REVIEW ARTICLE

Blastocystis hominis; Friend or Foe

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Abstract

Blastocystis hominis (*B. hominis*) remains the most common parasite identified through stool examination. A clinician will undoubtedly encounter the presence of this parasite numerous times in their career. Thus, it is vital to know if this organism is a 'friend or foe', or in other words, whether it is a commensal or a pathogen. This will help clinicians decide whether to treat or not. This literature review discusses the best available evidence of the association of *B. hominis* and two diseases- irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). Particularly, focus has been paid to the effect of antimicrobial therapy in improving disease activity/symptoms and concluding on the pathogenicity of *B. hominis* based on *in vitro*, observational studies, and randomized controlled trials. Most importantly, the review presents a concise set of recommendations for when and how to treat *B. hominis* in a patient presenting gastrointestinal ailments.

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Introduction

Blastocystis hominis (*B. hominis*) was first discovered in 1911 and characterized as an anaerobic protozoan parasite.[1] Seventeen subtypes of this parasite have been detected, with subtypes 1, 2, and 3 being the most common found in humans. Other subtypes affect insects, reptiles, birds, and other mammals, indicating that *B. hominis* can be transmitted by animal-to-human contact.[2] *B. hominis* is the most common parasite detected in ova and stool samples.[1] Therefore, there is a great deal of interest in determining whether it is a commensal or pathogenic organism.

There have been many studies, both randomized controlled trials and observational studies, that have examined the nature and potential pathogenicity of *B. hominis*. However, there are conflicting results and thus, the practicing clinician still needs a clear answer as to whether to treat this organism. With the advent and popularity of direct-to-consumer stool tests, it is vital for the gastroenterologist to properly understand how *B. hominis* does (or does not) play a role in disease and when to utilize antimicrobial therapy.

In this narrative review, the author evaluates the latest research on *B. hominis,* focusing on irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). This review aims to summarize the current literature as follows: (1) clarify the correlation between *B. hominis* with IBS and IBD, (2) understand when and how to treat positive findings, and (3) elucidate how to effectively counsel patients who test positive for this organism.

The review presents clinically relevant and practice-changing information for astute gastroenterologists and clinicians managing the sequelae of a dysfunctional GI ecosystem.

B. hominis and IBS

Blastocystis prevalence in IBS vs controls

One of the most common functional GI disorders a clinician may encounter is IBS, which affects 10-15% of the North American population.[3-9] Many have speculated that *B. hominis* contributes to IBS and eradication of this parasite is necessary in most cases to rectify IBS symptoms.

Although *B. hominis* and IBS are associated, the association seems to be modest at best. One meta-analysis of 29 observational studies showed a statistically significantly higher risk of IBS (odds ratio (OR) 1.78) in those with *B. hominis.*[10] Another meta-analysis of 17 studies, 5900 participants (2500 IBS, 3300 controls) also found an association between IBS and *B. hominis* (OR 2.19).[11] The greatest association was seen with subtype-1 (OR 4.4). The largest cross-sectional study the author has identified (454 participants), also suggested that subtype-1 was significantly associated with IBS-D (OR 2.9).[12] Many more observational studies have corroborated a higher prevalence of *B. hominis* in those with IBS as compared to healthy controls.[13–21]

Nonetheless, there is also evidence pointing to a null hypothesis of the association between *B. hominis* and IBS, although these studies are relatively smaller. A study of 79 participants found no statistical difference between IBS patients and healthy controls after measuring *B. hominis* using 7 different methodologies.[22] Another cross-sectional study of 36 IBS patients and 36 healthy controls also found no difference between IBS and controls irrespective of the techniques used (stool microscopy vs polymerase chain reaction (PCR)).[23] Khademvatan et al. also replicated such findings (17.2% healthy controls *vs.* 19.7% IBS) and found no difference in results depending on subtypes.[24]

