="list-style-type: none"> • Pleuritis • Interstitial lung disease with or without ARDS • Aseptic empyema • Diffuse alveolar hemorrhage 	<ul style="list-style-type: none"> • High-resolution computed tomography • Bronchoalveolar lavage (for differential diagnosis: in AoSD, nonspecific neutrophilic profile) • Pulmonary function tests 	<ul style="list-style-type: none"> • Supportive measures in ICU if ARDS • Rule out differential diagnoses: infections, cardiogenic causes (brain natriuretic peptide dosage, echocardiography), drug-related or iatrogenic causes, cancer • Specific treatment: <ul style="list-style-type: none"> – High-dose corticosteroids usually – \pmIL-1 or IL-6 inhibitors 	[42, 60]
AA amyloidosis	<ul style="list-style-type: none"> • Exceptional these days • Renal failure, proteinuria, edema, hydrops • Digestive involvement • Orthostatic hypotension, other neuropathies 	<ul style="list-style-type: none"> • Biopsy of minor salivary gland, or abdominal fat pad, or the kidney 	<ul style="list-style-type: none"> • Inflammation control with IL-1 or IL-6 inhibitors 	[89–93]

AoSD adult-onset Still's disease, ARDS acute respiratory distress syndrome, BAL bronchoalveolar lavage, CNS central nervous system, DIC disseminated intravascular coagulopathy, DRESS drug reaction with eosinophilia and systemic symptoms, ESR erythrocyte sedimentation rate, ICU intensive care unit,

IL interleukin, *IVIG* intravenous immunoglobulins, *LDH* lactate dehydrogenase, *NSAIDs* nonsteroidal anti-inflammatory drugs, *PAP* pulmonary arterial pressure, *PAPW* pulmonary artery wedge pressure, *RHL* reactive hemophagocytic lymphohistiocytosis, *TMA* thrombotic microangiopathy

^aWhereas in AoSD, fever is often remitting, with spikes (hectic)

^bWhereas in AoSD, skin rash is classically maculopapular and evanescent

^cWhereas in noncomplicated AoSD, white blood count is often $\geq 10,000/\text{mm}^3$, with mainly neutrophils, and thrombocytosis is frequent

^dWhereas in noncomplicated AoSD, ESR is high

^eHyperferritinemia is also seen in AoSD, but, in case of very high ferritin levels or sudden increase, an RHL or another systemic complication should be suspected

^fThis scoring system is a set of nine weighted criteria (known underlying immunosuppression, temperature, organomegaly, number of cytopenia, ferritin, triglyceride, fibrinogen, serum glutamic oxaloacetic transaminase, hemophagocytosis features on bone marrow aspirate) that have been elaborated and validated for the diagnosis of RHL in adults [94]. It is freely available online (<http://saintantoine.aphp.fr/score/>)

^gMainly infections, in particular viral reactivation (Epstein-Barr virus, cytomegalovirus), which may trigger AoSD or reactivated by immunosuppressive treatments

^hDrug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, potentially induced by interleukin (IL)-1 or IL-6 or another immunosuppressive agent, is a differential diagnosis that should always be ruled out because it can be responsible for a fulminant hepatitis and mimic AoSD systemic manifestations

ⁱKeeping in mind that tocilizumab-induced hepatic injury has also been reported [95]

6.5.3 Cardiac and Pulmonary Involvements

Although pleural effusion or pericarditis is frequent, other serious cardiac or pulmonary manifestations have been described.

Specific attention should be dedicated to a rare and very severe AoSD manifestation, pulmonary arterial hypertension (PAH), with several cases recently reported [77–88]. PAH, either idiopathic or occurring with AoSD or other connective tissue diseases, is thought to be related at least in part to immune-related alteration of the endothelium with overproduction of IL-1, IL-6, IL-18, and TNF [79, 80, 82, 83, 99]. PAH may occur at AoSD onset or later and seems to predominate in women. The diagnosis must be suspected with unexplained and often rapidly progressing dyspnea [59, 79, 81, 100, 101]. Electrocardiography is rarely contributive, eventually disclosing signs of right atrium hypertrophy. Echocardiography is more useful for detection by measuring systolic pulmonary artery pressure, which is >35 mmHg, and the exclusion of left ventricle dysfunction. The formal PAH diagnosis remains the right heart catheterization [100, 101].

6.5.4 Hepatitis

While liver abnormalities are most often limited to mild to moderate increases in aminotransferase activity which is frequent (up to 60% of cases), fulminant and fatal hepatitis have been reported [3, 59]. The potential role of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), or methotrexate has been mentioned by some authors [102]. Thus, clinicians should closely monitor liver function from the onset of the disease and particularly after prescription of potentially hepatotoxic drugs. Self-medication should be avoided.

Liver biopsy, if performed, reveals nonspecific portal infiltrates of lymphocytes, plasma cells, and polymorphonuclears [3, 59, 102]. Hepatocytic lesions or massive necrosis has been described in fulminant hepatitis with rapidly progressive hepatic insufficiency. Liver transplantation was necessary in a few exceptional cases [3, 103].

6.5.5 Exceptional Symptoms

Amyloid A amyloidosis is becoming extremely rare owing to the better ability of AoSD treatments to control inflammation [89–93]. It could be observed in refractory patients or in patients who did not have access to adequate treatments for long periods of time. Multiple organs can be involved.

