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Pediatrics 2007;119:e474-e483; originally published online Jan 22, 2007;
DOI: 10.1542/peds.2006-1434

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<http://www.pediatrics.org/cgi/content/full/119/2/e474>

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American Academy of Pediatrics

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Colchicine Use in Children and Adolescents With Familial Mediterranean Fever: Literature Review and Consensus Statement

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

The daily application of colchicine is the standard therapy for prophylaxis of attacks and amyloid deposition in familial Mediterranean fever. However, because of many issues (eg, dosage, time of introduction, etc), no standardized treatment recommendations have been established. In this work we review the available literature on colchicine use with respect to its indication, efficacy, mode of application, and safety in children and adolescents with familial Mediterranean fever. On the basis of this analysis, a consensus statement on the application of colchicine in children and adolescents with familial Mediterranean fever was developed by caregivers from Germany, Austria, and Turkey.

www.pediatrics.org/cgi/doi/10.1542/peds.2006-1434

doi:10.1542/peds.2006-1434

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Key Words

familial Mediterranean fever, colchicine, evidence-based guidelines, treatment

Abbreviations

FMF—familial Mediterranean fever

SAA—serum amyloid A

GFR—glomerular filtration rate

Accepted for publication Sep 14, 2006

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FAMILIAL MEDITERRANEAN FEVER (FMF) is the most common of the autoinflammatory syndromes and is characterized by recurrent inflammatory attacks of fever and serositis. The disease course can be complicated by development of amyloid depositions and organ failure.¹

Colchicine is the standard drug used to prevent febrile attacks and amyloidosis. We (an interdisciplinary group of German and Turkish physicians) analyzed the data and graded the evidence on the efficacy and adverse effects of colchicine therapy in children and adolescents with FMF.

Our analysis was intended to:

- grade the evidence of colchicine therapy in children and adolescents with FMF and discuss the potential for the development of standardized treatment guidelines from the available data;
- increase the awareness of colchicine use for FMF and improve the adherence to this medication;
- answer questions about the practical application of colchicine for FMF (eg, time of colchicine introduction, dosage for prophylaxis of attacks and amyloidosis, potential adverse effects and toxicity); and
- identify important unsolved issues to initiate additional studies on the use of colchicine for FMF.

A consensus statement on the application of colchicine in children and adolescents with FMF is provided.

METHODS

The analysis of evidence is based on the following elements:

1. Meetings of participating caregivers were held in Düsseldorf (January 31, 2004) and Berlin (October 1, 2004 and March 12–13, 2005), Germany.
2. An extensive literature search using PubMed's Medline with the keywords "familial Mediterranean fever" and "age 0–18 years" (June 2006) was conducted and produced 695 hits. In addition, cited references, standard text books, databases, and reviews were included.
3. Published results from colchicine-treatment trials in adult patients with FMF were used if data from children were scarce or not available.

Evidence collected from these 3 sources were graded as shown in Table 1.

The consensus statement was approved by the pharmacotherapy working group of the Scientific Society of Pediatric Rheumatologists in Germany and Austria (Gesellschaft für Kinder- und Jugendrheumatologie).

TABLE 1 Quality of Evidence

Quality	Evidence
I	One or more properly randomized, controlled trial
II	Well-designed controlled trial without randomization Well-designed cohort or case-control analytic study, preferably from >1 center or research group Comparisons between times or places with or without the intervention Dramatic results in uncontrolled experiments
III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Adapted from Feldmann W. *Evidence-Based Pediatrics*. 1st ed. Hamilton, Ontario, Canada: BC Decker; 2000.

MECHANISM AND PHARMACOKINETICS

Mechanism

The precise mechanism of colchicine in FMF is unknown. Colchicine interacts with the intracellular microtubuli, thus interfering with intracellular granula transport and secretion of mediators (reviewed in ref 3). It inhibits leukocyte chemotaxis at rather low concentrations and alters expression of adhesion molecules on the surfaces of neutrophils and their potential to produce cytokines.

Pharmacokinetic Studies

Fifteen percent to 30% of colchicine is excreted in the urine within the first 24 hours, and excretion is still measurable on day 10.⁴ It is metabolized in the liver via a cytochrome P450 3A4–dependent pathway.⁵ Up to two thirds of the drug is eliminated via feces.⁶

Bioavailability ranges from 24% to 88%.⁷ The maximum serum concentration is reached ~1 hour after oral application and varies between 2.2 and 6.7 ng/mL.^{8–10} The serum half-life time is estimated to be ~10 to 20 hours.^{10,11} In leukocytes the drug exhibits a terminal half-life of up to 35 to 40 hours.¹²

In patients with FMF with renal amyloidosis on hemodialysis, elimination half-life was significantly increased (400%) and total clearance was decreased compared with patients with normal renal function.¹³

Patients with alcoholic cirrhosis showed impaired colchicine clearance and prolonged half-life time compared with healthy controls.¹⁴

INDICATION AND EFFICACY OF COLCHICINE IN FMF

Prophylaxis of Attacks

The first indication for a beneficial role of colchicine in the prophylaxis of FMF attacks came from a number of open-labeled trials.^{15–21} In 3 independent placebo-controlled trials, colchicine led to a significant reduction in the number of attacks in adults (grade I).^{22–24}

In children, evidence for the effectiveness of colchicine came from open-labeled studies (grade II).^{25–32} Long-term application of colchicine led to a complete

remission in approximately two thirds and a partial remission (defined as significant decrease of attack frequency or remission of a single symptom) in approximately one third of the patients with FMF. A minority (~5% of patients) did not respond to this treatment (grade II).^{30,31}

There are several reasons for an early introduction of colchicine treatment in children (grade III): (1) protection from painful febrile attacks¹; (2) avoidance of potentially unnecessary medical interventions (eg, laparotomy, appendectomy, synovectomy, orchidopexy, intravenous antibiotics, etc)³³; and (3) protection from amyloidosis (refer to the next section), which can already occur in early childhood.¹

Prophylaxis of Amyloidosis

During an observation period of 4 to 11 years, 30% of adult patients without treatment developed proteinuria, whereas only 0.4% of patients taking colchicine showed kidney involvement (grade II).³⁴

None of the patients with persisting attacks despite colchicine treatment developed long-term proteinuria (grade III).³⁴ These findings point out that the regular intake of colchicine prevents amyloidosis, whereas it is less effective on the complete cessation of attacks.

