Blastocystis: To Treat or Not to Treat...

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Parasites in the genus Blastocystis comprise several subtypes (genotypes) and have a worldwide distribution. In some surveys, these are the most common parasites found in human stool specimens. An emerging literature suggests that the pathogenicity of Blastocystis is related to specific subtypes and parasite burden, although even individuals with small numbers of cysts may be symptomatic. Some data suggest an association between infection with Blastocystis and irritable bowel syndrome. However, there are few clinical studies demonstrating a direct relationship between the presence of this parasite and disease, few animal models to explore this relationship, and no consensus as to appropriate treatment. We recommend that asymptomatic individuals with few cysts not be treated. However, those who have gastrointestinal or dermatologic signs and symptoms and many cysts in stool specimens may require treatment. Metronidazole is the drug of choice. Additional studies are required to determine pathogenicity and appropriate therapy.

Members of the genus Blastocystis are ubiquitous parasites with a worldwide distribution that are transmitted via the fecal-oral route. Nine subtypes (genotypes) of Blastocystis are described on the basis of small-subunit ribosomal RNA gene analysis, and nonhuman primates, mammals, and birds seem to be the major reservoir hosts for most subtypes [1]. Because of this vast diversity, it has been suggested that the human parasite should no longer be referred to as Blastocystis hominis but instead should be called Blastocystis spp. or Blastocystis spp. subtype n (where n is the subtype number according to the Stensvold classification) [2]. In this article, we refer to this organism as Blastocystis to avoid confusion.

In many epidemiologic surveys, Blastocystis is the most frequently isolated parasite, with a higher prevalence in underdeveloped countries [3]. This may be attributed to poor hygiene, exposure to animals, and consumption of contaminated food or water. Blastocystis is the most common parasite identified in stool samples in many institutions in the United States. It is more common than Giardia lamblia and Dientamoeba fragilis. Within regions in the same country, the prevalence can vary widely [3].

The taxonomy of Blastocystis remained elusive for many years. It had been classified as flagellate, vegetable, yeast, or fungus, but in 1991, Zierdt et al [4] classified it as a protist on the basis of its morphologic features. With the advent of molecular data (on small-subunit ribosomal DNA and other genes), these organisms are now thought to belong to the stramenopiles, a branch of the Chromalveolata [5, 6]. This group includes both unicellular and multicellular protists, such as brown algae, diatoms, chrysophytes, water molds, and slime nets [7]. Blastocystis from humans and animals can be divided into at least 12 species, of which several are found in humans [8].

This classification of Blastocystis into several species on the basis of molecular data may explain the variations in symptoms and the response to treatment reported in Blastocystis infections. Humans can have zoonotic infections due to Blastocystis that are found in primates, pigs, cattle, and birds, as well as infection with the Blastocystis subtype 3 isolate, which is found only in humans [9]. Prevalence studies indicate that subtypes 1 and 3 predominate in human infection and suggest that...
subtype variation is constant and does not vary much between populations [10, 11]. Other genotypes have been isolated in other prevalence studies, but in decreasing frequency; these are subtypes 2, 4, 6, 7, 8, and 9 [2]. Most individuals seem to harbor a particular subtype, but combinations have also been reported. Pathogenesis may be associated with particular subtypes or species. Because subtypes of Blastocystis cannot be distinguished morphologically, molecular techniques are required for epidemiologic, clinical, and therapeutic studies to understand the dynamics of this infection.

CLINICAL SYMPTOMS AND EPIDEMIOLOGY

Some have suggested that certain populations may be more susceptible to Blastocystis infections. This parasite was the most common parasite found in Indonesian patients with human immunodeficiency virus infection and AIDS who had chronic diarrhea before receipt of antiretroviral therapy, but this study lacked a control group [12]. Similarly, Blastocystis was one of the parasites most frequently isolated from patients with cancer in a series from Turkey [13]. Similar to their susceptibility to other intestinal protozoa, children in underdeveloped countries have a higher incidence of infection [14]. Those who are in close contact with animals also seem to be at increased risk of acquisition of Blastocystis, reinforcing the notion that this is probably a zoonotic infection [2]. A few studies found that expatriates with traveler’s diarrhea had a high prevalence of Blastocystis, whereas some studies found that 25%–75% of those with Blastocystis have a history of recent foreign travel [15–19]; however, there was no association between Blastocystis and traveler’s diarrhea in a prospective case-control study performed in Nepal [16, 20].

