TITLE PAGE

Title: The 2021 EULAR and ACR points to consider for diagnosis, management and monitoring of the IL 1 mediated autoinflammatory diseases: CAPS, TRAPS, MKD and DIRA

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Abstract

Objective: The IL-1 mediated systemic autoinflammatory diseases (SAID) including the cryopyrin-associated periodic syndromes (CAPS), tumour necrosis factor receptor-associated periodic syndrome (TRAPS), mevalonate kinase deficiency (MKD), and deficiency of the IL-1 receptor antagonist (DIRA) belong to a group of rare immunodysregulatory diseases that primarily present in early childhood with variable multiorgan involvement. When untreated, patients with severe clinical phenotypes have a poor prognosis, and diagnosis and management of these patients can be challenging. However, recently approved treatments targeting the pro-inflammatory cytokine IL-1 have been life-changing and have significantly improved patient outcomes. Our aim was to establish evidence-based recommendations on diagnosis, treatment, and monitoring with the goal of standardizing management of these patients.

Methods: A multinational, multidisciplinary task force consisting of physician experts including rheumatologists, patients or caregivers, and allied health care professionals, used systematic literature review, Delphi questionnaires, and consensus methodology and formulated statements to guide patient care.

Results: The task force devised 5 overarching principles, 14 statements related to diagnosis, 20 points on therapy, and 14 items focused on long-term monitoring that were evidence and/or consensus-based for patients with IL-1 mediated diseases. An outline for disease-specific monitoring of inflammation-induced organ damage progression and reported therapies of CAPS, TRAPS, MKD and DIRA were also included.

Conclusion: These statements represent state-of-the-art knowledge based on published data and expert opinion to guide diagnostic evaluation, treatment and management of patients with CAPS, TRAPS, MKD and DIRA, and to inform the various stakeholders about optimized patient care with the ultimate goal to improve disease outcome.

INTRODUCTION

Systemic autoinflammatory diseases (SAID) are a group of genetically defined multisystem immunodysregulatory disorders caused primarily by the dysfunction of innate immune system[1]. Currently, SAID comprise a wide range of disorders with features of systemic and organ-specific inflammation in the absence of pathogenic infections or autoimmunity [2]. The pathogenesis of the earliest genetically defined group of SAID is driven by increased release or signaling of the pro-inflammatory cytokine interleukin-1 (IL-1)[3 4].

The conditions addressed by this task force are frequently seen by rheumatologists and include the cryopyrin-associated periodic syndromes (CAPS - also known as NLRP3-AID[5]), a spectrum of rare autosomal dominant autoinflammatory diseases caused by gain-of-function mutations in *NLRP3*[6-12], tumour necrosis factor receptor associated periodic syndrome (TRAPS) due to autosomal dominant mutations in *TNFRSF1A*[13 14] encoding the Tumour Necrosis Factor Receptor Type 1*,* mevalonate kinase deficiency (MKD), caused by autosomal recessive loss-of-function mutations in the mevalonate kinase gene (*MVK),* resulting in deficiency of mevalonate kinase enzyme[15-18], and deficiency of IL-1 receptor antagonist (DIRA) due to homozygous deleterious loss-of-function mutations in *IL1RN,* the gene encoding the IL-1 receptor antagonist (IL-1Ra)[19]. The most common IL-1 mediated autoinflammatory disease, Familial Mediterranean Fever (FMF) was not included, as EULAR-endorsed recommendations have already been published for this disease[20].

SAID are associated with chronic systemic and organ-specific inflammation leading to progressive organ damage and dysfunction[8 21-23]. In addition, acute disease flares can be life-threatening and contribute to the high mortality and morbidity in untreated patients with severe disease phenotypes[11 13 24]. With limited clinical expertise in this rapidly evolving group of rare diseases and barriers to genetic tools that allow for a timely genetic diagnosis in many areas of the world, there is a need to harmonize care that is reflective of our current knowledge related to diagnosis, treatment, and monitoring.

The natural history of untreated patients with pathogenic mutations leading to CAPS[25 26], TRAPS[14], MKD[27] and DIRA[19] has been characterized in the literature and forms the basis for the guidance on monitoring disease progression and organ damage. Disease severity is dependent on the level of systemic and organ-specific inflammation. Risk factors that are associated with adverse outcomes include certain mutations, clinically severe phenotypes, frequent and severe inflammatory episodes, and existing organ damage at the time of initial presentation[28]. The life-changing impact of therapies targeting IL-1 has been documented in patients with CAPS, TRAPS, MKD and DIRA. There is also mounting evidence on the impact of maintenance treatment on preventing the progression of organ damage thus pointing to the importance of identifying patients promptly and initiating treatment early in life[29 30] .

An early and accurate genetic diagnosis allows for referral for genetic counselling, screening for potential complications, informs prognosis and improves our ability to define individual treatment goals and tailor treatment decisions[28 31 32]. While most patients with CAPS, TRAPS, MKD and DIRA are historically managed by pediatricians and pediatric specialists due to their common early age of onset, for many, transitioning to adult care remains challenging for the young adults who are now reaching adulthood with the expectation of a normal life span in many treated patients. Furthermore, women's health and pregnancy and other subspecialty needs (i.e surgery), are often not addressed adequately in the context of SAID. A diagnosis of SAID in some patients may have been postponed for decades therefore requiring greater care needs that can include the management of permanent disabilities that developed due to delayed and inadequate treatment of these chronic inflammatory conditions. Therefore, the needs of the growing child, young adolescent, adult or even senior citizen should be addressed and should include age-appropriate measures that foster self-management skills, encourage shared medical decision-making, address reproductive health issues and facilitate the transition to adult medical care[8 33-35].

The above considerations led to the convening of a task force that was charged with developing standardized guidance for diagnosis, treatment and long-term management of patients with CAPS, TRAPS, MKD and DIRA that target pediatricians, internists, and subspecialists (particularly rheumatologists), involved in their chronic care. They should also provide knowledge and appropriate expectations for patients and caregivers. The statements were developed as a resource for physicians to facilitate management and for policy makers who have a role in authorizing patients' access to diagnostic tools and treatment options. Finally, these guidelines are aimed to standardize the level of care, and to uniformly assure improved quality of life and disease outcomes.

METHODS

The IL-1 mediated autoinflammatory diseases task force (TF) was convened to develop topics to consider for the diagnosis, monitoring, and management of four different IL-1 mediated SAID, after the approval by the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR) executive committee. The TF was led by two conveners (ED and RGM) and consisted of 19 internationally recognized experts from different countries across Europe, United States and Canada. The task force members were selected based on expertise in treatment and care of these patients.

