1. Introduction

Gastrointestinal pathologies constitute among the most frequent forms of disease in the World, especially enteric infections represent a significant burden of morbidity and mortality particularly in developing countries, where barriers between human feces and food and water supplies are inadequate. Enteric infections can be produced by a varied type of organisms, including bacteria, fungi, viruses and parasites. Among the parasites, two different types of them can produce gastrointestinal infections: helminths and protozoans. Inside the protozoans, these would be classified as flagellates (eg. *Giardia intestinalis*), spore-forming or coccidia (eg. *Cyclospora cayetanensis*), ciliates (eg. *Balantidium coli*) and amebas (eg. *Entamoeba histolytica*).

Amebas parasites include a large number of genuses and species among three subphyla of the phylum *Amoebozoa*: Conosa, Lobosa and Protamoebae. Pathogenic species are included in the families Acanthamoebidae (eg. *Acanthamoeba*), Vahlkampfiidae (eg. *Naegleria*), Balamuthiidae (eg. *Balamuthia*) and Entamoebidae (eg. *Entamoeba histolytica*). *Entamoeba histolytica* is the only recognized intestinal pathogenic ameba. Other species in the genus can be present in the human intestinal tract but are non-pathogenic (eg. *E. dispar*).

Over the past decade, since it was formally recognized, through molecular biology and phylogenetic analyses, that *Entamoeba histolytica* and *Entamoeba dispar* were two distinct species, studies in this field have made dramatic in-roads into the understanding of *E. histolytica* and the pathogenesis of invasive amebiasis (Adams & MacLeod, 1977), which in fact represent a low proportion of the cases of amebiasis; most of them are asymptomatic. Given this knowledge an extensive understanding of the epidemiology, pathophysiology, and the molecular and genetic biology of the organism has been reached, improving not just the diagnosis, medical and surgical treatment options but, ultimately, the development of a safe and efficacious vaccine, which is actually in process (Bercu, et al 2007; Blessmann & Tannich, 2002; Gonzales, et al 2009).
2. Epidemiology

In the last two decades too, it has also become clear that the true incidence of *E. histolytica* infection, particularly in vulnerable populations such as low socioeconomic children, is exceedingly high. Even more, in deprived areas of the World, especially in suburban and rural areas of the developing countries, particularly in tropical areas, amebiasis is a disease with a high burden of morbidity and mortality, with nations where prevalence estimates reach as high as 50% or more (eg. in Central and South America, Asia and Africa). However, this disease can be found worldwide and has been estimated that around 10% of the World’s population is infected.

Morbidity from amebiasis represent around 40-50 million estimated cases per year in the World (World Health Organization, WHO). Although most cases are asymptomatic, dysentery and invasive extraintestinal disease can occur (Lysy, et al 1991). Amebic liver abscess is the most common manifestation of invasive amebiasis, but other organs can also be involved, including pleuropulmonary, cardiac, cerebral, renal, genitourinary, and cutaneous sites (Kenner & Rosen, 2006). Mortality due to amebiasis is estimated in 40,000-100,000 deaths per year (WHO). Its lethality or case fatality ratio in amebic colitis is estimated in 2-10%, however would be increased up to 40% when amebic colitis evolves to fulminant necrotizing colitis or rupture (Aristizabal, et al 1991).

Actually, amebiasis is the second leading cause of death from parasitic diseases worldwide. In many countries, the epidemiology of amebiasis has been recognized as a significant public health problem, even in many countries, before the 1990s, being overestimated and overdiagnosed due to the confusion between *E. histolytica* and *E. dispar* that many times generated a false positive diagnosis of amebiasis when incorrectly *E. dispar* infection was diagnosed as amebiasis due to *E. histolytica*. This happened because these species cannot be differentiated by direct examination, mainly by molecular techniques more often used these days.

Although that today is still controversial of the role of *E. histolytica* in certain type of patients (eg. immunocompromised hosts, particularly in Human Immunodeficiency Virus, HIV infection/Acquired Immunodeficiency Syndrome, AIDS, but additionally in cancer and pregnant women). Additionally to this, has been stated that are certain groups of patients predisposed to amebic colitis: very young patients, malnourished subjects and recipients of corticosteroids, men who have sex with men and institutionalized individuals. Otherwise, race, sex and age, in general, do not affect significantly the epidemiology of disease.

