

Bowel habit changes in children with PFAPA Syndrome: Before and after treatment evaluation with the Bristol Stool Scale

¹Zelal Aydın¹, ²Elif Selcen Yabancı Erten², ¹Feray Kaya¹, ¹Elif Küçük¹, ¹Lütfiye Koru¹, ¹Eda Nur Dizman¹,
¹Hatice Kübra Dursun¹, ¹Merve Özen Balcı¹, ¹Ufuk Furkan Özdemir¹, ¹Fatih Haslak¹, ¹Kübra Öztürk¹

¹Department of Pediatric Rheumatology, İstanbul Medeniyet University, İstanbul, Türkiye, ²Department of Pediatrics, İstanbul Medeniyet University, İstanbul, Türkiye

Correspondence Address: **Kübra Öztürk**

e-mail: ozturk1209@gmail.com

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ABSTRACT

Objective: Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis (PFAPA) syndrome is one of the most common autoinflammatory diseases of childhood. Although gastrointestinal system (GIS) complaints are reported, bowel habits have not been objectively evaluated in these patients. This study investigated changes in bowel habits before and after treatment in children with PFAPA using the Bristol Stool Scale and daily stool frequency.

Materials and Methods: We included 101 children diagnosed with PFAPA according to the EUROFEVER/PRINTO criteria. Clinical, laboratory, daily stool frequency, and stool form were evaluated during febrile attacks before and after treatment. Stool form was evaluated using the Bristol Stool Scale and classified as hard (types 1–3), normal (type 4), and loose (types 5–7).

Results: Following treatment, median daily stool frequency during attacks decreased (2 [0.25–10] vs. 1 [0.25–6]; $p=0.008$), while stool form assessed by the Bristol Stool Scale remained unchanged (4 [1–7] vs. 4 [1–7]; $p=0.943$). No significant difference was observed in stool consistency categories ($p=0.174$). In the probiotic group, patients with normal stool form increased from 53.6% ($n=15$) pre-treatment to 57.1% ($n=16$) post-treatment.

Conclusion: To our knowledge, this study is the first to objectively evaluate bowel habits in children with PFAPA syndrome. Following treatment, stool frequency during episodes decreased significantly, while stool form remained unchanged. These results indicate that post-treatment alterations in bowel habits are primarily related to stool frequency. Future studies incorporating fecal biomarkers may provide further insights into gastrointestinal involvement and potential subclinical intestinal inflammation in PFAPA.

Keywords: Aphthous, colchicine, fever, pharyngitis, probiotics, stomatitis

Introduction

Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis (PFAPA) syndrome is one of the most common autoinflammatory diseases of childhood. This syndrome generally manifests before the age of five and is characterized by recurrent febrile episodes occurring at regular intervals (1,2). These episodes may be usually observed pharyngitis, aphthous stomatitis, and cervical lymphadenitis, whereas children remain entirely asymptomatic between episodes. In addition to the classical clinical features, children with PFAPA may present with gastrointestinal system (GIS) complaints, such as diarrhea, abdominal pain, nausea, and vomiting. Although PFAPA follows a generally self-limited course,

recurrent attacks are known to adversely affect the quality of life of both the patient and their families (3-6).

The Bristol Stool Scale is a diagnostic tool that classifies stool form into seven categories and is widely used in clinical practice for the objective assessment of bowel habits in children (7,8). Although GIS complaints have been described in the existing literature on PFAPA syndrome, to our knowledge, no study has evaluated stool form using the Bristol Stool Scale in these patients. In this study, we aimed to objectively evaluate changes in bowel habits during PFAPA attacks by assessing stool form with the Bristol Stool Scale and the average daily defecation frequency during pre-treatment and post-treatment attack periods.

Materials and Methods

This study was conducted at the Department of Pediatric Rheumatology, Istanbul Medeniyet University Göztepe Prof. Dr. Süleyman Yalçın City Hospital between January 2022 and June 2024. between January 2022 and June 2024. A total of 152 children who were classified as PFAPA syndrome according to the EUROFEVER/PRINTO criteria were initially enrolled (9). In our clinic, all patients presenting with GIS symptoms are routinely evaluated with additional tests for differential diagnosis, including celiac disease screening and fecal calprotectin testing. After excluding patients with incomplete data, concomitant GIS diseases, use of medications that could affect bowel habits, or secondary causes of diarrhea, 101 children constituted the final study cohort. Before treatment initiation, all families were informed about the international consensus recommended therapeutic options for PFAPA, and treatment decisions were made jointly with parents (10). Accordingly, patients were started on either colchicine or probiotic prophylaxis, and treatment was maintained throughout the follow-up period. In patients receiving probiotic prophylaxis, *Streptococcus salivarius* K12 (Bactoblis®) was administered orally once daily. The study flow diagram is presented in Figure 1.

