

## Recent advances in the management of children with familial Mediterranean fever

Familial Mediterranean fever (FMF) is the most frequent hereditary autoinflammatory disease characterized by self-limited episodes of fever and serositis. FMF is more prevalent among non-Askenazi Jewish, Turkish, Arabic and Armenian populations. FMF is inherited with an autosomal recessive pattern and is caused by mutations in the *MEFV* gene located on chromosome 16p13.3, encoding pyrin. AA type amyloidosis and the associated renal impairment are the most severe long-term complications. The diagnosis is established on the grounds of clinical findings. There have been a number of diagnostic criteria in the literature: the Tel Hashomer and Livneh criteria were first developed for the diagnosis of adult FMF patients. A new set of diagnostic criteria was recently proposed by Yalcinkaya *et al.* Colchicine is the best treatment option for the time being and some new agents have been tried in cases where there is colchicine resistance.

**KEYWORDS:** autoinflammatory disease ■ colchicine ■ familial Mediterranean fever ■ *MEFV* gene ■ pyrin/marenostrin

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### Learning objectives

Upon completion of this activity, participants should be able to:

- Characterize familial Mediterranean fever (FMF)
- Assess the diagnosis of FMF
- Report complications associated with FMF
- Describe the standard treatment of FMF

### Financial & competing interests disclosure

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Familial Mediterranean fever (FMF) is the most frequent hereditary autoinflammatory disease [1], affecting an estimated 100,000 people worldwide. It is characterized by self-limited intermittent episodes of fever and serositis, each lasting approximately 24–72 h. Historically, it was named ‘benign recurrent polyserositis’ and ‘familial paroxysmal polyserositis’ prior to the coining of the current name [2]. The name FMF reflects the fact that this disorder is more prevalent among Mediterranean countries and in non-Ashkenazi Jewish, Turkish, Arabic and Armenian populations. To date, the largest case series have been reported in Turkey, Armenia and Israel, and to a lesser extent in Italy, Greece and recently Japan [3]. FMF is rarely found in other regions.

FMF is inherited with an autosomal recessive pattern and is caused by mutations in the *MEFV* gene located on chromosome 16p13.3 [4,5]. Identification of *MEFV* and its protein called ‘pyrin/marenostrin’ was a major milestone in understanding and managing this disease. These studies, furthermore, led to the discovery of the protein complex called inflammasome, an intracellular protein complex that regulates IL-1 $\beta$  production and release. Pyrin is the main actor in FMF-associated inflammation by causing excessive IL-1 $\beta$  production. These findings became the foundation of the new field of autoinflammatory disorders (AIDs), and FMF continues to be the prototype [6,7]. The common manifestations of these disorders are the self-limited flares of systemic inflammation

manifested by fever and elevated acute phase reactants; and patients have normal health between these episodes. Although there is increased IL-1 $\beta$  and activation of the innate immune system [8], AIDs lack two key features of typical autoimmune disorders – that is, the inflammation does not lead to activation of specific immunity and does not cause self-recognizing immune memory in affected individuals [9]. Although FMF is not associated with immune-mediated tissue damage, these individuals are prone to develop AA type amyloidosis and associated renal impairment as the most severe long-term complications. Colchicine is the best treatment option for the time being and some new agents have been tried in cases where there is colchicine resistance.

In addition to FMF, some other conditions are also regarded as AIDs and these include TNF-receptor-associated periodic syndrome, hyper-IgD with periodic fever syndrome, cryopyrin-associated periodic syndrome, pyogenic arthritis, pyogenic gangrenosum and acne syndrome. In some of these disorders the specific genetic mutation and its relation to pyrin and inflammation has also been described; for example, PSTPIP1 (or CD2BP1) in pyogenic gangrenosum and acne syndrome [10] and NALP-3 or cryopyrin, in cryopyrin-associated periodic syndrome [8].

