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Review article

Blastocystis: A Mysterious Disregarded Parasite

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Abstract

Blastocystis is anaerobic protozoal parasite colonizing the intestinal tract of humans and many animals. It still has not been elucidated whether it is a commensal organism or a pathogen. Its prevalence varies both between the countries, and between certain population groups within individual countries. Due to poor hygienic conditions, common exposure to animals and intake of contaminated water and food, people in the developing countries have got a higher prevalence of *Blastocystis* but developed countries have not been spared either. 22 subtypes of *Blastocystis* have been so far identified, but only 10 subtypes were identified in humans. The parasite is transferred by the fecal-oral route. A variety of hosts have been identified, and animal-to-human transmission and vice versa have been documented. *Blastocystis* is polymorphic with only few of forms such as vacuolar, granular, amoeboid, and the cyst form being commonly known. It has been associated with the irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and urticaria. The diagnosis can be made using the microscopy, staining, cultivation, serodiagnosis, and by using molecular methods. The infection caused by the parasite does not always require treatment. In symptomatic patients, the first line medical treatment is metronidazole.

Keywords: *Blastocystis*, Blastocystosis, Subtype

1. Introduction

Blastocystis is a unicellular enteric protozoan. It is commonly present in human and animal stool specimens (in birds, rodents, reptiles, amphibians, fish, cockroaches). Infection with *Blastocystis* was demonstrated in both symptomatic and asymptomatic people (Roberts *et al*., 2014). For a long period, *Blastocystis* was considered a commensal organism with no pathogenic role

(Andersen and Stensvold, 2016) but recently, many studies linked it to different gastrointestinal symptoms (Noradilah *et al*., 2017). The association with irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) increased the surge of worldwide interest and study in *Blastocystis* (Rostami *et al*., 2017).

2. Taxonomy and Classification

During the infamous cholera epidemic of London in 1849, Brittan and Swayne observed the organism for the first time and wrongly suggested that it was the cause of cholera. In the early 1900s, the organism was specifically observed by Alexeieff and Emile Brumpt, who proposed it to be harmless yeast of intestinal tract. The genus name "*Blastocystis*" was coined by Alexeieff while Brumpt provided the species name, "*hominis*" (Parija and Jeremiah, 2013).

At first, it was classified as a protist by Zierdt *et al.,* (1967) but after the molecular analysis of its small subunit ribosomal RNA gene (SSU-rRNA), Silberman *et al.,* (1996) reclassified it within the phylum Stramenopiles which includes diatoms, slime moulds and algae. Since the stramenopiles have flagella surrounded by lateral hair-like mastigonemes, that is characteristically absent in *Blastocystis*, so Cavalier-Smith, (1998) placed it in a new separate kingdom "Chromista".

Deducing the identity of the organism to the species level is still an unresolved challenge. Earlier, the species name was given based on the host from which it was isolated such as *B. hominis* from humans, *B. ratti* from rats etc., Subsequently, *Blastocystis* was isolated from diverse hosts as well as human-animal; animal-human transmission was noted. These observations warranted a change in the specific names which prompted various reports attempting to classify the different species of *Blastocystis*, based on their ultra-structural electron microscopic morphology. It was later found that the host specificity and the pathogenic potential of different isolates correlated with sequence variations in the SSU-rRNA. Based on these variations, the members of the genus are classified into several subtypes, which could possibly be termed as species. More recently, the small subunit rDNA (SSU-rDNA) was found to have a better correlation with subtype (Parija and Jeremiah, 2013). At present it is appropriate to limit the nomenclature of the organism as "*Blastocystis* species" and it must further be characterized only by molecular subtyping of the SSU-rRNA or SSU-rDNA (Skotarczak, 2018).

Up to now, at least 22 different subtypes identified based on the SSU rRNA gene. These subtypes are found in various hosts, including humans, primates, birds, reptiles, and rodents (Deng *et al*., 2021). Only STs 1-9 and ST12 were found in human isolates (Roberts *et al*., 2014). Amongst these, STs 1-4 are more common in humans, appearing in 90% of isolations (Li *et al*., 2018) but ST1 is considered the most virulent (Popruk *et al*., 2013).