Among 809 pediatric patients on colchicine, no manifestation of amyloidosis was observed.^{30,35} In a cohort of 704 children, 1 patient developed end-stage renal disease, most likely because of poor compliance.³⁶ In the Turkish FMF registry, 2.3% developed amyloidosis and were noncompliant with respect to regular colchicine intake (grade II).³⁷

Treatment of Amyloidosis

In a subgroup of pediatric and adult patients it was demonstrated that colchicine treatment can stabilize or even improve proteinuria secondary to amyloidosis (grade II).^{30,34,35,38} Several reports have demonstrated a stabilization and/or improvement of renal function after introduction of colchicine in children and adults with already established nephrotic syndrome resulting from amyloidosis,^{38–48} but no improvement was documented in patients with end-stage renal disease (grade III).³⁸

COLCHICINE APPLICATION AND DOSE FINDING

Dosage for Prevention of Attacks and Amyloidosis

Majeed et al^{28,35} reported that 0.5 mg/day of colchicine in 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 was successful in the majority of children (grade II). In a large pediatric cohort the final colchicine dosage at the end of the observation period was 1.0 mg/day in 40%, 1.5 mg/day in 25%, and 2.0 mg/day in 35% of the patients (grade II). Patients in whom 2.0 mg/day was not sufficient to control attacks did not

benefit from an additional increase of dosage (grade III). It is important to note that the final dosage was assigned irrespective of age and body size.^{30,36}

In a small child, the colchicine dosage is established on an individual basis; a body size–adapted increase of dosage is not necessary to control the disease (grade II).⁴⁹

In large long-term cohort studies in adults and children, the dose was adjusted for control symptoms. When using this approach for dosage finding, development of proteinuria was rare (0.4%)³⁴ or not observed at all (grade II).^{28,30,35}

In the “high-risk” group of patients with kidney transplantation for secondary amyloidosis, the development of amyloid deposition was significantly associated with low colchicine doses (eg, ≤ 1.0 mg/day) (grade II).⁵⁰

No data exist on a “desired optimal average serum level of colchicine” in the treatment of FMF.⁵¹

Dosage for Control of Subclinical Inflammation (C-Reactive Protein, Erythrocyte Sedimentation Rate, and Serum Amyloid A)

For patients without clinical symptoms, the acute-phase response can still be elevated⁵² (grade II). To detect subclinical inflammation in children with FMF, serum amyloid A (SAA) might be more sensitive than erythrocyte sedimentation rate, C-reactive protein, or fibrinogen.⁵³ In adults, the prognosis of amyloidosis in various diseases is correlated to median SAA values (grade II).⁵⁴

Increased SAA levels may be controlled by adjustment of colchicine dosage (grade II).⁵³ However, because the influence of subclinical inflammation on amyloidosis, growth, and development has not been analyzed in prospective studies, the benefit of dose adjustment according to this parameter remains unknown.

Dosage for Treatment of Amyloidosis

In adult patients, deterioration of renal function is significantly associated with low daily colchicine dosage (≤ 1.5 mg/day) (grade II).³⁸

In children with amyloid nephropathy, high daily colchicine doses (1.5–2.0 mg/day) lead to an improvement of impaired renal function in approximately two thirds of patients (grade II).⁵⁵

Dosage According to Genetic Constellation

An association has been shown between the development of amyloidosis and the presence of mutations at position 694 within the *MEFV* gene^{56–64} (grade II), age of colchicine introduction⁵⁷ (grade III), and requirement of higher colchicine doses^{61,63} (grade III). However, secondary amyloidosis has also been demonstrated in patients with FMF harboring other mutations.^{65–68} Polymorphisms within the *SAA* gene (*SAA1 α / α* genotype) were also found to be significantly associated with the development of amyloidosis.^{63,64,69–72}

No prospective data are available regarding whether

colchicine dosage depends on the underlying mutation within the *MEFV* gene or the *SAA1α/α* genotype.

Dosage in Patients With Renal or Liver Failure

Renal impairment is associated with an increased risk of colchicine toxicity,^{38,73–77} but patients with preterminal chronic renal failure who exhibit no adverse effects were also reported^{34,38} (grade II). Reduction of the dosage in patients with a glomerular filtration rate (GFR) of <50 mL/minute and additional dose adjustment or cessation of colchicine therapy in patients with a GFR of <10 mL/minute have been recommended (grade III).^{78–80}

Colchicine was shown to be safe in patients with liver cirrhosis (grade II).^{81,82}

Use of Colchicine in Clinically Unaffected Children Showing Two Mutations in the *MEFV* Gene

Children who show 2 mutations in the *MEFV* gene but no clinical symptoms might develop clinical signs of FMF on follow-up (phenotype I) or might not show any clinical symptoms in adulthood (phenotype III⁸³). No data on the application of colchicine in these subjects are available.

Mode of application

Bioavailability of colchicine tablets versus suspension was found to be equivalent in 1 study⁸⁴ and slightly lower in another study.⁹ If small amounts of colchicine have to be applied (eg, 0.25 mg) liquid preparations, which usually contain alcohol, are available, or capsules might be produced by a local pharmacy. Intravenous application of colchicine prevented the occurrence of diarrhea, which is frequently associated with oral application, but it increases the risk of systemic toxicity.⁸⁰ A stepwise introduction of the starting dose seems to lower the rate of gastrointestinal adverse effects.²⁹

SAFETY OF COLCHICINE TREATMENT

Adverse Effects

Adverse effects of long-term colchicine treatment in >1225 pediatric patients with a total treatment time of

>2400 years are summarized in Table 2 (grade II). The occurrence of gastrointestinal adverse effects seems to be dose dependent (grade II).⁹ Mild steatorrhea and enzyme inhibition (eg, lactose malabsorption) may be responsible for part of the gastrointestinal adverse effects (grade III).^{85,86} In children with FMF, development of myopathy with progressive proximal muscle weakness and generalized myalgia was very rarely observed on regular colchicine dosage (grade III).⁸⁷ Myoneuropathy with involvement of the peripheral nervous system may be a sign of intoxication (grade III) but can also occur on a regular prophylactic dosage.⁸⁸ It seems to be reversible (grade II).⁸⁸ Bone marrow alteration (eg, hemolytic or aplastic anemia, pancytopenia, neutropenia, and thrombocytopenia) was reported in cases of acute intoxication but is rarely observed under adequate treatment (grade II).^{89,90} A combination of colchicine treatment and concomitant virus infection (for example cytomegaly) may cause blood cell alterations (grade III).⁹¹ Dermatological reactions such as urticaria, purpura, erythema, and edema may rarely be seen (grade III).⁹²

Growth is not negatively affected by colchicine treatment.^{30,93} Instead, treatment with colchicine leads to increased weight gain and growth velocity in children with FMF.⁹⁴ No differences were observed in terms of height velocity and levels of insulin-like growth factor 1 in children with FMF on colchicine and healthy controls (grade II).⁹³

Drug Interactions

Interactions are possible with drugs that interfere with cytochrome P450 family enzymes⁹⁵ (eg, macrolides⁹⁶ and cyclosporin⁹⁷) (grade III). Consumption of grapefruit juice can also interact with colchicine metabolism.⁹⁸

