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Recommendations

EULAR/PReS endorsed recommendations for the management of familial Mediterranean fever (FMF): 2024 update

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ARTICLE INFO

ABSTRACT

Objectives: Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease despite being a rare disease for many rheumatologists. These evidence-based recommendations update the ones issued in 2016 to account for the recent developments in the field and aim to guide rheumatologists and other health professionals in the treatment and follow-up of patients with FMF.

Methods: A multidisciplinary panel was assembled, including rheumatologists, internists, paediatricians, a nephrologist, an occupational therapist, a physiotherapist, 2 methodologists, and 2 patient representatives, all from the Eastern Mediterranean area and Europe. Several systematic reviews were performed on the pharmacological treatment of FMF and its complications. The previous recommendations were revised considering the updated evidence, and the new levels of evidence were incorporated. The agreement with the recommendations was obtained through a Delphi survey.

Results: The final set comprises 4 overarching principles and 12 recommendations, each presented with its degree of agreement (0-10), level of evidence, and rationale. The degree of agreement was greater than 9/10 in all instances, and the level of evidence improved in most updated statements. Improving adherence is emphasised as an important aspect in several statements. These new recommendations include a priority set, quality indicators, and other suggested implementation strategies.

Conclusions: This article presents a set of widely accepted recommendations for treating and monitoring FMF, supported by the best available evidence and expert opinion. These recommendations are valuable for guiding physicians in caring for patients with FMF.

INTRODUCTION

Familial Mediterranean fever (FMF) is a monogenic autoinflammatory disease characterised by recurrent attacks of fever and serosal inflammation, increased acute phase response, and the sequelae of chronic inflammation in untreated patients [1–3]. In 2016, a task force supported by the European Alliance of Associations for Rheumatology (EULAR) developed recommendations for managing FMF [4]. These recommendations provided rheumatologists, patients, and other stakeholders with the evidence-based views of international experts on managing FMF and summarised the state of the art. This was especially important because although FMF is the most common autoinflammatory disease, it is rare in most regions of the world and thus warrants awareness [5,6]. Hence, most physicians encountering FMF patients need guidance on managing the disease.

Several of the 2016 recommendations for FMF were based on publications with relatively low evidence levels. Over the past 8 years, novel data have been published on the management of resistant patients and the efficacy and safety of treatments, including their effects on fertility. In addition, a new definition of colchicine resistance and tolerance necessitated an update on the previous recommendations for FMF [7]. Today, biologics have become the main therapeutic choice in colchicine-resistant FMF patients, and treat-to-target strategies are being developed [8]. The emerging data on the efficacy and safety of biological agents in FMF and publications on treatment titration and amyloid A (AA) amyloidosis also warrant the update [9–11].

For these reasons, another task force was assembled, and EULAR supported its endeavours. We herein present the 2024 update of the EULAR recommendations for managing FMF.

METHODS

The present recommendation effort started in June 2023 after formal approval by the EULAR Council (QoC018) and was conducted according to the EULAR standard operating procedures (SOPs) for task forces [12]. The recommendations were led by a convenor (SO) and a methodologist (LC), assisted by 2 fellows (ES, TO) and a junior methodologist (FP) (these 5 formed the steering committee), and included expert adult and paediatric rheumatologists and internists from Europe and the Mediterranean area, a nephrologist (HL), 2 health professionals in rheumatology (DK, YP), 2 young rheumatologists from EMEUNET (CSS) and Emerge (ES), and 2 patient representatives (SY, ZY). The steering committee conducted the pertinent systematic reviews and all other necessary work to support the task force decisions. All task force members were requested to participate in a face-to-face meeting plus a virtual one and answer the Delphi survey.

The process started with a first meeting of the steering committee to define the initial systematic reviews needed to update the recommendations. Based on PICO (Population, Intervention, Comparison, Outcome) questions, protocols were prepared, and the fellows and the methodologist conducted searches in Medline (via PubMed), Embase, and Cochrane Library. The fellows conducted study selection, data extraction, and interpretation under the supervision of the senior and junior methodologists and the convenor, with weekly meetings. The detailed methods and results of the systematic reviews are reported separately [13,14].

The task force members then received a comprehensive document compiling the main results of the reviews. They met face-to-face to discuss overall and recommendation by recommendation how the evidence had changed and how it should be

incorporated. After the first panel meeting, additional quick reviews were carried out concerning the impact of FMF on the quality of life of patients and their families, nonpharmacological interventions, and barriers to the use of colchicine. This new evidence and the recommendations were discussed again in a second virtual meeting of the panel, including the level of evidence of each statement based on the Oxford Levels of Evidence, 2011 [15]. Following the new EULAR SOPs for recommendations development, the task force ranked the statements to identify the top 3 management priorities; this was done online during the meeting using SurveyMonkey. The scenario that prompted the ranking was "If only one or two recommendations were to be implemented, rank the statements by priority of impact, also thinking on their feasibility." The methodologists proposed 3 quality indicators to measure the implementation and outcome of the prioritised recommendations, and the group discussed them and formulated a fourth one encompassing the outcomes of several recommendations. Barriers to implementing the recommendations were discussed, and implementation strategies were suggested after further discussion with the methodologists. After the second meeting, a Delphi survey was launched among the task force members. All the statements were graded from 0 to 10, with a score from 8 to 10 reflecting agreement. The agreement was already very high in the first round, all >95%, with a threshold of 90% necessary for an item to remain. Based on the comments received, minor edits were made to improve readiness, and an overarching principle was passed through the second round by the suggestion of 2 panellists.

