ASTHMA ALLERGY IMMUNOLOGY
ASTIM ALLERJİ İMMÜNOLOJİ

doi: 10.21911/aai.2025.672
Asthma Allergy Immunol 2025;23:22-31

REVIEW

Received: 25.09.2024 • Accepted: 02.12.2024
Online Published: 10.03.2025

An Overview on *Blastocystis* spp: The Potential Hidden Cause of Chronic Urticaria

Ozlem ULUSAN BAGCI[1], Zeynep CELEBI SOZENER[2], Sevim BAVBEK[2], Gulay ARAL AKARSU[1]

[1] Ankara University Faculty of Medicine, Department of Microbiology, Division of Parasitology, Ankara, Türkiye
[2] Ankara University Faculty of Medicine, Department of Chest Diseases, Division of Immunology and Allergic Diseases, Ankara, Türkiye

Corresponding Author: Ozlem Ulusan Bagci ✉ drozlemulusan@gmail.com

ABSTRACT

Blastocystis spp., the most common protozoan discovered in human feces, has affected about one billion people worldwide so far. Despite significant advancements in the epidemiology and diagnosis of the parasite, no consensus has been reached over the pathogenecity and treatment approach. The most common symptoms related to the protozoan include nausea, vomiting, diarrhea, bloating, weight loss, and intestinal gas. Dermatological symptoms, such as skin rash and urticaria, may coexist with gastrointestinal complaints. *Blastocystis* spp. has evolved as an emerging parasite around the world in recent times. Research has revealed that the prevalence in urticaria patients was 21.3-61.1%, whereas that in healthy volunteers was 8-29.41%. The studies conducted in Egypt produced the highest prevalence among urticaria patients. The prevalence of *Blastocystis* spp. varied between 5.69 and 31.9% in urticaria patients and 1.56 and 14.8% in healthy individuals in Türkiye. The most prevalent subtype was subtype 3 worldwide and in Türkiye. Urticaria patients were generally shown to have a higher prevalence of *Blastocystis* spp. than control groups. Moreover, it was shown that urticarial lesions and urticaria scores improved in patients treated with metronidazole who had *Blastocystis* spp. *Blastocystis* spp. could be a part of a healthy microbiota, but there is also research that indicated *Blastocystis* spp. reduced the amount of beneficial bacteria. Gut microbiota in people with chronic urticaria shows a decrease in the diversity of the gut bacteria besides an increase in organisms that are usually referred to as pathogens, including Proteobacteria, Enterobacterales, Enterobacteriaceae, and Bacilli. Furthermore, by modifying the intestinal microbiota, *Blastocystis* spp. may indirectly contribute to the etiopathogenesis of urticaria. However, this relationship has not been searched yet, and further investigation is required to assess the correlation between the microbiota and *Blastocystis* spp. in patients with urticaria.

Keywords: *Blastocystis* spp., urticaria, metronidazole, microbiota, subtype

INTRODUCTION

Blastocystis spp. (Alexeieff, 1911) are anaerobic eukaryotic microorganisms that inhabit the intestines of humans and a wide range of animals, including birds, rodents, reptiles, amphibians, fish, insects, and other mammalian animals. They are the most abundant protozoan parasite found in human and animal feces, particularly in warm climates and countries with unsanitary conditions. An estimated one billion individuals globally are thought to be infected with *Blastocystis* spp. (1,2). *Blastocystis* spp. may cause gastrointestinal and urticarial complaints in people. The objective of this review is to summarize the morphological and biological characteristics of the etiological agent *Blastocystis* spp., provide an overview of the literature assessing the relationship between *Blastocystis* spp. and urticaria, and gain insight into the potential etiological role of the agent in urticarial patients.

MORPHOLOGY, TAXONOMY AND LIFE CYCLE OF *BLASTOCYSTIS* SPP.

Blastocystis spp. was once thought to be a harmless gastrointestinal tract yeast; however, five decades later, its morphological and cellular characteristics, inability to develop on a fungal culture, resistance to antifungal drugs,

ORCID Ozlem Ulusan Bagci / 0000-0002-9695-5703, Zeynep Celebi Sozener / 0000-0003-4188-0959, Sevim Bavbek / 0000-0002-7884-0830, Gulay Aral Akarsu / 0000-0003-0007-9006

and susceptibility to antiprotozoal medications led to its classification under the kingdom of Protista (3). Initially, the parasite's host of origin was taken into consideration when naming the species of *Blastocystis* spp., such as *Blastocystis hominis* of humans or *Blastocystis ratti* of rats, but later it was designated as *Blastocytis* spp. when the zoonotic transmission of the parasite was realized (4). Due to genetic diversity between isolates, 38 subtypes (ST) have been identified so far, and 14 of them have been isolated from both animals and humans (ST1-ST10, ST12, ST14, ST16, and ST23), with ST1-ST3 responsible for the majority of human carriage (5).

There are four distinct forms of the parasite: amoeboid, cystic, granular, and vacuolar. Ingestion of food and water contaminated with cysts, interaction with infected individuals directly, and environmental contamination with feces all contribute to the spread of the infection (1,3).

