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Adult-onset Still's disease in focus: Clinical manifestations, diagnosis, treatment, and unmet needs in the era of targeted therapies

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ABSTRACT

Background: Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disorder of unknown etiology, characterized by a clinical triad of high spiking fever, arthralgia (± arthritis), and evanescent skin rash. Management of AOSD poses several challenges, including difficulty in diagnosis and limited therapeutic options. In this review, we examined whether AOSD and systemic juvenile idiopathic arthritis (SJIA) represent a continuum of the same disease. We also explored the latest available evidence related to prevalence, clinical and laboratory manifestations, complications, diagnostic challenges, novel biomarkers, and treatment options in the era of biologics and identified the unmet needs of patients with AOSD.

Methods: A comprehensive systematic literature search was performed in the Embase and MEDLINE (via PubMed) literature databases. The search was limited to human studies published in English from inception up to March 2020. Additionally, abstracts presented at various conferences were screened and hand searches were performed. Publications were processed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Results: A total of 123 publications were identified through the literature search, majority of which were case series and retrospective observational studies. AOSD and SJIA are widely considered part of the same disease spectrum owing to similarities in their clinical and biological features. The clinical presentation of AOSD is highly variable, accompanied by a broad spectrum of disease manifestations. Recent evidence suggests that the AOSD disease course can be classified into two distinct categories: "systemic" and "articular." Furthermore, AOSD patients may experience various life-threatening complications, such as macrophage activation syndrome — reported in as high as 23% of AOSD patients and considered to be the most severe complication characterized by a high mortality rate.

The ambiguity in presentation and lack of serologic markers make the diagnosis of AOSD difficult, often leading to a delay in diagnosis. Given these limitations, the Yamaguchi and Fautrel criteria are the most widely used diagnostic tools in clinical practice. It has been observed that a clinical diagnosis of AOSD is generally reached by exclusion while investigating a patient with fever of unknown origin. Recent advances have demonstrated a major role of proinflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-18, and IL-37, and other biomarkers in the pathogenesis and management of AOSD.

Owing to the rarity of the disease, there are very limited clinical trials evaluating management strategies for AOSD. The current AOSD treatment paradigm includes non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids initially, conventional synthetic disease-modifying anti-rheumatic drugs in steroid-refractory patients, and biologics in those resistant to conventional treatment. Only a few country-specific guidelines for the management of AOSD have been published, and a treat-to-target approach, as previously recommended for SJIA, is still lacking. Canakinumab is the only FDA–approved biologic for the treatment of AOSD.

Abbreviations: ACR, American College of Rheumatology; ANA, antinuclear antibody; AOSD, adult-onset still's disease; CRP, C-reactive protein; Cyr61, cysteine-rich angiogenic inducer 61; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; FDA, Food and Drug Administration; FUO, fever of unknown origin; HLA, human leukocyte antigen; HLH, hemophagocytic lymphohistiocytosis; HO-1, heme oxygenase; IL, interleukin; IFN, interferon; JAK, Janus kinase; LRG, leucine-rich α2-glycoprotein; MAS, macrophage activation syndrome; NLR, neutrophil-to-lymphocyte ratio; NSAID, nonsteroidal anti-inflammatory drug; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RA, rheumatoid arthritis; RF, rheumatoid factor; RCT, randomized controlled trial; SJIA, systemic juvenile idiopathic arthritis; SLE, systemic lupus erythematosus; SLR, systematic literature review; USA, United States of America; US, United States

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Conclusion: Emerging evidence supports that AOSD and SJIA represent a continuum of the same disease entity. Despite advancements in the understanding of AOSD, it continues to pose a substantial burden on patients and the healthcare systems, and substantial unmet needs exist across key domains such as the pathway to diagnosis, use of biomarkers in clinical practice, and standardized treatment strategies. Further research and collaboration is crucial for optimizing the diagnosis and management of AOSD patients.

Introduction

Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disease of unknown etiology usually affecting young adults. AOSD was first described as a distinct clinical entity in the early 1970s by Eric Bywaters [1]. It is typically characterized by a triad of spiking fever, arthritis, and salmon-colored skin rash and closely resembles childhood-onset Still's disease, commonly known as systemic juvenile idiopathic arthritis (SJIA), which was first described by George Still in 1897 [2]. Although the exact pathogenic mechanisms of the disease are unknown, substantial advances have been made supporting the concept of a Still's disease spectrum, wherein SJIA and AOSD would be part of a continuum, delimited by the age at onset of disease presentation [3]. Several factors have been proposed to be involved in the etiology of this disease, including genetics (association with human leukocyte antigen [HLA] DRB1*1201 and 1501, B35, DR2 and DR5), infections (from viral and bacterial pathogens), and a dysregulated immune system [4–7]. Stressful life events related to work, family and health have also been suggested to be a potential trigger for AOSD [8]. With the advantage of understanding the role of the inflammasome in its childhood counterpart SJIA and in monogenic autoinflammatory diseases, there is growing evidence that AOSD is an autoinflammatory disorder [9,10].

In this systematic literature review (SLR), we focused on the epidemiology, clinical picture, complications, diagnosis, and possible treatment strategies for AOSD in the era of biologics. We also explored the relationship between AOSD and SJIA and new diagnostic biomarkers available for AOSD patients.

Methods

This SLR was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11]. Comprehensive searches were conducted in March 2020 using the Embase and MEDLINE (via PubMed) literature databases as well as abstracts presented at various conferences. We also performed hand searches for relevant additional references. The main search terms included "Adult Onset Still Disease," "AOSD," "Still's disease," "Wissler Fanconi syndrome," "epidemiology," "diagnosis," "clinical and laboratory manifestations," "disease continuum," "disease burden," "diagnostic biomarkers," and "treatment" (see Supplementary Material for the complete list of search terms). The search was limited to human studies published in English from inception up to March 2020. Two reviewers independently screened all the identified studies, and any disagreement was discussed and resolved.

The search identified 2178 articles, of which 2107 were assessed for eligibility after removal of duplicates and 123 publications fulfilling the requirements were selected for the present SLR (Fig. 1). A majority of the retrieved articles were case series, case reports, and retrospective observational studies; therefore, to ensure reliable data assessment, we included only those articles reporting data from ≥30 patients. Well-designed prospective studies in AOSD patients are very limited owing to the rarity of the disease. Furthermore, as the number of randomized controlled trials (RCTs) in AOSD patients is very limited, we included all available RCTs irrespective of the number of patients.

No ethical approval was required because no individual patient identifiers were disclosed in the publications included in this SLR.

Results

Continuum of sjia to AOSD

AOSD is a systemic inflammatory disorder analogous to SJIA. Both conditions encompass many common clinical and biological features, including the occurrence of macrophage activation syndrome (MAS; Table 1). Specifically, cohort studies across the spectrum depict that both AOSD and SJIA appear to affect a similar distribution of joints and are similarly associated with a constellation of systemic manifestations, including fever; a very characteristic salmon-colored, evanescent cutaneous eruption; splenomegaly; lymphadenopathy; myalgia; hepatomegaly; pericarditis; pneumonitis; and renal dysfunction. Collectively, these findings show that AOSD patients have a disease onset and course undistinguishable from that of SJIA patients, suggesting that these diseases represent a continuum of a single disease entity.

Epidemiology

AOSD is a rare multisystem disease; it is a relatively recently described condition and therefore lacks robust epidemiological data. Most of the information is based on data from retrospective observational studies or case series. The annual incidence of AOSD is estimated to be between 0.16 and 0.62 per 100,000 individuals worldwide, independent of ethnicity [18–20]. The estimated prevalence is between 0.73 and 6.77 per 100,000 individuals [18,19,21]. In two recent studies, the prevalence was reported to be 3.9 per 100,000 individuals in Japan and 6.77 per 100,000 individuals in Turkey [18,21]. Owing to an increased awareness about AOSD over the last 2 decades, incidence and prevalence rates were observed to be higher in recent studies compared with those reported before 2000 (Table 2).

Disease patterns

Conventionally, three major disease patterns have been observed in AOSD patients: monocyclic, polycyclic, and chronic articular (Table 3). The monocyclic pattern is characterized by a single systemic episode completely resolving within months; the polycyclic (also called intermittent) pattern is associated with one or more disease flares and characterized by complete remissions that can last up to a couple of years, and the chronic articular pattern is usually associated with long-lasting polyarthritis.

