Egyptian evidence-based consensus on clinical practice recommendations for the management of familial Mediterranean fever

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Abstract

Background: We aimed to provide a consensus, evidence-based recommendations for the diagnosis, evaluation, and treat-to-target management of children living with FMF.

This study was carried out to achieve an expert consensus on a treat-to-target management strategy for FMF using the Delphi technique. The preliminary scientific committee identified a total of 17 key clinical questions according to the Patient/Population, Intervention, Comparison, and Outcomes (PICO) approach. An evidence-based, systematic, literature review was conducted to compile evidence for the benefits and harms associated with JIA treatments. The core leadership team identified researchers and clinicians with expertise in FMF management. Delphi process was implemented (2 rounds) to reach a consensus on the management recommendations of FMF patients.

Results: Twenty-one expert panel participated in the 2 rounds with a response rate of 100%. A total of 12 recommendations, categorized into 2 sections (4 in the diagnosis section and 8 in management), were obtained. The agreement with the recommendations (rank 7–9) ranged from 85.7 to 100%. The consensus was reached (i.e., ≥75% of respondents strongly agreed or agreed) on all the clinical standards. Algorithms for management have been also developed.

Conclusion: A wide and representative panel of experts established a consensus regarding the management of FMF. The developed guidelines provide a comprehensive treat-to-target approach to the management of FMF for all healthcare professionals who are involved in its management.

Keywords: Familial Mediterranean fever, FMF, Colchicine, Egyptian guidelines for FMF

Background

Familial Mediterranean fever (FMF) is the most frequent monogenic autoinflammatory disorder [1]. Autoinflammatory diseases (AIDs) are rare clinical conditions. FMF is common, with a high incidence among Arabs, Turks, non-Ashkenazi Jews, and Armenians who live in the Mediterranean basin, particularly

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on the eastern side. However, it has become more common in recent years in countries that are not part of this region [2]. Recent advances in the understanding of the molecular basis of inflammatory mechanisms have made it easier to identify genetic changes that have a role in FMF pathogenesis. Since 1997, when (Mediterranean fever) MEFV gene mutations were discovered to be the underlying cause in FMF, roughly 310 sequence variants in the MEFV gene have been identified [3]. The pyrin protein is encoded by the MEFV gene, which is found on chromosome 16 [4, 5]. Uncontrolled interleukin-1 (IL-1) secretion is induced by a mutated pyrin, resulting in an exacerbated inflammatory response [6].

Unfortunately, there is a knowledge gap when it comes to categorizing the best management strategy for FMF patients. While FMF can be adequately controlled with the use of proper treatments and regular monitoring, there are differing perspectives on how the disease should be managed, depending on the treating healthcare professional's knowledge and experience. Such a disparity in management approaches may have a negative influence on clinical and treatment outcomes [7].

A consensus based on real-life data from an FMF-affected country could serve as a model for healthcare experts responsible for FMF diagnosis and management. For the accurate diagnosis and treatment of FMF in children, there are currently no Egyptian-wide, evidence-based, treat-to-target recommendations. This was the driving force for the creation of this work. The objective is to provide a consensus, evidence-based recommendations for the diagnosis, evaluation, and treat-to-target management of children living with FMF. The scope of this guideline includes FMF itself (in children and adults), its complications, comorbidities, and refractory cases that may affect its management. Although framed for Egyptian children with FMF, we hope that these guidelines will be valuable for pediatric rheumatologists across the globe.

Methods
Design
A multistep procedure was used to produce consensus, evidence-based treatment guidelines for FMF. The study design was created using the CEG guideline creation process procedure, which entails a scientific evidence and consensus-building process based on existing scientific data and clinical experience. For reporting systematic reviews and meta-analyses, the publication followed the recommended reporting items for systematic reviews and meta-analysis criteria [8].

Development stages
Core team
It was created by a group of four specialists with extensive experience in FMF management. The core team oversaw and directed the team's efforts; aided in the development of the project's scope and initial Patient/Population, Intervention, Comparison, and Outcomes (PICO) clinical questions; and came to an agreement on the important questions to include in the guidelines. The core team pre-identified outcomes as crucial for the systematic literature evaluation for each PICO question. The team was also in charge of selecting the expert panel and writing the manuscript.

Key questions used to develop the guideline
The target population, the intervention, the investigation, the comparison(s) employed, and the outcomes used to quantify efficacy, effectiveness, or risk were all defined in this guideline. Formulation of clinical questions, structure of questions, search for evidence, critical evaluation and selection of evidence, presentation of results, and suggestions were all used to gather evidence to answer the clinical questions. Table 1 shows the questions that guided the systematic literature search and, as a result, the clinical care guidelines. This guideline does not offer any evidence-based suggestions for the diagnosis and investigation of FMF.

Literature review team
The literature evaluation was conducted with the assistance of a methodology expert, under the guidance of an experienced literature review consultant, and was based on particular research questions designed to focus on FMF management. A systematic literature search was conducted utilizing the PubMed/MEDLINE, EMBASE, and Cochrane databases to get sufficient evidence-based baseline knowledge for considerations. Following data abstraction, evaluation of published recommendations, and quality of evidence grading [9, 10], the professionals in charge of the literature study offered a comprehensive list of proposals for FMF management based on available research evidence and their own clinical competence. The Oxford Centre for Evidence-based Medicine (CEBM) approach was used to determine the degree of evidence (Table 2) for each area [10].

Data sources and search strategies
The search strategy was planned to capture all studies in which the study population were children living with FMF. The PICO questions (Table 1) were used to conduct the literature search. Literature search strategies were carried out to locate randomized clinical trials

Table 1 Key questions used to develop the guideline

- What is FMF?
- What is the genetic predisposition for FMF?
- How FMF is diagnosed and what is the role of the MEFV gene in the diagnosis of FMF?
- How to classify FMF?
- What are FMF prognosis and complications?
- How could we assess FMF disease activity?
- What is the target of treatment?