Female Fertility

Colchicine is believed to affect fertility by its potential to inhibit cell division (grade III), but it also prevents the formation of peritoneal adhesion (demonstrated in rodents,⁹⁹) and the development of ovarian amyloidosis with subsequent ovarian dysfunction (grade III).¹⁰⁰

TABLE 2 Adverse Events of Colchicine in Long-term Treatment of Children

Reference	N	Follow-up (Total Nos. of Months)	Adverse Effects, No. of Patients							Growth
			Diarrhea	Nausea	Leukopenia	Thrombocytosis	Epistaxis	Angioneurotic Edema	Alopecia	
25	5	>30	^a	—	—	—	—	—	—	Normal
26	14	42	^a	—	—	—	—	—	—	Normal
28	32	921	3	—	—	—	—	—	—	NA
30	350	>25 200	^a	^a	1	—	—	1	1	Normal
29	94	NA	—	—	—	1	—	—	—	NA
33	192	NA	13	—	—	—	—	—	—	NA
35	476	NA	^b	—	—	—	—	—	2	NA
49	62	2901	6	5	1	—	—	—	—	NA
Total	1225	>29 094	>20	>5	2	1	1	1	2	

NA indicates that data are not available; —, no adverse effect reported.

^a Adverse effects reported but not specified.

No clear relationship between female infertility and colchicine therapy has been established. Several reports have described fertile women with FMF on colchicine therapy for FMF (grade III).¹⁰¹⁻¹⁰³ A lack of colchicine treatment is likely to bear a greater risk of female infertility compared with the tentative risk of infertility resulting from colchicine.

Pregnancy Loss

In pregnant women with FMF who were treated with colchicine, spontaneous abortions occurred in 12% compared with 20% in untreated women (grade III).¹⁰³ Pregnancy seems to aggravate amyloid nephropathy¹⁰⁴ with a significant risk for adverse maternal and fetal outcomes¹⁰⁵ (grade III).

Mutagenic and Teratogenic Effects of Colchicine

Because colchicine crosses the placenta, considerable concern exists about the potential mutagenic and teratogenic effects of this medication. In some reports, colchicine therapy during conception and the first trimester of pregnancy had no adverse effects on the offspring.^{102,106-109} In patients treated with colchicine, no increase was observed in mitotic rates, the percentage of tetraploidy, or the rate of chromosome breakage.¹⁰⁷

In a limited number of studies the rate of aneuploidy was analyzed further in women taking colchicine for FMF: there were 2 cases (trisomy 21) among 131 pregnant women,¹⁰³ no case of trisomy 21 in 430 amniocenteses,¹⁰³ 2 cases (trisomy 21 [1], Klinefelter syndrome [1]) among 444 pregnant women,¹¹⁰ 4 cases (trisomy 21) among 2000 pregnant women,¹¹¹ and 6 cases of numerical chromosomal abnormalities (2 of them trisomy 21) among 628 pregnancies¹¹² (grade III). Although a mutagenic and teratogenic potential of colchicine has been discussed along with some case reports, there is no clear evidence for human teratogenicity or increased rate of aneuploidy. Some authors recommend amniocentesis in women taking colchicine during pregnancy.^{111,112}

Among pregnancies fathered by men taking colchicine for FMF, no significant difference was observed regarding abortions or congenital malformations (grade III).¹¹³

Breastfeeding

Breastfed infants are exposed to colchicine. The drug concentrations in breast milk are similar to those in the mother's serum.¹¹⁴⁻¹¹⁶ Follow-up of these children has been unremarkable thus far (grade III).¹¹⁴

Male Fertility

When applying dosages of colchicine that highly exceed those applied for FMF, a toxic effect on sperm production and function can be measured in humans.¹¹⁷ Data on male fertility are conflicting: impaired male fertility in patients taking colchicine has been reported.¹¹⁸ In con-

trast, volunteers and patients with FMF who received colchicine in therapeutic doses showed normal sperm analyses (grade III).^{119,120} In summary, azoospermia resulting from colchicine seems to be a rare adverse effect. FMF itself might cause azoospermia and infertility (eg, by amyloid deposits in the testis) (grade III).¹²¹

ACUTE COLCHICINE INTOXICATION

After a latent asymptomatic period, colchicine intoxication leads to bone marrow hypoplasia, myocardial depression, acute respiratory distress syndrome, acute oliguric kidney failure, and various metabolic abnormalities (grade III).¹²² Lethal outcome after ingestion of as little as 7 mg of colchicine¹²³ as well as survival after ingestion of 60 mg of colchicine have been reported.¹²⁴ Toxic effects occur in association with serum colchicine levels >5 ng/mL (grade III).¹²⁵

Prevention of Absorption/Elimination Therapy

Administration of ipecacuanha directly after colchicine administration does reduce the serum level of the medication, but no controlled study on its beneficial role is available at this time (grade III).¹²⁶ Repeated administration of activated charcoal should prevent the absorption of potentially toxic colchicine ingestion¹²⁷; however, thus far, no impact on the clinical outcome was shown (grade III).¹²⁸ Gastric lavage represents an option within the first 60 minutes after ingestion. However, there are no data regarding its benefit in colchicine intoxication. The elimination of colchicine via hemodialysis, peritoneal dialysis, charcoal hemoperfusion, exchange transfusions, and plasma exchange seems to be impossible (grade III).¹²⁹

Supportive Therapy

Supportive therapy includes intensive care measures. Administration of granulocyte colony-stimulating factor can be beneficial in colchicine-caused bone marrow depression and pancytopenia (grade III).¹³⁰ An elevation of troponin I may be indicative for cardiac colchicine toxicity (grade III).¹³¹

TREATMENT OF ATTACKS AND ALTERNATIVE TREATMENT MODALITIES

Treatment of Attacks

Numerous drugs have been applied for symptomatic treatment of attacks without systematic evaluation.^{1,132} The effective use of nonsteroidal antiinflammatory drugs in mild attacks and opioids in severe events has been described (grade III).¹³² Steroids have not been beneficial.¹

Interferon- α treatment at the earliest signs of an attack does not consistently exhibit a beneficial effect on the course of an episode (grade II).^{133,134}

In large cohort studies, increasing colchicine dosages

during attacks had no beneficial effect on symptoms (grade II).^{1,132}

Alternative Treatment Strategies for Patients Who Have Not Responded to Colchicine

The effect of alternatives in patients who have not responded to prophylactic colchicine application were only reported in single cases and small series: effects have been described for additional thalidomide,¹³⁶ interferon- α ,¹³⁷ infliximab^{138,139} (grade III), and weekly intravenous colchicine.¹³⁵ In children, some effects were observed with the herbal drug ImmunoGuard on the severity of symptoms without altering attack frequency or duration (grade III).¹⁴⁰ Bone marrow transplantation has no present role in the treatment of FMF (grade III).^{141,142}

In summary, colchicine is effective in the prophylaxis of attacks and amyloidosis in children and adolescents with FMF. It is safe for long-term treatment. There is no alternative treatment option available.

