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# Unmet needs and research gaps in Still's disease across ages: proceedings from a pediatric and adult joint expert panel

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## Abstract

**Background** Still's disease (SD), including systemic juvenile idiopathic arthritis (sJIA) and adult-onset SD (AOSD), is an inflammatory condition typically characterized by daily fever, arthritis, and skin rash together with neutrophilic leukocytosis, thrombocytosis, and increased acute phase reactants. The reported differences between sJIA and AOSD appear to reflect variations along an inflammatory spectrum influenced by age, rather than differences in the underlying pathology.

**Methods** In February 2023, an expert meeting, including pediatric and adult rheumatologists, was held in Rome, Italy, with the aim of defining more precise and timely strategies for disease management. The following four topics were discussed: (1) early recognition and diagnosis of SD; (2) pathogenetic pathways and possible biomarkers for diagnosis and response; (3) refractory disease and risk factors, and (4) treatment of SD and its complications.

**Results** The development of improved diagnostic criteria and validation of biomarkers are important steps towards achieving early diagnosis, although several biomarkers remain to be universally validated and available for clinical practice. Additionally, awareness of important complications of SD, including macrophage activation syndrome and lung disease, is crucial for improving patient outcomes, alongside an improved understanding of risk factors for the development of refractory disease. While interleukin (IL)-1 and IL-6 inhibitors have improved the treatment landscape of SD, harmonizing the therapeutic approach across centers and countries, together with developing treatment strategies for refractory patients, still represents a challenge.

**Conclusions** Here, we summarize the results of discussions among experts, supplemented by relevant literature, and highlight unmet needs in the diagnosis and management of SD.

**Keywords** Adult-onset Still's disease, Biological agents, Diagnosis, Lung disease, Macrophage activation syndrome, Novel biomarkers, Still's disease, Systemic juvenile idiopathic arthritis, Treatment, Unmet needs

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## Introduction

Still's disease (SD), which encompasses systemic juvenile idiopathic arthritis (sJIA) and adult-onset SD (AOSD), is a rare, complex and polygenic inflammatory syndrome [1–6]. Currently, sJIA and AOSD are considered part of the same clinical spectrum, sharing key pathological and clinical features.

In both pediatric and adult patients SD is characterized by the overproduction of pro-inflammatory cytokines, mainly interleukin (IL)-1, IL-6, and IL-18 [1, 2]. Innate and adaptive immune mechanisms are both thought to contribute to disease pathology [6, 7]; more specifically, the innate immune system drives systemic febrile inflammatory syndrome that typically characterizes the first phase of the disease, while adaptative immune pathways seem to play a major role in chronic evolution, especially for articular manifestations [8]. Macrophage activation syndrome (MAS) remains the main and most severe complication of SD [1, 8], together with the more recently described SD-related lung disease (LD) [9].

SD is typically characterized by daily spiking fever, arthritis, and skin rash, together with laboratory markers of systemic inflammation [1]; however, some differences have been reported between pediatric (sJIA) and adult (AOSD) cohorts [3, 10]. These discrepancies most probably result from differences in age-specific immune manifestations or from variability in data collection across cohorts, rather than from differences in the underlying pathogenetic mechanisms. Indeed, a recent meta-analysis showed that in pediatric and adult SD, all clinical and laboratory features shared similar prevalence, with the only exceptions of myalgia, sore throat, and weight loss, which were more frequently reported in adults, and anemia, more commonly described in children [4]. Of note, while sore throat is a very common, but unspecific, symptom in pediatric patients, myalgia is often less reported in children, which could be a reason for underreporting by pediatric rheumatologists. Moreover, weight loss is rare in children and is more frequently deemed as growth failure.

Despite all these similarities, there is still a wide variability in the diagnostic and therapeutic approach between pediatric and adult centers. It is crucial for clinicians to share their respective experiences in the management of children and adults with SD, in order to develop more effective and timely strategies.

To this end, an expert meeting, including pediatric and adult rheumatologists, was held in Rome, Italy, in February 2023. The following topics were discussed: (1) early recognition and diagnosis of SD; (2) pathogenetic pathways and possible biomarkers for diagnosis and response; (3) refractory disease and risk factors; and (4) treatment of SD and its complications. This manuscript reports the clinical experiences of clinicians who manage SD in pediatric and adult patients, based on the most recent literature updates and on the discussions over the course of this two-day meeting. The objective was to provide an overview of the major clinical challenges and unmet needs in SD across ages, with the goal of improving disease management in both the pediatric and adult setting.

## Methods

The expert meeting, with the unconditional sponsorship of Sobi, was led by seven international clinical and translational researchers with high expertise in the field of SD across the age spectrum. The meeting involved 33 Italian pediatric and adult rheumatologists.

Over the course of two days, participants were divided into groups to discuss each of the four topics outlined above; two groups worked on each topic and each group was moderated by two of the expert leaders. Following discussion, each group developed a list of unmet needs within their topic and proposed possible actions and/or recommendations to address them.

## Results

### Early recognition and diagnosis of SD

Recent clinical and translational data increasingly support the hypothesis of a biphasic model in the pathogenesis of SD [8]. In the first phase, characterized by febrile spikes and systemic disease manifestations, it is now recognized that innate immune pathways are particularly activated with an overproduction of IL-1, IL-6, IL-18, and pro-inflammatory proteins (S100 A8/9 and S100 A12). If systemic inflammation is not adequately controlled and treated, SD can progress into a more chronic disease phase where more adaptive immune pathways get activated [8]. Increasing evidence that early treatment of SD can positively impact clinical outcomes [11–14] highlights the importance of early diagnosis, to enable treatment within this potential window of opportunity to alter the natural disease course.

Early diagnosis of SD is also important for clinical research. Detecting SD early in the disease course increases the likelihood of an accurate diagnosis and correct classification of patients in clinical trials, enhancing the ability to obtain approval for targeted therapies for SD across patient subtypes. However, early diagnosis of SD remains challenging, particularly as some of the main clinical symptoms of SD are also common among infectious, malignant, or other inflammatory conditions [1, 15]. Furthermore, typical clinical and laboratory features of the disease may not all be present at the time of diagnosis, and there is a lack of validated and widely accepted biomarkers [15].

