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# *Blastocytosis hominis*: The Summary From A to Z

***Muhammad Fakhrur Rozi[1], Dewi Masyithah Darlan[2]****

*[1]Faculty of Medicine Universitas Sumatera Utara, Medan, Indonesia*
*[2]Department of Parasitology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia*

**Abstract.** *Blastocystis hominis* is a unicellular parasite classified as stramenopiles found in human and other mammals. The prevalence varies depending on the region, higher in developing country. The transmission route is primarily fecal-oral via ingestion of oocyst contaminated food or water, but zoonosis transmission is also considered. Travelers also emerge vulnerable to *Blastocystis sp.* infection. Based on recent studies, several proposed pathogenesis and virulence factor remain unclear. The advanced molecular method has been introduced to determine the genetic variation and diversity that implicates the clinical significance of the infection. There are six distinct morphological forms of this microorganism, consisting of vacuolar, granular, ameboid, and cystic described as the infective stage. It can produce a diverse range of clinical manifestation, asymptomatic or self-limiting diarrhea until severe watery diarrhea, depends on host factors and the subtype. The organism also causes pruritus and urticaria, which reported in a few case reports. Notwithstanding unclear pathogenicity, *Blastocystis sp.* has a significant impact on human health. Therefore, the mainstay of therapy still applies the conservative management for asymptomatic as well as symptomatic *Blastocystis sp.* positive patients based on the patient's immune status and symptoms.

**Keyword:** Zoonosis, infection, parasitic

***Abstrak.*** *Blastocystic hominis merupakan parasite uniselular yang digolongkan sebagai stramenofila, ditemukan menginfeksi manusia dan hewan. Prevalensinya beragam tergantung dengan lokasi kejadian, cenderung tinggi di negara berkembang. Transmisi organisme ini melalui rute fekal-oral dengan cara menelan ookista yang menginfeksi makanan dan minuman. Pelancong juga cenderung memiliki risiko tinggi terinfeksi. Selain itu, virulensi faktor organisme ini telah dikemukakan oleh beberapa studi namun tetap tidak dapat dijelaskan secara akurat. Teknik mutakhir juga telah digunakan untuk menggambarkan variasi genetic dan keragaman organisme ini yang mungkin terkait dengan kemaknaan klinis. Ada 6 bentuk morfologi dari Blastocystis sp. termasuk vacuolar, granular, ameboid, dan bentuk kistik. Bentuk kistik diduga merupakan fase infektif organisme. Paparan terhadap mamalia yang terinfeksi ookista juga dapat menimbulkan infeksi. Selain itu, organisme ini dapat menyebabkan berbagai gejala tergantung dengan status imun pasien. Karena pada beberapa aspek masih belum dapat dijelaskan secara pasti, terapi pasien dengan blastositosis hanya dengan terapi konservatif.*

**Kata Kunci:** *Zoonosis, infeksi, parasit*

*Corresponding author at: dewi2@usu.ac.id ; dmasyithah57@gmail.com

## 1. Introduction

In the past few decades, the role of *Blastocystis hominis* as a pathogen causing gastrointestinal problems were unidentified. The classification, life cycle, mechanism of transmission, and the clinical significance are disputable, but recent studies have been barely successful in unfolding its pathogenicity. In the early 1900s, Alexeieff proposed *Blastocystis sp.* as a distinct organism and previously named as *B. enterocola*. Subsequently, *B. hominis* was suggested by Brumpt later in the same year. In recent phylogenetic studies, *B.hominis* has distinct features of fungi, which later classified the organism into protist as it does not grow on fungal media and its resistance properties to antifungal agents. The re-classification of *Blastocystis sp.* has put *Blastocystis sp.* into a separate group as stramenopile, a heterotrophic and photosynthetic protist. *Blastocystis* becomes the only one stramenopile lead to human infection. Its morphology similarly linked to Protista consisting of one or more nuclei, smooth and rough endoplasmic reticulum, Golgi complex, and mitochondrion-like organelles [1-2].