EPIDEMIOLOGY

In the World

The frequency of *Blastocystis* spp. infection varies widely between countries and even among different regions in the same country, depending on dietary and personal hygiene habits. Developing countries have a higher prevalence of the parasite caused by poor hygiene, intimate animal contact, and ingestion of food or water contaminated with cysts. According to Fonte Galindo et al. (6), the prevalence of *Blastocystis* spp. is reported to range from 5 to 20% in high-income countries and from 30 to 60% in low and middle-income countries. High incidence is observed in developing countries like Egypt (33.3%), Brazil (40.9%), Mexico (78.4%), and Nigeria (84%), whereas low frequency is found in developed nations like Singapore (3.3%) and Japan (0.5-1%) (7-12). Even within the same nation, prevalence can fluctuate depending on the subpopulation under investigation and the various diagnostic techniques used. In China, for instance, the positivity ratio was reported to range from 1.9% to 32.6% (13).

In Türkiye

Widely differing prevalence results have been obtained from research conducted in different regions of Türkiye with various patient groups. For instance, *Blastocystis* spp. was found in 7.3% of stool samples submitted to a laboratory in İzmir over a ten-year period (14). In Ankara, *Blastocystis* spp. was detected in 15.5% of the stool specimens by using molecular methods (15). *Blastocystis* spp. was found in 8.3% of stool samples that were sent to the laboratory over the course of a year, according to a study conducted in Mardin (16).

Every day, more research on the epidemiology of *Blastocystis* spp. is published in the literature. *Blastocystis* spp. has become an emerging parasite with global distribution due to a number of factors, including enhanced knowledge of the parasite, increased identification through the use of tests with high diagnostic sensitivity, and the ability to identify subtypes and alleles using molecular methods. However, no agreement has been established on the course of treatment, even with notable progress in the domains of diagnostic methods and epidemiology. There is still disagreement over whether it is a true pathogen or a part of the healthy microbiota (6). Studies have attempted to link subtypes or morphologies (vacuolar, granular, amoeboid, and cystic) to pathogenicity (17,18). Furthermore, it has been stated that quantification can serve as a reference for the pathogenicity being defined as the detection of more than five parasites in any field under a 40x objective (19). Treatment may be necessary if there are dermatological or gastrointestinal complaints and excessive cysts in stool specimens. Nonetheless, a definite agreement between the subtypes, morphologies, quantification, and necessity for treatment is not present. More study is required to determine pathogenicity and the need for therapy (20).

LABORATORY DIAGNOSIS OF *BLASTOCYSTIS* SPECIES

The diagnosis of *Blastocystis* spp. can be made by direct microscopic examination with or without Lugol's iodine, a permanent smear stained with trichrome, culture, or molecular technique. The tests used in the studies have significance since there are variations in the sensitivity of the methods. For example, in a study conducted in Ankara, the positivity rates of physiological saline, lugol, precipitation, and trichrome staining differed statistically significantly ($p<0.05$) when compared with the molecular technique and culture. However, there was no statistically significant difference in the positivity rate between the molecular technique and culture ($p = 0.14$) (15). In another study, the positivity ratio was detected as 20%, 26.6%, and 30.4% with microscopic examination, culture, and polymerase chain reaction (PCR), respectively (21). Culture seems like a sensitive and simple method for diagnosis. Nevertheless, molecular methods have gained popularity in recent times

as a sensitive, reliable, and rapid method for diagnosis, and they have also taken advantage of the differentiation *of Blastocystis* spp. subtypes (22).

BLASTOCYSTIS SPP. AND URTICARIA RELATIONSHIP

Nausea, vomiting, diarrhea, bloating, weight loss, and intestinal gas are among the most frequent symptoms caused by *Blastocystis* spp. It has been mentioned that gastrointestinal complaints may coexist with dermatological symptoms such as urticaria and itchy skin rashes (20). Numerous case reports and cross-sectional studies have proposed a causal relationship between urticaria and *Blastocystis* spp. infection. Pasqui et al. reported a case presenting with cutaneous and mild gastroenteric manifestations, all of which disappeared after antimicrobial therapy administered against *Blastocystis* spp (23). Another reported case was a 19-year-old male who presented with a three-week history of hives and abdominal pain that persisted for nearly 10 weeks (24). Antihistamine therapy failed to alleviate the patient's symptoms; however, metronidazole treatment, given upon detection of *Blastocystis* spp. subtype 3 in the patient's stool, caused the disappearance of urticarial lesions. Similarly, Verma and Delfanian (25) reported a 71-year-old man with a pruritic rash that began on his forehead with minor diarrhea. He was a farmer, taking care of farm animals such as cattle. After receiving metronidazole therapy for *Blastocystis* spp. that was found in his feces, he recovered within a week. The dramatic improvement in the urticaria with antiparasitic treatment implements the role of *Blastocystis* spp. in the etiology of urticaria. Studies on *Blastocystis* spp. in the literature have found three possible pathways for the parasite to cause chronic urticaria:

1-Type 1 hypersensitivity reaction: Th_2 cell activation brought on by *Blastocystis* spp. antigens increases the percentage of circulating eosinophils as well as the release of IL-3, IL-4, IL-5, and IL-13. Furthermore, mast cells degranulate when IgE, produced in response to the parasite, attaches to their Fc regions. Histamine, contained in mast cells, is responsible for the development of urticarial lesions (6).

2-Impaired permeability of the intestinal epithelial barrier: In a recent in vitro study, *Blastocytis* spp. antigens such as serin proteases have been demonstrated to dramatically upregulate the expression of proinflammatory cytokines, including IL-1b, IL-6, and tumor necrosis factor-α, by inducing the activation of three main mammalian mitogen-activated protein kinases, including ERK, JNK, and p38 in mouse macrophages. These cytokines break down the strong bonds that bind intestinal epithelial cells, increasing intestinal permeability and allowing some bacteria in the flora or metabolites in the lumen to enter the bloodstream (26).