CONSENSUS STATEMENT

A consensus statement on the application of colchicine in children and adolescents with FMF was developed on the basis of analysis of the data discussed above.

Consensus was reached by discussion at the consensus meetings in Düsseldorf and Berlin and mailing manuscript drafts to all conference attendees. Evidence and recommendations were graded as shown in Tables 1 and 3.

Indication and Efficacy in FMF

1. The continuous use of colchicine for prophylaxis of attacks and prevention of amyloidosis is recommended for children with FMF (grade IIA).
2. Colchicine should be introduced in children with FMF as soon as the diagnosis has been established and continued for life (grade IIIA).

3. Colchicine is recommended for the treatment of amyloidosis (grade IIA). Dosage should be adjusted for age and renal function.

Application and Dose Finding

1. A starting dose of ≤ 0.5 mg/day (for children < 5 years of age), 1.0 mg/day (for children 5–10 years of age), or 1.5 mg/day (for children > 10 years of age) should be administered orally (grade IIA).^{*} Colchicine dosage should be increased in a stepwise fashion (eg, 0.25 mg/step) up to a maximum of 2.0 mg/day to control disease in patients who do not clinically respond to the standard dosage (grade IIIC).
2. In high-risk patients (eg, after kidney transplantation, patients with amyloidosis), higher colchicine doses (up to 2 mg/day) should be applied independent of the dose needed for control of clinical symptoms (grade IIB).
3. Monitoring has to be careful in the presence of impaired renal or liver function. For patients with severe renal failure (GFR of < 10 mL/min), the dosage should be reduced by 50% (eg, ≤ 1 mg/day) (grade IIIB).

Safety

1. The most frequent adverse effect is diarrhea. Modification of diet (ie, temporary reduction of milk products), split doses, and dose reduction are recommended (grade IIA). Once symptoms resolve, the regular prophylactic dosage has to be introduced in a stepwise fashion (grade IIIA). Careful clinical workup with respect to possible adverse effects including laboratory examination should be performed every 4 to 6 months (grade IIB).
2. Special attention has to be attributed to possible drug interactions (grade IIIC).
3. It is recommended to continue colchicine treatment during conception, pregnancy, and breastfeeding (grade IIIB/C). There is no consensus on the need for karyotyping of the fetus (grade IIIC). However, a detailed fetal ultrasound is recommended (grade IIIA).

Acute Colchicine Intoxication

A patient with suspected colchicine intoxication should be taken to a hospital immediately. Activated charcoal should be administered within the first 60 minutes after ingestion (50 g in adults, 20–30 g in children) (grade IIIC). If the ingestion has occurred > 60 minutes ago, the repetitive administration of activated charcoal is recom-

TABLE 3 Classification of Recommendations

Grade	Recommendation
A	Good evidence to support the recommendation that the intervention should be performed
B	Fair evidence to support the recommendation that the intervention should be performed
C	Poor evidence regarding the value or harm of the intervention; recommendations may be made on other grounds
D	Fair evidence to support the recommendation that the intervention should not be performed
E	Good evidence to support the recommendation that the intervention should not be performed

Adapted from Feldmann W. *Evidence-Based Pediatrics*. 1st ed. Hamilton, Ontario, Canada: BC Decker; 2000.

^{*}In some countries, colchicine is available as a tablet containing 0.6 mg of the drug. In this case, the starting dose should be adapted (eg, ≤ 0.6 mg/day in children 6 years of age, 1.2 mg/day in children 6–12 years of age, and 1.8 mg/day in children > 10 years of age).

mended (grade IIIC). If possible, suction via a duodenal tube should occur within the first 60 minutes (grade IIIC).

Any patient with a colchicine overdose should be monitored as an inpatient for at least 12 hours after ingestion and at least 72 hours after an intravenous overdose (grade IIIB).

Treatment of Attacks

Attacks can be treated with nonsteroidal antiinflammatory drugs and, in severe cases, opioids (grade IIIA). It is not recommended to treat attacks with a high colchicine dosage at the beginning of an attack or to increase prophylactic dose (grade IIIE).

ACKNOWLEDGMENTS

Members of the pharmacotherapy working group of the Scientific Society of Pediatric Rheumatologists in Germany and Austria (Gesellschaft für Kinder und Jugendrheumatologie) included Susanne Bechtold-Dalla Pozza, Isa Feddersen, Johannes-Peter Haas, Dirk Hobusch, Gerd Horneff, Anton Hospach, Rolf Keitzer, Günter Klaus, Gerhard Koch, Kristina Mathony, Markus Metzler, Hartmut Michels, Tim Niehues, Ingrid Pilz, Johannes Roth, Michaela Sailer-Höck, Monika Schöntube, Werner Schoppel, Lothar Schuchmann, Claudia Sengler, Hannsjörg W. Seyberth, Andreas Urban, Norbert Wagner, and Elisabeth Weißbarth-Riedel.

We thank Dr M. Brockstedt for critically reading the "Acute Colchicine Intoxication" section.

