Ⅲ. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表（平成25年度）

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
Hamano, S. and William A. Petri Jr.	Amoebiasis	James Cherry, Gail J. Demmler-Harrison, Sheldon L. Kaplan, William J. Steinbach and Peter Hotez	"Feigin, Cherry, Demmler, Kaplan: Textbook of Pediatric Infectious Disease, 7th edition"	Elsevier	London	2013	2866-2874.
濱野真二郎	アメーバ症		今日の治療指針2014	医学書院	東京	2014	255
濱野真二郎	リンパ系糸状虫症、イヌ糸状虫症	熱帯病治療薬研究班	寄生虫症薬物治療の手引き　改訂8.0版		東京	2014	
Makoto HIRAI	Fertilization mechanisms of the rodent malarial parasite *Plasmodium berghei*.	Sawada H	***Sexual reproduction***	Springer	ドイツ	2014	印刷中
森稔幸 平井　誠	動植物・原生生物の受精に共通する配偶子融合機構	澤田　均	生物の受精	化学同人	日本	2014	印刷中
Angeles, JM., and Kawazu, S.	Insights into animal schistosomiasis: From surveillance to control.	A. Miele	Schistosomiasis: Epidemiology, Diagnosis and Treatment.	Nova Publishing Inc.	New York	in press	
山﨑 浩	抗寄生虫 IgG 抗体	和田 收, 大久保昭行, 矢崎義雄, 大内尉義	臨床検査ガイド	文光堂	東京	2013	878-880
杉山　広	肝蛭症，肺吸虫症（肺ジストマ症），肥大吸虫症，毛細虫症.	山崎修道ら	感染症予防必携（第 3 版）	日本食品衛生協会	東京	2014	印刷中
杉山　広	回虫，アニサキス.	上野俊治ら	獣医公衆衛生学 1（食品衛生学）	文永堂出版	東京	2014	印刷中

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杉山　広	顎口虫症，アニサキス症，日本住血吸虫症，肺吸虫症，肝蛭症.	上野俊冶ら	獣医公衆衛生学2（人獣共通感染症学）	文永堂出版	東京	2014	印刷中
杉山　広，小島荘明	アニサキス幼虫，旋尾線虫X型幼虫，肺吸虫，回虫	高谷　幸	食中毒予防必携（第3版）	日本食品衛生協会	東京	2013	pp.308-316 pp.337-340 pp.348-352
杉山　広	生食による寄生虫感染症のリスク.	一色賢司	生食のおいしさとリスク	エヌ・ティー・エス	東京	2013	pp.379-393

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渡辺恒二　他	Clinical Significance of High Anti-Entamoeba histolytica Antibody Titer in Asymptomatic HIV-1-infected Individuals	Journal of Infectious Diseases			2014 in press

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杉山　広，森嶋康之，大前比呂思，山﨑　浩，木村真也	アニサキスによる食中毒：届出に関わる法改正とレセプトデータによる患者数の推計.	Clinical Parasitology	24	44-46	2013
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水野麻衣，清水裕希，坂井浩志，調裕次，**杉山　広**，山﨑　浩	サブイレウスにて保存的加療されていた旋尾線虫による皮膚幼虫移行症の 1 例.	臨床皮膚科	67	539-542	2013
杉山　広	食品による寄生動物感染症 7. 蠕虫感染症 (2) 肺吸虫.	防菌防黴	41	165-171	2013
杉山　広	増えている？アニサキス食中毒	食と健康	57	8-16	2013

Ⅳ. 研究成果の刊行物・別刷

Paragonimus kellicotti (lung fluke endemic in the United States)
Paragonimus spp.
Metorchis conjunctus (North American liver fluke)

Trematodes—Blood

The schistosomes are acquired by penetration of the skin by the cercarial forms that are released from freshwater snails. Although they are not endemic within the United States, occasionally patients are seen who may have these infections.

Current Name

Schistosoma mansoni
Schistosoma haematobium
Schistosoma japonicum
Schistosoma intercalatum
Schistosoma mekongi

ARTHROPODS

See Tables 208-1 and 208-2.

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SUBSECTION 1 *PROTOZOA*

CHAPTER 209

AMEBIASIS

Shinjiro Hamano • William A. Petri, Jr.

Diarrheal diseases continue to be major causes of morbidity and mortality in children in developing countries. In Bangladesh, 10 percent of children in the first year of life have amebic diarrhea and 1 in 30 children dies of diarrhea or dysentery by age 5 years.[78] Amebiasis is an infection caused by the protozoan parasite *Entamoeba histolytica*. Infection occurs via ingestion of the parasite's cyst from fecally contaminated food, water, or hands. Approximately 50 million illnesses and 100,000 deaths occur annually from amebiasis, rendering it the third leading cause of death by parasitic disease in humans.[78] Although amebiasis is present worldwide, it occurs most commonly in underdeveloped areas, especially Asia, sub-Saharan Africa, and Central and South America. In the United States and other developed countries, cases of amebiasis are most likely to occur in immigrants from and travelers to endemic regions, but it can affect populations of the developed world, as shown by the epidemic that occurred

in Tbilisi, Republic of Georgia, caused by contaminated municipal water.[13] Currently, there is no vaccine to prevent the childhood morbidity and mortality resulting from infection with *E. histolytica.*