The main unmet needs regarding diagnosis of SD acknowledged by the board of experts, together with agreed proposals to implement management of SD in pediatric and adult settings, are summarized in Table 1 and discussed in detail below.

#### *Diagnostic and classification criteria*

The diagnosis of SD is still based on the recognition of a typical clinical phenotype and requires the exclusion of numerous mimicking conditions in both pediatric and adult patients, such as autoinflammatory diseases, infections, malignancies, and other hyperinflammatory conditions [18]. Indeed, diagnostic or classification criteria available for both pediatric and adult SD reflect the main clinical features of the syndrome (Table 2).

The 2004 International League of Associations for Rheumatology (ILAR) criteria [22] have long guided the diagnosis of SD in children; however, major shortcomings have led to a recent consensus effort to revise them. In particular, the main limitation of applying ILAR criteria is the requirement of arthritis, of a duration greater than 6 weeks, as a mandatory criterion. Indeed, a sizable proportion of children with SD do not have arthritis at disease onset [22]. Moreover, arthritis is often the last manifestation to occur in clinical practice [12], with a median delay of 1 month after disease onset (unpublished data, courtesy of Dr De Benedetti). Finally, evidence is increasingly robust supporting that no significant differences exist in the main features or in the course of disease in pediatric SD with or without arthritis at onset [13].

In 2018, a major international effort led to the proposal of new classification criteria for pediatric SD (2019 Paediatric Rheumatology INternational Trials Organisation [PRINTO] criteria; Table 2) [20]. Importantly, in this new set of criteria, arthritis is no longer considered a mandatory criterion, allowing earlier classification of patients without arthritis at onset, as well as a better alignment to the diagnostic criteria most commonly used for adult patients. In adults, Yamaguchi and Fautrel criteria (Table 2) [18, 21], have both revealed excellent diagnostic performance in their developmental sets; however, neither was validated in independent cohorts with a gold standard control group. The lack of a common set of criteria across ages is a major unmet need in SD management, given its key relevance in both clinical practice and research, and should represent the focus of a joint effort in the near future (Table 1).

#### *Early detection of MAS*

MAS is still the most important, life threatening complication of SD. MAS is recognized as a secondary form of hemophagocytic lymphohistiocytosis (HLH) [1, 23–25] and is characterized by rapid worsening of the patient's condition, typically accompanied by a sustained high-grade fever (i.e., no spiking pattern) and the development of cytopenias, hyperferritinemia, liver failure, coagulopathy, and central nervous system involvement [1, 23–25]. Given its potentially rapid progression to multiorgan failure and fatal outcome, a high suspicion for an early diagnosis of MAS is crucial to promptly start treatment, and improve morbidity and mortality [23–26]. However, diagnosis of MAS is a major challenge for clinicians, given its overlap with several mimicking conditions, such as a flare of the underlying SD itself and/or the presence of concurrent infections, which often trigger MAS. Furthermore, in a sizable proportion of children with SD-associated MAS, MAS occurs at the onset of SD, thereby increasing the complexity of the initial differential diagnosis [27].

For the timely detection of MAS in patients with SD, it is crucial to point out that MAS occurs in the context of a highly inflammatory underlying condition [24, 28]. For that reason, many patients with SD may have several laboratory parameters (platelets, fibrinogen, white blood cells) paradoxically still within normal range at the onset of MAS [29], and may not fulfil the well-known HLH- 2004 diagnostic criteria for hemophagocytic syndromes [30]. Thus, in this context, changes in the trend of laboratory parameters over time are considered more indicative of MAS than absolute laboratory values [31]. Against this background, an international effort led to the development of the 2016 European Alliance of Associations for Rheumatology/American College of Rheumatology/PRINTO (EULAR/ACR/PRINTO) criteria, specific for the classification of MAS in children with SD [32]. In order to speed up the recognition of SD-associated MAS and to increase sensitivity, the 2019 MAS/sJIA (MS) score, an electronic algorithm including seven variables (three clinical and four laboratory parameters), was developed and validated [28].

As there are no specific diagnostic criteria for MAS in adult patients with SD, the criteria defined for children [28] may represent an important tool that can also be applied to adults. Indeed, the 2016 criteria have proven useful in identifying adult patients with SD who are at risk of an unfavorable outcome and have demonstrated good sensitivity and specificity [33].

The role of biomarkers in supporting the diagnosis of MAS is increasingly robust [34–37]. These include the interferon (IFN)-γ–induced chemokine CXCL9, of which circulating levels are known to distinguish between SD-associated MAS and active SD [34]. Furthermore, the ratio between total IL-18 versus CXCL9 levels is a potential distinguisher between SD-associated MAS