Many other symptoms attributed to AoSD have appeared in the literature. As these are almost exclusively in case reports, drawing conclusions is difficult:

- Ophthalmologic involvement related to sicca syndrome, conjunctivitis, uveitis, or episcleritis [1, 5, 102].

- Neurological manifestations, such as ischemic stroke, aseptic meningitis, or encephalitis [3]. Such symptoms might reveal hepatic failure or coagulation dysfunction, as in DIC, RHL, or TMA.
- Renal involvement limited to isolated proteinuria or related to glomerular or interstitial nephritis [102, 103]. Acute renal failure is possible in the context of severe myositis, hepatic insufficiency, or hematological complications [21, 74, 102–104].
- Secondary amyloid A amyloidosis (AA amyloidosis) is nowadays exceptional and is related to sustained uncontrolled inflammation [89–93].

6.6 Differential Diagnoses

AoSD is an exclusion diagnosis. Because of presentation heterogeneity and of the lack of specificity of the clinical and biological manifestations, many other diagnoses might be evoked and afterward ruled out, before reasonably considering AoSD (Table 6.2) [3, 5, 6, 102]. Before finally diagnosing AoSD, it is thus essential to first rule out neoplastic, infectious, or inflammatory conditions that can mimic the disease.

Table 6.2 Differential diagnoses of AoSD and helpful tests to rule them out

	Diseases	Relevant workups	
<i>Infections</i>			
Bacteria	Pyogenic bacterial septicemia	Blood cultures, PCT	
	Infectious endocarditis	Echocardiogram	
	Biliary, colic, or urinary occult infections, tuberculosis	CT scan IGRAs, CT scan	
	Brucellosis, yersiniosis	Biopsy for bacteriology and histology Serology, PCR	
Viruses	HIV, viral hepatitis Parvovirus B19 Herpesviridae Measles, rubella	Serology, PCR	
	Parasites	Toxoplasmosis, abscessed parasitosis	Serology, PCR
	<i>Malignant diseases</i>		
	Hematological disease	Hodgkin's disease or non-Hodgkin's lymphoma	Biopsy of a large and asymmetrical lymphadenopathy
Angioimmunoblastic lymphadenopathy		Bone marrow smear or biopsy	
Castleman's disease		CT scan	
Myeloproliferative disorders		PET/CT scan	
Solid cancers	Kidney, colon, lung, etc. Paraneoplastic syndromes	CT scan, PET/CT scan	

(continued)

Table 6.2 (continued)

	Diseases	Relevant workups
<i>Systemic diseases</i>		
Autoimmune diseases	Systemic lupus erythematosus	Antinuclear autoantibodies
	Polymyositis, dermatomyositis	CPK, specific autoantibody, biopsy
	Rheumatoid arthritis	RF, ACPA, joint ultrasonography
	Polyarteritis nodosa or other vasculitides	ANCA, arteriography
Autoinflammatory disorders	Hereditary autoinflammatory syndromes:	Familial history and
	– Familial Mediterranean fever	– MEFV gene sequencing
	– Mevalonate kinase deficiency	– Urinary mevalonic acid, MVK gene sequencing
	– TNF receptor-associated periodic syndrome	– TNFRSF1A gene sequencing
	– Cryopyrin-associated periodic syndromes	– CIAS1 (NLRP3) gene sequencing
	Neutrophilic dermatosis, Sweet syndrome	Skin biopsy
Other	Post-streptococcal arthritis	ASLO
	Reactive arthritis	No fever, erythema nodosum
	Sarcoidosis	ACEs, lesion biopsy (granulomatosis)
	Schnitzler's syndrome	Monoclonal gammopathy
	Kikuchi-Fujimoto disease	Biopsy of a large and asymmetrical lymphadenopathy
	Drug-related hypersensitivity	Eosinophilia, drug investigation

ACEs angiotensin-converting enzymes, *ACPA* anti-citrullinated antibody, *ANCA* anti-neutrophil cytoplasmic antibodies, *ASLO* anti-streptolysin O antibody, *CPK* creatine phosphokinase, *CT* computed tomography, *HLA* human leukocyte antigen, *IGRAs* interferon gamma release assays, *MEFV* Mediterranean fever virus, *MVK* mevalonate kinase, *PCR* polymerase chain reaction, *PCT* procalcitonin, *PET* positron emission tomography, *RF* rheumatoid factor, *TNFRSF1A* tumor necrosis factor receptor superfamily member 1A

6.6.1 Infections

Infectious diseases represent the most complex issue in differential diagnoses because AoSD therapies can be highly deleterious. The most misleading diagnoses are probably deep occult infections (e.g., biliary tract abscess or bone marrow infestation) or subacute endocarditis [3]. Whole blood culture, urine testing, and synovial fluid culture seem the minimal workup, while other tests might be considered depending on the context.

6.6.2 Malignant Diseases

Among malignancies, malignant lymphomas—either Hodgkin's disease or non-Hodgkin's lymphomas—are probably the most misleading and the first to exclude

if nonsymmetrical, fixed, and indurated lymph node enlargement is present [3, 105]. Less frequently, systemic inflammatory conditions have been described in the course of lymphoid leukemia or in paraneoplastic syndromes associated with solid cancers of either the lung or the breast [3, 105].

6.6.3 Autoimmune or Autoinflammatory Disorders

Autoimmune diseases that can mimic AoSD include vasculitis, especially polyarteritis nodosa, and polymyositis [6]. For patients with mainly chronic arthritis, the distinction between seronegative RA and AoSD can be difficult.