RESULTS

The discussions identified several previous recommendations seen as principles, which were transformed into overarching principles. Some recommendations with very low levels of evidence or redundancy were moved from the core set to the text. Two systematic reviews support the statements [13,14]. We found no studies directly answering the questions posed after the first meeting (quality of life, nonpharmacological interventions, and barriers to colchicine adherence). However, we identified indirect evidence that was incorporated into the underlying text of the corresponding principles or recommendations. The final set comprises 4 overarching principles and 12 recommendations, each presented with its degree of agreement (0-10), level of evidence, and rationale. See the text below for details and rationale; Table 1 lists the recommendations and overarching principles. The degree of agreement was greater than 9/10 in all instances, and the level of evidence improved in most updated statements. Improving adherence is seen as an important part of several statements.

Overarching principles

OP1. FMF has complex clinical presentation and genetics, which requires expertise in diagnosis and management

This statement was directly derived from the first recommendation of the previous document [4]. However, it was noted that this is a factual observation rather than a suggestion. Although FMF is an autosomal recessive disease and its associated gene, *MEFV*, has been identified, the interpretation of the genetic result may be complex. This is mainly because there are many likely pathogenic variants and variants of unknown significance, complicating the interpretation of the genetic results. Furthermore, patients with one mutation may occasionally express the disease phenotype. Thus, the genetic result is not always confirmatory, and the differential diagnosis from other autoinflammatory conditions is indeed broad. Ideally, the diagnosis should be confirmed by a physician with experience in FMF, and the initial treatment should be discussed and planned with an expert. The French procedure for the diagnosis and management

Table 1
EULAR recommendations for the management of FMF: 2024 update

	Overarching principles	*A*[a]
OP1.	FMF has complex clinical presentation and genetics, which requires expertise in diagnosis and management.	100
OP2.	The treatment goal in FMF is to achieve minimal or no clinical activity and complete control of subclinical inflammation to prevent associated damage.	95
OP3.	FMF requires lifetime management, including long-term prophylaxis with colchicine; therefore, treatment adherence is the cornerstone of FMF management.	100
OP4.	Patient-centred management is required to promote a good quality of life and support health and well-being.	100
	Recommendations	***LE***[b] ***A***[a]
R1.	Treatment with colchicine should start as soon as a clinical diagnosis is made[c].	1 95
R2.	Colchicine dosing can be in single or divided doses depending on adherence and tolerance.	2 100
R3.	In adherent patients, the persistence of attacks or subclinical inflammation represents an indication to increase the colchicine dose within the recommended range. The maximum dose should not exceed 2 mg/d in children and 3 mg/d in adults.	2 100
R4.	Adherent patients not responding adequately to the maximum tolerated dose of colchicine should be considered for additional treatments; the highest level of evidence is for IL-1-targeting treatments.	1 100
R5.	Chronic inflammatory musculoskeletal involvement of FMF may need additional treatments.	4 95
R6.	Response, toxicity, and adherence should be monitored regularly, more often at diagnosis and when the disease is uncontrolled.	5 100
R7.	As overdose with colchicine can be fatal; intentional or accidental overdosing should be carefully assessed.	4 95
R8.	In AA amyloidosis, treatment aims to obtain complete and sustained control of the biochemical inflammation, measured by SAA or equivalent (CRP).	3 100
R9.	In FMF patients on biologics, doses should be optimised; if remission is achieved, tapering and discontinuation may be considered.	1 95
R10.	Colchicine should be continued during conception, pregnancy, and lactation; amniocentesis is not currently recommended.	3 95
R11.	During a characteristic attack, the usual dose of colchicine should be continued, and symptomatic treatment, such as NSAIDs, is recommended.	4 95
R12.	To standardise patient care and research, a minimum outcome set should include measures of clinical disease activity (eg, attack frequency per 3 mo, physician assessment), patient experience (eg, PROMs and PREMs), and biochemical markers (eg, CRP, SAA).	5 100

AA, amyloid A; CRP, C-reactive protein; FMF, familial Mediterranean fever; IL, interleukin; NSAID, nonsteroidal anti-inflammatory drug; PREM, patient-reported experience measure; PROM, patient-reported outcome measure; SAA, serum amyloid A.

[a] Percent agreement (ie, proportion of panellists who scored the item 8-10 on a 0-10 scale).