**Table 1** Unmet needs and suggested recommendations for the management of patients with SD

| Unmet need | Suggested recommendations for improvement |
|---|---|
| **1. Early recognition and diagnosis of SD** | |
| *Delayed referral* | |
| • Lack of awareness of the condition both in pediatric and adult general medicine | • Education<br>○ Spreading of currently available recommendations<br>○ Definition of red flags<br>○ Definition of diagnostic–therapeutic care pathways for fever of unknown origin<br>○ Raising awareness of the impact of ongoing treatments in masking symptoms (e.g., corticosteroids)<br>• Creation of multidisciplinary teams as a support and reference for specialists less familiar with the disease |
| *Diagnostic criteria* | |
| • Lack of common and validated diagnostic criteria for both pediatric and adult SD<br>○ A major limitation of ILAR classification criteria for sJIA is the requirement of arthritis as mandatory criterion<br>○ Lack of widely available and validated biomarkers included in the current diagnostic criteria | • Identification of the most relevant clinical signs/symptoms to be included in common diagnostic criteria<br>• Evaluation of the performance of currently available criteria in both pediatric and adult settings<br>• Implementation of available criteria:<br>○ Yamaguchi: including a weighted score (different relevance of criteria included)<br>• Joint effort to develop new common classification criteria, including promising biomarkers |
| • Difficulty in the use of CT, PET, or MRI PET in children<br>○ Requires sedation<br>○ Radiation exposure risks with use of CT | • Since only required in a few children, better identification of patients for whom imaging is useful |
| **2. Pathogenetic pathways and possible diagnostic and response biomarkers** | |
| *Pathogenesis of SD* | |
| • Pathogenetic mechanisms underlying the disease still not completely understood | • Investigation of the role of:<br>○ Innate immunity<br>○ Pro-inflammatory cytokines (e.g., the IL-1 family)<br>○ Adaptative immunity<br>• Clarification of the genetic profile of the disease |
| *Biomarkers* | |
| • Lack of widely available and validated biomarkers | • International cross-center validation of standardized assays and cut-offs for currently available biomarkers (e.g., S100, IL-18, CXCL9)<br>• Ensure timely availability of test results<br>• Identification of effective biomarkers for:<br>○ Prediction of disease evolution, response to therapy, remission, and treatment discontinuation<br>○ Recognition of patients at high risk of complications or refractory disease<br>• Assign specific biomarkers for different phases of the disease |
| • Lack of awareness regarding biomarkers for which scientific evidence is already available | • Education of physicians regarding currently available biomarkers and their role in diagnosis<br>○ Publication of a position paper (endorsed by scientific societies) to foster the use and availability of biomarkers<br>• Improvement of the availability of biomarkers<br>○ Mapping referral centers for specific biomarkers<br>○ Networking across centers |
| • Limited knowledge of the role of IL-18 | • Investigation of the role of IL-18 in:<br>○ Diagnosis<br>○ Response to biologicals<br>○ Development of complications (e.g., MAS, LD) and chronic joint disease |
| *Window of opportunity* to treat JIA | |
| • Limited knowledge regarding the 'window of opportunity' hypothesis | • Design *ad hoc* studies to:<br>○ Demonstrate its existence<br>○ Better define its duration<br>○ Clearly define early sJIA |
| **3. Refractory disease and risk factors** | |
| *Definition of refractory disease* | |
| • Lack of a validated definition of refractory disease | • Promote the use of Erkens' formulation [16], developed together with the sJIA Foundation, as a good reference point for the definition of refractory disease<br>• Further investigation to differentiate what is considered refractory disease in children from that in adults<br>• Types of disease:<br>○ Systemic: systemic symptoms that do not respond to any treatment except steroids |

**Table 1** (continued)

| Unmet need | Suggested recommendations for improvement |
|---|---|
| | ○ Joint (polyarthritic phenotype): can be more difficult to control<br>• Drugs referred to when defining refractory disease include: anti–IL-1 and anti–IL-6, non-steroids, NSAIDs, and methotrexate |
| *Diagnosis of refractory disease* | |
| • Physicians unaware of differential diagnoses | • Ensure physicians are alert to the possibility of differential diagnosis if patients fail to respond to therapy, especially in adults<br>○ Refractory systemic disease is predominantly a pediatric problem<br>○ Lack of response is rare in adults; thus, misdiagnosis should be suspected<br>• Educate physicians regarding differential diagnoses:<br>○ Whipple's disease in adults<br>○ Lysinuric protein intolerance in children |
| *Risk factors* | |
| • Currently unable to identify patients at risk of refractory disease | • Improve knowledge of pathogenetic mechanisms to help identify patients who might benefit from specific treatment approaches<br>• Identify biomarkers that would enable:<br>○ Stratification of patients at high risk for poor therapeutic response<br>○ Early identification of refractory disease<br>○ Selection of patients for possible new targeted treatments |
| *Role of hypereosinophilia* | |
| • The pathogenesis and importance of hypereosinophilia is currently unclear<br>○ Detected in children with refractory disease but not adults<br>○ Increase in eosinophils is significant (can reach 3000/μL)<br>○ Appears during the course of the disease, and seems to have an oscillating and non-persistent course<br>○ Possible association with pulmonary disease (intermittent course, resolved spontaneously without therapy changes) | • Clarify whether hypereosinophilia is related to a drug reaction or to a disease<br>○ Investigate potential temporal association with the use of biological agents and/or IL-1 and IL-6 inhibition<br>○ Investigate potential eosinophil sensitivity to steroids<br>○ Investigate whether it is mediated at the lung level by eosinophilic infiltrates<br>○ Investigate the significance of progressively worsening eosinophilia in children with non-systemic forms, treated with anti–TNF-alpha (particularly etanercept) |
| *Pulmonary involvement* | |
| • Optimal detection and diagnosis when pulmonary involvement is unknown<br>○ Observed in children but uncommon in adults (possibly because it is simply not investigated or confounded by smoking) | • Clarify how pulmonary involvement can be identified before symptoms appear<br>○ Define the role of total body CT scan<br>■ Interpretation by radiologist<br>○ Define criteria for appropriate use of chest CT scan in children to identify interstitial pneumopathy<br>■ Minimize radiation exposure<br>■ Uncontrolled ferritin as a potential risk factor for interstitial pneumopathy<br>• Establish diagnostic criteria for pulmonary involvement<br>• Recommend close monitoring of patients with pulmonary involvement due to tendency to develop recurrent MAS |
| **4. Treatment of SD and its complications** | |
| *Role of glucocorticoids (GCs)* | |
| • Use of GCs in the diagnostic phase can mask certain disease features and hamper diagnosis | • Further investigate the role of cortisone |
| *Differences in treatment in pediatric and adult settings* | |
| • A lack of common, shared guidelines and recommendations<br>○ Limited evidence from supporting literature | • Collection of data on the use of high-dose anakinra<br>• Update of current guidelines to permit early administration of biological agents in cases of strong diagnostic suspicion<br>• Clarify use of methotrexate<br>○ Used in adults with joint involvement<br>○ Not used in children<br>○ Not administered if fever present |
| *Use of anakinra* | |
| • Clarification of the use of anakinra needed<br>○ Currently anakinra use differs between children and adults | • Current use of anakinra in children<br>○ Anakinra monotherapy at a high dose (5–10 mg/kg), further increased if necessary<br>○ If no response after 24–48 hours or high ferritin levels are detected, cortisone is added<br>• Current use of anakinra in adults<br>○ Initial antibiotic therapy and screening for tumors<br>○ If no response, cortisone initiated before anakinra<br>○ Anakinra administered at a lower dosage than in children |
| • Clarification of anakinra dose and route of administration<br>○ Initial doses in children are high (5–10 mg/kg), regardless of the form of the disease<br>○ Initial doses in adults are generally lower than in children<br>○ No guidelines, thus reference is made to the AIFA data sheet<br>○ Often intermediate doses administered due to lack of guidance | • Common guidance and standardization of anakinra dose needed<br>○ High initial dose, then reduced<br>• Collection of experiences of high-dose IV administration |

