

Intestinal Amebiasis: Diagnosis and Management

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ABSTRACT

Intestinal amebiasis is an infection due to Entamoeba Histolytica and has the highest prevalence in tropical countries, including Indonesia. Amebiasis is responsible for approximately 70,000 deaths annually every year. High prevalence is found especially in endemic area which had poor hygiene and sanitation or crowded population. Human is the main reservoir, while the disease can be transmitted by mechanical vector such as cockroach and flies.

Making diagnosis of intestinal amebiasis sometimes can be a problem. Clinical presentation and disease severity may be varied. Complication due to late management of the disease can be fatal. Lifestyle education, early diagnosis and proper management of amebiasis are very important measures to promote by health workers.

Keywords: *intestinal amebiasis, diagnosis, management*

INTRODUCTION

Intestinal/colonic amebiasis or amebic colitis is an infection caused by *Entamoeba histolytica*, protozoan parasite which has capability to invade intestinal mucosa and spread to other organ specially the liver.¹ *Entamoeba histolytica* is currently found in all over the world, and high prevalence is in high risk region in tropical and subtropical countries.² The prevalence of amebiasis is greatly varied; estimating that 10% population are infected and has the highest prevalence in tropical countries accounting for 50-80%.³ *E histolytica* infection can also be found in developed countries and frequent infected groups are those who are immigrants, travelers, refugees, prisoners, patients at mental hospital and male homosexual.^{2,4} According to recent data of WHO, amebiasis is responsible for 70,000 deaths worldwide every year. This has made amebiasis to be the fourth leading cause of death due to protozoan infection after malaria, Chagas disease and leishmaniasis and it is also third cause of morbidity after malaria and trichomoniasis.¹

According to UNESCO, global burden of amebiasis currently is more than 50 million people infected symptomatically and up to 100,000 people die every year.⁵ Cohort study in developing countries underlined the critical health issue of amebiasis. For example in Dhaka, Bangladesh; diarrhea is main cause of death in children. A 2-years prospective study on preschool age children demonstrated that 55% subjects had *E histolytica* infection. Annual incidence of amebic colitis is 2.2% and similar to *Shigella dysenteriae* in this cohort study.⁵

Human is the main reservoir and host of *E histolytica* infection. Infection may be transmitted by feces contamination on food and drinking water by mechanical vectors such as flies, cockroach, or by person-to person contacts and anal-oral sexual contact. Poor hygiene, crowded population, inadequate and contaminated water supply, worse individual sanitation have all give access to transmission of amebiasis.^{1,3} This disease is more severe in very young

patients, elderly, neonatus, pregnant women, post partum, malignancy, malnutrition and patients on steroid treatment.^{6,7} The prevalence of colonic disease is not very much different between male and female. However, liver amebic abscess and other extra intestinal disease are 3-10 times higher in male.⁷

In Indonesia as developing and tropical country, intestinal amebiasis is an important matter and can be a critical health problem for its population. There are still some technical and non-technical problems in making diagnosis and management of amebiasis. This paper will review further on pathogenesis, clinical presentation, and current management of amebiasis.

PATHOGENESIS OF INTESTINAL/COLONIC AMEBIASIS

Intestinal/colonic amebiasis is infection of intestine/colon caused by protozoan *Entamoeba histolytica*. *E. histolytica* exists in two forms; cyst and motile trophozoites. The infection starts when contaminated food or water that containing cyst is swallowed by human. Inside intestinal lumen, cyst wall is broken down and thus releasing trophozoites which will become mature in colonic lumen (figure 1). Trophozoites is a causative agent of invasive disease but has no role in transmission of disease because of rapid degeneration of trophozoites outside the human body and destruction by gastric acid.⁷ Trophozoites use galactose and lectin specific N-acetyl-D-galactosamin (Gal/GalNAc) to adhere to colonic mucin and colonize in colon.^{1,2,5,6,7,8}

Amebic colitis occurs when trophozoites penetrate intestinal mucosal layer which is actually the barrier to invasion; by inhibit adherence of ameba to epithelial layer and inhibit the trophozoite motility. Invasion is mediated by the destruction of epithelial, neutrophils and lymphocyte cells by trophozoite if lectin of the parasite binds N-acetyl-D-Galactosamin at O-linked of surface cell of the host. The secretion through amebapore; a pore forming protein sized 5 kD has contribution to the destruction of the cells.^{7,8,9,10}

