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EULAR/PReS recommendations for the diagnosis and management of Still's disease, comprising systemic juvenile idiopathic arthritis and adult-onset Still's disease

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ABSTRACT

Systemic juvenile idiopathic arthritis (sJIA) and adult-onset Still's disease (AOSD) are considered the same disease, but a common approach for diagnosis and management is still missing.

Methods In May 2022, EULAR and PReS endorsed a proposal for a joint task force (TF) to develop recommendations for the diagnosis and management of sJIA and AOSD. The TF agreed during a first meeting to address four topics: similarity between sJIA and AOSD, diagnostic biomarkers, therapeutic targets and strategies and complications including macrophage activation syndrome (MAS). Systematic literature reviews were conducted accordingly.

Results The TF based their recommendations on four overarching principles, highlighting notably that sJIA and AOSD are one disease, to be designated by one name, Still's disease.

Fourteen specific recommendations were issued. Two therapeutic targets were defined: clinically inactive disease (CID) and remission, that is, CID maintained for at least 6 months. The optimal therapeutic strategy relies on early use of interleukin (IL-1 or IL-6 inhibitors associated to short duration glucocorticoid (GC). MAS treatment should rely on high-dose GCs, IL-1 inhibitors, ciclosporin and interferon-γ inhibitors. A specific concern rose recently with cases of severe lung disease in children with Still's disease, for which T cell directed immunosuppressant are suggested. The recommendations emphasised the key role of expert centres for difficult-to-treat patients. All overarching principles and recommendations were agreed by over 80% of the TF experts with a high level of agreement.

Conclusion These recommendations are the first consensus for the diagnosis and management of children and adults with Still's disease.

INTRODUCTION

Systemic juvenile idiopathic arthritis (sJIA), described by Sir George Still at the end of the XIX century,[1] and adult-onset Still's disease (AOSD), described in 1971 by Bywaters, have been initially considered as a continuum.[2] The age threshold of 16 years separating the two entities introduced in the initial AOSD description was arbitrary, corresponding to the age separating paediatrics department from adult medicine departments in the UK in the second half of the XXth century.[3 4] The two entities share common features such as the four major symptoms: recurrent spiking fever, skin rash, arthralgia and/or arthritis and high levels of inflammation—that is, high erythrocyte sedimentation rate (ESR) and C reactive protein (CRP), increased white cell count with high neutrophil count. Other shared features are common, even if not disease specific, especially serositis, elevated liver function tests (LFTs) and very high serum ferritin level, as well as the risk of macrophage activation syndrome (MAS). Rapid sJIA/AOSD diagnosis is a challenge.[5 6] Several classification/diagnostic criteria have been proposed to facilitate identification of patients with sJIA, as well as AOSD.[7–11] While some differences exist between these sets, they all refer to the features mentioned above. In terms of management, several clinical trials have been conducted in patients with sJIA, thanks to the efficiency of paediatric rheumatology networks.[12–14] This has not been possible for many years in adults, due to the rarity of the disease, together with its heterogeneous presentation, which frequently leads patients with AOSD to be hospitalised in units of different disciplines (rheumatology, dermatology, infectious diseases or internal medicine). This resulted in delayed and suboptimal management of patients, with a

potentially increased risk of life-threatening complications such as MAS, fulminant hepatitis, myocarditis or disseminated intravascular coagulation (DIC).[15–17] Drug approvals were obtained for several molecules in sJIA, but not in AOSD for several years, making advanced therapies only accessible for children and adults having started their disease before the age of 16 years.

Advances in the understanding of sJIA and AOSD identified a key role for interleukin (IL)-1, IL-6 and IL-18 overproduction possibly secondary to dysregulation of inflammasome activities and of innate immunity dysregulation. These observations have led some authors to include sJIA/AOSD into the spectrum of non-familial (polygenic) systemic autoinflammatory disorders.[5 18] However, pathogenic mechanisms involving adaptive immunity, particularly in, but not limited to, chronic persistent disease have also been shown, making it rather difficult at the present stage of knowledge to clearly categorise sJIA/AOSD.

In the recent years, growing interactions between paediatricians and adult rheumatologists led to the identification of common substantial unmet needs in the diagnosis and management of patients with both sJIA and AOSD, which deserve to be addressed by consensus. In 2022, the EULAR and the Paediatric Rheumatology European Society (PReS) decided to join their efforts to develop clinical practice guidelines for the diagnostic and management of sJIA and AOSD, with the aim to address four main questions: (1) Are sJIA and AOSD one single disease, for which one single name could be helpful? (2) How can sJIA/AOSD diagnosis be made, particularly during the early phase of the disease? (3) what is the optimal therapeutic strategy—including both the choice of the drugs and their management over time; (4) how to detect and manage disease complications as well as treatment-related side effects.

In this recommendation process, patient representatives, paediatricians and adult rheumatologists shared their views on sJIA and AOSD and addressed the four above-mentioned issues based on the best available evidence in a joint effort. The final aims were to align their positions into common recommendations for clinical practice and to define the research agenda for issues remaining to be addressed in the coming years. This recommendation document is targeted to (1) adult and paediatric rheumatologists, (2) patients, patient caregivers and patient associations and (3) institutional stakeholders such as drug agencies and health authorities.

METHODS

The present recommendation effort started in September 2022 after formal approval by both EULAR and PReS Councils (QoC011 task force (TF)) and was conducted according to the EULAR standard operating procedures (SOPs) for developing recommendations and the AGREE II document.[19 20] The TF was led by two convenors (BF for EULAR and FDB for PReS) and a methodologist (LC) and included expert adult (LD, EF, SGL, RG, YJ, KL, FOR, PAN, PR, SS, M-ET) and paediatric (JA, AB, CB, TC, DF, MG, AAG, CL, FM, PAN, SO, PQ, SJV, CW) rheumatologists/clinical immunologists from Europe or North America, 2 young rheumatologists (SB from Emeunet, ES from Emerge) and two patient research partners (ADB, T-CW). The steering committee (BF, FDB, LC) selected three fellows (SB, SM, ADM) to undertake the evidence reviews. All TF members were requested to attend the face-to-face meetings to facilitate efficient development of the recommendations; two members were not able to attend the second meeting due to logistical issues and participated online.

The process started with a first meeting of the TF in Paris in September 2022 to define the scope of the TF activities and to agree on the research questions that will be addressed by the preparatory systematic literature reviews (SLRs). The group validated the four main topics proposed by the steering committee to yield the scientific evidence on which the recommendations will be based. Three SLRs were conducted: (1) sJIA and AOSD clinical expression and diagnosis, including novel diagnostic biomarkers, to address the two first topics; (2) sJIA and AOSD treatments for topic 3; (3) MAS diagnosis, including novel biomarkers, and treatments for topic 4. All SLRs were conducted on Medline (PubMed), Embase and Cochrane libraries and explored scientific literature up to October 2022 (February 2023 for the biomarkers SLR). Study selection, data extraction and interpretation were conducted by the three fellows under the supervision of the methodologist (LC) and the two convenors (BF and FDB), with weekly or biweekly web conferences to monitor SLR progression. The detailed methods and results of the three SLRs were reported separately (Mitrovic SR1, Bindoli SR2, De Matteis SR3); all protocols were registered in PROSPERO.

At the end of the SLR process, the steering committee and the fellows prepared a comprehensive document compiling the main SLR results. On their basis, the steering committee wrote a set of candidate statements (overarching principles (OPs) and recommendation statements (RSs)) to be discussed, modified, and finalised by the TF experts during the second face-to-face meeting.