Besides autoimmune diseases, hereditary or nonfamilial autoinflammatory syndrome (AIS) can present with symptoms close to AoSD because of the combination of fever, skin lesions, and arthritis in addition to other symptoms that differ among the AIS [106–108]. Although the hereditary AIS often begins during childhood, the diagnosis tends to be made when the individual is an adult; examples are hyperimmunoglobulin D (IgD) syndrome or TNF receptor-associated periodic syndrome (TRAPS). Different mutations have been associated with different hereditary AIS, but, to date, none has been associated with AoSD. However, the similarities between these diseases and AoSD might suggest common pathogenic pathways and place AoSD as a nonfamilial, sporadic form of AIS.

Finally, in rare cases, the severe and systemic drug hypersensitivity reaction can mimic AoSD. The presence of urticarial skin lesions and increased eosinophilic PMN count are suggestive features, as is exposure to a potential agent within the previous days or weeks.

6.7 Classification Criteria and Biomarkers

After comprehensive investigations, no clinical sign or biological abnormality can be considered AoSD specific enough to ascertain the diagnosis. Thus, classification criteria may be helpful, although they have been developed more for clinical research than diagnosis.

6.7.1 Classification Criteria

Two sets of criteria have been validated (Table 6.3). The Yamaguchi criteria set, published in 1992, is the most widely used [109]; however, it contains exclusion criteria that are problematic in clinical practice. The Fautrel criteria set has the advantage of including ferritin and GF levels as diagnostic biomarkers and does not require exclusion criteria [13]. In a recent validation study, both sets showed high sensitivity and specificity [14].

Table 6.3 Classification criteria for adult-onset Still's disease

Yamaguchi et al. [109]	Fautrel et al. [13]
<i>Major criteria</i>	
1. Fever ≥ 39 °C lasting 1 week or more 2. Arthralgia lasting 2 weeks or more 3. Typical skin rash: maculopapular, nonpruritic, salmon-pink rash with concomitant fever spikes 4. Leukocytosis $\geq 10,000/\text{mm}^3$ with neutrophil polymorphonuclear count $\geq 80\%$	1. Spiking fever ≥ 39 °C 2. Arthralgia 3. Transient erythema 4. Pharyngitis 5. Neutrophil polymorphonuclear count $\geq 80\%$ 6. Glycosylated ferritin fraction $\leq 20\%$
<i>Minor criteria</i>	
1. Pharyngitis or sore throat 2. Lymphadenopathy and/or splenomegaly 3. Liver enzyme abnormalities (aminotransferases) 4. Negative for rheumatoid factor or antinuclear antibodies	1. Typical rash 2. Leukocytosis $\geq 10,000/\text{mm}^3$
<i>Exclusion criteria</i>	
1. Absence of infection, especially sepsis and Epstein-Barr viral infection 2. Absence of malignant diseases, especially lymphomas 3. Absence of inflammatory disease, especially polyarteritis nodosa	None
<i>At least five criteria, including two major criteria</i> <i>And</i> <i>No exclusion criteria</i>	<i>Four major criteria</i> <i>Or</i> <i>Three major criteria and two minor criteria</i>
<i>Classification performance</i> ^a Se, 96.3%; Sp, 98.2%; PPV, 94.6%; NPV, 99.3% <i>Modified Yamaguchi criteria</i> <i>Yamaguchi criteria and</i> – Ferritin > N:Se, 100%; Sp 97.1%; PPV, 87.1%; NPV, 100% – GF $\leq 20\%$:Se, 98.2%; Sp, 98.6%; PPV, 93%; NPV, 99.6%	<i>Classification performance</i> ^a Se, 87.0%; Sp, 97.8%; PPV, 88.7%; NPV, 97.5%

^aLebrun D et al. Semin Arthritis Rheum 2018 [14]

6.7.2 AoSD Biomarkers

The most relevant serum biomarkers identified to date are listed in Table 6.4.

6.7.2.1 Biomarkers for Routine Clinical Setting

Ferritins are the major biomarkers for AoSD. Serum ferritin level is a key biomarker to assess disease activity, but probably less relevant for diagnosis since its specificity is limited and no clear threshold has been identified so far [27, 28]. The diagnostic value of glycosylated ferritin level, with the threshold of GF $\leq 20\%$, is much more interesting [27, 30].

Table 6.4 Most relevant serum biomarkers identified to date in adult-onset Still's disease (AoSD) cohorts and their intended potential use

Biomarker	Diagnosis ^a	Disease activity monitoring	Prognosis: severity (i.e., predictive of life-threatening complications)	Prognosis: evolution (i.e., predictive of evolution pattern ^b (systemic versus arthritis; monophasic, recurrent, or progressive, either systemic or joint))	References
<i>Routine biomarkers</i>					
CRP	High sensitivity No specificity	+	-	-	[42]
Ferritins					
Ferritin >ULN ≥5ULN (≥1000 µg/L)	High sensitivity No specificity	+	+	±	[5, 12, 27, 28, 61, 110]
	Se 40.8% Sp 80%	+	+	High levels associated with systemic pattern ^c	
Glycosylated ferritin (GF) ≤20%	Se 79.5% Sp 66.4%	-	+	NA	[29, 30]
Ferritin >ULN and GF ≤20%	Se 70.5% Sp 83.2%	-	-	-	[29, 30]
Ferritin >5ULN and GF ≤20%	Se 70.5% Sp 92.9%	-	-	-	[29, 30]
Calprotectin (S100A8/S100A9 proteins)	± ^d	+	NA	NA	[111, 112]
Procalcitonin	Weak (rule out sepsis)	NA	NA	NA	[113]
SAA	NA	NA	+	NA	[42]
			Predictive of AA amyloidosis		