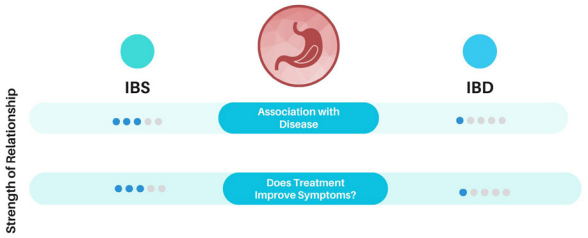
Some studies have even found that the prevalence of Blastocystis was higher in healthy controls compared to individuals with IBS. For example, a study of 419 individuals reported that healthy controls had higher levels of parasites (52% healthy controls *vs.* 39% IBS) and *B hominis* (27% healthy controls *vs.* 18% IBS).[25] In addition, a 2020 case-control study of 483 adults in Denmark found that *Dientamoeba fragilis* and Blastocystis were detected in a greater proportion of fecal samples in the asymptomatic group than the IBS group (22% healthy controls *vs. 15*% IBS).[26]

Does treating *B. hominis* improve IBS outcomes?

Even if *B. hominis* is associated with IBS, it would be crucial to know if treatment alleviates IBS symptoms. An analysis of 2 pooled randomized, double-blind, placebo-controlled studies found that *B. hominis* eradication was better at achieving clinical remission of symptoms compared to placebo (86% treatment *vs.* 38% placebo).[27] Another placebo-controlled trial with over 600 patients with diarrhea showed that symptom improvement correlated with eradication after metronidazole therapy; 80% of participants reported an eradication, and 88% became asymptomatic at 1-month follow-up.[28] However, the co-presence of another parasite in 24% of those with *B. hominis* confounded the findings. In another study of 138 children with *B. hominis* and functional abdominal pain, treatment with antimicrobials was effective in improving symptoms compared to no treatment (69% treatment *vs.* 35% no treatment).[29] However, this study was not placebo-controlled and was not looking at children with IBS specifically.

It is difficult to know if the improvement of symptoms in these studies is solely from the eradication of *B. hominis* or from some other factor. Most research suggests that symptom improvement is not always associated with the successful eradication of the parasite. A study of 39 patients with symptomatic *B. hominis* who received metronidazole therapy, reported symptom improvement in 79% of cases post-therapy.[30] However, only 48% had confirmed eradication of *B. hominis*. In another study of 10 IBS-D patients with *B hominis* who received 14 days of antibiotic therapy, 60% (6) of patients reported improvement in symptoms.[31] However, only 3 of them had eradication of *B. hominis*. This implies that a notable number of participants had improved symptoms without confirmed eradication of *B. hominis.*

Figure 1. Comparing *B. hominis* in IBS and IBD Research



Note: Figure 1 shows the relative strength of evidence of *B. hominis* association with disease (top bar) and how much treatment improves symptoms (bottom bar). On a scale of one to five, each blue colored circle represents the relative strength of evidence for each clinical question (one colored circle = low strength of relationship, five colored circles = high strength of relationship). While there has been no meta-analysis to quantify the answer to these questions, the author aims to show a graphical representation of the general strength of evidence.

In conclusion, the studies focusing on *B. hominis* and IBS suggest the following (Figure 1): (1) there is a modest association between *B. hominis* and IBS; (2) treatment of *B. hominis* is modestly associated with improved outcomes; and, (3) the improvement in symptoms may be independent of the actual eradication of the organism and may be a result of some other factor(s).

B. hominis and IBD

Blastocystis prevalence in IBD

Examining the link between *B. hominis* and IBD reveals a similar pattern to that of the relationship between *B. hominis* and IBS. While there are mixed results, the overall trend is that there is no increased prevalence of *B. hominis* in those who have IBD. Notably, most of the studies have centered on ulcerative colitis (UC) (*versus* Crohn's disease).

In a study of 616 healthy individuals and 107 IBD patients, *B. hominis* was more common in healthy controls (30% *vs.* 4%).[32] Similarly, another study reported almost two times higher rate of *B. hominis* in healthy controls compared to those with IBD.[33] Furthermore, it found no difference in *B. hominis* subtypes in IBD *versus* healthy controls. A third study found about a 2.5 times increased rate (32% *vs* 13%) of *B. hominis* in healthy controls compared to those with active UC.[34] Finally, a fourth study found a four times increased rate (19% vs 5%) of *B. hominis* in healthy controls.[35] In those with UC, *B. hominis* was more common in those in remission compared to those with active disease. The lack of association between *B. hominis* and IBD has been replicated by many more studies, which showed higher rates of *B. hominis* in healthy controls compared to IBD patients.[36-39]

In contrast to the above findings, a few studies show a potential connection. The largest study to date is a case-control study of 2334 patients with gastrointestinal symptoms including 335 with diagnosed IBD and 192 healthy controls.[40] *B. hominis* was more prevalent in those with IBD compared to controls. However, this finding was only observed in those with UC (not Crohn's disease).