3-Altered composition of the gut microbiome: Urticarial lesions may be caused by changes in the composition of the gut microbiota. When researchers compared the gut microbiomes of chronic urticaria patients with healthy volunteers, they found that people with the disease had higher concentrations of bacteria from the Enterobacterales family, whereas those in the healthy group had higher concentrations of *Faecalibacterium prausnitzii*, *Clostridium leptum*, and *Akkermansia muciniphila* (27). Studies on *Blastocystis* spp. have shown that the parasite modifies the gut microbiota by decreasing the bacterial diversity, increasing pathogenic bacteria such as *Escherichia coli*, and decreasing beneficial bacteria *such as Bifidobacterium* and *Lactobacillus* (28). As a result of its impact on the gut microbiota, *Blastocystis* spp. may indirectly cause urticaria.

Studies investigating *Blastocystis* spp. in stool samples of patients with urticaria around the world

It is evident that research on the relationship between *Blastocystis* spp. and urticaria worldwide has been conducted in developing nations where the parasite is endemic (Table I). As a result, greater prevalences have been identified in both urticaria patients and healthy participants. Studies revealed that urticaria patients had a prevalence of 21.3-61.1% and healthy volunteers, 8-29.41%, respectively (29-33). The study carried out in Egypt yielded the highest prevalence in urticaria patients (29). With the exception of the Shirvani et al. study (32), all of the studies mentioned in Table I indicated that patients with urticaria had a greater prevalence of *Blastocystis* spp. compared with healthy individuals (29,30,33). In respect to the STs found in urticaria patients, ST3 was found to be the predominant strain in most of the studies (29-31); nevertheless, several studies also highlighted the presence of ST2 (32,33). Although the most abundant life cycle form that is found in the stool of the patients is the vacuolar form, research from Egypt revealed an intriguing discovery, in that ameboid forms of the parasite predominated in the stools of urticaria pa-

Table I: The studies evaluating *Blastocystis* spp. in stool samples of patients with urticaria conducted in the world

Author(s)	Participants (n)	Country	Method	*Blastocystis* spp. positivity (%)	Subtype (%)	Recovery rate after treatment	Additional information
Hameed et al. (29)	**UP:** 54 -**Acute:** 18 -**Chronic:** 36 **HI:** 50	Egypt	Culture and PCR	**UP:** 61.1 -**Acute:** 50 -**Chronic:** 66.7 **HI:** 8	**UP:** ST3: 100 **HI:** ST3: 100	60 (after one course), 100 (two course treatment)	Amoeboid form was detected in 95.2% of symptomatic *Blastocystis* spp. urticarial patients
Casero et al. (30)	270 (Symp:UP and/or patient with GI complaints+ Asymp: control group)	Argentina	Native-lugol, precipitation, trichrome, PCR, sequence analysis	24.81 -Symp 58.2* -Control: 41.8*	ST 1:14.93 ST 2: 5.97 ST3: 71.64 -*Symp*: 71.43 -*Asymp:* 28.57 ST 6: 7.46	-	Allele 34 (ST3) was detected in 85.7% of symptomatic UP
Melo et al. (31)	**UP:** 58	Brazil	Microscopy, PCR, sequence analysis	53.5	ST 1: 25 ST 2:17.8 ST 3: 28.5 ST 4: 21.4 ST 6: 3.6 ST1+ST3: 3.6	-	-Allele sequence analysis: a4 (ST1), a9 and a12 (ST2), a34, a36 and a37 (ST3), a42 and a94 (ST4), a122 (ST6), a4 and a37 (ST1+ST3) -*Endolimax nana*:3.45%, *Entamoeba coli*:1.72%, *E. nana* and *E. coli*:5.17%, *Taenia* spp.: 1.72%, and *G. intestinalis*: 1.72%
Shirvani et al. (32)	**UP:** 59 **HI:** 51	Iran	Native-Lugol examination, PCR	**UP:** 25.42 **HI:** 29.41	**UP:** ST 1: 20 ST 2: 33.33 ST 3: 20 **HI:** ST 1: 26.67 ST 2: 20 ST 3: 33.33 ST1+ST3: 6.67	-	-
Jafari et al. (33)	**UP:** 94 **HI:** 285	Iran	Native-Lugol examination, precipitation, PCR, sequence analysis	**UP:** 21.28 **HI:** 17.19	**UP:** ST 1: 30 ST 2: 40 ST 3: 30 **HI:** ST 1: 8.33 ST 2: 25 ST 3: 66.67	Not available	The infected patients were treated with a course of metronidazole but the impact on the prognosis wasn't followed

UP: Urticaria patients, **HI:** Healthy individuals, **Symp:** Symptomatic, **Asymp:** Asymptomatic, **PCR:** Polymerase Chain Reaction, **ST:** Subtype
Subtype (%) calculated based on all *Blastocystis* spp. positive samples
* Since the number of symptomatic and asymptomatic groups was not obtained in the reference, the percentage distribution was calculated

tients (29). Previous research has similarly claimed that the etiopathogenesis of urticaria could be attributed to the ameboid form, which could be a more invasive and pathogenic form. However, prospective research is required to prove the pathogenicity of the ameboid form, since almost all of the studies with this claim are case reports (6,24,34).