ETIOLOGY

E. histolytica is the cause of amebiasis and was named for the pathologic evidence of "lysis" of tissues. Additional *Entamoeba* spp. that infect humans and that are identical in appearance microscopically to *E. histolytica* include *E. dispar*, which is nonpathogenic, *E. moshkovskii*, which may cause diarrhea,[95] and the recently identified enteric parasite *E. bangladeshi.*[91] The first demonstration of the organism in human tissues was made by Lambl in 1859 in the postmortem examination of the colon of a child who died as a result of having excessive diarrhea.[16,74] No connection of the organism with the disease was made until 1875, when Losch, in St. Petersburg, Russia, found the organism at autopsy in the colon of a woodcutter. Losch induced diarrhea and ulcerations in a dog given feces from the patient.[61] He did not think, however, that a connection existed between the organism and the disease. The first patient described in the United States was a physician treated by Osler for an amebic liver abscess in 1890.[74] Councilman and Lafleur described the organism and the disease in 1891.[20,45] Further investigation of the disease was delayed until a better understanding of the life cycle of *E. histolytica* could be obtained.[27] In recent years, the application of modern molecular biology techniques to the study of *E. histolytica* and *E. dispar* has resulted in an explosion of information about the mechanisms of virulence, pathogenicity, and immune responses to these organisms.[88,90]

E. histolytica is the pathogenic species, having the capacity to invade tissue and cause symptomatic disease, whereas *E. dispar* (and *E. histolytica*) is associated with the asymptomatic carrier state.[6,88] More recently, a study revealed that all genotypes of *E. histolytica* are not equally capable of causing disease.[6] Morphologically distinct members of the genus *Entamoeba*, such as *Entamoeba coli* and *Entamoeba hartmanni*, also are nonpathogenic. *Entamoeba moshkovskii*, *Dientamoeba fragilis*, and *Entamoeba polecki* have been associated with diarrhea, and *Entamoeba gingivalis* has been associated with periodontal disease.

Members of the genus *Entamoeba*, which are protozoan organisms belonging to the subphylum Sarcodina and close to *Dictyostelium discoideum* on one of the lowest branches of the eukaryotic tree, have trophozoite and cyst forms.[39] The cysts of *E. histolytica*, *E. dispar*, *E. moshkovskii*, and *E. bangladeshi* are almost spherical, being surrounded by a cell wall composed of chitin. The cysts may have one to four nuclei, although quadrinucleate cysts are most typical. This feature allows differentiation from *Escherichia coli*, which usually has 6 to 8 nuclei in the cysts and may have 32 nuclei.[75] Cysts of *E. histolytica* are 5 to 20 μm in diameter (average, 12 μm) and have a greenish tint in the unstained condition.[62] Young cysts contain chromatoid bodies, which are composed of ribosome particles in crystalline arrays.[12] The cysts of *E. hartmanni* appear identical to those of *E. histolytica* except for being a smaller size (4 to 10 μm). *E. histolytica* cysts can survive for days in the dried state at 30° C or for months at 0° C to 4° C. They can be killed by temperatures greater than 50° C retained for 5 minutes.[45] They are completely resistant to the concentrations of chlorine used in water supplies but may be killed with hyperchlorination or with iodine solutions.[62,75] They are filtered from water supplies that pass through a sand filtration phase. They resist acids well.

When these quadrinucleate cysts are ingested, they resist the acid pH of the stomach and ultimately excyst in the alkaline environment of the bowel. The process of excystation results in the release of four trophozoites that divide by binary fission to produce eight trophozoites. The usual trophozoites have a diameter of 25 μm (range, 10 to 60 μm).[27,88] They have a single nucleus that is 3 to 5 μm in diameter and contains fine peripheral chromatin with a slightly eccentric karyosome. They have a granular endoplasm that typically contains vacuoles in which bacteria and debris can be seen. Some glycogen is present and can be stained with periodic acid–Schiff stain.

Although amebae were thought to lack organelles, such as mitochondria, endoplasmic reticulum, and Golgi apparatus, evidence to the contrary is coming to light. The existence of nuclear-encoded mitochondrial genes and a remnant mitochondrial organelle was reported more recently.[63,102] The presence of ingested erythrocytes is a characteristic feature of *E. histolytica* but not *E. dispar.*[88] Movement is accomplished by extension of clear pseudopodia. Replication is by binary fission. These protozoa live in the colon of humans and other mammals. Trophozoites die quickly outside the body and are quite sensitive to acid—they generally are not considered to be infective.[32] When cooled (as when feces are expelled and gradually cooled from body temperature) or stimulated by as-yet-undefined luminal conditions, the trophozoites form cysts that can remain viable for weeks to months on excretion.[88]

Trophozoites of *E. coli* are 15 to 50 μm in diameter; have much more sluggish motility than the trophozoites of *E. histolytica*; and have blunt pseudopodia, rather than the sharp, finger-like pseudopodia of *E. histolytica.* Trophozoites of *E. hartmanni* are 4 to 14 μm in diameter and have much less glycogen than the trophozoites of *E. histolytica.*[27]

EPIDEMIOLOGY

Amebiasis is distributed throughout the world. The number of people infected with either *E. histolytica* or *E. dispar* per year is estimated to be 500 million. Although most individuals remain asymptomatic, perpetuating the natural cycle of the organism through fecal excretion of infective cysts, approximately 50 million people experience the severe morbidity associated with invasive disease, with an estimated 100,000 dying annually.[78,99] In the United States, 50 percent of amebiasis is observed in Hispanics, Asians, and Pacific Islanders. Travelers from developing countries, malnourished individuals,[72] men, and residents of institutions for the mentally retarded are considered to be at higher risk for amebiasis (Table 209-1).