Clinical response

Laboratory response

Functional response

- How frequent could we assess the response, toxicity, and compliance to treatment?
- What is the role of colchicine in FMF treatment?
- When and how to modify colchicine dose?
- What are complications that could occur with colchicine?
- Could colchicine be used during pregnancy and breastfeeding?
- How can we deal with colchicine-resistant patients?
- What other medications could be used in the treatment of FMF patient?
- What is the role of biological therapy in FMF management?
- How could we monitor FMF?
- How could we manage amyloidosis complicating FMF?

FMF familial Mediterranean fever, *MEFV* Mediterranean fever

Table 2 Levels of evidence

Level of evidence	
1	Systematic review of all relevant randomized clinical trials or *n*-of-1 trials
2	Randomized trial or observational study with dramatic effect
3	Non-randomized controlled cohort/follow-up study (observational)
4	Case series, case-control study, or historically controlled study
5	Mechanism-based reasoning (expert opinion, based on physiology, animal or laboratory studies)
Grades of recommendation	
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies, or extrapolations from level 1 studies
C	Level 4 studies, or extrapolations from level 2 or 3 studies
D	Level 5 evidence or troubling, inconsistent, or inconclusive studies of any level

evaluating the efficacy of FMF management as well as quality improvement outcomes/approaches. The search terms were related to Familial Mediterranean Fever OR Familial Mediterranean Fever, Autosomal Recessive OR Familial Paroxysmal Polyserositis OR Familial Paroxysmal Polyserositides OR Paroxysmal Polyserositides, Familial OR Paroxysmal Polyserositis, Familial OR Polyserositides, Familial Paroxysmal OR Mediterranean Fever, Familial OR Periodic Disease OR Periodic Diseases OR Wolff's Periodic Disease OR Periodic Peritonitis OR Periodic Peritonitides OR Peritonitis, Periodic OR Polyserositis, Familial Paroxysmal OR Polyserositis, Recurrent) AND Diagnosis; Therapy AND colchicine, Interleukin 1 Receptor Antagonist Protein OR Anakinra OR Urine-Derived IL1 Inhibitor OR IL1 Inhibitor, Urine-Derived OR Urine Derived IL1 Inhibitor OR IL1 Febrile Inhibitor OR Febrile Inhibitor, IL1); infliximab OR etanercept OR adalimumab OR golimumab OR certolizumab OR Tumor Necrosis Factor alpha OR Cachectin-Tumor Necrosis Factor OR Cachectin Tumor Necrosis Factor OR TNF alpha OR TNF-alpha OR Tumor Necrosis Factor OR Tumor Necrosis Factor Ligand Superfamily Member 2); AND Outcomes.

The PICO elements that were employed in various combinations defined the keywords that were used. Duplicate screening of literature search results was undertaken using an electronic method. Looking through the reference lists of studies obtained using database search tools yielded more research that met the inclusion criteria.

Study selection

Relevant studies were selected by applying inclusion and exclusion criteria to the literature retrieved with the

Table 3 EUROFEVER/PRINTO classification criteria for FMF [11]

EUROFEVER/PRINTO clinical + genetic criteria ≥ 6 criteria
Presence of confirmatory MEFV genotype and at least one among the following
    1. Duration of episodes 1:3 days
    2. Arthritis
    3. Chest pain
    4. Abdominal pain
OR
Presence of not confirmatory MEFV genotype and at least two among the following:
    1. Duration of episodes 1:3 days
    2. Arthritis
    3. Chest pain
    4. Abdominal pain
EUROFEVER/PRINTO clinical only criteria ≥ 6 criteria
Presence of:
    1. Eastern Mediterranean ethnicity
    2. Duration of episodes 13 days
    3. Arthritis
    4. Chest pain
    5. Abdominal pain
Absence of:
    1. Aphthous stomatitis
    2. Urticarial rash
    3. Maculopapular rash
    4. Painful lymph nodes

FMF familial Mediterranean fever, *MEFV* Mediterranean fever, *PRINTO* Paediatric Rheumatology INternational Trials Organization

search strategies (Table 3 shows the classification criteria for FMF).

Inclusion criteria

Articles included were systematic reviews; randomized controlled trials (RCTs); uncontrolled trials; observational studies including cohort, case-control, and cross-sectional studies; or those where economic evaluation was made. Trials were eligible if they included juveniles diagnosed to have FMF regardless of sex, from any healthcare setting receiving any therapy. The included studies should have the criteria of classification evidence and recommendations used identified. Also, the formal process for establishing recommendations (Delphi exercise, panel conference) is outlined.

Exclusion criteria

Editorials, commentaries, conference abstracts, and non-evidence-based narrative/personal reviews, and manuscripts lacking an English version, were excluded.

Expert panel

Twenty-one participants were nominated by the core leadership team. Professional expertise and experience (at least 8 years of experience) in the field of rheumatology, care of inflammatory arthritis, and in particular FMF, as well as active engagement in scientific research on rheumatic diseases, were among the criteria for their selection. The expert panel assisted in developing the project's scope and refining the PICO questions. PICO

questions were converted into recommendation statements and forwarded to the expert panel, which voted on the recommendations along with the evidence report.

Target audience

The guideline was created to help healthcare professionals, mainly rheumatologists and pediatricians with a special focus in pediatric rheumatology, treat and manage patients with FMF. The guideline should also serve as a useful resource for patients and those in charge of contracting FMF care in the National Health Service.

Developing the clinical care standard framework

A structured template was designed to assist the consistent identification of guideline components based on the answers to the structured key questions and the literature review. The format in which the recommendations/information will be delivered and extracted has been identified for each guideline component.