3. Morphology

The main morphological forms of *Blastocystis* are vacuolar, granular, amoeboid, and cyst. Other forms as avacuolar and multivacuolar forms have also been reported, but rarely seen (Ismai *et al.,* 2022).

a. Vacuolar form. It is spherical in shape with average size 5-15 µm, containing a central large vacuole, occupying approximately 90% of the cell, and a thin layer of peripheral cytoplasm. The nuclei (2-7 nuclei) are distributed peripherally throughout the cytoplasm.

b. Granular form. This form is very similar to vacuolar forms but contains granules within the

cytoplasm.

c. Cyst form. It is round or oval, and with smaller size (3–6 µm). The cytoplasm contains one to four nuclei, glycogen deposits, mitochondria-like organelles (MLOs), and small vacuoles.

d. Ameboid form. This form is rarely seen. It is irregular in shape and non-motile despite having 1-2 pseudopodia-like extensions (Sekar and Shanthi, 2015).

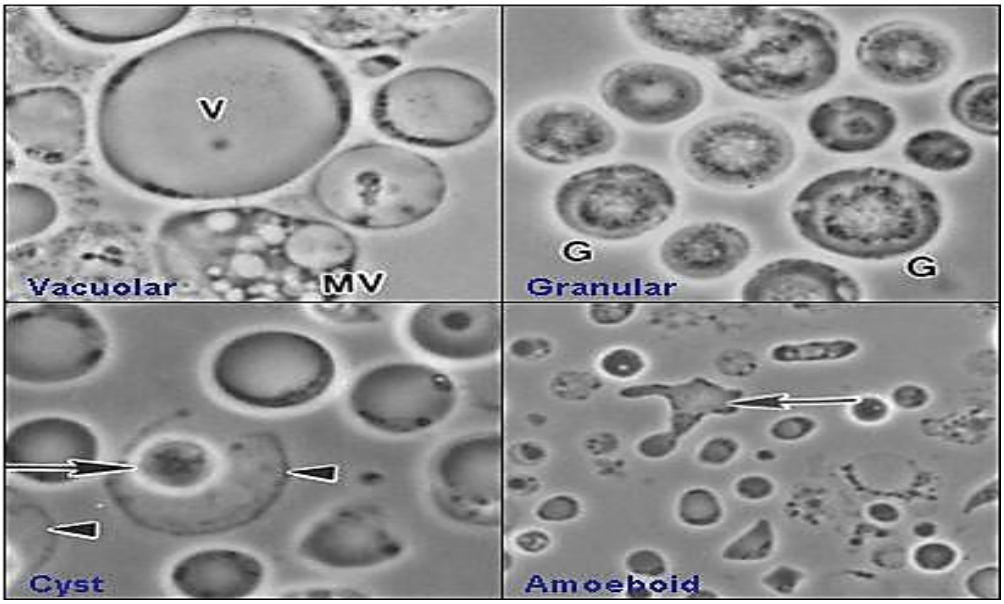
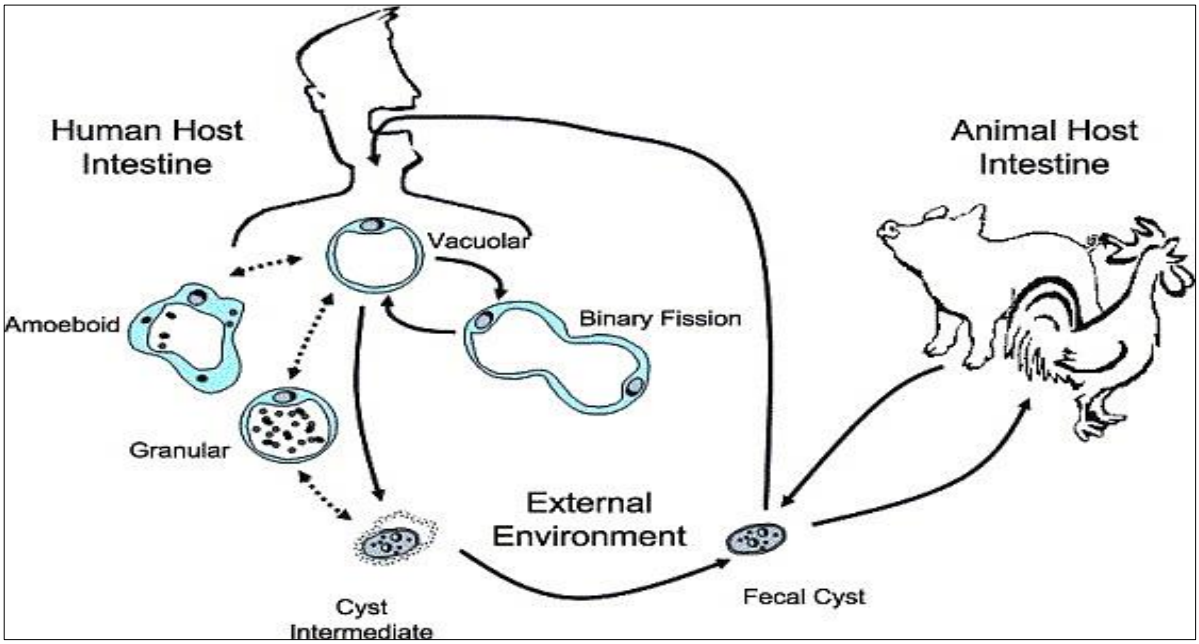