The second face-to-face meeting (Rome, March 2023) was divided into four parts corresponding to the four main topics (disease name, diagnosis, treatments, complications) to be addressed. Each of the four parts included: (1) the presentation of the SLR, (2) a general discussion on the results and their interpretation, (3) the modification or rewriting of the candidate statement(s), (4) a vote of the experts on their agreement on the final OP or RS, during which a 80% consensus among the TF members had to be reached (if consensus was less than 80%, the candidate statement, OP or RS, had to be rediscussed and redrafted). For each statement, the level of evidence (from 1b to 5) and the strength (from grade A to D) were attributed according to EULAR SOPs (table 1).[19]

Finally, the TF experts were sent the draft manuscript of the recommendations and asked to give their level of agreement to each OP or RS, ranging from 0 (fully disagree) to 10 (fully agree). At the end of the production process, as advised by EULAR SOPs,[21] the convenors, the methodologist and the fellows prioritized three quality indicators based on the literature reviews, their potential relevance in affecting clinical practice and the discussion with the TF around the treatment algorithm during the second F2F meeting. The TF experts were asked to vote (on-line) on their agreement on the three indicators.

RESULTS

Overarching principles

OP A: sJIA and AOSD are the same disease, that should be designated by the same unique name, Still's disease (formerly called sJIA/AOSD)

As mentioned above, AOSD was initially described as the adult counterpart of sJIA and the distinction of the two entities was mainly artificial based on the organisation of paediatric care, with an age limit of 16 years.[3] This led in the subsequent decades to the separation of the two entities in terms of definition,

Table 1 EULAR PReS recommendation for the management of Still's disease

		LoE	Strength	Agreement	LoA
Overarching principles					
A	sJIA and AOSD are the same disease, that should be designated by the same unique name, Still's disease (formerly called sJIA/AOSD).	2a	B	100%	9.7
B	The treatment targets and the therapeutic strategy should be based on shared decision making between the parents/patients and the treating team.	2b	C	100%	9.9
C	T2T by regularly assessing disease activity and adapting therapy accordingly is important. The ultimate goal is drug-free remission.	5	D	100%	9.7
D	MAS should be detected promptly and treated rapidly.	2b	D	100%	10
Recommendation statements					
Diagnosis					
1	To facilitate rapid diagnosis and initiate early treatment, operational definitions should be used to identify patients with Still's disease, ► Fever is typically spiking with temperature ≥39°C (102.2°F) for at least 7 days, ► Rash is transient and often coincides with fever spikes, preferentially involving trunk. It is typically erythematous (salmon pink), but other rashes (eg, urticarial) may be consistent with the diagnosis, ► Musculoskeletal involvement is usually present with arthralgia/myalgia. Overt arthritis is supportive but not necessary for diagnosis and may appear later, ► High levels of inflammation are typically identified by neutrophilic leucocytosis, increased serum CRP and ferritin.	2a	B	94%	9.6
2	Marked elevation of serum IL-18 and/or S100 proteins (eg, calprotectin) strongly supports the diagnosis, and therefore should be measured if available.	4	C	90%	8.9
3	Alternative diagnoses such as malignancies, infectious diseases, other immune-mediated inflammatory diseases and monogenic autoinflammatory disorders should be carefully considered.	5	D	83%	9.8
Targets and timing					
4	CID is defined as absence of Still's disease-related symptoms and normal ESR or CRP. Remission is defined as a period of at least 6 months with CID.	5	D	85%	9.4
5	In order to achieve the ultimate goal (drug-free remission), the following intermediate targets are recommended: ► At day 7, resolution of fever and reduction of CRP by >50%, ► At week 4, no fever, reduction of active (or swollen) joint count by >50%, normal CRP and physician and patient/parent global assessment less than 20 on a 0–100 VAS, ► At month 3, CID with glucocorticoids less than 0.1 or 0.2 mg/kg/day, ► At month 6, CID without glucocorticoids.	5	D	86%	9.0
Treatments					
6	To avoid prolonged systemic GC use for achieving and maintaining the target, the use of IL-1 and IL-6 inhibitors should be prioritised due to high evidence of efficacy.	1b	A	100%	9.8
7	An IL-1 or an IL-6 inhibitor should be initiated as early as possible when the diagnosis is established.	2b	B	96%	9.4
8	Maintenance of CID for 3 to 6 months without glucocorticoids should be achieved before initiating bDMARD tapering.	5	D	96%	9.2
Complications					
9	Severe/life-threatening complications, including MAS or lung disease, may develop at any point during the disease course. Patients should be actively screened and monitored.	2a	B	100%	9.9
10	MAS should be considered in patients with persistent fever, splenomegaly, elevated or rising serum ferritin, inappropriately low cell counts, abnormal LFT, intravascular activation of coagulation, elevated or rising serum triglycerides.	2a	B	100%	9.9
11	MAS treatment must include high dose glucocorticoids. In addition, treatments including anakinra, ciclosporin and/or IFNγ inhibitors should be considered as part of initial therapy.	2b	B	100%	9.8
12	Lung disease should be actively screened by search for clinical symptoms (eg, clubbing, persistent cough, shortness of breath) and pulmonary function tests (pulse oximetry, DLCO measurement), and investigated by high resolution CT scan in any patients with clinical symptoms.	2b	B	98%	9.7
13	Based on the available data, the presence of risk factors for Still's lung disease or the development of Still's lung disease should not be considered as a contraindication to IL-1 or IL-6 inhibitors.	2b	B	100%	9.4
14	Difficult-to-treat patients, those with severe MAS and those with lung disease should be managed in collaboration with Still's disease expert centres.	5	D	96%	9.9

LoE: level of evidence on which the statement is based, ranging from 1a (systematic review of randomized controlled trials) to 5 (expert opinion); Agreement: percentage of experts agreeing with the recommendation statement; LoA: level of agreement, ranging from 0 (fully disagree) to 10 (fully agree).
AOSD, adult-onset Still's disease; bDMARDs, biologic disease-modifying antirheumatic agents; CID, clinically inactive disease; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; IFNγ, interferon-γ; IL, interleukin; LFT, liver function test; MAS, macrophage activation syndrome; sJIA, systemic juvenile idiopathic arthritis; T2T, Treatment-to-target; VAS, visual analogue scale.

classification criteria, clinical trials and in some instances drug approval.

Several elements argue in favour of the unification of the two entities. Although epidemiological data are scarce, they indicate that sJIA/AOSD incidence peaks in young children, that is, before the age of 6, but remains stable in adolescents and young adults.[22] The SLR, conducted to identify similarities and discrepancies of clinical and biological features of the two diseases,[23] showed that all sJIA/AOSD manifestations had similar prevalence in both entities, with the exception of sore throat and myalgia (often difficult to elicit by history in young, and so rarely annotated by paediatricians), weight loss (rarer in children and more frequently expressed as growth curve break in children), leucocyte counts (different norms in children and adults) and AA amyloidosis, whose prevalence has dramatically decreased during the last decades. Additionally, striking similarities in gene expression profiles in sJIA and AOSD were described.[24]

It is important to point out that age does matter in sJIA/AOSD for disease expression; for example, very young children, that is, less than 18 months, are more likely to display high levels of inflammation and to develop MAS.[25] The same applies for differential diagnoses to be ruled out (see online supplemental table 1).

During the recommendation process, an online survey, conducted among the TF experts, revealed that 22 (92%) of the 24 experts who responded agreed on the principle of a unique name to identify sJIA and AOSD. During the survey, several names have been proposed and 'Still's disease' was the most frequent proposal among the respondents. This term was approved and incorporated in OP A during the second Face-to-Face (F2F) meeting.

OP B: the treatment targets and the therapeutic strategy should be based on shared decision-making between the parents/patients and the treating team.

The TF thought it was important to highlight a few key points that should drive the management of patients with Still's disease. As for all other systemic inflammatory diseases, it is important to engage patients and caregivers in the decision-making process of the therapeutic strategy in order to create a therapeutic alliance with health professionals and thus promote long-term adhesion to treatment.

OP C: treatment to target (T2T) by regularly assessing disease activity and adapting therapy accordingly is important. The ultimate goal is drug-free remission

Since Still's disease evolution is often characterised by flares, it appeared relevant to the experts to apply the T2T principle for Still's disease management. According to this principle, disease-modifying anti-rheumatic drugs (DMARDs) are dynamically increased or decreased (step-up or step-down approach) depending on disease activity. Sequential therapeutic targets were identified and will be addressed below; however, the experts wanted to emphasise that the ultimate goal of Still's disease management is drug-free remission, which is realistic for a substantial proportion of patients thanks to recent innovative therapies.