TABLE 209-1 Risk Factors for Amebiasis in the United States

Hispanic/Asian/Pacific Islanders—50% of U.S. cases reported to CDC
Travelers to endemic regions of the world—0.3% incidence in one study
Institutions for mentally retarded
Men who have sex with men
Men—90% amebic liver abscesses in men, but rare in children

CDC, Centers for Disease Control and Prevention.

During the 1990s, enough evidence had accumulated to support the formal separation of two morphologically identical species of ameba: the nonpathogenic *E. dispar* from the potentially pathogenic *E. histolytica.** Morbidity and mortality data in absolute numbers that existed before this time pertaining to cases of invasive disease were not greatly affected by this reclassification because all invasive disease was known to be caused by *E. histolytica.*[99] Because most prevalence and incidence data previously collected pertained to asymptomatic individuals, however, and it was clear that most asymptomatic individuals with cysts detected in their stool were infected with nonpathogenic *E. dispar*, the true prevalence and incidence of *E. histolytica* became a matter of speculation.[99]

Estimates of *E. histolytica* infections have been based primarily on examinations of stool for cysts and parasites, but these tests are insensitive and cannot differentiate *E. histolytica* from morphologically identical species that are nonpathogenic, such as *E. dispar* and *Entamoeba moshkovskii.*[5,22] Specific and sensitive means to detect *E. histolytica* in stool are now available and include antigen detection and polymerase chain reaction (PCR) analysis.[36,44,58]

A prospective study of preschool children in a slum of Dhaka, Bangladesh, showed *E. histolytica*–associated diarrhea in 9 percent and *E. histolytica*–associated dysentery in 3 percent of the children annually.[42] Not all individuals are equally susceptible to amebiasis, with a leptin receptor polymorphism and certain HLA-DR and HLA-DQ alleles associated with resistance to infection and disease.[23,24] The annual incidence of amebic liver abscess was reported to be 21 cases per 100,000 inhabitants in Hue City, Vietnam.[14] Carefully conducted serologic studies in Mexico, where amebiasis is endemic, showed antibody to *E. histolytica* in 8.4 percent of the population.[17] In the urban slum of Fortaleza, Brazil, 25 percent of all individuals tested carried antibody to *E. histolytica*; the prevalence of anti-amebic antibodies in children 6 to 14 years old was 40 percent.[15]

PATHOGENESIS AND PATHOLOGY

The cysts are transported through the digestive tract to the intestine, where they release their mobile, disease-producing form, the trophozoite. *E. histolytica* trophozoites can live in the large intestine and form new cysts without causing disease. They also can invade the lining of the colon, killing host cells and causing diarrhea, amebic colitis, acute dysentery, or chronic diarrhea. The trophozoites also can be carried through the blood to other organs, most commonly the liver and occasionally the brain, where they form potentially life-threatening abscesses (Fig. 209-1). Important virulence factors include the trophozoite cell surface galactose and *N*-acetyl-D-galactosamine (Gal/GalNAc)–specific lectin that mediates adherence to colonic mucins and host cells,[77,89] cysteine proteinases that likely promote invasion by degrading extracellular matrix and serum components, and amebapore pore-forming proteins involved in killing of bacteria and host cells.[59,92]

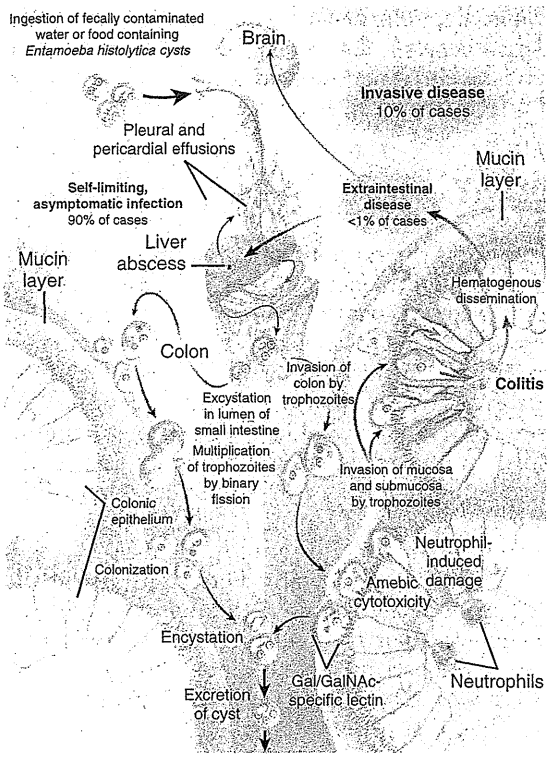

FIGURE 209-1 ■ Life cycle of *Entamoeba histolytica.* Infection normally is initiated by the ingestion of fecally contaminated water or food containing *E. histolytica* cysts. The infective cyst form of the parasite survives passage through the stomach and small intestine. Excystation occurs in the bowel lumen, where motile and potentially invasive trophozoites are formed. In most infections, the trophozoites aggregate in the intestinal mucin layer and form new cysts, resulting in a self-limited and asymptomatic infection. In some cases, adherence to and lysis of the colonic epithelium, mediated by the galactose and *N*-acetyl-D-galactosamine (Gal/GalNAc)–specific lectin, initiates invasion of the colon by trophozoites. Neutrophils responding to the invasion contribute to cellular damage at the site of invasion. When the intestinal epithelium is invaded, extraintestinal spread to the peritoneum, liver, and other sites may follow. Factors controlling invasion, as opposed to encystation, most likely include parasite "quorum sensing" signaled by the Gal/GalNAc-specific lectin, interactions of amebae with the bacterial flora of the intestine, and innate and acquired immune responses of the host. (From Haque R, Huston CD, Hughes E, et al. Amebiasis. *N Engl J Med* 2003;**348**:1565-73.)