Figure 1. Morphological forms of *Blastocystis* (Abd AL-Khaliq, 2019).

4. Life cycle and Mode of reproduction

Infectivity studies conducted on BALB/c mice, Wistar rats and chickens have proved that the cyst is the only transmissible form of *Blastocystis* and is transmitted feco-orally (Tan, 2008). Upon ingestion, the cyst undergoes excystation in the intestine to liberate the vacuolar form which can transform into any of the other forms. The vacuolar forms encyst in the intestinal lumen to form cysts which are shed in the feces for further transmission (Tan, 2004). Various modes of reproduction have been described for *Blastocystis* namely binary fission, budding, plasmotomy, multiple fission, endodyogeny and schizogony. However, binary fission is now the only accepted one



(Tasić *et al.,* 2016).

Figure 2. Life cycle of *Blastocystis* (Tan, 2004).

5. Pathogenicity

There is controversy about the pathogenicity of *Blastocystis spp*. It was reported to be part of intestinal microbiomes in healthy individuals (eubiosis), while other studies linked it to gut disorders (dysbiosis) (Ahmed *et al.,* 2022). More recently, there is some explanation of its pathogenicity in relation to subtypes and virulence. Symptomatic patients usually carry the STs 1, 2, 3, 4 and 6. Among them, ST3 is the most common, but ST1 is most virulent (Sekar and Shanthi, 2015). Intra-subtype variations in pathogenicity have also been observed, that is, not all the strains of a particular subtype are pathogenic. These observations suggest that subtyping alone does not predict the pathogenicity (Parija and Jeremiah, 2013). The pathogenic strains of *Blastocystis* secrete cysteine proteases that play an important role in intestinal inflammation and increased permeability. Proteases also cleave IgA, the prevalent immunoglobulin at the mucosal surface and this helps in immune evasion and promoting parasite survival (Roberts *et al*., 2014). In addition to proteases, other hydrolytic enzymes have been identified as lysates which lead to cytoskeletal changes and induce apoptosis in epithelial cells resulting in increased bowel permeability (Tasić *et al.,* 2016).