New contexts of disease include today the infection impact in transplant recipients (Franco-Paredes, et al 2010). Infection due to *Entamoeba histolytica* can occur in transplant recipients leading to severe colitis and liver abscesses.

Even more, in the context of globalization and migration, relevance of many gastrointestinal infections have been emphasised. Traveller’s diarrhoea represents 20-60% of the estimated incidence of illness during travel to developing countries, being 5-10% of its etiology due to protozoan agents. In this context, travel and migration from those countries with high prevalence of amebiasis have been also considered of risk for infection. Amebic liver abscesses have been reported in travel exposures as short as 4 days, with a median of 3 months. Whereas amebic colitis is not common in short-term travellers (Cascio, et al 2011).
3. Pathology

The causative protozoan parasite, *E. histolytica* (Figure 1), is a potent pathogen, transmitted via ingestion of the cystic mature form (Figure 2), the infective stage of this protozoan parasite (Dickson-Gonzalez, et al 2009).

![Entamoeba histolytica throphozoites, showing nucleus and karyosoma (arrow) (HF, 1000X)](image)

Viable in the environment for weeks to even months, cysts can be found in fecally contaminated soil, fertilizer, or water or on the contaminated hands of food handlers and contaminated elements that can be used during food preparation or ingestion (Dickson-Gonzalez, et al 2009).

Fecal-oral transmission can also occur in the setting of anal sexual practices, for which some series have been found a higher incidence in men who have sex with men (MSM), or in the context of direct rectal inoculation through colonic irrigation devices.

Excystation (Figure 2) occurs in the terminal ileum or colon (Figure 3), resulting in trophozoites, the invasive form.

The trophozoites can penetrate and invade the colonic mucosal barrier, leading to tissue destruction, secretory bloody diarrhea, and colitis resembling inflammatory bowel disease. In addition, the trophozoites can spread hematogenously via the portal circulation to the liver or even to more distant organs, which would include lungs, brain, kidneys and skin, among others (extraintestinal disease) (Figure 2) (Dickson-Gonzalez, et al 2009).
Fig. 2. Life cycle of *Entamoeba histolytica* infection

Fig. 3. *Entamoeba histolytica* trophozoites with a granulose cytoplasm (arrow), in the ileum producing an ulceration of the mucosa (HE, 200X) (Dickson-Gonzalez et al., 2009)
Today is well known that many pathogenic mechanisms are involved in the disease produced by this parasite, such as secreting proteinases that dissolve host tissues, killing host cells on contact, and engulfing red blood cells (Figure 4), leading to trophozoites to invade the intestinal mucosa, causing amebic colitis. Classically, the triad of Gal-lectin, cysteine proteinases and amoebapores of the parasite were thought to be the major proteins involved in the pathogenesis of amoebiasis (Accolla, 2006).

Regard to the pathophysiology, new evidences regard the interaction between *E. histolytica* and human polymorphonuclear neutrophils (PMN) has been investigated, based on *in vitro* and *in vivo* animal studies, which have found that PMN actively migrate toward amebae trophozoite cells (Al-Mofleh, et al 1989; Arbo, et al 1993; Guerrant, et al 1981). Later studies in tissue culture systems demonstrated that PMN were confirmed to play a vital role in amebic tissue invasion mechanisms (Accolla, 2006; Arbo, et al 1993).

Even more, at least axenic *E. histolytica* trophozoites and amebic protein preparations have been able to stimulate chemotaxis of human PMN *in vitro*. Additionally, *E. histolytica* inhibits the respiratory burst of PMN which represents a unique survival tactic and may contribute also to the pathogenesis of amebiasis (Dickson-Gonzalez, et al 2009).

More recently, some evidence has been reported on the findings regard to this interaction *in vivo* on human beings. In a study on biopsy samples taken by endoscopic surgical procedures from individuals with amebic colitis assessed histopathologically the relation...
between inflammatory infiltrating cells populations and the *E. histolytica* density in the intestinal lesions. PMN and lymphocytes are significantly associated with the extent of parasite presence (more significantly for PMN). Such findings support the theory that PMN interaction with *E. histolytica* contribute to the pathogenesis of lesions (Accolla, 2006).

