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Diagnosis and treatment of adult-onset Still's disease: a concise summary of the German society of rheumatology S2 guideline

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This article is a slightly modified translation of the original German guideline (https://doi.org/10.1007/s00393-022-01276-4), incorporating important aspects of the methodology report (https://doi.org/10.1007/s00393-022-01277-3).

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Introduction

Adult-onset Still's disease (AOSD) is a rare polygenetic disease with an annual incidence of 0.16–0.4/100,000 [57, 132]. Onset is typically sudden, peaking at 36 years of age with a relatively wide margin including all age groups [69]. Mortality and morbidity are clearly increased [23]. With the licensing of interleukin (IL)-1 inhibitors, effective treatment options have become available and are employed alongside other pharmacological options in off-label use. The German Society of Rheumatology (DGRh) therefore commissioned the development of guidelines to inform clinical decision-making regarding diagnosis and pharmacological treatment in AOSD for rheumatologists and specialists in internal medicine. Due to the paucity of international guidelines, the DGRh hereby additionally provides a concise English version in order to render these recommendations more easily accessible, thereby entertaining the hope of contributing to improved AOSD patient care.

Methods

A panel was assembled consisting of German rheumatology experts, two patient representatives from the German national patient organization Rheumaliga, and a delegate from the German Society of Internal Medicine (DGIM). The core issues "how should AOSD be diagnosed?" and "how should AOSD be treated?" were structured according to the PICO scheme (P: patients or population; I: intervention; C: comparison, control, or comparator;

Infobox 1

Association of the Scientific Medical Societies in Germany (*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften*, AWMF)—registration number: 060-011
Classification: S2e
https://www.awmf.org/leitlinien/detail/ll/060-011.html (in German)
Special note:
Medicine and medical practice are subject to continuous development. All statements, particularly those regarding therapeutic procedures, can only be based on the state of scientific knowledge at the time of print. Greatest care was taken during establishment of the treatment recommendations herein. Guideline users remain responsible for each diagnostic and therapeutic application, medication, and dose.

O: outcome) and a systematic literature search was conducted in the CENTRAL (Cochrane) and Pubmed databases up until 31 December 2020, according to national guidelines [11]. Due to anticipated limited evidence, broad search parameters were chosen to include any definition of AOSD, any clinical endpoint, any or no comparator therapy, case series and observational studies including three or more AOSD patients, randomized controlled trials, and systematic reviews provided PICO questions and detailed methods were reported. The details and results of the systematic literature research are outlined in ◘ **Fig. 1**. All abstracts were screened by at least two members of the panel before inclusion or exclusion. Risk of bias analysis was performed employing the Newcastle–Ottawa Scale [47], Cochrane tool [47], or AMSTAR [185], as appropriate. Overarching principles, statements, and recommendations were developed following a nominal group process. The levels of evidence for statements and recommendations were assessed according to the Oxford Centre for Evidence-Based Medicine 2009; grading of recommendations followed national guidelines [11], with translation from German into English as follows: grade A: "soll" to "strongly recommend"; grade B: "sollte" to "recommend"; grade 0: "kann" to "suggest" or "can." All members of the panel reviewed potential conflicts of interest to exclude members' votes from the final results in case of potential moderate or higher conflicts of interest. The guidelines were externally reviewed by the executive boards of the DGRh, DGIM, and Rheumaliga. The final guidelines were originally published in German in August 2022 online (www.awmf.orf/leitlinien/detail/060-11.html) and consecutively in the *Zeitschrift für Rheumatologie*. The present English concise version was assembled by representatives from the original guideline panel.

Supplementary Information

The online version of this article (https://doi.org/10.1007/s00393-022-01294-2) includes detailed information on the authors' potential conflicts of interest. The article and supplementary material are available at www.springermedizin.de. Please enter the title into the search field; additional online material can be found under "Supplementary Material."

Overarching principles, statements, and recommendations

The overarching principles, statements, and recommendations issued by the board are summarized in ◘ **Table 1**.