OP D: MAS should be detected promptly and treated rapidly

MAS is the main challenging and life-threatening complication of Still's disease, whatever their age—although more frequent in children under the age of 2.[25–28] This complication can be present at the onset of Still's disease or can occur during treatment, or during its course. This may happen even when the disease is in remission, since a relapse of Still's disease may present directly as MAS especially in a context of infection. Due to its severity and its prognostic impact, physicians in charge of patients with Still's disease should always be aware of this specific risk, monitor with adequate biological workups and be prepared to rapidly adjust treatment (see Recommendation Statements 10 and 11).

Recommendation statements

RS1: – To facilitate rapid diagnosis and initiate early treatment, operational definitions should be used to identify patients with Still's disease,

1. ***Fever is typically spiking with temperature ≥39°C (102.2°F) for at least 7 days.***
2. ***Rash is transient and often coincides with fever spikes, preferentially involving trunk. It is typically erythematous (salmon pink), but other rashes (eg, urticarial) may be consistent with the diagnosis.***
3. ***Musculoskeletal involvement is usually present with arthralgia/myalgia. Overt arthritis is supportive but not necessary for diagnosis and may appear later.***
4. ***High levels of inflammation are typically identified by neutrophilic leucocytosis, increased ESR, serum CRP and ferritin.***

Disease clinical expression may be heterogeneous and no symptom or biological feature is specific of Still's disease. However, some manifestations are key, namely fever, skin rash (which may be challenging on coloured skin), arthralgia or arthritis and highly elevated acute phase reactants, typically CRP, high neutrophil count (PMN) and ferritin, but also increased platelet count, fibrinogen and D-dimers. To facilitate early diagnosis, the TF proposed operational definitions for the most relevant manifestations. A specific attention was paid to joint manifestations: arthralgia is commonly present, but arthritis appears often later with a median delay of 1 month after disease onset (range 0 to several months) (26, F de Benedetti personal communication); additionally, the underlying pathogenic immunological mechanisms seem to be quite similar in patients with Still's disease with or without arthritis.[29] Thus, requiring arthritis to make the diagnosis of Still's disease leads to unnecessary and potentially deleterious diagnostic delays. For this reason, the TF strongly recommends that presence of arthritis is not mandatory for the diagnosis of Still's disease.

Although not developed for Still's disease diagnosis ascertainment, classification criteria may help clinicians to identify the disease. Several criteria sets have been proposed for sJIA or AOSD (table 2), and one—Yamaguchi—has been tested and validated in both sJIA and AOSD with high sensitivity.[30] Noteworthy, arthritis is not mandatory for the diagnosis in the Yamaguchi's criteria as well as in the recently proposed classification criteria for sJIA.[9] The working group recommends that a common set of classification criteria encompassing children and adults is needed; this is listed in the research agenda (table 3).

Table 2 Classification criteria sets proposed for Still's disease

Criteria set	ILAR	CARRA	PRINTO	Yamaguchi	Fautrel
Reference	Petty, J Rheumatol 2004	De Witt, Arthritis Care Res 2012	Martini A, J Rheumatol 2019	Yamaguchi, J Rheumatol 1992	Fautrel, Medicine 2002
Still's disease subtype	sJIA	sJIA	sJIA	AOSD	AOSD
Items	1. Age <16 years 2. Arthritis (>6 weeks) 3. Fever (>2 weeks) 4. Rash 5. LN 6. HM/SM 7. Serositis	1. Age <19 years 2. Arthritis (>1 week) 3. Fever (>2 weeks) 4. Rash 5. LN 6. HM/SM 7. Serositis	1. Age <18 years 2. Fever (>2 weeks) 3. Rash 4. Arthritis 5. LN, HM or SM 6. Arthralgia (>2 weeks) 7. PMN leucocytosis	1. Fever ≥39°C >1 week 2. Arthralgia >2 weeks 3. Typical skin rash 4. WBC ≥10×10^9/L and PMN ≥80% 5. Pharyngitis or sore throat 6. LN and/or SM 7. Elevated LFT (transaminases) 8. No auto-Ab† 9. No exclusion criteria‡	1. Spiking fever ≥39°C 2. Arthralgia 3. Transient erythema 4. Pharyngitis 5. PMN ≥80% 6. Glycosylated ferritin ≤20% 7. Typical rash 8. WBC ≥10×10x10^9/L
Minimal requirement	Items 1 to 3 AND ≥1 of items 4–7	Items 1 to 3 AND ≥1 of items 4–7	Items 1 to 4 OR Items 1, 2 AND 1 among 3 and 4 AND 1 among 5, 6, 7, 8	≥5 items with 2 among items 1 to 4	≥4 of items 1 to 5 OR ≥3 of items 1–5 AND items 6 and 7
Performance	Se 93.1% §	Se 91.1% §	Se 98.2% §	In adults: Se 96.3% – Sp 98.2%¶ + ferritin >N: Se 100% – Sp 97.1%¶ In children: Se 96.4%§	Se 87.0% – Sp 97.8% ¶

*Typical skin rash: maculopapular, nonpruritic, salmon-pink rash with concomitant fever spikes.
†Absence of antinuclear antibodies and rheumatoid factor.
‡Absence of infection, especially sepsis and Epstein-Barr virus infection; absence of malignant diseases, especially lymphomas; absence of inflammatory disease, especially polyarteritis nodosa.
§Pardeo M, A&R 2021.
¶Lebrun A, Semin A&R 2016.
AOSD, adult-onset Still's disease; HM, haepatomegaly; LFT, liver function test; LN, lymphadenopathy; PMN, polymorphonuclear; PMN leucocytosis, neutrophilic leucocytosis; Se, sensitivity; sJIA, systemic juvenile idiopathic arthritis; SM, splenomegaly; Sp, specificity; WBC, white cell count.

Table 3 Research agenda

1	Could a common set of classification criteria encompassing children and adults be used to ascertain Still's disease diagnosis for clinical research?
2	What biomarkers that should be validated for the diagnosis of Still's disease?*
3	What biomarkers that should be validated for the diagnosis of MAS?†
4	Could a common disease activity measure be used in children and adults to drive therapeutic decision and for clinical research?
5	What is the optimal therapeutic strategy for patients with Still's disease with inadequate response to IL-1 and IL-6 inhibitors?
6	Could cytokine measurements be used to choose the optimal treatment for a given patient, that is, a personalised medicine approach?
7	What are the roles of bDMARDs and HLA DRB1*1501 in the development of Still's lung disease and other severe Still's manifestations?
8	What is the optimal therapeutic strategy in Still's LD and MAS?

*The candidate diagnostic biomarkers for Still's disease include IL-18, S100 proteins, and other well characterised such as serum vascular endothelial growth factor (VEGF)-A, fibroblast growth factor (FGF)-2, granulocyte macrophage colony-stimulating factor (GM-CSF), neutrophil or platelet parameters, and miRNAs.
†The candidate biomarkers for MAS include CXCL-9, IL-18, adenosine deaminase 2 (ADA2) activity, soluble IL-2 receptor, and activated cells such as CD8 T cells (CD8 ^{pos}CD38^{high}/HLHDR^{high}, or CD8^{pos}, CD4^{dim}), CD4+ or NK cells.
bDMARDs, biologic disease-modifying antirheumatic agents; IL, interleukin; LD, lung disease; MAS, macrophage activation syndrome.

RS2: marked elevation of serum IL-18 and/or S100 proteins (eg, calprotectin) strongly supports the diagnosis, and therefore should be measured if available.