Maria et al. have proposed a dichotomous view of AOSD, distinguishing the AOSD subtypes according to the dominant clinical expression. Thus, it is possible to discriminate two different subsets of patients—those with predominant systemic clinical features, such as fever and skin rash, and those with predominant articular involvement, more similar to the classic features of rheumatoid arthritis (RA) [22]. Approximately 50–70% of patients develop a chronic polycyclic form of the disease or chronic polyarthritis, which can eventually induce joint destruction [21,23–25]. Similarly, *Ichida* et al. have described two subsets of patients with AOSD—the "non-RA subtype,"

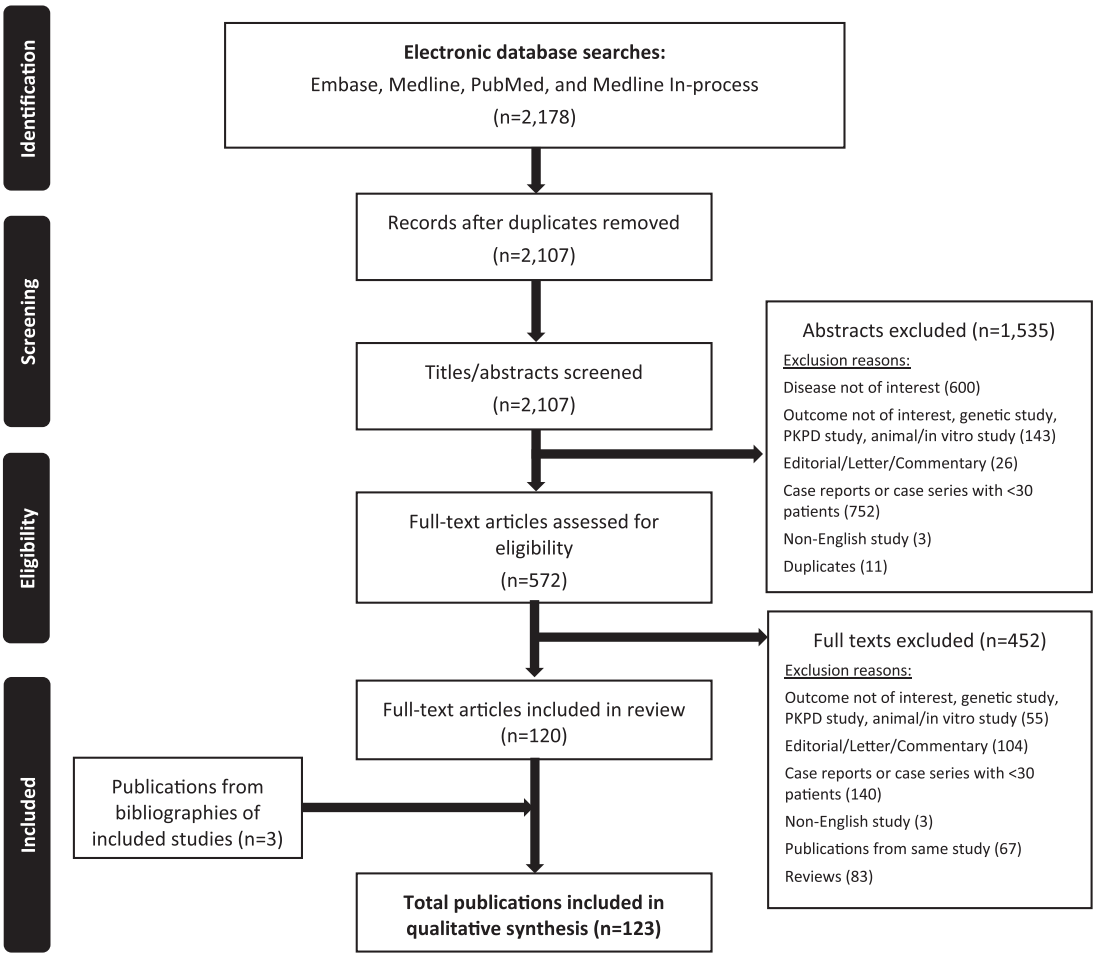

Fig. 1. Summary of search results: PRISMA flow diagram.
Abbreviations: PKPD: pharmacokinetic-pharmacodynamic; PRISMA: preferred reporting items for systematic reviews and meta-analyses.

characterized by severe systemic inflammation, and the "RA-like subtype," characterized by severe, sometimes erosive, arthritis [26].

In regard to disease progression, *Colina* et al. demonstrated that persistence of high ferritin levels after adequate treatment may be a predictor of the chronic articular course [27]. Furthermore, data from a large multicenter study suggested that a delayed diagnosis was an important factor associated with the development of chronic disease. Relapses or chronic articular patterns were found to be more common when the diagnosis had been delayed for >6 months [25–27].

Clinical and laboratory manifestations

Age at diagnosis

The disease occurs worldwide, usually affecting young adults with a mean age at diagnosis of approximately 38 years (range: 33.3–45.0 years); however, delayed diagnosis is common considering the nonspecific symptoms and the lack of awareness among patients and within the medical community. AOSD shows a bimodal age distribution with two peaks of onset—the first affecting people in the age group of 16–25 years and the second affecting people in the age group of 36–46 years. Most patients (45–80%) had disease onset between 16 and 35 years of age. Although onset after the age of 60 is rare, some case series have identified adult onset in patients >60 years of age as well, which constituted around 7–10% of the cases [23,35,37,44,45]. The sex ratio was almost balanced in some studies, while in some of the largest case series, a female predominance was observed (Table 4).

Clinical manifestations

AOSD patients generally present with the following triad of symptoms: a spiking fever (>39 °C), maculopapular salmon-colored rash, and arthritis or arthralgia. The most common features of AOSD are listed below:

- Fever: Fever is the most prominent symptom, occurring in 46–100% of patients, and usually precedes other manifestations. The fever is typically a high spiking quotidian fever (≥39 °C), which occurs daily or occasionally peaks twice daily, resolving within a few hours. In a large cohort of AOSD patients, the fever pattern was usually intermittent in most cases, and was remittent in up to 20% of the cases [37]. The diagnosis is often reached by exclusion while investigating a patient with a fever of unknown origin (FUO) [23,35,46]. Thus, awareness of this characteristic fever pattern can be a valuable clue to early recognition of the disease and to differentiate among other conditions such as lymphoma (Pel-Ebstein fever) and infections (tertian and quartan malarial infections and undulant fever in brucellosis).
- Musculoskeletal manifestations: Joint involvement is a common sign in AOSD patients (approximately 40–100%), with arthralgia and arthritis being the most frequently reported manifestations. Arthritis, which is usually mild and localized at the beginning, can aggravate through the course of the disease, becoming more severe and polyarticular. The most commonly involved joints are the knees, wrists, ankles, elbows, and proximal interphalangeal joints [35,37,38,41,44,47]. AOSD often spares the distal interphalangeal joints of the hands and shoulders. Narrowing of the

Table 1
Similarities and differences between AOSD and SJIA.

Publication	No. of patients AOSD	SJIA	Similarities	Differences
Inoue_2016 [12]	33	77	Clinical features: rash, lymphadenopathy, hepatomegaly, splenomegaly, and arthritis Laboratory findings: hyperleukocytosis and elevation of transaminase and ferritin levels MAS reported in both Similar cytokine release patterns in both clinical entities Markedly elevated serum IL-18 levels in patients with AOSD and SJIA during the active and inactive phases of the disease Elevated levels of serum neopterin, IL-6, IL-18, sTNF-RI, and sTNF-RII were observed in patients with AOSD and SJIA during the active phase; however, all these cytokine levels normalized once patients achieved clinical remission Significant increases in serum neopterin, IL-18, sTNF-RI, and sTNF-RII were observed during the MAS phases of both diseases	Significant female predominance among patients with AOSD ($p < 0.05$) Significantly increased serum ferritin levels, hepatomegaly, and splenomegaly were observed more frequently with AOSD ($p < 0.05$) Arthritis was more common among SJIA patients than among AOSD patients ($p < 0.05$)
Feist_2018 [13]	29	216 children; 56 young adolescents	Canakinumab had a similar efficacy in older adolescents/young adults and children and young adolescents, i.e., both diseases were highly responsive to IL-1β inhibition	–
Lin_2000 [14]	21	24	All children and adults with Still's disease had fever Affected joints were similar—the knees, ankles, wrists, elbows, proximal interphalangeal joints, and metacarpophalangeal joints (in order of frequency) The clinical and laboratory features were similar All children and adults received therapeutic dosages of NSAIDs (aspirin or naproxen) Chronic arthritis was comparable	More AOSD patients vs SJIA patients presented with a sore throat (81% vs 46%; $p = 0.03$) AOSD patients had a significantly higher serum ferritin concentration than SJIA patients during the active disease phase ($p < 0.01$)
Pay_2006 [15]	95	25	There were no significant differences in the pattern of fever and the type of skin rash or its localization between the groups	The frequency of fever (98.9% vs 84%; $p < 0.05$), skin rash (82.1% vs 64%; $p < 0.05$), myalgia (69.5% vs 20%; $p < 0.001$), weight loss (17.9% vs 0%; $p < 0.05$), and sore throat (66.3% vs 24%; $p < 0.001$) was found to be significantly higher in patients with AOSD compared with patients with SJIA The most commonly affected joints were the wrists, knees, and ankles (in order of frequency) in adult patients with AOSD and the ankles, knees, and wrists in patients with SJIA Liver dysfunction and neutrophilia were more common among adults A majority of the adult patients had an unclassified course in AOSD vs SJIA patients (21.1% vs 8.3%; $p < 0.05$), whereas children predominantly had a polycyclic disease pattern (41.7% vs 16.8%; $p < 0.001$)
Uppal_1995 [16]	31	23	The clinical picture, disease course, and outcomes in AOSD were similar to those in SJIA	AOSD had a significantly lower time interval from disease onset to remission compared with SJIA
Yang_2018 [17]	132	-	There was a fair concordance between the Yamaguchi and ILAR criteria for SJIA in patients with AOSD	–

Abbreviations: AOSD: adult-onset Still's disease; IL: interleukin; ILAR: International League of Associations for Rheumatology; MAS: macrophage activation syndrome; NSAID: nonsteroidal anti-inflammatory drug; SJIA: systemic juvenile idiopathic arthritis; sTNF-RI: soluble tumor necrosis factor receptor I; sTNF-RII: soluble tumor necrosis factor receptor II.

intercarpal or carpometacarpal joint spaces was observed in up to 75% of patients, being more characteristic of AOSD and unlikely in other inflammatory joint diseases of young adults, such as systemic lupus erythematosus (SLE) [35,37].

