

## **Defining colchicine resistance/intolerance in patients with familial Mediterranean fever: a modified-Delphi consensus approach**

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**Rheumatology Key Messages:**

- There is no standard definition for colchicine intolerance/resistance in familial Mediterranean fever (FMF)
- Using a Delphi consensus-based approach, eight core statements defining colchicine resistance/intolerance in FMF were developed
- These statements may serve as a guide for the management of patients with FMF

## ABSTRACT

**Objectives.** Colchicine is the main treatment for familial Mediterranean fever (FMF). Although a number of individuals with FMF are intolerant/resistant to colchicine, there is no standard definition of colchicine resistance/intolerance. We developed a set of evidence-based core statements defining colchicine resistance/intolerance in patients with FMF that may serve as a guide for clinicians and health authorities.

**Methods.** A set of statements was identified using a modified-Delphi consensus-based approach. The process involved development of an initial colchicine resistance/intolerance-related questionnaire derived from a systematic literature review. The questionnaire, which was completed by an international panel of 11 adult and pediatric rheumatologists with expertise in FMF, was analysed anonymously. The results informed draft consensus statements that were discussed by a round-table expert panel, using a nominal group technique to agree on the selection and wording of the final statements.

**Results.** Consensus among the panel was achieved on 8 core statements defining colchicine resistance/intolerance in patients with FMF. A definition of resistance was agreed upon that included recurrent clinical attacks (average one or more attacks per month over a 3-month period), or persistent laboratory inflammation in between attacks. Other core statements recognize the importance of assessing treatment adherence, and the impact of active disease and intolerance to colchicine on quality of life.

**Conclusion.** Based on expert opinion, a set of evidence-based core statements defining colchicine resistance/intolerance in patients with FMF were identified to help guide clinicians and health authorities in the management of patients with FMF.

## INTRODUCTION

Familial Mediterranean fever (FMF) is an autoinflammatory disease characterised by recurrent episodes of fever and serositis, accompanied by elevated biomarkers of inflammation usually with childhood onset and a markedly increased prevalence in individuals of Mediterranean and Middle Eastern descent [1]. Although the clinical phenotype is characterised by discrete attacks, there may be persistent inflammation in patients who are inadequately treated. Colchicine has been the standard therapy for over 40 years and has been shown to suppress clinical and laboratory findings of inflammation and prevent amyloid A (AA) amyloidosis [2–6]. However, reports suggest that up to 5% of patients do not respond to colchicine and are at risk of persistent inflammation and its complications [6, 7]. This may be due to genetic and/or environmental factors that may impact disease severity and/or colchicine bioavailability [8].

Recent advances in the understanding of the mechanisms leading to inflammation have revealed that increased interleukin (IL)-1 $\beta$  production is pivotal in driving signs and symptoms and systemic inflammation in FMF. Indeed, several observations have shown that inhibiting IL-1 is highly effective in FMF patients. Some attempts have been made to define colchicine-resistant FMF [7, 9–13], with the aim of identifying patients who should be offered additional treatments, such as those targeting IL-1 [9, 14]. However, there is no standard and validated definition for colchicine resistance [15]. Our aim was to achieve consensus on a set of evidence-based core statements defining ‘colchicine resistance’, as well as adherence and intolerance, to serve as a guide for rheumatologists and other health professionals in the treatment and follow-up of FMF patients.

## MATERIALS AND METHODS

The following methodologies were used to reach a consensus on colchicine resistance/intolerance definitions in FMF patients: systematic literature review and Delphi consensus-based consultation with an expert committee (Figure 1) [16, 17].

**Systematic Literature Review:** In January 2018, a steering group consisting of 2 rheumatologists (SO and JBKD) defined the questions that were to be addressed through a systematic literature review, namely, to identify different definitions of colchicine resistance/intolerance/compliance in FMF patients. The systematic literature review was conducted between August-October 2018. The term 'colchicine resistance' or 'colchicine failure' was coined in 2004 [10]; the search covered all studies, in English, published up until October 2018. Database searches were conducted using PubMed, Embase and the Cochrane library. The following search terms were used: (familial mediterranean fever[MeSH Terms] OR 'familial mediterranean fever'[tiab] OR FMF[tiab]) AND (Colchicine[tiab]) AND (resistance[tiab] OR resistant[tiab] OR intolerance[tiab] OR intolerant[tiab] OR ineffective[tiab] OR fail[tiab] OR unresponsive[tiab] OR response[tiab]) in English. Following removal of duplicates, titles and abstracts were screened and final inclusion of articles was based on review of the full text. Levels of evidence for each article were determined using the Oxford Centre for Evidence-Based Medicine (CEBM) standards [16]. The literature search, title and abstract screening, as well as data extraction, was conducted by ES. The results of the title and abstract screening process were discussed with an experienced author (SO). The summary of findings

of the systematic literature review were presented to SO and FdB, who formulated the Delphi survey based on this information.