Several inflammatory molecules are elevated in numerous case series and are proposed as diagnostic biomarkers.[23 29] The list of candidate biomarkers is quite long.[23] Among these, serum IL-18 levels and S100 proteins levels are the most studied biomarkers in both children and adults. IL-18, a proinflammatory cytokine produced by inflammasome activation, drives IFNγ overproduction. Alarmins such as S100 proteins, that is, S100 A8/A9 (also called serum calprotectin) and S100 A12, which are produced by innate immunity cells (monocytes and neutrophils), act as danger-associated molecular patterns to amplify inflammation.[31] Highly elevated levels of these biomarkers appear to identify Still's disease with high sensitivity and specificity. However, there is no consensual or validated threshold for these biomarkers as sensitivity and specificity were assessed by comparison with different control groups (fever of unknown origin, other autoinflammatory disorders, autoimmune diseases including vasculitis, infections, haematological diseases, neoplasia, liver diseases).[23] Serum levels of IL-18 and S100 proteins are presently used for diagnosis in selected tertiary centres.[31] To enable widespread use, assays and cut-off values need to be validated. This was included in the research agenda (table 3).

RS3: alternative diagnoses such as malignancies, infectious diseases, other immune-mediated inflammatory diseases and monogenic autoinflammatory disorders should be carefully considered.

Still's disease diagnosis relies on a combination of clinical and biological findings, none of them being in isolation specific of the disease. Other diseases such as infectious diseases, malignancies or other immune-mediated diseases (IMIDs) can mimic Still's disease. In general, this includes also monogenic (germline or somatic, inherited or acquired) inflammatory disorders. In the adult patients, VEXAS and CHIP should be considered.[32–35] This has important consequences when Still's disease treatment has to be initiated, glucocorticoids (GC) or immunomodulating agents being potentially deleterious if Still's disease is misdiagnosed, particularly in the presence of malignancies. Thus, the TF highlighted the need to carefully consider potential differential diagnoses, without inadequately delaying treatment initiation. Based on previous expert consensus documents on fever of unknown origin[36] or Still's disease,[37] a comprehensive list of these alternative diagnoses is proposed (online supplemental table 1), as well as a list of potentially relevant investigations according to the alternative diagnostic hypotheses (online supplemental table 2).

RS4: clinically inactive disease (CID) is defined as absence of Still's disease-related symptoms and normal ESR or CRP. Remission is defined as a period of at least 6 months with CID.

Several outcome measures have been used in Still's disease clinical trials and longitudinal observational studies, usually developed for juvenile idiopathic arthritis or for rheumatoid arthritis and adapted to the systemic nature of Still's disease by adding fever to the other items. These measures include the American College of Rheumatology (ACR) responses, the JIA ACR responses (JIA-ACR), EULAR responses, CID, and remission with different definitions in different studies.[38] However, the TF favoured to use the same outcome irrespectively of patient age, and proposed to define two main targets derived from the consensus proposals of Wallace *et al* for JIA.[39]

CID is a single point-in time (snapshot) measure, defined as absence of any Still's disease-related manifestation including normal acute phase reactants such as ESR or CRP. If multiple acute phase reactant measures are performed, all have to be normal (except if another explanation exists to explain abnormal value, such as anaemia for ESR). Some TF members proposed to include physician global assessment with a value equal to or less than 10 on a 0–100 visual analogue scale (VAS), that is, less than 1 on a 0–10 VAS.

Remission is a time-integrated measure defined as the maintenance of CID over a period≥6 months, irrespective of treatment status. Remission can thus be defined as on or off treatment (ie, drug-free remission).

RS5: in order to achieve the ultimate goal (drug-free remission), the following intermediate targets are recommended:

1. ***At day 7, resolution of fever and reduction of CRP by >50%,***
2. ***At week 4, no fever, reduction of active (or swollen) joint count by >50%, normal CRP and physician and patient/parent global assessment less than 20 on a 0–100 VAS,***
3. ***At month 3, CID with GCs less than 0.1 (adults) or 0.2 (children) mg/kg/day,***
4. ***At month 6, CID without GCs.***

A stepwise T2T approach should be implemented, adapting treatments according to disease activity. Due to Still's disease potential severity and the risk of life-threatening manifestations, the TF was in favour of defining intermediate targets to monitor disease-related symptoms (fever, active (swollen) joints if present, CRP, physician or patient global assessment, and so on) and their evolution during the first weeks of treatment.

Several disease activity scores have been used in clinical trials or longitudinal observational studies, some derived from other IMID such as Disease Activity Score (DAS), some being more

specific of Still's disease, such as the systemic Juvenile Arthritis Disease Activity Score (sJADAS)[40] or the modified Pouchot's score,[41] both exploring the whole spectrum of Still's disease manifestations. The TF experts were uniformly in favour of using the same tool to quantify disease activity in children or adults with Still's disease, but they acknowledged that the scientific evidence is not robust enough to recommend one single tool for the moment. The TF identified this as an issue for the research agenda (table 3).

Taking this into consideration and based on existing recommendations proposed by German or North American paediatric rheumatologists,[8 42] the TF defined four pragmatic targets, at day 7, week 4 and month 3 and 6 of treatment, based on simple and clinically relevant criteria, rather than disease activity composite measures. These were developed to guide optimal patient management throughout the first 6 months of disease in a newly diagnosed patient or in a patient relapsing during drug-free remission. When interpreting these targets, it should be taken into account that IL-6 inhibitors may blunt CRP increase.[43 44] The definition and management of refractory or difficult-to-treat patients will be addressed below. The target dose of GCs at 3 months depends on age, and was set, consistently for adults and children to respectively, at 0.1 mg/kg/day and 0.2 mg/kg/day.[45 46] Patient management should include monitoring of safety in addition to disease activity.

RS6: to avoid prolonged systemic GC use for achieving and maintaining the target, the use of IL-1 and IL-6 inhibitors should be prioritised due to high evidence of efficacy.

The introduction of IL-1 and IL-6 inhibitors has changed the course of the disease so that nowadays GC use can be markedly limited, or even avoided. The TF acknowledges the efficacy of GCs in managing Still's disease. Available evidence, although low-level, and real-world experience suggest that high-dose (ie, ≥1 mg/kg/day of prednisone equivalent) are more efficacious than low-dose GCs. High dose should be considered at disease onset and particularly in the presence of severe symptoms, impending MAS, and severe pericarditis. The TF also acknowledges that some patients may not require GCs, particularly when an IL-1 or IL-6 targeted biologic disease-modifying antirheumatic agents (bDMARDs) can be initiated. While short-term use of GCs (for a few weeks) may not necessarily be associated with clinically relevant side effects, their long-term use often causes severe side effects, some of which are common to both children and adults, while others are more specific to children (eg, growth retardation and bone mineralisation defects) or adults (eg, metabolic syndrome). Whatever the situation, the TF emphasised that GC use to maintain the target at any time during the treatment course must be avoided: in other terms, in the presence of GC dependence, other therapies should be added to achieve the goal of disease control without GCs.

Despite the small number of randomised controlled trials (RCTs) with IL-1 or IL-6 inhibitors performed in sJIA or AOSD, the TF strongly recommends their use based also on the overwhelming body of evidence from real-world experience supporting their efficacy to control all aspects of the disease—including both systemic and joint manifestations—and to limit exposure to GC.[38] Their safety profile is well established, and the overall benefit–risk balance is extremely favourable. Serious adverse events appear to be more frequent during IL-6 inhibition than during IL-1 inhibition (table 4). Also, infectious adverse events, serious and non-serious, are more frequent during IL-6 inhibition compared with IL-1 inhibition (table 4). Among the IL-1 inhibitors, anakinra appears to have the most reassuring safety profile.[38] It is also worth to note that anakinra has been used in critically ill patients with sepsis admitted in intensive care unit with no safety concern[47] and that IL-1 and IL-6 inhibitors have been proven to be safe in patients with severe COVID-19.[48–50]

Evidences supporting the use of conventional synthetic DMARDs (csDMARDs) in Still's disease is scarce. In the one RCT available (performed in sJIA), methotrexate (MTX) was not superior to placebo even at a low response threshold (ACR30).[51] DMARDs have been traditionally used, particularly in patients with prominent joint involvement. Several observational studies have reported some response with MTX or with MTX in combination with other DMARDs.[52] They can be used as GC-sparing agent, although, nowadays, bDMARDs targeting IL-1 or IL-6 are the treatment of choice. csDMARDs should be considered in countries where IL-1 and IL-6 inhibitors are not available.