REFERENCES

1. Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever: a survey of 470 cases and review of the literature. *Am J Med.* 1967;43:227–253
2. Feldmann W. *Evidence-Based Pediatrics*. 1st ed. Hamilton, Ontario, Canada: BC Decker; 2000
3. Ben Chetrit E, Levy M. Colchicine: 1998 update. *Semin Arthritis Rheum.* 1998;28:48–59
4. Ertel NH, Mittler JC, Akgun S, Wallace SL. Radioimmunoassay for colchicine in plasma and urine. *Science.* 1976;193:233–235
5. Tateishi T, Soucek P, Caraco Y, Guengerich FP, Wood AJ. Colchicine biotransformation by human liver microsomes: identification of CYP3A4 as the major isoform responsible for colchicine demethylation. *Biochem Pharmacol.* 1997;53:111–116
6. Hunter AL, Klaassen CD. Biliary excretion of colchicine. *J Pharmacol Exp Ther.* 1975;192:605–617
7. Sabouraud A, Rochdi M, Urtizberea M, Christen MO, Achtert G, Scherrmann JM. Pharmacokinetics of colchicine: a review of experimental and clinical data. *Z Gastroenterol.* 1992;30(suppl 1):35–39
8. Rochdi M, Sabouraud A, Girre C, Venet R, Scherrmann JM. Pharmacokinetics and absolute bioavailability of colchicine after i.v. and oral administration in healthy human volunteers and elderly subjects. *Eur J Clin Pharmacol.* 1994;46:351–354
9. Ferron GM, Rochdi M, Jusko WJ, Scherrmann JM. Oral absorption characteristics and pharmacokinetics of colchicine in healthy volunteers after single and multiple doses. *J Clin Pharmacol.* 1996;36:874–883
10. Girre C, Thomas G, Scherrmann JM, Crouzette J, Fournier PE. Model-independent pharmacokinetics of colchicine after oral administration to healthy volunteers. *Fundam Clin Pharmacol.* 1989;3:537–543
11. Thomas G, Girre C, Scherrmann JM, Francheteau P, Steimer JL. Zero-order absorption and linear disposition of oral colchicine in healthy volunteers. *Eur J Clin Pharmacol.* 1989;37:79–84
12. Chappey ON, Niel E, Dervichian M, et al. Colchicine disposition in human leukocytes after single and multiple oral administration. *Clin Pharmacol Ther.* 1993;54:360–367
13. Ben Chetrit E, Scherrmann JM, Zylber-Katz E, Levy M. Colchicine disposition in patients with familial Mediterranean fever with renal impairment. *J Rheumatol.* 1994;21:710–713
14. Leighton JA, Bay MK, Maldonado AL, Schenker S, Speeg KV. Colchicine clearance is impaired in alcoholic cirrhosis. *Hepatology.* 1991;14:1013–1015
15. Goldfinger SE. Colchicine for familial Mediterranean fever. *N Engl J Med.* 1972;287:1302
16. Eliakim M, Light A. Letter: colchicine-aspirin for recurrent polyserositis (familial Mediterranean fever). *Lancet.* 1973;2(7841):1333
17. Manialawi M. Colchicine for familial Mediterranean fever. *N Engl J Med.* 1973;289:752
18. Hassan A, Trabolsi B, Farid Z. Letter: colchicine for familial Mediterranean fever. *N Engl J Med.* 1974;290:973
19. Hovsepian JM. Letter: colchicine for familial Mediterranean fever. *N Engl J Med.* 1974;290:973
20. Reimann HA. Letter: colchicine for familial Mediterranean fever. *N Engl J Med.* 1974;290:973
21. Ozkan E, Okur O, Ekmekci A, et al. A new approach to the treatment of periodic fever. *Med Bull Istanbul Med Fac.* 1972;5:44–49
22. Goldstein RC, Schwabe AD. Prophylactic colchicine therapy in familial Mediterranean fever: a controlled, double-blind study. *Ann Intern Med.* 1974;81:792–794
23. Zemer D, Revach M, Pras MA, et al. A controlled trial of colchicine in preventing attacks of familial Mediterranean fever. *N Engl J Med.* 1974;291:932–934
24. Dinarello CA, Wolff SM, Goldfinger SE, Dale DC, Alling DW. Colchicine therapy for familial Mediterranean fever: a double-blind trial. *N Engl J Med.* 1974;291:934–937
25. Levy M, Eliakim M. Long-term colchicine prophylaxis in familial Mediterranean fever. *Br Med J.* 1977;2(6090):808
26. Lehman TJ, Peters RS, Hanson V, Schwabe A. Long-term colchicine therapy of familial Mediterranean fever. *J Pediatr.* 1978;93:876–878
27. Branski D, Gross-Kieselstein E, Abrahamov A. Colchicine therapy in familial Mediterranean fever: prophylactic benefit in 6 childhood patients. *Clin Pediatr (Phila).* 1978;17:14–15
28. Majeed HA, Carroll JE, Khuffash FA, Hijazi Z. Long-term colchicine prophylaxis in children with familial Mediterranean fever (recurrent hereditary polyserositis). *J Pediatr.* 1990;116:997–999
29. Gedalia A, Adar A, Gorodischer R. Familial Mediterranean fever in children. *J Rheumatol Suppl.* 1992;35:1–9
30. Zemer D, Livneh A, Danon YL, Pras M, Sohar E. Long-term colchicine treatment in children with familial Mediterranean fever. *Arthritis Rheum.* 1991;34:973–977
31. Majeed HA, Barakat M. Familial Mediterranean fever (recurrent hereditary polyserositis) in children: analysis of 88 cases. *Eur J Pediatr.* 1989;148:636–641
32. Ertekin V, Selimoglu MA, Pirim I. Familial Mediterranean fever in a childhood population in eastern Turkey. *Pediatr Int.* 2005;47:640–644