**Expert panel.** The expert committee was formed by an international panel of 11 adult and pediatric rheumatologists with extensive experience of FMF, who run clinics for FMF patients and have a strong publication record in FMF. Two experts were chosen from each of the two countries with a high incidence of FMF (Turkey and Israel), with 1 expert per country selected from other countries (France, Italy, United Kingdom, Greece, Canada and Germany). Another expert from Italy, FdB, was invited as the Moderator.

**Delphi techniques.** Delphi techniques were used to consult the expert panel [17, 18]. A survey was conducted from 30 October 2018 to 6 November 2018, with questionnaires regarding potential statements derived following the systematic literature review circulated via email (Table 1). The Delphi questionnaire included open-ended questions, with experts asked to provide their input on parameters relating to colchicine resistance/intolerance/compliance derived from the literature. Analysis of the survey was conducted anonymously by SO.

The expert panel convened in November 2018 (Figure 1) for a round-table discussion using a nominal group technique (led by FdB who did not vote) to form consensus on statements defining colchicine resistance/intolerance in FMF patients. Draft consensus statements, based on the results of the questionnaire and prepared in advance of the meeting, were edited as required at the meeting, based on the discussions. If there was consensus on the statement wording following the first

round of discussion, a vote would take place, with consensus defined as  $\geq 8$  (80%,  $n = 10$  [FdB moderated the discussions and voting and edited the statements and so did not vote]) votes in agreement. When consensus was not reached after the initial round of discussion and voting, another round of discussion took place followed by a second vote.

## RESULTS

**Systematic literature review.** The systematic literature review identified 264 unique papers (Figure 2), of which 38 were considered for expert review. The list of studies considered for expert review can be found in Supplementary Data S1, available at *Rheumatology* online. All articles were analysed according to the level of evidence and grade of recommendation based on the Oxford CEBM standards.

**Delphi techniques.** Nine topics were identified from the completed questionnaires; two “additional symptoms associated with colchicine resistance” and “Autoinflammatory Disease Activity Index (AIDAI) score”, were excluded and eight draft statements covering the remaining topics were prepared for round-table expert panel discussion (Table 2). Statements were edited, if required, during round-table panel discussion, and iterations of voting and discussion conducted until the consensus of  $\geq 80\%$  was reached. Consensus was achieved on 8 core statements (Table 2); panel discussions relating to the development of each statement are provided below.

**Adherence.** Panellists were in agreement that high-level evidence supports colchicine as an effective treatment for FMF [4–6], with adherence identified as a key

issue in determining the success of treatment. The panel acknowledged that adherence is difficult to define and monitor.

Statement 1: Colchicine is the drug of choice for the treatment of FMF, and adherence is a critical issue. For the following statements, it is assumed that the patients are adherent with their prescribed colchicine treatment.

**Dose adjustment criteria.** Discussions regarding the starting dose, particularly in children, centred on the need for a standard dose, and the need for expert advice before adjusting the dose. It was agreed that the statement needed to incorporate two key aspects, namely that the dose is adjusted based on clinical activity (evaluated according to European recommendations), and secondly, that the dose is adjusted based on additional factors including age and weight. The latter were based on expert feedback that the FMF phenotype is affected by age, mutations and environment.

Statement 2: When utilizing colchicine to treat FMF, it is recommended to adjust the dose based on disease activity, with the adjustment of maximal dose in children depending on age (and weight).