### Epidemiology

FMF mostly affects four populations of the south-eastern Mediterranean region: non-Ashkenazi

Jews, Turks, Armenians and Arabs [1]. The prevalence of FMF is one in 250 to one in 500 among non-Ashkenazi Jewish [11], and one in 1073 among Turkish populations [12]. Higher rates were reported among the residents of central Anatolia (Turkey). The carrier frequency is similar in Turkish [13] and north African Jewish [11] populations and the carrier frequency is one in seven among Armenians [14], and one in 11 in Ashkenazi Jews [11]. The disease is very rare in other populations, but recent reports suggest it can be found among some European populations including Italian [15] and Greek [16] populations and to a lesser extent in some other ethnic groups such as Japanese individuals [17]. Although some studies report male predominance, in general, FMF affects both genders equally [8].

### Pathogenesis

The *MEFV* gene was discovered in 1997 by two independent groups from the USA [4] and France [5]. The gene is located on chromosome 16p13.3, and includes ten exons. There have been approximately 200 mutations and polymorphisms described for the *MEFV* gene [201]. The most common mutations are located in exon 10 and include M694V, M694I, M680I, E148Q and V726A. The study by the Turkish FMF group has shown M694V (51.4%) to be the most common mutation in Anatolia, followed by M680I (14.4%) and V726A (8.6%) [8]. Some other studies have also shown the M694V mutation as the most prevalent not only among Turkish, but also among non-Ashkenazi Jewish populations [13,18–28]. Some recent studies indicated another mutation, R202Q located on exon 2, to be of importance and should take place in routine molecular diagnosis of FMF. The study also noted a significant association with homozygous AA type genotype [29].

Pyrin is composed of four domains, PYD at the N terminal, B30.2 at the C terminal and B-box and coiled coil (CC) domains in the middle [30]. After transcription in the nucleus, pyrin is transported into the cytoplasm through nuclear pores [31].

The pyrin (or marenostriin) protein interacts with the apoptosis-associated speck-like (ASC) protein by its PYD domain as a negative regulator. ASC contains the caspase recruitment domain that activates caspase-1, which acts as the converting enzyme of IL-1 and induces production of active IL-1 $\beta$  [32]. Thus, it can be said that pyrin inhibits the interaction between ASC and caspase-1 and modulates the production of IL-1 $\beta$  [33]. However, a recent study performed on

the pyrin knock-in mouse suggested that FMF was due to gain-of-function mutations in pyrin that lead to IL-1 $\beta$  activation [34]. The main function of the B30.2 domain of pyrin is not fully understood, but it has been shown to inhibit the production of the active form of IL-1 $\beta$ . Accordingly, patients carrying mutation of B30.2 can have high levels of IL-1 $\beta$  [7]. In addition, pyrin is expressed in neutrophils, eosinophils, monocytes, dendritic cells and fibroblasts and can affect the microtubules of the cytoskeleton. This latter effect may seem to be similar to the effect of colchicine on the tubular system of the cell, but the exact function of pyrin and the pathogenetic mechanism of *MEFV* mutation is still not fully understood [28,30].

### Clinical manifestations

The disease generally occurs in the first decade of life and 90% of cases have their first attack before the age of 20 years [2]. The disease manifests with fever (96%), peritonitis (91%), pleurisy (57%), arthritis/arthralgia (45%), erysipelas-like erythema (13%) and amyloidosis (2%) [35]. Rare symptoms are headache, aseptic meningitis, purpura and, in laboratory evaluation, proteinuria. Clinical features occur, last between 6 and 96 h and resolve gradually without any treatment. Some prodromal symptoms such as nausea, vomiting, myalgia, arthralgia, headache, dyspnea, back pain, constipation and diarrhea may occur. Between attacks patients feel totally well [36].

Attacks may be triggered by some events such as cold exposure, stress, menstrual cycle, infections, exercise and fat-rich meals [37]. Patients infected by *Helicobacter pylori* have been shown to have more frequent and severe attacks [38].

### Characteristics of FMF manifestations

#### ■ Fever

The fever varies between 38 and 40°C and lasts between 12 and 72 h. Fever is the cardinal finding of FMF attacks and was shown to be the most frequent manifestation in a study from Turkey, which had the largest series of patients reported from a single country [8].

#### ■ Abdominal pain

Abdominal pain is another frequently observed clinical feature of FMF and is seen in 95% of patients. The pain may be focal and then may spread and become generalized. Constipation, and less frequently diarrhea, may be observed. Attacks last from approximately 1 to 3 days. Although the peritonitis resolves spontaneously,

recurrent attacks may cause bowel obstructions and female infertility due to pelvic adhesions [39].