(continued)

Biomarker	Diagnosis ^a	Disease activity monitoring	Prognosis: severity (i.e., predictive of life-threatening complications)	Prognosis: evolution (i.e., predictive of evolution pattern ^b (systemic versus arthritis; monophasic, recurrent, or progressive, either systemic or joint))	References
<i>Nonroutine biomarkers</i>					
IL-18 > 150 ng/L >366 ng/L	Se 88% Sp 78% Se 91.7% Sp 99.1%	+	+	High levels potentially associated with systemic pattern	[110, 111, 114–124]
IL-1 β *	- ^c	+	\pm	High levels potentially associated with systemic pattern	[115, 116, 125]
IL-6*	- ^c	+	\pm	High levels potentially associated with arthritis pattern	[115, 116]
TNF- α *	- ^c	-	-	-	[115, 116]
S100A12 protein*	\pm ^f	+	NA	NA	[43, 45, 126]
AGEs and sRAGE*	\pm	+	NA	+	[50]
				Higher AGE levels in serum with polycyclic or chronic articular patterns (compared to monocyclic pattern)	
CXCL10*	+	+	NA	NA	[127]
CXCL13*	+	+	NA	NA	[127]
sCD163*	\pm	NA	NA	NA	[128, 129]
MIF*	+	+	NA	NA	[130]
ICAM1*	\pm	+	NA	NA	[131]

+ yes, - no, ± tested but contradictory results, *NA* not assessed, *ULN* upper level of normal, *se* sensitivity, *sp* specificity, *reference range according to manufacturer
AA amyloid A, *AGEs* advanced glycation end products, *CRP* C-reactive protein, *ICAM1* intracellular adhesion molecule-1, *IL* interleukin, *MIF* macrophage inhibitory factor, *RHL* reactive hemophagocytic lymphohistiocytosis, *SAA* serum amyloid A protein, *sRAGE* soluble receptors for AGEs, *TNF* tumor necrosis factor

^aA good diagnostic biomarker helps rule out the differential diagnoses of infection, malignancy, and other inflammatory disorders

^bIdentifying the disease subset might orientate the therapeutic strategy

^cSerum ferritin levels are significantly higher in the systemic subtype [110], but high ferritin levels after adequate treatment may predict chronic articular course [61]

^dCalprotectin levels help rule out rheumatoid arthritis, but further studies are needed to validate it as a diagnostic biomarker because of no statistical difference between AoSD and septic patients, although the populations were small [42]

^eElevated plasma levels of IL-1 β , IL-6, and TNF α have been found during AoSD, but the cytokine profile is not specific and cannot differentiate AoSD patients from those with sepsis

^fS100A12 was found an efficient diagnostic and monitoring biomarker in systemic juvenile arthritis, but further studies are needed for validation in AoSD

Procalcitonin, a marker of severe systemic infection, was also found elevated in patients with active AoSD and does not appear relevant to distinguish acute infection from AoSD flare [42, 113].

Serum level of calprotectin (i.e., S100A8/S100A9 protein) could be an additional disease activity biomarker because alarmins seem to play a key role in AoSD pathogenesis. However, it is not specific to AoSD and may be elevated in many other inflammatory conditions [42, 44, 111, 112]. Finally, serum amyloid A protein (SAA) is an inflammatory biomarker found predictive of amyloidosis [42].

6.7.2.2 Potential Biomarkers for Future Clinical Research

Several research works assessed serum cytokine levels. High serum levels of IL-1, IL-6, and IL-18 have been found in systemic forms of AoSD and can be considered activity biomarkers. However, their additional value on top of CRP level and other inflammatory biomarkers is unclear, and these cytokines are clearly not specific to AoSD. Thus, they are not recommended in routine investigation. Of importance, IL-18 seems to play a key role in RHL.

AGE products and RAGEs, involved in AoSD pathogenesis, may be elevated in other inflammatory disorders. High serum levels have been associated with polycyclic or chronic/progressive evolution patterns [42]. Serum level of soluble CD163, a macrophage activation biomarker, is elevated in AoSD but is not specific to the disease. Finally, several chemokines (C-X-C motif chemokine ligands 10 and 13, macrophage inhibitory factor) have been found to be diagnostic biomarkers for AoSD, which needs to be confirmed in larger patient samples [42].

6.8 Disease Evolution and Prognosis

AoSD evolution can be quite diverse and currently is impossible to predict. Several patterns of evolution have been described, mainly based on case series and not robust epidemiological studies [5, 9, 102, 132, 133]:

6.8.1 Evolution Patterns

6.8.1.1 Self-Limited, Monocyclic Evolution

It combines systemic manifestations and joint involvement: the initial flare evolves over a few weeks; remission is achieved with steroids or other immunomodulatory agents after a few days or weeks; and treatments can be progressively tapered and then stopped without relapse after a few months. The pattern may represent 19–44% of cases.