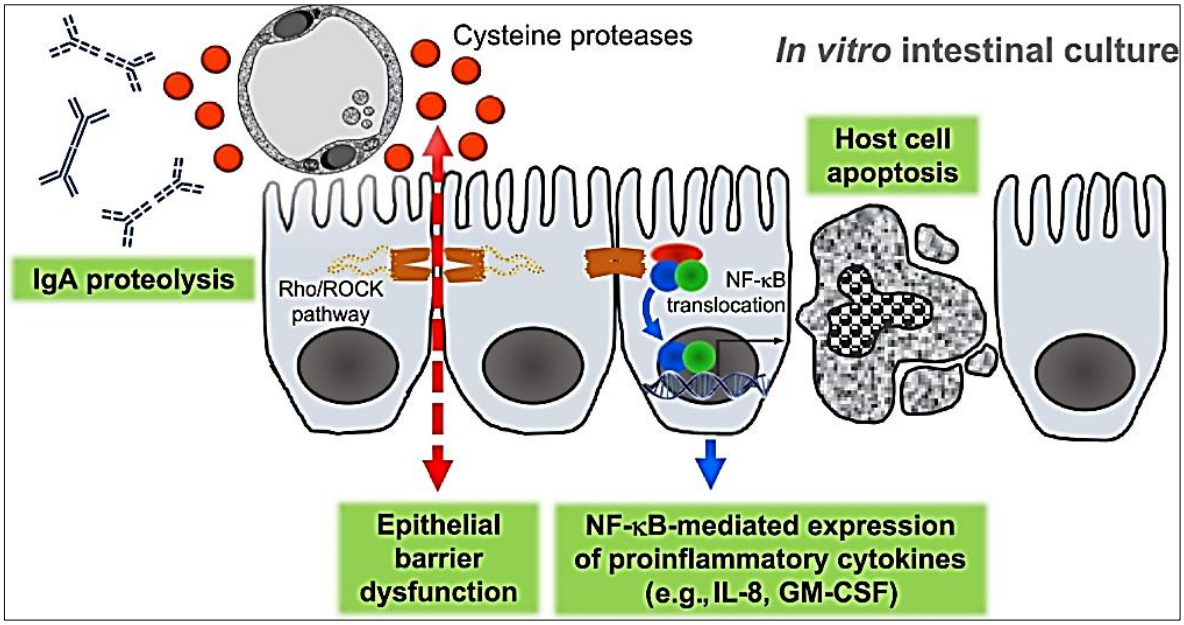


Figure 3. Pathogenesis of *Blastocystis* (Stensvold *et al.,* 2020).

6. Clinical manifestations

Blastocystosis has a wide range of manifestations, it may be asymptomatic, or present with non-specific gastrointestinal symptoms, including diarrhea, nausea, vomiting, flatulence, cramps, discomfort, abdominal pain, or anorexia (Poirier *et al.,* 2012). It was found that this parasite plays an important role in IBS and IBD (Shirvani *et al.*, 2020). Cutaneous manifestations in the form of acute or chronic urticaria are also reported (Vezir *et al*., 2019). However, the exact mechanism through which *Blastocystis* may cause these cutaneous manifestations is still not understood, an association was found between urticaria and amoeboid forms (Katsarou-Katsari *et al.,* 2008). It was suggested that the amoeboid form adheres efficiently to the intestinal epithelium, affecting

gut immune homeostasis and causing an inflammatory response against the parasite that led to urticaria (Sheela Devi and Suresh, 2019). *Blastocystis* infection is also reported as a risk factor for iron deficiency anemia (El deeb and Khodeer, 2013).

7. Laboratory diagnosis

i. Microscopic examination

Direct fecal smear is quick and cost-effective method for detecting *Blastocystis*. However, this method has low sensitivity and can give false-negative results as some forms are misinterpreted as yeast, pus cells or fat globules (Tan, 2008).

Permanent staining of fecal smears with acid-fast, Giemsa, Field's, or trichrome stains have been described, with trichrome being the most sensitive stain (Maghawry, 2020).

ii. *In vitro* cultivation

Culture is the most sensitive method for the detection of *Blastocystis*. Various media are available for cultivating *Blastocystis* namely, Locke-egg medium, Iscove's modified Dulbecco's medium, Robinson's medium and modified Jones' medium. However, the preferred medium is the modified Jones' as it is composed of the simplest constituents and can be stored for a longer time in a refrigerator if sterilized. In addition, it is also cost-effective and do not require any specific technique and equipment (Parkar *et al.,* 2007).

iii. Immunodiagnosis

Blastocystis can be detected using serological methods, such as indirect fluorescent antibody (IFA) and enzyme-linked immunosorbent assay (ELISA) as the parasite can trigger IgG and IgA responses (Tasić *et al.*, 2016).

iv. Molecular diagnosis

PCR has high specificity and sensitivity in the detection of *Blastocystis*. It also can be used to determine the different subtypes (Tasić *et al.,* 2016).