Studies investigating *Blastocystis* spp. in stool samples of patients with urticaria in Türkiye

In our country, studies evaluating the relationship between *Blastocytis* spp. and urticaria have been carried out, particularly in the past five years (Table II).

Table II: The studies evaluating *Blastocystis* spp. in stool samples of patients with urticaria conducted in Türkiye

Author(s)	Participants (n)	Method	Blastocystis spp. positivity (%)	Subtype (%)	Recovery rate after treatment (%)	Additional information
Aykur et al. (21)	**UP:** 135 **HI:** 54	Native-Lugol, trichrome, culture, PCR, sequence analysis	**UP:** 31.9 **HI:**14.8	**UP:** -ST1: 18.92 -ST2: 27.03 -ST3: 45.95 -ST7: 8.11 **HI:** -ST1: 37.5 -ST3: 62.5	-	Allele 34 (ST3) was found most in the patients with UP, contrary to allele 36 (ST3) and allele 4 (ST1) in HI
Doğruman et al. (35)	**UP:** 55 **HI:** 43	Native-lugol, precipitation, and trichrome	**UP:** 20 **HI:** 11.6	-	45.45	*Giardia intestinalis* was found in 9.1% of UP
Dilek et al. (36)	**UP:** 49 **HI:** 36	Native-lugol, precipitation, and trichrome	**UP:** 14.29 **HI:** 2.78	-	-	*E. coli* and *G. intestinalis* were found in 18.3% and 6.1% of UP, respectively
Arik Yilmaz et al. (37)	**UP:** 211	Native-Lugol	5.69	-	76.19 (not only for *Blastocystis* spp., for all parasites)	-Intestinal complaints were more frequent in patients with parasites such as *Blastocystis* spp. than in those without -*Giardia:* 2.37%, *Dientamoeba fragilis*: 1.42%, *Enterobius vermicularis*: 2.37%, *Entamoeba* spp.:0.47%
Vezir et al. (38)	**UP:** 114 (76 children, 38 adult)	Native-lugol, precipitation, and trichrome	18.4	-	**Pediatric:** 57.1 **Adult:** 60	*D. fragilis* and G. *intestinalis* were also detected in 2.6%, and 1.3% of UP, respectively
Aydin et al. (39)	**UP:** 137 -Acute: 72 -Chronic: 65 **HI:** 129	Native-Lugol, trichrome, PCR, sequence analysis	**UP:** 12.03 -**Acute:** 43.75 -**Chronic:** 56.25 **HI:** 1.63	**UP:** ST1: 25 ST2: 6.25 ST3: 68.75 **HI:** ST3: 100	-	There were no statistically significant differences between the acute and chronic urticaria groups for neither *Blastocystis* spp. positivity (P = 0.60) nor ST distribution (P = 0.15).
Cakir et al. (40)	**UP:** 80 **HI:** 81	Native-Lugol, trichrome, culture and PCR	**UP:** 22.5 **HI:**14.6	**UP:** ST 1: 15.38 ST 2: 7.69 ST 3: 38.46 ST1+ST2: 3.85 ST1+ST3: 11.54 Non-ST: 23.08	-	The non-ST ratio in the urticaria group was seen as very high. The reason for this could be the STs that aren't currently identified
Tuzer et al. (43	**UP** **-Group A:** 70 (*Blastocystis* spp. +*)* **-Group B:** 70 (*Blastocystis* spp. -)	Not available	-	-	-Group A: given metronidazole treatment -Group B: no treatment -UAS7 (p: 0.007) ve MS (p < 0.001) scores were lower in Group A	-Total IgE and eosinophil level were lower in group A1 - Food hypersensitivity reactions were higher in group A

UP: Urticaria patients, **HI:** Healthy individuals, **PCR:** Polymerase Chain Reaction, **ST:** Subtype, **UAS-7:** Urticaria Activity Score-7, **MS:** Medication Score

Subtype (%) calculated based on all *Blastocystis* spp. positive samples

Upon analysis of the research, it can be observed that the prevalence of *Blastocystis* spp. varied between 5.69 and 31.9% in urticaria patients, and 1.56 and 14.8% in healthy individuals. Although very different prevalences have been reported in studies carried out by different study groups from various regions of our country, the prevalence was found to be higher in patients with urticaria when compared with control groups (21,35,36,39,40).

Various characteristics of patient groups, the use of different diagnostic techniques with varying degrees of sensitivity, and the expertise of microscopists in identifying parasitic forms may have contributed to the conflicting prevalences in these studies. Older research tended to use only conventional methods (35-38), but more current studies tend to practice the diagnostic algorithm, including high-sensitivity molecular techniques like PCR and sequence analysis (21,39,40).

Humans are primarily infected with ST1, ST2, and ST3 of the 38 identified subtypes of the parasite (5). Compatible with the world, the most prevalent subtype in our country among both urticaria patients and healthy participants was ST3, followed by ST1 and ST2, though their alignment varied throughout the documents (21,39,40).

Studies investigating the effect of antiparasitic treatment on urticaria

The advised therapy for *Blastocystis* spp. is metronidazole ranging from 250 to 750 mg three times a day for 10 days. Combination therapy using trimethoprim-sulfamethoxazole and paromomisin may also be utilized to treat *Blastocystis* spp. (41). There are also studies in the literature regarding that probiotic treatment such as yeast *Saccharomyces boulardii* could be used for the eradication of *Blastocystis s*pp. (42) . In patients with gastrointestinal and dermatological problems, treatment may be recommended if more than five *Blastocystis* spp. forms are found in a single field in the 40x objective (19). Additionally, research has been done to assess the connections between urticaria and the parasite's forms and subtypes. However, there is no consensus regarding whether treatment is necessary against *Blastocystis* spp. (20, 41).