6.8.1.2 Recurrent or Polycyclic Evolution

It is characterized by AoSD relapses after a few months or years, under immunomodulatory treatment or after its discontinuation. In this pattern, one classical presentation is a first flare during childhood-diagnosed SoJIA, followed by sustained drug-free remission for several years, and then a relapse in adulthood. In most of

these cases, recurrences combine systemic and joint involvement. The pattern represents 10–41% of cases.

6.8.1.3 Chronic and Progressive Evolution

In this form, a continuous inflammation is responsible for chronic and frequently erosive joint involvement with regular systemic flares. This pattern was the most frequent, estimated at 35–67% of cases, in old series [1, 102, 134]. Although no new estimates are available, this pattern should be less likely with the most recent targeted therapies.

6.8.2 Prognosis

The prognosis of AoSD is dominated by potential life-threatening events as well as progressive functional impairment.

6.8.2.1 Life Prognosis

The life prognosis is dominated by the severity of the following visceral involvements, in isolation or combination: hematological complications, such as DIC, TMA, or severe RHL; fulminant hepatitis with rapid liver failure; and acute respiratory distress syndrome, extensive myocarditis, or multiorgan failure [3, 59]. Importantly, exacerbation of these serious symptoms has been reported within the first days of treatment initiation, especially of biological therapies. This necessitates a close and very careful monitoring of such patients at the start of treatment. In addition to organ involvements, the development of secondary amyloidosis of the AA type remains possible in long-standing refractory chronic articular AoSD [59].

6.8.2.2 Functional Prognosis

Functional prognosis depends mainly on erosion and joint destruction in chronic articular AoSD, which affects approximately one-third of patients [3, 7, 102]. No clear predictor of erosive joint disease has been identified, but, as joint involvement is often limited, functional prognosis in AoSD seems to be less severe than in RA or other inflammatory arthritides [135].

6.8.2.3 Iatrogenicity

Corticosteroid side effects are also common because steroids are usually prescribed in high doses and the long term, which might contribute to the overall prognosis in AoSD.

6.9 AoSD Treatment

AoSD is rare, and no randomized controlled trial has been performed. Thus, the only information on therapy is from observational studies and retrospective case series. Recently, the management of AoSD benefited from the proofs of the efficacy of targeted biotherapies.

6.9.1 Symptomatic Treatments

Although NSAIDs, including aspirin, have been effective in systemic JIA, they are rarely effective in AoSD; only 20% of patients have achieved control with this therapy [1, 102, 103].

Of the NSAIDs, indometacin 150–250 mg/day seems to be the most effective [3, 102]. Liver enzymes must be monitored at the initial stages of the disease because severe hepatitis has been suggested to be related to treatment with NSAIDs [3, 102, 103].

Acetaminophen may help to reduce fever, although it is often not enough to suspend it. Other analgesics might be necessary to relieve intense myalgia and joint pain.

6.9.2 Corticosteroids

Once the diagnosis is established, corticosteroids are usually required to induce symptom remission. Optimal dosing relies on medium to high doses (i.e., 0.5–1 mg/kg/day of prednisone equivalent) [3, 5, 6, 16, 102]. Patients with serious visceral involvement might achieve a quick response with intravenous infusion of high-dose methylprednisolone [3, 102, 103]. Response to corticosteroids is often dramatic—within a couple of hours or a few days [3, 102].

The consensus is lacking on a therapeutic tapering scheme once clinical remission is achieved. However, owing to the potentially serious side effects of cumulative corticosteroid therapy, many others currently recommend to achieve the dose of 0.1 mg/kg/day after 6 weeks of therapy and to stop completely after three months. If this is not possible, the response should be considered inadequate, and a disease-modifying treatment, especially a targeted therapy, should be started (Fig. 6.6) [16].

6.9.3 Methotrexate

Methotrexate is used as an immunomodulatory agent in rheumatoid arthritis. It is efficient in controlling AoSD disease activity and allowing for steroid dose sparing [3, 136–138]. However, whether methotrexate can prevent or limit joint structural damage in the erosive form of AoSD, as has been shown for RA, is unclear. The presence of liver enzyme abnormalities does not contraindicate methotrexate prescription, but close biological monitoring is necessary [3, 102, 136, 137].

Of importance, methotrexate can be associated with anti-IL-1- or anti-IL-6-targeted therapies.

6.9.4 Targeted Therapies for AoSD

Different targeted therapies have been used to treat refractory AoSD (Table 6.5). The medical need is high, keeping in mind the unsatisfactory rates provided by