EULAR[7] and the ACR standardized operating procedures (SOPs) were followed during the project (see online supplementary methods). The first meeting was convened on August 2019, in Bethesda, United States to define the focus of the TF, and identify the target population for four different IL-1 mediated SAID. Then group worked to determine the PICO (Population, Intervention, Comparison, Outcome) questions related with diagnosis, monitoring and management of diseases for the systematic literature review (SLR). Using the PICO questions defined during the first meeting, SLR was performed by the research fellows (MR, ZSA, DP) with support from a librarian (DH) and the senior methodologists (ED, DA) to identify relevant publications through August 2020. Utilizing the Delphi technique, a series of well-defined open questionnaires with semi-structured, anonymous Delphi questionnaire was sent via REDCap to members of the TF. A second Delphi questionnaire with refined statements based on comments received in the first survey was circulated to the task force members. Similar to the first round, participants were asked to indicate their agreement and comments before the consensus meeting. Statements that reached ≥80% agreement were formulated into draft statements included in the virtual consensus meeting, statements that reached between 20% and 80% agreement were included for discussion in the second part of the consensus meeting, those with below 20% agreement were dropped.

Due to the COVID-19 pandemic three consensus meetings were held online between September and November 2020. During the consensus meetings, if a statement reached ≥80% agreement, it was accepted as a point to consider. If a statement did not reach ≥80% agreement, it was discussed in a Round Robin discussion. The discussed statements were voted during the second round, and again if the statement reached ≥80% agreement, it was accepted as a point to consider, and if not, it was dropped from the final list. The Oxford Levels of Evidence (LoE) were applied for each point to consider. Subsequently, the strength of the statement (GoR) was assigned ranging from A (directly based on level I evidence) to D (directly based on level IV evidence or extrapolated recommendations from level I, II or III evidence)[36]. Finally, members of the task force were asked to provide their level of agreement (LoA) for each point to consider, through an online survey, on a scale of 0 (absolutely disagree) to 10 (absolutely agree). The mean and SD of the LoA with each statement were calculated. The manuscript was reviewed and approved by all task force members and the EULAR/ACR Executive Committee before submission.

RESULTS

Systematic literature review

The details for the literature search strategy and summary of results are described in the online supplementary material. Briefly, the search was performed using Pubmed, Embase and the Cochrane Library through August 2020. For CAPS, among 2041 references identified, 66 studies were selected for inclusion. For TRAPS, among 1161 references identified, 47 studies were selected for inclusion. For MKD, among 1806 references identified, 51 studies were selected for inclusion and for DIRA among 557 references identified, two studies were selected for inclusion. In total, from among 5565 references identified, 165 were included.

OVERARCHING PRINCIPLES

After a group discussion that included the results of the SLR, the consensus process was initiated and the full task force agreed on a final set of 5 overarching principles (Table 1) and 33 points to consider (Table 2, 3, 5). The initial presentation of patients with CAPS, TRAPS, MKD and DIRA occurs typically in the perinatal period or in early childhood with overlapping features of systemic and disease specific inflammation[11 13 19 24] including early onset of fever, abdominal pain, rash, joint pain, neurologic manifestations, and elevated inflammatory markers[13 37-42]. Elevation of acute phase reactants (including high sensitive C-reactive protein (hsCRP), erythrocyte sedimentation rate (ESR) and serum amyloid A (SAA)[43]), correlates with disease activity and is required for diagnosis[33 37 44], long-term monitoring of disease activity, adjusting treatment intensity and risk assessment for the development of complications[13 32 45-47]. Delayed treatment can result in progressive organ damage[8 21-23], early morbidity and increased mortality[31 48 49]. Overlap of clinical features among IL-1 related disorders, particularly early in life, stress the need of an accurate genetic diagnosis, that in many countries may also be required to access IL-1 blocking biologics that can prevent life-threatening complications[33 50 51]. NGS-based sequencing platforms are now widely used and are replacing the increasingly outdated “gene by gene” approach[50-54].

Disease and organ-specific assessment often require a multidisciplinary team of subspecialists and supportive care providers to make a diagnosis and initiate effective treatment that can improve outcome[8 21 33]. The goals of therapy are rapid control of disease activity and prevention of disease progression and treatment related organ damage[48 55]. As IL-1 blocking treatments have been FDA and EMA approved for CAPS, TRAPS, MKD and DIRA, rapid disease control (i.e. of disease symptoms and systemic inflammation) using IL-1 blocking treatments is critical to prevent early inflammation related organ damage and side effects from the use of drugs that are not effective or have substantial toxicities.

There are currently no cures for these diseases, and patients need continuous and developmentally appropriate care during and beyond adolescence. Long-term monitoring focuses on evaluating disease activity, assessing signs and symptoms, disease-specific organ inflammation, growth and development, and of adjusting therapeutic doses for growth. Patient-related outcomes[56-58] should be assessed and should include measures of health-related quality of life[33 59 60] (HRQoL), disease activity[61], (i.e. AIDAI), global assessment scales for physicians and patients/parents[62] (PGA, PPGA) and assessment of disease-related organ damage[58] (i.e. ADDI) are also useful for monitoring.

Transfer of adolescents with SAID to adult specialists can be challenging and may put patients at risk for unfavorable outcomes. Therefore, we stress the need to include management goals that foster self-management skills and medical decision-making (i.e including reproductive health) and a transition plan to adult specialist care[63].

The management of patients particularly with severe organ damage, including cognitive (i.e. learning and behavioral disorders) and physical disabilities (i.e. short statue, bone deformities, hearing and vision loss)[11 64] can be overwhelming and affect physical, mental, psychosocial health, and social functioning of entire families. Individualized support services including but not limited to psychosocial support, genetic counseling, cognitive and learning support and occupational and physiotherapy may be needed to address ad manage these issues[34 56 65 66].

Table 1 Overarching principles for the diagnosis, monitoring and management of CAPS, TRAPS, MKD and DIRA				
	Overarching principles	**LoE**	**GoR**	**LoA (0-10) mean ± SD**
A	Patients with the IL-1 mediated diseases CAPS, TRAPS, MKD and DIRA present with chronic or intermittent flares of systemic and organ inflammation, that if untreated results in progressive organ damage, early morbidity and increased mortality. A multidisciplinary team is required to diagnostically evaluate and manage patients with CAPS, TRAPS, MKD and DIRA, which includes evaluation of systemic inflammation, disease-associated complications and long-term treatment and management.	5	D	9.5±0.7
B	Patients presenting with chronic or episodic flares of unexplained systemic inflammation (including elevations of CRP and ESR) and clinical features suggestive of CAPS, TRAPS, MKD and DIRA should receive a prompt diagnostic work up comprising: • genetic work up • clinical work up focusing on the extent of inflammatory organ involvement • screening for disease and treatment-related comorbidities	5	D	9.8±0.6
C	Genetic testing using a next generation sequencing platform should be used to diagnose patients with CAPS, TRAPS, MKD and DIRA, which facilitates initiation of targeted treatments, genetic counselling, and informs prognosis.	4	C	8.9±1.6
D	The goal of therapy is to control clinical signs and symptoms and normalize laboratory biomarkers of systemic inflammation by using a treat-to-target approach.	5	D	9.6±0.8
E	Long-term monitoring goals should focus on: • adequate treatment adjusted to the needs of the growing child and prevention of systemic and organ-specific inflammatory manifestations, • fostering of self-management skills and medical decision-making, • initiating a transition program to adult specialist care in adolescent patients.	5	D	9.6±0.9