Based on isoenzyme pattern, *E. histolytica* is classified into 2 groups: pathogenic and non-pathogenic zymodeme.³ Although Brumpt postulated in 1925 that there were 2 species of *Entamoeba* that could not be differentiated morphologically. One was known to cause the disease and the other one could not. Later in 1990, genetic molecular examination had confirmed from the two isoenzymes that they were actually two genetically different species but had the same morphology. One that cause invasive amebiasis is called *E. histolytica* and the other one *E. dispar* which is a nonpathogenic protozoan paracyte.^{7,8}

Invasive disease is characterized by the release of toxic substance that cause inflammation and destruct mucosal layer.^{1,11,12} If the process continue,

flask-shaped ulceration will occur extending to sub mucosa or muscularis layer. In some cases, amebic invasion extends more to portal circulation in the liver, thus causing amebic liver abscess. The edge of ulcer is slightly condensed with inflammation. Mucosa between ulcers appears normal. Ulceration may be found in all parts of colon but most frequent is in caecum, followed by ascending colon, sigmoid, appendices and terminal ileum. Due to amebic invasion to intestine wall, humoral immune reaction and cell-mediated amebicidal will occur such as macrophage lymphokine-activated and CD8 cytotoxic lymphocyte.^{1,13} Several studies demonstrated that cystein protein of *E. histolytica* had important role in amebic invasion to intestinal tissue and stimulate inflammation by activating interleukin-1 (IL-1) of the host.^{5,7} After the adherence of trophozoites to colonic mucin, amebic cystein proteinase will degrade mucin and facilitate penetration. Contact with epithelial cells will kill host cell by mechanism of apoptosis and necrosis. It also will activate epithelial inflammation that characterized by activation of NF- κ B, pre-IL- β , IL-1 α , IL-8, IL-6, COX-2, GRO-a and GM-CSF secretion and leukocyte involvement.^{5,13,14} Amebic cytotoxicity and tissue destruction induced by neutrophils allow deep penetration of ameba^{5,6,7} (see figure 2). Invasion that reach muscularis layer of colon can cause granulation mass that is known as ameboma frequently found in caecum and ascending colon. *E. histolytica* can also induce severe inflammation and make it difficult to differentiate with inflammatory bowel disease (IBD). Severe amebic invasion is likely to be found in immunosuppressed patients such as those who are on steroid treatment.^{1,7}

During chronic infection, *E. histolytica* avoid host response immune by various mechanisms. Lectin specific Gal/GalNAc has similarity in chain and antigenic cross reaction with CD 59, a human leukocyte antigen which prevent formation of complement C5b-C9 membrane. Glycosylphosphatidylinocytol bindslypophosphoglycan/proteophosphoglycan (LPG) which covers trophozoites and functioning as protection to complement. Amebic cystein proteinase also degrades serum IgA and IgG that might protect ameba from opsonisation. Ameba might also inhibit macrophage breakdown and suppress antigenic presentation by major histocompatibility complex (MHC) molecules class II.^{2,5}

Model for the step-wise invasion of the colonic mucosa by the *Entamoeba histolytica* in figure 1. Infection begins with excystation and adherence of trophozoites to colonic mucins. Amebic proteinases degrade mucins and facilitate penetration. Contact with epithelial cells lead to apoptotic and necrotic host cell