*References 1, 14, 30, 31, 38, 99.

The interface of the Gal/GalNAc lectin with the host mucins lining the intestine is the defining moment of the infection.[19] If the parasite lectin attaches to the host mucin glycoproteins that line the intestinal lumen, a noninvasive gut infection ensues. The life cycle continues as the trophozoites reproduce by clonal expansion in the mucin layer. Subsequently, the Gal/GalNAc lectin, along with mucin glycoproteins or other gut bacteria, initiates the developmental pathway leading to encystment.[26,99]

Colitis is caused when the trophozoite penetrates the intestinal mucous layer, which otherwise acts as a barrier to invasion by inhibiting amebic adherence to the underlying epithelium and by slowing trophozoite motility.[19] Invasion is mediated by the killing of epithelial cells, neutrophils, and lymphocytes by trophozoites, which occurs only after the parasite lectin engages host GalNAc on O-linked cell surface oligosaccharides.[78] The interaction of the lectin with glycoconjugates is stereospecific and multivalent.[107] The identity of the high-affinity intestinal epithelial cell receptor is unknown. Secretion of amebapore, a 5-kDa pore-forming protein, by the ameba may contribute to killing.[57] Activation of human caspase 3, a distal effector molecule in the apoptotic pathway, occurs rapidly after amebic contact, and caspases are required for cell killing in vitro and for the formation of amebic liver abscesses in vivo.[47,106]

Interaction of the parasite with the intestinal epithelium causes an inflammatory response marked by the activation of nuclear factor κB and the secretion of cytokines.[25,93] The development of this epithelial response may depend on trophozoite virulence factors, such as cysteine proteinase, and leads to intestinal abnormalities through neutrophil-mediated damage. Neutrophils also can be protective, and activation of neutrophils or macrophages by tumor necrosis factor-α or interferon-γ kills amebae in vitro and limits the size of amebic liver abscesses.[7,21] In contrast to the intense inflammatory response typical of early invasive amebiasis, inflammation surrounding well-established colonic ulcers and liver abscesses is minimal, given the degree of tissue damage.[16]

The initial lesions of clinical amebiasis often are small interglandular ulcers with a diameter of approximately 1 mm. They extend only to the muscularis mucosa.[16,66] The margins may be hyperemic, and slight edema of the surrounding mucosa is present. *E. histolytica* organisms seen in these ulcers stain well with periodic acid–Schiff stain.[79] Bleeding and friability are not prominent at this stage, although proctoscopic examination may find mucus coming from these ulcers, with an abundant number of amebae present.

The next stage of intestinal disease is the production of deeper ulcers. These "buttonhole" ulcers may be 1 cm in diameter and may extend into the submucosa.[16,79] The ulcer often extends laterally under normal-appearing mucosa, forming a characteristic flask shape. Occasional perforation through the serosa leads to peritonitis or pneumoperitoneum.[96] Extensive necrosis may be present, but usually only very little inflammation occurs. The edema is more intense, but the mucosa between ulcers is normal, in contrast to the marked inflammatory response seen in bacterial enteritis. When ulceration is more extensive, the edema surrounding the ulcers becomes confluent and the mucosa appears gelatinous. In young children, this condition can progress to a fulminant necrotizing colitis associated with transmural necrosis. The pathologic events associated with this phenomenon are not understood. Rarely, an inflammatory response is present, resulting in granulation of the tissue with a fibrous outer wall.[75] It is given the name *ameboma.* Occasionally, an ameboma fills a significant portion of the lumen, which causes stricture or obstruction. Other complications of intestinal amebiasis result from direct extension of the ulcers. This extension may result in cutaneous involvement of the perianal area or lesions of the penis, vulva, vagina, or cervix.[2,75] Cutaneous and ophthalmologic amebiasis also is caused by fecal contamination of the face.[69]

Amebae disseminate to the liver in 50 percent of patients with fulminant amebiasis.[2,3] Dissemination to other organs directly from the intestine probably does not occur, but dissemination from the liver to lung, heart, brain, spleen, scapula, larynx, stomach, and aorta has been described.[16] Amebic abscess of the liver occurs more often in men than in women by a ratio of 16:1 but occurs equally often in prepubertal children of both sexes.[3,16] Abscesses occur more commonly in adults but occur in children as young as 4 months of age.[73] These abscesses vary from microscopic lesions to massive necrosis of 90 percent of the liver. Fever, right upper quadrant pain, and the presence of serum antibodies to amebae point to hepatic amebic abscess.[87] Examination of the fluid from such an abscess frequently reveals a reddish, "anchovy paste" fluid that rarely may appear white or green. The fluid is acidic, with a pH ranging from 5.2 to 6.7.[85] Amebae are found in the walls of the abscess and only rarely in the fluid of the abscess. Many patients with amebic liver abscess also have anaerobic bacteria in the abscess fluid.[86] The walls are composed of a thin connective tissue capsule. The right lobe of the liver is involved with amebic liver abscess about six times as often as the left lobe. Abscesses in the right lobe can perforate and cause disease below the diaphragm or in the thoracic cavity. Abscesses in the left lobe can lead to pericardial effusions, which are less common than pleural effusions.[34,49]

Pleural effusions can remain loculated or lead to cutaneous fistulas or to bronchopleural fistulas. Drainage from these fistulas is acidic, in contrast to the neutral secretions in the normal lung. Seeding of the cardiac valves and of the brain has been described.[16] Cerebral abscesses have the same microscopic findings as do liver abscesses, with a thin capsule of connective tissue surrounding a fluid with little or no associated inflammatory response.