CAPS, cryopyrin-associated periodic syndromes; TRAPS, tumour necrosis factor receptor associated periodic syndrome; MKD, mevalonate kinase deficiency; DIRA, deficiency of the IL-1 receptor antagonist; LoE: 1a: systematic review of randomized controlled trials (RCTs); 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (including low-quality RCT); 3a: systematic review of case-control studies; 3b: individual case-control study; 4: case-series (and poor-quality cohort and case-control studies); 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'; GoR: A: based on consistent level 1 studies; B: based on consistent level 2 or 3 studies or extrapolations from level 1 studies; C: based on level 4 studies or extrapolations from level 2 or 3 studies; D: based on level 5 studies or on troublingly inconsistent or inconclusive studies of any level; LoA: level of agreement; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Points to consider 1-14 focus on the diagnosis of IL-1 mediated SAID, including recognizing clinical and damage features of the respective diseases, genetic testing, disease-specific clinical and laboratory work up and initiation of early treatment.

Disease-specific clinical features for untreated CAPS, TRAPS, MKD and DIRA and the resulting organ damage have been characterized in clinical descriptions of patient cohorts before anti-IL-1 treatment was used in patients with all 4 diseases[13 19 67 68]. These signs and symptoms have been used for evidence-based classification criteria for CAPS, TRAPS and MKD[37] and are listed in Table 2 recommendations 8 (CAPS), 10 (TRAPS), 11 (MKD) and 13 (DIRA) respectively. These features in combination with the molecular analyses help physicians in recognizing the disease-specific features and in differentiating these conditions from clinically complex diseases that can present with overlapping inflammatory disease manifestations, including systemic JIA, adult-onset Still's disease, neoplasms, infections, and autoimmune disorders[69 70].

Genetic work up: Points to consider 2-6

Suggestive clinical features should trigger a genetic work up, as a genetic diagnosis needs to be established for and accurate diagnosis of CAPS, TRAPS, MKD and DIRA[37 71]. Next generation sequencing (NGS) is generally recommended and largely replacing historical gene-by gene Sanger sequencing approaches[51 52 69 72 73]. In certain conditions, especially when the clinical suspicion is high, Sanger sequencing of a single gene may be cost-effective in patients with known familial disease or classic disease features, and may be the only modality for genetic testing that is available[51 74-77].

CAPS and TRAPS are autosomal dominant diseases caused by gain-of-function mutations in *NLRP3* and *TNFRSF1A*[14], respectively and can be familial[69 78] or caused by *de novo* mutations, that in CAPS are most frequently found in patients with severe phenotypes[79]. Somatic mutations in patients with CAPS or TRAPS phenotypes may be undetected by standard coverage of NGS and may require deep sequencing[46 50 78 80 81]. In contrast, MKD and DIRA are caused by recessive

loss-of-function mutations in *MVK*[82 83] and *IL1RN*[19], respectively. In patients with suggestive clinical symptoms of MKD or DIRA, Sanger sequencing as well as WES and WGS may not detect large deletions[19]. Therefore, gene deletions should be carefully screened for, if needed, using chromosomal microarray analysis (CMA) by comparative genomic hybridization (CGH) array or by single nucleotide polymorphism (SNP) array[19]. For the genetic diagnosis of DIRA, PCR and sequencing using specific deletion breakpoint primers for the screening of reported *IL1RN* large deletions in selected ethnic backgrounds (i.e. Puerto Rico, Brazil, India) may aide the genetic evaluation[19 84 85]. If a genetic diagnosis cannot be made, patients should be referred to tertiary centers with expertise in managing patients with SAID.

One significant challenge for the diagnosis of SAID is the interpretation of genetic results that have not been classified or validated as pathogenic mutations including variants of unknown significance (VUS) that have not been described previously or studied functionally, or likely benign variants that may be present in the general population and could be low penetrance mutations with inconsistent clinical significance. Patients with these genetic findings may display distinct clinical and biologic phenotypes, including IL-1β and non-IL-1β-mediated inflammatory pathway activation, which has clinical implications for their management.

Clinical work up: Points to consider 7-14

Patients present with systemic inflammation that typically accompanies clinical signs and symptoms and can be episodic/periodic or chronic/persisting [67 86]. MKD, TRAPS and the mildest form of CAPS, known as familial cold autoinflammatory syndrome (FCAS) may in rare cases present with intermittent episodes separated by periods of perceived well-being [2 13 37 71 87 88]. However, most of these patients have evidence of chronic subclinical inflammation between episodes. Patients with more severe CAPS such as Muckle-Wells Syndrome (MWS) or neonatal-onset multisystem inflammatory disease/chronic infantile neurologic cutaneous articular syndrome (NOMID/CINCA), or with severe MKD and almost complete absence of the enzymatic activity of mevalonate kinase, or with DIRA all present with chronic systemic inflammation that

almost never spontaneously remits and correlate with disease symptoms[9 46 89 90]. Historically, hsCRP, ESR, and if available SAA[43] have been used in assessing systemic inflammation. Additionally, S100 proteins[91] have been used in some countries as sensitive markers in research settings, but their use in clinical settings requires further validation. Hepatosplenomegaly can be present in patients with severe systemic inflammation. The diagnostic work-up across all four diseases is broadly similar and can be synchronized. Typical signs and symptoms of active disease, organ inflammation and damage should prompt a diagnostic work up (Table 2 and 6).

The CAPS disease spectrum features include urticaria-like rash with histologic features of a neutrophilic dermatosis involving eccrine glands as well as systemic inflammation that is present in almost all patients[9 21 39 46 90 92-94]. Cold-induced flares often last less that 24 hours and are observed in patients at the mild end of the disease spectrum (FCAS)[10 38]. A negative localized cold challenge (ice cube test) is observed in patients with CAPS-FCAS differentiating them from patients with cold urticaria[38]. Progressive sensorineural hearing loss is often seen in moderately (CAPS-MWS) and severely (CAPS-NOMID/CINCA) affected patients[11 21 46 64] while neurologic findings (chronic aseptic meningitis, increased intracranial pressure, cognitive impairment[89 95] and skeletal abnormalities (distal femur overgrowth, frontal bossing) are typically seen in CAPS-NOMID/CINCA[9 46]. Ophthalmologic involvement can vary and most typically include conjunctivitis, but keratitis, episcleritis, anterior and posterior uveitis have been described. Increased intracranial pressure may cause papillary edema and subsequent optic disc atrophy. Therefore, a slit lamp exam and retinal evaluation should be performed in all patients at baseline[8 39 90]. In patients with suspected neurologic involvement, brain imaging[24 96 97] and lumbar puncture may be needed to evaluate for elevated intracranial pressure or aseptic meningitis, while specialized brain MRI can detect cochlear enhancement, cerebral atrophy and ventriculomegaly[89 98]. Epiphyseal bony overgrowth especially of the knees is assessed by bone MRI or x-ray[8 22 94].