Overarching principles concerning fundamental concepts of AOSD pathogenesis and treatment were developed based on clinical experience alongside literature review without grading the level of evidence or recommendation. AOSD is delineated as a rare, polygenetic autoinflammatory disorder. Diagnosis and treatment constitute an interdisciplinary challenge relying on rheumatological expertise. The role of shared decision-making and supportive therapies are further stressed (see overarching principles 1–3 in ◘ **Table 1**).

Multiple observational studies on patients with AOSD showed (i) that the disease often has a variable course and (ii) that arthralgia is a very common symptom (median, interquartile range [IQR]: 100%, 86–100%), whereas (iii) arthritis is observed in approximately two thirds of patients (66.6%, 50.5–86.2%). Polyarticular disease is more common (56.5%, 29.9–90.3%) than oligoarticular (29.0%, 2.3–41.8%) or monoarticular involvement (8.9%, 2.0–11.5%) [5, 7, 65, 129, 137, 142, 197, 201] (see statement 1 in ◘ **Table 1**). The most commonly affected joint regions are, in decreasing order, knees, ankle, elbows, shoulders, and fingers [58, 61, 65, 69, 74, 77, 83, 89, 98, 100, 109, 111, 119, 121, 126–129, 133, 134, 136, 137, 142, 162, 169, 177, 181, 197, 200–202, 217] (see statement 2 in ◘ **Table 1**). The patient representatives stressed that fatigue is of paramount importance from the patients' point of view. Although there was no evidence to support this notion, the board decided to include this patient concern in a statement (see statement 3 in ◘ **Table 1**).

The clinical picture of AOSD has been analyzed in multiple cohort studies, with varying clinical signs and symptoms. In summary, a characteristic clinical pattern emerges, including a combination of very common (> 50%), common (> 20%), and less common characteristic findings. In most studies, the exclusion of hemato-oncological diagnoses, alternative rheumatological diseases, and infections is highlighted. In order to diagnose AOSD, the board strongly recommends consideration of this combination of clinical signs and symptoms after exclusion of the conditions mentioned above. The grade of recommendation (GoR) was thus upgraded from the comparatively low level of evidence (LoE), because no alternative validated diagnostic instrument or tests exist to date [58, 61, 65, 69, 74, 77, 83, 89, 98, 100, 109, 111, 119, 121, 126–129, 133, 134, 136, 137, 142, 162, 169, 177, 181, 197, 200–202, 217] (see recommendation 1 in ◘ **Table 1**).

The Yamaguchi classification criteria have shown good diagnostic precision compared to other criteria and diagnostic approaches in cohort studies [10, 85, 119]. Therefore, these criteria can be employed to ascertain the clinical diagnosis of AOSD made by an expert [10, 85, 119] (see recommendation 2 in ◘ **Table 1**). Of interest, a European Alliance of Associations for Rheumatology (EULAR) working group is currently developing an AOSD activity score. Alternative multidimensional scores such as the "systemic score" by Pouchot do not include important complications such as macrophage activation syndrome (MAS) or lung involvement, and have not been sufficiently assessed as a disease activity parameter on an individual basis in AOSD for clinical purposes. The board