IMMUNITY

Protection from amebiasis, including acquired immunity to infection and invasion by *E. histolytica,* is associated with a mucosal IgA antibody response against the carbohydrate recognition domain of the parasite Gal/GalNAc lectin.[33,37,39,55] Cell-mediated immunity in protection

from invasive amebiasis, but not infection per se, also has been shown. There is substantial evidence from an in vitro animal model and most recently from human studies of an important role for interferon-γ and IL-17 in protection from amebic colitis, acting in part by activating of macrophages to kill the parasite.[33,43,46] Invasive amebiasis rarely occurs in individuals with human immunodeficiency virus infection/acquired immunodeficiency syndrome, even in areas where amebiasis is common, suggesting an important role also exists for natural immunity or innate immune responses, or both, in protection from infection.[7,36]

CLINICAL MANIFESTATIONS

Intestinal Amebiasis

Asymptomatic Intraluminal Amebiasis

The most common type of amebic infestation is an asymptomatic cyst-passing carrier state. All *E. dispar* infections and 90 percent of *E. histolytica* infections are asymptomatic, manifesting as only *Entamoeba* cysts in the feces.[30,81]

Entamoeba histolytica*–Associated Diarrhea*

Diarrhea is the most common manifestation of amebic disease, present in 9 percent of children in the Mirpur cohort each year, compared with only 3 percent of children having amebic colitis each year.[42] *E. histolytica*–associated diarrhea is defined as three or more unformed stools in a 24-hour period accompanied by a new episode of *E. histolytica* infection. This definition was validated previously in the cohort by (1) showing that diarrhea was approximately five times more common in the setting of a new infection (age-adjusted odds ratio for the association of new *E. histolytica* infection with diarrhea of 4.7; 95% confidence interval 2.9 to 7.6), and (2) showing by a complete bacteriologic, virologic, and parasitic workup that only 32 percent of patients with *E. histolytica*–associated diarrhea were coinfected with another pathogen compared with identification of an enteropathogen in 59 percent of all cases of diarrhea.[39]

Acute Amebic Colitis

Amebic dysentery was defined as a diarrheal stool sample containing occult or gross blood that was positive for *E. histolytica* antigen. Seventy percent of patients have a gradual onset of symptoms over 3 or 4 weeks after infestation, with increasingly severe diarrhea as the primary complaint, accompanied by general abdominal tenderness. Occasionally, the onset may be acute or may be delayed for several months after infestation. This onset differs from bacterial causes of dysentery, in which patients usually have only symptoms of 1 to 2 days' duration. The diarrhea is usually associated with pain in children. Pain may be of such severity that an acute abdomen is suspected.[50,79] The stools contain blood and mucus in virtually all cases.[2,79,80] Fever is present in only a few patients with amebic colitis. Abdominal distention and dehydration occur in less than 10 percent of patients. In young children, intussusception, perforation, peritonitis, or necrotizing colitis may develop rapidly.[10,50,96] Amebic colitis has been shown to be associated with cognitive disability as a long-term sequelae.[101]

Ameboma

Unusual manifestations of amebic colitis include toxic megacolon (0.5% of cases, usually requires surgical intervention), ameboma (granulation tissue in colonic lumen mimicking colonic cancer in appearance), and a chronic nondysenteric form of infection that can manifest as years of waxing and waning diarrhea, abdominal pain, and weight loss (easily misdiagnosed as inflammatory bowel disease).

Extraintestinal Amebiasis

Amebic Liver Abscess

The typical patient with an amebic liver abscess in the United States is an immigrant, usually a Hispanic/Asian/Pacific Islander; is male; is 20 to 40 years old; and has fever, right upper quadrant pain, leukocytosis, abnormal serum aminotransferase and alkaline phosphatase levels, and a defect on hepatic imaging study. Roughly 90 percent of patients with liver abscesses are men. The abscess usually is single and is in the right lobe of the liver 80 percent of the time.[51] Most frequently, patients have liver abscess without concurrent colitis. Amebae are seen infrequently in the stool at the time of diagnosis of liver abscess.[3] Liver abscess can manifest acutely as fever and right upper abdominal tenderness and pain or subacutely as prominent weight loss and less frequently fever and abdominal pain. The peripheral white blood cell count is elevated, as is the alkaline phosphatase level, in many patients.

Early evaluation of the hepatobiliary system by ultrasonography or computed tomography (CT) is essential to show the abscess in the liver. The differential diagnosis of the lesion in the liver includes pyogenic abscess, hepatoma, and echinococcal cyst. Aspiration of the abscess occasionally is required to diagnose amebiasis (although amebae are visualized in the pus in only a few cases; if the abscess is pyogenic, the responsible bacteria are seen or cultured). Antibodies to *E. histolytica* are present in the serum of 70 to 90 percent of patients on acute presentation with amebic liver abscess and are useful diagnostically, especially in combination with antigen detection or PCR tests.[41] Unusual extraintestinal manifestations of amebiasis include direct extension of the liver abscess to pleura or pericardium and brain abscess. In a patient who has right upper quadrant pain, ultrasonography, CT, or magnetic resonance imaging (MRI) should be performed to examine the liver and gallbladder.