[b] Level of evidence, according to the Oxford Levels of Evidence 2011.

[c] The starting dose of colchicine is ≤0.5 mg/day (≤0.6 mg/day in case when available tablets contain 0.6 mg in some countries) for children <5 years of age, 0.5–1.0 mg/day (1.2 mg/day in case tablets contain 0.6 mg) for children 5–10 years of age, 1.0–1.5 mg/day (1.8 mg/day in case tablets contain 0.6 mg) in children >10 years of age and in adults.

of FMF has a detailed protocol that could be useful for the diagnosis of FMF [16].

OP2. The treatment goal in FMF is to achieve minimal or no clinical activity and complete control of subclinical inflammation to prevent associated damage

This overarching principle was derived from the previous set of recommendations. While controlling attacks is crucial for the patient's quality of life, subclinical inflammation—reflected in the elevation of sensitive acute phase reactants such as serum amyloid A protein (SAA), which is more specific, or C-reactive protein (CRP)—is important to prevent complications, such as AA amyloidosis, vasculitis, chronic arthritis, liver damage, and other comorbidities. We acknowledge that treat-to-target strategies are crucial in this context and that not all patients can achieve this goal [8]. We also acknowledge that an accepted definition of minimal disease activity does not exist at the time of the issue of these recommendations (see Research Agenda).

OP3. MF requires lifetime management, including long-term prophylaxis with colchicine; therefore, adherence to treatment is the cornerstone of FMF management

FMF is a genetic disorder, and the risk of complications continues lifelong; management will continue into the adult years. Long-term colchicine prophylaxis is essential to control inflammation and prevent attacks of clinical manifestations as well as AA amyloidosis. Management includes treatment, routine follow-up visits, and discussions with the patient as required.

A crucial element of management is assessing the patient's adherence to treatment. This may be especially relevant in adolescence and adulthood [17]. We encourage the rheumatology team to observe the EULAR points to consider for the screening, monitoring, and management of nonadherence [18]. For this, education of the patient and the family is crucial [19]; the goals cannot be reached without a lifelong therapeutic alliance with the patient and the family. This alliance includes offering shared decisions, effective communication, and considering the disease's physical, psychological, and social aspects and impact.

OP4. Patient-centred management is required to promote a good quality of life and support health and well-being

FMF attacks and the ongoing subclinical inflammation can markedly impair the health-related quality of life (HRQoL) of affected individuals, involving physical, emotional, and social dimensions [20,21]. Even though attacks are the main concern in individuals with FMF, recent studies have shown the negative effects of the disease on exercise capacity, fatigue, physical activity levels, and emotional status [21–26]. The EULAR guidelines advocate for integrating nonpharmacological therapies to manage chronic rheumatic diseases, emphasising the role of physical activity and addressing fatigue as one of the key components [27,28]. Physical activity, tailored to the individual's capabilities and disease state, can help maintain functional capacity, reduce inflammation, and enhance overall well-being [29,30]. Furthermore, strategies for managing fatigue include energy conservation, sleep hygiene, and cognitive-behavioural approaches [31]. The EULAR guidelines underscore the holistic management of chronic conditions such as FMF, for which nonpharmacological interventions, including physiotherapy, occupational therapy, and psychological approaches, are crucial in improving HRQoL and functional status alongside conventional medical treatments [27,28]. "Holistic" was a preferred term over "patient-centred" by the patients; however, there were discussions to protect patients from "natural remedies" with unproven efficacy, and therefore, the term patient-centred prevailed.

Recommendation statements

R1. Treatment with colchicine should start as soon as a clinical diagnosis is made

This recommendation remains unchanged; however, the level of evidence was increased after the up-to-date systematic literature review [14]. The clinical diagnosis is based on symptoms and family history—including first-degree relatives with AA amyloidosis—whereas laboratory and radiographic studies may help to support the diagnosis or exclude other causes. Typical laboratory results reveal elevated white blood cell count with neutrophil predominance, acute phase reactants such as CRP, SAA, and fibrinogen, and erythrocyte sedimentation rate. If possible, genetic testing is advised for every patient with suspected FMF [32,33].

The starting dose of colchicine is ≤0.5 mg/d (≤0.6 mg/d when tablets contain 0.6 mg, available in some countries) for children <5 years of age, 0.5 to 1.0 mg/d (1.2 mg/d in case tablets contain 0.6 mg) for children 5 to 10 years of age, and 1.0 to 1.5 mg/d (1.8 mg/d in case tablets contain 0.6 mg) in children >10 years of age and in adults. In principle, this drug is widely accessible and prescribed with clinical diagnosis; however, genetic corroboration is necessary in some countries for subsequent treatments in colchicine-resistant patients.

R2. Colchicine dosing can be in single or divided doses, depending on adherence and tolerance

This recommendation was slightly edited ("adherence" instead of "compliance"), but the evidence level remained the same—it is based on a single randomised controlled trial (RCT) [14,34]. A single dose is accepted to be effective; however, it may be associated with more gastrointestinal intolerance [35].