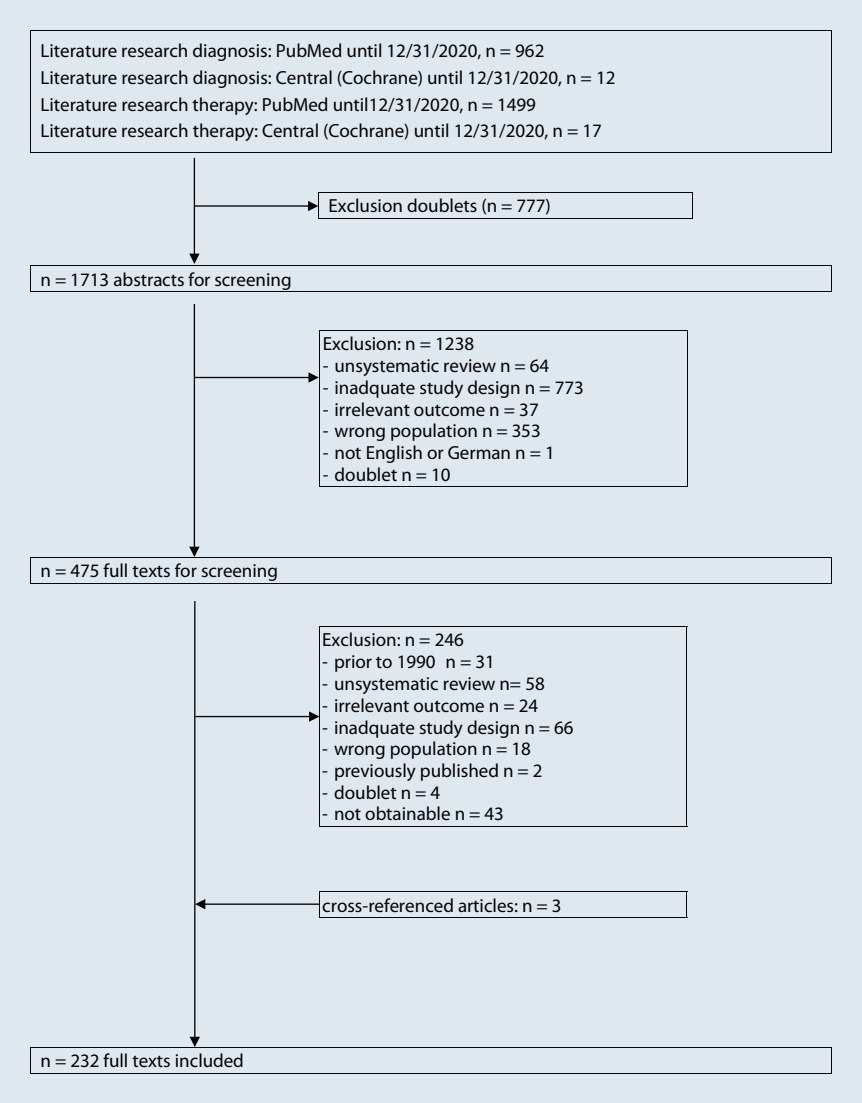

Fig. 1 ▲ Systematic literature research adult-onset Still's disease

therefore recommends assessing disease activity based on the presence of typical clinical signs and symptoms as outlined in the other recommendations and statements of this guideline [44, 55, 100, 174, 177] (see recommendation 3 in ◘ **Table 1**).

Various risk factors for MAS (synonym acquired hemophagocytic lymphohistiocytosis [HLH] or MAS-HLH) complicating AOSD have been identified in different cohort studies. Evaluation for MAS is advised in case of risk factors [2, 13, 15, 53, 55, 59, 100, 122, 139, 177, 198, 217] (see recommendation 4 in ◘ **Table 1**). Most consistently, high disease activity [2, 53, 55, 59, 100, 139, 177, 216], cytopenia (especially leukopenia) [2, 15, 15, 100, 216], raised liver enzymes [2, 13, 15, 216], elevated lactate dehydrogenase (LDH) [2, 13, 100], high ferritin serum levels [2, 13, 15, 55, 216], low fibrinogen [2, 15, 216], and high triglyceride values [2, 122, 216] have been identified. The guidelines do not include further specific recommendations concerning MAS-HLH, as guidelines on this potentially severe complication are already available [114].

Perimyocardial and pulmonary complications in AOSD are of concern and are associated with an unfavorable prognosis and/or treatment resistance [22, 149, 174, 198] (see statement 4 in ◘ **Table 1**). Perimyocardial disease complications in AOSD include pericarditis, pericardial effusion, cardiomyopathy, and non-infectious endocarditis [22]. Interstitial lung disease in AOSD is associated with a higher disease activity and ferritin levels [174, 198], pulmonary hypertension is rarely observed [149]. In a systematic literature review covering 1971–2018, the prevalence of AA amyloidosis in AOSD was estimated to be relatively low, at 0.88% (95% confidence interval [CI] 0.49–1.28) [54]. The main risk factor is high clinical disease activity. Due to the adverse prognosis associated with systemic AA amyloidosis, the board recommends excluding this rare complication in AOSD patients in case of persistently active disease [54] (see recommendation 5 in ◘ **Table 1**).