If a space-filling defect in the liver is observed, the differential diagnosis includes (1) amebiasis (most common in men with a history of travel or residence in a developing country); (2) pyogenic or bacterial abscess (suspected in women, patients with cholecystitis, elderly individuals, individuals with diabetes, and patients with jaundice); (3) echinococcal abscess (an incidental finding

because echinococcal abscess should not cause pain or fever); and (4) cancer. Most patients with amebic liver abscess have detectable circulating antigen in serum and serum anti-amebic antibodies.[36]

In children, abdominal pain is reported infrequently with amebic liver abscess.[35,70] More commonly, high fever, abdominal distention, irritability, and tachypnea are noted. Some children are admitted to the hospital with a fever of unknown origin. Hepatomegaly occurs frequently, but elicitation of hepatic tenderness is not well documented. In one report, four of five children younger than age 5 years died with amebic liver abscesses because the diagnosis was not suspected.[56] Death usually results from rupture of the liver abscess into the peritoneum, thorax, or pericardium but may follow extensive hepatic damage and liver failure.[3,84]

Metastatic Amebiasis

Extra-abdominal amebiasis presumably follows direct extension from liver abscesses, rather than direct dissemination from the intestine.[3,16] Thoracic amebiasis is the most common type of extra-abdominal amebiasis and occurs in less than 10 percent of patients with amebic liver abscess.[16,49] Symptoms depend on the type of involvement. Empyema, bronchohepatic fistulas, or extension of a pleuropulmonary abscess into the pericardium may occur.

Pericardial amebiasis is the next most common form of extraintestinal involvement and may result from rupture of a liver abscess in the left lobe of the liver into the pericardium or through extension of the right-sided pleural amebiasis.[16,28,29,34] It is estimated to occur in 3 percent of patients with hepatic abscesses.[29] It manifests as acute pericarditis with tamponade and, occasionally, as pneumopericardium.[28] Amebic liver abscess in the left lobe also may rupture directly into the left side of the chest.[65]

Cerebral amebic abscesses are seen only in individuals with amebic liver abscess and were found in 8 percent of patients with liver abscess discovered at autopsy in one study.[60] In other studies, lower rates of 0.66 to 4.7 percent of patients with amebic liver abscess having brain abscesses were reported.[48,98] Patients with cerebral amebiasis frequently are so ill from the intestinal, liver, and possibly lung involvement that neurologic signs are not always assessed easily. In 18 patients with proven cerebral amebiasis, initial neurologic examination was normal in 13 and only 1 patient later developed seizures.

Other foci of infection are rare findings, but amebic rectovesical fistula formation and involvement of pharynx, heart, aorta, and scapula have been reported. Cutaneous extension after the adherence of perforated, inflamed bowel to the skin is an extremely painful and rare complication.[16,75] This situation also may arise after invasion of the skin occurs from trophozoites emerging out from the rectum.[69]

DIAGNOSIS

The prevalence of diarrhea due to *E. histolytica* in the first year of life in impoverished children in the developing world may be as high as 10 percent.[71] A heightened suspicion of amebiasis should be present if the patient has been in a developing country as a resident or traveler. The diagnosis of amebiasis should be considered in any child with risk factors who has diarrhea, bloody stools, or stools with mucus; with a hepatic abscess; and/or with right upper quadrant pain, abdominal distention, or tachypnea.[56,70] In a patient with diarrhea, if blood is present in the stool (grossly bloody or occult blood positive), infectious (Shiga toxin–producing *E. coli*, *Salmonella*, *Shigella*, *Campylobacter*, and *E. histolytica*) and noninfectious (inflammatory bowel disease, diverticulosis, arteriovenous malformations, cancer) causes should be considered.

Serologic Tests

Serologic tests for anti-amebic antibodies also are a very useful tool in diagnosis, with sensitivity of 70 to 80 percent early in disease and approaching 100 percent sensitivity on convalescence.[97,100] The combined use of serology and stool antigen detection or PCR analysis offers the best diagnostic approach.

Microscopic Examination of Stool

Before the development of new antigen detection tests and PCR analysis, amebiasis was diagnosed by examining a stool sample through a microscope to determine whether *E. histolytica* cysts were present. This method often requires more than one specimen, however, because the number of cysts in the stool varies greatly. In addition, stool microscopy has limited sensitivity and specificity. The body's own immune system produces macrophage cells that can look like the amebae. Four different amebae—*E. histolytica*, which causes amebiasis, *E. dispar*, which does not cause disease, and *E. moshkovskii* and *E. bangladeshi*, which may cause diarrhea—look identical under a microscope.[22,91,95]