The clinical picture of abdominal pain can be confusing because it may resemble acute peritonitis. Sometimes the x-ray imaging results indicate ileus. Due to these clinical uncertainties, some patients undergo unnecessary operations and appendectomies [2,8,40].

#### ■ Chest pain

Chest pain might be due to inflammation of the pleura, referred pain from subdiaphragmatic inflammation or pericarditis. Unilateral pleuritic chest pain is generally seen in patients with inflamed pleura. In this case, a small amount of transient pleural effusion will be appreciated. This pleural pain will usually subside within 3 days, but may last 1 week. Pericarditis may develop in 2.4% of patients, but usually does not cause a tamponade or constructive pericarditis. Colchicine seems to be an effective standard treatment option for recurrent idiopathic pericarditis [8].

#### ■ Arthritis

This is another frequently observed clinical feature of FMF. The frequency of its occurrence differs with ancestry. It is seen in 16% of Sephardic patients as the first symptom of the disease and 75% of Sephardic patients suffer from arthritis at some time during the disease [2,41]. The incidence of arthritis in other ancestries is lower compared with Jewish populations (TABLE 1) [42]. Patients with arthritis have been demonstrated to have a higher risk of amyloidosis.

The knee, elbow, ankle and hip are the most affected joints in order of frequency and the arthritis generally emerges with a monoarticular or oligoarticular pattern. Trauma or long-lasting exercise of the legs may trigger arthritis. The affected joint generally recovers without any chronic joint change. Only 5% of arthritis causes destruction in the joint, and most of the destruction is in the hip joint [43,44].

Some patients with chronic arthritis may present with sacroiliac joint involvement, enthesitis and with slight changes in the spinal image on x-ray. However, the patients with this clinical picture are seronegative for HLA-B27 [40,45].

#### ■ Protracted febrile myalgia

Protracted febrile myalgia is one of the possible severe features of FMF that is rarely seen, but if untreated may last for up to 6 weeks. It is seen in the lower extremities and characterized by muscle pain and tenderness. To alleviate the symptoms, high-dose prednisone is the drug of choice [46].

#### ■ Erysipelas-like erythema

Erysipelas-like erythema can be described as erythematous, hot, tender and raised from the skin. It is a 10–15 cm<sup>2</sup> lesion that occurs on the lower extremity over the foot and ankle. The lesion generally lasts for 24–48 h and resolves without any treatment. The frequency is approximately 7–40% in FMF patients [2].

#### ■ Other manifestations

Splenomegaly [40], orchitis and aseptic meningitis can also be seen in FMF patients.

### Assessing disease severity & activity

Scoring systems have been developed to quantify disease severity among adult patients with FMF. Modified versions of severity scores for children with FMF were developed based on expert opinion approaches, but these versions still await validation. In a recent study, the clinical consistency of the two most commonly used severity scoring systems, Pras and Mor, were compared with pediatric FMF patients. The results revealed that these scoring systems were not statistically consistent. There has been some progress on the development of a new and improved scoring system for children [47].

Disease activity scoring is essential for clinical trials in order to standardize the assessment in

**Table 1. The prevalence of main clinical features in familial Mediterranean fever patients among different populations.**

Symptom	Turkish (%) [8]	Jewish (%) [2]	Arabic (%) [109]	Armenian (%) [110]	Japanese (%) [111]
Fever	93	100	100	100	95
Peritonitis	94	95	82	96	62
Arthritis	47	77	37	37	31
Pleuritis	31	40	43	87	36
Erysipelas-like erythema	21	46	3	8	0

studies and evaluate the efficacy of new treatment strategies. For the time being, no activity scores for autoinflammatory syndromes have been described, which limits both the assessment of the efficacy of treatment modalities currently used and foreseeing long-term complications. In a recent study, a disease activity index (Auto-Inflammatory Diseases Activity Index) for four hereditary autoinflammatory syndromes (FMF, mevalonate kinase deficiency, TNF-receptor-associated periodic syndrome, cryopyrine-associated periodic syndrome) was proposed and the authors stated that they would be in charge of conducting a prospective validation phase of Auto-Inflammatory Diseases Activity Index [48].