Elevated serum ferritin levels were evaluated in many cohorts [18, 19, 77, 126, 141, 154, 184, 192, 198, 202, 204] and case–control studies [20, 58, 61, 73, 98, 217]. For instance, in one case–control study that included patients with fever of unknown origin, raised ferritin values >5 times the upper level of normal were associated with a diagnosis of AOSD and with an odds ratio (OR) of 132.8 (95% CI 7.1–2502.9) [20]. However, in a large cohort of US patients, raised ferritin serum levels >1000 µg/l were most commonly caused by malignancy, iron overload, infections, and renal failure [143]. This finding stresses the importance of accompanying clinical signs for a diagnosis of AOSD. Despite its limited availability outside of France, a low fraction of glycosylated ferritin has been shown to support the diagnosis of AOSD in several studies [61, 69, 113]. Normalization of these parameters is associated with an improvement in clinical signs and symptoms. In summary, ferritin levels, especially markedly increased levels, support a diagnosis of AOSD [18–20, 45, 50, 51, 55, 58, 61, 69, 73, 77, 88, 95, 98, 113, 115, 119, 121, 126, 141, 154, 184, 192, 198, 202, 204, 204, 217] (see recommendation 6 in ◘ **Table 1**).

Elevated IL-18 serum levels were reported in several cohort and case–control studies with AOSD patients including various rheumatic diseases as comparators [30, 38, 45, 48, 73, 88, 92, 93, 95, 112, 164, 179] as well as sepsis [104, 165]. In most studies, IL-18 serum levels were also associated with clinical disease activity [73, 88, 92, 112, 165]. However, the use of IL-18 in daily practice is currently limited by the lack of a validated and certified com-

Table 1 Overview of overarching principles, statements, and recommendations on AOSD

Overarching principles

No.	*Principle*	*c (%)*
1	Adult-onset Still's disease (AOSD) is a rare, polygenetic, autoinflammatory disorder	100
2	Diagnosis and treatment of AOSD are interdisciplinary tasks which need rheumatological expertise	100
3	Treatment of AOSD follows the principles of participatory decision-making within a holistic therapeutic approach including pharmacological therapy alongside accompanying measures such as analgetic and physical therapy, rehabilitative measures, functional training, and the involvement of patient support groups	100

Statements

No.	*Statement*	*LoE*	*c (%)*
1	AOSD follows a variable course including monocyclic, polycyclic, and chronic patterns	3b	100
2	In AOSD, arthralgias are very common (> 80%) and arthritis is common (> 50%). A polyarticular course is observed more often than oligo- or monoarticular involvement. Very commonly involved regions (> 50%) are knees, ankles, and wrists, followed by (> 20%) elbows, shoulders, and fingers	3b	100
3	From patients' perspective, fatigue constitutes a substantial disease burden	5	100
4	Lung involvement and perimyocarditis are severe complications of AOSD which are associated with an unfavorable prognosis	4	93

Recommendations

No.	*Recommendation*	*LoE*	*GoR*	*c (%)*
1	Diagnosing AOSD based on the typical combination of (a) very common symptoms (> 50%) such as fever > 39 °C, rash, arthralgia, arthritis, pharyngodynia, lymphadenopathy, myalgia; (b) common symptoms (> 20%) such as splenomegaly, hepatomegaly, weight loss; and (c) less common characteristic symptoms (< 20%) such as pleuritis, pericarditis, abdominal pain, after (d) exclusion of alternative rheumatological, hemato-oncological, and infectious diseases is strongly recommended	3b	A	100
2	The clinical diagnosis of AOSD can be supported by fulfillment of the Yamaguchi classification criteria	3a	0	100
3	Assessment of disease activity in patients with AOSD is recommended to be based on the presence of typical clinical signs and laboratory markers	3b	B	100
4	Evaluation for macrophage activation syndrome (MAS) as a complication of AOSD is recommended in case of risk factors such as high clinical disease activity and laboratory markers such as a high ferritin serum level and cytopenia	2c	B	93
5	In case of persistently active disease in AOSD, exclusion of the rare complication of AA amyloidosis is recommended	2b	B	100
6	Assessment of serum ferritin levels for diagnosis and follow-up of patients with AOSD and assessment of disease activity in conjunction with markers of inflammation such as C-reactive protein (CRP) are recommended. A markedly elevated serum ferritin level (≥ 5 × upper limit of normal) and, if available, markedly reduced fraction of glycosylated ferritin (< 20%) further support the diagnosis of AOSD	2b	B	100
7	Measurement of interleukin-18 (IL-18) levels can be employed to substantiate the diagnosis and disease activity of patients with AOSD	2b	0	85
8	Non-steroidal anti-inflammatory drugs (NSAID) and eventually other analgesics and antipyretics can be used temporarily to control symptoms such as pain and fever	4	0	100
9	Systemic glucocorticoids are recommended as part of the initial therapy of acute-onset AOSD	2b	B	100
10	Consideration of glucocorticoid-sparing agents and/or alternative pharmacological therapies is recommended to prevent unwanted glucocorticoid side effects	4	B	100
11	Consideration of tocilizumab (1b), anakinra (2a), canakinumab (2b), methotrexate (2b), or calcineurin inhibitors, especially ciclosporin (2b), as glucocorticoid-sparing agents is strongly recommended	1b–2b	A	100
12	Use of agents blocking interleukin-1 and/or interleukin-6 in case of an insufficient response to glucocorticoids and conventional therapies such as methotrexate and/or ciclosporin is recommended	2b	B	100
13	Anakinra (2b) or canakinumab (5) can also be used as primary treatment options in AOSD prior to conventional disease-modifying antirheumatic drugs	2b/5	0	100