There is no RCT evidence supporting the efficacy of non steroidal anti-inflammatory drugs (NSAIDs) in Still's disease. However, the TF recommends to limit their use as symptomatic treatments to manage fever and arthralgia during the diagnostic work-ups.

RS7: an IL-1 or an IL-6 inhibitor should be initiated as early as possible when the diagnosis is established.

No formal RCT has addressed the timing of initiation of IL-1 or IL-6 inhibitors in Still's disease. Indeed, controlled trials have invariably enrolled patients with long-disease duration. However, real-life data have shown that early initiation of IL-1 or IL-6 inhibitors is associated with very favourable short-term outcome with high rates of CID off GCs.[38] Low-level evidence

Table 4 Pooled analysis of the incidence rate of SAEs, infectious AEs, infectious SAEs and MAS with IL-1 inhibitors (anakinra, canakinumab and rilonacept) or with the IL-6 inhibitor tocilizumab in patients with Still's disease

		SAEs	Infectious AEs	Infectious SAEs	MAS
Intervention		Number of patient years Rate/100 patient-years (95% CI)			
IL-6 inhibition	Tocilizumab	1141 36.5 (33.1–40.2)	855 104.6 (97.9–111.8)	1083 12.9 (10.9–15.3)	1141 2.7 (1.8–3.9)
IL-1 inhibition	All IL-1 inhibitors	1447 22.6 (20.2–25.2)	1447 94.5 (89.5–99.6)	1399 4.1 (3.1–5.3)	1447 3.2 (2.3–4.2)
IL-1 inhibition	Anakinra	739 10.4 (8.2–13.0)	739 18.1 (15.2–21.5)	739 3.2 (2.1–4.8)	739 2.2 (2.4–3.5)
IL-1 inhibition	Canakinumab	605 38.9 (34.0–44.1)	605 190.2 (179.3–201.4)	605 4.8 (3.2–6.9)	605 4.8 (3.2–6.9)
IL-1 inhibition	Rilonacept	103 14.6 (8.2–24.0)	103 80.6 (64.2–99.9)	103 3.9 (1.1–9.9)	103 2.9 (0.6–8.5)

IL, interleukin; MAS, macrophage activation syndrome; sAEs, serious adverse events.

from observational studies suggest that these drugs should be initiated before 3 months from symptoms onset.[30] Comparisons with historical data, and with patients in whom treatment with bDMARDs is delayed, suggest that early initiation of IL-1 or IL-6 inhibitors may also decrease the number of patients with a chronic persistent course. These data are consistent with the hypothesis of a therapeutic window of opportunity in the course of Still's disease. Translational data generated in murine models, namely IL-1RN-deficient mice, also support this window of opportunity. These mice develop spontaneous arthritis associated with increased number of activated Th17 cells. Arthritis development, as well as Th17 cell increase, was prevented by early, but not late, initiation of with an IL-1 inhibitor.[53] Consistently, in sJIA increased Th17 and increased γ/δ T cells with a Th17 profile are associated with chronic persistent disease.[54 55] Based on the efficacy data and the GC sparing effect, and since the safety profile of IL-1 and IL-6 inhibitors is reassuring and their use does not interfere with the diagnostic work-up at onset, the TF recommends to initiate an IL-1 or an IL-6 inhibitor as early as possible.

RS8: maintenance of CID for 3–6 months without GCs should be achieved before initiating bDMARD tapering.

With presently available IL-1 and IL-6 inhibitors, many patients achieve persistent remission on medication. The TF reiterates that withdrawal of GCs is a mandatory first step. Many physicians and patients want to attempt bDMARD tapering or withdrawal. Very few studies address the issue of drug management after achieving remission, that is, bDMARD maintenance, tapering or discontinuation. Based on their experience in Still's disease, the TF members preferentially recommended to progressively taper as performed in other inflammatory joint disease: a relapse will lead to an end-of-dose effect, that the patient will directly manage by bringing back bDMARD injections closer. With regards to patient empowerment, this strategy is preferable to a complete bDMARD discontinuation. In case of insufficient disease control, progressive bDMARD tapering would more likely lead to loss of efficacy in the last hours or days before the next injection, while complete and abrupt discontinuation could lead to a more severe disease flare. The TF recommends that bDMARD tapering should be considered in patients who have maintained CID off GCs for at least 3 months, possibly 6 months for patients with severe and difficult-to-treat Still's disease. Tapering should be conducted progressively, that is, stepwise by steps of 3–6 months, either by dose reduction or injection interval prolongation. The latter appears more appropriate as it leads to reduced number of injections (relevant for the patients whatever their age) and drug wastage. Possible schedule of tapering, based on published studies or real-life experience, is proposed in online supplemental table 3.

RS9: severe/life-threatening complications, including MAS or LD, may develop at any point during the disease course. Patients should be actively screened and monitored.

The TF considered important to warn physicians that Still's disease is a challenging condition in which severe or life-threatening complications may occur abruptly at any time during the disease course, that is, at disease onset, during the first weeks of course while diagnostic investigations are being performed, during bDMARD treatment (see table 4) even when Still's disease is well controlled, or later when drug tapering is implemented. MAS is the most frequent complication occurring in 15%–20% of patients with Still's disease. In addition, other rarer complications have been described including cardiac involvement (tamponade, myocarditis), lung involvement (Still's disease-related lung disease (LD), pulmonary hypertension, acute respiratory distress syndrome), fulminant hepatitis, DIC and thrombotic microangiopathy.[5 17 56] For this reason, the TF highlighted that patient monitoring and follow-up should be careful and that the patients should be advised to contact the treatment team in case of relapse/flare or new unexpected symptoms.

RS10: MAS should be considered in patients with persistent fever, splenomegaly, elevated or rising serum ferritin, inappropriately low cell counts, abnormal LFTs, intravascular activation of coagulation, elevated or rising serum triglycerides.

The term MAS identifies secondary haemophagocytic lymphohistiocytosis (HLH) occurring in the context of rheumatic diseases. MAS and in general all forms of HLH are considered prototypical hyperinflammatory syndromes caused by excessive activation of the innate and adaptive immune response. The pattern of hyperinflammation is recognisable in MAS and includes the items listed in RS10. None of these laboratory abnormalities in isolation is specific for MAS. The TF wants to emphasise that, in order to identify early MAS, it is important to pay attention to the pattern as a whole and particularly to the evolution over time of the laboratory parameters,[57] as also pointed out in a recent EULAR/ACR endorsed consensus effort on the early diagnosis of hyperinflammation.[58] The available classification criteria and diagnostic scores (H-scores and M-scores) for MAS,[59 60] derived with statistical analyses based on different sets of patients and disease controls, capture these laboratory abnormalities (online supplemental table 5) and could be used to help in the diagnosis. The TF underscores that MAS can occur also in patients receiving IL-1 or IL-6 inhibitors and emphasises that, in patients receiving canakinumab or tocilizumab, clinical and laboratory abnormalities may be blunted or delayed, particularly fever and ferritin increase.[61] During withdrawal and/or tapering of GCs, IL-1 or IL-6 inhibitors, patients might be at risk for MAS and therefore should be carefully monitored.

In all patients with Still's disease, ferritin should be measured routinely. In patients at risk or with suspected MAS, ferritin measurements should be repeated on a daily or even on a bidaily basis to allow for a tight monitoring.[57 58] Although other rarer causes of hyperferritinaemia have been described, ferritin remains very important in the diagnosis of MAS with high sensitivity and specificity.[62] Ferritin trends over time should always be interpreted in the context of the other laboratory abnormalities that are part of hyperinflammation.[57 58] Other modern biomarkers can be used when available: serum sIL-2R, CXCL-9, IL-18 levels and percentages of activated CD8 T lymphocytes, or possibly activated CD4+or monocytes.[62–64] All these biomarkers display high sensitivity and specificity.[62]

RS11: MAS treatment must include high dose GCs. In addition, treatments including anakinra, ciclosporin and/or IFNγ inhibitors should be considered as part of initial therapy.