**Table 1** (continued)

| Unmet need | Suggested recommendations for improvement |
|---|---|
| • Optimal timing of anakinra administration and treatment response are unknown | • Confirm the existence and duration of the 'window of opportunity'<br>○ Evidence supporting early initiation of the biological agent<br>• A significant response (i.e., reduction of fever and rash, improvement of general clinical condition) is observed 48 hours after initiation of biological agents |
| *Remission and discontinuation of therapy* | |
| • The definition of disease remission differs in adults and children<br>○ In adults, patients can be classified as being in remission when a joint with active arthritis is present<br>○ Children are defined as being in remission if the patient has no symptoms at all | • Investigation of biomarkers to guide the decision on when and how to reduce and discontinue therapy |
| • A lack of clear guidance regarding timing of discontinuation of biological therapy and GCs<br>○ Therapy generally discontinued after 1 year in patients with inactive disease for ≥ 6 months | • Timing of discontinuation is decided by treating physician according to disease severity |
| • No evidence to support the use of the current stair-step strategy (i.e., increasing intervals between doses rather than reducing the dosage) to achieve discontinuation<br>○ Current data generated in rheumatoid arthritis not SD | • Conduct targeted studies to generate objective data in adults and children<br>• Organize an international consensus conference aimed at defining criteria for therapy discontinuation |
| *Treatment of systemic disease* | |
| • Avoidance of GCs if MAS is observed until malignancies are ruled out | • In children, the usual starting dose of anti–IL-1 therapy of ≥ 5 mg/kg can be increased to 10 mg/kg if MAS is observed<br>○ If no response within 24–48 hours, steroid can be added |
| • Approximately 20% of children do not respond to anti–IL-1 or anti–IL-6 therapies | • Define the characteristics (including biochemical) that can help identify cases of refractory systemic disease |
| • Adults present more frequently with visceral symptoms (serositis, hepatosplenomegaly) and have a lower prevalence of erosive arthritis; thus, there is a greater tendency to develop systemic disease | • Confirmation of preliminary data required |
| *Management of non-responders to anakinra* | |
| • A lack of guidelines for managing non-responders<br>○ Generally pediatric patients | • Define recommendations for non-responders<br>○ Currently, children who do not respond to anakinra receive anti–IL-6 (no response) or canakinumab (partial response) |
| *Treatment of refractory disease* | |
| • Early initiation of therapy is important for prevention of persistent forms of the disease from becoming refractory; however, the best early treatment strategy is currently unknown | • Development of EULAR guidelines required<br>• Identify best early treatment:<br>○ Monotherapy with anakinra, or;<br>○ Glucocorticoid–anakinra combination<br>• Identify optimal starting dose in children:<br>○ Hospitalization period (IV administration): lower (2 mg/kg) or higher dose (10 mg/kg)<br>○ At discharge (SC administration): reduced dose once symptoms and inflammation have resolved |
| • Difficulty in accessing innovative (experimental) therapies, especially for adults | • Improve regional certification of rare diseases to ensure access to innovative new drugs<br>• Improve communication of ongoing trials to enable referral of patients to centers participating in clinical studies |
| • Difficulties associated with off-label use of drugs or combinations of biological therapies | • Ensure timely publication of information regarding successful off-label use:<br>○ Combination of anakinra and abatacept [17]<br>○ Publications needed of experience with combination therapies with cytokine inhibitors + JAKis and bispecific anti–IL-1/IL-18<br>○ Modern conditioning regimens may be useful for reducing the complex courses observed in some patients<br>• Expert opinion required to develop indications for rescue therapy (e.g., combinations of biological agents) in patients with refractory disease |

*AIFA* Agenzia Italiana del Farmaco, *CRP* C-reactive protein, *CT* computed tomography, *ER* emergency room, *ESR* erythrocyte sedimentation rate, *EULAR* European Alliance of Associations for Rheumatology, *GCs* glucocorticoids, *GPs* general practitioners, *IL* interleukin, *ILAR* International League of Associations for Rheumatology, *IV* intravenous, *JAKis* Janus kinase inhibitors, *LD* lung disease, *MAS* macrophage activation syndrome, *MRI* magnetic resonance imaging, *NSAIDs* nonsteroidal anti-inflammatory drugs, *PET* positron emission tomography, *SC* subcutaneous, *SD* Still's disease, *sJIA* systemic juvenile idiopathic arthritis, *TNF* tumor necrosis factor

from both familial as well as secondary HLH [35, 37]. In patients with systemic hyperferritinemic inflammatory diseases, chronically elevated IL-18 levels are correlated with an increased risk for MAS development [36]. Recently, elevated $CD38^{high}$/HLA-DR+ CD8+ T cells have demonstrated good performance in distinguishing patients with HLH from those with sepsis [38], and $CD4^{dim}$ CD8+ T cells were not only found to be significantly increased in patients with all forms of secondary HLH, but also reliably able to separate patients with MAS

from those with active SD [39, 40]. Although routine use of these biomarkers is not yet available in most clinical settings and the validation of standardized assays and cut-offs is ongoing, these insights and measurements will significantly impact our performance in detecting MAS in SD in the near future.

## Pathogenetic pathways and possible biomarkers for treatment response

While there are already several available biomarkers to support the early differential diagnosis of SD, they need to be internationally validated, with standard cut-off values identified and included in diagnostic guidelines. The lack of widely accepted and universally validated biomarkers is an important unmet need in SD (Table 1).