- Rash: The characteristic rash in Still's disease is transient, nonpruritic, salmon-colored, and with macular or maculopapular lesions, which are often observed during febrile episodes, predominantly in the late afternoon or evening. The typical rash appears mainly on the trunk and proximal extremities, occasionally on the palms and soles, and tends to accompany fever [46], in some occasions being misdiagnosed as a drug eruption. Another common finding in many AOSD patients is an exaggerated urticarial response to cutaneous stimuli, which is referred to as dermatographism (reported in as high as 31% and 59% of patients) [27,35]. The Koebner phenomenon (the appearance of new lesions on areas of cutaneous injury or trauma, in otherwise healthy skin) was also observed in almost all patients in one case series [37].
- Sore throat/pharyngitis: This condition is commonly reported in up to 91.9% of patients. It usually coincides with the fever spike and subsides as the body temperature returns to normal [44,48].
- Lymph node enlargement and hepatosplenomegaly: These conditions are also very common. Lymphadenopathy develops in around 42.8–56.3% of AOSD patients, frequently involving the cervical region, and may raise a suspicion of lymphoma initially. Hepatomegaly may present in 6.6–71% of patients and is usually accompanied with splenomegaly in up to 44% of the cases. Splenomegaly alone was found in up to 83.7% of patients. Lymph node biopsy in AOSD patients may reveal reactive hyperplasia or

Table 2
Incidence and prevalence of AOSD.

Publication	Country	Study type	N	Annual incidence (per 100,000)	Prevalence (per 100,000)
Asanuma_2015 [21]	Japan	Retrospective	169	NR	3.9
Balci_2015 [18]	Turkey	Retrospective	42	0.62	6.77
Wakai_1997 [19]	Japan	Retrospective	146	0.22 (M), 0.34 (F)	0.73 (M), 1.47 (F)
Magadur-Joly_1995 [20]	France	Retrospective	62	0.16	NR

Abbreviations: AOSD: adult-onset Still's disease; F: female; M: male; NR: not reported.

Table 3
Clinical course in AOSD patients.

Publication	N	Disease pattern (% of patients)		
		Monocyclic systemic/self-limited (%)	Polycyclic systemic/intermittent (%)	Chronic articular (%)
Kalyoncu_2016 [25]	356	45.9	36.1	18.0
Sfriso_2016 [28]	245	23.9	40.8	35.3*
Asanuma_2015 [21]	169	39.7	34.2	26.1
Kim_2012 [29]	141	–	44.4	55.6
Colafrancesco_2017 [30]	140	–	74.2**	25.8
Kim_2013 [31]	137	27.0	49.6	23.4
Ruscitti_2018 [32]	119	30.3	31.1	22.7
Ruscitti_2016 [33]	100	29.0	22.0	33.0
Pay_2006 [15]	95	21.1	16.8	41.1
Cagatay_2009 [34]	84	33.3	33.3	27.4***
Chen_2004 [35]	82	34.0	45.0	21.0
Kim_2014 [36]	82	40.2	40.2	17.1
Colina_2011 [27]	76	26.0	30.0	44.0
Franchini_2010 [37]	66	20.0	40.0	40.0
Pouchot_1991 [6]	62	33.9	24.2	35.5
Magadur-Joly_1995 [20]	62	44.0	32.0	24.0
Zeng_2009 [38]	61	44.3	29.5	16.4§
Gerfaud-Valentin_2014 [24]	57	30.0	44.0	26.0
Kim_2012 [39]	54	53.7	9.3	27.7
Franchini_2010 [40]	45	–	64.0**	36.0
Balci_2015 [18]	42	64.3	23.8	11.9
Riera_2011 [41]	41	44.0	26.0	30.0
Mitamura_2009 [42]	34	50.0	35.0	15.0
Tejera_2013 [43]	30	50.0	50.0	–
Lin_2000 [14]	45	57.0	43.0	–
Overall range		**21.1–64.3%**	**9.3–50.0%**	**11.9–55.6%**

* Chronic articular monocyclic pattern in 4.6% and chronic articular polycyclic pattern in 30.7% of patients.
** Systemic disease pattern.
*** Chronic articular monocyclic systemic pattern in 6% and chronic articular polycyclic systemic pattern in 21.4% of patients.
§ Chronic articular monocyclic pattern in 4.9% and chronic articular polycyclic pattern in 11.5% of patients.
Please note that a specific percentage was not mentioned for some subtypes in the actual publication, which is presented as "-" in the above table.
Abbreviations: AOSD: adult-onset still's disease.

nonspecific chronic inflammation [44,46,48]. Lymphoma is always a differential diagnosis since fever is a key symptom in both diseases in addition to splenomegaly. Mild, transient elevations in liver enzyme levels are commonly observed, with a few cases of liver dysfunction being reported [37,44,45].

- Other manifestations: In different case series, myalgia was present in 13–95% of patients and was often associated with temperature elevation. Several other manifestations such as weight loss (11.5–66.1%), serositis (7.2–29%), pericarditis (2.6–37.1%), and pleuritis (2.9-53.2%) were also reported in the literature. Other relatively rare manifestations reported in few case series are interstitial pneumonia (1.0–15.0%), abdominal pain (1.2–24.0%), pulmonary arterial hypertension (2.9%) [49], myocarditis (14%) [49], encephalopathy (8.8%) [49], asthenia (35.3%) [50], gastrointestinal symptoms (26.8%) [36], and peritonitis (2.7%) [44]. Rare presentations related to lung disease have been observed to be more frequent in SJIA patients compared with AOSD patients [51,52].

General characteristics and disease manifestations reported in most recent and published series with largest number of patients are compared in Table 4.

Overall, AOSD is a multisystem disorder, and although considered a benign condition, it can present with life-threatening complications and lead to chronic disabilities.

Laboratory manifestations

A typical laboratory panel of a patient with AOSD presents leukocytosis with neutrophilia, elevated levels of acute-phase reactants such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), elevated liver enzymes, and markedly elevated ferritin levels in the absence of rheumatoid factor (RF) and antinuclear antibodies (ANAs) (Table 5).

CRP was elevated in 70–100% of patients and ESR was ≥40 mm/h in 68.9–100% of patients. Neutrophilic leukocytosis was found in 73–100% of AOSD patients. Ferritin levels were found to be elevated in a majority of AOSD patients, with 34.0–97.6% of patients having serum ferritin levels ≥1000 ng/mL and 19.5–60.0% of patients having serum ferritin levels ≥3000 ng/mL. It is not clear whether ferritin only reflects an acute-phase reaction or if it has a role in the pathogenesis of the disease. An elevated ferritin level is a nonspecific but common finding in AOSD and could be useful in helping make the diagnosis, particularly in the presence of other typical signs and symptoms. Abnormal liver function and anemia of chronic disease

Table 4
Characteristics of AOSD patients among the largest published series in the last 5 years.

	Asanuma_2015 [21]	Hu_2019 [47]	Kalyoncu_2016 [25]	Nakamura_2020 [53]	Sfriso_2016 [28]	Zhang_2016 [54]
Country/Nationality	Japan	China	Turkey	Japan	Italy	China
N	169	517	356	178	245	305
General characteristics						
Infant onset: Adult onset	4.8%: 95.2%	NR	NR	NR	NR	NR
Age at onset, median, years	46	37.7	30	42	38.8	33.2
Female (%)	72.0	72.0	59.0	70.0	47.3	71.7
Clinical characteristics (%)						
Fever >39.0 °C	91.6	91.3	95.8	96.0	92.6	100.0
Arthralgia	83.1	73.1	94.9	74.0	93.0	47.2
Arthritis	50.7	–	64.6	–	–	–
Typical rash	62.2	79.9	66.9	63.0	67.7	73.1
Sore throat	59.3	60.5	63.5	39.0	62.0	31.8
Lymphadenopathy	44.7	51.1	28.1	37.0	60.4*	33.4
Splenomegaly	32.3	34.4	25.0	37.0**	60.4*	43.3
Pericarditis	3.1	14.1	6.2	–	17.3	–
Myalgia	25.9	32.5	52.8	–	–	25.6
Laboratory findings						
Leukocytosis (>10,000/μL)	79.4	85.6	84.9	55.0	81.0	–
Leukocytosis (>15,000/μL)	–	60.8	–	–	70.3	–
Neutrophils >80%	71.5	78.4	66.7	–	–	–
Anemia <10 g/dL	40.2	27.3	65.4	–	–	68.9
Thrombocytopenia (platelets $<15 \times 10^4$)	13.6	–	–	–	–	0
Thrombocytosis (platelets >40,000/mm^3)	–	–	37.6	–	46.0	–
Elevated ESR	68.9	91.9	98.2	–	87.0	97.0
Elevated CRP	91.5	93.8	98.2	–		97.0
Hyperferritinemia	88.5	95.8	96.7	–	56.4	94.8
Serum ferritin >3000 ng/mL	60.0	78.8	NR	–	80.1	–
Abnormal liver function/raised ALT and/or AST	–	61.6	50.4	54.0	53.5	56.1

* Lymphadenopathy/splenomegaly.
** Hepatosplenomegaly.
Abbreviations: ALT: alanine aminotransferase; AOSD: adult-onset Still's disease; AST: aspartate aminotransferase; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; N: total number of patients; NR: not reported.

are usually reversible once the disease subsides. Hypoalbuminemia (albumin ≤3.5 mg/dL) was also commonly observed.

Clinical complications

Similar to SJIA, inadequate control of inflammatory activity is associated with a risk of serious complications in AOSD patients [55]. MAS is one of the most serious and potentially life-threatening complications among AOSD patients, with a reported mortality rate ranging between 20% and 42% [55–57]. MAS represents an acute systemic inflammatory response caused by a cytokine release syndrome; its occurrence has been associated with a significant reduction in survival rate in patients with AOSD ($p < 0.0001$) [32,56,57]. In a retrospective hospital-based study, overall survival was significantly lower in patients with MAS than in those without MAS (67% vs 100%; $p < 0.001$) [58]. MAS is also known as hemophagocytic syndrome and is considered to be a form of secondary hemophagocytic lymphohistiocytosis (HLH) [59].