AOSD adult-onset Still's disease, *MAS* macrophage activation syndrome, *c* consensus, *LoE* level of evidence, *GoR* grade of recommendation

mercially available assay [30, 38, 45, 48, 73, 88, 92, 93, 95, 104, 112, 164, 165, 179] (see recommendation 7 in **Table 1**).

Concerning treatment, the use of non-steroidal anti-inflammatory drugs (NSAIDs) in cohort studies [4, 24, 49, 52, 66, 90, 142, 171, 187, 191] has led to their being reported to be sufficiently efficient in a wide range of 7–54% of AOSD cases [4, 66, 90, 142, 171, 191]. Therefore, NSAIDs can be tried for temporary symptomatic relief [4, 24, 49, 52, 66, 90, 142, 171, 187, 191] (see recommendation 8 in **Table 1**). The studies in AOSD were too small to address safety, but the safety is unlikely to be much different from other indications. However, the concomitant use of glucocorticoids deserves attention.

Glucocorticoids have been used as part of the treatment approach in virtually all AOSD studies so far [3, 4, 14, 17, 22, 25–27, 46, 56, 63, 66, 71, 80, 82, 87, 90, 91, 94, 103, 105, 107, 110, 117, 118, 124, 125, 140, 141, 144, 147, 148, 150–153, 158, 163, 166, 168, 170, 176, 182, 187, 190, 191, 193, 196, 199, 203, 205, 207, 208, 210, 215]. Their effectiveness has been reported to be higher than that of NSAIDs, with a range of 38–95% [60, 66, 67, 90, 151, 171, 191], albeit with a high risk of flare after discontinuation [141, 144, 151]. The use of glucocorticoids is therefore recommended as part of an initial treatment regime in AOSD [3, 4, 7, 14, 17, 22, 25–27, 46, 56, 63, 66, 71, 80, 82, 87, 90, 91, 94, 103, 105, 107, 110, 117, 118, 124, 125, 140, 141, 144, 147, 148, 150–153, 157, 158, 163, 166, 168, 170, 171, 175, 176, 182, 187, 190, 191, 193, 196, 199, 203, 205, 207, 208, 210, 215] (see recommendation 9 in **Table 1**). Due to known adverse effects of glucocorticoids, the panel recommends consideration of glucocorticoid-sparing agents [81, 209, 213] despite very limited evidence, especially in AOSD (see recommendation 10 in **Table 1**).