Most studies have reported the prevalence of *Blastocystis sp* only in a small region; it was estimated that one episode of infection occurred in 58% of Indonesia population [3]. The infection was also related to animal contact as the organism considered as a zoonotic infection. In developing countries, the most prevalent of *Blastocystic hominis* prevalence found among children [4]. Besides, the high prevalence of HIV infection also adds the vulnerability of a person infected by the organism, the primary immune pathogenesis of *Blastocystis* infection involves CD4+ cell lineage so it could make drawback if there is loss of immune function via CD4+ cell destruction. The series study conducted in Turkey showed that the infection was frequently found in cancer patients or impaired cellular immune function. Travelers diarrhea also admitted having a relationship with *Blastocystis hominis* infection, a study conducted in Nepal found more than 50% of Blastocystis positive patients had recent foreign travel but unsuccessful to reveal the significant relationship between *Blastocystis sp.* and travel history [5-7].

*Blastocystis hominis* has been widely isolated from diverse species of mammals, birds, reptiles, amphibians, fish as well as human. Its genetic and classification variation caused the organism could trigger an infection in a wide range of hosts species. In a study, there is a tendency that the infection caused by *Blastocystis hominis* manifests in human mainly limited to serogroup I and II, pigs with serogroups III and IV [8]. Furthermore, clinical manifestation during the infection is currently under surveillance. A clinical study proved that of 23 patients infected with *Blastocystis sp.*, only 19 individuals complained abdominal discomfort, anorexia, diarrhea, and excessive flatus while no significant eosinophilia occurred among the study population [9].

A large number of studies related to *B.hominis* showed its pathogenicity. Since its existence remains positive in human while there is no significant symptom produced during the infection.

Broad clinical manifestation can be produced by the organism depend on host factor and the *Blastocystis sp*. serotype per se. Immunocompetent and adult patients are common with self-limiting diarrhea, but for the patients which suffered from immunocompromised condition, prolonged, and severe form diarrhea can take place [10]. Extraintestinal symptoms are also noted by a few studies, such as diffuse pruritus and urticaria [11]. Additionally, inflammatory bowel syndrome has also been linked to the organism [12].

Several aspects related to the organism are susceptible to be questioned, particularly its clinical significance. Because of some controversies, our article provides some information related to the organism. It consists of *Blastocystis sp.* classification, morphology, life cycle, several proposed virulence factors, clinical manifestation, and dubious medication.

## 2. Classification

In the previous era, the researchers described *Blastocystis sp.* as yeast, fungus, and protozoan. In 1967, *Blastocystis hominis* was identified as polymorphic protozoa with its phylum can not be defined as Sporozoa or Sarcodina. During the advancement of molecular technique, some studies revealed its nucleic acid sequence not belong to either category. Stramenopiles are now more than considered as a phylum for *Blastocystis sp.* Stramenophila is a group of protist in which the organism in this phyla has unicellular and multicellular form of protists; it includes slime nets, water molds, and brown algae [2][13].

Small subunit rDNA analysis (SSU rDNA) of *Blastocystis sp.* demonstrates various subtypes with its pathogenicity and habitat. It consists of 17 subtypes (STs) which found in animal and human isolates; nine subtypes infect human. There are several molecular techniques used to determine the molecular diversity of the organism, particularly PCR-restriction fragment length polymorphism (RFLP). Multilocus Sequence Typing (MLST) of the Mitochondria-Like Organelle (MLO) has been used to differentiate the genetic variation in its species. From the studies, ST3 MLST sequences consisting of five loci and six loci for ST4 MLST [2][14-15]. The controversies related to the clinical significance of the organism results in the distinct pattern of infection by both the subtype (ST) or particular virulence factor of *Blastocystis sp.* ST1 and ST3 are discovered in human while ST2, 5, and 8 found in both human and mammals, such as primate, pig, and cattle pig. Rodent-infested Blastocystis has been isolated for ST4 and ST6, 7, and 8 are also found among avian population. Therefore, it has been outdated to classify the organism only based on its reservoir rather than its DNA-sequence or mitochondrial-like organelle (MLO) [16].

## 3. Life cycle and morphological form

The life cycle analysis of *Blastocystis sp.* discovers that the organism could transmit in several

varieties of morphology; nevertheless, it is still disputable in some particular stages. The primary route of transmission is fecal-oral, whereas the incubation period and infection duration have not yet been elucidated in the literature, but cyst is postulated to be its infective stage. Virulence genotype, immunosuppressed host, host genotype by the organism interaction, virus or bacteria associated with the organism, high-burden infection, host response, and dysbiosis are several factors related to the high susceptibility of the severe form of the symptomatic disease [8].