**Recommended maximum colchicine dose.** Several panellists outlined that while it would be preferable to base maximum dose categories on the age of paediatric patients, there is a lack of firm data to support such categorisation. EULAR recommendations for the management of FMF advocate a standard starting dose of colchicine  $\leq 0.5$  mg/day (0.6 mg/day with tablets containing 0.6 mg colchicine) in



children younger than 5 years of age, 0.5–1 mg/day (1.2 mg/day with tablets containing 0.6 mg colchicine) in children 5–10 years of age, and 1–1.5 mg/day (1.8 mg/day with tablets containing 0.6 mg colchicine) for children older than 10 years and adults [9].

The panel acknowledged that the maximum dose of colchicine recommended to avoid toxicity is low (oral colchicine doses: 3 mg daily in adults and 2 mg daily in children) [9,19]. A more general dose range for the maximum recommended colchicine dose was agreed, with limiters of age, tolerability and signs of toxicity, and the importance of physician expertise when prescribing maximal doses also being discussed.

Statement 3: The maximum recommended colchicine dose for the treatment of FMF is 1–3 mg per day, depending on age and, to a lesser degree, weight, limited by signs of toxicity and tolerability (see below).

**Resistance to colchicine.** Panellists discussed the value of a number of clinical parameters for defining colchicine resistance, including proteinuria (an indicator of the early signs of AA amyloidosis), high fever, attack frequency and duration, and AIDAI. Proteinuria was excluded as it was not believed to be a true indicator of FMF activity, while attack duration was believed to represent FMF severity rather than colchicine resistance. It was also agreed to exclude high fever from a definition of colchicine resistance. AIDAI was not included as it is currently not validated to define colchicine resistance and the panel felt that there were no clear data demonstrating an association between AIDAI score and colchicine resistance.

The panel agreed that colchicine resistance is represented by ongoing clinical disease activity, in addition to elevated C-reactive protein (CRP) and serum amyloid A protein (SAA) in between attacks, reflecting ongoing inflammation. The panel discussed the number of attacks that would reflect an inadequate response or non-response to colchicine treatment.

Statement 4: For a patient receiving the maximum tolerated dose of colchicine, resistance to colchicine is defined as ongoing disease activity (as reflected by either recurrent clinical attacks [average one or more attacks per month over a 3-month period], or persistently elevated CRP or SAA in between attacks [depending on which is available locally]) in the absence of any other plausible explanation.

**Additional symptoms associated with colchicine resistance.** There was a discussion on the significance of the type of inflammatory attack or additional symptoms, such as arthritis, abdominal pain, chest pain, erysipelas-like rash, post-exertional leg pain and vasculitis, but the panel agreed that it was not necessary to include a statement on the manifestations or specific symptoms.

**Inclusion of secondary amyloidosis in the definition of colchicine resistance.**

The panel discussed the need to include AA amyloidosis (formerly known as secondary amyloidosis) in the definition of colchicine resistance. AA amyloidosis is the most severe complication of ongoing inflammation; and is associated with insufficient treatment and more severe scores. The statement was intended to reflect that there are many reasons for AA amyloidosis, not only colchicine resistance; for

instance, AA amyloidosis may present if colchicine treatment is started too late or if there is insufficient disease control.

Statement 5: AA amyloidosis develops as a consequence of persistent inflammation, which may be a complication of colchicine resistance.

**Colchicine intolerance.** The panel agreed that it is necessary to differentiate gastrointestinal symptoms (e.g. diarrhoea, nausea and abdominal pain), which are suggestive of colchicine intolerance and prevent patients from reaching an effective dose, from markers of toxicity, including elevated liver enzymes, leukopenia, azoospermia and neuromyopathy. Panellists acknowledged that colchicine intolerance is common while toxicity (e.g. leukopenia) is rare.

Statement 6: Colchicine intolerance, which generally manifests as mild gastrointestinal symptoms (such as diarrhoea and nausea), is common but can limit the ability to achieve or maintain the effective dose. Dose-limiting toxicity is rare and may include serious gastrointestinal manifestations (such as persistent diarrhoea), elevated liver enzymes, leukopenia, azoospermia, neuromyopathy, etc.

**Impact on quality of life (QoL).** The panel discussed the importance of QoL but acknowledged the difficulties in measuring this parameter.

Statement 7: Active disease and intolerance to colchicine affect QoL.