There has been debate in the literature concerning the question of the pathogenicity of Blastocystis. Some studies suggest an association between the parasite and disease, but others do not [3, 18, 21]. The limitations of these studies have included adequate sample size, diagnostic methods details, case definitions, duration of organism carriage, and an absence of culture studies to rule out other causes [22]. Many of these studies have lacked data on the specific concentration of organisms and the Blastocystis subtype. Recently, a 29-kDa parasite protein and a parasite-associated protease have received attention as potential markers of pathogenicity [23, 24]. There is a lack of reliable animal models for this infection that would allow adequate and detailed investigation of its pathogenesis [25].

It has been suggested that finding >5 parasites per high-power field (40× objective) or, less commonly, by oil immersion (100× objective) is associated with the presence of gastrointestinal disease [3]. Many studies were done in hospitals located in developing countries where the risk of infectious diarrhea is high. A causal relationship has never been established for Blastocystis and diarrhea, and no reliable animal model exists, so Koch’s postulates have not been demonstrated for this organism. Interestingly, in some studies the clinical presentations have been shown to be subtype dependent, adding to the confusion and possible underestimation of the organism’s importance in the literature [26]. Recent studies have focused on correlating disease pathogenicity with subtypes irrespective of parasite density, but the results have been discrepant [26–29].

A variety of signs and symptoms, ranging from intestinal symptoms to cutaneous disorders, have been attributed to Blastocystis infection [30, 31]. The most common intestinal symptoms described are diarrhea and abdominal pain [2, 3, 22]. Nonspecific symptoms such as nausea, anorexia, abdominal pain, bloating, flatulence, and acute or chronic diarrhea, have also been reported [2, 3, 26, 32]. Diarrhea may be mild and self-limited or chronic, with reports of acute gastroenteritis [2, 3]. Blastocystis does not seem to be invasive, despite 2 case reports describing its recovery in deep tissue. In both of these cases, there were coexisting conditions predisposing to disruption of the gut barrier that probably led to coinfection with Blastocystis [33, 34]. In addition, there are no reports of Blastocystis-associated dysentery or endoscopic evidence of invasion [2, 35, 36]. Allergic cutaneous lesions, particularly urticaria, have been associated with this organism. In these reports, the resolution of dermatologic signs and symptoms were reported after treatment and eradication of the parasite from the stool [37–39]. It has been suggested that cutaneous manifestations in the setting of Blastocystis carriage are probably immune mediated, although the mechanism is unclear [2].

Irritable bowel syndrome (IBS) is defined as a functional group of bowel disorders in which abdominal pain is associated with defecation or alterations in bowel habits in the absence of an organic cause [40]. An association between Blastocystis and IBS has been suggested in the recent literature [2, 22, 36, 41–43]; however, in some studies, Blastocystis was detected more frequently in patients with IBS than in a control group [27, 32, 35], whereas in other studies there was no association [18, 44]. The pathophysiologic of IBS remains elusive, and there are probably several factors causing the constellation of signs and symptoms associated with this clinical entity. These include altered gut reactivity (colonic and/or small-bowel motility) in response to luminal or psychological stimuli, visceral afferent hypersensitivity, a hypersensitive gut with enhanced visceral perception and pain [45], and chronic immune activation [46, 47]. It has been suggested that low-grade inflammation due to ongoing immune activation caused by carriage or infection with Blastocystis providing persistent antigenic exposure could play a role in IBS [45]. For example, one study found levels of immunoglobulin G2 directed against Blastocystis in IBS patients when compared with asymptomatic controls [48]. Other researchers have speculated that the increased incidence of Blastocystis is not a cause of IBS but is rather an indicator of intestinal dysfunction [18].
Thus, current studies do not suggest a clear role for Blastocystis as an etiologic agent of IBS, and controlled trials demonstrating a resolution of symptoms in Blastocystis-infected IBS patients with eradication of the organisms are needed [2].

DIAGNOSIS

Blastocystis is a polymorphic organism, and 4 major morphologic forms—vacuolar, cyst, granular, and amoeboid—can be seen in stool and axenic cultures. Blastocystis is detected using standard clinical parasitologic techniques that are used to detect other enteric parasites, including direct smears stained with trichrome (Figure 1) [49]; various concentration techniques, such as formol-ether (ethyl acetate) concentration technique [32]; and in vitro culture [50]. Culture techniques are, most likely, more sensitive than direct smears. Amplification of Blastocystis-specific DNA by polymerase chain reaction directly from stool has been reported and permits identification of the Blastocystis subtypes [2, 9]. In comparative studies of diagnosis, polymerase chain reaction–based methods coupled with short-term axenic in vitro culture had the highest diagnostic utility in characterizing stool specimens [1, 32]. As with other enteric pathogens, the examination of multiple stool specimens increases the diagnostic yield. Blastocystis infection results in a serologic response, which can be detected by enzyme-linked immunosorbert assay or other assays; however, serologic testing is not currently used for diagnosis of this infection [51]. Fecal immunoassays are under development but have not been commercialized. Remarkably, many laboratories do not report Blastocystis because of the long-held view by some in the medical community that it is always nonpathogenic.