Other than supporting the initial diagnosis, biomarkers in SD should help to predict response to treatment and determine when treatment should be discontinued. While our understanding of relevant disease mechanisms in SD is increasing, many aspects still remain incompletely understood [6]. Several biomarkers have promising utility for prediction of the course of SD and treatment response.

### *Genetic markers*

One large genome wide genetic study, identified an association between SD and the *HLA-DRB1 *11* alleles in various populations across North America, South America, and Europe, with an odds ratio (OR) of 2.3 (95% confidence interval [CI] 1.9–2.8), representing the strongest association with the risk of developing SD of any identified marker to date [41]. This finding suggests a strong autoimmune component in the pathophysiology of SD and may highlight how both innate and adaptive immune systems can be involved in the disease pathogenesis [41]. Even though limited, there are some data to suggest a role for *HLA-DRB1 *11* in T cell activation and an autoimmune-like process, particularly in patients with arthritis-predominant SD [41]. *HLA-DRB1 *11* as a risk factor for SD has also been validated in other cohorts [42].

In addition to variations in major histocompatibility complex (MHC) II, polymorphisms in the *IL1RN* gene (encoding the IL-1 receptor antagonist [IL-1RA]) have been reported to be associated with susceptibility to SD (OR 1.3; 95% CI 1.1–1.4) [43]. The presence of *IL1RN* polymorphisms (as a common haplotype in most patients) results in lower expression of IL-1RA, which

**Table 2** Currently available diagnostic/classification criteria for SD

| | sJIA | | AOSD | |
|---|---|---|---|---|
| | **ILAR 2004 [19]** | **PRINTO 2018 [20]** | **Yamaguchi 1992 [21]** | **Fautrel 2002 [18]** |
| **Major criteria** | • Arthritis in ≥ 1 joint with or preceded by fever ≥ 2 weeks (documented to be daily for ≥ 3 days), with ≥ 1 day of:<br>○ Evanescent (non-fixed) erythematous rash<br>○ General lymph node enlargement<br>○ Hepatomegaly and/or splenomegaly<br>○ Serositis | • Onset before age 18 years<br>• Fever for ≥ 3 consecutive days, reoccurring over 2 weeks<br>• Evanescent (non-fixed) erythematous rash<br>• Arthritis | • Fever ≥ 39 °C lasting ≥ 1 week<br>• Arthralgia or arthritis lasting ≥ 2 weeks<br>• Typical rash<br>• Leukocytosis ≥ 10,000/μL with ≥ 80% neutrophils | • Spiking fever ≥ 39 °C<br>• Arthralgia<br>• Transient erythema<br>• ≥ 80% granulocytes<br>• Pharyngitis<br>• Glycosylated ferritin < 20% |
| **Minor criteria** | – | • Generalized lymph node enlargement and/or hepatomegaly and/or splenomegaly<br>• Serositis<br>• Arthralgia lasting ≥ 2 weeks (in the absence of arthritis<br>• Leukocytosis (≥ 15,000/$mm^3$) with neutrophilia | • Sore throat<br>• Lymphadenopathy<br>• Hepatomegaly or splenomegaly<br>• Abnormal liver function tests<br>• Negative RF and ANA | • Maculopapular rash<br>• Leucocytes ≥ 10,000/μL |
| **Exclusion criteria** | • All other forms of JIA must be excluded | • Other known conditions | • Infections, malignancies, and all other conditions that may mimic AOSD | – |
| **Additional criteria** | – | • Fever (as described) accompanied by either the 2 other major criteria, or 1 of the major criterion and 2 minor criteria | • The presence of 5 criteria listed above, including ≥ 2 major criteria | • The presence of 4 major criteria listed above, or 3 major and 2 minor criteria |

*ANA* antinuclear antibodies, *AOSD* adult-onset Still's disease, *ILAR* International League of Associations for Rheumatology, *JIA* juvenile idiopathic arthritis, *PRINTO* Paediatric Rheumatology International Trials Organisation, *RF* rheumatoid factor, *SD* Still's disease, *sJIA* systemic juvenile idiopathic arthritis

leads to excessive IL-1β signaling and consequently an increased risk for developing SD. In contrast, individuals without *IL1RN* polymorphisms and normal IL-1RA expression, but nevertheless develop SD, are thought to be less likely to respond to anakinra therapy [43]. However, this association does not appear to be consistent in other cohorts, possibly due to the differences in populations. The highest associations were found in Spanish and Italian populations, but no association was found in the German [43, 44] and Dutch populations [42]. In all these reports, early IL-1 inhibition has been associated with excellent clinical outcomes at least in the short term (first year of the disease) [12, 42, 44].

#### *Protein markers and interleukins*

The phagocytic S100 proteins S100 A8/A9 (MRP8/14) and S100 A12 (MRP6) are highly overexpressed in patients with SD compared with healthy controls and patients with other inflammatory or malignancy-associated conditions [45, 46]. Once released from overactivated and/or necrotic cells, these proteins can operate as damage-associated molecular pattern (DAMP) molecules (also termed alarmins) [47–50]. Via binding to and signaling through toll-like receptor 4 (TLR- 4), S100 A8/A9 and S100 A12 are thought to perpetuate sterile inflammation. Next to S100 proteins, IL-18 is a cytokine that is strongly expressed in SD and can distinguish SD from other inflammatory conditions [51]. Moreover, IL-18 can help to identify SD patients with high risk of developing MAS. At present, serum IL-18 levels are being tested for their ability to reliably support decisions to stop treatment in SD (unpublished data, courtesy of the authors).

#### *Other markers*

Next to protein markers, it is also possible to monitor immune cell frequencies and effector function in SD; however, at present such data can rather inform on disease mechanisms, than serve as reliable biomarkers. In this context, overexpression of IL-17 A by T cells has been demonstrated in SD patients, which was driven by disease-related inflammatory signaling and was sensitive to IL-1 inhibition [52]. Prolonged IL-1 exposure in SD has been demonstrated to result in reprogramming of regulatory T cells to Th17-like effector cells [53]. Along with IL-17–expressing cells, a preferential differentiation of naïve SD T-helper cells towards follicular or peripheral T-helper cells has been reported [54]. *Ex vivo* cell, gene, and cytokine expression, as well as serological data, may argue for a role of these T cells, which are canonically involved in supporting (auto)antibody production, in the pathophysiology of SD [54].