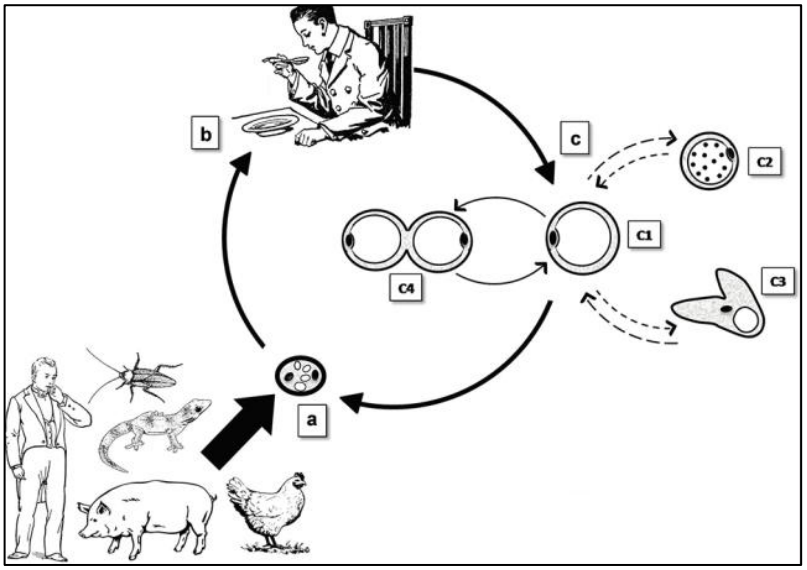


Figure 1. *Blastocystis sp.* life cycle (*Courtesy of* Parija and Jeremiah, 2013; Reference 17).

The subsequent stage is encystation that provokes the organism to transform into avacuolar forms or ameboid and a multivacuolar, consecutively. Multivacuolar and vacuolar change becoming infective form, a cyst. The life cycle largely ensues in the large intestine with no invasion to enterocyte producing a more silent infective form of the disease. Meanwhile, the vacuolar stage only grows in culture. Some sources disputably describe the life cycle involving in vitro studies or using the more advanced technique, particularly explaining its step-by-step life cycle and how this organism could reproduce itself. In recent studies, the binary fission, budding, plasmotomy, multiple fission, endodyogeny, schizogony are suggested as reproductive modes of *Blastocystis sp.*[18-19].

There are at least six distinct morphological forms of *B.hominis* described in the literature. Dormant cyst form is suggested as the infective stage. Whereas, vacuolar, granular, ameboid, and cystic forms have been described in literature and the morphological form can be found directly using light microscope except for particular form including avacuolar and multivacuolar in which can only be identified using electron microscope [16]. Vacuolar form (2- >200 µm) is a cell with sizeable central vacuole consisting of two nuclei. Mitochondrion-related organelles and Golgi apparatus present in the peripheral region of the cytoplasm. Mitochondria forms '*rose*

*appearance'* which encircle the nucleus. Based on several studies, the asymptomatic individual carrier is commonly positive for vacuolar phase. Granular form (3-80 µm) consists of several granules within the cytoplasm in addition to the two nuclei in the cytoplasm, and it is similar to the vacuolar type. Furthermore, the appearance of the granular phase indicates cell death, and it is commonly observed in older cultures or the media supplied with antibiotics. Ameboid form (2.6-7.8 µm) characteristically resembles macrophage and neutrophil equipped with two pseudopodia and large vacuole within the cytoplasm. Pseudopodia is essential for the attachment to bowel mucosa. Ameboid form present in the pathogenic subtype of *Blastocystis sp* cultures, and patients suffer from several gastroenterology problems. Cystic form (3-6 µm) has 1-4 nuclei and multilayered-wall that could survive for a month outside of the human body. Thus, it can cause outbreaks among the vulnerable population, including children [14][20].