Delphi process

The Delphi method is a structured method for gathering vital information about a certain issue that is extensively used. It is predicated on the premise that collective estimates are more accurate than individual projections. The Delphi method aims to generate consensus forecasts from a group of experts through a structured iterative process. Its methodology is based on a series of "rounds" of expert questions. The stages of the Delphi technique are usually as follows: (1) A group of experts is put

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together. (2) Forecasting tasks/challenges are assigned to professionals and spread. (3) Experts provide preliminary predictions and justifications. In order to provide input, these are collated and summarized. (4) The experts receive comments, which they consider when revising their forecasts. This process can be repeated until there is a reasonable degree of consensus. (5) The final forecasts are created by combining the forecasts of the experts. The key features of this method are the anonymity of participants and the controlled feedback [12–14].

Consensus process
To get a consensus on the T2T (treat to target) strategy in FMF, three Delphi rounds were conducted. The structured Delphi method ensures that all participants' opinions are taken into account equally. Online surveys were used to conduct the Delphi procedure. The electronic questionnaire's first round covered eight primary items related to FMF's T2T strategy.

Voting process
Live online voting was conducted in two rounds, each with a strict time limit. All members of the task force were invited to participate, and the start and end times of each round of voting were announced ahead of time. Anonymous votes were gathered and evaluated, and unique access links were sent out. At the same time as the voting procedure, comments on rephrasing, potential ambiguity, and unidentified overlaps were received for each statement. The task force members were the only ones who could vote on the statements.

Rating
Each statement was rated between 1 and 9 with 1 indicative of "complete disagreement" and 9 indicating "complete agreement." Generally, 1–3, 4–6, and 7–9 represent disagreement, uncertainty, and agreement, respectively. Voting on all statements was not mandatory, and the members were encouraged to refrain if they feel that a statement falls outside their area of expertise. An "uncertainty" vote represents "inconvenience about the accuracy of the recommendation." All statements allowed for the submission of comments, which the scientific committee assessed following each round of voting. Members were encouraged to leave comments during all of the voting rounds, especially where there was a vote of dissent. This allowed the panel to spot a case of statement misinterpretation and invalidate the vote on that statement.

Definition of consensus
Definition of consensus was established before data analyses. It was determined that consensus, consequently to become a recommendation in this guideline, would be achieved if at least 80% of participants reached an agreement (score 7–9) or disagreement (score 1–3) [12–14]. A statement was retired if it had a mean vote below 3 or a "low" level of agreement. Statements whose rate came in the uncertainty score, (4 –6), were revised in view of the comments. The levels of agreement on each statement of recommendation were defined as "high" if after the second round of votes, all votes on a statement fell into the agreement bracket (7-9) [14, 15].

Chronogram of Delphi rounds
The first round took place between 20 and 24 December 2021 (5 days). The aspects about which respondents did not reach consensus in this first round were revised in view of the comments and included in the second round. The second round took place on 31 December 2021 (1 week after the first round) and lasted for 4 days (3 January 2022).

Ethical aspects
This study was performed in accordance with the Helsinki Declaration. The Clinical, Evidence-based, Guidelines (CEG) initiative protocol was approved by the local ethical committee: ethical approval code: 34842/8/21, ethical board Tanta University. Written ethics approval from the experts sharing in this work was deemed unnecessary according to national regulations. As per the Egyptian National Ethical Committee regulations, written informed consent was required from all the participants included in the study. All the participants were kept anonymous, in compliance with data protection regulations. All participating personnel declare no any conflict of interest.
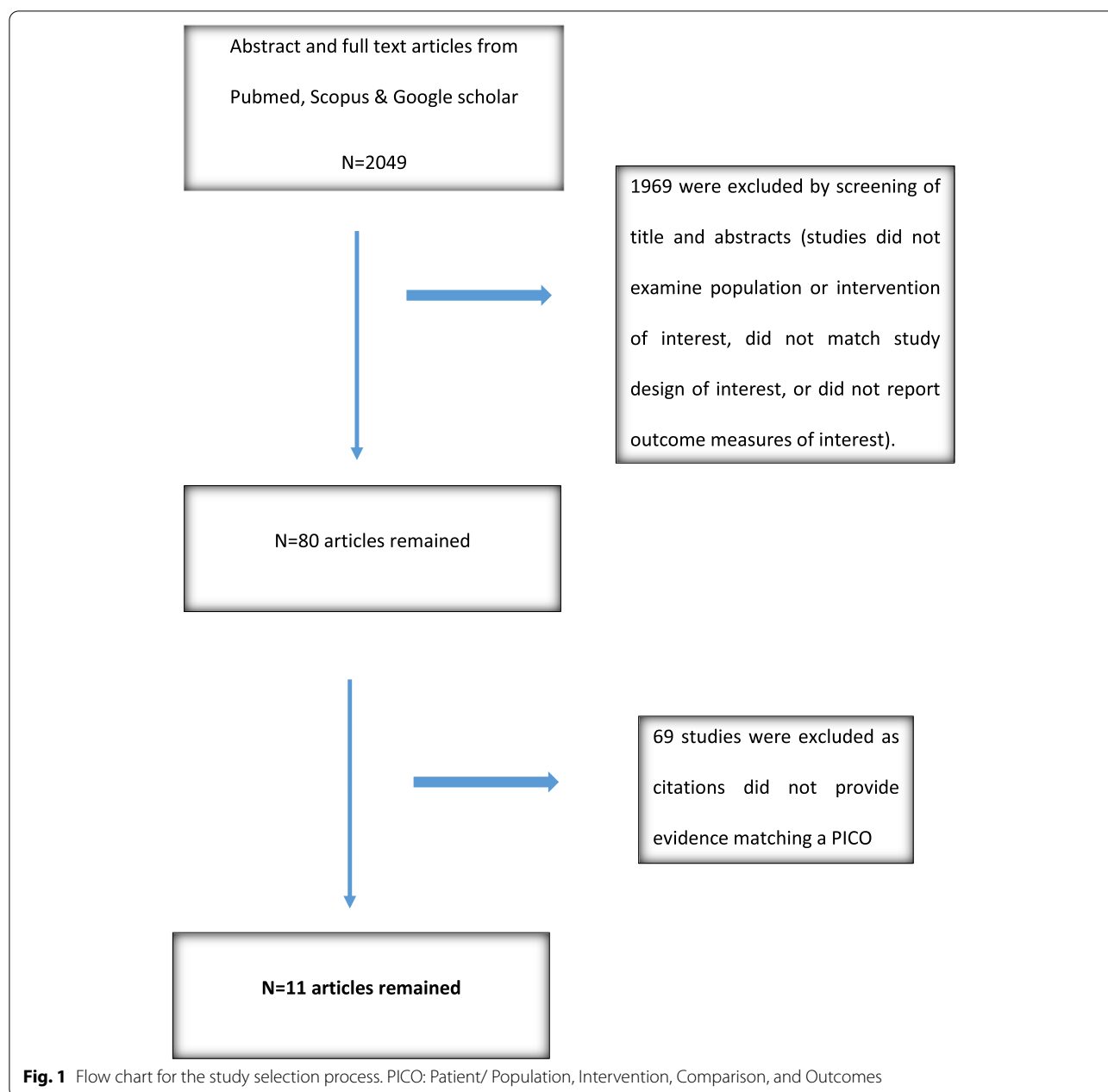
Results
Literature research and evidence selection
In the study selection process, we found 2049 potentially relevant studies by search strategy. A total of 1969 were excluded for duplicate or after screening of title and abstracts (studies did not examine population or intervention of interest, did not match study design of interest, or did not report outcome measures of interest). Therefore, relevant 80 studies were included for full article review. Sixty-nine studies were excluded as citations did not provide evidence matching a PICO. Therefore, we included 11 studies in this work (Fig. 1).