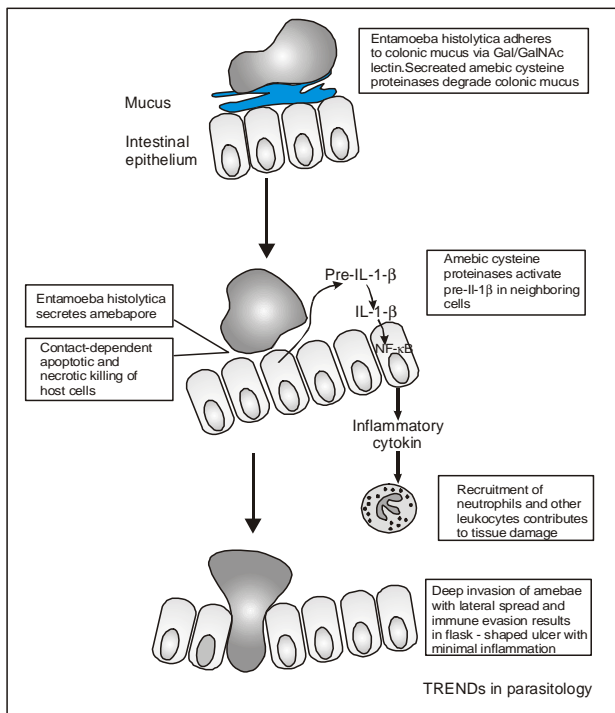


Figure 1. Pathogenesis of intestinal amebiasis⁵

killing and activation of an epithelial cell inflammatory program marked by: (i) activation of NF-κB; (ii) secretion of per-IL-1β, IL-1-α, IL-8, IL-6, COX-2, GRO-α and GM-CSF; and (iii) recruitment of leukocytes. Amebic cytotoxicity and neutrophil-induced tissue damage enable deep penetration by amebae and lateral spread. During chronic infection, amebae evade the host immune response, and inflammation is often minimal given the tissue destruction. However T cells and macrophages recruited to the sight of chronic infection might contribute to disease by autoimmune mechanisms. Abbreviations: COX-2, cyclooxygenase 2; Gal/GalNAc, D-galactose/N-acetyl-D-galactosamine; GRO, growth-related oncogene; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; NF-κB, nuclear factor-κB.

CLINICAL SYMPTOMS

The clinical manifestations of intestinal amebiasis range from mild diarrhea to classic dysentri intestinal disease.^{1,2,3,5,6} Patients with amebic colitis usually complaint of abdominal tenderness for few weeks, weight loss, diarrhea and bloody stool.^{3,15,16} Onset of disease is not very clear. The various clinical presentations have made difficulties in making diagnosis because sometimes patients have no fever or bloody stool.²

Some clinical conditions of patients with amebiasis:

1. Carrier (cyst passer)

Ameba does not invade to intestine wall. Usually patients are asymptomatic or having mild complaints

such as bloating, flatulence, obstipation, and sometimes diarrhea. Ninety percent of patients are self-limiting disease in a year, and the rest 10% develop amebic colitis.³

2. Mild amebic dysentri

Patients' complaint of abdominal fullness, mild abdominal tenderness, mild fever, and mild diarrhea with stinky stool mixed with blood and mucus. The general condition of patients is good

3. Moderate amebic dysentri

Patients may complaint of abdominal rigidity, fever, hepatomegaly with pain

4. Severe amebic dysentri

Clinical presentations such as diarrhea with bloody stool, high fever, nausea and anemia

5. Chronic amebic dysentri

The symptoms are similar to mild amebic dysentri with asymptomatic period interval. It may last for months or even years. Sometimes with neurasthenia, diarrhea occurs in association of fatigue, fever or maldigestive food.

Other manifestations of more severe amebiasis but rarely occur are acute necroticans, toxic megacolon, ameboma, and perianal ulceration which can develop fistulae. Acute necrotican colitis is rare, accounts less than 0.5% of cases with mortality rate more than 40%. In general, patients are in severe condition, have fever, mucous bloody diarrhea, abdominal tenderness and sign of peritoneal irritation. Surgical intervention is indicated if there were intestinal perforation or unresponsive to anti ameba therapy. Toxic megacolon in amebic colitis is rare and usually related to administration of corticosteroid in intestinal amebiasis.⁷ Early detection of complication and surgical intervention is important for such patients who are frequently unresponsive to anti amebic therapy. Rarely, a localized amebic colonic infection results in a segmental mass of granulation tissue forming an ameboma. Amebomas are found in decreasing order of frequency in the caecum, ascending colon, rectosigmoid, transverse colon, and descending colon. The ameboma can be mistaken for a carcinoma.^{2,7} It can be detected on physical examination as a tender palpable mass.⁷

DIAGNOSIS

In patients suspected of intestinal amebiasis, first laboratory examination is stool analysis to detect erythrocyte in stool. If result of stool examination were positive, then other supporting examination can be done (as seen in diagnosis algorithm). Intestinal amebiasis is diagnosed if cyst or motile trophozoites are identified in stool analysis. The lack of this method is low sensitivity and high false positive for infections of *E dispar* or *E moshkowskii*. Ideally, the diagnosis should be based on serologic test of specific antigen or

DNA of *E histolytica* and the presence of anti ameba antibody in the sera (see table 1). At least 3 specimens of feces which are taken at 3 different times are needed for the examination because organism is intermittently secreted and not well-distributed in the feces.