**Patient-reported outcomes (PROs).** A number of PROs that can be used to guide FMF disease management were outlined, including the AIDAI. Juvenile Autoinflammatory Disease Multidimensional Assessment Report (JAIMAR) – a multidimensional questionnaire for assessing children with auto-inflammatory disease in standard clinical care [20] – was proposed as a suitable assessment tool that reflects QoL in FMF. Other practical measures that were discussed included restriction in daily activity, fatigue and chronic pain, missed work/school days, and generic QoL measures.

Statement 8: The following PROs can be used to guide FMF disease management: restriction in daily activity, fatigue and chronic pain, missed work/school days, AIDAI, JAIMAR, generic QoL measures.

## **DISCUSSION**

A set of core statements were developed as a guide for physicians, other healthcare professionals, and regulatory health authorities involved in the treatment and follow-up of FMF patients with persistent inflammation following treatment with colchicine. The statements were derived using a Delphi consensus-based consultation with an expert committee.

Colchicine remains the mainstay of treatment for FMF [7] and should be continued at a tolerated dose, regardless of additional treatments started. Non-adherence to colchicine treatment is a major issue, particularly in adults [21,22]; therefore, and in accordance with the literature, adherence should be thoroughly evaluated before attributing a lack of treatment efficacy to colchicine resistance [23]. For instance,

patients with repeatedly elevated acute phase reactants or with unstable disease should be monitored more regularly for adherence [9]. However, assessing adherence is not easy due to a paucity of reliable detection methods and a lack of correlation between plasma and intracellular concentrations of colchicine [7]. The panel recommended that physicians give this aspect due consideration, discussing the importance of adherence with patients (e.g. in preventing AA amyloidosis) and explaining how skipping doses may result in an attack. The value of adherence to colchicine medication may be reinforced by regular patient education during visits and performing tests to follow disease activity and complications (e.g. CRP and SAA in serum and urinalysis to detect proteinuria) [9]. The future use of electronic pill-counting technology, assessment of centralised pharmacy reports of the filling of scripts and measurement of colchicine levels in the blood may aid in monitoring adherence. Simplifying colchicine regimens (once-daily use rather than divided doses), use of soon to be available liquid colchicine (especially for children), dealing promptly with adverse effects, reminder apps and various emotional or psychologic techniques may be among the strategies to improve adherence.

The dose range achievable with colchicine depends on the pill formulations available; oral formulations in Europe contain 0.5 mg colchicine but those in the US contain 0.6 mg colchicine. The panel discussed how age ranges, similar to those used in starting dose recommendations (i.e. < 5, 5–10 and ≥ 10 years), could be used to provide more specific dose adjustment recommendations. However, it was widely acknowledged that more work is needed to inform dose adjustment and that higher doses should only be prescribed by specialists because of the potential significant toxicity associated with the colchicine dose. While the statement included

weight as a factor in dose adjustment, it was noted that the vast majority of experts adjust the dose based on disease activity and age and not on weight. Furthermore, the specific mutation was not considered a major factor for dose adjustment but was for actual disease activity.

The panel discussed basing maximum potential colchicine doses on patients' age in the absence of dose-limiting side effects, with a potential maximum dose in young children of 1 mg/day, versus a maximum dose of 2 mg/day in older children, and 3 mg/day in adults. The importance of physician expertise was reiterated by the panel with regards to prescribing maximal doses; there is a lack of evidence on the maximal doses in specific paediatric age groups and the statement therefore stated a dose range. Concomitant medications and liver/renal function are also important considerations in the calculation of the maximal dose.

The number of attacks the panel recommended to define resistance is in alignment with relevant literature on this topic [9,13,21,24]. While the panel agreed that the definition of an attack and its severity is beyond the scope of this paper, they outlined that an attack should reflect acute clinical inflammatory findings with raised acute phase reactants, as has been reported in patients with colchicine resistance [15,25]. CRP and SAA (when available) were considered to be key laboratory markers of inflammation, erythrocyte sedimentation rate (ESR) was not believed to be suitable because of its low specificity [26-28]. For the laboratory marker criteria, it is important to measure the serum concentrations between attacks (preferably at least 2 weeks after an attack).

The aetiology underlying colchicine resistance are not completely clear but are likely to be multifactorial, including the type of genetic variants and factors relating to colchicine absorption and intracellular transport. Pathogenic variants in the *MEFV* gene have a clear effect on the severity of FMF, with those in exon 10, especially p.Met694Val, being associated with a severe disease phenotype [29]. It is therefore unsurprising that many patients with colchicine resistance are those with variants in exon 10 [30]. Indeed, in an analysis of long-term data from the CLUSTER study of canakinumab in patients with FMF, 96.7% of these colchicine resistant patients had an exon 10 variant and 70% were homozygous for p.Met694Val [31].