The TF highlighted the need for a search for triggering factors (most frequently infections), while initiating specific MAS treatments.[65] Infections, if identified, should be aggressively treated with appropriate antimicrobial therapy as their control facilitates the management of MAS. Regarding potential infectious triggers, many infectious agents can trigger MAS.[58] The presence of an active infection should not delay the initiation of MAS treatment.

High-dose GCs are the mainstay of the treatment in patients with MAS. In MAS, GCs are usually administered by intravenous pulses of methylprednisolone (15 to 30 mg/kg/day, maximum dose 1 g/infusion). Dexamethasone should be considered in the presence of central nervous system involvement as it better crosses the blood–brain barrier. High-dose GCs may achieve

satisfactory results in a substantial number of patients, particularly if initiated early.

Additional treatments include ciclosporin, or possibly another calcineurin inhibitor (tacrolimus), anakinra and IFN-γ neutralising monoclonal antibody (online supplemental table 6). Ciclosporin has been proven to be ineffective in primary familial HLH and has been dropped from the standard of care approach in this specific condition.[66] However, despite the absence of formal clinical trial in secondary HLH/MAS, the TF acknowledges the large and often positive experience with ciclosporin in MAS and recommends that ciclosporin should considered in case of inadequate response to GC.[58] Indeed, it is particularly valuable in less resourced countries. Ciclosporin can be administered orally or intravenously, particularly in the critical care setting. Similarly to ciclosporin, anakinra has not been tested in clinical trial in MAS. However, there is a large real-world experience on its use in MAS. In these patients it should be used at doses higher than the standard 1 to 2 mg/kg/day, and possibly in intravenously repeated doses; this approach resulted in satisfactory responses in several patients.[62 67] Emapalumab, an anti-IFN-γ antibody, is the only targeted therapy that has been tested in a clinical trial (open-labelled single arm) in Still's disease-related MAS.[68] In patients with severe MAS and who had failed standard of care with high-dose GCs, treatment with emapalumab was associated with achievement of MAS remission in the great majority of the patients with a marked GC sparing effect and a reassuring safety profile. It is important to point out that emapalumab is not yet approved in Europe. Additionally, the potential interest of JAK inhibitors should be mentioned, since a few case reports reported efficacy of JAK1/JAK2 inhibitors—that is, ruxolitinib or baricitinib—in such patients[69 70] (online supplemental table 6). Finally, in refractory MAS, low-dose etoposide may also be considered[71] (online supplemental table 6).

The TF recommends that the addition of the above-mentioned treatments is considered in patients with initial unsatisfactory response to high dose GCs and in patients with severe MAS and rapid worsening. The TF highlights that combination therapies with multiple agents on a background of high dose GCs are often necessary and should be considered also as initial therapy. The higher mortality of patients with MAS reported in adults[72] may also be considered when choosing a treatment or a combination therapy. Such decisions should be discussed with experts of a reference centre.

RS12: LD should be actively screened by search for clinical symptoms (eg, clubbing, persistent cough, shortness of breath) and pulmonary function tests (pulse oxygenometry, diffusing capacit of carbon monoxyde (DLCO) measurement), and investigated by high-resolution CT-scan in any patients with clinical symptoms.

In the last decades, physicians have been recognising, with progressively increasing frequency, patients, particularly children, with Still's disease and inflammatory LD.[73 74] LD was initially described in North America; however, cases have now been recognised in Europe and other regions of the world.[75] Still's LD is characterised by interstitial inflammatory infiltrates of CD4 and CD8 lymphocytes and by intra-alveolar deposition of proteinaceous material. LD appears to be associated with younger age at onset, Down's syndrome, occurrence of MAS and particularly of recurrent MAS, as well as high serum IL-18 levels.[74] Data are also accumulating, partly still unpublished, suggesting that carriage of the HLA DRB1*1501 is strongly associated with LD.[75 76] Given the potential strength of the association, the TF believes that HLA typing should performed in several different populations with Still's disease in order to provide information on the pathogenic and the clinical significance of this association. This issue has been included in the research agenda (table 3). Although the exact pathogenesis of Still's LD is not yet understood, there is increasing evidence of a role for the IL-18/IFNγ pathway and activated T cells.[77]

All patients with Still's disease should be evaluated carefully for the occurrence of LD.[78] Particular attention must be paid to the patients with the above-mentioned risk factors. Clinical symptoms are important, but may present lately when LD is already advanced. Pulmonary function tests are useful; in children and particularly in small children pulse oximetry (specifically continuous overnight pulse oximetry) is useful to detect early functional impact of LD. Given the potential severity of Still's LD, the TF recommends that a high-resolution CT scan is performed in any patients with clinical concerns. The TF also highlighted that echocardiography is useful to screen and detect pulmonary hypertension, or other rarer complications, such as myocarditis. No evidence-based screening protocol is available. A proposal for such a protocol has been recently published and could represent a guide for treating physicians.[78]

Finally, as the field of Still's LD is rapidly evolving from both clinical and therapeutic perspectives, the TF emphasised that patients with LD should be managed in collaboration with expert centres (see RS 14).

RS13: based on the available data, the presence of risk factors for Still's LD or the development of Still's LD should not be considered as a contraindication to IL-1 or IL-6 inhibitors.

One current hypotheses on the pathogenesis of Still's LD is based on the occurrence of hypersensitivity-like reactions to IL-1 and/or IL-6 inhibitors and postulates that LD is a consequence of a Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)-like reaction to these drugs.[73 76] DRESS-like reactions would imply withdrawal of IL-1 and IL-6 inhibitors in patients with Still's LD, so it is important to emphasise that the hypothesis remains unproven and indeed may be difficult to reconcile with all available data. Furthermore, IL-1 and IL-6 inhibitors have been shown to be very effective in Still's disease and led to substantial improvement in patient quality of life and in long-term outcome. Withdrawal of these effective drugs was not associated with notable improvement of LD in the great majority of the patients. Moreover, withdrawal would make it very difficult to manage the patients with no other options than using markedly higher doses of GCs. It also exposes the patients to a significant risk of severe flares, which can be associated with severe MAS. In such occasions, fatalities have already been reported. Considering the overall benefit–risk ratio, the TF recommends that IL-1 and IL-6 inhibitors should not be withdrawn and thus should be continued in patients with Still's LD. This is in line with a recent observation in a Dutch prospective study.[79] The TF also acknowledges that there is insufficient evidence to withhold first-line IL-1 or IL-6 inhibitors in patients with new onset Still's disease and LD risk factors. Additionally, given the potential involvement of T cells in LD pathogenesis, some TF experts felt that it is reasonable to initiate T cell-directed immunosuppression in patients at high risk for LD or developing LD, although direct clinical evidence for this strategy is still absent. Benefits of JAK inhibitors in patients with Still's LD has been reported in two single cases.[80 81]

RS14: difficult to treat (D2T) patients, those with severe MAS and those with Still's LD should be managed in collaboration with Still's disease expert centres.

The course of the disease may be challenging since its beginning, with MAS often presenting at onset. D2T patients, that is, those who have failed IL-1 and IL-6 inhibitors, those with

severe/recurrent MAS and those with LD may represent a major challenge. For such patients, intermediate targets might be less ambitious. Therapeutic strategies in D2T patients may include repeated intra-articular GC injections, periodic GC pulses, JAK inhibitors, combination of csDMARDs and bDMARDs and novel IL-18 or IFNγ inhibitors. Some of these are experimental, and there is no evidence supporting one specific strategy. During the last decades, rare disease networks have been developed in Europe (European Reference Networks) and outside Europe with the objective of facilitating the access to both expert physicians and patients with disease specific expertise, through specific consultations or multidisciplinary rounds. Physicians are therefore encouraged to contact centres with Still's disease expertise (in Europe through the ERN-RITA; https://ern-rita.org/) to discuss treatment escalation and in general the management of patients with inadequate response to standard of care. This will enable optimisation of Still's disease management, allowing also to foster research on difficult patients and to favour the access to innovative therapies (compassionate access or enrolment in clinical trials).