Another study found a higher rate of *B. hominis* in UC patients compared to healthy controls (65% *vs* 18%).[41] Similar results were found in a one-year case-control study of 125 IBD patients and 125 healthy controls.[42] In fact, UC participants who also had *B. hominis* colonization, were more likely to have an active disease compared to being in remission (76% *vs* 24%). One potential reason that may account for these potential differences (as will be reviewed later) is that *B. hominis* subtype differences may lead to different phenotypic changes in the microbiome.

Does treating *B. hominis* improve IBD outcomes?

There is a paucity of evidence to answer this question. Antibiotic therapy may improve IBD outcomes, but clinical improvement is not always associated with the eradication of the organism.

In one small study of 6 UC patients who had *B. hominis* and were refractory to conventional IBD treatment were given metronidazole. All patients improved 3 weeks later.[43]

In 1993, a small retrospective study comprising 12 IBD patients with *B. hominis* found that only 3 of the 7 who received metronidazole had symptom improvement.[44] In a randomized clinical trial of 100 UC patients, those treated with a combination of nitazoxanide and mesalazine showed better mucosal healing compared to those treated with mesalazine alone.[41] However, no difference in symptom improvement was reported between the two therapies. Another limitation of this study is that UC patients had notable rates of *Entamoeba nana* and *Entamoeba dispar* colonization. In the few examples where, antimicrobial therapy led to improvement, it could be possible that symptom improvement was related to other mechanisms such as microbiome changes and/or immunomodulatory effects of the antimicrobial agent, and not eradication of *B. hominis.*

Overall, these findings do not strongly indicate that *B. hominis* eradication leads to symptom improvement in those with IBD (Figure 1).

Is *B. hominis* A Pathogen?

To better understand whether *B. hominis* is a 'friend or foe', this review will discuss the potential pathogenicity of this organism. Conclusions will be drawn to help answer the question of how and when to treat *B. hominis* found in a patient. In this section, five elements will be discussed: (1) the prevalence of *B. hominis* in the general population, (2) species subtype factors, (3) virulence factors, (4) criticizing whether *B. hominis* presence is a result or cause of dysbiosis, (5) and briefly discussing the association between eradication and symptom improvement.

B. hominis in the general population

Blastocystis species have been identified worldwide. The prevalence in the general population depends on many risk factors including temperature, water/food hygiene practices, and exposure to animals.[45] In general, *B. hominis* is found at higher rates in resource-limited locations (30-60% prevalence) compared to resource-rich locations (0.5-55%).[45,46] For example, 36% of 244 asymptomatic healthy children from six non-western countries were found to have *B. hominis* using PCR,[47] and similar findings were also reported by other studies.[48,49]

Although *B. hominis* remains the most prominent parasitic organism identified through epidemiologic studies,[45] the prevalence of *B. hominis* remains variable and dependent on the type of method used for stool analysis as well as the age of the population studied.

Does the type of Blastocystis matter?

Blastocystis species subtype differences were first noted *in vitro* and animal studies. For example, using a murine model of experimental colitis, Deng et al. found that ST-7 infection exerts a phenotypic expression different from that of ST-4 infection.[50]

Human studies suggest that subtype-1 (ST1) and subtype-3 (ST3) are the most common subtypes found in humans and they are most likely to exhibit symptoms.[51,52,53] It is important to note that not all studies suggest the association between specific subtypes and the presence of symptoms.[46,54-56] Some parasitologists argue that ST-4 may be more pathogenic in Western regions.[57]

Overall, these findings suggest subtype and host region may account for the heterogeneity found in the IBS and IBD literature; and there remains a strong association between a specific subtype and the presence of disease.