33. Rawashdeh MO, Majeed HA. Familial Mediterranean fever in Arab children: the high prevalence and gene frequency. *Eur J Pediatr*. 1996;155:540–544
34. Zemer D, Pras M, Sohar E, Modan M, Cabili S, Gafni J. Colchicine in the prevention and treatment of the amyloidosis of familial Mediterranean fever. *N Engl J Med*. 1986;314:1001–1005
35. Majeed HA, Carroll JE, Khuffash FA, Hijazi Z. Familial Mediterranean fever in children: the expanded clinical profile [published correction appears in *QJM*. 1999;92:545]. *QJM*. 1999;92:309–318
36. Padeh S. Periodic fever syndromes. *Pediatr Clin North Am*. 2005;52:577–609
37. Saatci U, Ozen S, Ozdemir S, et al. Familial Mediterranean fever in children: report of a large series and discussion of the risk and prognostic factors of amyloidosis. *Eur J Pediatr*. 1997;156:619–623
38. Livneh A, Zemer D, Langevitz P, Laor A, Sohar E, Pras M. Colchicine treatment of AA amyloidosis of familial Mediterranean fever: an analysis of factors affecting outcome. *Arthritis Rheum*. 1994;37:1804–1811
39. Skrinkas G, Bear RA, Magil A, Lee KY. Colchicine therapy for nephrotic syndrome due to familial Mediterranean fever. *Can Med Assoc J*. 1977;117:1416–1417
40. Ravid M, Robson M, Kedar I. Prolonged colchicine treatment in four patients with amyloidosis. *Ann Intern Med*. 1977;87:568–570
41. Familial Mediterranean fever and amyloidosis. *Kidney Int*. 1981;20:676–685
42. Herlin T, Storm K, Hamborg-Petersen B. Remission of progressive renal failure in familial Mediterranean fever during colchicine treatment. *Arch Dis Child*. 1985;60:477–479
43. Sirera G, Tural C, Bonal J, Caralps A. Regression of nephrotic syndrome in amyloidosis secondary to familial Mediterranean fever during maintenance therapy using colchicine [in Spanish]. *Med Clin (Barc)*. 1989;92:757
44. Gertz MA, Kyle RA. Secondary systemic amyloidosis: response and survival in 64 patients. *Medicine (Baltimore)*. 1991;70:246–256
45. Zemer D, Livneh A, Langevitz P. Reversal of the nephrotic syndrome by colchicine in amyloidosis of familial Mediterranean fever. *Ann Intern Med*. 1992;116:426
46. Zemer D, Livneh A, Pras M, Sohar E. Familial Mediterranean fever in the colchicine era: the fate of one family. *Am J Med Genet*. 1993;45:340–344
47. Rozenbaum M, Rosner I. Regression of amyloidosis with colchicine in familial Mediterranean fever in an Ashkenazi patient. *Clin Exp Rheumatol*. 1995;13:126
48. Simsek B, Islek I, Simsek T, Kucukoduk S, Cengiz K. Regression of nephrotic syndrome due to amyloidosis secondary to familial Mediterranean fever following colchicine treatment. *Nephrol Dial Transplant*. 2000;15:281–282
49. Ozkaya N, Yalcinkaya F. Colchicine treatment in children with familial Mediterranean fever. *Clin Rheumatol*. 2003;22:314–317
50. Livneh A, Zemer D, Siegal B, Laor A, Sohar E, Pras M. Colchicine prevents kidney transplant amyloidosis in familial Mediterranean fever. *Nephron*. 1992;60:418–422
51. Wallace SL, Ertel NH. Occupancy approach to colchicine dosage. *Lancet*. 1970;2(7685):1250–1251
52. Korkmaz C, Ozdogan H, Kasapcopur O, Yazici H. Acute phase response in familial Mediterranean fever. *Ann Rheum Dis*. 2002;61:79–81
53. Duzova A, Bakkaloglu A, Besbas N, et al. Role of A-SAA in monitoring subclinical inflammation and in colchicine dosage in familial Mediterranean fever. *Clin Exp Rheumatol*. 2003;21:509–514
54. Gillmore JD, Lovat LB, Persey MR, Pepys MB, Hawkins PN. Amyloid load and clinical outcome in AA amyloidosis in relation to circulating concentration of serum amyloid A protein. *Lancet*. 2001;358:24–29
55. Oner A, Erdogan O, Demircin G, Bulbul M, Memis L. Efficacy of colchicine therapy in amyloid nephropathy of familial Mediterranean fever. *Pediatr Nephrol*. 2003;18:521–526
56. International FMF consortium. Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. *Cell*. 1997;90:797–807
57. Shohat M, Magal N, Shohat T, et al. Phenotype-genotype correlation in familial Mediterranean fever: evidence for an association between Met694Val and amyloidosis. *Eur J Hum Genet*. 1999;7:287–292
58. Cazeneuve C, Sarkisian T, Pecheux C, et al. MEFV-gene analysis in Armenian patients with familial Mediterranean fever: diagnostic value and unfavorable renal prognosis of the M694V homozygous genotype-genetic and therapeutic implications. *Am J Hum Genet*. 1999;65:88–97
59. Livneh A, Langevitz P, Shinar Y, et al. MEFV mutation analysis in patients suffering from amyloidosis of familial Mediterranean fever. *Amyloid*. 1999;6:1–6
60. Mimouni A, Magal N, Stoffman N, et al. Familial Mediterranean fever: effects of genotype and ethnicity on inflammatory attacks and amyloidosis. *Pediatrics*. 2000;105(5). Available at: www.pediatrics.org/cgi/content/full/105/5/e70
61. Shinar Y, Livneh A, Langevitz, et al. Genotype-phenotype assessment of common genotypes among patients with familial Mediterranean fever. *J Rheumatol*. 2000;27:1703–1707
62. Ben Chetrit E, Backenroth R. Amyloidosis induced, end stage renal disease in patients with familial Mediterranean fever is highly associated with point mutations in the MEFV gene. *Ann Rheum Dis*. 2001;60:146–149
63. Gershoni-Baruch R, Brik R, Zacks N, Shinawi M, Lidar M, Livneh A. The contribution of genotypes at the MEFV and SAA1 loci to amyloidosis and disease severity in patients with familial Mediterranean fever. *Arthritis Rheum*. 2003;48:1149–1155
64. Medlej-Hashim M, Delague V, Chouery E, et al. Amyloidosis in familial Mediterranean fever patients: correlation with MEFV genotype and SAA1 and MICA polymorphisms effects. *BMC Med Genet*. 2004;5:4
65. Yalcinkaya F, Akar N, Misirlioglu M. Familial Mediterranean fever: amyloidosis and the Val726Ala mutation. *N Engl J Med*. 1998;338:993–994
66. Yalcinkaya F, Cakar N, Misirlioglu M, et al. Genotype-phenotype correlation in a large group of Turkish patients with familial Mediterranean fever: evidence for mutation-independent amyloidosis [published correction appears in *Rheumatology (Oxford)*. 2000;39:1170]. *Rheumatology (Oxford)*. 2000;9:67–72
67. Ozen S. Renal amyloidosis in familial Mediterranean fever. *Kidney Int*. 2004;65:1118–1127
68. Atagunduz MP, Tuglular S, Kantarci G, Akoglu E, Direskeneli H. Association of FMF-related (MEFV) point mutations with secondary and FMF amyloidosis. *Nephron Clin Pract*. 2004;96:c131–c135
69. Cazeneuve C, Ajrapetyan H, Papin S, et al. Identification of MEFV-independent modifying genetic factors for familial Mediterranean fever. *Am J Hum Genet*. 2000;67:1136–1143
70. Yilmaz E, Balci B, Kutlay S, et al. Analysis of the modifying effects of SAA1, SAA2 and TNF-alpha gene polymorphisms on development of amyloidosis in FMF patients. *Turk J Pediatr*. 2003;45:198–202
71. Akar S, Soyuturk M, Onen F, Tunca M. Serum amyloid A1 and tumor necrosis factor-alpha alleles in Turkish familial Medi-