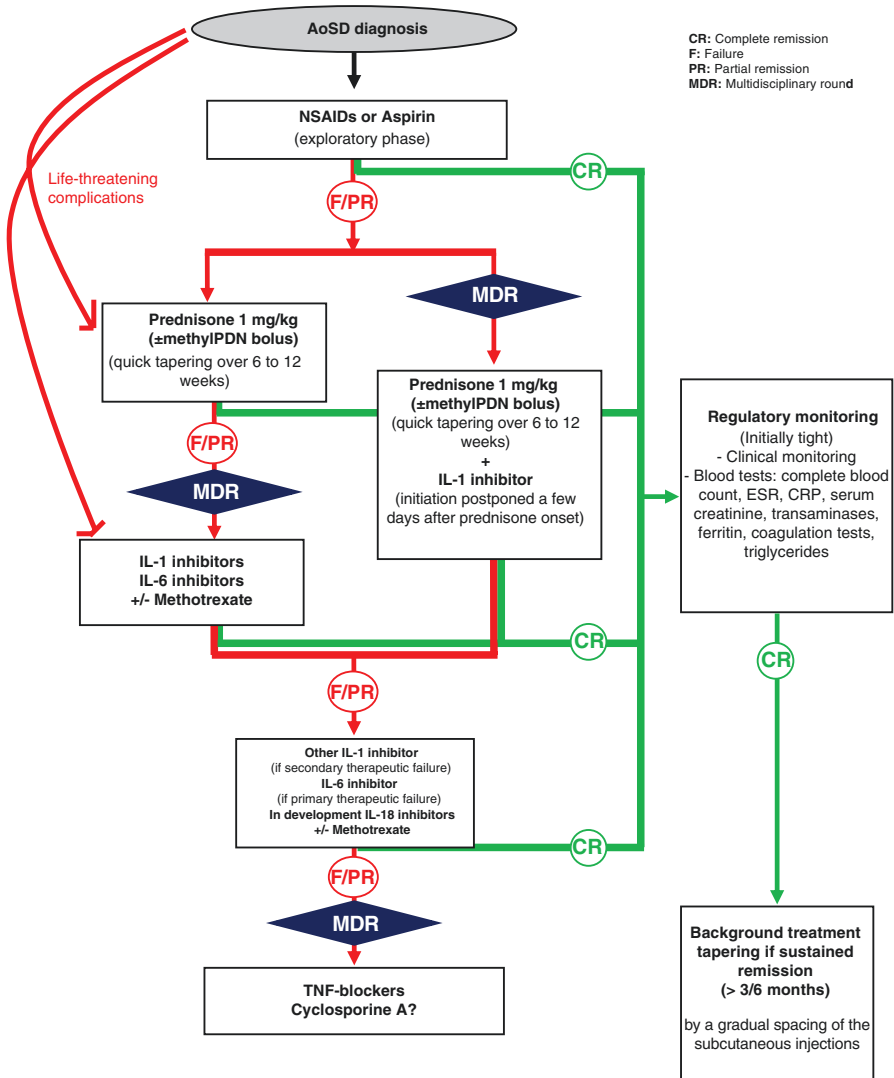


Fig. 6.6 Therapeutic strategies to manage AoSD patients. *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *IL* interleukin, *methylPDN* methylprednisolone, *NSAIDs* nonsteroidal anti-inflammatory drugs, *TNF* tumor necrosis factor

classical therapies with NSAIDs or conventional disease-modifying antirheumatic drugs (DMARDs). The use of glucocorticoids is also limited by the known long-term safety issues, especially with higher doses. In fact, for at least 30–40% of patients, the disease cannot be controlled by glucocorticoids even when combined with conventional DMARDs, such as methotrexate.

Table 6.5 AoSD targeted therapies

Targeted therapy	International nonproprietary name and usual dose	Reported no. of patients	Preferential AoSD pattern	Follow-up (months)	Complete remission (%)	Steroid dose reduction	References
IL-1 receptor antagonists	Anakinra 100 (sometimes 200) mg/day SC	>250	Systemic and articular	>12	80	Yes	[46, 68, 69, 139–144]
Anti-IL-1 β	Canakinumab 150 (sometimes 300) mg/month SC	<5	Systemic and articular	>12	100	Yes	[145–147]
IL-1 trap	Rilonacept Loading dose of 100–320 mg and then 100–320 mg/week	<5	Systemic and articular	>12	100	Yes	[148]
TNF blockers	Infliximab 3–7.5 mg/kg at W0–W2–W6 and then every 6–8 weeks IV Or Etanercept 50 mg/7 days SC	<100	Articular	>12	0–100	n.k.	[149–154]
IL-6 receptor antagonists	Tocilizumab 8 mg/kg/month IV Or 162 mg/week SC	<150	Systemic and articular	>12	60–85	Yes	[155–162]
Anti-IL-18	Tadekinig alfa 80 mg/week SC Or 160 mg/week SC	<25	NA	4	n.k.	n.k.	[163]
B cell directed	Rituximab 1 g D1–D15 every 6 months	Single case	NA	12	n.k.	n.k.	[164]
T cell directed	Abatacept 500–1000 mg/month IV ^a Or 125/week SC	Single case	NA	>12	n.k.	n.k.	[165, 166]

D day, IV intravenously, SC subcutaneously, W week, NA not available, IL interleukin, TNF tumor necrosis factor, n.k. not known

^aAbatacept dose depends on patient's weight: <60 kg = 500 mg, 60–100 kg = 750 mg, \geq 100 kg = 1000 mg

6.9.4.1 IL-1 Inhibition

The use of IL-1 inhibitors for AoSD contributed to the revival of considering this mode of action in rheumatology and now represents the primary choice for treating autoinflammatory diseases in general. However, it took surprisingly long until clinical development moved forward from cohort studies to randomized, placebo-controlled trials. Currently, two IL-1 blocking compounds are the focus of phase 2/phase 3 studies with different designs.