## Complications

### ■ Amyloidosis

Progressive AA type secondary amyloidosis and its deposition in the kidneys is the main cause of mortality of FMF [49]. SAA protein, the source of amyloid A fibrils, is produced in the liver as an acute phase reactant. However, it is not clear whether amyloidosis is a result of recurrent inflammation or whether there are additional genetic risk factors influencing the outcomes. It is likely that both components are in effect. The incidence of amyloidosis has decreased after colchicine became the main treatment option. However, amyloidosis is still observed in some countries, probably because of the delay in diagnosis or inadequate adjustment to treatment [8,50]. Some genetic factors have also been shown to be involved in the development of amyloidosis. Mutations such as V726A [51] and E148Q have been shown to be associated with a lower incidence of amyloidosis and milder disease presentation. However, some mutations detected on codon 694 were shown to be prone to a more severe disease presentation [18,19,52,53]. Two different studies showed another effective genetic factor, the SAA1 $\alpha/\alpha$  genotype would increase the risk for renal amyloidosis [52,53]. Another study is about SAA1 and the association of TNF- $\alpha$ , which is one of the main inducers of the amyloid production. The study revealed a higher carrier frequency of the TNF- $\alpha$ -308 G-A allele among FMF amyloidosis patients homozygous for SAA1 compared with FMF patients without amyloidosis [54].

Although initial studies indicated that some mutations (mainly M694V) were more pathogenic and prone to development of amyloidosis, the following studies showed that mutations of the *MEFV* gene were not the only factors causing a tendency for renal amyloidosis [35].

These findings brought up questions about genotype–phenotype correlation in FMF. Consecutive studies showed that the country of a patient is more effective than *MEFV* genotype for the development of renal amyloidosis in FMF [55]. Some other contributing factors were also defined that influence the development of renal amyloidosis. Male patients were shown to have a higher risk for amyloidosis than females. A study revealed that the place where an FMF patient lives could also be a contributing factor for the development of this complication. In that study, amyloidosis was less frequent among Jewish and Armenian patients who were living in USA [56].

Clinically, amyloidosis presents with proteinuria as the initial sign of renal involvement; hematuria and hypertension are not associated with this condition. Gradually, these patients progress to develop nephrotic syndrome and eventually renal failure within 2–13 years after onset of proteinuria [2]. In general, the diagnosis of amyloidosis requires a renal biopsy [57]. Some studies showed that the sensitivity of renal biopsy was 88%, while that of the rectal and bone marrow biopsy was close to 75%, and reported that the confirmation of the diagnosis of amyloidosis by using the abdominal fat tissue and the gingival biopsies were not favorable [58,59]. On the other hand, when a clinically active FMF patient requiring long-term treatment with colchicine develops persistent proteinuria, it is most likely from amyloidosis and the pathological investigation is generally not carried out in everyday practice. Although amyloidosis is the most common kidney disease in patients with FMF, observations from different countries indicated that FMF patients can develop a variety of glomerular diseases other than amyloidosis [60] thus nonamyloid glomerular diseases should be considered in the differential diagnosis of FMF patients with renal involvement.

### ■ Other complications

Depression, cardiac autonomic dysfunction and decline in school or job performance can be listed as other possible complications of FMF [61].

## FMF-associated vasculitides

FMF patients are known to be prone to vascular injury. In fact, immune complex positivity among FMF patients is approximately 50%. Furthermore, high TNF levels, excessive complement consumption and inadequate down-regulation of complement activation observed in FMF patients are likely to contribute in vasculopathy [62–64]. It has been well documented

that Henoch–Schonlein purpura (HSP), polyarteritis nodosa (PAN), and Behçet's disease are frequently seen in FMF patients although the exact mechanisms for the association of each vasculitis are not well understood [65–67]. For instance, HSP (a small vessel vasculitis), and PAN (a medium size vasculitis), were observed in 2.6–5.0% and 0.8–1.0% of FMF patients, respectively [2,68–73]. Likewise, a study from Israel reported a high frequency of Behçet's disease among Israeli FMF patients [74]. It is likely that an *MEFV* mutation contributes to disease susceptibility and disease severity – that is, evidence suggests that a *MEFV* mutation can cause subclinical inflammation that might contribute to susceptibility and severity of vasculitis [75]. In fact, the literature suggests an increased incidence of *MEFV* mutations in patients with HSP [76] and Behçet's disease [77].