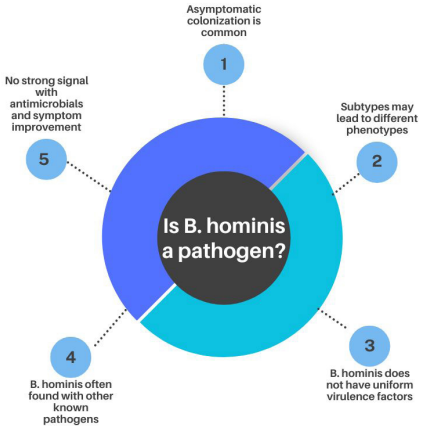
Virulence factors

If *B. hominis* is a frank pathogen, then it would be expected that the species would express virulence factors. It is hypothesized that antigens from *B. hominis* can induce a predominant T-Helper 2 Th2 cell response which may be implicated in IBS etiology.[58,59] However, Andersen and Stenvold reported that *B. hominis* has "*... no striking phenotypic virulence properties, such as the presence of flagella, lectins, or rhoptries, have been identified, and phagocytosis has been described only once*".[48]

Cause or effect?

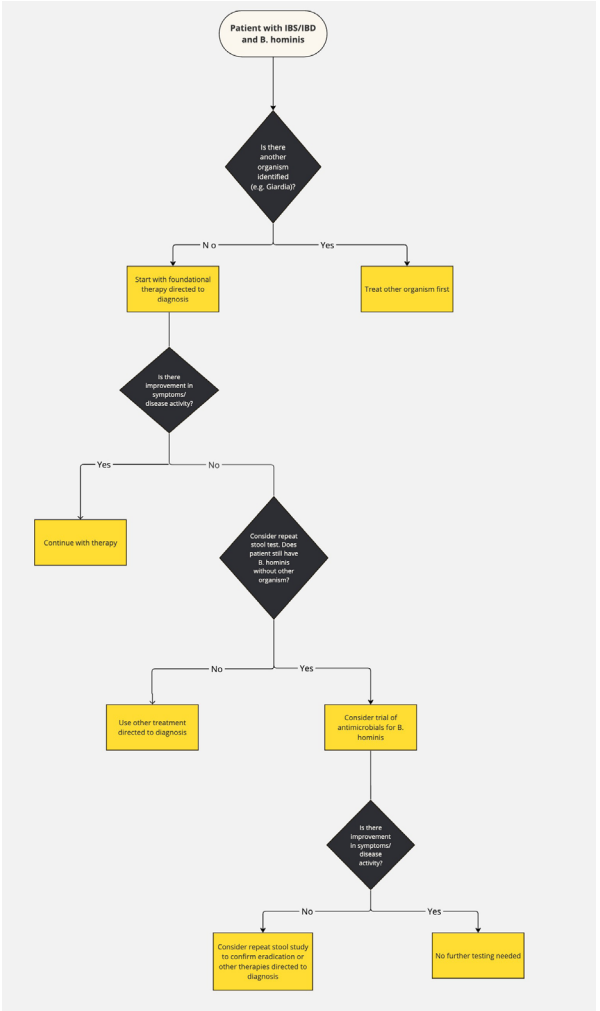
It is also important to note that *B. hominis* is commonly found in the presence of other dysbiotic findings. For example, a study of 115 IBS patients found that *Helicobacter pylori* was present in 73% of those who were identified to have *B. hominis*.[60] Another study found that 24% of those infected with *B. hominis* had co-infection with another organism (e.g., Giardia).[28] This suggests that perhaps there is another root cause of why *B. hominis* can colonize the GI tract (e.g. impaired immune function, unhealthy host, and generalized dysbiosis). One narrative review even suggested that *"Blastocystis can only be considered an indicator of dysbiosis"*.[13] Thus, the presence of *B. hominis* may be a *result* of dysbiosis rather than the root *cause*.

Figure 2. Assessing the Pathogenicity of *B. hominis*?



Note: Figure 2 summarizes five key aspects of research pointing to the author's conclusion that *B. hominis* is likely not a frank pathogen.

Figure 3. Proposed Algorithm of Approach to Blastocystis



Note: Figure 3 is the author's proposed algorithmic approach to managing a patient with IBS or IBD, with *B. hominis* identified using stool testing.