R3. In adherent patients, the persistence of attacks or subclinical inflammation represents an indication to increase the colchicine dose within the recommended range

This is revised from previous recommendation number 5 by adding "In adherent patients. . .." This was deemed necessary to stress the importance of adherence to a lifelong oral drug. The aim is to increase the dose but not to exceed the daily dose of 2 mg in children and 3 mg in adults or up to the maximum tolerated dose. It should be increased gradually to reach the target, no more frequently than weekly. Intravenous colchicine is discouraged. An expert group defined colchicine resistance as recurrent clinical attacks (average ≥1 attacks per month over a 3-month period) or persistent laboratory inflammation in between attacks [7]. This recommendation highlights the need to regularly assess both adherence and subclinical inflammation (see recommendation R6).

R4. Adherent patients not responding adequately to the maximum tolerated dose of colchicine should be considered for additional treatment; the highest level of evidence is for IL-1-targeting treatments

The previous recommendation, number 6, underwent some fine-tuning to reflect the newly available data. The systematic literature review on efficacy has increased this recommendation's evidence level [14]. There are 6 RCTs in FMF patients with interleukin (IL)-1 blockers (1 anakinra, 4 canakinumab, 1 rilonacept) [36–41] and 2 RCTs with an anti-IL-6 treatment

[42,43]. A therapeutic algorithm has been suggested with the relevant literature (Fig). The starting dose of biologics should be: anakinra, 100 mg/day or 2 mg/kg subcutaneously daily; canakinumab, 150 to 300 mg or 2 to 4 mg/kg subcutaneously every 4 to 8 weeks; rilonacept, 2.2 mg/kg (maximum, 160 mg) by weekly subcutaneously; tocilizumab, 162 mg or 4 to 8 mg/kg by weekly subcutaneously; or tofacitinib, 5 mg twice a day orally. However, other than IL-1 inhibitors, these latter drugs have not been approved for use in colchicine-resistant FMF and thus require expert advice before they can be initiated.