- terranean fever patients with and without amyloidosis. *Amyloid*. 2003;10:12–16
72. Bakkaloglu A, Duzova A, Ozen S, et al. Influence of Serum Amyloid A (SAA1) and SAA2 gene polymorphisms on renal amyloidosis, and on SAA/C-reactive protein values in patients with familial Mediterranean fever in the Turkish population. *J Rheumatol*. 2004;31:1139–1142
 73. Montseny JJ, Meyrier A, Gherardi RK. Colchicine toxicity in patients with chronic renal failure. *Nephrol Dial Transplant*. 1996;11:2055–2058
 74. Kuncel RW, Duncan G, Watson D, Alderson K, Rogawski MA, Peper M. Colchicine myopathy and neuropathy. *N Engl J Med*. 1987;316:1562–1568
 75. Boomershine KH. Colchicine-induced rhabdomyolysis. *Ann Pharmacother*. 2002;36:824–826
 76. Schiff D, Drislane FW. Rapid-onset colchicine myoneuropathy. *Arthritis Rheum*. 1992;35:1535–1536
 77. Wallace SL, Singer JZ, Duncan GJ, Wigley FM, Kuncel RW. Renal function predicts colchicine toxicity: guidelines for the prophylactic use of colchicine in gout. *J Rheumatol*. 1991;18:264–269
 78. Anderson-Haag T, Patel B. Safety of colchicine in dialysis patients. *Semin Dial*. 2003;16:412–413
 79. Lange U, Schumann C, Schmidt KL. Aspects of colchicine therapy. 1: Pharmacology, toxicology, classic indications [in German]. *Z Arztl Fortbild Qualitatssich*. 2002;96:59–63
 80. Wallace SL, Singer JZ. Review: systemic toxicity associated with the intravenous administration of colchicine—guidelines for use. *J Rheumatol*. 1988;15:495–499
 81. Kaplan MM, Alling DW, Zimmerman HJ, et al. A prospective trial of colchicine for primary biliary cirrhosis. *N Engl J Med*. 1986;315:1448–1454
 82. Kershenovich D, Uribe M, Suarez GI, Mata JM, Perez-Tamayo R, Rojkind M. Treatment of cirrhosis with colchicine: a double-blind randomized trial. *Gastroenterology*. 1979;77:532–536
 83. Kogan A, Shinar Y, Lidar M, et al. Common MEFV mutations among Jewish ethnic groups in Israel: high frequency of carrier and phenotype III states and absence of a perceptible biological advantage for the carrier state. *Am J Med Genet*. 2001;102:272–276
 84. Achtert G, Scherrmann JM, Christen MO. Pharmacokinetics/bioavailability of colchicine in healthy male volunteers. *Eur J Drug Metab Pharmacokinet*. 1989;14:317–322
 85. Ehrenfeld M, Levy M, Sharon P, Rachmilewitz D, Eliakim M. Gastrointestinal effects of long-term colchicine therapy in patients with recurrent polyserositis (familial Mediterranean fever). *Dig Dis Sci*. 1982;27:723–727
 86. Fradkin A, Yahav J, Zemer D, Jonas A. Colchicine-induced lactose malabsorption in patients with familial Mediterranean fever. *Isr J Med Sci*. 1995;31:616–620
 87. Sayarlioglu M, Sayarlioglu H, Ozen S, Erkok R, Gul A. Colchicine-induced myopathy in a teenager with familial Mediterranean fever. *Ann Pharmacother*. 2003;37:1821–1824
 88. Harel L, Mukamel M, Amir J, Straussberg R, Cohen AH, Varsano I. Colchicine-induced myoneuropathy in childhood. *Eur J Pediatr*. 1998;157:853–855
 89. Dixon AJ, Wall GC. Probable colchicine-induced neutropenia not related to intentional overdose. *Ann Pharmacother*. 2001;35:192–195
 90. Ferrannini E, Pentimone F. Marrow aplasia following colchicine treatment for gouty arthritis. *Clin Exp Rheumatol*. 1984;2:173–175
 91. Ben Chetrit E, Navon P. Colchicine-induced leukopenia in a patient with familial Mediterranean fever: the cause and a possible approach. *Clin Exp Rheumatol*. 2003;21:S38–S40
 92. Guven AG, Bahat E, Akman S, Artan R, Erol M. Late diagnosis of severe colchicine intoxication. *Pediatrics*. 2002;109:971–973
 93. Savgan-Gurol E, Kasapcopur O, Hatemi S, et al. Growth and IGF-1 levels of children with familial Mediterranean fever on colchicine treatment. *Clin Exp Rheumatol*. 2001;19(5 suppl 24):S72–S75
 94. Zung A, Barash G, Zadik Z, Barash J. Familial Mediterranean fever and growth: effect of disease severity and colchicine treatment. *J Pediatr Endocrinol Metab*. 2006;19:155–160
 95. Leighton JA, Bay MK, Maldonado AL, Johnson RF, Schenker S, Speeg KV. The effect of liver dysfunction on colchicine pharmacokinetics in the rat. *Hepatology*. 1990;11:210–215
 96. Rollot F, Pajot O, Chauvelot-Moachon L, Nazal EM, Kelaidi C, Blanche P. Acute colchicine intoxication during clarithromycin administration. *Ann Pharmacother*. 2004;38:2074–2077
 97. Menta R, Rossi E, Guariglia A, David S, Cambi V. Reversible acute cyclosporin nephrotoxicity induced by colchicine administration. *Nephrol Dial Transplant*. 1987;2:380–381
 98. Goldbart A, Press J, Sofer S, Kapelushnik J. Near fatal acute colchicine intoxication in a child: a case report. *Eur J Pediatr*. 2000;159:895–897
 99. Granat M, Tur-Kaspa I, Zylber-Katz E, Schenker JG. Reduction of peritoneal adhesion formation by colchicine: a comparative study in the rat. *Fertil Steril*. 1983;40:369–372
 100. Ismajovich B, Zemer D, Revach M, Serr DM, Sohar E. The causes of sterility in females with familial Mediterranean fever. *Fertil Steril*. 1973;24:844–847
 101. Zemer D, Pras M, Sohar E, Gafni J. Letter: colchicine in familial Mediterranean fever. *N Engl J Med*. 1976;294:170–171
 102. Ehrenfeld M, Brzezinski A, Levy M, Eliakim M. Fertility and obstetric history in patients with familial Mediterranean fever on long-term colchicine therapy. *Br J Obstet Gynaecol*. 1987;94:1186–1191
 103. Rabinovitch O, Zemer D, Kukia E, Sohar E, Mashiach S. Colchicine treatment in conception and pregnancy: two hundred thirty-one pregnancies in patients with familial Mediterranean fever. *Am J Reprod Immunol*. 1992;28:245–246
 104. Cabili S, Livneh A, Zemer D, Rabinovitch O, Pras M. The effect of pregnancy on renal function in amyloidosis of familial Mediterranean fever. *Am J Reprod Immunol*. 1992;28:243–244
 105. Sanders CL, Lucas MJ. Renal disease in pregnancy. *Obstet Gynecol Clin North Am*. 2001;28:593–600
 106. Ben Chetrit E, Levy M. Colchicine prophylaxis in familial Mediterranean fever: reappraisal after 15 years. *Semin Arthritis Rheum*. 1991;20:241–246
 107. Cohen MM, Levy M, Eliakim M. A cytogenetic evaluation of long-term colchicine therapy in the treatment of familial Mediterranean fever (FMF). *Am J Med Sci*. 1977;274:147–152
 108. Akar S, Soyuturk M, Onen F, Tunca M. The relations between attacks and menstrual periods and pregnancies of familial Mediterranean fever patients. *Rheumatol Int*. 2006;26:676–679
 109. Tutuncu L, Atasoyu EM, Evrenkaya R, Mungen E. Familial Mediterranean fever-related nephrotic syndrome and successful full-term pregnancy. *Arch Med Res*. 2006;37:178–180
 110. Barkai G, Meital Y, Chetrit A. Clinical and chromosomal outcome following colchicine exposure before and during pregnancy. Paper presented at: the 11th annual meeting of the European Network of Teratology Information Services. September 19–21, 2000; Jerusalem, Israel
 111. Ben Chetrit E, Levy M. Reproductive system in familial Mediterranean fever: an overview. *Ann Rheum Dis*. 2003;62:916–919
 112. Berkenstadt M, Weisz B, Cuckle H, Di-Castro M, Guetta E, Barkai G. Chromosomal abnormalities and birth defects among couples with colchicine treated familial Mediterranean fever. *Am J Obstet Gynecol*. 2005;193:1513–1516