TRAPS is characterized by fever episodes lasting more than 7 days, abdominal pain that can mimic an acute abdomen, variable chest pain and, rarely, testicular pain[13 37 73]. Especially in

adults, a sub-chronic disease course might be observed, with fatigue, leg pains and persistent slight elevation of acute phase reactants[13]. Typical findings include migratory tender skin plaques with hazy edges that are erythematous, swollen and warm[99] and affect predominantly the upper and lower limbs. Periorbital edema and myalgias that might herald the onset of an attack and correlate with fasciitis imaged on MRI can also occur[100]. There is now a general consensus that variants of unknown significance, such as R92Q should not be considered as pathogenic [13 41 101-106]. Therefore, the interpretation of these variants should occur in the context of the inflammatory phenotype by an expert in the field if available.

Patients with MKD present, usually in the first year of life[107 108], with recurrent episodes of fever usually lasting 4 to 6 days[108] that are associated with gastrointestinal symptoms (severe abdominal pain with vomiting and diarrhea), cervical lymphadenopathy, aphthous stomatitis, skin rash (urticarial or maculopapular)[27 56 70 87 109-113]. The most severe form of MKD, namely mevalonic aciduria presents with severe cognitive impairment, and chronic inflammation along with the clinical features described above[56 87 114]. Febrile attacks triggered by vaccinations suggest a diagnosis of MKD[67 88 115-118].

High levels of circulating immunoglobulin D that were described early and even led to the name Hyper IgD syndrome, have low sensitivity and specificity for MKD, and are no longer recommended in the diagnostic work-up[86 109 119 120]. However, elevated urine mevalonate levels during disease flares, due to reduced MVK enzyme activity and accumulation of mevalonic acid, are more specific for MKD[121 122].

DIRA patients classically present with early-onset pustular rashes that can be triggered by mechanical stress (pathergy), sterile osteomyelitis, and nail changes (onychomadesis)[19 123]. Although the inflammatory markers are typically highly elevated, fever may be absent. Vertebral involvement can include odontoid osteomyelitis resulting in destruction and neck instability, vertebral block formation and gibbus-like spinal changes that need to be screened for by MRI or CT[19 123]. In contrast with patients with CAPS, TRAPS and MKD, patients with DIRA rarely present

with flare-associated fever episodes. In patients with presumed DIRA, a diagnostic workup includes assessment of peripheral neutrophilia and elevated inflammatory markers, determination of bone involvement (i.e. x-ray or bone MRI) and genetic testing[19 123]. The differential diagnosis for DIRA should include CRMO[124 125], SAPHO[126] and pustular psoriasis[127] and include genetic testing for the many genetic causes including *LPIN2, FGR, FBLIM1* for CRMO[128 129] and *CARD14 for CARD14* Mediated Psoriasis (CAMPS)[130 131]*, IL36RN for* Deficiency of IL-36 Receptor Antagonist (DITRA)[130 131]*, AP1S3*[131] for other pustular psoriasis and *MEFV* for Pyrin-Associated Autoinflammation with Neutrophilic Dermatosis (PAAND)[132] related mutations.

Table 2 Points to consider for the diagnosis of CAPS, TRAPS, MKD and DIRA				
		LoE	**GoR**	**LoA (%)**
1	Patients with clinical symptoms of CAPS, TRAPS, MKD and DIRA who do not carry any of the disease-causing mutations described here should be referred to specialty/research centers that can guide further work up and treatment.	**5**	**D**	9.4±1
Genetic Work up				
2	Genetic testing[1] using a NGS platform[2], if available, should be used to make a genetic diagnosis. • Sanger sequencing of targeted genes known to cause CAPS (NLRP3), TRAPS (TNFRSF1A), MKD (MVK) and DIRA (IL1RN) can be used if the clinical suspicion is strong or to validate NGS.	**4**	**D**	9.4±1.1
3	Deep sequencing in patients with CAPS and TRAPS may be needed to detect some somatic mutations that may not be identified by standard NGS or Sanger sequencing.	5	D	9.5±1.1
CAPS specific				
4	Patients with low penetrance variants in *NLRP3* may present with clinical manifestations different from CAPS; their treatment response and prognosis may differ from "canonical" CAPS.	5	D	9.4±1.2
TRAPS specific				
5	Patients with low penetrance variants in *TNFRSF1A* (i.e.R92Q) may present with clinical manifestations different from TRAPS and their treatment response and prognosis may differ from "canonical" TRAPS.	2	B	9.5±1.2
DIRA specific				
6	In patients with DIRA, Sanger sequencing as well as WES or WGS may not detect large deletions in *IL1RN,* thus complicating a genetic diagnosis. • In cases with a high clinical suspicion of DIRA and negative Sanger Sequencing or WES/WGS, chromosomal microarray analysis (CMA) is recommended for the detection of large deletions. • The use of deletion-specific primer in countries with founder variants that include large deletion may also be recommended.	3	B	9.3±1.2
Clinical Workup				
7	The clinical work up of systemic inflammation should include hsCRP, ESR and CBC and differential; if available SAA and S100 proteins may be assessed. • Older patients with long-standing untreated systemic inflammation need to be screened for the presence of amyloidosis.	5	D	9.7±0.6

CAPS Specific				
8	The following clinical features in the presence or absence of autosomal dominant inheritance should prompt consideration of a diagnostic workup of CAPS: • urticarial rash, • cold/stress-triggered episodes, • sensorineural hearing loss, • chronic aseptic meningitis, • skeletal abnormalities	2	B	9.8±0.5
9	The initial diagnostic work-up should include an audiogram and an ophthalmologic exam. Lumbar puncture and a head MRI should be performed if clinically indicated.	5	D	9.8±0.5
TRAPS Specific				
10	The following clinical features should prompt consideration of a diagnostic workup of TRAPS: • long lasting fever episodes, • migratory rash, • periorbital edema, • myalgia, • a positive family history	2	B	9.8±0.5
MKD Specific				
11	The following clinical features should prompt consideration of a diagnostic workup of MKD: • age at onset < 1 year, • gastrointestinal symptoms, • painful lymph nodes, • aphthous stomatitis, • a history of triggers of the periodic fever attack (i.e post-vaccination), and • a maculopapular rash should prompt diagnostic work up for MKD	2	B	9.8±0.5
12	In patients with unexplained/undifferentiated inflammatory diseases, the presence of mevalonate in urine should prompt further diagnostic work up for MKD	4	C	9.5±0.7
DIRA Specific				
13	The following clinical features particularly if occurring sporadically should prompt consideration of a diagnostic workup of DIRA: • pustular-psoriasis like rashes, • osteomyelitis (i.e. CRMO-like disease, rib flaring and cloaking of the femoral head, odontoid lesions/osteomyelitis • absence of bacterial osteomyelitis, • nail changes (i.e. onychomadesis)	5	D	9.6±0.8