According to the related research, patients with urticaria who received therapy for *Blastocystis* spp. in their stool samples had positive outcomes. In three investigations conducted in Türkiye, treatment was given upon detection of *Blastocystis* spp. in the stool, and all studies yielded quite favorable outcomes (35,38,43). In one of these studies, intestinal parasites were investigated in patients with urticaria, and regression of urticarial lesions was observed in 57.1% of pediatric and 60% of adult patients after treatment of all parasites, including *Blastocystis* spp. (38). The predominant investigation regarding how metronidazole treatment affected urticaria was conducted by Tuzer et al. in 2022. In this study, chronic urticaria patients with *Blastocytis* spp. detected in their feces were assigned to group A, and patients with persistent urticaria and no *Blastocystis* spp. discovered in their stools were assigned to group B. In addition to the laboratory test results, patients' urticaria activity (UAS-7) and medication scores (MS) were recorded. Patients in group A also received antiparasitic medicine besides urticaria treatment. All scores were reassessed eight months after the treatment began. They were divided into two groups following this treatment: group A1, whose urticaria symptoms disappeared, and group A2, whose symptoms continued. Eight months later, it was shown that patients in group A had lower scores than those in group B, although the initial UAS-7 and MS scores were the same. Additionally, total IgE and eosinophil levels decreased in group A1 (43).

It was reported that the rate of cure success after antimicrobial treatment in urticaria patients rises especially with repeated treatment regimens. Hameed et al. revealed that after receiving a single course of metronidazole, the parasite in the stool of 12 out of 20 symptomatic individuals with urticaria symptoms disappeared and their symptoms recovered. The remaining eight patients needed multiple doses to recover (29).

Studies investigating fecal microbiota in patients with chronic urticaria

There are contradictory findings from studies on the connection between gut microbiota and *Blastocystis* spp. In addition to the studies suggesting that *Blastocystis* spp. may be a component of the healthy microbiota, there are studies showing that *Blastocystis* spp. decreases the quantity of beneficial bacteria in the intestine (44). *Blastocystis* spp. has the ability to affect urticaria either directly or indirectly through interaction with the gut microbiota. The hypothesis that *Blastocystis* spp. has the potential to contribute indirectly to the etiopathogenesis of urticaria by reducing beneficial bacteria in the intestine has not been examined so far.

Table III: The studies investigating the fecal microbiota of patients with urticaria

Author(s)	Participants (n)	Country	Method	Findings	Additional information
Nabizadeh et al. (27)	**UP:** 20 **HI:** 20	Iran	PCR	1) *Akkermansia muciniphila, Clostridium leptum, and Faecalibacterium prausnitzii*: HI>UP 2) Enterobacteriaceae family members: UP>HI	It was the first study, that evaluate the change of microbiota in patients with urticaria
Zhu et al. (45)	**UP:** 16 **HI:** 26	China	Metagenomic sequencing, short-chain fatty acids metabolomics	1) Opportunistic pathogens such as *Escherichia coli, Klebsiella pneumoniae, and Bacteroides stercoris*: UP>HI 2) SCFA producer bacteria like Rikenellaceae, Alistipes, and *Roseburia hominis*: HI>UP 3) The level of SCFA: HI> UP 4) The level of LPS: UP>HI 5) *K. pneumoniae* transplantation increases MC-driven skin inflammatory response while *R. hominis* decreases	The etiopathogenesis of urticaria is associated with lower levels of SCFA-producing bacteria and higher levels of bacterial LPS-producers
Lu et al. (46)	**UP**: 10 **HI:** 10	China	16S rRNA sequence analysis	1) Pathogenic strains such as *E. coli*: UP>HI 2) *F. prausnitzii*, *Prevotella copri*, and *Bacteroides* spp.: HI>UP	The difference in microbiota between UP and HI indicates the reason leading to the different responses to probiotic treatment
Wang et al. (47)	**UP:** 100 **HI:** 100	China	16S rRNA sequence analysis	1) Enterobacteriaceae: UP>HI 2) *Bacteroides, Faecalibacterium, Bifidobacterium*, and *Ruminococcaceae:* HI>UP	The alterations in metabolites and gut microbiota can hamper immunological response and cause inflammation, which could exacerbate urticaria
Zhang et al. (48)	**UP:** 20 **HI:** 20	China	16S rRNA sequence analysis	1) Firmicutes, Bacteroidetes, Proteobacteria, and Verrucomicrobia were dominant in UP 2) Proteobacteria, Bacilli, Enterobacterales, Enterobacteriaceae: UP>HI 3) *Megamonas*, *Megasphaera*, and *Dialister*: HI>UP	The bacterial taxa that increased in UP might play a role in the pathogenesis of the disease and could be beneficial for future microbial-based therapies
Rezazadeh et al. (49)	**UP**: 20 **HI:** 20	Iran	PCR	1) *Lactobacillus* and *Bifidobacterium* load*:* HI>UP 2) The two groups did not differ in terms of the presence of *Bacteroides*	Urticaria may develop as a result of a reduction in the *Bifidobacterium* and *Lactobacillus*
Liu et al. (50)	UP: 25 HI: 25	China	16S rDNA sequence analysis	1) *Subdoligranulum* and *Ruminococcus bromii* were lower in UP 2) *Enterobacteriaceae* and *Klebsiella* were positively correlated with the duration of the disease 3) *Clostridium disporicum* was positively correlated with the DLQI	*Subdoligranulum* and *Ruminococcus bromii* could be used as biomarkers in the diagnosis of urticaria
Kwon et al. (51)	**UP:** 84 **HI:** 30	Korea	16S rRNA sequence analysis	1) Firmicutes: UP>HI 2) Bacteroidetes: HI> UP 3) Bacterial metabolites were higher in UP	The alterations in gut microbiome were associated with the severity of urticaria