Serologic examination to detect the presence of ameba is positive in 85-95% of patients with invasive amebic infection or liver abscess. Because antiamebic antibodies may persist for months and years after the eradication of infection, a positive serology requires more rigid clinical and diagnostic correlation in endemic areas. Indirect hemagglutination (IHA) is the most sensitive assay, and it yields positive results in 90% to 100% of subjects with liver abscess, 75% to 90% of subjects with symptomatic intestinal infection, and 5% to 50% of subjects with asymptomatic infection.⁷ Antibody may be negative early in the course of an acute infection. It is therefore important to repeat the serology 5 to 7 days later if the initial study results are negative.

Endoscopy is useful in making diagnosis of colitis ameba and should be performed without previous bowel preparation in order to increase the chance of detecting amebas in the colonic mucus. Discrete shallow-based ulcers covered with yellow or white exudates with intervening areas of edematous mucosa are often found in invasive amebic colitis. Mucosa around the ulcers is usually normal. Trophozoite form can be found at the base of ulcer by scrapping or aspiration to obtain the specimen. The diagnostic yield from endoscopic biopsy samples or scrapings is high.⁷ Trophozoites are usually easily identified in these specimens by routine light microscopy, but immunohistochemical staining for *E histolytica* may further increase the yield.⁶

Radiologic examination is not very useful because the appearance may be varied and non specific. Ameboma may appear as filling defect. The scanning procedure should be performed in all cases of suspected liver abscess. Abdominal CT usually

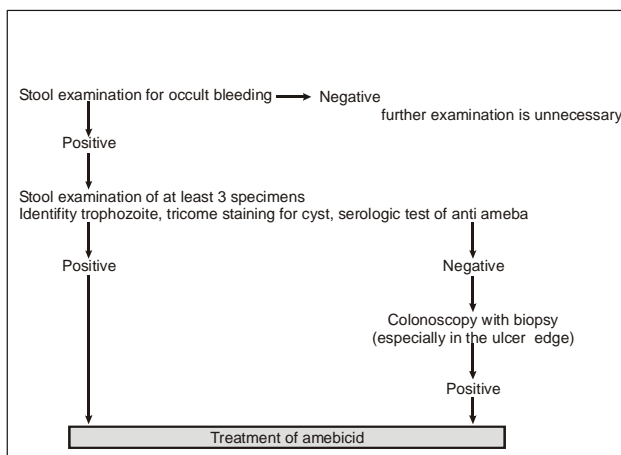


Figure 2. Amebic colitis diagnosis algorithm

Table 1. Sensitivity of test for the diagnosis of amebiasis

Test	Colitis (%)	Liver absces (%)
Microscopy		
Stool	25 – 60	10 – 40
Abscess fluid	NA	≤ 20
Antigen detection		
Stool	90	- 40
Serum	65 (early)	- 100 (before treatment)
Abscess fluid		- 40
Indirect hemagglutination (antibody)		
Serum obtained during acute illness	70	70 – 80
Serum obtained during convalescence	> 90	> 90

* NA denotes not applicable

demonstrates localized, low density lesion with definite borderline.

Antigen detection test to diagnose *E histolytica* infection shows the three methods have almost the same yield. The important things in antigen detection test and PCR based test are serum antibody to ameba detection that is found in 70-90% patients with symptomatic *E histolytica* infection.⁶

DIFFERENTIAL DIAGNOSIS

The similarities in symptoms between amebiasis and inflammatory bowel disease have made amebiasis should be excluded by examination of stools or amebic serology in all patients before a diagnosis of inflammatory bowel disease is made and especially before corticosteroid therapy is begun.⁷

The differential diagnosis of invasive intestinal amebiasis includes infection with *Shigella*, *Campylobacter*, and other invasive bacteria, as well as pseudo membranous colitis secondary to *Clostridium difficile*, CMV colitis.^{3,7}

The ameboma can be mistaken for a carcinoma on barium enema. Amebic strictures are most commonly observed in the anus, rectum, or sigmoid colon and must be differentiated from those due to lymphogranuloma venereum (*chlamydia*) or malignancy.⁷

COMPLICATIONS

1. Intestinal, colonic bleeding, perforation, peritonitis, ameboma, intussusceptions, and stricture.
2. Extraintestinal. With the most common manifestation is liver abscess. Usually, patients are complaint of fever, upper quadrant abdominal pain, leukocytosis, and abnormal liver function test and elevated phosphatase alkaline level.⁷

Most of complications are associated with abscess rupture. Brain amebic abscess is rarely occurred. But has high mortality rate. There had been many medical reports on the involvement of genitourinary tract including perinephric abscess, splenic abscess, rectovaginal fistula, cervicis ulcer, uterine involvement and vaginal lesion. There

had also been some reports on skin, nail, and pleuropulmonal amebiasis.