14	For patients with suspected DIRA, X-rays of chest and upper and lower limbs and/or MRI/CT to assess the spine including odontoid should be included in the diagnostic work up to assess the extent of the inflammatory bone involvement. A dermatology consult and skin biopsy should be considered as the presence of neutrophilic dermatosis with exocytosis of neutrophils and subcorneal pustules is highly suggestive of DIRA.	5	D	9.7±0.8

CAPS, cryopyrin-associated periodic syndromes; TRAPS, tumour necrosis factor receptor associated periodic syndrome; MKD, mevalonate kinase deficiency; DIRA, deficiency of the IL-1 receptor antagonist; LoE: 1a: systematic review of randomized controlled trials (RCTs); 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (including low-quality RCT); 3a: systematic review of case-control studies; 3b: individual case-control study; 4: case-series (and poor-quality cohort and case-control studies); 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'; GoR: A: based on consistent level 1 studies; B: based on consistent level 2 or 3 studies or extrapolations from level 1 studies; C: based on level 4 studies or extrapolations from level 2 or 3 studies; D: based on level 5 studies or on troublingly inconsistent or inconclusive studies of any level; LoA: level of agreement; CNS, central nervous system; COVID-19, Coronavirus disease 2019; CRP, C-reactive protein; CSF, cerebrospinal fluid; CT, computerized tomography; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; NA, not applicable;

Points to consider 15-24 focus on treatment of IL-1 mediated diseases.

Disease management involves a shared decision-making approach and a combination of pharmacologic and non-pharmacologic approaches. The current standard of care for patients with CAPS, TRAPS, MKD, and DIRA is injectable IL-1 targeted biologic therapy when available[24 48 133-135]. While the specific pharmacologic mechanisms, pharmacokinetics, availability, and disease indications differ for each of the 3 available drugs, anakinra (Kineret^{R}), rilonacept (Arcalyst^{R}) and canakinumab (Ilaris^{R}), all block the effect of IL-1β alone (anakinra, rilonacept and canakinumab) or in addition to IL-1α (anakinra and rilonacept) on IL-1 receptor downstream signaling resulting in improved symptom control and reduced systemic and tissue/organ inflammation. The availability of these drugs varies significantly between different countries. Anakinra is a recombinant IL-1 receptor antagonist with a short half-life that binds to the IL-1 receptor and blocks both IL-1α and IL-1β signaling[47 97 136 137]. Rilonacept is a recombinant fusion protein with a relatively longer half-life that binds to both IL-1α and IL-1β[133 138 139] . Canakinumab is a human monoclonal antibody to IL-1β with a long half-life[48 134 140 141]. Pivotal studies including a randomized study in CAPS[142 143] (MWS and FCAS), in TRAPS and MKD[62] and others which have confirmed with a high level of evidence that the anti–interleukin-1β monoclonal antibody was efficacious in controlling and preventing flares in patients with CAPS[142] and with MKD and TRAPS[62] respectively.

Treatment aims are early control of diseases activity, prevention of disease and treatment related damage and optimal health-related quality of life (HRQoL)[55 62]. The target of treatment is complete remission. In the absence of a consensus definition of remission or minimal disease activity for these diseases, remission has been defined for clinical studies and clinical monitoring as absence of clinical symptoms and normal inflammatory markers. The instruments used to measure disease activity include daily diary scores[24 97] or AIDAI score <9[61], and a PGA and PPGA of <1/10cm) and for inflammatory markers CRP less than 10mg/L or less than 5mg/L have most commonly

been used [62]. Minimal disease activity has suggested to be used as alternative target if remission cannot be achieved. Definitions of remission and minimal disease activity and their validations are on the research agenda for autoinflammatory diseases[61 62].

Treat-to-target strategies are effective in many inflammatory diseases and [32] are used in the treatment of patients with IL-1 mediated autoinflammatory diseases to find individualized and optimal dosing regimens for each patient and disease. Control of inflammation in the absence of corticosteroids is archived with IL-1 blocking therapies[62 136 144]; treatment can retard or even prevent development or progression of organ damage in patients with moderate or even severe disease activity[64 97 145]. This is best achieved in a multidisciplinary team that included subspecialists and resulted in better disease control in patients with CAPS[32]. To achieve and maintain optimal disease control, IL-1 blocking treatment needs to be administered continuously in most patients and should be adjusted frequently. On demand regimens may be used in selected patients with MKD, TRAPS and FCAS who have very mild disease and/or episodic disease manifestations and who maintain normal inflammatory markers in between treatment[146 147]. Dose adjustments for weight gain and growth and higher mg/kg doses to optimize treatment regimens may be required and needs to be individualized for each patient[32 97]. Patients with severe disease manifestations including severe NOMID may require frequent adjustments and higher doses than patients with less severe diseases (Table 4)[32 97 143]. Patients with *NLRP3* variants that have not been validated as pathogenic may respond to IL-1 blockade and specific recommendations have previously been published[30 148]. NSAIDs may be efficacious for initial, partial symptomatic control, when used together with IL-1 targeted therapy to improve control of some symptoms. The long-term use of all three IL-1 blockers (anakinra, rilonacept, and canakinumab) in CAPS have been demonstrated ongoing efficacy and a beneficial long-term safety profile, although direct comparative studies are lacking among them [40 48 133 136 138-141 149-154]. There is a potential clinical advantage of using anakinra for severe CAPS patients, especially those with neurologic

disease[155 156] and strong evidence for the use of anakinra and rilonacept in DIRA[19 84 85 123] with those two drugs having the advantage of blocking both IL-1α and IL-1β.

A large body of evidence suggests that IL-1 inhibitors should be considered as treatment of choice for TRAPS[103]. Although anakinra was the first IL-1 blocker that was successfully used in TRAPS patients in small series and observational registries[103 134 145 157], the long-acting anti-IL-1β monoclonal antibody, canakinumab is currently the only IL-1 blocker that has been approved by the FDA and EMA for treatment of patients with TRAPS. Individual patients with TRAPS may respond to treatment with etanercept or short-term glucocorticoids. Responses often wane and should be monitored with a view to change the treatment if required[41 103 158]. Disease control in patients carrying *TNRFS1A* variants that are not validated as pathogenic (i.e. D12E, I28S, P46L, R92Q, N116S) can be challenging, and escalating therapy including the addition of colchicine or other biologics may be needed to control inflammatory symptoms[103].