Demographic information, clinical characteristics, and laboratory data of the patients were obtained from their medical records. Disease activity in PFAPA patients was assessed using the Autoinflammatory Diseases Activity Index (AIDAI) (11). Stool form was assessed using the Bristol Stool Scale and classified as hard (types 1–3), normal (type 4), or loose (types 5–7) (12).

To establish pre-treatment status, patients were evaluated during the month prior to treatment initiation, and data on clinical features, AIDAI scores, stool form assessed by the Bristol Stool Scale, average daily stool frequency, and inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were recorded during febrile attacks. After treatment initiation, patients were followed with regular follow-up visits over a 6-month period. During this follow-up, the same parameters were reassessed during febrile attacks, and the mean values obtained across this period were calculated for each patient. These post-

treatment averages were then compared with the baseline pre-treatment values to evaluate treatment outcomes.

In addition, to investigate the association between disease activity and stool form assessed by the Bristol Stool Scale, correlation analyses were performed using pre-treatment and post-treatment average values.

Statistical analysis

Statistical analyses were performed using SPSS for Windows, version 26.0 (SPSS Inc., Chicago, IL, USA). The distribution of continuous variables was assessed with the Kolmogorov–Smirnov test. Continuous variables were expressed as mean and standard deviation when normally distributed and as median (minimum–maximum) when non-normally distributed, while categorical variables were presented as frequencies and percentages. Comparisons of pre-treatment and post-treatment values within the same group were performed using the paired t-test for normally distributed data or the Wilcoxon signed-rank test for non-normally distributed data. For comparisons between two independent groups, Student's t-test was applied to normally distributed variables, while the Mann-Whitney U test was used for non-normally distributed variables. Correlation analyses were conducted using Spearman's correlation test, given the non-normal distribution of the variables. Categorical stool form, which was categorized into three groups according to the Bristol Stool Scale (hard: types 1–3, normal: type 4, loose: types 5–7), was analyzed using the McNemar–Bowker test to evaluate pre- and post-treatment changes. This test was selected to determine whether stool form categories differed between two time points within the same individuals in the presence of more than two categorical outcomes. A p value of less than 0.050 was considered indicative of statistical significance in all analyses.

Results

The study cohort consisted of 101 patients, of whom 73 (72.3%) were female. The median age at symptom onset was 30 (2–92) months, and the mean age at diagnosis was 52.9 ± 24.4 months. Parental consanguinity was present in 18 (17.8%) patients. A family history of periodic fever syndromes was observed in 61.3% (n=62) of the patients, while a family history of tonsillectomy was reported in 41.4% (n=42). During febrile attacks prior to treatment, the most common clinical manifestation was sore throat in 100 (99%). This was followed by lymphadenitis in 79 (78.2%), fatigue in 60 (59.4%), oral aphthae in 53 (52.5%), abdominal pain in 50 (49.5%), myalgia in 47 (46.5%), arthralgia in 44 (43.6%), nausea/vomiting in 31 (30.7%), headache in 30 (29.7%), diarrhea in 18 (17.8%), constipation in 6 (5.9%), chest pain in 5 (5%), and conjunctivitis in 5 (5%). Colchicine was administered to 73 patients (72.3%), whereas 28 patients (27.7%) received probiotic therapy.