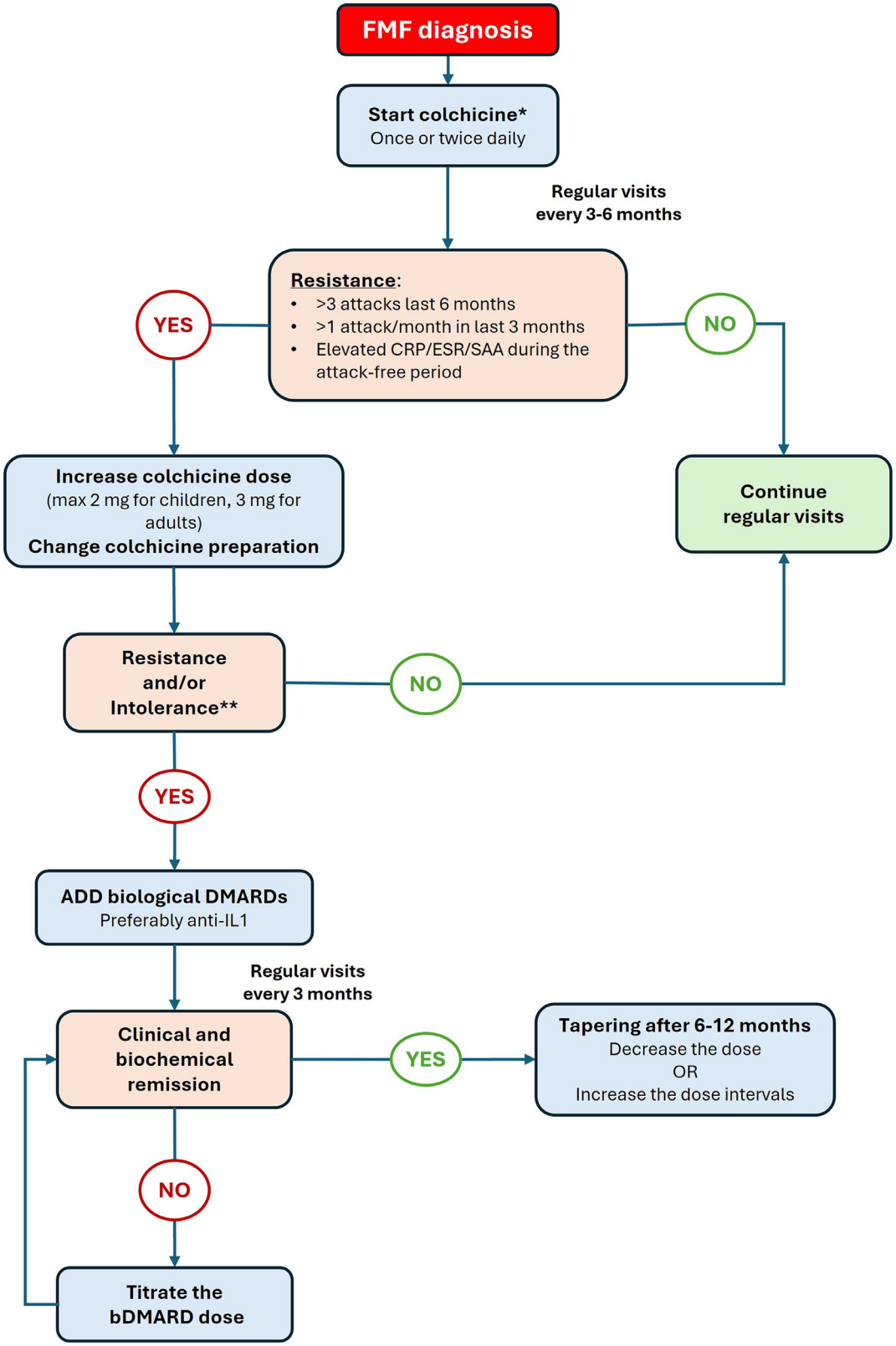

Figure. Therapeutic algorithm for familial Mediterranean fever (FMF). CRP, C-reactive protein; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; SAA, serum amyloid A. *Starting dose for colchicine. ≤0.5 mg/d (≤0.6 mg/d in case tablets contain 0.6 mg) for children <5 years of age, 0.5-1.0 mg/d (1.2 mg/d in case tables contain 0.6 mg) for children 5-10 years of age, 1.0-1.5 mg/d (1.8 mg/d in case tablets contain 0.6 mg) in children >10 years of age. **Intolerance. Treatment-related conditions preventing the patient from reaching effective dose (ie, diarrhoea, elevated liver enzymes, leukopenia, etc).

R5. Chronic inflammatory musculoskeletal involvement of FMF may need additional treatments

The previous recommendation 16 was slightly modified to reflect the evidence better. Recent data suggests that chronic inflammatory joint involvement in FMF, such as spondyloarthropathy, may indeed need additional treatments [44]. These musculoskeletal features may be less responsive to colchicine and IL-1 inhibitors. Hence, other disease-modifying antirheumatic drugs (DMARDs), conventional-synthetic or biologic-targeted, may need to be considered.

Protracted febrile myalgia is a complex situation that requires an expert consultation. In mild cases, nonsteroidal anti-inflammatory drugs (NSAIDs) may be used, but usually, glucocorticoids lead to the resolution of symptoms. IL-1-blockade might also be a treatment option [45–48]. NSAIDs are suggested to treat exertional leg pain.

R6. Response, toxicity, and adherence should be monitored regularly, more often at diagnosis and when the disease is not controlled

This recommendation was revised from the previous recommendation 9. Patients should be monitored regularly for their response to the medication and adverse effects. Treat-to-target strategies are being developed to define the desired response [8,16,49]. In any case, the response to treatment should be evaluated based on attack frequency, HRQoL, and laboratory parameters of inflammation.

Colchicine is a safe drug in the suggested doses [50,51]. The toxicity of colchicine should be assessed using complete blood counts and liver function tests. If liver enzymes are elevated >2-fold the upper normal limit, the colchicine dose should be reduced, and the possible causes should be further investigated carefully, which may require expert opinion. On the other hand, poorly controlled FMF has also been suggested to be a cause of liver dysfunction, especially in the adult literature [52]. In patients with decreased renal function, the risk of toxicity is high, and therefore, signs of colchicine toxicity, as well as serum creatine kinase concentrations, should be monitored carefully, and the colchicine dose should be reduced accordingly. The caring physician should be aware of the drug interactions with colchicine (Supplemental File; Table S1). Colchicine intolerance, which generally manifests as gastrointestinal symptoms (such as diarrhoea and nausea), is common and can limit the ability to achieve or maintain the effective dose.

Follow-up visits should be scheduled at frequent intervals following the initial diagnosis and if the disease is unstable. If the disease is under control, follow-up visits every 6 months may suffice.

In addition, adherence should be monitored regularly. The EULAR points to consider for screening, monitoring, and managing adherence recommend setting up a safe environment and open questions [18]. In addition, it may be possible to measure colchicine levels in hair samples, but this is only in an experimental phase and is costly [53].

R7. As overdose with colchicine can be fatal, intentional or accidental overdosing should be carefully assessed

This was recommendation 12 in the previous set. Colchicine is the mainstay of the treatment, and it is very effective and safe at suggested doses. However, the therapeutic index is rather narrow and thus, accidental overdose can be fatal [54]. Suicidal ideation or intent may also need to be evaluated.