### Diagnosis

The diagnosis of FMF is established on the grounds of clinical findings and requires a minimum of three episodes of short-term fever associated with serositis. The supportive evidence includes disease onset before the age of 20 years, family history of amyloidosis or FMF, and the absence of features of the other periodic fever syndromes. Mutational analysis of the *MEFV* gene is usually reserved for patients without typical clinical phenotypes and can be useful in differential diagnosis. It is important to point out that FMF patients almost always respond well to colchicine and this property is often used in daily practice to confirm the diagnosis in the absence of genetic analysis. There have been a number of diagnostic criteria in the literature: The Tel Hashomer [2] and Livneh [78] criteria were developed first for the diagnosis of adult FMF patients (Box 1). The Tel Hashomer criteria are the most commonly used diagnostic criteria for FMF and named after the city where they were proposed for the first time in 1997. Another diagnostic criteria was described by Pras [79] and included short-term episodes of fever, serositis and a positive response to colchicine treatment. Recently, a new set of diagnostic criteria was proposed by Yalcinkaya *et al.* (Box 1) [80].

### Laboratory investigations

Follow-up of FMF patients should include measurement of serum levels of acute phase reactants (e.g., ESR and CRP), fibrinogen, urine analysis and complete blood count. Repeating urine analysis every 4–6 months to rule out proteinuria as an early sign of amyloid nephropathy is

recommended. In addition, a complete blood count should be carried out in order to monitor leukopenia, which can be a side effect of colchicine treatment, and normocytic normochromic anemia, which is the result of chronic inflammation (i.e., anemia of chronic inflammation).

Children with FMF should be monitored for acute phase reactants (APRs) during attacks. These laboratory parameters should also be measured periodically between attacks, as some patients might present with high levels of APRs, which suggests that FMF is not only an episodic disease with inflammatory attacks, but also a chronic immune activation with subtle inflammation [81]. This subclinical inflammation might result in the following clinical and laboratory findings: splenomegaly [82], chronic normocytic normochromic anemia [83], high fibrinogen levels and elevated ESRs [84], decreased bone density [83] and growth retardation [85].

The levels of some inflammatory proteins or cytokines might indicate subclinical inflammation that persists between attacks of FMF. SAA is one of these proteins and can be used as a marker to detect and monitor treatment response and continuous inflammation [86].

### Treatment

Daily colchicine treatment has been the standard therapy for FMF since 1972 [87,88]. Colchicine, a fat soluble alkaloid, is mainly metabolized by the liver [88]. It was first used to treat gout, then used in the treatment of primary biliary cirrhosis (PBC), Behçet's disease, Sweet's syndrome and amyloidosis [89]. The response to prophylactic treatment with colchicine consists of reductions in the frequency, severity and duration of attacks. Prevention of complications, such as amyloidosis, and potentially unnecessary surgical interventions due to severe abdominal pain (e.g., laparotomy and appendectomy, among others) can be provided by colchicine treatment in FMF patients [2,90]. Prior to colchicine treatment, most patients with FMF would progress to renal failure due to amyloidosis before the age of 40 years [91].

### Dose of colchicine

The recommended dose of colchicine is 0.5 mg/day for children <5 years of age, 1 mg/day for children between 5 and 10 years of age, and 1.5 mg/day for children >10 years of age [92]. In cases where the patient does not respond to treatment, the dose should be increased gradually (e.g., 0.25 mg/step). The maximum drug dose is defined as 2.0 mg/day and does not depend