Comparison of pre-treatment and post-treatment findings during attacks

In the total cohort, following treatment, a significant reduction was observed in the median number of stools per day (2 [0.25–10] vs. 1 [0.25–6]; $p=0.008$). In contrast, stool

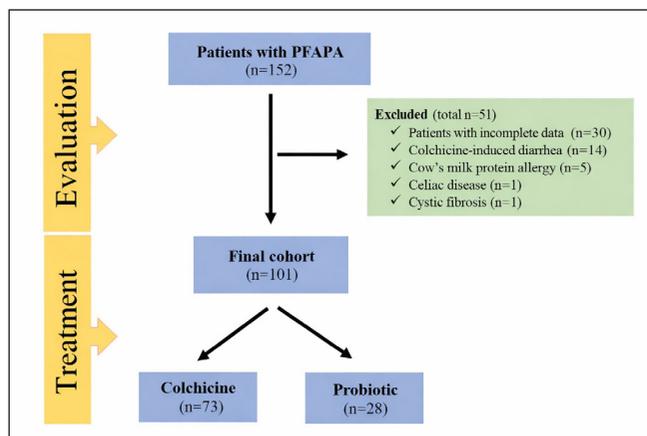


Figure 1: Flowchart illustrating the patient selection process (PFAPA: Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis).

Table I: Comparison of laboratory and clinical findings during attacks before and after treatment

	Pre-treatment*	Post-treatment*	p [‡]
Total Cohort (n=101)			
Duration of attacks [†]	4 (1-10)	3 (0-10)	<0.001
Interval between attacks [†]	20 (7-90)	30 (7-180)	<0.001
Number of stool/day	2 (0.25-10)	1 (0.25-6)	0.008
Bristol Stool Scale	4 (1-7)	4 (1-7)	0.943
AIDAI score	24 (0-128)	3 (0-60)	<0.001
CRP (mg/l)	54.9 (7.9-191)	46.9 (2.2-212)	0.050
ESR (mm/h)	32 (12-63)	21 (5-46)	0.080
Colchicine Group (n=73)			
Duration of attacks [†]	4 (2-10)	3 (1-10)	<0.001
Interval between attacks [†]	20 (10-90)	30 (7-180)	<0.001
Number of stool/day	2 (0.25-10)	1 (0.25-6)	0.034
Bristol Stool Scale	4 (1-7)	4 (1-7)	0.675
AIDAI score	24 (0-80)	4.5 (0-60)	<0.001
CRP (mg/l)	51.5 (7.9-190)	46 (2.2-208)	0.062
ESR (mm/h)	39 (12-63)	19 (5-46)	0.655
Probiotic Group (n=28)			
Duration of attacks [†]	4.5 (1-10)	2 (0-4)	<0.001
Interval between attacks [†]	15 (7-60)	30 (10-90)	0.001
Number of stool/day	1.5 (0.33-5)	1 (0.33-3)	0.078
Bristol Stool Scale	4 (1-7)	4 (2-7)	0.776
AIDAI score	27.5 (6-128)	2 (0-15)	<0.001
CRP (mg/l)	87.7 (8.7-191)	48 (11.5-212)	0.062
ESR (mm/h)	22 (12-47)	22 (21-39)	0.655

*: median (min-max), †: days, ‡: Wilcoxon signed-rank test, **AIDAI**: Auto-Inflammatory Diseases Activity Index, **CRP**: C-Reactive Protein, **ESR**: Erythrocyte sedimentation rate

form assessed by the Bristol Stool Scale showed no significant change (4 [1-7] vs. 4 [1-7]; p=0.943). Similarly, in the colchicine group, a significant reduction was observed in the median number of stools per day following treatment (2 [0.25-10] vs. 1 [0.25-6]; p=0.034), while stool form assessed by the Bristol Stool Scale showed no significant change (4 [1-7] vs. 4 [1-7]; p=0.675). In the probiotic group, however, no significant change was observed following treatment in either the median number of stools per day (1.5 [0.33-5] vs. 1 [0.33-3]; p=0.078) or stool form assessed by the Bristol Stool Scale (4 [1-7] vs. 4 [2-7]; p=0.776). Detailed results for the total cohort and subgroups are presented in Table I.

Similarly, no significant difference was observed in stool consistency categories in both the colchicine and the probiotic group (p=0.247 vs. p=0.311). The number of patients with hard stools decreased from 9 (8.9%) in the pre-treatment period to 6 (5.9%) post-treatment, while patients with normal stools decreased from 65 (64.3%) to 63 (62.4%). In contrast, the number of patients classified as having loose stools increased from 27 (26.7%) before treatment to 32 (31.7%) after treatment. Nevertheless, in the probiotic group, the proportion of patients with normal stool form showed an increase from 53.6% (n=15) pre-treatment to 57.1% (n=16) post-treatment. The detailed data are given in Table II. No significant difference was observed between the colchicine and probiotic groups in the difference of daily stool frequency from pre- to post-treatment (Colchicine groups: 0 (-2 to 6); Probiotic groups: 0 (-0.5 to 3); p=0.957).