UP: Urticaria patients, **HI:** Healthy individuals, **PCR:** Polymerase Chain Reaction, **DLQI:** Dermatology Life Quality Index, **SCFA:** Short Chain Fatty Acids, **LPS:** Lipopolysaccharide, **MC:** Mast cell

The group of bacteria known as the gut microbiota has been linked to several diseases. Table III provides an overview of research that compares the fecal microbiota of urticaria patients to that of healthy participants. However, the exact role of the gut microbiota in the etiology of chronic urticaria and the relevant mechanisms remain inadequately characterized and understood. Four points summarize the evidence suggesting that the fecal microbiota may play a role in the pathophysiology of chronic urticaria:

- Patients with chronic urticaria have a noticeable reduction in the diversity of their gut flora.
- Short-chain fatty acids, also referred to as inhibitors of mast cell activation, are present in lower concentrations in the serum of the urticaria patients.
- Inflammation, the duration of the disease, and the patient's response to treatment have all been linked to alterations in the gut microbiome of individuals with chronic urticaria.
- Probiotics may help patients with persistent urticaria (45).

A reduction in the diversity of the gut microbiota is a frequent observation in research examining the gut microbiota in individuals with chronic urticaria (45-47). There is a rise of organisms that are commonly referred to as pathogens, such as Enterobacterales, Enterobacteriaceae, Proteobacteria, and *Bacilli* (27,45,48). Further, it was discovered that the blood samples from the individuals with chronic urticaria had reduced amounts of the short-chain fatty acids such as acetate, propanoate, and caproate. Furthermore, it was found that individuals with chronic urticaria had a more active lipopolysaccharide production pathway and that their blood lipopolysaccharide levels were higher than those of the control group, inversely correlated with short-chain fatty acids.

CONCLUSION

In most research, the urticaria patient group has a higher prevalence of *Blastocystis* than the control group, and the regression of urticaria lesions and scores after therapy indicates that *Blastocystis* spp. might play a part in the pathogenesis of urticaria. For this reason, it is believed that performing parasitic examinations in the stools of urticaria patients with undetermined cause and treating *Blastocystis* spp. positive patients may be beneficial for the patients. However, since there is disagreement on this topic, additional research is required to investigate the relationship between *Blastocystis* spp. presence and urticaria, including its various forms and subtypes.

Conflict of Interest

The authors declare no conflict of interest.

Funding

No financial support has been received by the authors.

Authorship Contributions

Concept: **Ozlem Ulusan Bagci, Zeynep Celebi Sozener, Sevim Bavbek, Gulay Aral Akarsu,** Design: **Ozlem Ulusan Bagci, Zeynep Celebi Sozener, Sevim Bavbek, Gulay Aral Akarsu,** Data collection or processing: **Ozlem Ulusan Bagci, Gulay Aral Akarsu,** Analysis or Interpretation: **Ozlem Ulusan Bagci, Zeynep Celebi Sozener, Sevim Bavbek, Gulay Aral Akarsu,** Literature search: **Ozlem Ulusan Bagci, Gulay Aral Akarsu,** Writing: **Ozlem Ulusan Bagci, Gulay Aral Akarsu,** Approval: **Ozlem Ulusan Bagci, Zeynep Celebi Sozener, Sevim Bavbek, Gulay Aral Akarsu.**

REFERENCES

1. Barati M, KarimiPourSaryazdi A, Rahmanian V, Bahadory S, Abdoli A, Rezanezhad H, et al. Global prevalence and subtype distribution of Blastocystis sp. in rodents, birds, and water supplies: A systematic review and meta-analysis. Prev Vet Med 2022;208:105770.
2. Popruk S, Adao DEV, Rivera WL. Epidemiology and subtype distribution of Blastocystis in humans: A review. Infect Genet Evol 2021;95:105085.
3. Parija SC, Jeremiah S. Blastocystis: Taxonomy, biology and virulence. Trop Parasitol 2013;3(1):17-25.
4. Clark CG, van der Giezen M, Alfellani MA, Stensvold CR. Recent developments in Blastocystis research. Adv Parasitol 2013;82:1-32.
5. Maloney JG, Molokin A, Seguí R, Maravilla P, Martínez-Hernández F, Villalobos G, et al. Identification and molecular characterization of four new Blastocystis subtypes designated ST35-ST38. Microorganisms 2022;11:46.
6. Fonte Galindo L, Aleaga Santiesteban Y, Ginori Gilke M, Molina Y, Hernández Barrios Y. Blastocystosis and Urticaria: An Overview from a Syndemic Perspective. Arch Gastroenterol Res 2023;4(1):36-42.
7. Rayan HZ, Ismail OA, El Gayar EK. Prevalence and clinical features of Dientamoeba fragilis infections in patients suspected to have intestinal parasitic infection. J Egypt Soc Parasitol 2007;37(2):599-608.
8. Aguiar J, Goncalves A, Sodre F, Pereira Sdos R, Boia M, De Lemos E, et al. Intestinal protozoa and helminths among Terena Indians in the State of Mato Grosso do Sul: high prevalence of Blastocystis hominis. Rev Soc Bras Med Trop 2007;40:631-4.
9. Hidalgo-Gonzalez LA, Salgado-Lopez J, Pineda-Rodriguez SA, Martinez A, Romero-Valdovinos M, Martinez-Hernandez F, et al. Identification of Blastocystis sp. in school children from a rural Mexican village: subtypes and risk factors analysis. Parasitol Res 2023;122:1701-7.
10. Poulsen CS, Efunshile AM, Nelson JA, Stensvold CR. Epidemiological Aspects of Blastocystis Colonization in Children in Ilero, Nigeria. Am J Trop Med Hyg 2016;95(1):175-9.
11. Wong K, Ng G, Lin R, Yoshikawa H, Taylor M, Tan K. Predominance of subtype 3 among Blastocystis isolates from a major hospital in Singapore. Parasitol Res 2008;102:663-70.