R8. In AA amyloidosis, the aim of treatment is to obtain complete and sustained control of the biochemical inflammation, measured by SAA or equivalent (CRP)

This recommendation is revised from the previous recommendation 7 and rephrased to introduce a more precise objective. When AA amyloidosis develops as a complication of FMF, the target is to decrease overt or subclinical inflammatory findings to the normal ranges [11]. Subclinical inflammation is suggested to be monitored by SAA and proteinuria. AA amyloidosis develops due to ongoing inflammation that is not adequately suppressed, therefore, in patients who are resistant or nonadherent to colchicine. FMF treatment needs to be intensified in AA amyloidosis using the maximal tolerated dose of colchicine and supplemented with biologics as required [14]. When SAA measurements are not available or are costly, a sensitive CRP measurement can also be used to monitor low-level inflammatory response.

R9. In FMF patients on biologics, doses should be optimised; if remission is achieved, tapering and discontinuation may be considered

The previous recommendation 18 was revised to make it clearer. We performed a systematic review of tapering strategies in FMF, which showed they were feasible [14]. Tapering of colchicine may not be appropriate for patients with biallelic pathogenic *MEFV* mutations, and consideration of tapering is suggested only for biologics in FMF patients. If the dose of biologics is tapered or the administration intervals are increased, close monitoring (ideally every 3 months) is needed for flare-ups or worsening of inflammatory findings. Optimisation of treatment may also include the up-titration of biological doses in selected patients when the clinical findings and inflammatory parameters cannot be controlled with the standard doses and intervals.

Some uncertainties remain, as there is no standard strategy for defining sustained remission or an acceptable state to start tapering.

R10. Colchicine should be continued during conception, pregnancy, and lactation; amniocentesis is not currently recommended

This was the previous recommendation number 14, but we found more evidence in our systematic review [13]. Female fertility is not affected by colchicine, and causes of infertility in patients with FMF under colchicine are not different from those expected in the general population [13]. The data on biologics is similar but needs a risk assessment (US Food and Drug Administration categories differ for each biological). Fertile women who are on biologics can get pregnant.

R11. During a characteristic attack, the usual dose of colchicine should be continued, and symptomatic treatment, such as NSAIDs, is recommended

During a characteristic attack, the colchicine dose should not be increased; only the usual dose should be continued. Glucocorticoids are not recommended. NSAIDs are suggested as appropriate. Opioids should not be used. This recommendation expects the patient to be conscious of a typical attack. There are some reports about the on-demand use of anakinra in severe attacks, but further data are required for a recommendation [55,56].

R12. To standardise patient care and research, a minimum outcome set should include measures of clinical disease activity (eg, attack frequency per 3 months, physician assessment), patient experience (eg, PROMs and PREMs), and biochemical markers (eg, CRP, SAA)

The expert group recognises the challenges of assessing the patient HRQoL measures in FMF, both patient-reported outcome measures (PROMs) and patient experience measures (PREMs). Outcome measures in RCT and observational studies have included the number of attacks (per 3 months), the attack site, quality of life, autoinflammatory diseases activity index (AIDAI), modified FMF50 score, physician global visual activity score (physician VAS) and patient VAS, CRP, SAA, SF-36 score, Child Health Questionnaire, or the short-form 12 (SF-12). We also acknowledge that the only validated activity assessment score, AIDAI, has problems reflecting the activity of the disease. Some physicians may depend on patient diaries as well.

Research agenda

The panel recognises there are still many uncertainties in the diagnosis and management of FMF that require continuing research efforts. Table 2 shows the items that the task force members encourage the community to pursue by research.

Implementation strategies

EULAR SOPs for recommendations emphasise the need to not only disseminate the recommendations but also to enhance their implementation at the local level. Two tables describe the top priorities for implementation, their proposed quality indicators to be used, for instance, in quality audits to measure the implementation at the centre, region, or country level (Table S2), and the barriers to the FMF recommendations and suggested implementation strategies to overcome them (Table 3).

Table 2
Research agenda

Aspect	Details
Aetiology	- Environmental factors that may lead, trigger, or worsen FMF or its complications
Diagnosis	- Genetic definition
Management	- Effect of nonpharmacological approaches - Better studies on dosing alternatives - How to manage fatigue
Safety	- Long-term safety of biologics in FMF - Better studies about the impact of disease and treatments on male fertility (with proper controls)
Prognosis	- Biomarkers of colchicine resistance - Differences across populations/subgroups and across sexes - Geriatric patients
Assessment	- Failure/response - Minimal disease activity - Acceptable state - Attack severity - Add the number of attacks as an endpoint in RCTs and prognostic studies - Composite scores - Patient-reported outcomes measuring: ○ Quality of life ○ Participation (children and adults) ○ Patient experience
Comorbidities	- Liver disease (eg, whether it is related to FMF or treatments) - Impact of fibromyalgia on disease activity
Adherence	- Tools to improve patient education

FMF, familial Mediterranean fever; RCT, randomised controlled trial.

DISCUSSION

This manuscript presents the revised recommendations for the diagnosis and management of FMF. This work's major strengths include the endorsement by the adult and paediatric European rheumatology societies (EULAR and PReS) and the involvement of a large team of paediatric and adult rheumatologists with other health professionals and patient representatives. We also facilitate their implementation at the local level by suggesting strategies based on barriers and ways to measure uptake.