The glucocorticoid-sparing potential of conventional disease-modifying drugs in AOSD has been shown in case series: for methotrexate in approximately 60% of cases [67, 171] and for calcineurin inhibitors [66, 147]. In a randomized controlled trial on the use of anakinra in AOSD, the cessation of glucocorticoids was a predefined secondary endpoint, which was reached in 3 of 12 patients in the verum group but by no patient of the placebo group (not significant [n. s.]) [153]. Two meta-analyses including the aforementioned trial and seven or eight observational studies, respectively, showed a significant dose reduction of glucocorticoids with the use of anakinra [78, 178]. Canakinumab has shown its glucocorticoid-sparing potential in two cohorts [117, 205]. Tocilizumab met a predefined secondary endpoint of glucocorticoid reduction in week 12 in a randomized controlled trial (46% vs. 21%, $p = 0.017$) [91]. With the indicated variable level of evidence, these substances are therefore recommended as glucocorticoid-sparing agents [17, 46, 49, 56, 63, 66, 67, 71, 78, 91, 103, 110, 117, 118, 124, 125, 130, 147, 150, 152, 153, 157, 158, 166, 171, 178, 193, 194, 196, 203, 205, 210] (see recommendation 11 in **Table 1**). An additional multicenter registry study, which was published after the formal literature review for the present guidelines was closed, confirmed a significant dose reduction of daily prednisone from 18 to 4 mg in 31 AOSD patients on tocilizumab [195].

The efficacy of methotrexate was assessed in AOSD case series, with at least partial remission reported in 9–88% [4, 14, 66, 67, 90, 140]. The efficacy of calcineurin inhibitors was estimated to be between 33 and 75% in case series [66, 140, 151]. The use of biologics in AOSD studies is so far largely restricted to treatment-resistant cases, which were most often defined as a non-response to a conventional immunosuppressive medication such as methotrexate. Anakinra was assessed in a randomized controlled trial including 22 AOSD patients. The primary endpoint, defined as the percentage of patients in remission, was not met (6 of 12 vs. 3 of 12, n. s.) [153]. A meta-analysis including the above study alongside seven observational studies showed a significantly increased chance of remission, with an OR of 0.16 (95% CI 0.06–0.44). In a randomized controlled trial on canakinumab, 36 instead of the initially planned 68 patients were included due to slow recruitment and early licensing of the substance. Moreover, 2 patients in the placebo group were erroneously treated with canakinumab. The primary endpoint, the percentage of patients with a significant improvement in Disease Activity Score 28 (DAS28) of > 1.2, was not met (67% vs. 41%, $p = 0.18$). However, a post hoc per-protocol analysis showed a significant American College of Rheumatologists 30/70% (ACR30/70) response already at week 2 [62]. The IL-6 receptor blocker tocilizumab was tested in patients with AOSD in a randomized controlled trial. The primary endpoint, an ACR50% response at week 4, was not met (61.5% vs. 30.8%, $p = 0.24$). However, secondary endpoints consisting of clinical improvement (e.g., fever, rash, lymphadenopathy, serositis, splenomegaly), C-reactive protein (CRP) reduction, and reduction of glucocorticoids were significantly different, favoring tocilizumab [91]. In summary, the board therefore recommends anakinra, canakinumab, or tocilizumab in case of insufficient response to glucocorticoids and conventional therapies such as methotrexate and/or ciclosporin [4, 14, 17, 27, 29, 46, 49, 52, 56, 62, 63, 66, 66, 67, 70, 71, 78, 90, 91, 94, 103, 110, 117, 118, 124, 125, 130, 140, 147, 150–153, 157, 158, 166, 168, 170, 171, 173, 183, 187, 196, 199, 203, 205, 206, 208, 210] (see recommendation 12 in **Table 1**).

Concerning first-line therapeutic options, an IL-1-targeted therapeutic strategy with anakinra was assessed as a first-line treatment option prior to conventional immunosuppressants in AOSD cohort studies, demonstrating effectiveness for anakinra [151, 205]. In accordance with the licensing situation, the board therefore recommends that anakinra or canakinumab can be used as treatment options prior to conventional disease-modifying antirheumatic drugs [151, 207] (see recommendation 13 in **Table 1**).

Only a limited body of evidence is available to support therapeutic strategies in AOSD. In retrospective cohorts, tocilizumab responders were more likely to suffer from chronic articular disease, while anakinra responders were more likely to suffer from systemic disease [203]. In another cohort, the number of swollen joints was negatively associated with anakinra retention rates, while the presence of a rash was associated to improved anakinra retention rates [206].