12. Hirata T, Nakamura H, Kinjo N, Hokama A, Kinjo F, Yamane N, et al. Prevalence of Blastocystis hominis and Strongyloides stercoralis infection in Okinawa, Japan. Parasitol Res 2007;101: 1717-9.
13. Li L, Zhang X, Lv S, Zhang L, Yoshikawa H, Wu Z, et al.Cross-sectional surveys and subtype classification of human Blastocystis isolates from four epidemiological settings in China. Parasitol Res 2007;102:83-90.
14. Ulusan Ö, Zorbozan O, Yetişmiş K, Töz S, Ünver A, Turgay N. The Distribution Of The Intestinal Parasites Detected In Ege University Medical Faculty Parasitology Direct Diagnosis Laboratory; 10-Years Evaluation. Journal of Turkish Society of Microbiology 2019;49(2):86-91.
15. Sarzhanov F, Dogruman-Al F, Santin M, Maloney JG, Gureser AS, Karasartova D, et al. Investigation of neglected protists Blastocystis sp. and Dientamoeba fragilis in immunocompetent and immunodeficient diarrheal patients using both conventional and molecular methods. PLoS Negl Trop Dis 2021;15(10):e0009779.
16. Ergezen Alas S, Taş Cengiz Z, Yılmaz H. Investigation of Presence of Intestinal Parasites in Patients Applying to Derik State Hospital. East Black Sea Journal of Health Sciences 2022;1(1).
17. Tan TC, Suresh KG. Predominance of amoeboid forms of Blastocystis hominis in isolates from symptomatic patients. Parasitol Res 2006;98:189-93.
18. Delshad A, Saraei M, Alizadeh SA, Niaraki SR, Alipour M, Hosseinbigi B, et al. Distribution and molecular analysis of Blastocystis subtypes from gastrointestinal symptomatic and asymptomatic patients in Iran. Afr Health Sci 2020;20(3):1179-89.
19. Tan KS. New insights on classification, identification, and clinical relevance of Blastocystis spp. Clin Microbiol Rev 2008;21:639-65.
20. Coyle CM, Varughese J, Weiss LM, Tanowitz HB. Blastocystis: To Treat or Not to Treat. Clin Infect Dis 2012;54(1):105-10.
21. Aykur M, Camyar A, Türk BG, Sin AZ, Dagci H. Evaluation of association with subtypes and alleles of Blastocystis with chronic spontaneous urticaria. Acta Trop 2022;231:106455.
22. Dagci H, Kurt Ö, Demirel M, Mandiracioglu A, Aydemir S, Saz U, et al. Epidemiological and diagnostic features of Blastocystis infection in symptomatic patients in İzmir province, Turkey. Iran J Parasitol 2014;9(4):519-29.
23. Pasqui AL, Savini E, Saletti M, Guzzo C, Puccetti L, Auteri A. Chronic urticaria and blastocystis hominis infection: a case report. Eur Rev Med Pharmacol Sci 2004;8(3):117-20.
24. Katsarou-Katsari A, Vassalos CM, Tzanetou K, Spanakos G, Papadopoulou C, Vakalis N. Acute urticaria associated with amoeboid forms of Blastocystis sp. subtype 3. Acta Derm Venereol 2008; 88(1):80-1.
25. Verma R, Delfanian K.Blastocystis hominis associated acute urticaria. Am J Med Sci 2013;346(1):80-1.
26. Lim MX, Png CW, Tay CY, Teo JD, Jiao H, Lehming N, et al. Differential regulation of proinflammatory cytokine expression by mitogen-activated protein kinases in macrophages in response tointestinal parasite infection. Infect Immun 2014;82:4789-801.
27. Nabizadeh E, Jazani NH, Bagheri M, Shahabi S. Association of altered gut microbiota composition with chronic urticaria. Ann Allergy Asthma Immunol 2017;119:48-53.
28. Mayneris-Perxachs J, Arnoriaga-Rodríguez M, Garre-Olmo J, Puig J, Ramos R, Trelis M, et al. Presence of Blastocystis in gut microbiota is associated with cognitive traits and decreased executive function. ISME J 2022; :2181-97.
29. Hameed DMA, Hassanin OM, Zuel-Fakkar NM. Association of Blastocystis hominis genetic subtypes with urticaria. Parasitol Res 2011;108:553-60.
30. Casero RD, Mongi F, Sánchez A, Ramírez JD. Blastocystis and urticaria: Examination of subtypes and morphotypes in an unusual clinical manifestation. Acta Trop 2015;148:156-61.
31. Melo GB, Malta FM, Maruta CW, Criado PR, Castilho VLP, et al. Characterization of subtypes of Blastocystis sp. isolated from patients with urticaria, São Paulo, Brazil. Parasite Epidemiol Control 2019;7:e00124.
32. Shirvani G, Fasihi-Harandi M, Raiesi O, Bazargan N, Zahedi MJ, et al. Prevalence and Molecular Subtyping of Blastocystis from Patients with Irritable Bowel Syndrome, Inflammatory Bowel Disease and Chronic Urticaria in Iran. Acta Parasit 2020;65:90-6.
33. Jafari A, Bahrami F, Nasiri-Kalmarzi R, Abdoli A.Chronic urticaria associated with Blastocystis hominis infection. Arch Dermatol Res 2024;316:413.
34. Kantardjiev V, Galev A, Broshtilova V. Urticaria Associated With Amoeboid Forms of Blastocystis Spp. Asian J Res Infect Dis 2019;2:1-4.
35. Doğruman Al F, Adışen E, Kuştimur S, Gürer MA. The Role of Protozoan Parasites in Etiology of Urticaria. Turkish Journal of Parasitology 2009;33(2):136-9.
36. Dilek AR, Dilek N, Saral Y, Ekşi S. The role of protozoa in the etiology of chronic urticaria. Dermatol Sin 2012;30(3):90-2.
37. Arik Yilmaz E, Karaatmaca B, Sackesen C, Sahiner UM, Cavkaytar O, Sekerel BE, Soyer O. Parasitic Infections in Children with Chronic Spontaneous Urticaria. Int Arch Allergy Immunol 2016;171(2):130-135.
38. Vezir S, Kaya F, Vezir E, Karaosmanoğlu N, Adiloğlu AK. Evaluation of intestinal parasites in patients with chronic spontaneous urticaria in a territory hospital in Turkey. J Infect Dev Ctries 2019;13(10):927-32.
39. Aydin M, Yazici M, Demirkazik M, Koltas IS, Cikman A, Gulhan B, Duran T, Yilmaz A, Kara M. Molecular characterization and subtyping of Blastocystis in urticarial patients in Turkey. Asian Pac J Trop Med 2019;12(10):450-6.
40. Cakir F, Cicek M, Yildirim IH. Determination the Subtypes of Blastocystis sp. and Evaluate the Effect of These Subtypes on Pathogenicity. Acta Parasit 2019;64:7-1.
41. Roberts T, Stark D, Harkness J, Ellis J. Update on the pathogenic potential and treatment options for Blastocystis sp. Gut Pathog 2014;6:17.