Table II: Stool form categories pre-treatment and post-treatment in the Colchicine and Probiotic groups

	n	Post-treatment [†]			p [‡]
		Hard	Normal	Loose	
Colchicine Group*					
73	5	47	21		
Hard	6	5 (6.8)	0 (0)	1 (1.3)	0.247
Normal	50	0 (0)	46 (63)	4 (5.4)	
Loose	17	0 (0)	1 (1.3)	16 (21.9)	
Probiotic Group*					
28	1	16	11		
Hard	3	1 (3.5)	0 (0)	2 (7.1)	0.311
Normal	15	0 (0)	14 (50)	1 (3.5)	
Loose	10	0 (0)	2 (7.1)	8 (28.5)	

*: Pre-treatment, †: n(%), ‡: McNemar-Bowker test

In the total cohort, no significant association was found between AIDAI scores and Bristol Stool Scale values at pre-treatment (r=0.043, p=0.667) or at post-treatment average values (r=-0.044, p=0.665). Similarly, no significant association was observed between AIDAI scores and Bristol Stool Scale values in the colchicine or probiotic groups at pre-treatment (colchicine group r=-0.015, p=0.899; probiotic group: r=0.132, p=0.512) or at post-treatment average values (colchicine group r=-0.004, p=0.974; probiotic group: r=-0.001, p=0.997).

Discussion

In our study, patients were evaluated during attack periods both before and after treatment. Following treatment, a significant decrease was observed in attack frequency and in AIDAI scores reflecting disease activity. With this clinical improvement, there was a significant reduction in daily stool frequency, but no change in stool form as assessed by the Bristol Stool Scale. A statistically significant reduction in stool frequency was observed in the colchicine group. Although not significant, a similar trend was noted in the probiotic group. Moreover, the proportion of patients classified as normal according to the Bristol Stool Scale (type 4) increased after treatment in this group. However, this change also did not reach statistical significance, which may be partly attributable to the smaller sample size in the probiotic group. Overall, these findings suggest that the post-treatment changes in bowel habits in PFAPA are primarily related to stool frequency, and that probiotic treatment may also exert a more favorable effect in achieving normal stool form.

Although aphthous stomatitis is defined to be one of the typical features of PFAPA syndrome, GIS symptoms such as diarrhea, abdominal pain, nausea, and vomiting have been reported during PFAPA attacks (5,13). Oral ulcers and GIS symptoms are well-documented manifestations of diseases such as Crohn's disease (CD) and Behçet's disease (BD), which may overlap and mimic each other (14-17). Moreover, significant genetic similarities indicating common mechanisms between PFAPA syndrome and BD were discovered (18). These similarities and overlapping clinical features raise the question of whether the GIS complaints observed in PFAPA represent merely transient symptoms or reflect an underlying intestinal involvement resembling colitis, an issue that warrants further investigation.

One of the most noteworthy findings of our study is that the post-treatment increase in the proportion of patients with normal stool form represents, to our knowledge, the first report suggesting that probiotic therapy may have a beneficial effect on bowel habits during PFAPA attacks. This finding is consistent with the literature reporting that probiotics may be beneficial in the regulation of GIS symptoms. Indeed, probiotics have been shown to strengthen the intestinal mucosal barrier, modulate immune responses, and possess significant potential in the prevention and treatment of various diseases (19,20). Therefore, we suggest that probiotics may be considered as an option, particularly for PFAPA patients with gastrointestinal complaints. However, it should be emphasized that the mechanisms of action of colchicine and probiotics differ: colchicine exerts a direct anti-inflammatory effect in autoinflammatory diseases, whereas probiotics primarily act through immunomodulatory pathways linked to the gut microbiota. Although probiotics are not approved for autoinflammatory diseases, clinical studies have demonstrated that they can reduce attack frequency and provide clinical benefit in PFAPA (20-22).

In the colchicine group, there was an observed increase in the proportion of patients experiencing loose stools following treatment. This phenomenon may be attributed to diarrhea being reported as one of the GIS side effects associated with colchicine (22). However, since patients who had diarrhea due to colchicine were excluded from our study, the observed increase is more likely to reflect a softening of stool consistency rather than a true adverse event. This finding suggests that the effect of colchicine on stool form may exist along a spectrum, with only some patients progressing to clinically overt diarrhea.