However, further studies are necessary in order to improve the knowledge of pathophysiology as well the systemic and local immune response of this worldwide public health problem which may cause potentially life-threatening diseases (Accolla, 2006; Adams, et al 1993; Jhingran, et al 2008).

### 4. Gastrointestinal manifestations

The most common presentation of amebic colitis is gradual onset of bloody diarrhea, abdominal pain, and tenderness spanning several weeks’ duration. Besides that, rectal bleeding without diarrhea can occur, especially in children. Other manifestations include heme-positive stools (seen in approximately 70-100%), diffuse abdominal tenderness (12-85%), weight loss (40%), fever (10-30%) and anorexia.

In the case of fulminant or necrotizing colitis, severe bloody diarrhea and widespread abdominal pain with evidence of peritonitis and fever are usually observed. Predisposing factors for this form of colitis include pregnancy, malnutrition, corticosteroid use and very young age (Hsu, et al 1995).

Fig. 5. Colon mucosa with mixed inflammatory infiltrate and congestion with presence of *E. histolytica* (HE, 400X, in the zooming, 1000X) (Dickson-Gonzalez et al., 2009)
Colonic findings in amebiasis have varied from thickening of the mucosa to flask-shaped ulceration, mostly in the cecum or appendix or near the ascending colon, but rarely in the sigmoidorectal area. These intestinal lesions can include: a colonic mucosa with mixed inflammatory infiltrate and congestion with presence of *E. histolytica* (Figure 5), inflammatory infiltrate in the superficial epithelium of the colon, with absorptive cells denuded (Figure 6), interglandular corion with abundant inflammatory infiltrate rich in PMN and eosinophils (Figure 7), erosions of colonic mucosa with fibrinousleucocitary exudate in the surface (Figure 8), necrotic material and fibrinousleucocitary exudate (Figure 9) and the presence abundant eosinophils and edema in the interglandular corion (Figure 10).

The development of fulminant colitis, ameboma, cutaneous amebiasis and rectovaginal fistulas can occur as medical and surgical complications of intestinal amebiasis (Kenner & Rosen, 2006; Lejeune, et al, 2009).

### 5. Diagnosis

Differential diagnosis of amebiasis include a large list of infectious and non-infectious causes (Table 1). Then multiple studies can be performed to confirm or rule-out the diagnosis, including stools microscopy, cultures, antigen detection, histopathology, serology and molecular biology techniques (Dickson-Gonzalez, et al 2009).

Microscopic evaluation using trichrome stain of stools is able to detect trophozoites in amebic colitis in 33-50%. Then serial stool samples (≥3) over no more than 10 days increase the sensitivity to 85-95%. Besides the trophozoite ingesting red blood cells, mostly happening in *E. histolytica* infection, leukocytes may be found (Burchard, et al 1993).

At cultures infection diagnosis can be achieved in 50% to 70%. Culture is not a routine process and is less sensitive than microscopy in detection. Then, it should be understood that cultures of *Entamoeba* are primarily research tools rather than diagnostic ones.

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Non-infectious</th>
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<tr>
<td>Abdominal Abscess</td>
<td>Arteriovenous Malformations</td>
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<tr>
<td><em>Campylobacter</em> Infections</td>
<td>Diverticulitis</td>
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<td>Cholecystitis</td>
<td>Hepatocellular Adenoma</td>
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<td>Echinococcosis</td>
<td>Inflammatory Bowel Disease</td>
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<td><em>Escherichia coli</em> Infections</td>
<td>Ischemic Colitis</td>
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<td>Hepatitis A</td>
<td>Perforated abdominal viscus</td>
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<td>Other Viral Hepatitis</td>
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Table 1. Differential diagnoses of amebiasis
Antigen detection through enzyme-linked immunosorbent assay (ELISA) is another test currently more available with multiple kits commercially available. In addition to it, kits using monoclonal antibodies against the GAL/GalNAc-specific lectin and the serine-rich antigen of *E. histolytica* yield an overall sensitivity up to 71%-100% and specificity up to 93%-100% (Dickson-Gonzalez, et al 2009).