MANAGEMENT

Medical treatment

Patients with *E histolytica* infection should receive antiamebic therapy, but there is no evidence that patients with *E dispar* infection require treatment.⁷ Prior to the general availability of assays that distinguish between infection with *E histolytica* and *E dispar*, treatment decisions must be based primarily on the clinical presentation. The goals of treatment are to treat the invasive disease and eradicate intestinal carriage of the organism. Based on the site of actions, amebicid is divided into 3 categories:¹⁷

1. Tissue amebicid

Drugs that mainly act on intestinal wall, liver and other extraintestinal tissues include dehydroemetine, emetin, and chloroquine.

2. Luminal amebicid

It works in lumen of intestine and is called contact amebicid. Drugs that included in this category are diiodohydroxyquine, iodochlorhydroxyquin, chiniofphone, glycobiarsol, carbarsone, emetine bismuth iodide, clefamide, diloxanid furoat, and some other antibiotics such as tetracycline and paromomycine.

3. Amebicid of intestinal lumen and tissue (e.g. metronidazole)

According to severity of clinical symptoms, recommended treatment is as follow:

a. Asymptomatic or carrier^{3,18}

Amebiasis without clinical symptoms should be treated because ameba that lives commensally in colon can change to be pathogenic at any time. Besides, carrier could be the main source of infection. Recommended drugs given as luminal amebicid are:

- 1) Iodoquinol (diiodohydroxyquin) 650 mg tid for 20 days
- 2) Diloxanil furoat, 500 mg tid for 10 days. Now this is the treatment of choice because it is highly effective (80%-85%), while the minimal side effects are only nausea and abdominal bloating
- 3) Carbarsone, 500 mg tid for 7 days
- 4) Clefamide, 500 mg tid for 10-13 days
- 5) Paromomycine, 500 mg tid for 5 days

Because the risk of amebic invasion to intestinal mucosa is high although it does not disturb peristaltic movement, addition of tissue amebicid is recommended. The choices of drugs are as follows;

- 1) chloroquine diphosphate, 500 mg bid for 1-2 days, continue with dose of 250 mg bid for 7-12 days
- 2) Metronidazole, 35-50 mg/kgBW or 500 mg tid

for 5 days

- 3) Trinitadazole, 50 mg/kgBW or 2 g/day for 2-3 days
- 4) Ornidazole, 50-60 mg/kgBW or 2 g/day for 3 days

- b. Mild to moderate intestinal amebicid
Tetracycline 500 mg tid for 5 days or metronidazole 500 mg tid for 5-10 days
- c. Severe intestinal amebiasis
Metronidazol 750 mg tid for 5-10 days.^{17,19,20}
Tetracycline 500 mg tid for 5 days and emetine 1 mg/kgBW/day IM (maximal 60 mg) for 10 days
- d. Extraintestinal amebiasis, using 3 regimens of drugs
 - Metronidazole 750 mg tid for 5-10 days
 - Chloroquine phosphate 1 g/day for 2 days continued by 500 mg/day for 4 weeks
 - Emetine 1 mg/kgBW/day IM (maximal 60 mg) for 10 days

Metronidazole is (1b-hydroxy-ethyl)-2 methyl-5-nitroimidazole which has yellowish crystal form and mildly dissolve in water or alcohol.¹⁷ The half time ranges from 9 to 10 hours. Beside thricomoniacid effect, metronidazole is also effective for treatment of *Giardia lamblia*. To date, resistance of *E histolytica* to metronidazole has not become a problem yet.⁷ Other drugs that have similar structure and activity with metronidazole are tinidazole, nimorazole, and ornidazole. These three drugs have longer half time than metronidazole, so that they can be given once daily.^{7,17} Common side effects of metronidazole include nausea, headache, metallic taste, and abdominal discomfort; ataxia, confusion, insomnia, and paresthesias may occasionally occur. The most serious side effects are central nervous system effects (psychosis, seizures), which mandate cessation of the drug.