Anakinra, a recombinant IL-1 receptor antagonist, was the first biologic showing beneficial effects in treating the systemic and articular features of AoSD in many case series, uncontrolled trials, and different national surveys. Although the evidence for its efficacy has not been proven by controlled trials, the overall number of more than 250 published cases provides convincing results. In fact, a clear and sustained improvement was described for systemic and also arthritic symptoms in most treated cases [68, 139–143]. Systemic features seem to show a more rapid response, and longer exposure seems usually required for improvement of arthritis. Of major importance for long-term safety were consistent reports of a reduction or even discontinuation of glucocorticoids use as well as NSAIDs. In this context, meta-analyses from eight case series and three national surveys meeting predefined quality standards and including more than 100 anakinra-treated AoSD patients revealed a remission rate of approximately 80% and a reduced use of steroids in approximately 35% of patients [69]. Recently, a large observational retrospective multicenter study from Italy added evidence for a strong impact on disease activity with the Pouchot score as well as clinical and serological features regardless of sex, age, disease pattern, or co-medication [46]. Since September 2017, a randomized, double-blind, placebo-controlled, multicenter, phase 3 study in the United States has recruited patients for investigating two different doses of anakinra (2 mg/kg/day [max 100 mg/day] or 4 mg/kg/day [max 200 mg/day]) to evaluate its efficacy and safety in patients newly diagnosed with SoJIA and AoSD. The primary end point, American College of Rheumatology 30 (ACR30) response, has already been evaluated at week 2; however, the overall treatment period is short, with only 12 weeks of exposure followed by a 4-week safety follow-up [167]. Of note, anakinra is the only IL-1 blocker for which we have substantial long-term results in terms of efficacy and safety in AoSD [144], and it has now been approved in this indication. In contrast to monogenic autoinflammatory diseases, in AoSD, remission can continue in some cases even after treatment is stopped. However, a relatively high withdrawal rate of 40% has been reported owing to loss of response over time and also to frequent injection site reactions to the required daily administrations.

The other approved biologic for AoSD is canakinumab, a fully human antibody against IL-1 β [145]. Furthermore, canakinumab is also approved for treating other autoinflammatory diseases including cryopyrin-associated periodic syndromes, familial Mediterranean fever, TNF receptor-associated periodic syndrome, and hyper-IgD syndrome as well as SoJIA. Although the overall experience with canakinumab in AoSD is still limited, the reported response of systemic features and arthritis was rapid and sustained over many months to years in most patients, frequently allowing for tapering of steroids [145–147]. Of note, canakinumab was

found highly effective for patients with AoSD who were difficult to treat, including those showing failure of NSAIDs, glucocorticoids, and other IL-1 inhibitors. With these promising results, a placebo-controlled, randomized, multicenter, phase 2 study of canakinumab in AoSD is ongoing [168]. The dosage of canakinumab with monthly injections of up to 4 mg/kg body weight (maximum dose of 150 mg) is based on the pharmacokinetic profile in adolescent patients with SoJIA. The primary aim is to investigate the efficacy of canakinumab in patients with AoSD and active joint involvement in terms of the proportion of patients with a clinically significant reduction in disease activity (Disease Activity Score in 28 joints [DAS28] > 1.2) following a treatment period of 12 weeks. The overall placebo-controlled period is 24 weeks, but nonresponders can be unblinded and show treatment rescue at week 12. The core study is followed by an optional long-term extension over 2 years to provide additional safety results in the adult population.

In summary, the published data for anti-IL-1 agents in refractory AoSD clearly show a consistently high rate of full or partial remission with the additional achievement of lowering or stopping glucocorticoid medication [169].

6.9.4.2 IL-6 Inhibition

Inhibition of IL-6 signaling is possible by two different approaches, the direct neutralization of the cytokine or the blockade of the respective receptor. None of these mechanisms has been investigated in AoSD in a controlled setting of clinical trials in detail. For the two different IL-6 receptor antagonists currently available in daily practice for treating rheumatic diseases, only the tocilizumab AoSD case series has been published and reported at conferences [155–158]. To summarize, the observed anti-inflammatory effects were strong, rapid, and sustained for most of the cases. Usually, the systemic features disappeared entirely, but also the arthritic manifestations improved, and the serologic activity decreased [159, 160]. However, because of limited data, the likelihood of response cannot be estimated as clearly as for IL-1 inhibitors and seems to be between 60% to 80% in terms of full remission. A recently published meta-analysis of ten original studies (147 individuals) on the efficacy of tocilizumab and AoSD revealed overall high partial and complete remission rates of 85–77%, respectively. Tocilizumab prevented new flares, was well tolerated, and could significantly reduce the need for corticosteroids [161, 162].

Whether other IL-6 inhibitors have similar effects remains unknown. As shown for RA treatment, with AoSD, differences could exist with respect to safety, especially in comparison to the direct cytokine inhibitors. Also, the advantages or disadvantages that distinguish IL-6 and IL-1 inhibition are unclear. Although clearly IL-6 as well as IL-1 inhibitors have high response rates and represent alternative approaches in AoSD, we have no way to predict the individual effects and define the ideal treatment algorithm.

6.9.4.3 IL-18 Inhibition

A novel compound is Tadekinig alfa, a recombinant human IL-18 binding protein [163]. This drug was tested in healthy volunteers and patients with psoriasis and

RA in phase I studies and demonstrated a good safety and tolerability profile with only mild adverse events at the injection site. Because of the postulated role of IL-18 in the pathogenesis of AoSD, it was a logical step to investigate the effects of Tadekinig alfa in this condition. A first open-label, dose-finding phase 2 study involving multiple centers in Europe was designed to capture safety information as the primary outcome. Two doses (80 and 160 mg) were administered during 12 weeks, and patients were followed up for 4 more weeks. As a secondary outcome measurement, the efficacious dose at 3 weeks was defined as normalization of body temperature and decrease of CRP level by 50% or more of baseline values.