The IL-1 blocking therapy, including anakinra and canakinumab, have been employed in children with MKD with success, but only canakinumab has been evaluated in a randomized study, and is approved by FDA and EMA[62 146]. Some MKD patients wtih milder disease phenotype characterized by occasional attacks separated by symptom-free periods can be managed wtih on-demand treatment [146]. Glucocorticoids can also be beneficial during flares but their extended use is limited because of side-effects[146]. The panel suggested the use of anti-IL 1, but noted that treatment could be switched to anti-TNF agents, if anti-IL1 treatment is not available or not effective[146].

Recently the FDA approved anakinra and rilonacept for treatment of DIRA. Both drugs block IL-1α and IL-1β; Blocking IL-1a seemed necessary to completely block bone inflammation in a patient who developed osteitis on canakinumab, which only blocks IL-1β[124]. While anakinra has been used in all patients initially to achieve disease control, rilonacept can be used to maintain remission[123]. Overall doses for disease controls in DIRA are lower than in severe CAPS-

NOMID/CINCA and long-term sustained and complete remission is an achievable goal of treatment.

Overall, individualized dose adjustments for IL-1 blocking agents in patients with severe disease or early in life may be necessary. Particularly in infants twice a day (bid) dosing of anakinra is sometimes needed. This is thought to be due to the higher liver blood flow in infants and preschool children compared with adults which increases the hepatic clearance of drugs owing to the larger ratio of liver to total body mass[159]. However, some older patients with severe and difficult to control disease including CNS disease may also achieve improved disease control on bid dosing.

Table 3 Points to consider for the treatment of CAPS, TRAPS, MKD and DIRA				
		LoE	**GoR**	**LoA (%)**
15	IL-1 blocking therapy has become the treatment of choice and a therapeutic trial with IL-1 blocking treatment may be started when a strong clinical suspicion of a diagnosis of either CAPS, TRAPS, MKD or DIRA is entertained.	4	C	9.5±0.9
16	In the context of viral infections, including COVID-19, IL-1 blocking therapy should not be altered, as stopping treatment may lead to rebound inflammation.	4	C	9.5±0.8
CAPS Specific				
17	Treatment with IL-1 blockers is recommended standard of care and currently includes anakinra[1], canakinumab[2] and rilonacept[3].	[1]2 [2]1 [3]1	A B B	9.9±0.3
18	Anakinra may be the most effective anti-IL-1 treatment for CNS disease.	2	B	9.6±0.8
19	Higher and more frequent dosing with IL-1 blockers may be required to control disease activity in more severe cases and/or younger children to prevent complications. Less frequent dosing may be appropriate for patients with milder disease.	1	B	9.8±0.5
TRAPS Specific				
20	Anti-IL-1 drugs are more effective than traditional DMARDS and other biologic DMARDS in achieving disease remission and preventing long-term complications.	4	C	9.6±0.9
MKD Specific				
21	In children with MKD, IL-1 blocking therapy is generally required. In patients without chronic systemic inflammation, on demand IL-1 blockade should be attempted at the onset of flares.	4	C	9.4±1.0
22	If anti-IL1 is not effective or available, then anti-TNF agents should be considered.	1/3	B/B	9.3±0.9
23	Glucocorticoids on demand may be effective in treating acute flares, however frequent or long-term use is limited by side effects.	2	B	9.3±1.0
DIRA Specific				
24	In patients with DIRA, treatment with the IL-1α and IL-1β blocking agents, anakinra and rilonacept has shown benefit in controlling disease flares and in preventing long-term complications.	4	C	9.6±0.8

CAPS, cryopyrin-associated periodic syndromes; TRAPS, tumour necrosis factor receptor associated periodic syndrome; MKD, mevalonate kinase deficiency; DIRA, deficiency of the IL-1 receptor antagonist;LoE: 1a: systematic review of randomized controlled trials (RCTs); 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (including low-quality RCT); 3a: systematic review of case-control studies; 3b: individual case-control study; 4: case-series (and poor-quality cohort and case-control studies); 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles';GoR: A: based on consistent level 1 studies; B: based on consistent level 2 or 3 studies or extrapolations from level 1 studies; C: based on level 4 studies or extrapolations from level 2 or 3 studies; D: based on level 5 studies or on troublingly inconsistent or inconclusive studies of any level; LoA: level of agreement; CNS, central nervous system; COVID-19, Coronavirus disease 2019; CRP, C-reactive protein; CSF, cerebrospinal fluid; CT, computerized tomography; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; NA, not applicable;

Table 4. Approved treatments and doses

Disease	Treatment	Recommended dosing	FDA	EMA	LoE
CAPS					
• FCAS	Canakinumab	2-4 mg/kg/q8w*	+	+	**1B**
	Rilonacept	2.2 or 4.4mg/kg/q1w	**+**	-	**1B**
	Anakinra	1.5-3mg/kg/day	-	**+**	**NA**
• MWS	Canakinumab	2-4 mg/kg/ q8w*	+	+	**1B**
	Rilonacept	4.4mg/kg/q1w	**+**	-	**1B**
	Anakinra	2.5-5mg/kg/day	-	**+**	**2B**
• CINCA/NOMID	Anakinra	4.5-10mg/kg/day	+	+	**2A**
	Canakinumab	2-8 mg/kg/ q8w*	-	+	**1B**
TRAPS	Canakinumab	2-4 mg/kg/q4w**	+	+	**1B**
MKD	Canakinumab	2-4 mg/kg/q4w**	+	+	**1B**
DIRA	Anakinra	2-4 mg/kg/day	+	-	**4C**
	Rilonacept	2.2 or 4.4mg/kg/q1w	+	-	**4C**

CAPS, cryopyrin-associated periodic syndromes; TRAPS, tumour necrosis factor receptor associated periodic syndrome; MKD, mevalonate kinase deficiency; DIRA, deficiency of the IL-1 receptor antagonist; FCAS, Familial cold autoinflammatory syndrome; MWS, muckle-wells syndrome; CINCA, Chronic infantile neurologic cutaneous articular syndrome; NOMID, neonatal onset multisystem inflammatory disease FDA, US Food and Drug Administration; EMA, European Medicines Agency LoE: 1a: systematic review of randomized controlled trials (RCTs); 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (including low-quality RCT); 3a: systematic review of case-control studies; 3b: individual case-control study; 4: case-series (and poor-quality cohort and case-control studies); 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'

Points to consider 25-33 focus on monitoring of IL-1 mediated SAID CAPS, TRAPS, MKD and DIRA

Long term management includes adjustment of pharmacologic therapy, monitoring of disease activity and development of disease related complications and drug toxicity and are required long term. Additionally, individual focus on the needs of the growing child, young adolescent, adult or even senior citizen and should include age-appropriate measures that foster self-management skills, encourage shared medical decision-making, address reproductive health issues and facilitate an early and effective transition to adult medical care[8 33-35].