Expert panel characteristics
The Delphi form was sent to the expert panel ($n = 21$), who participated in the two rounds. Respondents were drawn from different governorates and health centers across Egypt: Cairo University (19.1%), Ain Shams University (14.4%), Tanta University (9.5%), Benha University

Fig. 1 Flow chart for the study selection process. PICO: Patient/ Population, Intervention, Comparison, and Outcomes

(4.75%), Alexandria University (4.75%), Suez Canal University (9.5%), Zagazig University (9.5%), Minia University (4.75%), Mansoura University (4.75%), Fayoum University (4.75%), Assiut University (4.75%), Menofeya University (4.75%), and Sohag University (4.75%). Thirteen of the experts' panel (61.9%) were adult rheumatologists with special interest in pediatric rheumatology, 7 (33.3%) were pediatric rheumatologists, and 4.7% was a methodologist.

Delphi round 1

The response rate for round 1 was 100% (21/21). Consensus was reached on the inclusion of clinical standards on 92% of the items (i.e., ≥ 75% of respondents strongly agreed or agreed). There were 17 key questions and the comments raised regarding the wording of some of the recommendations. Comments (excluding minor editing suggestions) were more frequent for key points, monitoring of disease, and treatment target. There was no diversity of opinion in round 1.

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Delphi round 2

The response rate for round 2 was 100% (21/21). The percentage of those who received a high-rank recommendation (rank 7–9) ranged from 85.7 to 100%. Due to a similarity with another statement, two statements were retired. On all of the clinical standards, there was agreement (i.e., 75% of respondents strongly agreed or agreed). Table 2 displays the amount of evidence attributed to each statement, as well as the mean, standard deviation, and level of agreement, as determined by the Oxford Centre for Evidence-Based Medicine (CEBM) guidelines [9]. The wording of the remarks was unanimously agreed upon (>80% agreement).

Recommendations for the management of FMF

At the end of round 2, a total of twelve recommendation items, categorized into 2 sections (4 recommendations in the diagnosis section and 8 in management), were obtained. Regarding management, we categorize disease definition, genetic predisposition, disease activity, and prognosis. Regarding the management section, we categorize the target of treatment, drugs used, treatment of acute attack, monitoring of therapy, and amyloidosis management.

Regarding FMF definition, familial Mediterranean fever (FMF) is a monogenic autoinflammatory disease that causes recurrent fevers and serosal inflammation of the abdomen, lungs, and joints. Its prevalence varies among different ethnicities being most common among the East Mediterranean territory including Egypt *(LE 1, GoR: A, mean rate± SD 8.85 ± 0.35, % of agreement 100%, level of agreement H).*

What is the genetic predisposition for FMF? *(LE 1, GoR: A, mean rate± SD 8.47 ± 0.74, % of agreement 100%, level of agreement H)*

FMF is an autosomal recessive disease, it is caused by gain of function mutations in the (Mediterranean fever) MEFV gene, which encodes pyrin protein. About 10% of patients with FMF who are clinically diagnosed have no known mutation in the MEFV gene. On the MEFV gene, there are more than 300 mutant variations. The majority of the mutations occur between amino acids 680 and 761 in exon 10. The most common gene mutation is M694V (valine for methionine at position 694), which was discovered to be the most prevalent. Also, E148Q was found in heterozygous and homozygous groups in Egypt.

How FMF is diagnosed and what is the role of the MEFV gene in the diagnosis of FMF? *(LE 1, GoR: A, mean rate± SD 8.28 ± 1.45, % of agreement 90.5%, level of agreement H)*

FMF should be diagnosed and managed only by a physician who is experienced in FMF (either pediatric rheumatologists or adult rheumatologists with interest in pediatric rheumatology; however, management can be carried out in a multidisciplinary teamwork and other specialties can be included like clinical geneticists, internists, nephrologists, and gastroenterologists.)