42. Dinleyici EC, Eren M, Dogan N, Reyhanioglu S, Yargic ZA, Vandenplas Y. Clinical efficacy of Saccharomyces boulardii or metronidazole in symptomatic children with Blastocystis hominis infection. Parasitol Res 2011;108:541-5.
43. Tuzer C, Yegit O, Ozturk NS, Demir S, Demirpek U, Boral OB, et al. Relationship between Blastocystis spp. with Accompanying Food Hypersensitivity and Chronic Spontaneous Urticaria. Int Arch Allergy Immunol 2022;183(12):1259-69.
44. Deng L, Wojciech L, Gascoigne NRJ, Peng G, Tan KSW. New insights into the interactions between Blastocystis, the gut microbiota, and host immunity. PLoS Pathog 2021;17(2):e1009253.
45. Zhu L, Jian X, Zhou B, Liu R, Muñoz M, Sun W, et al. Gut microbiota facilitate chronic spontaneous urticaria. Nat Commun 2024;15:112.
46. Lu T, Chen Y, Guo Y, Sun J, Shen W, Yuan M, et al. Altered Gut Microbiota Diversity and Composition in Chronic Urticaria. Dis Markers 2019;2019:6417471.
47. Wang D, Guo S, He H, Gong L, Cui H. Gut Microbiome and Serum Metabolome Analyses Identify Unsaturated Fatty Acids and Butanoate Metabolism Induced by Gut Microbiota in Patients With Chronic Spontaneous Urticaria. Front Cell Infect Microbiol 2020; 10:24.
48. Zhang X, Zhang J, Chu Z, Shi L, Geng S, Guo K. Gut Microbiome Alterations and Functional Prediction in Chronic Spontaneous Urticaria Patients. J Microbiol Biotechnol 2021;31(5):747-55.
49. Rezazadeh A, Shahabi S, Bagheri M, Nabizadeh E, Jazani NH. The protective effect of Lactobacillus and Bifidobacterium as the gut microbiota members against chronic urticaria. Int Immunopharmacol 2018;59:168-73.
50. Liu R, Peng C, Jing D, Xiao Y, Zhu W, Zhao S, et al. Biomarkers of Gut Microbiota in Chronic Spontaneous Urticaria and Symptomatic Dermographism. Front Cell Infect Microbiol 2021;11:703126.
51. Kwon JW, Park Hİ, Young H. Alteration of gut microbiome in chronic urticaria. J Allergy Clin Immunol 2024;153(2).