113. Ben-Chetrit E, Berkun Y, Ben-Chetrit E, Ben-Chetrit A. The outcome of pregnancy in the wives of men with familial Mediterranean fever treated with colchicine. *Semin Arthritis Rheum.* 2004;34:549–552
114. Ben Chetrit E, Scherrmann JM, Levy M. Colchicine in breast milk of patients with familial Mediterranean fever. *Arthritis Rheum.* 1996;39:1213–1217
115. Milunsky JM. Breast-feeding during colchicine therapy for familial Mediterranean fever. *J Pediatr.* 1991;19:164
116. Guillonneau M, Aigrain EJ, Galliot M, Binet MH, Darbois Y. Colchicine is excreted at high concentrations in human breast milk. *Eur J Obstet Gynecol Reprod Biol.* 1995;61:177–178
117. Ben Chetrit A, Ben Chetrit E, Nitzan R, Ron M. Colchicine inhibits spermatozoal motility in vitro. *Int J Fertil Menopausal Stud.* 1993;38:301–304
118. Haimov-Kochman R, Ben Chetrit E. The effect of colchicine treatment on sperm production and function: a review. *Hum Reprod.* 1998;13:360–362
119. Bremner WJ, Paulsen CA. Colchicine and testicular function in man. *N Engl J Med.* 1976;294:1384–1385
120. Levy M, Yaffe C. Testicular function in patients with familial Mediterranean fever on long-term colchicine treatment. *Fertil Steril.* 1978;29:667–668
121. Ben Chetrit E, Backenroth R, Haimov-Kochman R, Pizov G. Azoospermia in familial Mediterranean fever patients: the role of colchicine and amyloidosis. *Ann Rheum Dis.* 1998;57:259–260
122. Stapczynski JS, Rothstein RJ, Gaye WA, Niemann JT. Colchicine overdose: report of two cases and review of the literature. *Ann Emerg Med.* 1981;10:364–369
123. MacLeod JG, Phillips L. Hypersensitivity to colchicine. *Ann Rheum Dis.* 1947;6:224–229
124. Baud FJ, Sabouraud A, Vicaut E, et al. Brief report: treatment of severe colchicine overdose with colchicine-specific Fab fragments. *N Engl J Med.* 1995;332:642–645
125. van der Naalt J, Haaxma-Reiche H, van den Berg AP, Hazenberg BP, Molenaar WM. Acute neuromyopathy after colchicine treatment. *Ann Rheum Dis.* 1992;51:1267–1268
126. Tenenbein M, Cohen S, Sitar DS. Efficacy of ipecac-induced emesis, orogastric lavage, and activated charcoal for acute drug overdose. *Ann Emerg Med.* 1987;16:838–841
127. Putterman C, Ben Chetrit E, Caraco Y, Levy M. Colchicine intoxication: clinical pharmacology, risk factors, features, and management. *Semin Arthritis Rheum.* 1991;21:143–155
128. Chyka PA, Seger D, Krenzelok EP, Vale JA; American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. Position paper: single-dose activated charcoal. *Clin Toxicol (Phila).* 2005;43:61–87
129. Maxwell MJ, Muthu P, Pritty PE. Accidental colchicine overdose: a case report and literature review. *Emerg Med J.* 2002;19:265–267
130. Critchley JA, Critchley LA, Yeung EA, et al. Granulocyte-colony stimulating factor in the treatment of colchicine poisoning. *Hum Exp Toxicol.* 1997;16:229–232
131. Mullins ME, Robertson DG, Norton RL. Troponin I as a marker of cardiac toxicity in acute colchicine overdose. *Am J Emerg Med.* 2000;18:743–744
132. Schwabe AD, Peters RS. Familial Mediterranean fever in Armenians: analysis of 100 cases. *Medicine (Baltimore).* 1974;53:453–462
133. Tunca M, Tankurt E, Akbaylar Akpınar H, Akar S, Hizli N, Gonen O. The efficacy of interferon alpha on colchicine-resistant familial Mediterranean fever attacks: a pilot study. *Br J Rheumatol.* 1997;36:1005–1008
134. Tunca M, Akar S, Soyuturk M, et al. The effect of interferon alpha administration on acute attacks of familial Mediterranean fever: a double-blind, placebo-controlled trial. *Clin Exp Rheumatol.* 2004;22:S37–S40
135. Lidar M, Kedem R, Langevitz P, Pras M, Livneh A. Intravenous colchicine for treatment of patients with familial Mediterranean fever unresponsive to oral colchicine. *J Rheumatol.* 2003;30:2620–2623
136. Seyahi E, Ozdogan H, Masatlioglu S, Yazici H. Successful treatment of familial Mediterranean fever attacks with thalidomide in a colchicine resistant patient. *Clin Exp Rheumatol.* 2002;20(4 suppl 26):S43–S44
137. Calguneri M, Apras S, Ozbalkan Z, et al. The efficacy of continuous interferon alpha administration as an adjunctive agent to colchicine-resistant familial Mediterranean fever patients. *Clin Exp Rheumatol.* 2004;22(4 suppl 34):S41–S44
138. Daysal S, Akcil G, Goker B, Haznedaroglu S, Ercan N, Ozturk MA. Infliximab therapy in a patient with familial Mediterranean fever and chronic hip arthritis. *Arthritis Rheum.* 2005;53:146–147
139. Metyas S, Arkfeld DG, Forrester DM, Ehresmann GR. Infliximab treatment of familial Mediterranean fever and its effect on secondary AA amyloidosis. *Clin Rheumatol.* 2004;10:134–137
140. Amaryan G, Astvatsatryan V, Gabrielyan E, Panossian A, Panosyan V, Wikman G. Double-blind, placebo-controlled, randomized, pilot clinical trial of ImmunoGuard: a standardized fixed combination of *Andrographis paniculata* Nees, with *Eleutherococcus senticosus* Maxim, *Schizandra chinensis* Bail. and *Glycyrrhiza glabra* L. extracts in patients with familial Mediterranean fever. *Phytomedicine.* 2003;10:271–285
141. Touitou I. Should patients with FMF undergo BMT? *Blood.* 2003;101:1205–1206
142. Touitou I, Ben-Chetrit E, Gershoni-Baruch R, et al. Allogeneic bone marrow transplantation: not a treatment yet for familial Mediterranean fever. *Blood.* 2003;102:409

**Colchicine Use in Children and Adolescents With Familial Mediterranean Fever:
Literature Review and Consensus Statement**

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Pediatrics 2007;119:e474-e483; originally published online Jan 22, 2007;
DOI: 10.1542/peds.2006-1434

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