Possible triggers of attacks: Emotional stress, intense physical activity, viral infection, and menstruation *(LE 3, GoR: B, mean rate ± SD 8.61 ± 0.81, % of agreement 95.2%, level of agreement H)*

The prognosis of FMF is variable and depends mainly on the attack frequency and the development of complications. Usually, the attacks decrease in frequency with age and improve with the treatment. Certain genotypes as M694V are associated with a higher disease activity and higher incidence of developing amyloidosis if not properly treated, while early treatment and patient compliance carry good prognosis *(LE 3, GoR: B, mean rate± SD 8.47 ± 0.74, % of agreement 100%, level of agreement H).*

Disease activity *(LE 3, GoR: B, mean rate ± SD 8.61 ± 0.81, % of agreement 95.2%, level of agreement H)*

Disease activity measurement using the Autoinflammatory Diseases Activity Index (AIDAI): score ≥9 points

Table 4 The treatment target in FMF management

Treatment target		LE	GoR	Mean Rate±SD	% of agreement	Level of agreement
Clinical target	• **Complete response**: ≤ 1 FMF attack in 6 months • The alternate target is **nearly a complete response**: one attack in 3 months	4	C	8.09±1.41	85.7%	H
Laboratory response	Serum amyloid A (SAA) < 10 mg/L					
Functional response	**Patient-Reported Outcomes Measure (PROMs):** functional ability (CHAQ/HAQ), and quality of life assessment A minimum clinically important difference (MCID) of 0.22 is used to consider functional outcome improvement					

LE level of evidence, *GoR* Grade of Recommendation, *FMF* familial Mediterranean fever, *CHAQ* Child Health Assessment Questionnaire, *SAA* serum amyloid A, *MCID* minimum clinically important difference, *PROMs* Patient-Reported Outcomes Measure

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Table 5 Summary of recommendations of FMF management

Standard	Statement	LE	GoR	Mean rate ± SD	% of agreement	Level of agreement
General considerations	- Start treatment of FMF at the time of clinical diagnosis, without waiting for genetic testing, except if the attacks are not severe or frequent, a period of 3-month observation is recommended to confirm the pattern of the attacks before starting treatment. - Treatment with colchicine should be started as soon as possible as the first line of treatment	1	A	8.8 ± 0.51	100%	H
Colchicine therapy considerations	- Colchicine is very efficacious in preventing FMF attacks and associated amyloidosis. - The treatment with colchicine is usually lifelong, and a trial to reduce the dose may be attempted after five years of complete clinical and subclinical remission.	1	A	8.8 ± 0.51	100%	H
	- Colchicine should not be discontinued before conception, during pregnancy or lactation; also, men do not need to stop colchicine before conception except if conception delayed as its effect on sperm count is still a controversy.	3	C	8.8 ± 0.51	100%	H
	- **Dose of colchicine:** a) A dose of 0.05 mg/kg/day can be used (maximum 2 mg/day). Start gradually and use the least dose to control disease. Single dose is better for compliance. b) Starting dose of ≤ 0.5 mg/day for children < 5 years of age c) 0.5–1.0 mg/day for children 5–10 years of age d) 1.0–1.5 mg/day in children > 10 years of age e) Start with a low dose and increase the dose according to: a. The patient's response b. Tolerance f) Patients with amyloidosis or very high disease activity may start with higher doses. g) The maximum dose in children 2 mg/day - Dosing can be in single or divided doses, depending on: • Tolerance (divide if diarrhea or related abdominal pain) • Patient compliance	3	C	8.61±0.86	95.2%	H
	- **Colchicine side effects:** • The most common side effects of the treatment are diarrhea and vomiting. These side effects are dose-dependent and more common at higher doses. Other uncommon side effects are myelosuppression, myopathy, neuropathy, hepatotoxicity, nephrotoxicity, and hypersensitivity reaction • If liver enzymes are elevated more than twofold the upper limit of normal, colchicine should be reduced and the cause of elevation should be further investigated.	3	C	8.71 ± 0.46	100%	H

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Table 5 (continued)

Standard	Statement	LE	GoR	Mean rate ± SD	% of agreement	Level of agreement
	- **Colchicine tolerance and compliance:** a) There is a high rate of poor compliance with colchicine therapy among patients. Reason includes concerns about: I. Lifelong use of the drug II. Adverse effects such as bloating and diarrhea III. Fertility IV. Embarrassment and laziness b) Lack of compliance should be considered in all patients with FMF in with colchicine ineffectiveness. c) Lactose intolerance and diarrhea have been reported and may affect compliance; in these patients, we may try: I. Temporary reduction of dairy products II. Split doses III. Dose reduction IV. Anti-diarrheal and spasmolytic V. Once resolved return to regular dose in a gradual stepwise fashion d) Increasing compliance and decreasing side effects may be through: I. Dietary modification (i.e., temporary reduction of dairy products) II. Increase the dose in a gradual stepwise fashion III. Gastric prokinetics substances and spasmolytic agents IV. Patient education (particularly for teenagers)	4	C	8.33±0.79	100%	H
	- **Colchicine resistance and failure** • Ensure: a. Optimum patient compliance and adherence to therapy b. The dose has been increased up to a maximum tolerated dose of colchicine (up to 2mg in children up to 3mg in adults) • Compliant patients not responding to the maximum tolerated dose of colchicine for more than 6 months can be considered non-respondent or resistant (7) • Those non-responders or resistant patients; additional biological treatments are indicated (after confirming compliance)	2	B	8.61±0.6	95.2%	H
	- **Dose reduction after remission:** • If a patient is in complete remission with no attacks for more than 5 years and no elevated APR especially serum amyloid A, gradual dose reduction could be considered after expert consultation with strict continued monitoring to avoid subclinical amyloidosis. • Dose reduction after remission is considered extremely rare and appropriate only in a small minority of patients	5	D	8.29 ± 1.87	90.5%	H