Intriguingly, in a subpopulation of patients with SD, the transient occurrence of autoantibodies targeting IL-1RA has been reported [55]. These antibodies are associated with a depletion of IL-1RA plasma levels and result in increased IL-1β signaling. However, the presence of anti-IL-1RA antibodies in SD does not appear to be associated with non-response to treatment or disease severity. Importantly, therapies that block IL-1 (anakinra, canakinumab) can override the detrimental and transient effects of these antibodies [55].

### Refractory disease and risk factors

SD presents several phenotypes and pathological courses [47–50]. The monocyclic or monophasic type (occurring in 30–40% of patients) has a severe inflammatory course that subsides and does not recur [3, 15, 56, 57]. Alternatively, the disease may follow a polycyclic (10–20% of patients) or a persistent (50% of patients) course [15, 56, 57]. One proposed model for chronic forms of SD is the widely accepted biphasic model, which highlights a predominant role for IL-1 in the early phase of the disease [8]. While there is almost no evidence of autoantibody or autoreactive T cell involvement in the first phase of SD, they may play a role in later stages, including in patients with refractory disease [55]. In a large prospective cohort treated with IL-1 inhibition (anakinra) in first line, almost 90% of patients showed positive responses, with approximately 50% of patients maintaining disease inactivity thereafter without further treatment for up to 5 years [13, 14]. However, 20–25% of children with SD still experience a refractory disease course [56].

There are several unmet needs relating to refractory disease and its risk factors (Table 1). The experts' discussion and points to consider for addressing them are reported in detail below.

#### *Toward a definition of refractory SD*

Currently, there is no consensus on the definition of refractory SD. Some preliminary definitions, including those encompassing refractory arthritis, recurrent/refractory MAS, and the occurrence of recently recognized pulmonary involvement, have been proposed and are summarized in Table 3 [16, 56], though they are not yet validated. Moreover, further studies are needed to compare refractory disease in children and adults.

So far, at SD diagnosis it is not possible to identify patients most likely to subsequently develop refractory disease. However, a longer duration of symptoms prior to diagnosis (and thus a longer time to first treatment) and lower neutrophil levels at diagnosis have been associated with a higher risk of developing refractory disease [13].

**Table 3** Proposed definitions of refractory SD

| Erkens R et al, Rheum Dis Clin N Am, 2021 [16] | Ambler W et al, Ann Med, 2022 [56] |
|---|---|
| 1. **Refractory sJIA-arthritis:**<br>• Patients with sJIA whose arthritis fails to respond to both IL-1 and IL-6 inhibitor therapy, defined as continued arthritis disease activity requiring maintenance therapy with GCs | **Refractory sJIA:**<br>• Failure to respond to IL-1 and/or IL-6 inhibitors, or;<br>• Need for ongoing treatment with long term GCs (> 6 months) with persistence of systemic and/or arthritic feature |
| 2. **Refractory sJIA-MAS:**<br>• sJIA-related MAS, requiring long-term adjunctive therapy with GCs, or;<br>• Recurrent (≥ 2 episodes) sJIA-related MAS | **sJIA associated complications:**<br>• MAS<br>• LD<br>• Amyloidosis |
| 3. **sJIA-LD:**<br>• Suspected sJIA-LD: objective findings on clinical examination (including but not limited to tachypnea, cough, or clubbing) or diffuse abnormalities on chest imaging<br>• Probable sJIA-LD: both clinical findings and chest imaging findings as in suspected sJIA-LD, or pulmonary hypertension as measured by echocardiogram<br>• Definite sJIA-LD: tissue biopsy consistent with interstitial LD, pulmonary alveolar proteinosis/endogenous lipoid pneumonia, or pulmonary artery hypertension | |

*GC* glucocorticoid, *IL* interleukin, *LD* lung disease, *MAS* macrophage activation syndrome, *sJIA* systemic juvenile idiopathic arthritis

Moreover, persistently elevated IL-18 levels have been reported in children with recurrent/refractory MAS and pulmonary involvement [58].

#### *Emerging issues: lung involvement and hypersensitivity-like reactions*

In the past 10 years we have seen a surge in the reporting of SD-associated lung disease (SD-LD), especially in children [9, 59, 60]. This intriguing and serious complication seems to affect patients with refractory disease courses and its evolution is insidious at the initial stages. One of the first clinical signs of LD in patients with SD is digital clubbing with finger erythema [59–61], but it often occurs once pulmonary involvement is already established and severe. High resolution computed tomography (HRCT) chest scan is considered the gold standard for imaging evaluation, and common radiographic patterns in SD-LD include pleural thickening, peribronchovascular thickening, septal thickening, and ground glass opacities [9, 60]. Careful infectious screening is required, in particular to rule out atypical respiratory infections in patients on long-term immunosuppressive therapy. As patients may also develop pulmonary hypertension, a cardiological evaluation should be included in the diagnostic work-up [59–61].

Compared with SD patients without this complication, LD-SD patients were more likely to be diagnosed with SD at < 2 years of age, to have a history of recurrent MAS and drug adverse reactions [59], and to have persistently and markedly elevated levels of IL-18 [60]. Despite relatively mild symptoms at onset, lung involvement in SD may severely affect the disease course and can be fatal in a substantial percentage of affected children [59].

Recent data have suggested that an *HLA-DRB1 *15* background may represent a risk factor for the development of lung involvement and delayed hypersensitivity reactions to IL-1 and IL-6 inhibitors [62]. However, validation of these data in external cohorts showed controversial results. In particular, in a prospective cohort study of 65 children with new-onset SD, early outcomes (at 6 and 12 months after the start of therapy) were not significantly different in patients with a non-*HLA-DRB1 *15* background ($n$= 48) compared with those with an *HLA-DRB1 *15* background ($n$= 17) [42]. Although further studies are required to better understand the role of *HLA-DRB1* in refractory SD, available data currently do not support neither to withhold or to withdraw biologic treatment in SD based on *HLA-DRB1* background. All patients with SD should be carefully and actively evaluated and screened for the occurrence of LD, with particular attention to patients with the above-mentioned risk factors (Table 4) [63, 64].