The incidence of MAS in patients with AOSD has been reported to be as high as 23% in some studies [49]. AOSD patients may present with MAS at the time of diagnosis or during the disease course [32]. Almost all AOSD patients with MAS were reported to have fever. A change in the typical pattern of fever occurs in patients with Still's disease who develop MAS (from intermittent to nonremittent fever), and this change can help to differentiate between underlying disease flare-ups and MAS. A diagnosis of MAS should be increasingly suspected in patients presenting with continuous high fever, lymphadenopathy, hepatosplenomegaly, liver dysfunction, significantly elevated levels of serum ferritin, and elevated triglycerides but low number of platelets or neutrophils [32,55,56,60]. In patients with AOSD who develop MAS, a greater risk of aggressive disease symptoms, therapeutic recalcitrance, and mortality was noted [32,56–58,61]. Thus, a clinician's suspicion is critical for early detection and proper management.

Table 5
Laboratory manifestations.

Laboratory manifestations	Frequency range (%)
Elevated CRP	70–100
Elevated ESR (≥40 mm/h)	68.9–100
Hyperferritinemia	
Ferritin > normal range	43.1–100
Ferritin ≥1000 ng/mL or >5 times normal level	34.0–97.6
Ferritin ≥3000 ng/mL (severe)	19.5–60.0
Leukocytosis/increased WBCs	
WBC ≥10,000/mm^3	23.6–96.8
WBC ≥15,000/mm^3	31.7–93.5
Leukocytosis + neutrophilia	73–100
Neutrophils ≥80%	32.0–98
Abnormal liver function/liver dysfunction	10.4–91.2
Anemia (hemoglobin ≤10 g/dL)	13.0–74.5
ANA negative	9.0–100
ANA positive	2.9–25.8*
Glycosylated ferritin (≥20%)	72.2–79.5
Hypoalbuminemia (albumin ≤3.5 mg/dL)	41–72
PMN cells (≥80%)	69.4–78.0
Proteinuria	2.9–11.0
Raised LDH	69.0–81.5
RF positive	0–20.1*
RF negative	56.5–100
Thrombocytosis (platelets ≥400,000/μL)	8.0–48.4

* In some case series, a small proportion of patients reported positive RF and ANA. Thus, although AOSD is considered as a seronegative disorder (as per the Yamaguchi criteria), it should also be taken into consideration in seropositive patients with typical clinical presentation and other compatible findings.
Abbreviations: ANA: antinuclear antibody; AOSD: adult-onset Still's disease; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase; PMN: polymorphonuclear; RF: rheumatoid factor; WBC: white blood cell.

Other complications of AOSD reported in >10% of patients included multiple relapses, myocarditis, pericardial effusion, cardiac tamponade, cardiopulmonary shock, fulminant hepatitis, multiple

Table 6
Clinical complications of AOSD.

Clinical complications	Frequency range (%)
MAS	1.7–23.5
Hemophagocytic syndrome/HLH*	7.0–83.3
Multiple relapses	35.3
Myocarditis	1.9–21.1
Pericardial effusion	21.0
Cardiac tamponade	15.8
Cardiopulmonary shock	10.5
Fulminant hepatitis	10.5
Multiple organ failure	10.5
Disseminated intravascular coagulation	0.9–7.0
Interstitial lung disease	1.9
Joint deformities	14.7
Acute respiratory distress syndrome	3.0–21.1
Pancytopenia	5.7
Renal dysfunction	6.6
Secondary amyloidosis	1.0
Thrombotic thrombocytopenic purpura	1.0

* HLH is a hyperinflammatory condition characterized by inappropriate survival of histiocytes and cytotoxic T lymphocytes. HLH may be familial (fHLH) or secondary/acquired (sHLH); sHLH is termed as MAS when associated with rheumatological disease [62].
Abbreviations: AOSD: adult-onset Still's disease; HLH: hemophagocytic lymphohistiocytosis; MAS: macrophage activation syndrome.

organ failure, joint deformities, and acute respiratory distress syndrome (Table 6).

Disease journey of patients with AOSD

Primary diagnosis of patients with AOSD

As observed across multiple case series, AOSD patients were primarily diagnosed by rheumatologists, as patients commonly complain of arthralgia as the initial symptom; however, no substantial data are available [24,47,63]. Considering the appearance of skin rashes and joint pain along with fever in AOSD, many patients might first seek dermatologic treatment, given that their skin lesions are clearly visible and thus have a more immediate impact on their daily lives [64]. Thus, if dermatologists are familiar with the associated rheumatological manifestations, they can help in early diagnosis of AOSD. Other specialists, such as those treating infectious diseases and hematologists, are frequently consulted to opine on the possibility of an underlying infection or hematologic malignancy. Rarely, patients initially present with MAS requiring hospitalization and extensive workup before rendering an AOSD diagnosis.

Diagnosis of AOSD

Diagnostic tools used in clinical practice. The diagnosis of AOSD is highly dependent on the physician's judgment. A diagnosis of AOSD is usually made based on a thorough clinical evaluation, assessment of patient history, identification of characteristic findings, and exclusion of other possible and more common disorders (i.e., a diagnosis of exclusion). Affected individuals present with a high spiking fever, maculopapular rash, arthralgia or arthritis, and pharyngitis and often have elevated levels of acute-phase reactants such as ESR and CRP, serum ferritin, neutrophils, leukocytes, and/or platelets.

The clinical diagnosis of AOSD is generally reached by exclusion while investigating a patient with FUO. From the publications retrieved on FUO and Still's disease that met the criteria for our review, almost all AOSD patients presented with fever at the initial stage, and approximately 10-20% of patients evaluated for FUO had a diagnosis of AOSD per data from different cohort studies (Table 7).

Bilgin et al. have proposed an algorithm to differentiate AOSD patients from patients with other causes of FUO [84,85] (Fig. 2). The presence of arthralgia, hyperferritinemia, sore throat, and neutrophilia strongly favors AOSD in patients presenting with FUO.

Table 7
AOSD patients presenting with initial complaint of FUO.

Publication	Country	Number of patients with FUO (N)	Final AOSD diagnosis in patients with initial complaint of FUO (%)
Bilgin_2019 [65]	Turkey	106	18.9
Bosilkovski_2016 [66]	Republic of North Macedonia	123	4.9
Bosilkovski_2019 [67]	Republic of North Macedonia	106	7.6
Crispin_2005 [68]	Mexico	161	16.1
Goto_2007 [69]	Japan	51	11.8
Hung_2017 [70]	Taiwan	58	3.4
Pedersen_2011 [71]	Denmark	31	16.1
Kim_2013 [72]	Korea	77	5.2
Kucukardali_2008 [73]	Turkey	154	13.6
Mert_2003 [74]	Turkey	130	15.4
Mir_2014 [75]	India	66	3.0
Saltoglu_2004 [76]	Turkey	87	4.6
Schonau_2017 [77]	Germany	72	15.3
Sethi_2014 [78]	India	101	13.9
Shoji_1994 [79]	Japan	80	7.5
Tabak_2003 [80]	Turkey	117	11.1
Vanderschueren_2012 [81]	Belgium	447	4.9
Zhai_2018 [82]	China	215	17.2
Zhiyong_2003 [83]	China	158	11.4

Abbreviations: AOSD: adult-onset Still's disease; FUO: fever of unknown origin.

Similarly, *Crispin* et al. proposed a scale to identify patients with AOSD (Table 8). The scale comprises five criteria—arthritis, pharyngitis, Still's rash, splenomegaly, and neutrophilia—to differentiate AOSD from other causes of FUO. The presence of each of these criteria confers a different number of points, and the points are added to obtain a total score. If the score equals 30, a diagnosis of AOSD may be confirmed [68]. This scale appears to be highly specific (~98%), with predictive values greater than 90% and ease of use in clinical practice.

Since the nonspecific clinical features of AOSD may pose a diagnostic challenge, several criteria have been developed for the identification of AOSD patients (Table 9). The Yamaguchi and Fautrel classification criteria are the most widely used criteria for AOSD [86,87]. The diagnosis of AOSD depends largely on a combination of major and minor criteria, requiring the exclusion of other clinical conditions that may mimic AOSD, including infection, malignancy, and other rheumatologic disorders such as autoimmune diseases and systemic vasculitis (Table 9). The sensitivity of the Yamaguchi criteria (96.2%) is hampered by a large number of clinical conditions that should be excluded, whereas the Fautrel diagnostic criteria require measurement of glycosylated ferritin, which may not be available in many healthcare facilities. Additionally, these criteria were designed based on retrospective data, and none of them have been compared or validated using an appropriate "gold standard" control group, which raises questions on their diagnostic capabilities. Results from a retrospective study by *Bilgin* et al. [88] demonstrated that when the current Yamaguchi criteria were applied to patients with AOSD, 93.5% met the criteria for AOSD. However, when "neutrophilia > upper normal limit" was used instead of "leukocytosis with neutrophilia >80%," all patients met the revised criteria for AOSD. Consequently, using "neutrophilia > upper normal limit" as a criterion instead of "leukocytosis with neutrophilia >80″ may be more appropriate for the diagnosis of AOSD in real-life settings. Thus, specialists have not yet reached a consensus as to what would be the most effective diagnostic pathway for AOSD, and a robust diagnostic tool is still a major unmet need for this clinical condition.