The treatment goal in FMF is complete control of attacks and subclinical inflammation, thus preventing associated damage and comorbidities. We highlighted the need for lifelong management to control subclinical inflammation in the overarching principles. This is crucial to prevent complications such as AA amyloidosis and ensure a good quality of life. Thus, in FMF, patient-centred care is a holistic approach, and this was specifically addressed in the revised set. Patient education should cover disease, medication, adherence, prevention, and self-management. The overarching principles remind us that management may be challenging because of diagnostic and therapeutic problems. For the challenges in diagnosis that require an expert opinion, we refer to the clinical heterogeneity and the complexity of assessing the *MEFV* genetic analysis results, such as variants of unknown significance, variants in exons other than exon 10, or patients displaying FMF phenotype with one exon 10 mutation only, or conversely patients with pathogenic *MEFV* variants but a phenotype not compatible with FMF. The management may also be challenging, particularly considering comorbidities and issues complicating dose adjustment or evaluation of response to treatment [57,58]. As we have suggested in the research agenda, future research should address definitions for assessing the disease so that we can have set goals in treat-to-target strategies.

The task force highlighted the need to check treatment adherence in this set of recommendations. A starting dose of colchicine had been previously suggested [59]. Subsequently, the individual dose should be titrated according to the patient's response and tolerance. We aim to achieve minimal clinical activity and complete control of subclinical inflammation, which is assessed with a sensitive test such as CRP or SAA. An increase in subclinical inflammation represents an indication to increase the colchicine dose within the recommended range. However, we suggest not to exceed a daily dose of 2 mg in children and 3 mg in adults or up to the maximum tolerated dose. Intravenous colchicine is not recommended.

An expert group has defined the ongoing disease activity despite the highest tolerable doses of colchicine (which is referred to as "colchicine resistance") as recurrent clinical attacks (average ≥1 attack/month over a 3-month period) or persistently elevated serum CRP or SAA in between attacks in the absence of any other plausible explanation. If disease control cannot be reached with colchicine, recent data justifies using IL-1 inhibitors, based on our systematic review [14]. Long-term follow-ups of the patients have also been published, confirming the ongoing efficacy without further safety signals [41]. The biologic dose should be titrated until disease control is achieved, and after achieving sustained remission, tapering and even cessation can be considered for biologics. However, there is yet no definition for sustained remission, and close monitoring is necessary in those patients followed with tapered doses or after the discontinuation of biologic drugs. On the other hand, colchicine should be continued if the diagnosis has been confirmed with

Table 3
Barriers to the FMF recommendations and suggested implementation strategies to overcome them

Barriers	Implementation strategies suggested
Lack of knowledge/training in FMF.	- Public and professional awareness campaigns. - Include FMF in rheumatology curricula. - Develop educational materials for medical students and rheumatologists (slide kits). - Prepare an algorithm and disseminate it (eg, social media, via ERN Connect, patient associations). - Identify knowledge champions (eg, lead campaigns).
Delay of genetic testing.	- Develop and implement tools for quality monitoring to be embedded in clinical records/IT systems (eg, an FMF blood test profile that includes CRP, SAA, and genetics in fever of unknown origin). - Not-to-do campaigns.
Lack of adequate patient information on colchicine (may lead to initiation non-adherence).	- Develop educational material for patients with information on treatment (eg, shared decision-making aids). - Prepare patients to become active participants.
Lack of standardisation/measure, including the absence of minimal disease activity definition.	- More research and better-quality studies.
The misconception that colchicine is contraindicated in pregnancy.	- Develop educational material for patients with information on treatment (eg, shared decision-making aids). - Develop educational materials for medical students and rheumatologists (slide kits).
Difficulties in knowing adherence.	- Check for the level of implementation of EULAR recommendations for adherence.
Insurance/price of drugs	- Advocate for accessibility.
Lack of head-to-head studies.	- More research and better-quality studies.

CRP, C-reactive protein; ERN, European Reference Networks; EULAR, European Alliance of Associations for Rheumatology; FMF, familial Mediterranean fever; SAA, serum amyloid A.

the detection of biallelic pathogenic and/or likely pathogenic variants.

Chronic musculoskeletal manifestations or comorbidities may require the use of other DMARDs or biologic DMARDs to manage FMF patients. For example, spondyloarthritis may require the use of tumour necrosis factor inhibitors in addition to conventional treatments, or coexistent inflammatory bowel disease may require other specific treatment modalities [60,61].

