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

REVIEW ARTICLE

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 attacks[1]; (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 elevated[52] (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 introduction[57] (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 (*SAA1α/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 III[83]). 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 study[84] 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 enzymes[95] (eg, macrolides[96] and cyclosporin[97]) (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 nephropathy[104] with a significant risk for adverse maternal and fetal outcomes[105] (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 pregnancies[112] (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 contrast, 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 colchicine[123] 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 ingestion[127]; 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.

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.

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-

*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 Weiβbarth-Riedel.

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

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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