Therapeutic algorithm

The above RSs lead to propose a two-part algorithm (figure 1). At onset or during a flare a patient should receive an IL-1 or IL-6 inhibitor as early as possible. Since there is no clear predictor at disease onset to identify patients who will develop a chronic disease course, the TF recommends considering first-line biologic therapy irrespective of disease severity. When bacterial infection remains on the differential diagnosis, an IL-1 blocker is preferred. Anakinra is very often used initially because of its short half-life and its reassuring safety profile. High-dose GCs are indicated in patients with high disease severity (high spiking fever, wide-spread polyarthritis, high levels of pain (VAS >6–7/10), pericarditis, impending MAS (elevated LFT and/or high serum ferritin levels). In milder presentations, GC may be used at low or intermediate doses, but are not mandatory. When they are started, GC should be progressively tapered as soon as possible with the aim of achieving CID on low dose GC at 3 months and, subsequently, CID off GC at 6 months from treatment initiation. Failure to achieve one of these two targets should prompt IL-1 or IL-6 inhibitors rotation during which slow progressive GC tapering should be continued. A patient who fails to achieve CID off GC after IL-1/IL-6 inhibitor rotation should be considered as D2T and should be discussed in multidisciplinary rounds with an expert in Still's disease, for example, at a reference centre (in Europe through the ERN-RITA, https://ern-rita.org/); the use of less well-established therapeutic options should be discussed. These include JAK inhibitors, haematopoietic stem cell transplantation and immunosuppressants.[82–86]

If at any time CID off GC is achieved, IL-1 or IL-6 inhibitors or the experimental therapy should be maintained for 3–6 months (until remission is achieved). At least 6 months of CID off GC should be maintained before tapering of bDMARDS or of experimental therapies is initiated. A patient who presents a major flare while in CID off GC should be induced again similarly as if at onset.

A patient who develops MAS at any time before initiation and during treatment should be treated promptly as described.

Quality indicators

Based on the recommendation statements and TF discussions during the production process, three quality indicators were identified: (1) proportion of patients achieving CID off GCs at 6 months; (2) proportion of patients having started early IL-1 or IL-6 inhibitors, that is, in the first 3 months after disease onset; (3) proportion of severe patients with Still's disease (D2T patients, severe/recurrent MAS, Still's LD) referred to or managed in collaboration with an expert centre. These were voted on line with percent consensus of 96.8%, 96.8% and 100%, respectively.

DISCUSSION

This is the first set of recommendations for the diagnosis and management of children and adults with Still's disease, two entities previously named sJIA and AOSD and distinguished primarily based on an arbitrary cut-off of age at onset.

The endorsement by both the adult and the paediatric European rheumatology societies (EULAR and PReS) and the involvement of a large team of paediatric and adult rheumatologists, together with patient's representatives are major strengths of this work. Even though the introduction of the arbitrary cut-off caused a disconnect between paediatric and adult rheumatologists in the management of Still's disease for several decades, the experts worked to overcome this disconnection, with the aim to homogenise patient management and therapeutic strategies across all ages. The ultimate goal is to improve Still's disease outcomes through (1) the facilitation of rapid and accurate diagnosis and the definition of realistic and timely therapeutic targets, and (2) the optimisation of the prevention, screening and eventually management of complications and of the evolving phenotypes of Still's disease, such as LD. For all these considerations, a unique name, that is, Still's disease, already largely acknowledged by the medical community, was chosen by the TF to identify the disease across all ages. This decision will also have beneficial implications for future clinical trials of new innovative therapies. It implies the design of a single trial across all ages, enabling more rapid completion and, in case of positive results, quicker approval by regulatory agencies across all ages.

The past disconnect led to the definition and use of different sets of diagnostic/classification criteria in children and adults. The TF discussed the issue at length and eventually chose to propose operational definitions for fever, rash, joint involvement and systemic inflammation, which are the typical features of Still's disease. All these definitions achieved high levels of agreement. In addition, the TF emphasises that the presence of arthritis is not essential to make the diagnosis. At present, arthritis is required by the ILAR classification criteria used in children, but not by other sets of criteria used in adults[10 11] or recently proposed in children.[9] In this respect, the TF felt that defining a common set of diagnostic/classification criteria for Still's disease across all ages is needed, but it was beyond the scope of the present effort. However, given the important implications, ranging from clinical practice to trials and drug labels, this issue should be the focus of an effort in the near future.

The TF emphasised that drug-free remission is the ultimate goal for patients across all ages, and is now feasible for many given the efficacy of IL-1 or IL-6 inhibitors. The TF agreed on the definition of CID to be used and on the identification of intermediate targets to be achieved during treatments to guide therapy adjustments. The TF acknowledges that measures of disease activity are important. However, reflecting the above-mentioned disconnection, different measures have been developed for children and adults. Again, the TF recommends that this issue should be the focus of an effort in the near future.

Current therapeutic approaches are based on a vast body of evidence pointing to the pathogenic role of IL-1 and IL-6 in Still's