Overall, our findings indicate that post-treatment changes in bowel habits in PFAPA are primarily related to daily stool frequency. In both treatment groups, a decreasing trend in stool frequency during attacks was observed after treatment, but a statistically significant reduction was noted only in the colchicine group. Nevertheless, no significant difference was found between the colchicine and probiotic groups in terms of the change in daily stool frequency from pre- to post-treatment. This suggests that, independent of stool form categories, both treatments may exert similar effects on bowel habits.

Limitations

Our study has certain limitations. The Bristol Stool Scale may be useful in collecting information on bowel habits; however, it does not provide information on intestinal inflammation. In addition, we did not include fecal biomarkers, which could have provided a more objective assessment of GIS involvement in PFAPA. Moreover, dietary intake during attacks was not assessed in detail, even though certain foods are known to predispose to diarrhea or constipation and thereby influence stool consistency. Nevertheless, to our knowledge, this study is the first to objectively evaluate changes in bowel habits during attacks in children with PFAPA syndrome through pre- and post-treatment comparisons of stool frequency and stool form assessed using the Bristol Stool Scale.

Conclusion

In conclusion, we demonstrated that, in children with PFAPA syndrome, treatment resulted in a significant reduction in attack frequency and disease activity during febrile episodes, along with a decrease in daily stool frequency. While stool form assessed by the Bristol Stool Scale showed no overall significant change, our data revealed an increase in the proportion of patients with normal stool form after treatment, in the probiotic group. These findings suggest that post-treatment changes in bowel habits in PFAPA are primarily related to stool frequency. Future studies incorporating fecal biomarkers may help to better elucidate gastrointestinal involvement in PFAPA syndrome, as well as possible subclinical intestinal inflammation.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by İstanbul Medipol University (18/07/2024, reference number: 725).

Contribution of the authors

Study conception and design: ZA, FH, KO; Data collection: ZA, ESYE, FK, EK, LK, END, HKD, MOB, UFO; Analysis and interpretation of results: ZA, FH, KO; Literature search: ZA, ESYE, FK, EK, LK, END, HKD, MOB, UFO; Draft manuscript preparation: ZA, FH, KO. All authors reviewed the results and approved the final version of the article

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Conflict of interest

The authors declare that there is no conflict of interest.

References

1. Koru L, Erten ESY, Dursun HK, et al. Colchicine treatment in PFAPA: how long should we wait for the clinical response? *Eur J Pediatr.* 2025;184(5):322. <https://doi.org/10.1007/s00431-025-06158-w>.
2. Yıldız M, Haslak F, Adrovic A, et al. Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis Syndrome: A Single-Center Experience. *Turk Arch Pediatr.* 2022;57(1):46-52. <https://doi.org/10.5152/TurkArchPediatr.2021.21229>
3. Vanoni F, Theodoropoulou K, Hofer M. PFAPA syndrome: a review on treatment and outcome. *Pediatr Rheumatol Online J.* 2016;14(1):38. <https://doi.org/10.1186/s12969-016-0101-9>
4. Wang A, Manthiram K, Dedeoglu F, Licameli GR. Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome: A review. *World J Otorhinolaryngol Head Neck Surg.* 2021;7(3):166-73. <https://doi.org/10.1016/j.wjorl.2021.05.004>
5. Rydenman K, Fjeld H, Hätting J, Berg S, Fasth A, Wekell P. Epidemiology and clinical features of PFAPA: a retrospective cohort study of 336 patients in western Sweden. *Pediatr Rheumatol Online J.* 2022;20(1):82. <https://doi.org/10.1186/s12969-022-00737-z>
6. Yıldız M, Haslak F, Adrovic A, Barut K, Kasapçopur Ö. Autoinflammatory Diseases in Childhood. *Balkan Med J.* 2020;37(5):236-46. <https://doi.org/10.4274/balkanmedj.galenos.2020.2020.4.82>
7. Chumpitazi BP, Lane MM, Czyzewski DI, Weidler EM, Swank PR, Shulman RJ. Creation and initial evaluation of a Stool Form Scale for children. *J Pediatr.* 2010;157(4):594-7. <https://doi.org/10.1016/j.jpeds.2010.04.040>