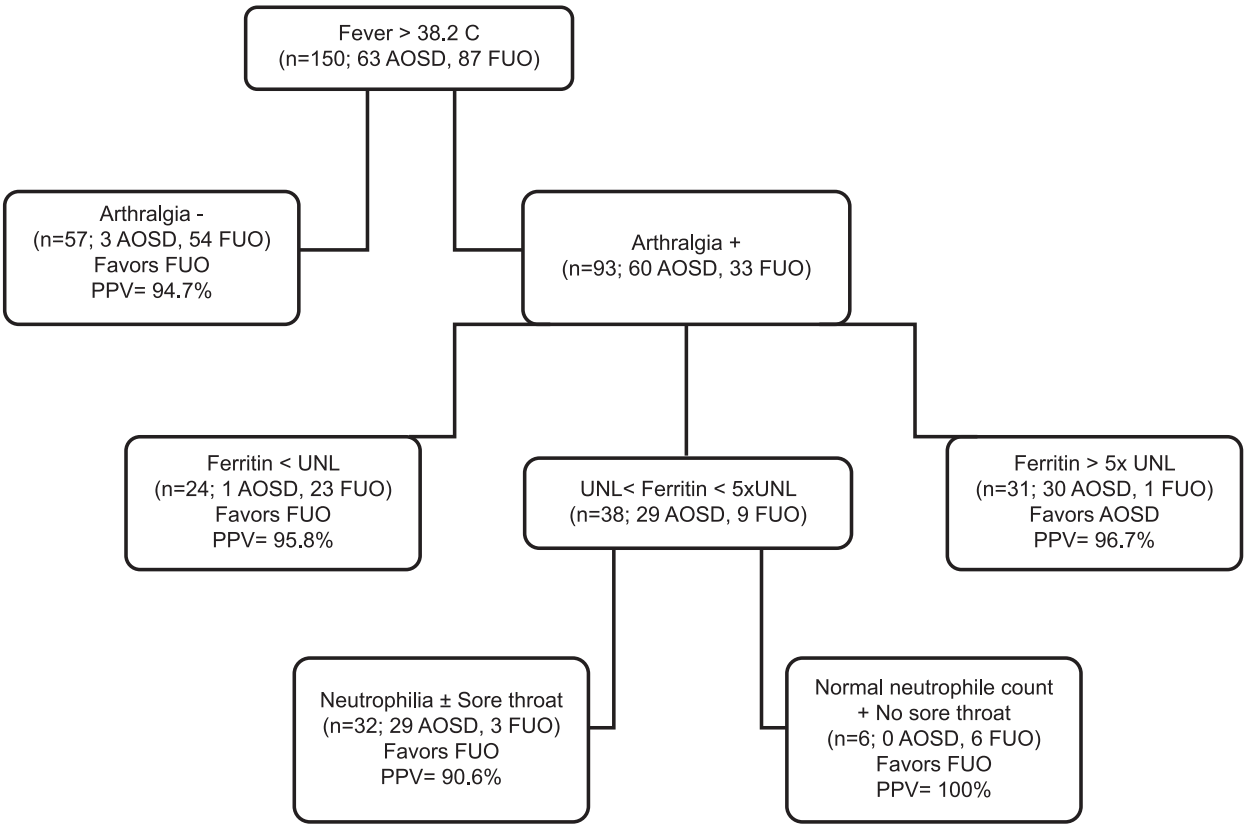

Fig. 2. Algorithm for differentiating AOSD from FUO [85].
Abbreviations: AOSD: adult-onset Still's disease; FUO: fever of unknown origin; PPV: positive predictive value; UNL: upper normal limit.
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Table 8
Clinical scale for the diagnosis of AOSD in the setting of FUO proposed by Crispin et al. [68].

Criterion	Description	Points
Arthritis	Presence of synovitis	10
Pharyngitis	Present at the beginning of the disease	7
Still's rash	Macular or maculopapular pink-salmon rash that accompanies the fever	5
Splenomegaly	Detected clinically or by imaging studies (>11 cm)	5
Neutrophilia	Total neutrophil count higher than $9.5 \times 10^3/\mu L$	18
Total		**45**

If a patient with FUO has ≥30 points, the diagnosis of AOSD can be established without further diagnostic workup, with a high specificity (~98%).
Abbreviations: AOSD: adult-onset Still's disease; FUO: fever of unknown origin.

In a study that investigated the characteristic pathologic findings from the skin, lymph nodes, liver, and bone marrow to assist in proper diagnosis of AOSD, the relatively specific findings with respect to cutaneous manifestations of AOSD were mild inflammatory cell infiltration in the upper dermis, basal vacuolization, keratinocyte necrosis, presence of karyorrhexis, and mucin in the dermis. In all cases, the pathologic findings in the lymph nodes included paracortical hyperplasia with vascular and immunoblastic proliferation. Skin and lymph node pathology along with clinical findings can aid in the diagnosis of AOSD [64], in particular by excluding other more common diseases. Kikuchi-Fujimoto disease, also known as histiocytic necrotizing lymphadenitis and characterized by subacute necrotizing regional lymphadenopathy, and Castleman disease, a poorly understood lymphoproliferative disease, are rare conditions that can be differentiated from AOSD based on a lymph node biopsy [89,90].

Novel biomarkers

To date, the serum levels of nonspecific acute-phase reactants, including CRP, ESR, and ferritin, have been useful biomarkers for AOSD in daily practice, as part of a bigger clinical picture composed of a characteristic combination of signs, symptoms, and laboratory findings. Nevertheless, recent advances have demonstrated a major role of proinflammatory cytokines, such as interleukin (IL)–1, IL-6, IL-18, and IL-37, and other biomarkers in the diagnosis and management of AOSD.

Glycosylated ferritin. Hyperferritinemia has been observed in cases of AOSD (refer Table 5) and may serve as an indicator of disease activity. However, ferritin has poor predictive value when used to diagnose AOSD in the absence of characteristic clinical features, regardless of the threshold used [91,92]. In addition, increased levels of ferritin have been noted in other diseases, such as infectious, liver, and kidney diseases, as well as malignancies, which can complicate the differential diagnosis process. Some studies suggest the use of ferritin as a predictive factor for disease progression to the chronic form. A potentially more useful biomarker might be glycosylated ferritin, which has comparatively higher sensitivity and specificity (Table 10). In healthy adults, 50–80% of ferritin is glycosylated. A decrease in the percentage of ferritin glycosylation can be observed in inflammatory diseases, malignancies, infections, or liver disease but is rarely less than 20%. Levels of glycosylated ferritin below 20% have been described in patients with AOSD and HLH. A retrospective multicenter study evaluated the concordance of ferritin and glycosylated ferritin levels with a final diagnosis of AOSD (using the Yamaguchi criteria). The sensitivity and specificity of the glycosylated ferritin test in the diagnosis of AOSD was found to be 80% and 66%, respectively, when tested alone, and 43% and 93%, respectively, when

Table 9
Most commonly used classification criteria for AOSD.

Yamaguchi et al. classification criteria for AOSD [86]	*Fautrel* et al. classification criteria for AOSD [87]
Sensitivity: 96.2% Specificity: 92.1% Major criteria: 1. Fever ≥39 °C lasting at least 1 week 2. Arthralgia or arthritis for ≥2 weeks 3. Typical nonpruritic salmon-pink skin rash 4. Leukocytosis ≥10,000/mm^3 with ≥80% polymorphonuclear cells	Sensitivity: 80.6% Specificity: 98.5% Major criteria: 1. Spiking fever ≥39 °C 2. Arthralgia 3. Transient erythema 4. Pharyngitis 5. Polymorphonuclear cells ≥80% 6. Glycosylated ferritin ≤20%
Minor criteria: 1. Sore throat 2. Lymph node enlargement 3. Hepatomegaly or splenomegaly 4. Abnormal liver function tests 5. Negative ANA and RF tests	Minor criteria: 1. Maculopapular rash 2. Leukocytes ≥10,000/mm^3
Exclusion criteria: 1. Infections (especially, sepsis and infectious mononucleosis) 2. Malignancy (mainly malignant lymphoma) 3. Other rheumatic disorders (mainly polyarteritis nodosa and rheumatoid vasculitis with extraarticular features)	
For diagnosis of AOSD, patient should meet "5 or more criteria, of which at least 2 should be major"	For diagnosis of AOSD, patient should meet "4 or more major criteria OR 3 major criteria + 2 minor criteria".

Abbreviations: ANA: antinuclear antibody; AOSD: adult-onset Still's disease; RF: rheumatoid factor.

combined with a total ferritin level greater than five times the normal value [91].

Heme-oxygenase 1 (HO-1). In a recent retrospective study conducted in Japan, serum ferritin and HO-1 levels were assessed in 110 AOSD patients and 46 disease controls. Results revealed that serum ferritin and HO-1 levels were significantly higher in active and relapsed AOSD cases compared with the disease controls and were reduced by the treatment. Serum ferritin level >819 ng/mL showed a sensitivity of approximately 80% and specificity of 71% for AOSD, whereas serum HO-1 level >30.2 ng/mL yielded a sensitivity of 86% and specificity of 83% [93]. Thus, typical skin rash and high-grade fever, neutrophilia, RF/ANA negativity, sore throat, and serum HO-1 with serum ferritin can serve as strong indicators for AOSD diagnosis and predictors of disease relapse.

Interleukins. High levels of serum cytokines such as IL-1, IL-6, IL-18, and IL-37 have been detected in AOSD patients. Several studies have shown that serum levels of free IL-18 are extremely high in AOSD patients (up to 1000-fold higher) as well as SJIA patients with active disease and clearly correlated with other biomarkers of disease activity [94–97]. Additionally, normalization of IL-18 serum levels was observed in the remission stage [96]. Findings suggest that IL-18 could be helpful as a diagnostic biomarker for AOSD as well as a differential diagnosis marker with respect to other inflammatory disorders such as RA and ankylosing spondylitis [94–97]. Also, IL-18 can be used as an indicator of disease activity because serum IL-18 levels are known to be associated with disease severity and serum ferritin levels in AOSD patients [95,97].