The panel acknowledged that FMF patients who develop associated inflammatory diseases or manifestations should receive additional treatment. For instance, a patient who develops vasculitis or sacroiliitis should receive specific treatments in addition to colchicine; it should be noted that these patients require additional treatment not because of colchicine resistance but because of manifestations attributable to the associated condition [32].

It was agreed that the term AA amyloidosis rather than secondary amyloidosis should be used. AA amyloidosis is the result of ongoing inflammation, with many reports demonstrating that this complication can almost always be prevented if the inflammatory activity is controlled with adequate dose of colchicine treatment, even in patients with continued FMF attacks. This is reflected in a declining incidence of AA amyloidosis over time [9]. There was also discussion regarding other factors, not associated with colchicine resistance that may impact the development of amyloidosis. AA amyloidosis, therefore, remains an important complication of FMF.

Intolerance is mainly due to gastrointestinal symptoms including diarrhoea, nausea and abdominal discomfort, leading occasionally to weight loss. The panel discussed how certain measures can be taken to alleviate these symptoms before introducing a new treatment to the patient. For instance, in patients with suspected lactose intolerance, dietary modification (i.e. temporarily reducing the intake of dairy products) may prove beneficial; alternatively, dose reduction and anti-diarrhoeal and spasmolytic agents are recommended. The prophylactic dosage should be re-administered gradually, upon symptom resolution. Changing the pharmaceutical formulation of colchicine pills, including other brands or those from other countries, can occasionally help. As a last resort to overcome problems with intolerance, treatment with colchicine can be initiated at 0.5 mg/day, with gradual increments in divided daily doses [9]; however, this approach is not favoured as adherence is improved with simpler treatment regimens.

EULAR recommendations for the management of FMF advise that complete blood counts and liver enzymes are routinely monitored in patients receiving colchicine [9]. The panel believed that other causes of intolerance and toxicity should also be ruled out; for example, elevated liver enzymes in adults can often be due to fatty liver or concomitant medications, in which case it is not necessary to reduce the dose of colchicine. Concomitant medications, particularly most macrolides, and renal function may result in rare toxicities such as bone marrow suppression (leukopenia), myopathy and neuropathy.



The panel acknowledged that the patient is at the centre of treatment decisions and proposed a number of tools that could be used for its assessment. Such QoL assessments should be used to inform decisions regarding biologic or other treatments. Damage indices may also play a role in the assessment of QoL. The autoinflammatory disease damage index (ADDI) has been developed to measure persisting damage caused by chronic inflammation in patients with autoinflammatory diseases [33]. Although the panel did not specifically address damage, ADDI is the appropriate measure to assess damage in patients with FMF as well. As noted in Statements 7 and 8, there are various measures to assess QoL in FMF; however, these have not been validated in the context of determining colchicine resistance.

To date, there has been no standard and validated definition for colchicine resistance. Based on expert opinion, a set of core statements were developed defining colchicine resistance/intolerance in FMF patients. These core statements are intended to improve patient care in FMF and may be used by health professionals and health authorities to guide treatment.

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## FIGURE LEGENDS

**Figure 1. Delphi consensus approach used to produce a set of evidence-based core statements to define colchicine-resistant FMF.** Process leading to the generation of a set of core statements defining colchicine resistance/intolerance in patients with FMF.

**Figure 2. Systematic literature review.** Flow chart of articles (published between January 2004 and December 2018) that were selected to identify the different definitions of colchicine resistance/intolerance/adherence in patients with FMF.



**TABLE 1** Delphi survey questionnaire used to propose definitions for colchicine resistance/intolerance in familial Mediterranean fever.<sup>a</sup>

- 
1. What is your maximum colchicine dose per day?
    - 1.0 mg
    - 1.5 mg
    - 2.0 mg
    - 2.5 mg
    - 3.0 mg
    - 3.5 mg
  
  2. How do you adjust colchicine dose?
    - Age
    - Weight
    - Mutation
    - Other
  
  3. For a patient on the maximum tolerated dose of colchicine, at what point would you declare resistance?
    - > 1 per month
    - > 3 /month
    - Other
  
  4. Is attack duration important?
    - Yes
    - No
-

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If yes, after how many days do you consider the patient to be resistant?