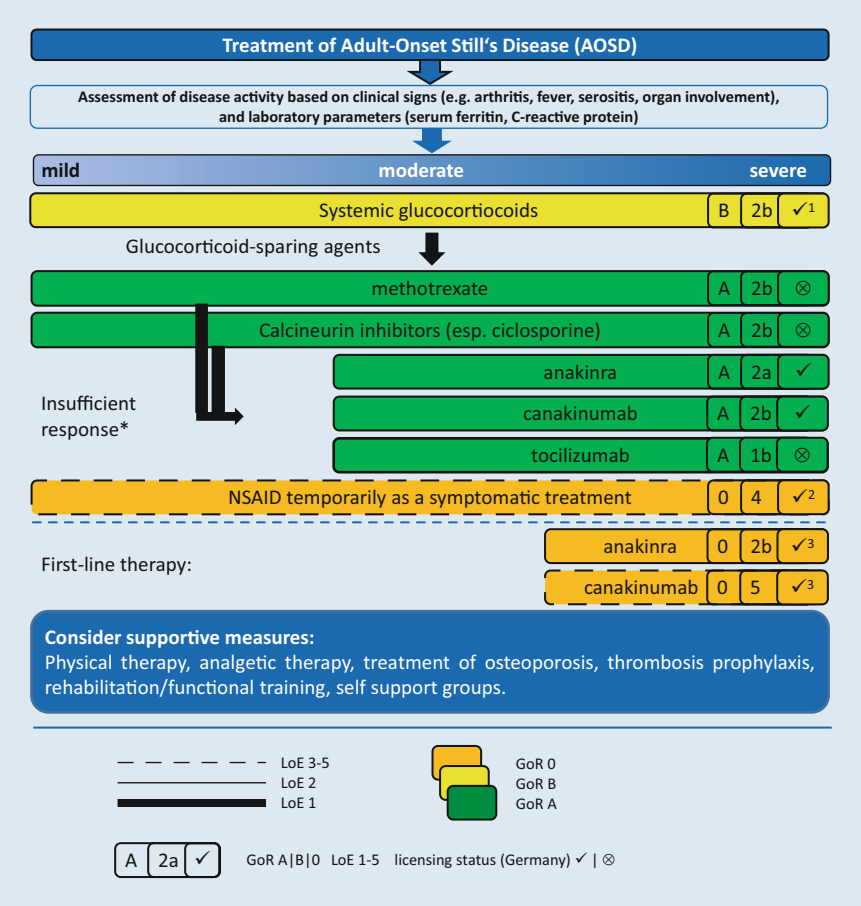

Fig. 2 ▲ Treatment of adult-onset Still's disease (AOSD; Level of evidence (LoE) 5—expert opinion). After determination of disease activity, treatment is usually commenced with glucocorticoids ([1]licensed for active disease states of rheumatic diseases). Methotrexate (MTX) or calcineurin inhibitors (CNI), in case of higher disease activity, additionally anakinra, canakinumab, or tocilizumab, are introduced as glucocorticoid-sparing agents. *In case of a non-response to MTX/CNI, anakinra, canakinumab, or tocilizumab should subsequentially be used even in cases of lower disease activity states. Non-steroidal anti-inflammatory drugs (*NSAIDs*; [2]licensed for pain and fever) can be used temporarily for symptom control. Anakinra and canakinumab can be used as a first-line option in case of severe disease activity ([3]licensed in case of non-response to glucocorticoids and NSAIDs; in the case of anakinra, additionally in case of moderate to high disease activity even before glucocorticoids and NSAIDs). *GoR* grade of recommendation, *LoE* level of evidence, *LoE 5* expert opinion; 100% consensus was obtained for the treatment algorithm

Since confounding by indication is a potentially important bias in these studies, the board did not favor IL-1- or IL-6-targeted therapy in case of certain clinical AOSD scenarios.