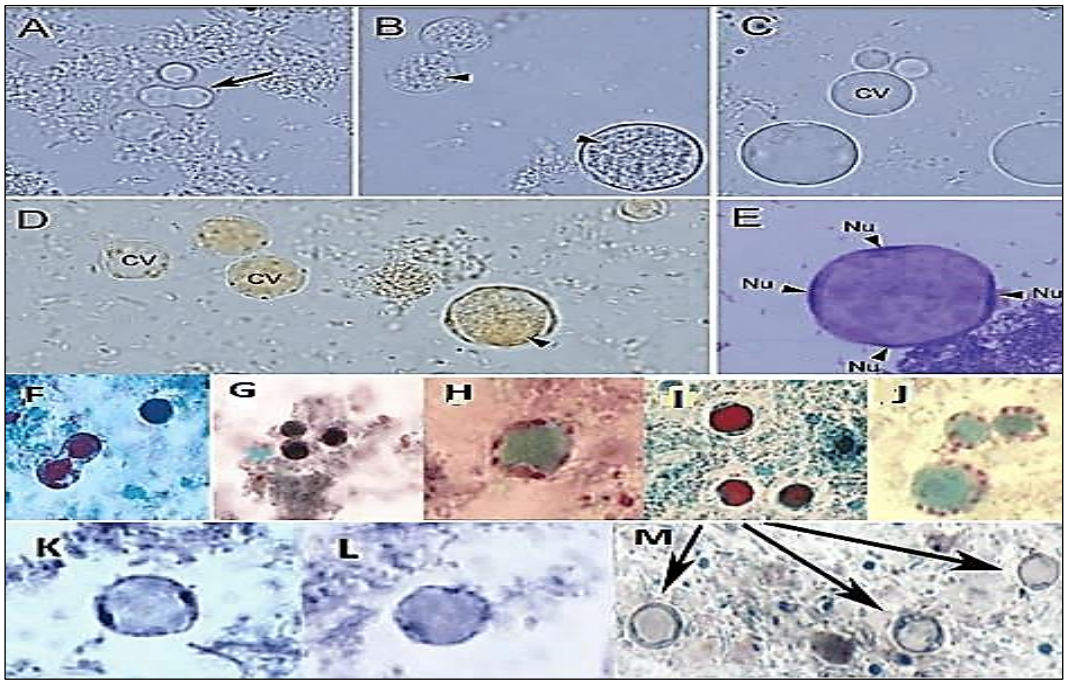


Figure 4. Light microscopy of *Blastocystis* cultured in Jones' medium. (A) Cells undergoing binary fission (arrow). (B) Granular forms commonly seen in laboratory culture. (C) Vacuolar forms with virtually indiscernible thin cytoplasmic rims. (D) Iodine-stained wet mount revealing granular

forms (arrowhead). (E) Giemsa-stained permanent smear of the large vacuolar form (F J) Trichrome-stained permanent smear of vacuolar forms. (K–M) vacuolar forms stained with hematoxylin, edited from (Tan, 2008).

8. Treatment

Treatment is required only for the symptomatic cases. There are numbers of antimicrobial agents have been used to treat blastocystosis. This includes metronidazole, nitazoxanide, trimethoprim sulfamethoxazole (TMP-SMX), paramomycin, ketoconazole, tinidazole and the probiotic *Saccharomyces boulardii* (Sekar and Shanthi, 2015).

9. Prevention and control

Due to the uncertain infective nature and transmission pathways of the parasite, there are no widespread public health or prevention strategies directly aimed at *Blastocystis.* CDC does list the followings, however, as potentially useful preventative and control measures, including hand wash with soap and water before handling food and after using the toilet. If employed in a child-care center, also wash after each diaper change even if gloves were used, avoid potentially infected water and food, wash and peel all raw fruits and vegetables, avoid untreated water in countries with less established water-safety (Abd AL-Khaliq, 2019).

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مقال مرجعي

الملخص العربي

المتبرعمة الكيسية: طفيل غامض مُهمل

شيماء رفاعي محمد عبد العال*، هناء أحمد الهادي، أمل مصطفى أحمد، أسماء كمال عبداللاه
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يُعتبر طفيل المتبرعمة الكيسية من الأوليات أحادية الخلية اللاهوائية التي تصيب الجهاز الهضمى للإنسان والكثير من الحيوانات وتتم العدوى به من خلال الفم ولايزال الجدل واسعًا حول كونه **غيرمُمْرِضًا**. ويختلف انتشاره بين البلدان المختلفة ومع أن معدل انتشاره أعلى في البلدان النامية إلا أن البلدان المتقدمة **لم تنج**. حتى الآن، تم اكتشاف 22 من الانماط الجينية المختلفة للمتبرعمة الكيسية ولكن عشرة أنماط فقط هي التي تم عزلها من **الإنسان**. تم ربط المتبرعمة الكيسية بالعديد من الأمراض مثل متلازمة القولون العصبى، **مرض الأمعاء الإلتهابي والطفح الجلدى**.

يمكن تشخيص المتبرعمة الكيسية بالفحص الميكروسكوبي، الصبغة، الزرع وكذلك بالتحليل الجزيئى. لا تتطلب العدوي بالمتبرعمة الكيسية العلاج دائما، ولكن يوصى بمعالجة المرضى الذين يعانون من أعراض **بالميترونيدازول**.

الكلمات الرئيسية: المتبرعمة الكيسية، داء المتبرعمة الكيسية، النوع الفرعي.