on age or body size [93,94]. If the patient has renal amyloidosis then it is crucial to use the maximum dose possible while following serum creatinine levels and liver function tests (transaminase levels) closely. Renal failure develops in two-thirds of children with amyloid nephropathy while on high daily colchicine doses (1.5–2.0 mg/day) [95]. The colchicine dose should be decreased to an appropriate level when there is a compromise of renal function. For example, in patients with end-stage renal failure (glomerular filtration rate of <10 ml/min), the dosage should be decreased by up to 50%. Optimal serum levels of colchicine have not been determined for prophylactic colchicine treatment in FMF [96]. Some authors recommend treatment with colchicine regardless of age or body weight. However, young children might need higher doses of the medication in order to control the disease manifestations and so the physicians should be more careful about the dosage of colchicine in this age group [97,98]. Colchicine doses specified according to the body weight and surface area ( $0.03 \pm 0.02$  mg/kg/day and  $1.16 \pm 0.45$  mg/m<sup>2</sup>/day, respectively) should be recommended in childhood, especially in small children [99].

### Side effects of colchicine

The most common side effects of colchicine includes those affecting the gastrointestinal system such as abdominal pain, diarrhea, nausea and vomiting. Generalized myalgia and myoneuropathy, which are less frequent adverse effects, may be a sign of intoxication, but can also be seen during regular use for prophylaxis [100,101]. Dermatological side effects (e.g., alopecia, urticaria, purpura, erythema and edema, among others), hematological side effects (e.g., thrombocytopenia, leukopenia and coagulopathy, among others), bone marrow suppression and renal and liver failure are very rarely observed [101–103]. Studies suggest that there are no adverse effects of colchicine treatment on the growth and development of children with FMF [93,104,105].

The drugs (e.g., lovastatin, midazolam, estrogen, steroids, diltiazem, nifedipine, lidocaine, erythromycin and grapefruit juice, among others) that are used concurrent with colchicine may lead to toxicity by inhibiting cytochrome CYP3A4 [93]; caution is recommended to prevent liver damage.

Colchicine is not contraindicated in pregnancy or during breastfeeding. By contrast, the use of colchicine during pregnancy may reduce the risk of abortion and preterm birth [106]. However,

### Box 1. Commonly used diagnostic criteria for familial Mediterranean fever.

#### Tel Hashomer criteria<sup>†</sup>

- Major criteria:
  - Recurrent episodes of fever accompanied by serositis
  - AA type of amyloidosis without predisposing disease
  - Response to colchicines
- Minor criteria:
  - Recurrent febrile attacks
  - Erysipelas-like erythema
  - Family history in first-degree relatives

#### Livneh criteria<sup>‡</sup>

- Major criteria:
  - Peritonitis (generalized)
  - Pleurisy (unilateral) or pericarditis
  - Monoarthritis (hip, knee or ankle)
  - Isolated fever
- Minor criteria:
  - Incomplete attacks affecting one or more sites:
    - Abdomen
    - Lungs
    - Joints
  - Exertion-related leg pain
  - Response to colchicine

#### Yalcinkaya–Ozen criteria for pediatric patients<sup>§</sup>

- Fever: axillary temperature >38°C, duration 6–72 h and ≥three attacks
- Abdominal pain: duration 6–72 h and ≥three attacks
- Chest pain: duration 6–72 h and ≥three attacks
- Arthritis: duration 6–72 h, ≥three attacks and oligoarthritis
- Family history of familial Mediterranean fever

<sup>†</sup>The definitive diagnosis requires at least two major criteria or one major plus two minor criteria.

<sup>‡</sup>The definitive diagnosis requires at least one major criterion or at least two minor criteria.

<sup>§</sup>The definitive diagnosis requires at least two criteria.

Data taken from [2,78,80].

decreasing the drug dose to 0.5–1.0 mg/day is recommended.

### Alternative treatment modalities

For the patients unresponsive to standard colchicine therapy, alternative approaches such as weekly intravenous colchicine, anti-IL-1, anti-IFN- $\alpha$ , TNF-blocking agents (thalidomide, etanercept and infliximab) and even selective inhibitors of serotonin reuptake, and can be tried, but further clinical trials are required to determine their efficacy. Bone marrow transplantation is not effective in the treatment of FMF [107,108]. Currently, there is no proven alternative agent to daily colchicine for the treatment of children with FMF.