IL-37 is a unique IL-1 family member functioning as a regulatory cytokine which can help in differentiating AOSD patients from healthy controls [98,99]. A recent study of 62 patients demonstrated that upregulation of IL-37 serum levels positively correlated with the systemic score and laboratory features that represented AOSD disease activity. IL-37 levels decreased when disease activity reduced in follow-up patients [98]. Thus, increased expression of IL-37 and its positive correlation with disease activity suggest its involvement in AOSD pathogenesis [98,99,100]. Several studies have demonstrated that IL-18, interferon (IFN)-γ, IL-10, and IL-4 are associated with systemic AOSD, whereas IL-6, IL-17, and IL-23 are associated with arthritic AOSD [27,100]. However, serum levels of IL-37 were comparable between patients who had a chronic articular pattern and those who had a systemic pattern [98]. IL-37 inhibits the expression of proinflammatory cytokines in peripheral blood mononuclear cells (PBMCs) from patients with SJIA/AOSD, indicating the potential anti-inflammatory role of IL-37 in AOSD [101]. Furthermore, a recent study demonstrated that IL-37 acts as a regulator of trained immunity, emerging as a potential therapeutic target in immune-mediated pathologies [102]. Thus, IL-37 plays a promising role as novel disease activity biomarker as well as therapy for AOSD [98,103].

Other potential biomarkers. Serum levels of calprotectin (a heterodimer of the S100A8 and S100A9 proteins), leucine-rich α2-glycoprotein (LRG), and cysteine-rich angiogenic inducer 61 (Cyr61) could be useful biomarkers for monitoring disease activity and might play a key role in the pathogenesis of AOSD [97,104–106].

In a study of 164 patients with suspected AOSD, clinical symptoms and blood test results were retrospectively assessed. Of these, 127 had a final diagnosis of AOSD. The neutrophil-to-lymphocyte ratio (NLR) was compared between AOSD patients and non-AOSD patients and was found to be higher in AOSD patients than in non-AOSD patients. Thus, NLR can be a potential diagnostic tool and a marker for evaluation of disease activity [104]. NLR showed a sensitivity of 91.7% and specificity of 68.4% as a diagnostic tool for AOSD, which were significantly higher than those of other inflammatory markers such as ESR, CRP, and ferritin. Multivariate analysis also revealed the utility of the NLR in differential diagnosis of HLH [107]. The NLR was significantly higher in patients with MAS than in patients with HLH.

Delay in diagnosis

Although early diagnosis tends to lead to a better prognosis, diagnosis is often delayed, with most patients being diagnosed only after the appearance of relapsing symptoms. Long delays in the diagnosis of AOSD patients have been reported across multiple studies (Table 11). The median interval between onset of symptoms and a definite diagnosis of AOSD ranged between 1 and 4.1 months across studies (Table 11). Owing to the heterogeneity in clinical presentation, the lack of a specific diagnostic test, and the rarity of the disease, a delayed diagnosis is common among AOSD patients.

Some of the causes for the delay in diagnosis of AOSD are summarized below:

Table 10
Novel biomarkers in AOSD.

Publication	Future diagnostic biomarkers	Sensitivity (%)	Specificity (%)	Overall remarks
Chi_2018 [98]	Serum IL-37			Serum IL-37 levels were dramatically higher in patients with AOSD than in healthy controls, and levels of IL-37 positively correlated with the systemic score and laboratory features that represented AOSD disease activity Serum IL-37 protein levels also correlated with expression of the proinflammatory cytokines IL-1β and IL-18 as well as with the anti-inflammatory cytokine IL-10 Serum levels of IL-37 were comparable between patients who had a chronic articular pattern and those who had a systemic pattern
Fautrel_2001 [91]	Ferritin > normal limit (N)	67.3	35.8	Glycosylated ferritin level ≤20% appears to be a better diagnostic marker of AOSD than an elevated level of serum ferritin, and the combination of both abnormalities can be especially helpful for the differential diagnosis of AOSD The specificity of ferritin levels greater than the upper normal limit (35.8%) is too unspecific to be helpful in clinical practice
	Ferritin >5N	40.8	80	
	Glycosylated ferritin ≤20%	79.5	66.4	
	Ferritin > *N* and glycosylated ferritin ≤20%	70.5	83.2	
	Ferritin >5 N and glycosylated ferritin ≤20%	43.2	92.9	
Girard_2016 [94]	Serum IL-18			Free IL-18 serum levels were significantly higher in AOSD patients (median 8.89 pg/mL) than in healthy and disease controls (other inflammatory disorders; 1.37 pg/mL; $p < 0.01$) Free IL-18 serum levels correlated with clinical and biological markers of AOSD activity
Guo_2016 [104]	Serum calprotectin	63.0	80.1	Calprotectin is considered to be "good" or "fair" at differentiating AOSD patients from patients with other rheumatic diseases and healthy controls
Ha_2015 [105]	Serum LRG	92.3	97.9	Serum LRG levels were significantly elevated in patients with AOSD (128.8 ± 40.8 ng/mL) compared to those in patients with RA and in healthy controls ($p < 0.001$) Elevated serum LRG levels correlated well with disease activity measures
Jung_2014 [96]	IL-18	85.0	97.0	Serum IL-6, IFN-γ, IL-18, IL-18BP, and free IL-18 levels were elevated in AOSD patients compared with RA and AS patients
	Free IL-18	86.0	97.0	IL-18 is an efficient marker for diagnosis and follow-up in AOSD patients and may be a useful predictive marker of remission, especially in the inactive stage
Kim_2012 [97]	S100A8/A9	69.4	98	Serum S100A8/A9 correlates with leukocyte count, ESR, CRP, ferritin, and systemic disease score
	IL-18	91.7	99.1	Serum levels of S100A8/A9 and IL-18 in patients with AOSD were significantly higher than those in patients with RA and healthy controls
Kirino_2018 [93]	Serum ferritin	76.1	73.8	Serum ferritin and HO-1 may serve as highly specific and sensitive biomarkers for AOSD
	HO-1	84.8	83.3	
Kudela_2019 [95]	IL-18	63.3	96.9	IL-18 levels were significantly increased in patients with active AOSD compared with patients in remission. For diagnosis of SJIA in children, a cutoff value of 10,000 pg/mL was chosen, with a specificity of 100% and a sensitivity of 60%
Lian_2012 [92]	Combined Yamaguchi criteria and hyperferritinemia Ferritin ≥750 μg/L	83.5	98.8	Ferritin level ≥2500 μg/L appeared to be highly specific for a diagnosis of AOSD When the Yamaguchi criteria and hyperferritinemia were combined, they helped in better AOSD diagnosis
	Ferritin ≥1250 μg/L	70.9	99.3	
	Ferritin ≥2500 μg/L	43.0	99.9	
Su_2019 [106]	Cyr61			Serum levels of Cyr61 were inversely correlated with disease activity in AOSD patients, i.e., significantly increased serum levels of Cyr61 were observed in inactive AOSD patients than those in active patients and healthy controls Can be a potential biomarker of AOSD disease activity

Abbreviations: AOSD: adult-onset Still's disease; AS: ankylosing spondylitis; CRP: C-reactive protein; Cyr61: cysteine-rich angiogenic inducer 61; ESR: erythrocyte sedimentation rate; HO-1: heme oxygenase-1; IFN: interferon; IL: interleukin; IL-18BP: interleukin 18 binding protein; LRG: leucine-rich α2-glycoprotein; RA: rheumatoid arthritis; SJIA: systemic juvenile idiopathic arthritis.

- Diagnostic difficulty: The initial symptoms of AOSD are similar to those of other diseases such as infections, malignancies, and other inflammatory conditions. Bacterial infection and FUO have been the most common misdiagnoses at the time of investigation, followed by allergy, including drug eruption, and autoimmune diseases, including either SLE or RA [23,27,35,47,108,109]
- Absence of specific clinically available biomarkers for diagnosis of AOSD [108]
- All known clinical and laboratory features of AOSD may not be present at the same time as the disease presents itself; thus, diagnosis could be delayed for several weeks or months, especially in patients with a polycyclic disease course [37,39,110]. Virtually all children and adults with Still's disease have fever at disease onset, while arthritis may not be evident during the initial stages of the disease [14–16]

Burden of disease

The burden of AOSD is not well documented in the literature. In one of the largest nationwide studies of AOSD in the United States (US), 5-year retrospective data of AOSD patients hospitalized between 2009 and 2013 revealed an inpatient mortality of 2.6%. Inpatient mortality was reported to be significantly higher among Asian patients compared with White patients [111]. As observed across multiple studies, AOSD was associated with significant morbidity and

Table 11
Time to diagnosis of AOSD.

Publication	Sample size (N)	Time to diagnosis/delay in diagnosis				
		Mean	SD	Median	SD	Range
Chen_2004 [35]	82	3.3 mo	–	–	–	(10 d to 4 y)
Colina_2011 [27]	76	21 mo	25 mo	–	–	–
Dwivedi_2017 [110]	34	12.24 mo	–	–	–	–
Ekbote_2018 [49]	34	3.5 mo	–	–	–	0.5–5.5 mo
Franchini_2010 [37]	66	–	–	4 mo	–	1 mo to 20 y
Gerfaud-Valentin_2014 [24]	57	–	–	4 mo	–	0–312 mo/26 y
Hu_2019 [47]	517	–	–	4.6 mo	–	0.5–96 mo
Iliou_2013 [23]	44	3.5 mo	–	–	–	0.5–6 mo
Kim_2012 [39]	54	41.1 d	87.5 d	–	–	–
Kim_2014 [36]	82	–	–	1 mo	46 mo	0.2–336 mo
Lin_2000 [14]	21	4.6 mo	2.3 mo	–	–	–
Pay_2006 [15]	95	–	–	3 mo	–	0.5–84 mo
Tamai_2017 [108]	51	50.4 d	–	–	–	–
Tamai_2019 [109]	65	21 d	–	–	–	–
Uppal_1995 [16]	31	4.34 y	4.04 y	3 y	–	–

Abbreviations: AOSD: adult-onset Still's disease; d: days; mo: months; SD: standard deviation; y: years.