5. Is fever important?

- Yes
- No

If yes, do you define fever as higher than 39 degrees?

6. Which acute phase reactants should be part of the definition for resistance?

- CRP
- SAA
- ESR
- Other

If yes, at what concentration (mg/L)?

7. Other symptoms associated with, or relevant to, resistance?

- Chest pain
- Abdominal pain
- Other

8. Which of these features would you use when defining colchicine

intolerance?

- Abdominal pain
  - Diarrhoea
  - Elevated liver enzymes
  - Leukopenia
  - Nausea
-

- 
- Secondary amyloidosis
  - Other
9. How would you define the quality of life (QoL) in a patient that you consider resistant to colchicine?
- 0 – no effect
  - 1
  - 2
  - 3
  - 4
  - 5 – intolerable
10. Should disease activity (defined by the Autoinflammatory Diseases Activity Index [AIDAI] score) be part of the criteria for determining resistance to colchicine?
- Yes
  - No
11. Do you use an AIDAI score of < 9 as a measure of inactive disease?
- Yes
  - No
12. Do you use the following patient input to determine management – restriction in daily activity
- Yes
  - No
13. Do you use the following patient input to determine management – fatigue
-

- Yes
- No

14. Do you use the following patient input to determine management – missed work/school days

- Yes
- No

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<sup>a</sup>Responder comments were allowed on each question and formed the basis for much of the discussion at the consensus meeting.

SAA: serum amyloid A.

**TABLE 2** Statements presented, discussed and voted on at the expert panel round-table meeting.

<b>Topic</b>	<b>Draft statement</b>	<b>Action taken following expert panel discussion and Delphi voting</b>	<b>Final core statement</b>	<b>LoE</b>	<b>GoR</b>
Adherence	For the following statements, it is assumed that the patient is fully adherent with colchicine treatment	Revised	<b>Core statement 1:</b> Colchicine is the drug of choice for the treatment of FMF, and adherence is a critical issue. For the following statements, it is assumed that the patients are adherent with colchicine treatment	<b>1a</b>	<b>A</b>
Dose adjustment criteria	When utilizing colchicine to treat FMF, it is recommended to adjust dosing according to...	Revised	<b>Core statement 2:</b> When utilizing colchicine to treat FMF, it is recommended to adjust the dose based on disease activity with the maximal dose in children depending on age (and weight)	<b>3</b>	<b>C</b>
Recommended maximum colchicine dose	What is the recommended maximum dose of colchicine ___ mg per day	Revised	<b>Core statement 3:</b> The maximum recommended colchicine dose for the treatment of FMF is between 1–3 mg per day depending on age and, to a lesser degree, weight,	<b>3</b>	<b>C</b>

			limited by signs of toxicity and tolerability		
Resistance to colchicine	For a patient receiving the maximum tolerated dose of colchicine, resistance to colchicine can be defined as_____.	Revised	<b>Core statement 4:</b> For a patient receiving the maximum tolerated dose of colchicine, resistance to colchicine is defined as ongoing disease activity (as reflected by either recurrent clinical attacks (average one or more attacks per month over a 3-month period), or persistently elevated CRP or SAA in between attacks (depending on what is available locally), in the absence of any other plausible explanation	<b>3</b>	<b>D</b>
Additional symptoms associated with colchicine resistance	Additional symptoms associated with, or relevant to, colchicine resistance include_____	Excluded			
Inclusion of secondary amyloidosis in the definition of colchicine resistance	The definition of colchicine resistance includes secondary amyloidosis	Revised	<b>Core statement 5:</b> AA amyloidosis develops as a consequence of persistent inflammation, which may be a manifestation of colchicine resistance	<b>3</b>	<b>D</b>
Colchicine intolerance	The following clinical features can be used to define	Revised	<b>Core statement 6:</b> Colchicine intolerance, which generally manifests	<b>3</b>	<b>D</b>