Based on the statements and recommendations, the board therefore suggested a treatment algorithm with LoE 5 (expert opinion; ◘ **Fig. 2**): AOSD activity should be assessed based on clinical symptoms and laboratory changes by physicians experienced in the treatment of AOSD. Systemic glucocorticoids should initially be used in acute-onset AOSD. Glucocorticoid-sparing pharmacological options in case of low disease activity are methotrexate (MTX) and calcineurin inhibitors, especially ciclosporin (CSA). With increasing disease activity, anakinra (ANA), canakinumab (CAN), and tocilizumab (TCZ) may be considered. In case of initially high disease activity, ANA and CAN can also be considered as primary options before MTX and/or CSA. NSAIDs may be used for temporary symptomatic relief. Supportive measures include pain management, physical therapy, patient support groups, etc. (◘ **Fig. 2**).

Discussion

AOSD is a rare systemic autoinflammatory disease with increased morbidity and mortality. Recently, novel targeted treatment options have become available, which are in part already licensed for this situation in some countries. The German Society of Rheumatology (DGRh) therefore commissioned the development of guidelines, as summarized here in a concise English version, to improve the management of AOSD and to stimulate interaction with other societies of rheumatologists. These AOSD guidelines are addressed primarily to rheumatologists and specialists in internal medicine, with the aim of improving AOSD patient care by providing evidenced-based recommendations.

Besides the diagnostic procedures mentioned in the recommendations, data also exist on the utility of procedures such as positron-emission tomography (PET) with or without computed tomography (PET-CT) [8, 21, 86, 155, 180], as well as on biopsies of liver [9], skin [64, 96, 116, 120, 131, 167, 214], mucous membranes [181], lymph nodes [84], and bone marrow [138], all of which may have a role in the differential diagnostic process of individual patients. Furthermore, multiple biomarkers other than ferritin or IL-18 have been assessed [16, 19, 30, 32–38, 38–41, 43, 45, 68, 74–76, 79, 88, 95, 101, 102, 104, 108, 135, 160, 161, 186, 188, 197], but validation studies are largely lacking. In certain cases, genetic studies may be useful to exclude hereditary autoinflammatory diseases, but do not show sufficient diagnostic precision to be routinely recommended in AOSD work-up [12, 31, 42, 97, 189, 211]. From a diagnostic perspective, it is noteworthy that flares or primary manifestations of AOSD have been noted in temporal relation to COVID vaccinations during the course of the current pandemic [99, 123, 145, 159, 172, 212]. Concerning therapeutic options, the board decided against phrasing a recommendation for or against tumor necrosis factor (TNF)-blocking agents. Most cohort studies showed a high rate of non-responders between 53 and 81% [25, 176, 187], which has been confirmed in most [28, 171, 196] but not all case series [1, 3, 26, 60, 82, 106]. Case series with tofacitinib [80], rilonacept

[163], and clarithromycin [182] were also not taken into account. A recent analysis of Janus kinase (JAK) inhibitors (published after the systematic literature review) in nine combined AOSD and systemic juvenile idiopathic arthritis (sJIA) patients showed a mixed response of two complete remissions, three partial remissions, and four (44%) treatment failures [72]. Another interesting study, which was published after the systematic literature review for the current guidelines, assessed the response of ASOD patients with pericarditis to NSAIDs and colchicine combination therapy [146]: a remission rate of 65% was observed in this cohort. Of note, amongst conventional antirheumatic drugs, sulfasalazine was associated with a high degree of adverse events (60%), including even one fatal outcome [87]. Evidence on IL-1- and IL-6-targeted therapies in AOSD is scarce, since randomized trials have mostly failed to reach their primary endpoint. However, at the same time, trends towards effectiveness of the respective cytokine blockade were shown, and important secondary endpoints were met [91, 94, 153]. The body of evidence supporting cytokine blockade is substantially better in children with Still's disease (sJIA) [6, 156]. Licensing of canakinumab and anakinra in adults is also based on the assumption that AOSD and sJIA represent the same disease, with age-specific variation in clinical presentation and prognosis. The board stated that important milestones to improve AOSD patient care comprise an internationally accepted definition of active vs. inactive disease states, a definition of treatment resistance, consolidation of the body of evidence favoring advanced treatment options in adults, and a consensus on an activity score for clinical and/or study purposes. Succinctly, there are still many open questions to address in the management of AOSD in the near future.

With the English translation and concise summary, the DGRh aims to support specialists involved in the management of this challenging disease to further improve patient care.

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