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Eradication of *Blastocystis* in humans: Really necessary for all?

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ABSTRACT

Blastocystis (initially named as *Blastocystis hominis*) has long been known as a protist without any clinical significance. However, there is now a huge pile of case reports where *Blastocystis* is blamed for the symptoms and the infection described in the patients. Introduction of the presence of as many as 17 *Blastocystis* subtypes while many infected individuals are non-symptomatic initially brought about the correlation between the subtypes and pathogenicity; however, the outcomes of these trials were not consistent and did not explain its pathogenicity. Today, it is mostly acknowledged that *Blastocystis* may colonize many individuals but the infection's onset depends on the interaction between the virulence of parasites and host's immune competence. Eradication of *Blastocystis* is essential in some cases where it is the only infectious agent and patient is suffering from some symptoms. In such cases, metronidazole is the drug of choice but its efficacy is relatively low in some cases. Other agents used include trimethoprim–sulfamethoxazole, paromomycin, and furazolidone. Recent studies on the interactions between human health and the role of gut microbiota introduces new data which may significantly change our point of view against some protists, which we tend to see as "parasites requiring urgent eradication for cure". May the presence or absence of some *Blastocystis* subtypes necessary for human health, or is the absence or presence of certain *Blastocystis* subtypes in human gut is associated with certain diseases/infections? The answers of these questions will surely guide us to select patients requiring treatment against *Blastocystis* infection in future.

1. Introduction

Blastocystis is the species name of a group of intestinal protists that inhabit the gastrointestinal system of humans and many animals worldwide. It is probably the most common intestinal protist in parasitological surveys throughout the world, with prevalence rates ranging between 3% and 100% in different countries [1–3]. It has long been named as *Blastocystis hominis*; however, intensive molecular studies unveiled as many as 17 *Blastocystis* subtypes, all of which look alike under the microscope. Due to this extensive genetic diversity, the researchers reached a consensus to name it as "*Blastocystis*", to cover all subtypes, identified and may yet be so [3–6].

Despite being firstly described more than 100 years ago, there are still many obscurities about *Blastocystis* and its clinical significance. It is well-known that *Blastocystis* may colonize the bowels and commonly identified in the stool examinations of individuals with neither any gastrointestinal complaints nor symptoms. However, *Blastocystis* was also identified as the only causative agent in some gastrointestinal and dermatological infections, and patients may complain of gastrointestinal symptoms such as abdominal pain, diarrhea, nausea, vomiting, bloating and anorexia, or less commonly of dermatological complaints such as urticaria and intense itching [4,5,7–10]. These data obviously show that it is not always an innocent colonizer of human gut, but under which circumstances or interactions with the host does such colonization becomes clinically-important infections are yet to be defined.

There is currently no consensus about the treatment of patients with blastocystosis; however, it is mostly acknowledged that there is no need for treating the non-symptomatic ones [1]. Spontaneous remission has been reported in 22% of a cohort of individuals having *Blastocystis* in stools [11]. Treatment is limited to symptomatic patients infected only with *Blastocystis* and no other causative agent has been identified [7,12]. Successful treatment is defined as the complete resolution of symptoms reported by the patient and disappearance of *Blastocystis* in stool examinations [2,7,13]. In the present review, the current debate on the necessity of treating all *Blastocystis*-positive cases is discussed in the light of recent findings and well-established data, together with the role of *Blastocystis* in human health.

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2. Pathogenicity of *Blastocystis*: how or when?

Regarded long time as a commensal in human gut, *Blastocystis* was not the subject of any clinical research for decades. Its role in the pathophysiology of intestinal diseases has been in focus lately, and despite a reported case of a child where *Blastocystis* was associated with mucosal and peritoneal irritation [14], it is typically not correlated with intestinal mucosa during endoscopic examination [15]. *Blastocystis* may exert its pathologic effects through increasing intestinal permeability [16], degradation of epithelial barrier and secretory IgA by its protease enzymes, immunomodulatory and toxic effects, and through cytokine release from the colonic cells [17,18]. There are protease enzymes in *Blastocystis*, as in many infectious agents, and they were shown to take part in the induction of virulence [19,20].

The subtypes of *Blastocystis* isolates were initially associated with the pathogenicity. Despite numerous studies were conducted worldwide to differentiate pathogenic subtypes from the non-pathogenic ones, conflicting data, even within the same country, were obtained; today, subtype of *Blastocystis* is considered as a contributing factor of pathogenicity in concordance with other factors [6–8,21–24].

Most *Blastocystis* isolates found in stool samples are in vacuolar and granular forms; ameboid forms are rarely seen but mostly associated with symptomatic cases. Therefore, ameboid forms of *Blastocystis* are probably pathogenic isolates and patients require treatment [13,25,26].