Table 12
Mortality rates among AOSD patients.

Publication	Country	Type of study	Total patients	Mortality (%)
Balci_2015 [18]	Turkey	Retrospective	42	2.3
Ekbote_2018 [49]	India	Retrospective	34	8.8
Gerfaud-Valentin_2014 [24]	France	Retrospective	57	5.2
Kim_2012 [39]	Korea	Retrospective	54	9.3
Kim_2014 [36]	Korea	Retrospective	82	2.4
Mehta_2019 [111]	USA	Retrospective	5820	2.6
Ruscitti_2016 [33]	Italy	Retrospective	100	16
Ruscitti_2018 [32]	Italy	Retrospective	119	16
Wang_2020 [56]	China	Retrospective	447	4.5
Zeng_2009 [38]	China	Retrospective	61	9.8

Abbreviations: AOSD: adult-onset still's disease.

mortality and life-threatening manifestations and hence impacted the health-related quality of life of patients (Table 12).

Data on the economic burden of AOSD are very scarce. Only one study conducted in the US reported the mean cost of hospitalization due to AOSD as USD 30,857 [111].

Treatment pattern

Nonsteroidal anti-inflammatory drugs and corticosteroids

Most AOSD patients in the identified literature were treated with glucocorticoids. While patients presenting with the monocyclic pattern easily achieve remission with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, patients presenting with the polycyclic systemic pattern or chronic arthritis are relatively difficult to treat and may require further treatment with conventional immunosuppressants and/or biologic drugs [46]. Studies showed that >80% of AOSD patients did not achieve remission with NSAIDs and approximately 20% suffered from adverse events [3,46,112,113]. Systemic corticosteroid therapy (prednisone, dexamethasone, and methylprednisolone) led to remission in approximately 65% of the patients, showing greater efficacy in resolving systemic symptoms (as opposed to articular symptoms) [113].

Conventional disease-modifying antirheumatic drugs

A majority of AOSD patients were treated with at least one disease-modifying antirheumatic drug (DMARD), with methotrexate being the most commonly used DMARD. In a chart review, methotrexate was found to be effective for disease control in systemic and chronic articular AOSD, particularly in 40–70% of steroid-dependent AOSD patients [24]. Methotrexate use in AOSD patients with liver involvement is not an absolute contraindication, but continuous monitoring of transaminase is warranted [114,115].

Other conventional DMARDs such as cyclosporine A, azathioprine, leflunomide, and hydroxychloroquine have been shown to be beneficial in AOSD patients, but methotrexate is still the preferred choice as a first-line steroid-sparing treatment [116].

Biologics

Treatment with biologics is recommended in AOSD patients refractory to conventional corticosteroid and DMARD therapy [116]. Currently, both IL-1 inhibitors canakinumab and anakinra are approved in Europe, and only canakinumab is approved in the USA, for the treatment of AOSD. Rilonacept, tumor necrosis factor-α blockers, and tocilizumab are used off-label.

Most patients achieved partial response rather than remission with tumor necrosis factor-α blockers. Patients with arthritis lacking systemic manifestations, lower IL-18 levels, and lower serum ferritin are more likely to respond to tumor necrosis factor-α blockers [116,117,118]. Switching from one tumor necrosis factor-α blocker to another does not provide any additional effect [116,118].

Treatment with anti–IL-1 agents is significantly effective in patients with AOSD refractory to conventional treatment [30,40,118,120]. First-line biologic therapy for AOSD with canakinumab resulted in rapid and marked efficacy, ultimately leading to full clinical remissions [121]. Prompt initiation of IL-1-blocking therapies was reported to be associated with better disease outcomes, and optimal retention rates [122,123,124].

Response to IL-1 inhibitors is rapid and sustained and allows patients to reduce their dependence on corticosteroids. Failure of one IL-1 inhibitor does not preclude the achievement of a therapeutic response with another IL-1 inhibitor. IL-1 inhibitors are generally safe [30,125]. In an RCT among AOSD patients, treatment of active AOSD with canakinumab led to improvements in several outcome measures, with two-thirds of patients on canakinumab achieving the primary outcome, defined as the proportion of patients with a clinically relevant reduction in disease activity at week 12 [119,120].

Other biologics including tocilizumab, abatacept, rituximab, and tofacitinib have also been investigated in AOSD. A randomized, double-blind, placebo-controlled phase III trial suggested that tocilizumab is effective in AOSD, although the primary endpoint was not met, and solid conclusion was not drawn [126]. Tocilizumab should be considered as an alternative to IL-1 antagonists, particularly when joint involvement is present [115,127]. Abatacept (a modulator of T-lymphocyte activation) and rituximab (a monoclonal anti-CD20 antibody) have been assessed in refractory AOSD patients with very little benefit [125]. A recent case report concluded that application of the

Table 13
AOSD treatment options (24,112,115–119).

Line of treatment	Treatment	Pros	Cons
First line	NSAIDs and corticosteroids	• Monocyclic pattern • Systemic corticosteroids achieve remission in 65% of patients • Corticosteroids are the first line of treatment for AOSD	• Polycyclic systemic pattern or chronic arthritis • NSAIDs do not achieve remission in >80% of patients • Steroid dependency occurs in approximately 45% of cases • Steroid dependence was associated with splenomegaly, low glycosylated ferritin, an elevated ESR, and young age at onset of AOSD
First line	Methotrexate	• First-line steroid-sparing treatment in AOSD • Systemic and chronic articular AOSD, especially steroid dependent	• Slow to induce remission, especially of systemic symptoms • Can cause severe adverse events, including liver toxicity and pneumonitis • Blood count, renal function, and liver enzymes should be monitored
Second line	IL-1 inhibitors* including anakinra and canakinumab	• Patients refractory to conventional corticosteroid and DMARD therapy • Polycyclic or chronic AOSD • Canakinumab and anakinra are the only approved biologics** • Are relatively safe	• Patients receiving anakinra are more likely to relapse as soon as treatment is stopped compared with those receiving canakinumab due to a shorter half-life (4–6 h vs 26 days) • Injection site reactions are more frequent with anakinra

* Rilonacept is currently not approved.
** Canakinumab is the only approved biologic for AOSD in the US, while in Europe, both canakinumab and anakinra are approved for AOSD.
Abbreviations: AOSD: adult-onset Still's disease; DMARD: disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; IL: interleukin; NSAID: nonsteroidal anti-inflammatory drug.

Janus kinase (JAK) inhibitor tofacitinib in refractory AOSD patients contributes to disease remission and decrease in corticosteroid dose in those with polyarthritis [126,128].

Summary of treatment options available for AOSD patients is provided in Table 13.

Efficacy and safety outcomes

Efficacy data in AOSD were mostly reported from case reports and case series. There were only two RCTs conducted in AOSD patients on tocilizumab and canakinumab versus placebo [119,120,126]. The primary efficacy outcome reported in the tocilizumab trial was the American College of Rheumatology (ACR) 50 response at week 4, while the primary efficacy outcome reported in the canakinumab trial was the proportion of patients with a clinically relevant reduction in disease activity at week 12 [119,120,126,129].

A significant improvement in systemic manifestations (systemic feature score) was reported in patients on tocilizumab at week 4 and week 12 compared with patients on placebo [126]. Patients on anakinra achieved remission in systemic manifestations (fever, rash, and raised inflammatory markers) and corticosteroid tapering [23]. The Pouchot score was significantly reduced at 3 months compared with baseline among patients on anakinra as well as among patients on canakinumab [30]. A higher ACR response was reported among patients on canakinumab in a pooled analysis of RCTs [129]. Very few studies reported serious adverse events among AOSD patients on biologics [113,119,120,126-131]. In a randomized, placebo-controlled trial, the safety profile of canakinumab in AOSD was similar to that reported in SJIA patients, with no unexpected safety issues observed [120].

Clinical management in AOSD

To date, there are no internationally recognized guidelines for the management of AOSD.

The first clinical practice guidelines for AOSD (as part of a Still's disease continuum that encompasses SJIA) were developed in Japan in 2017 by the Ministry of Health [132]. They recommended systemic glucocorticoids for improving clinical symptoms with high-dose intravenous pulse glucocorticoid therapy for AOSD patients with severe organ involvement. For steroid-refractory patients, methotrexate was strongly recommended. The main limitation of the guideline was that owing to the rarity of AOSD, only a few global reports with high-quality evidence were available [132].

Table 14
Clinical management recommendations for AOSD [132,133].

Reference	Country	Key recommendations
Mimura_2018	Japan	Systemic glucocorticoids ameliorate clinical symptoms and manifestations of AOSD-High-dose intravenous pulse glucocorticoids ameliorate clinical symptoms and manifestations of AOSD in patients with severe organ damage • It is recommended to concomitantly use methotrexate for the management of clinical symptoms and manifestations, which has a glucocorticoid-sparing effect in glucocorticoid-resistant refractory AOSD • Tocilizumab and canakinumab are useful for the improvement of symptoms and disease states, and they have an effect in reducing the glucocorticoid dose. They also improve growth in SJIA cases that show resistance to conventional therapy
Colafrancesco_2019	Italy	AOSD and SJIA may be considered as the same disease Data from SJIA suggest that early treatment with IL-1 inhibitors is associated with a better therapeutic response IL-1 inhibitors (anakinra, canakinumab, and rilonacept) are significantly effective in patients with AOSD refractory to conventional treatment

Abbreviations: AOSD: adult-onset Still's disease; IL: interleukin; SJIA: systemic juvenile idiopathic arthritis.