TREATMENT

Treatment of Blastocystis infection remains a complicated issue. Because there is still a great deal of debate about the true pathogenicity of Blastocystis, there is still much debate about the need for treatment. Further knowledge about the genotyping and subtyping of Blastocystis and the impact that various subtypes may have on pathogenicity and antimicrobial efficacy is still being sought [22]. In a symptomatic patient, isolation of cysts in stool specimens should trigger a thorough evaluation for other causes of the patient’s gastrointestinal tract complaints, given the possibility for coinfection with other pathogens. Patients with Blastocystis isolated in the stool can be coinfected with other pathogens, such as G. lamblia, Entamoeba histolytica, and D. fragilis [52]. It is quite possible that patients who respond to treatment for Blastocystis with metronidazole or trimethoprim-sulfamethoxazole (TMP-SMX) may actually have clinical improvement owing to treatment of a secondary pathogen.

To date, a number of antimicrobial agents have been used for treatment of Blastocystis infection (Table 1); however, randomized, controlled trials are limited. Metronidazole is considered first-line treatment, but the success of eradicating Blastocystis with this drug has been reported to be anywhere from 0% to 100% [53]. There have been 2 published placebo-controlled studies, and both concluded that resolution of symptoms was associated with eradication of the organism. Nigro et al [54] conducted a placebo-controlled trial evaluating 76 patients with Blastocystis infection, of whom 88% treated with metronidazole had resolution of clinical symptoms, compared with only 14% in the placebo group, 1 month after treatment. Microbiologic resolution was found in 80% of metronidazole-treated patients, compared with only 3% of the placebo group. In addition, when patients were evaluated 6 months after initiation of treatment, 30 (75%) of 40 in the metronidazole-treated group were still asymptomatic, compared with 12 (33%) of 36 in the placebo group. It is not clear whether any of these patients harbored resistant subtypes or were reinfected [54]. In a study by Mogaddham et al [55], 28 of 104 Blastocystis-infected patients were classified as having severe infection. Twelve of these patients were treated with metronidazole, with infection eradicated in only 4. It is possible that metronidazole is effective for certain patients but does not provide complete eradication, particularly in those with severe infection, or that patients who did not respond may have been infected with resistant subtypes.

TMP-SMX has been used as a second-line agent in patients who may not be able to tolerate or do not respond to treatment with metronidazole. Ok et al [56] examined 38 children and 15 adults with symptomatic infection with Blastocystis (stool specimens were negative for other parasitic or bacterial infections) treated with TMP-SMX for 7 days. Blastocystis was eradicated from stool in 36 (94.7%) of 38 children and in 14 (93.3%) of 15.
Table 1. Antimicrobials Reported as Useful in the Treatment of Blastocystis Infection

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
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<tbody>
<tr>
<td>Metronidazole</td>
<td>Adult dose: 750 milligrams thrice daily for 10 days; or 500 milligrams thrice daily for 10 days; or 1.5 grams daily for 7 days</td>
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<tr>
<td></td>
<td>Pediatric dose: 15 mg/kg twice daily for 10 days</td>
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<tr>
<td>TMP-SMX</td>
<td>Adult dose: 2 double strength tablets daily for 7 days (320 milligrams TMP: 1600 milligrams SMX)</td>
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<tr>
<td></td>
<td>Pediatric dose: 6 mg/kg TMP daily for 7 days</td>
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<tr>
<td>Nitzoxanide</td>
<td>Adult dose: 500 milligrams twice daily for 3 days</td>
</tr>
<tr>
<td></td>
<td>Pediatric dose: 100–200 milligrams twice daily for 3 days</td>
</tr>
<tr>
<td>Paromomycin</td>
<td>25 mg/kg thrice daily for 10 days; 500 milligrams thrice daily for 7 days</td>
</tr>
<tr>
<td>Iodoquinol</td>
<td>650 milligrams thrice daily for 10–20 days</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>200 milligrams daily for 14 days</td>
</tr>
<tr>
<td>Tinidazole</td>
<td>Adult dose: 2 grams daily for 5 days</td>
</tr>
<tr>
<td></td>
<td>Pediatric dose (&lt;40 kg body weight): 50 mg/kg/day for 5 days</td>
</tr>
<tr>
<td>Saccharomyces boulardii</td>
<td>250 milligrams twice daily for 10 days</td>
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</table>

Given the variable agreement regarding the pathogenicity of Blastocystis, there is no consensus as to which patients should undergo treatment for Blastocystis infection.