Histopathological diagnosis of amebic colitis has been, until now, based on the demonstration of the amebic throphozoites in the histological sections, mostly without considering the environment of the parasite. However, cell populations such as PMN and eosinophils (Figure 6) would be predictive of the parasitic infection, which would change the diagnostic approach and criteria in the future.

Serology is also another form of diagnosis for amebiasis. Multiple serologic assays are currently available, being the ELISA the most used of them. This, measures the presence of serum IgG antibodies antilectin. Its sensitivity is high for extraintestinal disease up to 98%, but very low for active amebic colitis particularly in endemic areas due repeated exposure and development of some immunity, limiting antibody-based testing for diagnosing currently active disease, since antibodies can persist for years after infection. Other techniques for extraintestinal disease available include immunofluorescent assay (IFA),
indirect hemagglutination (IHA) immunoelectrophoresis, counter-immunoelectrophoresis (CIE), immunodiffusion tests and complement fixation (CF) is less sensitive than other techniques.

Fig. 7. Interglandular corion with abundant inflammatory infiltrate rich in PMN and eosinophils (HE, 400X, in the zooming 1000X) (Dickson-Gonzalez et al., 2009)

Molecular biology techniques can directly identify RNA and DNA of the parasite, being specific for the species. Right now using multiple targeting genes, including a small-subunit rRNA gene (18S rDNA), serine-rich protein gene, chitinase gene, 30-kDa antigen gene, hemolysin gene, and extrachromosomal circular DNA, among others, *E. histolytica* can be differentiated from other species. Although that, its wide application is still very limited for the routine diagnosis given the cost as well the availability of facilities for these technologies.

6. Treatment and prospects for a vaccine

Additionally to the clinical, epidemiological and diagnostic issues, therapeutic management of amebiasis is currently showing new options. For amebic colitis the main choice drug is still metronidazole (given for 5 to 10 days). Treatment requires the use of two groups of antiparasitic drugs: luminal and tissue agents. Asymptomatic intestinal colonization with *E. histolytica* can be treated with luminal agents alone. Drugs used for the treatment of luminal
infections and generally prescribed for asymptomatic cyst passers include iodoquinol, diloxanide furoate, and paromomycin (5 to 20 days to eradicate colonization). Secnidazole has been used in some countries, but most studies coincide in that metronidazole, although more side effects such as headaches, anorexia, nausea, metallic taste, a disulfiram-like reaction to alcohol, and vomiting, is more effective than secnidazole. Recently some studies have also indicated a potential use of ivermectin for amebiasis (González-Salazar, et al 2009).

In a systematic review published recently, information relating to the effectiveness and safety of the following interventions was described: diiodohydroxyquinoline (iodoquinol), diloxanide, emetine, metronidazole, nitazoxanide, ornidazole, paromomycin, secnidazole, and tinidazole.

Fig. 8. Erosions of colonic mucosa with fibrinousleucocitary exudate in the surface (HE, 400X) (Dickson-Gonzalez et al., 2009)

Even more, in a recent review of the Cochrane Database Systematic Reviews, tinidazole was found as more effective in reducing clinical failure compared with metronidazole and has fewer associated adverse events. Combination drug therapy was found to be more effective in reducing parasitological failure compared with metronidazole alone. However, these results were based on trials with poor methodological quality so there is uncertainty in these conclusions. Further trials of the efficacy of antiamoebic drugs, with better methodological quality, are recommended.
The addition of broad-spectrum antibiotics to the treatment of acute amebic colitis may be appropriate if perforation is suspected. The possibility of coexisting bacteria causing dysentery must always be considered (Mackey-Lawrence & Petri 2011). Amebic colitis and some of its complications, such as ameboma, generally respond to medical treatment without surgical intervention, but for acute necrotizing colitis with toxic megacolon, partial or complete colectomy may be necessary.

Although not currently a significant problem, is expected that in the future antiparasitic drug resistance can emerge as a threat in the therapeutic management of amebiasis.

Recently, the genome of *E. histolytica* has been sequenced, which has widened the scope to study additional virulence factors. *E. histolytica* genome-based approaches have now confirmed the presence of Golgi apparatus-like vesicles and the machinery for glycosylation, thus improving the chances of identifying potential drug targets for chemotherapeutic intervention. Gal-lectin-based vaccines are under development, but additionally, promising vaccine targets such as serine-rich *E. histolytica* protein have yielded encouraging results. Considerable efforts have also been made to skew vaccination responses towards appropriate T-helper cell immunity that could augment the efficacy of vaccine candidates.