Patients complain mostly of gastrointestinal symptoms, such as abdominal pain, diarrhea and nausea, and less commonly of dermatological symptoms, such as itching, redness and urticaria [1,2,8]. Disappearance of urticaria and related symptoms was demonstrated after appropriate antimicrobial therapy [26–28]. How *Blastocystis* is involved in the emergence of clinical disease or how it is silent, are yet to be clarified. The review of the published studies indicates that some individuals are more sensitive to *Blastocystis* infection, such as HIV (+) patients, cancer patients, tourists and children [3,29–31]. As its zoonotic potential and presence in some animals are well-known, close contact with animals is also a significant risk factor [7,32–34]. Its role in the pathogenesis of irritable bowel disease (IBD) has been a subject of debate for a long time. Due to conflicting results, there is an urgent need to unveil the effects of *Blastocystis* eradication in IBD patients with large-scale, controlled studies. Until that time, it is better to see it as an indicator of the dysfunction observed during IBD instead of a causative agent for the arousal of IBD symptoms [1,35–39].

In addition to many case reports of blastocystosis which declare confirmed eradication of *Blastocystis* with antimicrobial agents, there is also a contrary report of a case infected with *Blastocystis* subtype 9 which persisted in the gut after antimicrobial treatment with mebendazole, metronidazole, paromomycin, TMP-SMX and tetracycline for three years [40]. This may be due to different drug sensitivities of *Blastocystis* subtypes or their quick adaptability to human intestinal microbiota, which consequently creates irresponsiveness to treatment. Research directed to the interactions of *Blastocystis* and intestinal microbiota will no doubt bring out priceless data about the pathophysiology of *Blastocystis* infection in clinical cases [41,42].

3. Eradication of *Blastocystis*: which agent is the best?

The list of all agents used in the eradication of *Blastocystis* in clinical cases is shown in Table 1. As *Blastocystis* does not interact with the colonic mucosa and is present in the lumen of the colon, an effective drug should reach high concentrations in colonic lumen, have short small intestine transit time and should not be inactivated by the intestinal flora [43].

3.1. Metronidazole

Today, metronidazole is the first choice for the eradication of *Blastocystis*, as for other protozoal infections. Firstly used in 1959 for the treatment of a case of *Trichomonas* vaginitis, metronidazole is a small, highly-lipophylic molecule which is active against anaerobic, electron-carrying cells with lower reduction potential. It turns into toxic compounds after interacting with ferrodoxin, an electron-carrying protein, and these toxic compounds may inhibit DNA synthesis in bacteria and protists, together with damaging their energy-producing pathways [44]. It may also induce apoptosis in *Blastocystis*, which was claimed after the trials on axenic cultures of *Blastocystis* [45].

The mode of metronidazole's action on *Blastocystis* isolates has not been described clearly; therefore, the ongoing debate whether metronidazole acts directly on *Blastocystis* or indirectly through the inhibition/eradication of *Blastocystis*-related microorganisms in the gut is yet to be identified [12,43]. While there are reports that show high efficacy of metronidazole against *Blastocystis* even in placebo-controlled trials [46,47], there is also an increasing number of reports which indicate that metronidazole may not be effective in the eradication of *Blastocystis* [43,48,49], This may be due to several reasons such as; inability of *Blastocystis* isolates to induce the production of toxic form of metronidazole due to the absence of ntr and/or nim genes that are present in *Entamoeba* and *Giardia* species [43, 50]; metronidazole's inability of reaching high concentrations in colonic lumen [51], higher risk of reinfection in endemic regions [48], differences of virulence of *Blastocystis* isolates from different geographic regions [52] and finally with interactions of intestinal flora and *Blastocystis* isolates [41,42,53,54].. Resistance to metronidazole has been described among the cyst forms of *Blastocystis* [52,55,56]. However, as there are many unidentified points in the efficacy of metronidazole against *Blastocystis*, it is better to describe this situation as “poor drug efficacy of metronidazole”, rather than drug resistance [43]. This complicated issue will probably be solved after large-scale, controlled studies using isolates from different geographical regions. Dunn et al. [57] have recently developed metronidazole-resistant *Blastocystis* series that were originated from subtype 4. These series will be used to assess the efficacy of novel drug candidates against *Blastocystis* isolates.

3.2. Trimetoprim–sulfamethoxazole (TMP–SMX)

It is the second commonly selected drug for the eradication of *Blastocystis*. Again, it is reported as an effective option [51, 58,59], as well as an option with limited efficacy in some patients [46]. Indeed, TMP-SMX was not found to be superior to placebo in the treatment of pediatric patients with recurring abdominal pain and *Blastocystis* infection [60].

3.3. Paromomycin

It is a large-spectrum antimicrobial, which has also been used against *Blastocystis* infection. There are studies that indicate both paromomycine as superior to metronidazole [11] and effective only through its bactericidal activity on the intestinal flora, which is crucial for the survival of *Blastocystis* in the colonic lumen [2]. It was shown to be effective in patients with *Blastocystis* infection and chronic urticaria [27,28]. Paromomycine can be used safely in pregnant ladies [5].

3.4. Other agents and options

Other agents which were found to be effective against *Blastocystis* include tinidazole, ornidazole, secnidazole, ketoconazole, pentamidine, paromomycine, quinine, iodoquinol and emetin. Emetin use is currently limited due to its serious side-effects, for which furazolidone may be a good option [13].

Assessment of new treatment options were assessed in the eradication of *Blastocystis* lately. A well-known probiotic agent, *Saccharomyces boulardii* is a non-pathogenic yeast and act as a regulator of homeostasis in the gut through preventing the colonization of pathogenic agents on