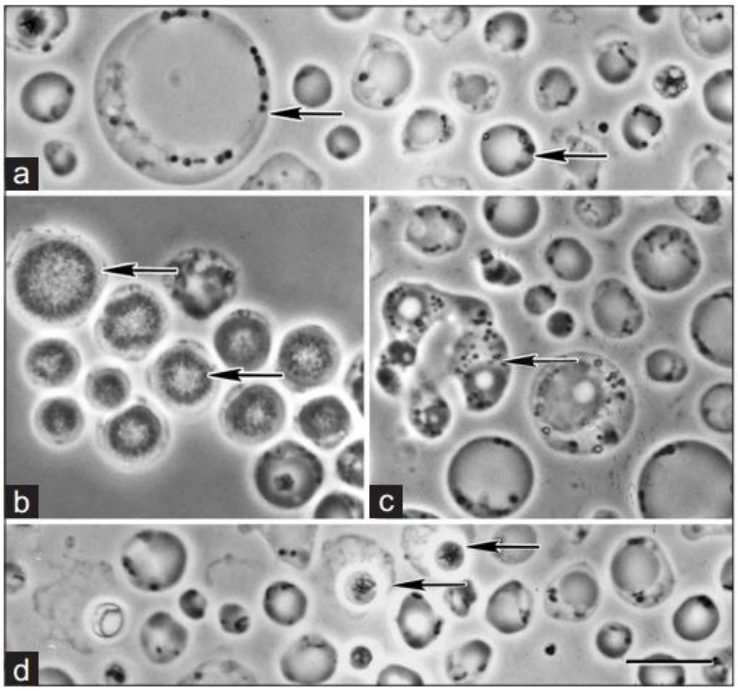


Figure 2. Morphological form of *Blastocystis hominis* (a) Vacuolar form; (b) Granular form; (c) Cyst forms (*Courtesy of* Tan KS, 2008; Reference 2).

It has also been uncovered that cysts form as the infective form of *Blastocystis sp* infection in human. Suresh and Smith proved that only 20.9 % of *B.hominis* positive patients excreted cysts. In one study conducted by Stensvold et al., it concluded that cyst excretion rate and morphological transformation during the life cycle also depend on its organism subtype, but it discovered that the excretion rate of cyst is low among infected individuals [21-22].

## 4. Pathogenesis

In DNA sequencing era, the use of the advanced molecular technique to disclose some unknown pathogenesis is inevitable. There must be an endpoint describing how the organism could initiate symptomatic infectious disease. Based on some research, the pathogenesis of *Blastocystis sp*. is highly associated with the organism subtype. Pavanelli et al. also describes that *Blastocystis sp.* infection also depends on inoculum size and period of the infection. The substantial amount of inocula induce early inflammatory response (seven days) while smaller inocula could produce slow-response of disease (21 days). There is a distinct clinical scenario caused by the existence of subtype resulting in different virulence factors. Nevertheless, most studies conducted in the form of epidemiology demonstrate infective vulnerability, pathogenesis, and clinical manifestation is highly associated with *Blastocystis sp*. subtype, for instance, infection with profound symptoms was found to be related to the subtype 1-4 and 6 with subtype 3 as the most prevalent subtype followed by ST1 and ST2, but subtype 1 become the main contributor to infect human in Brazil [23-24].

The pathogenesis of the infection begins after some protease production during ameboid stage; it directly involves in producing gastrointestinal symptoms. Rascon and McKerrow found that the pathogenic variation of *B.hominis* is highly linked with *cysteine protease* secretion during the infection [5]. In vitro studies using *Caco-2 cell line*, secreted proteases could undermine the epithelial barrier resistance that ultimately leads to the increase of permeability in the gut wall. Therefore, the inhibition of proteases activation could also disrupt the cytological effect of this substance. In another study, proteases provoked the degradation of immunoglobulin A (IgA) and, subsequently, the surge of the pro-inflammatory cytokine, such as interleukin-8 (IL-8), is on the brink of activation [25-26].

Histopathological analysis of infected-gut wall reveals the hallmark of the infection consisting of hyperemia and hyperplastic lymphoid aggregates in accordance with the physiologic immune response to *B.hominis*. The study also concluded that small intestine is predominant predilection of the pathological event during the initiation of the disease, whereas it previously demonstrated that the habitat of *B.hominis* is in the large intestine and becoming the major infection site [27].