Symptom response to eradication

As discussed previously, *B. hominis* eradication does not always lead to significant improvement in clinical symptoms. For both IBS and IBD, there is only a modest improvement in symptom severity, at best. Importantly, this improvement may be independent of actual eradication, suggesting that antimicrobials may exert other effects that improve symptoms. If *B. hominis* was a true pathogen (like *C. difficile* or *Cryptosporidium*), we would expect a stronger indication of disease improvement upon eradication of the microorganism.

Is *B. Hominis* A Pathogen Or A Commensal?

Overall, most of the research suggests that *B. hominis* is more of a commensal than an overt pathogen. This is supported by the following points as discussed above (figure 2): (1) Asymptomatic colonization is very common as evident from epidemiological studies. To date, no "Blastocystis outbreaks" have been identified.[48] (2) Subtype differences may account for the heterogeneity of association between *B. hominis* prevalence and disease. (3) There is no presence of uniform virulence factors in Blastocystis species. (4) *B. hominis* is often found in the presence of other dysbiotic findings that may be the true cause of symptoms. (5) There is no strong correlation between eradication and symptom improvement. Since, if *B. hominis* was a true pathogen, eradication is expected to lead to a more robust improvement in the clinical trials.

To Treat Or Not To Treat *B. hominis*?

There has historically been a great deal of conjecture over the pathogenicity of *B. hominis*. While this review does not present a definitive answer to this question, the author hopes to portray how the discussed literature may be implemented into practice (figure 3). These recommendations are based upon three key takeaways from this literature review: (1) *B. hominis* has a modest relationship with IBS. There is a modest improvement in IBS symptoms with antimicrobials, however, this may be independent of the actual eradication of *B. hominis.* (2) *B. hominis* has a null to weak relationship with IBD. There is no strong indication that antimicrobial therapy improves symptoms. (3) *B. hominis* lacks typical features of being a pathogen and in many cases, may be a commensal organism. However, data is lacking.

In general, the antimicrobials used to treat *B. hominis* are non-toxic and moderately effective. If the clinician decides to recommend antimicrobial treatment, the target should be the resolution of symptoms instead of complete eradication of the parasite. If treatment is chosen, identifying successful eradication (i.e., repeat stool test) may not be mandatory. However, if symptoms persist, repeat stool analysis may help to determine whether symptoms are linked to *B. hominis* or some other etiology.

Having said that, antimicrobial therapy may not always be required for clinical improvement. Rather, more

"foundational" GI therapies may be a better starting point for many patients with non-severe symptoms given the lack of strong evidence pointing to the pathogenicity of *B. hominis*. For example, one study comparing Metronidazole to *Saccharomyces boulardii* found better outcomes with the probiotic.[61] In addition, there are many other therapies for both IBS and IBD that have better evidence to support their use first before antimicrobial therapy. Thus, the author suggests utilizing antimicrobial therapy under the following conditions: (1) The patient exhibits some sort of GI symptom(s). There is stronger evidence for IBS than IBD. Treatment is not indicated in asymptomatic individuals. (2*) B. hominis* is detected through culture, microscopy, or PCR analysis; culture and PCR techniques are the most sensitive. (3) Other foundational GI therapies (e.g. changes to diet/lifestyle, pharmacotherapy directed to their diagnosis) have exhibited limited efficacy in improving patient condition.

Limitations To Current Research

More research is certainly necessary to conclusively determine the pathogenicity of *B. hominis*. Critical analysis of the studies suggesting a positive association between *B. hominis* and IBS showed that none of them utilized PCR technology, and instead relied upon microscopy and culture-based techniques, despite PCR having superior sensitivity compared to culture and microscopy.[45,62,63] Poirier et al. suggested that cultures usually flag as positive at a PCR value of 4.85×10^4. Instead of detecting the "presence/absence" of *B. hominis* colonization, PCR technology can help quantify *B. hominis* and thus, assess whether individuals may or may not benefit from treatment. Unfortunately, the existing literature does not offer good evidence of a cutoff to help identify "high" *versus* "normal" counts. Additional attention should be paid to conducting further clinical trials using antimicrobial therapy with a particular focus on pre- and post-treatment of *B. hominis* analysis using PCR technology, to better understand whether symptoms are due to *B. hominis* colonization or other factors.

Author Disclosure Statement

The author declares that they have no competing interests.

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