Although limited by the low patient number and short observation period in the study, the safety profile of Tadekinig alfa was overall acceptable, with injection site reactions and infections being the most frequent adverse events. In terms of efficacy, reduced level of CRP as well as other inflammatory markers (including IL-18, ferritin) was detected in some patients. Furthermore, an improvement in skin rash and a slight but significant reduction in the prednisolone doses were reported. In summary, inhibition of IL-18 by Tadekinig alfa could be a promising new approach in ASOD that needs to be investigated in a controlled setting.

6.9.5 Other Potential Agents with Less Validated Indication

Many other treatments have been tried in AoSD, with varying degrees of success.

6.9.5.1 TNF Inhibition

Stimulated by encouraging results from other chronic inflammatory joint diseases, especially RA, TNF inhibitors have been the first biologics used for AoSD [149–154]. However, driven by the deceptive impression that AoSD, with a predominant arthritic phenotype, is a subgroup of seronegative RA, the results from uncontrolled trials involving usually small cohorts of patients were inconsistent. Since favorable outcomes have been seen in only a few patients without any specific characteristics, TNF inhibitors can only be considered third-line drugs, preferentially for patients with chronic arthritis.

6.9.5.2 Cyclosporine A

Cyclosporine A has been proposed before the era of biotherapies, in patients with systemic features of AoSD or with RHL, with an interesting efficacy. However, the tolerance of this drug limits its use, but it certainly can be of interest in complex or refractory situations.

6.9.5.3 Intravenous Immunoglobulins

There is henceforth no place for intravenous immunoglobulins in AoSD treatment, owing to the efficacy of the other therapies available.

6.9.6 Treatment Strategies

The strategy we propose for AoSD patients is summarized in Fig. 6.6.

6.9.7 Treatment and Management of Life-Threatening Complications

6.9.7.1 Reactive Hemophagocytic Lymphohistiocytosis (RHL)

Management should include, firstly, symptomatic care in a medicine department or intensive care unit (ICU); secondly, active and rapid search for an infection; and, thirdly, introduction of high-dose steroids. Since RHL has described under IL-1 therapy, it appears prudent to introduce this treatment only after RHL control by a few days of high-dose steroids.

6.9.7.2 Coagulation Disorders

DIC is a medical emergency whose care combines:

1. Supportive measures, which could include platelet transfusion, coagulation factors (or fresh frozen plasma), and fibrinogen (in cryoprecipitate) infusion to control severe bleeding or sometimes heparin if no active bleeding is present [70].
2. Specific anti-inflammatory agents often decided in multidisciplinary rounds, with mainly high-dose corticosteroids, either intravenous (methylprednisolone 15 mg/kg/day) or oral (prednisone 1 mg/kg/day) [59]. To limit steroid exposure, the addition of other immunomodulatory agents, such as IL-1 or IL-6 blockers or cyclosporine, is recommended [68, 69, 71–73].

TMA treatment is complex and mandatorily includes [60]:

1. Supportive care in an ICU, with plasma exchange being central [75]
2. High-dose steroids intravenously and then orally

Other immunomodulatory agents proposed for refractory cases include anakinra [74], tocilizumab [76], intravenous immunoglobulins, cyclophosphamide, azathioprine, cyclosporine A, and rituximab [60, 74]. Despite this treatment, mortality associated with TMA remains high, up to 20% [60].

6.9.7.3 Cardiac and Pulmonary Involvements

Their treatment combines supportive care, high-dose steroids, and frequently IL-1 or IL-6 inhibitors.

Regarding PAH, early diagnosis is central for the prognosis of this complication, with mortality remaining as high as 40% [60]. The diagnosis includes [80, 82, 83, 85, 86, 100, 101]:

1. Hospitalization in an ICU and rapid referral to a specific reference center for multidisciplinary round discussions.

2. Vasodilating therapies frequently combining endothelin receptor antagonists (bosentan, ambrisentan), phosphodiesterase-5 inhibitors and other guanylate cyclase stimulators (sildenafil or others), and prostacyclin analogues.
3. High-dose steroids, initially intravenously and then orally.
4. Rapid introduction of biologic immunomodulatory agents targeting IL-1 or IL-6 or other immunosuppressive agents, such as methotrexate, azathioprine, cyclophosphamide, cyclosporine, or rituximab. However, these treatments must be carefully monitored because a few cases of PAH worsening have been described after their introduction.

PAH deserves to be well known by physicians caring for AoSD patients because it was not described in most of the initial AoSD case series for several reasons: now better diagnostic tools for PAH; differential efficacy of large-spectrum immunomodulatory agents, such as steroids, as compared with more targeted therapies, such as IL-1 or IL-6 blockers; and exposure to microorganisms as an additional target whose ecology may have evolved in recent years.

6.9.7.4 Amyloidosis

Even administered late, AoSD therapy, such as steroids and above all IL-1 and IL-6 blockers, may at least in part improve the clinical and biological symptoms.

6.10 Conclusion

In the last 15 years, substantial progress has been made in the diagnosis and prognosis of AoSD. The coming years will likely contribute to a better understanding of the disease and its complications, notably in disease pathogenesis, identification of diagnostic and prognostic biomarkers, and new targets for preventing both life-threatening manifestations and chronicity.

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