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Table 5 (continued)

Standard	Statement	LE	GoR	Mean rate ± SD	% of agreement	Level of agreement
Anti-interleukin 1 (IL-1) therapy: Anakinra and Canakinumab.	- IL-1 inhibitors are considered the second line of treatment of FMF in patients who showed intolerance to colchicine or have colchicine-resistant FMF. • Dose: Anakinra: - children ≥2 years and adolescents: subcutaneous: 1 to 2 mg/kg/ dose once daily. Canakinumab: 2 mg/kg SC q2-4wk; may increase to 4 mg/kg q4wk if the clinical response is not adequate. >40 kg: 150 mg SC q4wk. • Duration: continuous therapy in addition to colchicine • Il-1 inhibitors can be used as bridging therapy for 1–3 months in addition to colchicine then continue colchicine monotherapy.	2	C	8.57±0.81	95.2%	H
Tumor necrosis factor (TNF)-alpha inhibitors and IL-6 inhibitor (tocilizumab):	- They have been used with promising results in some cases, but the real efficacy is still not established.	5	D	8.28 ± 1.14	90.5%	H
Management of acute attacks	- When suspecting an attack, always consider other possible causes. - During the attacks: a) Continue the usual dose of colchicine and use NSAID b) In protracted febrile myalgia, low dose steroids lead to the resolution of symptoms; NSAID and IL-1-blockade might also be a treatment option. c) NSAIDs are suggested for the treatment of leg pain d) Chronic arthritis in a patient with FMF might need additional medications, such as DMARDS (e.g., methotrexate), intra-articular steroid injections or biologics (anti-TNF) without preference of specific type of anti-TNF than another.	4	C	8.61 ± 0.67	100%	H
Monitoring of therapy	a) At the onset of treatment, follow up patients for 3–6 months to monitor its therapeutic effect on attack frequency and severity (clinical diary and APR) b) In controlled compliant patients, follow-up frequency may be up to 1 year. c) Identifying possible trigger may help in preventing possible attacks through temporarily increasing the colchicine dose. d) The persistence of attacks and/or of subclinical inflammation represents an indication to increase the colchicine dose e) Monitoring for possible colchicine toxicity especially with possibility of: • Drug interactions (as with cyclosporine and CYP3A4 inhibitors) • Consumption of grapefruit or grapefruit juice f) CBC with differential, liver enzymes (elevated greater than twofold the upper limit reduce colchicine AND investigate the cause), CRP, urine analysis, kidney functions, and serum amyloid are investigations needed in follow-up visits every 3 months	3	C	8.71±0.56	100%	H

Table 5 (continued)

Standard	Statement	LE	GoR	Mean rate ± SD	% of agreement	Level of agreement
A. Amyloidosis complicating FMF	a. **Prevention** • By good control of FMF and maintaining normal SAA protein concentration between attacks b. **Treatment** • Colchicine is still the corner stone which can stabilize or even improve proteinuria in FMF-associated amyloidosis • IL-1 inhibitors could be used • End-stage renal disease should be treated the same way as other causes of renal failure, including transplantation. After renal transplantation, tight control of inflammation should be continued	4	C	8.61 ± 0.8	95.2%	H

LE level of evidence, *GoR* Grade of Recommendation, *FMF* familial Mediterranean fever, *MEFV* Mediterranean fever, *PRINTO* Paediatric Rheumatology INternational Trials Organisation, *GoR* Grade of Recommendation, *DMARDS* disease-modifying anti-rheumatic drugs, *TNF* tumor necrosis factor, *IL* interleukin, *SAA* serum amyloid A, *CRP* C-reactive protein, *APR* acute phase reactant, *CYP3A4* cytochrome P3A4

identifies active patients, while an AIDAI total score <9 points identifies patients as inactive.

Table 4 shows the treatment target in FMF management, while Table 5 shows the summary of recommendations of FMF management.