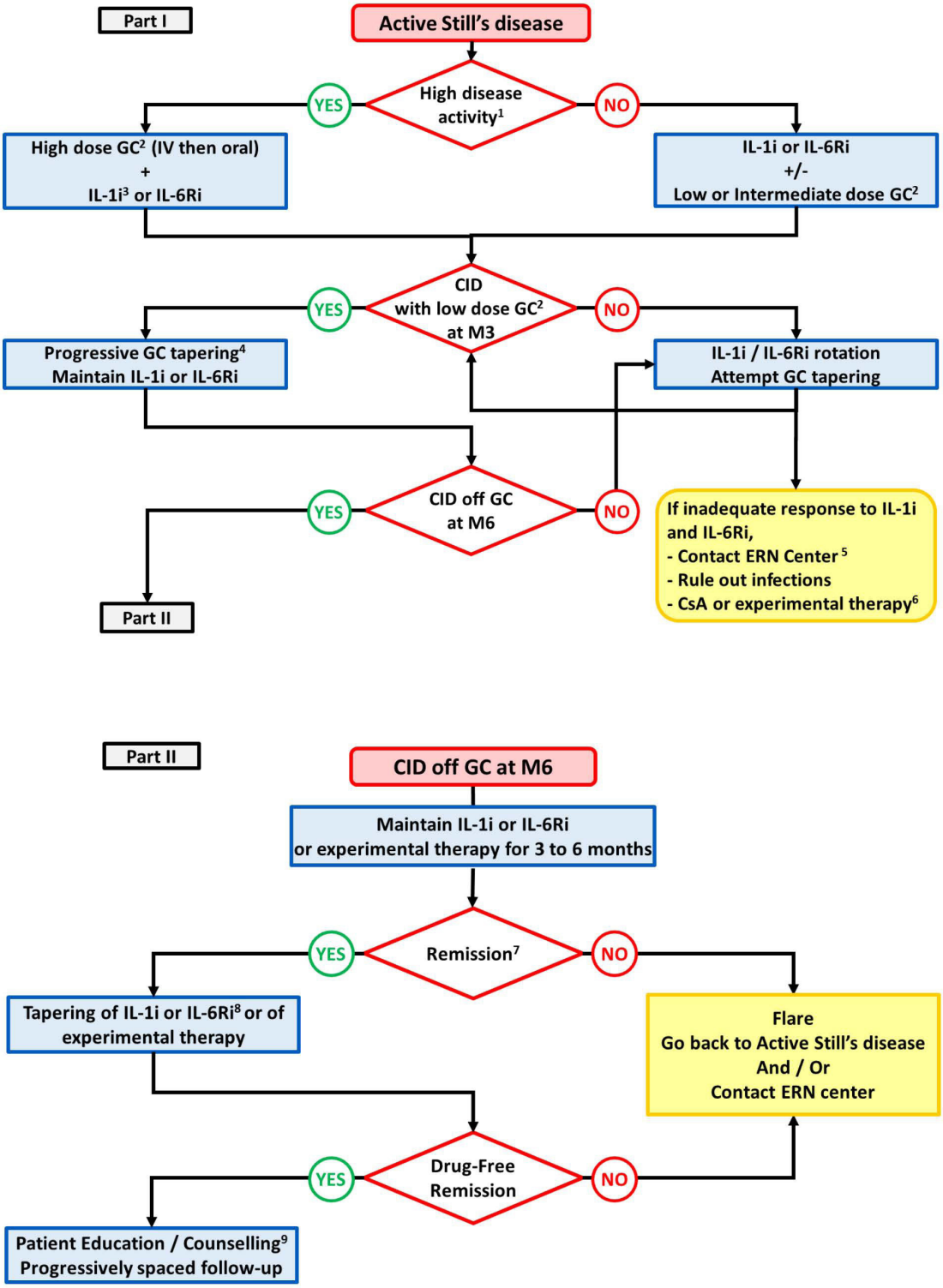

Figure 1 Treatment algorithm to manage people with Still's disease footnotes. [1]High disease activity includes: high spiking fever, wide-spread polyarthritis, high levels of pain (VAS >6–7/10), pericarditis, impending MAS (elevated LFT and/or high serum ferritin levels). [2]High-dose GC is equal to or greater than 1 mg/kg/day of prednisone equivalent in adults and 2 mg/kg/day in children. Low-dose GC is equal to or lower than 0.1 mg/kg/day of prednisone equivalent in adults and 0.2 mg/kg/day in children. [3]Anakinra would be the preferred choice for a patient with impending MAS. High-dose anakinra (> 4 mg/kg/day in children or 100 mg twice a day in adults) are often used in these circumstances. [4]GC tapering should be started as soon as the first intermediate target (see RS5) is reached (no fever and decrease by 50% of active joints). [5]Difficult-to-treat Still's disease requires discussion in multidisciplinary round of a ERN reference centre. [6]Experimental therapy may include JAK inhibitors, emapalumab, bispecific antibody to IL-1/IL-18. The choice among these possible therapies is driven by the features of the disease (eg, chronic relapsing MAS, severe and persistent joint involvement, lung disease) in consultation with ERN experts. [7]Remission defined as CID maintained for 6 months or more. [8] Tapering of IL-1i, IL-6Ri or experimental therapy is usually based on progressive injection spacing. [9]Patient education and counselling aims to learn to the patients the signs and symptoms that could indicate Still's disease relapse and the ways to reach the medical team to manage it. CID, clinically inactive disease; GC, glucocorticoid, IL, interleukin; LFT, liver function test; MAS, macrophage activation syndrome.

disease. Indeed, the use of IL-1 and IL-6 inhibitors has dramatically changed the outcome of these patients.[87] Despite the very limited number of RCTs, mostly performed in children and with different designs and outcomes, IL-1 and IL-6 inhibitors lead to CID in more than half of the patients. Given the efficacy of these approaches the TF identified pragmatic and simple therapeutic targets that should be achieved particularly in the first months of treatments. The TF acknowledges the need to identify, for both patient management and clinical research, a common disease activity measure, assessing all the disease features, particularly the systemic ones. The presently available measures such as the sJADAS or the modified Pouchot's score indeed do so, but they were developed specifically for children and adults, respectively.

It should be pointed out that inhibiting IL-6 or IL-1 may not cover the full spectrum of the pathogenic pathways involved in Still's disease. This is particularly relevant for the D2T patients who fail to respond to IL-1 and IL-6 inhibitors. Indeed, the proposed unified strategy to manage and treat patients with Still's disease should not occult that there is definitely some heterogeneity in Still's disease, both from a clinical and a pathogenic perspective. In the latest years, different patient clusters were proposed according to age of onset, diverse clinical manifestations, and presence of life-threatening complications.[17 88–92] To date, these attempts to cluster patients with Still's disease are not robust enough to be implemented in clinical practice. Therefore, the TF believes that a better understanding of pathogenic pathways is needed, with a view to developing new targeted approaches, particularly aimed at managing severe complications and D2T patients.

Despite the lack of controlled trials, the TF recognised that a large body of real-life data indicate that early initiation of an IL-1 or IL-6 inhibitor leads to high levels of rapid GC-free CIDs. Considering these data, an IL-1 or IL-6 inhibitor should be initiated as soon as the diagnosis of Still's disease is made. Initial data suggest that early initiation leads to a decrease in the percentage of patients with a persistent course, although this remains to be proven. An effort should be made to continue the validation process of the currently tested diagnostic biomarkers, that is, serum levels of IL-18 and S100 proteins, a process that could allow their widespread use of to support the clinical diagnosis. The same applies to MAS diagnosis where novel biomarkers are emerging (serum levels of CXCL9 and IL-18 or percentages of activated CD8+T lymphocytes). A validated method (score or biomarker) to identify patients with Still's disease at higher risk for MAS development, and who will require tight monitoring, is also needed

A similar tool would also be particularly useful for Still's LD. In this respect, different sets of data point to carriage of the DRB1*15 allele as being a risk factor for LD. These issues are included in the research agenda (table 3). The above-mentioned tools, as well as a better understanding of the pathogenic pathways underlying Still's disease, particularly the D2T patients, and the most frequent and severe complications (ie, MAS and LD) are needed in order to enable personalised strategies targeting the most relevant pathogenic pathway in each individual patient, as well as to adjust the treatment depending on the presence of an evolution of the disease towards MAS or LD.

MAS still represents a severe and potentially fatal complication of Still's disease. The TF recommends to be particularly vigilant for MAS with appropriate periodic blood screening and careful and tight monitoring of patients with impending MAS. High-dose GCs are the mainstay of the treatment of MAS. In addition to the well-known and extensively used ciclosporin, the TF acknowledges the efficacy of novel therapies targeting IL-1 or IFNγ and recommends that these should be used in patients who failed high-dose GCs and considered also at MAS onset for patients with severe and/or life-threatening MAS.

Therapeutic considerations are also particularly relevant for the recently emerging Still's LD. This severe complication is being observed more frequently in the last 10 years. It may lead to severe respiratory failure and death. Its pathogenesis is still unclear, although an increasing body of evidence points to an IL-18 and IFNγ driven inflammatory pathology in the lung.[74 93] Two hypotheses have been raised to explain this LD. One proposes hypersensitivity to IL-1 and IL-6 inhibitors, the 'DRESS hypothesis', and a second focuses on the biological impact of IL-1 and IL-6 blockade, potentially via skewing T cell differentiation, the 'cytokine plasticity hypothesis'.[77] The TF emphasises that the presently available evidence is not sufficient to withdraw efficacious therapies with IL-1 or IL-6 inhibitors, considering the fact that their withdrawal is not associated with significant improvement in most patients, that there is a significant risk for severe flares, often with MAS, and the burden of long-term high-dose GCs that represents the only alternative for many of these patients. In such situations, on the basis of expert experience and despite the lack of robust data in the literature, some experts in the TF would favour adding T cell-directed immunosuppressants to IL-1 or IL-6 blockers in patients with Still's-LD.

The last and always challenging issue is the recommendation implementation in daily practice.[21] The EULAR/PReS recommendations have already been presented in several national or international Pediatric or Adult Rheumatology scientific meetings in Europe, North America and in the coming months in Asia. Besides their publication in the Annals, several review papers will be issued in the coming months to make a large public of physicians, scientists, patient representatives or decision-makers aware of the important changes that the EULAR/PReS recommendations have proposed. In addition, three major quality indicators were proposed with the aim of assessing the improvement in the management of patient with Still's disease in daily practice.

In conclusion, this is the first set of recommendation for diagnosing and managing patients with Still's disease across all ages. This effort reconciles views and positions of paediatricians and adult rheumatologists. Importantly, this effort sets new goals to address key issues in order to achieve optimal patient management: a common set of diagnostic/classification criteria, possibly including modern biomarkers, a common disease activity measure and, last but not least, a better understanding of the pathogenic pathways, with particular focus on D2T patients, MAS and LD.

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