### Conclusion

FMF continues to be the prototype of the AIDs. The common manifestations of these disorders are the self-limited flares of systemic inflammation manifested by fever and elevated acute phase reactants; these individuals have normal

health between the episodes. Therefore, FMF should be considered in the evaluation of any child who has had recurrent attacks of fever plus serositis. Although clinical findings have an important role in the diagnosis of FMF, *MEFV* mutation analysis is a key element to confirm the diagnosis, especially in an atypical presentation form of the disease. On the other hand, it should be noted that patients suspected of FMF may have unidentified mutations. The most serious complication of FMF is the development of progressive AA type secondary amyloidosis and its deposition in the kidneys. Colchicine treatment can decrease the number and severity of attacks and can prevent amyloidosis.

### Future perspective

The future needs to include identifying other susceptible genes associated with FMF and international validation of the new set of diagnostic criteria which were set up by Yalcinkaya *et al.* [80]. The application of new treatment modalities (i.e., biologic agents and IL-1 receptor antagonists) in unresponsive cases to standard colchicine treatment is another requirement of FMF management. Furthermore, describing the resistance or response to treatment; developing and validating instruments for assessing outcome are also becoming important in FMF, as well as in other rheumatologic diseases of childhood.

### Executive summary

- The most common mutations are located in exon 10 and include M694V, M694I, M680I, E148Q and V726A.
- Pyrin is composed of four domains, PYD at the N terminal, B30.2 at the C terminal and B-box and coiled coil domains in the middle.
- Pyrin is the main actor in familial Mediterranean fever (FMF)-associated inflammation by causing excessive IL-1 $\beta$  production.
- The contributing factors that increase the risk of developing of renal amyloidosis are M694V homozygosity, SAA1 $\alpha/\alpha$  genotype and male gender.
- Henoch–Schönlein purpura, polyarteritis nodosa and Behçet’s disease are frequently seen in FMF patients.
- Tel-Hashomer and Livneh criteria were developed first for the diagnosis of adult FMF patients. A new set of diagnostic criteria was proposed by Yalcinkaya *et al.*
- There has been some progress on the development of a new and improved scoring system for pediatric FMF patients.
- The recommended dose of colchicine is 0.5 mg/day for children <5 years of age, 1 mg/day for children between 5 and 10 years of age, and 1.5 mg/day for children >10 years of age.
- Bone marrow transplantation is not effective in the treatment of FMF.
- SAA levels can be used as a marker to detect and monitor the treatment response and continuous inflammation.
- Further data are needed to determine the efficacy of more recently introduced biologic therapies in patients who are unresponsive or intolerant to standard colchicine therapy.

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## Recent advances in the management of children with familial Mediterranean fever

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### Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.

	1	2	3	4	5
The activity supported the learning objectives.					
The material was organized clearly for learning to occur.					
The content learned from this activity will impact my practice.					
The activity was presented objectively and free of commercial bias.					

1. A 16-year-old female presents to your office complaining of fever of 38 C for the last 2 days. Additionally, she complains of abdominal pain and left knee pain since the fever started. She denies any injury. She reports that she has had this illness before and resolved without further treatment. You suspect this patient may have familial Mediterranean fever (FMF); however, you need to ask additional questions. Which of the following would be most appropriate to ask to confirm your diagnosis?

- A Has anyone else in your family experienced similar symptoms?
- B Is she of Spanish descent?
- C Did the last episode last greater than 1 week?
- D Have you traveled outside of the country recently?

2. Which of the following is correct regarding the diagnosis of FMF?

- A It requires a minimum of 2 episodes of short-term fever associated with serositis
- B It only responds to colchicine 50% of the time
- C The Tel Hashomer criteria are the most commonly used diagnostic criteria for FMF
- D The Yalcinkaya-Ozen criteria are the oldest utilized for the diagnosis of FMF
- E Testing for mutations in the *MEFV* gene is always required to diagnose FMF

3 Which of the following is a major complication associated with FMF?

- A Cardiac autonomic dysfunction
- B Depression
- C Henoch-Schonlein purpura
- D Progressive AA type secondary amyloidosis

4 The standard treatment for children with FMF is:

- A Bone marrow transplant
- B Daily colchicine
- C Tumor necrosis factor (TNF)-blocking agents
- D Selective serotonin reuptake inhibitors (SSRIs)