Appropriate management of patients with SAID necessitates a multidisciplinary team of local primary care givers working together with experienced physicians including local primary care givers, rheumatologists and/or immunologists and other specialists on a case-by case basis that can include, but is not limited to ophthalmologists, otolaryngologists, nephrologists and genetic

counsellors, as well as physiotherapists, occupational therapists and psychosocial specialists[33 34 66].

Long-term monitoring requires adjustment of IL-1 blocking treatment to maintain long-term control of systemic and organ-specific inflammatory manifestations including adequate treatment adjustments to meet the needs of each age group[48 133 136 137 141 154]. Disease-specific monitoring plans take into account the different disease manifestations in CAPS, TRAPS, MKD and DIRA and are outlined in Table 5. Systemic inflammation should be monitored by following inflammatory markers including peripheral neutrophilia[160], hsCRP and ESR. SAA and S100 protein may be used as inflammatory markers where available and were internal normalized values are available[41 134].

Complications related to chronic systemic inflammation can have significant effects on growth and development in children, adolescents and adults and ongoing inflammation may predispose to amyloidosis[8 23]. Although amyloidosis has become less frequent with the initiation of early anti-IL-1 treatment, adults who have had long-standing uncontrolled disease should be closely monitored[48 103 142]. The task force recommended in patients with IL-1 mediated AID, proteinuria should be tested every six months, particularly in patients with a positive family history of amyloidosis.

In CAPS patients, hearing loss, CNS disease, bone deformities, renal failure due to amyloidosis and visual loss are the most serious organ manifestations[68]. Prevention or halt of progress are therapy challenges along with the achievement of the best possible quality of life[34].

TRAPS is distinguished from other monogenic and multifactorial recurrent fevers (FMF, MKD, PFAPA, CAPS) by long lasting fever episodes, a characteristic migratory and painful rash and an autosomal pattern of inheritance. Over time, TRAPS patients may progress into a more chronic disease course with a persistent and indolent inflammation in the absence of the typical fever episodes. This condition may still represent an important risk factor for the development of AA amyloidosis[23].The recurrence of long-lasting fever episodes with the consequent impact on the

quality of life and the risk of long-term complications, such as AA amyloidosis, represent an indication for long-term treatment with biological DMARDs[134 145].

Rare MKD-associated manifestations include retinopathy pigmentosa and hearing loss. Therefore, ophthalmologic evaluations and audiograms should be included as clinically indicated[27 42 67 121]. Secondary hemophagocytosis in the context of infections has been reported and should be considered in the context of severe disease flares[42 67 86] .

Patient reported outcomes including health related quality of life can help in monitoring disease symptoms and relevant instruments include AIDAI for CAPS, TRAPS and MKD[57 60 61 103 151 161] (Table 6). Questions regarding performance at school and workplace as well as recording missing school/workdays are useful for assessing burden of disease[66] .

The safety profile for IL-1 blocking treatment has generally been favorable. However, monitoring for infection, specifically respiratory tract infections with *Streptococcus pneumoniae* and skin infections due to *Staphylococcus* is recommended[62]. Even if in some conditions, such as MKD, vaccine could lead to a disease flare, patients should receive vaccinations in accordance with regional recommendations [162] . It is recommended that patients who are on anti-IL-1 targeted therapy or planning to start IL-1 blocking therapy receive pneumococcal vaccinations. Prior to starting is preferable but it is also acceptable to administer these vaccines while receiving anti-IL-1 targeted therapy[48] since there is preliminary data suggesting that an adequate antibody response to vaccines occurs in patients on canakinumab[48]. There is concern related to the use of pneumococcal vaccines, particularly the polysaccharide vaccine (Pneumovax®) in CAPS patients due to several reports of significant local and systemic reactions[48 163]. Ribonucleic acid (RNA) based SARS-Cov-2 vaccines are not live vaccines, suggesting that they may be safe for immunosuppressed patients. Whether vaccines against COVID-19 have the potential to provoke a disease flare is unknown, theoretical concerns about disease flare in IL-1 mediated AID caused by RNA vaccines exist; again, however, there are currently no data to base any recommendations regarding this specific issue.

Data on IL-1 treatment in pregnancy is limited[35 103 164]. In women with IL-1 mediated SAID who require biological treatment and are considering pregnancy, a risk benefit discussion should be held before conception and include the risk of untreated disease to mother and baby against the risk of continuing biologics. At present, regulatory advice and clinical case series support the use of anakinra rather than any other anti -IL-1 agent in pregnancy[103].

Children with SAID need continuous and developmentally appropriate care during and beyond adolescence. However, the literature informs us that currently up to half of the youth do not make a successful transfer to adult specialist care and are therefore at particular risk of unfavorable outcomes. Particularly relevant for this group are complications related to amyloidosis, hearing loss, and vision loss.

Table 5 Points to consider for the monitoring of CAPS, TRAPS, MKD and DIRA				
		LoE	**GoR**	**LoA (%)**
25	Disease activity and burden of disease should be monitored regularly depending on disease activity and severity, often requiring a multidisciplinary team. • Symptom control can be monitored with validated tools that asses disease-specific symptoms, with patient reported outcome and quality of life assessments and by recording missing school or work days. • The frequency of the follow up evaluations should be tailored to disease severity and clinical needs.	5	D	9.7±0.6
26	Growth and development of children should be monitored at each visit	5	D	9.9±0.3
27	Systemic inflammation should be monitored by following inflammatory markers including peripheral neutrophilia, hsCRP and ESR. SAA and S100 protein may be used as inflammatory markers where available.	5	D	9.8±0.5
28	Systemic inflammation may predispose to the development of amyloidosis and patients should be monitored for the development of amyloidosis by monitoring proteinuria and microalbuminuria.	5	D	9.8±0.5
29	Physicians should be aware of the increased risk of infections in patients with IL-1 targeted therapy, including respiratory tract infections with Streptococcus pneumoniae and skin infections due to Staphylococci.	1	B	9.8±0.4
30	Patients should receive immunizations, in particular live-attenuated vaccines, in accordance with their regional policy, prior to beginning anti-IL-1 targeted therapy when possible.	5	D	9.2±1.4
CAPS Specific				
31	Monitoring of organ damage should be established based on disease manifestations and can include monitoring of hearing loss, eye disease, aseptic meningitis, CNS disease and bone disease.	5	D	9.7±0.6
32	Patients with CNS and/or bone involvement should be assessed for the development of developmental delay, the development of bone deformities and the development of limb-length discrepancies	5	D	9.7±0.6
DIRA Specific				
33	In patients with DIRA, normalization of acute phase reactants and absence of inflammatory skin and bone findings is required to determine the adequate dose of IL-1 blocking treatment, and to monitor disease activity long-term.	5	D	9.5±0.8