When using colchicine, patients should be cautioned against the use of certain drugs that may lead to toxic elevations in serum concentration of colchicine. The medications interacting with colchicine are shown in Table S1 (Supplemental File). Children may experience toxicity, especially during viral infections, when they may experience elevated liver function tests or leukopenia, not only because of the infection per se but also because of the NSAIDs and possibly antibiotics that are administered. The task force discussed the interpretation of elevated liver function tests in FMF. Most paediatricians regarded this as a possible side effect of colchicine in children who were subject to extra insults, as discussed above. On the other hand, adult rheumatologists may regard elevated liver function tests as reflecting inadequate control of inflammation in that patient. Further research is needed to enlighten the controversy on this subject (Table 2). Patients and families should be enlightened about the narrow therapeutic index of colchicine to prevent accidental overdose; suicide risk also needs to be evaluated.

Urinalysis should be checked at least yearly and more often for patients with poorly controlled disease. The task force agrees that the suppression of subclinical inflammation is again mandatory in a patient who has developed AA amyloidosis. We do not recommend a repeat biopsy for the follow-up of AA amyloidosis [11]. In the case of renal transplantation due to end-stage renal failure, IL-1 inhibitors are continued for the prevention of the progression of the disease to the transplanted kidney and other organs; the interaction with immunosuppressants requires close monitoring (see Table S1; Supplemental File) [62].

It is essential to share with obstetricians that colchicine is safe during pregnancy. There are no increased safety signals; however, the literature shows a trend for preterm births, more likely in relation to the continuation of inflammation, ie, FMF itself and not colchicine [13,63]. Although we still await further research on the subject, current data and expert opinion agree that men do not need to stop taking colchicine at the recommended doses. More data on sperm counts and fertility outcomes in men are needed to provide further evidence on this subject.

FMF is a lifelong disease, and thus, psychosocial support for the care of patients and families is essential. The existing disease activity tools lack the patient perspective. Future research needs to concentrate on assessing health care and HRQoL from the patient's perspective (Table 2).

Thus, EULAR and the PReS endorsed the update of the FMF recommendations, especially regarding the recent data on the efficacy of treatments, AA amyloidosis, pregnancy, and fertility issues in disease management. Again, we aimed at global input and invited rheumatologists from different countries with expertise in this disease. The major focus of this updated version has been to introduce some modifications in the previous set of recommendations because of the new data. We have also introduced a set of overarching principles and some new recommendations. We have emphasised the importance of adherence. We have also further highlighted the importance of quality of life and that more work is needed as research agenda items.

In this recommendation process, patient representatives, paediatricians, adult rheumatologists, and internists addressed the issues mentioned above based on specific systematic reviews in a joint effort. This recommendation document targets adult and paediatric rheumatologists, patients, patient caregivers, patient associations, and health authorities. We aimed to suggest recommendations that would benefit the practice of experts and those with less experience with FMF. 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 further addressed.

In conclusion, this is the revised set of recommendations for managing FMF across all ages. These recommendations

highlight the need for a *holistic* approach and attention to compliance in these patients and the need for IL-1 inhibitors in patients who have uncontrolled disease despite the highest tolerable doses of colchicine treatment. Twenty-seven years after defining the causative gene, we still have an extensive research agenda to pursue.

Competing interests

AG: speaker fees and consultancy from SOBI, Novartis, and R-Pharm. JKD: speaker fees and research grants from Novartis and SOBI. LC and TO: have no conflicts of interest with the topic and do not prescribe; nevertheless, they work for an institute that delivers services for many stakeholders, including pharmaceutical companies that produce drugs listed here, such as Roche or Novartis. MG: speaker fees and research grants from Novartis and SOBI, speaker fees from Fresenius Kabi, and consultancy from Kiniksa and Boehringer. SGL: speaker fees from SOBI, and Novartis. HL: speaker fees from SOBI, and Novartis. SO: speaker fees and consultancy from SOBI and Novartis. OK: speaker fees and consultancy from Novartis, AbbVie, Pfizer, UCB. ES: consultancy from Novartis. TK: speaker fees from SOBI and Novartis paid to institutional accounts. VH: consultancy and speaker fees from Novartis and SOBI. All other authors (CSS, FNP, SY, SK, DB, TS, YP, YU, ZY) declare no competing interests.

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Contributors

SO was the convenor of the taskforce and, as such, directed all works and is the guarantor of the content. ES and TO acted as fellows and performed the systematic reviews. LC acted as methodologist and FNP as methodologist in training, and together with SO, they drafted this manuscript. ZY and SY represented the patient perspective, CSS represented the young rheumatologist's perspective (EMEUNET), and YP and DB represented the health professionals in rheumatology. All others represented their views as experts. All authors were involved in the discussions leading to the recommendations and revised the manuscript prior to submission.

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Patient consent for publication

Not applicable.

Patient and public involvement

As required by the EULAR SOPs, 2 patients were involved in the meetings, the Delphi, and the online discussions, and their priorities, experiences, and preferences were considered.

Ethics approval

Not applicable.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

We have not produced specific data for this manuscript; however, its previous versions, minutes of meetings, search strategies of quick reviews, and Delphi surveys are available for inspection upon reasonable request.

Supplementary materials

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