Noninvasive Diagnosis of Extraintestinal Amebiasis

Amebiasis outside the intestine has been even more difficult to diagnose. Clinical manifestations of extraintestinal disease vary widely, and less than 10 percent of individuals with amebic liver abscesses have identifiable *E. histolytica* in their stools. The TechLab *E. histolytica* II test, which differentiates the true pathogen *E. histolytica* from *E. dispar*, was reported to detect Gal/GalNAc lectin in the sera of 22 of 23 (96%) patients with amebic liver abscess tested before treatment with the anti-amebic drug metronidazole and 0 of 70 (0%) controls. After 1 week of treatment with metronidazole, more than 80 percent of patients became serum lectin antigen negative. Detection of *E. histolytica* Gal/GalNAc lectin in the sera using the TechLab *E. histolytica* II kit is sensitive to diagnose hepatic and intestinal amebiasis before the institution of metronidazole treatment.[41] A real-time PCR assay detected *E. histolytica* DNA in 49, 77, and 69 percent of blood, urine, and saliva specimens, respectively, from the amebic liver abscess patients.[40]

Noninvasive diagnostic procedures such as ultrasound, CT, and MRI can detect extracolonic amebiasis in the liver, paracecal masses, brain, and other sites, but they cannot distinguish between abscesses caused by amebae and those caused by bacteria, hampering proper treatment of the condition. Most patients with amebic liver abscess have a single abscess in the right lobe of the liver, although multiple lesions also can occur.[4] Chest radiographs show elevation of the right diaphragm in 56 percent of patients with hepatic abscess.[3] The diagnosis of cerebral amebiasis requires careful neurologic evaluation and radiographic evaluation with either CT or MRI.[16,48,60] In one case, *E. histolytica* DNA was detected by PCR in CNS to make the diagnosis.[98] Because of the risk for perforation, barium studies are relatively contraindicated in patients with amebic colitis.

Biopsy Studies

The colonic and rectal mucosa in amebic colitis usually reveals ulcerations with a diameter of 1 to 10 mm. Amebic trophozoites often are at the periphery of these necrotic areas, which can be sampled through a biopsy specimen taken during sigmoidoscopy or colonoscopy.[45,51] Because of the potential for perforation, colonoscopy should be undertaken with caution.

In patients with amebic liver abscesses, amebic trophozoites are found near the capsule of the abscess. Until more recently, the most accurate diagnostic test involved the examination by microscopy of a sample collected from the abscess tissue by needle aspiration, a procedure that is relatively insensitive, identifying amebic trophozoites only 20 percent of the time. PCR in contrast is a sensitive and specific means to identify *E. histolytica* in liver abscess material.[40]

DIFFERENTIAL DIAGNOSIS

Invasive amebic colitis may resemble ulcerative colitis, Crohn disease of the colon (inflammatory bowel disease), bacillary dysentery, or tuberculous colitis.[11,18,45,93] Stool *E. histolytica* antigen or PCR analysis, colonoscopic examination with biopsies, and serologic examination should be able to differentiate amebic colitis from these diseases. Histologic examination of involved colonic mucosa should differentiate amebic colitis, with its lack of inflammation and rare granulation tissue, from the inflammatory responses seen in ulcerative colitis, bacillary dysentery, and Crohn disease of the colon. Tuberculous colitis and Crohn disease are more likely to show granuloma formation than amebiasis. Ileocecal or small bowel involvement as seen on barium studies would suggest Crohn disease or tuberculosis of the gastrointestinal tract, rather than amebiasis. Tuberculous colitis usually is associated with pulmonary tuberculosis and with a strong reaction to tuberculin skin testing. In some cases, differentiating between invasive amebic colitis and inflammatory bowel disease may be impossible. If a patient with this differential diagnosis is placed on corticosteroids and his or her condition deteriorates, the corticosteroids should be stopped and repeat investigation for amebiasis should be performed.[18,70,75]

Amebic liver abscess must be differentiated from pyogenic abscesses and neoplastic lesions. Detection of *E. histolytica* Gal/GalNAc lectin in the sera using the TechLab *E. histolytica* II kit was helpful in one study to diagnose hepatic and intestinal amebiasis before the institution of metronidazole treatment.[41] Total leukocyte counts and cultures of blood may help to differentiate pyogenic and amebic abscesses. Many children with pyogenic liver abscesses have negative blood cultures, however. Often, amebic and pyogenic liver abscesses show similar features on CT and MRI. Occasionally, nuclear imaging with gallium is helpful because, in contrast to a pyogenic abscess, very few neutrophils are contained within an amebic liver abscess.[88,90] Gallium scanning of an amebic liver abscess may reveal a cold spot, possibly with a bright rim. For an individual with risk factors for amebiasis, several investigators recommend instituting treatment for amebic abscess for 3 or 4 days while serologic, antigen detection, or PCR results are awaited.[40,70] Patients with amebic liver abscess should respond to treatment in this length of time by becoming afebrile. No change in size of the liver or size of the abscess should be noted at this time because resolution of the abscess usually takes 2 months to several years.[4,82,83,94,105]

COMPLICATIONS

Complications of amebiasis may be prevented by early establishment of diagnosis and initiation of treatment with appropriate agents.[48,70] When complications occur, the prognosis generally is worse.

Invasive intestinal amebiasis has been associated most commonly with perforation and peritonitis,* which apparently are an end result of "necrotizing" or "toxic" amebic colitis. In children, perforation may be heralded by the appearance of an acute abdomen or pneumoperitoneum, with rapid progression to death, presumably from sepsis.[8,70,104] Surgical resection and therapy for endotoxic shock improve the prognosis.[104] This complication is not rare and accounts for more than 30 percent of deaths from amebiasis in children.[11,52] Massive intestinal hemorrhage causes approximately 3 percent of deaths from amebiasis. Multiple colonic strictures also can occur and cause obstructive symptoms. Fistulas to other organs or to the skin may develop.