A panel of experts from Italy developed recommendations based on the Delphi process for the management of patients with AOSD with IL-1 inhibitors (Table 14). The panel concluded that the literature is consistent in demonstrating a beneficial effect of IL-1 inhibitors, with a high proportion of patients achieving rapid and sustained remission of systemic symptoms and normalized inflammatory markers [133].

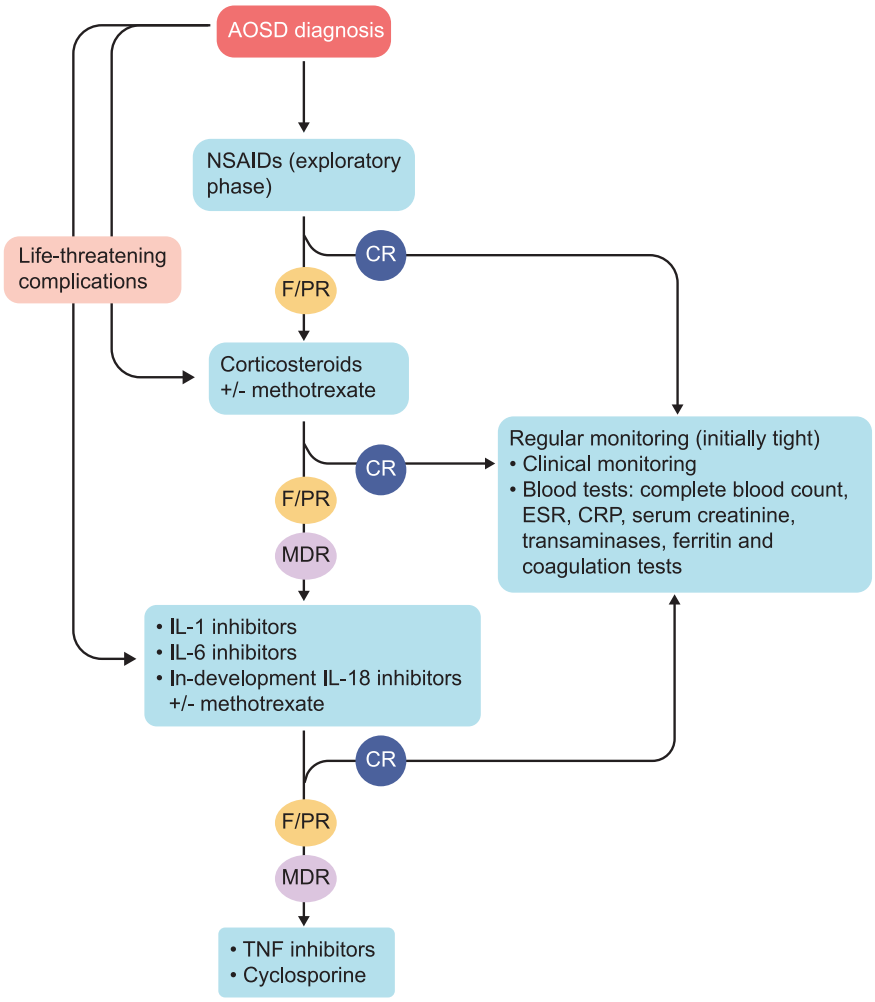

Fig. 3. Treatment algorithm for AOSD.

Abbreviations: AOSD: adult-onset Still's disease; CR: complete response; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; F: failure; IL: interleukin; MDR: multidisciplinary round; NSAID: nonsteroidal anti-inflammatory drug; PR: partial response; TNF: tumor necrosis factor.

The management of AOSD varies widely depending on various clinical presentations of the disease. *Feist* et al. proposed a treatment algorithm showing a targeted strategy with early use of biologics for AOSD (Fig. 3) [134].

Unmet needs and research agenda

The understanding of AOSD has advanced considerably over the past 10–15 years; however, there are still very important unmet needs to be addressed.

- Early detection of AOSD.
- Lack of understanding of the patient journey; due to the diverse presentation of AOSD, some patients might have to undergo a long journey before any suspicion of AOSD.
- Limited information about the disease burden of AOSD in terms of mortality, and a lack of data about the direct economic burden of the disease.
- The role of genetics and/or biomarkers for accurate and timely diagnosis and to monitor disease progression and treatment response.
- A targeted treatment approach, aiming for a comprehensive disease control (articular and systemic manifestations) and prevention of complications and chronic, irreversible disability.

Discussion

AOSD is a rare systemic inflammatory condition that is poorly recognized. Significant advances have been made in the understanding of the pathogenesis of the disease (i.e., key cytokines involved and the role of the inflammasome), but important unmet needs related to diagnosis and optimal management still remain.

There is a paucity of robust epidemiological data on AOSD, and the true disease burden is difficult to estimate owing to the lack of national disease registries and prospective databases and considering that most of the published data are retrospective in nature. Moreover, there are no studies that have evaluated the direct or indirect healthcare costs associated with AOSD at the country level.

AOSD poses many diagnostic challenges as it presents with a combination of nonspecific symptoms that can be caused by a wide variety of other diseases. Diagnostic delays and disease complications are exacerbated by the lack of pathognomonic serologic or clinical disease markers. However, the key point to remember is that for patients who present with prolonged and unexplained fever combined with musculoskeletal symptoms and evanescent rash, the differential diagnoses should include AOSD.

Advances in immunology have enhanced our knowledge on the role of cytokines in disease pathogenesis. To date, many biomarkers, including calprotectin, ILs (IL-6, IL-18, and IL-37), Cyr61, soluble S100A12, neutrophils (CD64+), and CXCL-10(+)/CXCL-13(+) cells, have been evaluated to monitor AOSD disease activity. However, their utilities in clinical practice have not been validated adequately owing to technical or economic reasons. Furthermore, MAS is a rare life-threatening syndrome that can complicate the course of AOSD. Early recognition of MAS in AOSD patients still remains diagnostically challenging as there is no diagnostic test or even a set of uniform disease diagnostic criteria to differentiate MAS from the underlying systemic inflammatory condition. Future research in this disease area should aim for the identification and validation of tools for the early diagnosis of AOSD and optimized treatment to prevent chronic articular inflammation as well as irreversible joint damage.

For AOSD management, glucocorticoids are suggested initially, while methotrexate is recommended for steroid-refractory patients. For patients resistant to conventional therapy, biologics are recommended. The treatment response to biologics may depend on disease phenotype: arthritis and a chronic articular phenotype have been associated with a substantial response to IL-6 inhibition, whereas the systemic phenotype has been associated with a substantial response to IL-1 inhibition [135].

In SJIA, the primary target for treatment is recommended as clinical remission [136]. In SJIA, use of biologics as the first line of therapy has demonstrated rapid attainment of inactive disease compared with conventional therapy and has also led to the avoidance of glucocorticoids [137]. AOSD management can possibly emulate that of SJIA and incorporate early treatment with biologics. Further studies are needed to assess if early treatment with biologics leads to better patient outcomes and a change in the natural history of the disease process.

There are only a few guidelines on the clinical management of AOSD, which is possibly due to fewer RCTs reporting efficacy and safety data. *Colafrancesco* et al. (2019) recommended the use of IL-1 inhibitors (canakinumab and anakinra) in AOSD refractory to conventional treatment [133]. At the moment, canakinumab is the only Food and Drug Administration (FDA)–approved biologic for AOSD in the USA, while in Europe, both canakinumab and anakinra are approved for AOSD.

Overall, there were some limitations in this systematic review concerning the quality of the data found in the literature. Majority of the articles included were case reports, case series, and cohort or case-control studies. In addition, heterogeneity was evident among the articles owing to a lack of standard parameters of assessment.

Conclusion

AOSD being a rare disease is challenging to treat, but it is even more difficult to diagnose. AOSD patients usually have to go through a journey of ambiguous symptoms, misdiagnosis or delay in diagnosis, and a series of ineffective therapies before an accurate diagnosis and effective treatment plan is implemented. This delay in diagnosis can lead to prolonged hospitalization and increase the financial burden for patients. Besides this, it may trigger the emergence of rare and potentially life-threatening complications of AOSD. Thus, a high index of suspicion is necessary for this disease at clinical presentation for timely, accurate diagnosis and prompt initiation of optimal therapy. At the moment, canakinumab is the only FDA-approved drug for AOSD in the USA, while in Europe both canakinumab and anakinra are approved for AOSD.

Furthermore, although the understanding of AOSD has evolved over the last decade, there are still significant gaps in our understanding of its diagnosis, most useful biomarkers, and treatment approach. An accurate depiction of the AOSD burden is needed to drive healthcare interventions and strategies. Since conducting large-scale prospective studies is very challenging in the context of rare diseases, nationwide registries, and good-quality RCTs with a smaller number of patients can be helpful to fill the knowledge gap that still exists.

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Author contributions

All authors contributed to researching data for the article, discussion of content, writing and reviewing and/or editing the manuscript before submission.

Declaration of Competing Interest

Dr. Petros Efthimiou has served on the advisory board of Novartis and Kiniksa.

Dr. Apostolos Kontzias has served on the advisory board of Novartis and Kiniksa.

Peter Hur and Priscila Nakasato are employees of Novartis Pharmaceuticals Corporation.

Kavita Rodha and GS Ramakrishna are employees of Novartis Healthcare Pvt Ltd.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2021.06.004.

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