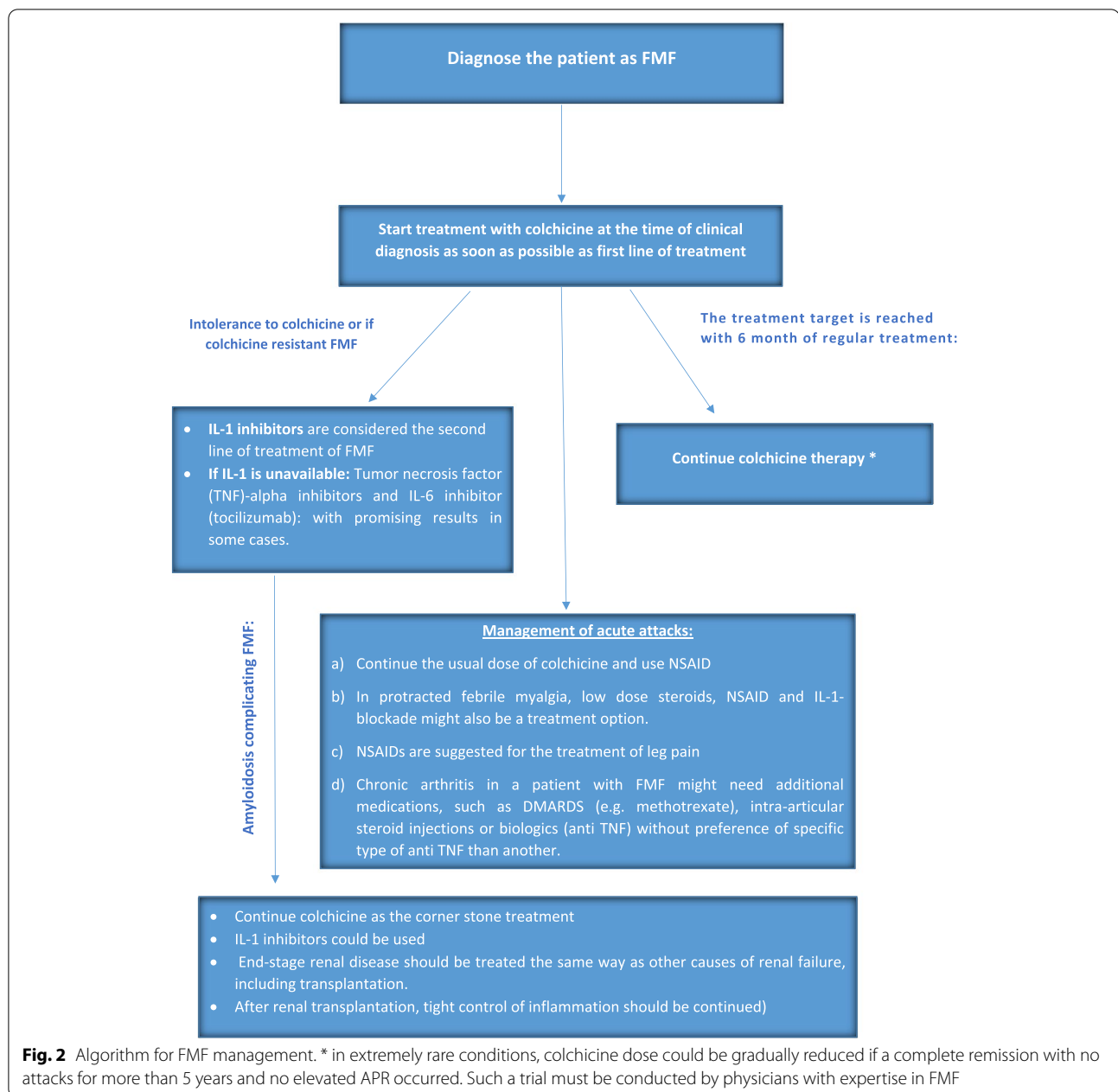### Application of the primary recommendations to clinical practice guidelines

Figure 2 shows an algorithm for the management of familial Mediterranean fever.

Discussion

Familial Mediterranean fever (FMF) is the most common hereditary autoinflammatory disease in the world and is characterized mainly by recurrent short-lived episodes of peritonitis, pleuritis, arthritis, and rash, and usually with accompanying fever [16]. This study was carried out to provide a consensus, evidence-based recommendations for the diagnosis, evaluation, and treat-to-target management of children living with FMF. The overarching principles were to provide practical evidence-based statements that enable treating healthcare professionals to implement the treat-to-target strategy for the management of their FMF patients in their standard practice, as well as to cover as many aspects of FMF patient treatment as possible after their diagnosis was confirmed. The validity of the guidelines was endorsed by a multifaceted expert panel (including rheumatologists, pediatricians, and a methodologist) who took part in this study, the Delphi process development group's high level of agreement, and the inclusion of the various therapeutic options available with their benefits, risks, and side effects.

T2T is a medical method for achieving remission through the identification of specific illness management targets. The ultimate goal of FMF treatment is to eliminate spontaneous attacks and reduce subclinical inflammation in between attacks. Three categories were highlighted as targets in this guideline: (1) clinical target (complete response: ≤ 1 FMF attack in 6 months; the alternate target is nearly a complete response: one attack in 3 months); (2) laboratory response (serum amyloid A (SAA) 10 mg/L); and (3) Functional response Patient-Reported Outcomes Measure (PROMs) (Functional Ability (CHAQ) and quality of life. Based on the heterogeneity between the FMF patients for the type and severity of attacks, such stratification of treatment targets and modalities of therapy are important to be able to tailor the management approach and monitoring of the cases to the individual patient's condition [17]. Broadly, this is in agreement with the EULAR guidelines [7] which identified the target of improvement of quality of life based on two main goals in the treatment of FMF. The first is to prevent the clinical attacks and the second is to suppress.

Chronic subclinical inflammation and elevation of acute-phase reactant: In agreement with the outcome of the study carried out by the EUROFEVER, EUROTRAPS, and the Paediatric Rheumatology INternational Trials Organisation (PRINTO) networks [18], this guideline endorsed the use of the Autoinflammatory Diseases Activity Index (AIDAI) in monitoring the patients' clinical response. The AIDAI score is a valid and straightforward method of determining disease activity in FMF/MKD/TRAPS/CAPS patients. This instrument is said to be simple to use in clinical practice and could be utilized as the standard efficacy measure in future clinical trials.

Fig. 2 Algorithm for FMF management. * in extremely rare conditions, colchicine dose could be gradually reduced if a complete remission with no attacks for more than 5 years and no elevated APR occurred. Such a trial must be conducted by physicians with expertise in FMF

FMF is an autosomal recessive disease; it is caused by gain of function mutations in the (Mediterranean fever) MEFV gene, which encodes pyrin protein.

Clinical manifestations of FMF vary from one patient to another, influenced by gene penetrance and environmental and epigenetic factors; negative genetic testing does not exclude FMF.

FMF patients who are carrying two of the commonly mutated alleles (homozygotes or compound heterozygotes), *M694V* mutation or mutations at 680 to 694 position on exon 10, are at higher risk of severe disease.

Asymptomatic patients with two pathogenic FMF mutations and risk factors for AA amyloidosis (such as family history; chronically increased acute phase reactants, particularly serum amyloid A protein) should be thoroughly evaluated and managed. Negative mutation does not exclude FMF.