	colchicine intolerance: _____		as mild gastrointestinal symptoms (such as diarrhoea and nausea), is common but can limit the ability to achieve or maintain the effective dose. Dose-limiting toxicity is rare and may include serious gastrointestinal manifestations (such as persistent diarrhoea), elevated liver enzymes, leukopenia, azoospermia and neuromyopathy.		
<b>AIDAI score</b>	An AIDAI score of ___ can be used as a measure of inactive disease in patients with FMF	Excluded			
<b>Patient QoL and patient-reported outcomes</b>	Patient quality of life is _____ affected by both colchicine resistance and colchicine intolerance in patients with FMF	Revised	<p><b>Core statement 7:</b> Active disease and intolerance to colchicine affect QoL</p> <p><b>Core statement 8:</b> The following patient-reported outcomes can be used to guide FMF disease management: Restriction in daily activity Fatigue and chronic pain Missed work/school days AIDAI, JAIMAR Generic QoL measures</p>	<p><b>3</b></p> <p><b>4</b></p>	<p><b>D</b></p> <p><b>D</b></p>

AA: amyloid A; AIDAI: auto-inflammatory diseases activity index; CRP: C-reactive protein; FMF: familial Mediterranean fever;

GI: gastrointestinal; GoR; grade of recommendation; JAIMAR: juvenile auto-inflammatory disease multidimensional assessment report; LoE: level of evidence; QoL: quality of life; SAA: serum amyloid A.



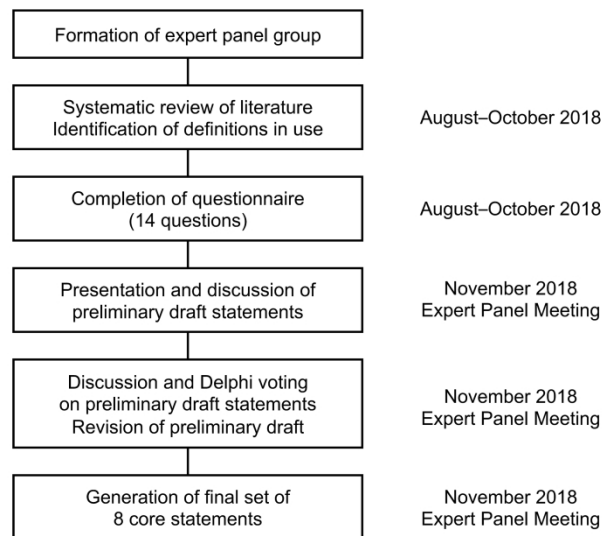


Figure 1. Delphi consensus approach used to produce a set of evidence-based core statements to define colchicine-resistant FMF. Process leading to the generation of a set of core statements defining colchicine resistance/intolerance in patients with FMF.

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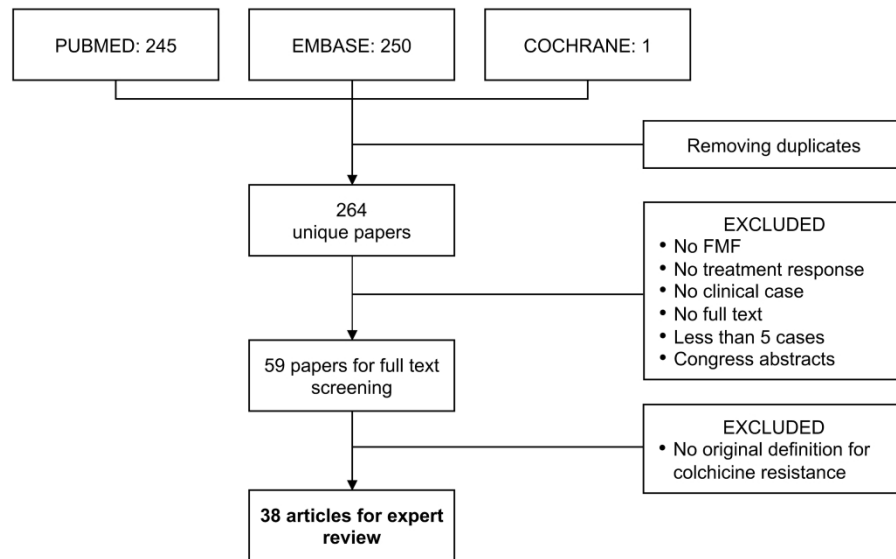


Figure 2. Systematic literature review. Flow chart of articles (published between January 2004 and December 2018) that were selected to identify the different definitions of colchicine resistance/intolerance/adherence in patients with FMF.

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