### Treatment of SD and its complications

In the context of the Pediatric Rheumatology European Society (PReS)-EULAR taskforce on developing guidelines on the diagnosis and treatment of SD (including both sJIA and AOSD), expert-based and literature-supported recommendations on the diagnosis and treatment of SD were recently published [5]. An overview of unmet needs and expert recommendations regarding the treatment of SD and its complications are summarized in Table 1 and discussed in more detail below.

#### *The impact of early treatment in SD*

The goal of treating SD is to control inflammation, thus preventing long-term complications associated with

chronic inflammation [22, 65]. Early treatment is crucial for reducing potentially damaging inflammation in the early disease stages [22, 65]. In particular, early treatment with cytokine inhibitors may take advantage of the so called 'window of opportunity', thus influencing achievement of clinically inactive disease and altering the progression to chronic arthritis [8].

First-line treatment at disease onset, when the diagnostic process is ongoing, are nonsteroidal anti-inflammatory drugs (NSAIDs) [22, 65]. Intravenous and oral glucocorticoids are still commonly used but are associated with serious side effects, especially with long-term use [22, 65]. IL-1 and IL-6 inhibitors have completely changed the natural history of SD [22, 65]. Both tocilizumab and canakinumab, have demonstrated, in randomized clinical trials, high response rates in glucocorticoid-refractory children with SD, thus enabling glucocorticoid tapering [66, 67].

The early use of anakinra was first reported in a retrospective clinical case series [11]. In this international collection of 46 cases of SD treated early in the disease course with anakinra, approximately 59% of patients achieved a complete response and 41% achieved a partial response [11]. Moreover, patients who received early treatment with IL-1 and IL-6 inhibitors have been shown to achieve higher rates of clinically inactive disease than those who received later treatment [12, 13, 68]. Furthermore, a retrospective multicenter Italian study investigating canakinumab in patients with sJIA showed that approximately 60% of patients achieved clinically inactive disease, with a trend towards early treatment being associated with better responses [39].

**Table 4** Proposed risk factors for lung involvement in patients with diagnosis of SD [63, 64]

| Proposed risk factors |
|---|
| • Age at SD onset < 2 years |
| • Predominant systemic features |
| • Recurrent or smoldering MAS |
| • ICU admission |
| • Atypical pruritic rash |
| • Peripheral eosinophilia (>500≥ 2 occasions) |
| • Drug reaction (any drug) |
| • Persistently high IL-18 levels |
| • Elevated CXCL9 levels |
| • *HLA-DRB1*15* |
| • Trisomy 21 |
| • Periungual erythema |
| • Acute digital clubbing |

*CXCL9* C-X-C motif chemokine 9, *ICU* intensive care unit, *IL* interleukin, *MAS* macrophage activation syndrome, *SD* Still's disease

### *Treatment of MAS in SD*

There are currently no validated guidelines for the treatment of MAS. It is crucial to stabilize a patient with MAS as soon as possible to avoid multi-organ failure and potentially death. In patients with rapidly progressive MAS, treatment with high-dose glucocorticoids, anakinra, cyclosporine, and/or intravenous immunoglobulin should be considered. However, glucocorticoids should be avoided if a diagnosis of SD is not yet clear, and if malignancies need to be ruled out (via total-body imaging and bone marrow aspirate). The course of MAS in SD can vary from a single event, well-responsive to first-line treatment, to a life-threatening complication requiring combined immunosuppressive drugs (including prolonged and high doses of glucocorticoids), as well as a more smoldering, but longstanding condition with specific organ involvement (e.g., the liver) [16].

Appropriate antimicrobial (broad spectrum and/or *Pneumocystis jirovecii pneumonia*) and/or antiviral prophylaxis should be considered in patients with smoldering MAS receiving longstanding combined immunosuppression. Biological agents used in the context of MAS act against self-inflammation contributing to inflammation (targeted neutralization of IL-1 and IL-18), and against hyperinflammation (broad-spectrum inhibition of Janus kinases [JAKs] and targeted neutralization of IFN-γ) [11, 25, 69–75].

Except for the emapalumab trial published in 2023 [76], there are currently no data from clinical trials on the use of cytokine inhibitors for the treatment of MAS. The incidence of MAS does not seem to decrease in patients who are receiving treatment with IL-1 inhibitors. Although some case series show the efficacy of anakinra in treating MAS, there remains a lack of data on dosing regimens and background therapies. Anakinra seems to be safe, even when used intravenously at high doses (up to 10–15 mg/kg/day), and does not interfere with differential diagnoses [11, 70–73, 77]. The inhibition of IL-18 through the recombinant IL-18 binding protein (tadekinig-α) was reported in one patient with resistant SD with long disease duration, interstitial LD, and recurrent severe MAS [78]. A novel bispecific monoclonal antibody (MAS825), targeting both IL-18 and IL-1β, is reported to be effective in a few patients with SD complicated by LD and recurrent MAS [79, 80]. The large spectrum inhibition of hyperinflammation through JAK inhibitors (JAKis) has been reported in different case series in both pediatric and adult patients with SD [81–85]. The patients in these reports tended to have a difficult-to-treat disease, with multiple lines of treatment failures. No one JAKi seemed to be more effective than another.

Data in humans and in animal models suggest a pathogenic role of IFN-γ in primary and secondary HLH,

including MAS [34, 75, 86]. Based on these preclinical observations, a clinical trial conducted with the anti–IFN-γ monoclonal antibody, emapalumab, in children with primary HLH reported efficacious results [87]. Emapalumab is now approved by the United States Food and Drug Administration for adult and pediatric use in patients with primary HLH [88]. An open-label, single-arm, multicenter trial evaluated the efficacy and safety of emapalumab in patients with MAS in the context of SD and who had inadequate response to prior standard high-dose glucocorticoid therapy [76]. In this study, eligible patients were enrolled in Europe ($n$= 11) and the United States (i= 3); emapalumab treatment resulted in rapid IFN-γ neutralization, as demonstrated by a decrease in serum CXCL9 levels. By week 8, 13 of the 14 patients (93%) achieved MAS remission at a median time of 25 days after emapalumab initiation. Glucocorticoids were tapered in all patients, and by the end of the long-term follow-up, five patients stopped glucocorticoids, while six were receiving a prednisone-equivalent dose of < 0.3 mg/kg/day. All patients were alive at the last visit and no patients discontinued emapalumab for safety reasons [76].