CAPS, cryopyrin-associated periodic syndromes; TRAPS, tumour necrosis factor receptor associated periodic syndrome; MKD, mevalonate kinase deficiency; DIRA, deficiency of the IL-1 receptor antagonist;LoE: 1a: systematic review of randomized controlled trials (RCTs); 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (including low-quality RCT); 3a: systematic review of case-control studies; 3b: individual case-control study; 4: case-series (and poor-quality cohort and case-control studies); 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles';GoR: A: based on consistent level 1 studies; B: based on consistent level 2 or 3 studies or extrapolations from level 1 studies; C: based on level 4 studies or extrapolations from level 2 or 3 studies; D: based on level 5 studies or on troublingly inconsistent or inconclusive studies of any level; LoA: level of agreement; CNS, central nervous system; COVID-19, Coronavirus disease 2019; CRP, C-reactive protein; CSF, cerebrospinal fluid; CT, computerized tomography; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; NA, not applicable;

Table 6. Disease specific monitoring of the IL-1 mediated AID, CAPS, TRAPS, MKD and DIRA

Monitoring Table		
For all diseases systemic inflammation needs to be monitored		
A. Monitoring of systemic inflammation in all diseases		**Frequency**
	ESR, CRP, CBC+Diff (granulocytosis), S100 proteins and SAA where available, hepatosplenomegaly and lymphadenopathy, fatigue	each visit
	Urinalysis to monitor proteinuria (amyloidosis)	Every 6-12 months
	Monitor growth, BMD, sexual development	each visit as indicated
B. Monitoring of disease-specific symptoms* and patient related outcomes		**each visit**
CAPS	Fever, rash (urticaria-like), progressive hearing loss, headaches, early morning nausea and vomiting, musculoskeletal symptoms, conjunctivitis, cognitive development (severe disease)	each visit
TRAPS	Fever, rash (migratory), periorbital edema, pain (abdomen, chest, testicular), myalgia	each visit
MKD	Periodic fever attacks (including triggered post vaccination), rash (urticarial or maculopapular), gastrointestinal symptoms (abdominal pain, diarrhea, vomiting), cervical lymphadenopathy, aphthous stomatitis, cognitive impairment in severe cases	each visit
DIRA	Pustular-psoriasis like rashes (pathergy), musculoskeletal (bone) pain (caused by osteomyelitis), nail changes	
Patient related outcomes for all 4 diseases	QoL, PGA, PPWA, missing school-/workdays	each visit
C. Monitoring of organ manifestations/damage		
CAPS		
Amyloidosis	Urinalysis	each visit

Hearing loss	Audiogram	3-6 months till stable then every 6-12 months
Eye disease	Ophthalmologic exam (vision, retina evaluation and slit lamp exam)	6-12 months
CNS disease	Lumbar puncture, head MRI (with special evaluation of cochlea, cerebral atrophy and ventriculomegaly)	12-36 months depending on symptoms
Bone deformity	Bone MRI, scanogram to monitor limb length, epiphyseal overgrowth	12-36 months depending on symptoms
TRAPS		
Amyloidosis	Urinalysis	each visit
Bone deformity	Bone MRI, X-Ray	12-36 months depending on symptoms
MKD		
Amyloidosis	Urinalysis	each visit
Eye disease	Ophthalmologic exam	as needed
Neurologic involvement	Neuropsychological testing	as needed
DIRA		
Spinal and bone deformities	Neck, spine MRI (vertebral osteomyelitis), bone x-ray/MRI, corrective surgery or spinal fusion	as needed
D. Monitoring of treatment related complications (IL-1 blocking treatments)		
Infections	Clinical history, skin infections, other infections	
Laboratory work	CBC+Diff, LFTs, Urinalysis, renal function, Lipid profile	

* The following instruments can be used for symptom monitoring: …….(AIDAI), for damage assessment the autoinflammatory disease damage index ….(ADDI), for quality of life (QoL), physician global assessment (PGA),…..(PPWA)

CAPS, cryopyrin-associated periodic syndromes; TRAPS, tumour necrosis factor receptor associated periodic syndrome; MKD, mevalonate kinase deficiency; DIRA, deficiency of the IL-1 receptor antagonist; CNS, central nervous system; COVID-19, Coronavirus disease 2019; CRP, C-reactive protein; CSF, cerebrospinal fluid; CT, computerized tomography; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; NA, not applicable;

CONCLUSION

The task force aims to raise awareness and to assist specialists or primary health care providers involved in the management of patients with IL-1 mediated SAID. These points to consider attempt to address the unmet needs for guidance on the basis of EULAR and ACR consensus procedures for the diagnosis, management and the treatment of SAID which include CAPS, TRAPS, MKD and DIRA. Unfortunately, most medical curricula and training in many tertiary medical centres do not cover the identification and management of these rare conditions. The consequence is that many physicians, including rheumatologists, lack the knowledge for optimal management of these patients. In recent years we have learned more about the extent of the phenotype and pathogenesis of SAID. This enables us to be more efficient with diagnosis and management of these diseases.

The panel has also highlighted the distinguishing clinical features of SAID in the suggested recommendations. The task force included specialists with broad expertise in relevant disease and representing different countries, disease interests, and practice environments. Due to the rarity of these disorders, statements have often been developed based on low level of evidence and mainly on expert opinion which will likely require updates regularly, including in the next few years. Multi-centre collaborative efforts, prospective registries and randomized trials will help to define the optimal treatment strategies to relieve patient symptoms. The panel also suggests areas for future research:

Research Agenda
• To set up specific transition clinics for these rare disorders to optimize the treatment strategies and care for patients with SAID
• To evaluate best treatment options during pregnancy and its effect on the newborn
• To establish biobanks for biomarker studies to validate best markers to show disease related activity and severity
• To evaluate the effect of vaccination in triggering or exacerbating disease activity in patients with IL-1 mediated SAID while on or off treatment with biologic DMARDS and/or glucocorticoids.
• To identify novel therapeutic targets and treatments
• To establish multicentre collaborative efforts for prospective registries

- To describe better phenotype-genotype correlations
- To define long term outcomes of related diseases
- To assess long term safety of biologics in IL-1 mediated disorders
- To develop disease specific outcome instruments for measuring disease activity and severity
- To understand pathophysiology of IL-1 related disorders
- To develop validated remission criteria for each disease including patient reported outcome measures
- To develop minimal disease activity criteria, response criteria
- To understand additional factors (epigenetics, environment) defining the disease course

Author affiliations

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