Emetine is an effective drug to kill throphozoites in tissue or intestinal wall but ineffective for ameba in the intestinal lumen.^{3,14} It is relatively toxic, may cause diarrhea, abdominal cramps, tachycardia, hypotension, precordial pain and ECG abnormalities such as T wave inversion and prolonged QT interval. Other manifestation of arrhythmia such as wide QRS complex is more rarely. Patients who are given emetine should be bed rest and have ECG monitor. Avoid the use of emetine if there is kidney, heart, or muscular disorder, or in pregnancy or children unless other drugs are considered failed.³

The need for vaccine

Ideally, amebiasis is prevented by eradicating feces contamination of food and water. However, to provide uncontaminated food and water in developing countries need huge investments and social changes. Vaccine is urgently needed. Human will naturally get the partial immunity against intestinal infection. In this

Table 1. Drug therapy for the treatment of amebiasis²⁰

Drug	Adult dosage	Pediatric dosage	Side effect
Amebic liver abscess			
Metronidazole	give		Primarily gastrointestinal: anorexia, nausea, vomiting, diarrhea, abdominal discomfort, or unpleasant metallic taste; disulfuram-like intolerance reaction with alcohol; rarely, neurotoxicity, including seizure; peripheral neuropathy, dizziness, confusion, irritability
	750 mg orally 3 times a day for 7-10 days	35-10 mg/kg of body weight/day in 3 divided doses for 7-10 days	
Tinidazole †	or		Primarily gastrointestinal and disulfuram-like intolerance reaction for metronidazole
	800 mg orally 3 times a day for 5 days	60 mg/kg/day (max 2 g) for 5 days	
Paromomycin	followed by a luminal agent		Primarily gastrointestinal: diarrhea, gastrointestinal upset
	25-35 mg/kg/day in 3 divided doses for 7 days	25-35 mg/kg/day in 3 divided doses for 7 days	
Dilocanide furate ‡	or second-line agent		Primarily gastrointestinal: flatulence, nausea, vomiting, pruritus, urticaria
	500 mg orally 3 times a day for 10 days	20 mg/kg/day in 3 divided doses for 10 days	
Amebic colitis			
Metronidazole	give		As for amebic liver abscess
	750 mg orally 3 times a day for 7-10 days	35-50 mg/kg/day in 3 divided doses for 7-10 days	
followed by a luminal agent (as for amebic liver abscess)			
Asymptomatic intestinal colonization			
Paromomycin	give		Primarily gastrointestinal: diarrhea, gastrointestinal upset
	25-35 mg/kg/day in 3 divided doses for 7 days	25-35 mg/kg/day in 3 divided doses for 7 days	
Dilocanide furate ‡	or second-line agent		Primarily gastrointestinal: flatulence, nausea, vomiting, pruritus, urticaria
	500 mg orally 3 times a day for 10 days	20 mg/kg/day in 3 divided doses for 10 days	

† This drug is not yet available in the United States

‡ This drug is not available in the United States

case, according to several studies, there are some recombinant antigen including lectin specific Gal/GAINac can be used.^{5,21} However, further studies are needed to develop this vaccine.

CONCLUSION

The high prevalence of colonic amebiasis due to protozoa; *Entamoeba histolytica* is found in tropical countries. Ameba infection begins by swallowing of infected cysts containing amebas in food or water which are contaminated by feces. Colitis occurs as trophozoite penetrates intestinal mucosal layer mediated by neutrophils and infection binding to N-acetyl-D-galactosamin of O-linked oligosaccharide on cell surface.

During chronic infection of *E histolytica* is against immune response by various mechanisms including lectin specific of Gal/Gal/Nac which has similarity of chains and antigenic cross reactivity to CD 59 with clinical symptoms of intestinal amebiasis are varied from asymptomatic, dysenteric diarrhea and intestinal involvements

Diagnosis is made from anamnesis, physical examination, supporting examinations including stool analysis, serologic examination, endoscopic and radiologic examinations. Management of intestinal amebiasis includes medical treatment of metronidazole, chloroquine, emetin, and tetracycline. Lifestyle education and good sanitation are also important to be promoted. In the future vaccination will be highly needed to decrease prevalence of intestinal amebiasis.

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