#### *Therapeutic approaches for SD-associated LD*

The optimal treatment of lung involvement in the context of SD is unknown. As there are no studies that show benefit of a specific treatment, therapy should be intensified in patients with SD-LD and this decision should be made by the treating physician [64]. The association of this complication with high disease activity, including MAS, and the activation of the IFN-γ pathway and T cells, support the use of immunomodulatory treatment [63]. There are only few case reports regarding the treatment of SD complicated by LD. Systemic glucocorticoids are the mainstay treatment. Calcineurin inhibitors, such as cyclosporine and tacrolimus, have been used in recurrent MAS and in SD-LD. However, their efficacy in controlling disease progression is not known [63]. Considering the extremely high IL-18 levels in this condition, treatments that neutralize IL-18 would be potentially efficacious [63]. To date, there is one case report on the use of tadekinig-α in a patient with SD-LD but the effect on lung involvement is unclear [78]. Neutralization of both IL-1β and IL-18 by MAS825 has been reported to be efficacious in some patients with SD-LD [79, 80]. JAKis have also been used for treatment of SD-LD even though it is not clear which one is the most effective [81–83]. In addition, emapalumab has been reported for the treatment of SD-LD in one case before hematopoietic stem cell transplantation (HSCT). The use of HSCT in patients with SD-LD has also been reported in a small case series of nine patients with refractory SD with MAS and lung involvement [89].

## Discussion

In recent decades, there has been great progress in the management of patients with SD. The current paper, reflecting discussions and recommendations of an expert meeting in 2023 in which specialists gathered to compare and discuss data on the adult and pediatric forms of the disease, further contributes to this progress. Here, we examine SD from different perspectives and highlight the similarities and differences in diagnosis and treatment. However, there are still unmet needs in the management of SD. Delayed diagnosis is a problem linked both to diagnostic criteria (essentially in pediatric patients) and late referral (mainly affecting adults). Early diagnosis of SD remains challenging due to the clinical overlap with a broad spectrum of other systemic conditions. Importantly, delayed diagnosis can result in an overuse of glucocorticoids in adults, even in the absence of a final diagnosis.

A lack of validated diagnostic biomarkers is another important aspect. Integration of highly reliable and widely validated biomarkers (e.g., MRP8/14 and IL-18) in the diagnostic work-up could have a significant impact on clinical care in SD. To this end, an ongoing PReS-Childhood Arthritis and Rheumatology Research Alliance (CARRA) (Speaking the Same Language)-funded project aims to validate a set of biomarkers for real-life clinical use in SD [6]. The goal of this project is to identify tests that clinicians can use in clinical settings.

The attendees of the expert meeting also highlighted several similarities and some differences in the diagnosis of SD between children and adults, given the patterns and mechanisms of disease [90, 91]. The incidence of SD in adults is much lower than in children [15, 92], which complicates the comparison. Whenever possible, studies on SD should include both adults and pediatric patients, but overall accessibility can be a problem. While evaluation of large retrospective cohorts provides interesting data, critical differences in patient populations, diagnostic criteria, and local accessibility to treatment need to be considered. This lack of consistent, high-quality data is particularly relevant for the development of evidence-based treatment guidelines in SD.

Based on our current understanding of SD, patients should be treated as early as possible with targeted therapies. Real-life studies may offer deeper insights and be useful for examining the validity of the 'window-of-opportunity' hypothesis, in terms of both optimal short-term response and the ability to prevent irreversible damage. Recommendations regarding multiple lines of treatment and possible combination therapies should be

established, along with the role of new targeted therapies, with a particular focus on such treatments for SD complications, MAS, and LD.

The heterogeneous nature of this systemic disease complicates its management. For example, long-term treatment of patients, especially children with monophasic SD who may go into spontaneous remission within a few months, is a concern. However, it is currently not possible to predict the disease course due to a lack of validated biomarkers or clinical indicators. Additionally, there is currently no validated indicators for treatment withdrawal in patients who achieve remission.

Importantly, there is still a lack of understanding of how to prevent and treat interstitial LD at an early stage, which is of particular concern, as this potentially serious complication is being observed more often in recent years [9, 60, 93, 94]. Clinical and pathogenetic studies are needed in this area.

## Conclusion

This article provides a comprehensive overview of the diagnostic/classification criteria for SD, specific strategies to optimize disease management, and the unmet needs related to its management in patients of all ages, regardless of disease stage. In addition, understanding the complications of SD, such as MAS and lung involvement, and the risk factors for the development of refractory disease could drastically improve patient outcomes in future.

### Abbreviations

| | |
|---|---|
| ACR | American College of Rheumatology |
| AOSD | Adult-onset Still's disease |
| EULAR | European Alliance of Associations for Rheumatology |
| HLH | Hemophagocytic lymphohistiocytosis |
| IFN | Interferon |
| IL | Interleukin |
| ILAR | International League of Associations for Rheumatology |
| JAKi | Janus kinase inhibitor |
| LD | Lung disease |
| MAS | Macrophage activation syndrome |
| NSAIDs | Nonsteroidal anti-inflammatory drugs |
| PReS | Pediatric Rheumatology European Society |
| PRINTO | Paediatric Rheumatology INternational Trials Organisation |
| RA | Receptor antagonist |
| SD | Still's disease |
| sJIA | Systemic juvenile idiopathic arthritis |

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### Authors' contributions

CB, FM, BV, and CK reviewed the whole manuscript. AR, LD, and FDB led the meeting discussions and supervised the whole project. All authors read and approved the final manuscript.

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### Data availability

No datasets were generated or analysed during the current study.

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

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