8. Gulati R, Komuravelly A, Leb S, Mhanna MJ, Ghori A, Leon J, et al. Usefulness of Assessment of Stool Form by the Modified Bristol Stool Form Scale in Primary Care Pediatrics. *Pediatr Gastroenterol Hepatol Nutr*. 2018;21(2):93-100. <https://doi.org/10.5223/pghn.2018.21.2.93>
9. Gattorno M, Hofer M, Federici S, Vanoni F, Bovis F, Aksentijevich I, et al. Classification criteria for autoinflammatory recurrent fevers. *Ann Rheum Dis*. 2019;78(8):1025-32. <https://doi.org/10.1136/annrheumdis-2019-215048>
10. Amarilyo G, Rothman D, Manthiram K, et al. Consensus treatment plans for periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome (PFAPA): a framework to evaluate treatment responses from the childhood arthritis and rheumatology research alliance (CARRA) PFAPA work group. *Pediatric Rheumatology*. 2020;18(1):31. <https://doi.org/10.1186/s12969-020-00424-x>
11. Piram M, Koné-Paut I, Lachmann HJ, et al. Validation of the auto-inflammatory diseases activity index (AIDAI) for hereditary recurrent fever syndromes. *Ann Rheum Dis*. 2014;73(12):2168-73. <https://doi.org/10.1136/annrheumdis-2013-203666>
12. Saps M, Nichols-Vinueza D, Dhroove G, Adams P, Chogle A. Assessment of commonly used pediatric stool scales: a pilot study. *Rev Gastroenterol Mex*. 2013;78(3):151-8. <https://doi.org/10.1016/j.rgmx.2013.04.001>
13. Feder HM, Salazar JC. A clinical review of 105 patients with PFAPA (a periodic fever syndrome). *Acta Paediatr*. 2010;99(2):178-84. <https://doi.org/10.1111/j.1651-2227.2009.01554.x>
14. Mitchel EB, Rosh JR. Pediatric Management of Crohn's Disease. *Gastroenterol Clin North Am*. 2022;51(2):401-24. <https://doi.org/10.1016/j.gtc.2021.12.013>
15. Feuerstein JD, Cheifetz AS. Crohn Disease: Epidemiology, Diagnosis, and Management. *Mayo Clin Proc*. 2017;92(7):1088-103. <https://doi.org/10.1016/j.mayocp.2017.04.010>
16. Cheon JH, Kim WH. An update on the diagnosis, treatment, and prognosis of intestinal Behçet's disease. *Curr Opin Rheumatol*. 2015;27(1):24-31. <https://doi.org/10.1097/BOR.0000000000000125>
17. Valenti S, Gallizzi R, De Vivo D, Romano C. Intestinal Behçet and Crohn's disease: two sides of the same coin. *Pediatr Rheumatol Online J*. 2017;15(1):33. <https://doi.org/10.1186/s12969-017-0162-4>
18. Manthiram K, Preite S, Dedeoglu F, et al. Common genetic susceptibility loci link PFAPA syndrome, Behçet's disease, and recurrent aphthous stomatitis. *Proc Natl Acad Sci U S A*. 2020;117(25):14405-11. <https://doi.org/10.1073/pnas.2002051117>
19. Peters VBM, van de Steeg E, van Bilsen J, Meijerink M. Mechanisms and immunomodulatory properties of pre- and probiotics. *Benef Microbes*. 2019;10(3):225-36. <https://doi.org/10.3920/BM2018.0066>
20. Li W, Zeng Y, Zhong J, et al. Probiotics Exert Gut Immunomodulatory Effects by Regulating the Expression of Host miRNAs. *Probiotics Antimicrob Proteins*. 2025;17(2):557-68. <https://doi.org/10.1007/s12602-024-10443-9>
21. Batu ED, Kaya Akca U, Basaran O, Bilginer Y, Özen S. Probiotic use in the prophylaxis of periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome: a retrospective cohort study. *Rheumatol Int*. 2022;42(7):1207-11. <https://doi.org/10.1007/s00296-021-05084-y>
22. Stewart S, Yang KCK, Atkins K, Dalbeth N, Robinson PC. Adverse events during oral colchicine use: a systematic review and meta-analysis of randomised controlled trials. *Arthritis Res Ther*. 2020;22(1):28. <https://doi.org/10.1186/s13075-020-2120-7>