Abbreviations: kg, kilograms; SMX, sulfamethoxazole; TMP, trimethoprim.

adults. Clinical symptoms resolved in 39 (73.6%) and improved in 10 (18.9%) of 53 patients evaluated.

Similar outcomes were observed in a study using nitzoxanide, but this study did not follow patients over a long period, so the effect may have been short-lived. Although these studies provide the best evidence to date for the pathogenic potential of this parasite, both studies used broad-spectrum antiparasitic agents, and thus the response to treatment could be attributed to the clearance of another possible enteric pathogen [2].

Additional agents, such as iodoquinol, tinidazole, nitzoxanide, emetine, pentamidine, iodochlorhydroxyquin, and furazolidone, have been used and have shown variable efficacy in eradicating Blastocystis infection [55, 57]. One of the difficulties in assessing therapeutic efficacy is the tremendous variability in posttreatment follow-up of patients treated for Blastocystis infection [22]. Posttreatment microbiologic analysis showing Blastocystis-positive stools may not reflect treatment failure or resistance but could represent reinfection. Patients may also have a secondary process that responded initially to treatment with subsequent treatment failure.

There have been several studies examining the use of alternative agents in the treatment of Blastocystis infection. For example, Yakoob et al [58] studied the in vitro efficacy of garlic and other dietary herbs, compared with that of metronidazole, in the treatment of Blastocystis infection in both control subjects and patients with IBS. The authors evaluated the efficacy of garlic and metronidazole at concentrations of 0.01 and 0.1 mg/mL in suppressing the growth of Blastocystis. They found that garlic and metronidazole were equally effective at both concentrations. The isolates of Blastocystis were not as sensitive to the other herbs tested, which included ginger, black pepper, and white cumin.

Saccharomyces boulardii (a probiotic) has also been studied for Blastocystis treatment [59]. In a study by Dinleyici et al [59], children with a 2-week history of gastrointestinal symptoms and isolation of Blastocystis from the stool were randomized to treatment with Saccharomyces, metronidazole, or placebo for 10 days. Patients were evaluated for clinical and microbiologic cure at days 15 and 30 after initiation of treatment. Clinical cure was found in 77.7% of the Saccharomyces group and 66.6% of the metronidazole group at 15 days, compared with 40% in the placebo group. Persistence of cysts in stool was noted in 20% of the metronidazole group and 27.8% of the Saccharomyces group, compared with 73.4% of the placebo group. Thirty days after initiation of treatment, clinical cure was found in 94.4% of subjects in the Saccharomyces group, compared with 73.3% of those in the metronidazole group. Resolution of cysts in the stool was found in 94.4% in the Saccharomyces group and 93.3% in the metronidazole group, and the difference was not statistically significant ($P = .43$) [59].

Given the variable agreement regarding the pathogenicity of Blastocystis, there is no consensus as to which patients should undergo treatment for Blastocystis infection. In the asymptomatic individual, treatment is not necessarily indicated. Isolation of Blastocystis in stool from a symptomatic individual should lead to a thorough investigation for other causes of the gastrointestinal complaints. It is reasonable to initiate a trial of antimicrobial therapy in patients who have persistent diarrhea or who have undergone an extensive work-up without any other pathogen or gastrointestinal source identified. Reasonable first-line agents include metronidazole or TMP-SMX. Additional randomized, controlled trials are needed to better assess the therapeutic efficacy of the additional antiparasitic drugs and their use in this infection.

The relation of Blastocystis to human disease remains unclear, and many of the drugs used in the treatment of Blastocystis infection have significant side effects. A minimum of 3 stool examinations separated in time and performed in a reliable parasitology laboratory constitute an adequate examination. If the individual is asymptomatic, we do not recommend specific antiparasitic therapy. However, we understand that a counter-argument to this recommendation may be made, because most experts recommend treatment of asymptomatic individuals who pass cysts, such as those with E. histolytica and G. lamblia.
infection. If the individual patient indeed has gastrointestinal signs and symptoms and has a significant number of cysts in the stool (ie, >5 cysts per high-power field), this patient may be a candidate for therapy. In those cases, other potential causes need to be ruled out. Thus, these patients may require additional stool specimens for parasite analysis, as well as cultures for bacterial pathogens. We have observed patients with Blastocystis in the stool who have G. lamblia or E. histolytica detected at subsequent examinations. Some of these patients may require endoscopy and imaging studies to rule out entities such as inflammatory bowel disease and IBS. Those with Blastocystis in the stool who have an associated skin eruption should be considered for treatment in the absence of other causes, but this recommendation is based on scant data. When treatment is given, we usually use metronidazole as first-line treatment, based on the available clinical trial data. If metronidazole is not effective, we usually use either TMP-SMX or nitazoxanide as second-line treatment.

Note

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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