## 5. Clinical manifestation

The distribution of *Blastocystis sp.* is a fastidious organism which prevalently found as a silent organism or commensal with the profound infection higher in developing country, particularly Indonesia, but genetic surveillance of *B.hominis* has not yet been performed in the country. In some literature, the organism infects a particular population, including foreign traveler, individuals with close contact with pets or animals, and living in a large dormitory place [28]. *Blastocystic sp.* can produce debilitating symptoms or severe watery diarrhea among the

immunocompromised host. Nonspecific symptoms, such as abdominal discomfort, bloating, cramping, diarrhea, and vomiting are commonly associated with mild infection. The resolution will spontaneously occur while it is still common that the infection does not produce symptoms. The severity of symptoms represents the high burden of infection, ingested large inoculum size, in a short period time [29].

Al-Fellani et al. and Salvador et al. concluded a similar result that diarrhea is the most prominent symptom, 84.94% and 66.3% consecutively. However, Salvador et al. found that more than 50% of patients are asymptomatic concurrent with the positive cyst in their feces. Meanwhile, abdominal pain was the most common symptom (76.9%) during the infection followed by diarrhea and abdominal distention which becoming a result of a study conducted by Arikan et al., 50% and 32.6% respectively yet surprisingly there are six patients complained about urticaria and perianal pruritus symptoms. Besides, Vogelberg et al. also reported a case, a 20-year old male was positive for blastocysts and generalized chronic urticaria associated with ST2 *Blastocystis sp*. infection [30-32].

*Blastocystis sp.* and irritable bowel syndrome (IBS) are distinct clinical entities, but its association has been studied in recent studies, so-called as post-infection IBS. Poirier et al. showed through genome analysis that some genes which encoded *hydrolases*, *serine*, and *cysteine proteases*, and substance potentially transformed the mucus layer and tight junctions to a different physiologic bowel mucosa [12][33].

## 6. Management

There are no guidelines provided to suggest the definitive treatment for *B.hominis* infection while the therapy still emphasizes on the conservative management to reduce symptoms severity appeared during the episode of disease. The basic principle of giving medication is only applied for all symptomatic patient as well as left untreated the asymptomatic or carrier individuals, but it is such a controversy whether or not the initiation of therapy should begin promptly without evaluating the symptoms [34]. However, chronic diarrhea which accompanied with abdominal pain has put the patient to the consideration of giving anti-protozoal drugs. Symptomatic positive with the severe form of acute debilitating diarrhea patient must undergo further examination for another causative agent. The infection could be found with the other invasive organism including *Entamoeba histolytica*, *Dientamoeba fragilis*, or *Giardia lamblia* so considering the supplementary anti-protozoal drugs is mandatory. Moreover, the self-limiting nature of the disease is evident from the study, vacuolar form was diminished suddenly without any intervention after 60 days of incubation still the cystic phase remains positive in feces for the extended period after the absence of symptoms [35,36].

The effective therapy used for colonic infection must have some specific properties, including high concentrated in colonic lumen, brief small intestine transit time, and intact activity after the exposure of intestinal flora. The randomized clinical trials among *B.hominis* patients are scarce, but it is summarized that metronidazole, nitazoxanide, paromomycin, and trimethoprim-sulfamethoxazole (TMP-SMX) are among the most effective drugs for eradicating the organism. Katsarou et al. found that using metronidazole 750 mg three times daily found that the eradication rate nearly 100%. Similarly, another study was also discovered that using metronidazole 1500 mg single dose was as effective as the lower but longer regiment. Nitazoxanide 500 mg, paromomycin (25mg/kg), TMP-SMX (80 mg TMP, 400 SMX) are suggested to be the alternative for metronidazole thrice daily. Nonetheless, there is a wide range of respond to therapy, particularly in relation to the organism subtype [11][37].

## 7. Conclusions

Several aspects related to *Blastocystis hominis*, including its pathogenicity, virulence factor, clinical significance, and management, still become problematic issues. The emergence of the infection are also highly associated with the genetic and molecular diversity of the organism. The physician could consider *B.hominis* infection with a prolonged watery diarrhea in an immunocompromised individual. Meanwhile, abdominal symptoms are the second most prevalent of B.hominis symptoms but the exclusion of the other etiologies is compulsory. Additionally, the organism has been reported for its role causing inflammatory bowel syndrome (IBS) and dermatologic disorder.

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