Fig. 9. Necrotic material and fibrinousleucocitary exudate (HE, 200X) (Dickson-Gonzalez et al., 2009)
under study. Thus, ongoing efforts mining the information made available with the sequencing of the *E. histolytica* genome will no doubt identify and characterize other important potential vaccine and drug targets and lead to effective immunologic strategies for the control of amebiasis.

Over the past decade, progress in vaccine development has been facilitated by new animal models that allow better testing of potential vaccine candidates and the application of recombinant technology to vaccine design. Oral vaccines and DNA-based vaccines have been successfully tested in animals models for immunogenicity and efficacy.

There has been significant progress on a number of fronts, but there are unanswered questions regarding the effectiveness of immune responses in preventing disease in man and, as yet, no testing of any of these vaccines in humans has been performed. In addition, there are strong economic barriers to developing an amebiasis vaccine and questions about how and where an effective vaccine would be utilized.

Fig. 10. Abundant eosinophils and edema in the interglandular corion (HE, 1000X) (Dickson-Gonzalez et al., 2009)
7. Conclusions

Amebiasis has been recently suggested as one of the new proposed neglected tropical diseases (NTDs), beyond the original list. Neglected tropical diseases include in order of decreasing prevalence: soil transmitted helminths (these include roundworms such as *Ascaris lumbricoides* which causes ascariasis, whipworm which causes trichuriasis, hookworms which, depending on the species, cause necatoriasis and ancylostomiasis), snail fever (schistosomiasis), lymphatic filariasis, trachoma, kala-azar black fever (and other clinical forms of leishmaniasis), Chagas disease (american trypanosomiasis), leprosy, African sleeping sickness (human African trypanosomiasis), Guinea-worm (dracunculiasis), and Buruli ulcer. The World Health Organization (WHO) list of neglected tropical diseases is including the following additional diseases: cysticercosis, dengue and dengue haemorrhagic fever, echinococcosis, fascioliasis, onchocerciasis, rabies, yaws, podoconiosis and snakebites.

Although its distribution is cosmopolitan, highest burden of amebiasis occurs in developing tropical countries, then, adding the low interest in research and in developing new drugs for its treatment, this pathology would be considered as neglected.

Additionally to these considerations, right now is not just important in endemic countries, but also in and non-endemic ones, due to international migration, which makes now that amebiasis would represents a global phenomenon with a changing geography of its epidemiology.

For all these reasons a high level of suspicion should be established into the medical practice not just in endemic countries in symptomatic and asymptomatic patients with epidemiological risk factors, but also in non-endemic countries in travellers and migrants from endemic countries.

Early diagnosis and prompt treatment is highly important in an adequate resolution of disease and avoidance of extraintestinal pathology. More on, deep research is needed in different clinical and epidemiological settings such as in immunosuppressed individuals.

Fortunately recent insights into vaccine development promise potential candidates that would be effectively used in human beings in the next following years or decades, making a significant intervention into reduction of its high burden of morbidity and mortality especially in developing countries.

8. Acknowledgements

We would like to thank S. Dickson-Gonzalez for her review on the manuscript.

9. References


Yu Y, Chadee K. *Entamoeba histolytica* stimulates interleukin 8 from human colonic epithelial cells without parasite-enterocyte contact. *Gastroenterology* 1997;112:1536-1547.
Inflammation of the colon is collectively called "Colitis". Since a variety of conditions may cause colitis and its manifestations are similar among the causes, selection of the right treatment based on the correct diagnosis is important in the management of this group of illnesses. Over the last few decades, a major shift has been observed in the clinical attention to the pathogenesis of colitis from infectious to idiopathic inflammatory bowel diseases. Colitis cases that are associated with chemical therapeutics and specific pathogens such as amoeba, have become prominent in hospitalized individuals and immune deficient patients, respectively. In addition, a great deal of progress has been made in colitis research triggering the need for updating our knowledge about colitis. This book Colitis provides comprehensive information on the pathogenesis, mechanism of resolution, and treatment strategies of colitis.

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