The most commonly encountered gene mutations in heterozygous and homozygous groups in Egypt are E148Q. Clinical criteria are thought to be sufficient for diagnosing FMF in normal practice, particularly in endemic countries, and so FMF treatment should begin at the time of clinical diagnosis, rather than waiting for genetic testing [19]. However, using clinical criteria, or if the treating healthcare provider has limited familiarity with FMF symptoms, or if the patient presents with vague or atypical symptoms, diagnosing FMF might be difficult or delayed. Following the molecular cloning of MEFV, genetic testing became available as a diagnostic adjunct, particularly in unusual instances like the ones described above, as well as phenotypic 2 patients (those who show with AA amyloidosis in the absence of other conventional FMF disease signs). In different cohorts, this trait accounts for less than 2% of patients [20]. Genetic testing and the elimination of other causes of persistent inflammation are required for diagnosis [21]. In non-endemic instances, however, genetic testing is recommended to support or confirm the diagnosis of FMF. Genetic testing can also reveal important details regarding the severity of the condition, such as the reaction to colchicine, the likelihood of disease complications, and, ultimately, the prognosis in the long run [22, 23].

This guideline emphasized the care of cases with colchicine resistance and failure, in addition to the management of established cases and acute attacks. Although there is no clear definition of "colchicine resistance," the most frequently recognized description is monthly attacks or consistently increased inflammatory markers despite adherence to a maximally tolerated colchicine regimen [7, 21]. Patients who are colchicine-resistant (crFMF) or colchicine-intolerant (ciFMF) may benefit from biologic treatments. In resistant or intolerant instances, interleukin (IL)-1 antagonists are the preferred treatment. IL-1 antagonists, such as anakinra and canakinumab, have now reached thousands of FMF patients who are resistant to or intolerant to colchicine, with clinical evidence of their efficacy and safety. However, information on their long-term utility in terms of preventing damage and practice guidelines for the rational use is still lacking. Although FMF is considered an IL-1-mediated disease, serum IL-6 concentrations have been found to be elevated in FMF. Tumor necrosis factor (TNF)-alpha inhibitors and IL-6 inhibitor (tocilizumab) have been used with promising results in some cases, but the real efficacy is still not established [24–28].

FMF may be accompanied by various inflammatory conditions. When they accompany FMF, treatment of these conditions is the same as their usual treatment in non-FMF patients. In FMF, chronic arthritis not responding to colchicine monotherapy may require addition of other therapy, such as disease-modifying anti-rheumatic drugs (DMARDs), or intra-articular steroid injections, or biologics. Similarly, protracted febrile myalgia that is resistant to colchicine can be treated with glucocorticoids, NSAIDs, and IL-1 antagonists. The treatment of FMF-related amyloidosis was the emphasis of this recommendation. There is a link between elevated serum SAA levels and an increased risk of amyloidosis-related death. The desired SAA value would be less than 10 mg/L, as this cut-off is associated with a 60% chance of amyloid deposit regression and increased survival [29]. CRP values of 5 mg/L in FMF children during attack-free periods can be an adequate substitute for SAA in guiding therapy decisions if SAA is not available [30]. The use of IL-1 inhibitors improves renal function in AA amyloidosis patients, according to previous studies [31, 32].

The main strengths of the study are related to the diversity as well as the expertise of the participants, the high levels of consensus achieved, and the agreement with the most recently published FMF treatment recommendations. However, caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations in this report. Several new therapeutic alternate options are currently being studied for patients unresponsive to colchicine. In the interests of specific patients and special circumstances, it may be necessary or even advantageous to deviate from the standards. Deviation from rules should not necessarily be considered negligent, just as conformity to guidelines may not be a defence against an allegation of negligence.

In conclusion, FMF is an enigmatic disorder in both its pathogenesis as well as clinical manifestations. Though FMF usually presents with intermittent acute attacks, good percentage of the patients suffer from the disease complications. Early diagnosis and adherence to therapy are key points for the patients' well-being. This guideline provides an opportunity to set out best practice based on current evidence and expert consensus. In addition, they will help to increase consistency in practice and promote the highest standards of care.

Abbreviations
AIDAI: Autoinflammatory Diseases Activity Index; APR: Acute phase reactant; CEBM: Centre for Evidence-based Medicine; CHAQ: Child Health Assessment Questionnaire; ciFMF: Colchicine-intolerant; CrFMF: Colchicine-resistant; CRP: C-reactive protein; CYP3A4: Cytochrome P3A4; DMARDs: Disease-modifying anti-rheumatic drugs; FMF: Familial Mediterranean fever; GoR: Grade of Recommendation; IL: Interleukin; MEFV: Mediterranean fever; NSAIDs: Non-steroidal anti-inflammatory drugs; PICO: Patient/Population, Intervention, Comparison, and Outcomes; PRINTO: Paediatric Rheumatology INternational Trials Organisation; PROMs: Patient-Reported Outcomes Measure; RCTs: Randomized controlled trials; SAA: Serum amyloid A; T2T: Treat to target; TNF: Tumor necrosis factor.

Availability of data and materials
The data will be available upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was performed in accordance with the Helsinki Declaration. This was a multistep process which followed the "Clinical, Evidence-based, Guidelines" (CEG) initiative protocol (ethical approval code: 34842/8/21, ethical board Tanta University) aiming at setting up an actionable clinical gold standard for treat-to-target management of rheumatic and bone diseases. As per the Egyptian national Ethical Committee regulations, verbal informed consent was required from all the participants included in the study. All the participants included in the study gave their verbal informed consent. All the participants were kept anonymous, in compliance with data protection regulations.

Consent for publication
Not applicable

Competing interests
The authors declare that the corresponding author is associate editor in the Egyptian Rheumatology and Rehabilitation, Mohammed Mortada, and Yasser El Miedany are among editorial board of the journal.

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