Liver abscesses are an unusual manifestation of amebiasis in children, but their resultant complications account for approximately 40 percent of all deaths from amebiasis.[52] Liver abscess also was found in 13 percent of patients with amebiasis at postmortem examinations. Liver abscess with rupture into the abdomen was present in 8 percent of patients who died with amebiasis, and rupture of a liver abscess into the right pleural space was found in 12 percent.[52] Many patients with amebic liver abscess also have anaerobic bacteria in the abscess fluid.[86]

*References 8, 10, 50, 70, 96, 104.

In cases free of bacterial contamination, the fluid has few inflammatory cells and an acidic pH. Amebic pericarditis or pneumopericardium occurs rarely and is found in only 1 percent of patients whose deaths were caused by amebiasis.[28,29,34,52] The fluid is similar to that found in the pleural space. A cerebral abscess was found in 4 percent of patients with amebiasis who died.[52] It has been reported in fewer than 10 children, only 1 of whom survived.[9,16,48,60] Other complications include infections of the retroperitoneal space, stomach, spleen, esophagus, and duodenum.[60]

TREATMENT

Intestinal Amebiasis

Asymptomatic Intraluminal Amebiasis

Therapy for asymptomatic colonization differs from therapy for invasive infection. Asymptomatic infections may be treated with intraluminal agents, such as paromomycin or diloxanide furoate. Each agent has a high rate of success for eradication of cyst passage.[67,68] Paromomycin is a nonabsorbable aminoglycoside that is active against the cyst and trophozoite stages. High cure rates have been reported with a 7-day oral dose of paromomycin at 25 to 35 mg/kg/day in three divided doses (Table 209-2). Diloxanide furoate (Furamide) is a poorly absorbed agent that is quite active against only intraluminal amebiasis.[64] Cure rates have been greater than 90 percent with a 10-day oral course of diloxanide furoate at 20 mg/kg/day in three divided doses (maximum, 1500 mg/day).[67,68,76]

Acute Amebic Colitis

Nitroimidazoles, particularly metronidazole, are the mainstay of therapy for invasive amebiasis.[39] The oral dosage of metronidazole is 35 to 50 mg/kg/day (maximum, 2250 mg/day) in three divided doses for 7 to 10 days for severe intestinal or extraintestinal amebiasis. Metronidazole is concentrated in the ameba, probably via reduction of its nitro group by ferredoxin or flavodoxin-like electron transport proteins, which maintain a gradient for the entry of the unchanged drug. Metabolic intermediates of metronidazole damage DNA and possibly other macromolecules, and they deprive the organism of reducing equivalents by acting as an electron sink. Nitroimidazoles with longer half-lives (tinidazole, secnidazole, and ornidazole) are better tolerated and allow shorter periods of treatment.[41] For children 3 years of age or older, the oral dosage of tinidazole is 50 mg/kg/day (to a maximum of 2000 mg/day) for 5 days for severe intestinal or extraintestinal amebiasis (see Table 209-2).

Approximately 90 percent of patients who present with mild-to-moderate amebic dysentery have a response to nitroimidazole therapy. In the rare case of fulminant amebic colitis, adding broad-spectrum antibiotics to treat intestinal bacteria that may spill into the peritoneum is prudent; surgical intervention occasionally is required for acute abdomen, gastrointestinal bleeding, or toxic megacolon.[39] Agents such as metronidazole that are active against invasive and extraintestinal amebiasis are well absorbed and do not stay in the lumen long enough to have an effect on intestinal amebiasis. Parasites persist in the intestine in 40 to 60 percent of patients who receive nitroimidazole. Nitroimidazole treatment should be followed with paromomycin or the second-line agent diloxanide furoate to cure luminal infection.[41] Metronidazole and paromomycin should not be given at the same time because the diarrhea that is a common side effect of paromomycin may render assessing the patient's response to therapy difficult.[52-54]

Extraintestinal Amebiasis

Amebic Liver Abscess and Metastatic Amebiasis

Extraintestinal and severe intestinal amebiasis must be treated with the tissue-active agents. Metronidazole 35 to 50 mg/kg/day in three divided doses for 7 to 10 days is preferred because it is effective and relatively free of serious side effects (see Table 209-2).[2,3,64,88,90] It is effective for extraintestinal amebiasis in any location, although amebic brain abscesses usually are not treated successfully with any medications. Most patients with amebic liver abscess respond to metronidazole within 72 hours. For amebic colitis, follow-up therapy with a luminal agent is very important because of the high rates of asymptomatic intestinal colonization in patients with amebic liver abscess.

Therapeutic aspiration of an amebic liver abscess occasionally is required as an adjunct to antiparasitic therapy. Drainage of the abscess should be considered in patients who have no clinical response to drug therapy within 5 to 7 days or patients with a high risk of experiencing rupture of the abscess, as defined by a cavity with

TABLE 209-2 **Pediatric Dosage of Drugs for Amebiasis**

Type of Disease	Drug	Dosage
Asymptomatic colonization	Paromomycin	25-35 mg/kg/day in 3 doses × 7 days
Mild-to-moderate intestinal disease	Metronidazole	35-50 mg/kg/day in 3 doses × 7-10 days
	Tinidazole	50 mg/kg/day (maximum, 2000 mg) × 3 days
Severe intestinal and extraintestinal disease	Metronidazole	35-50 mg/kg/day in 3 doses × 7-10 days
	Tinidazole	50 mg/kg/day (maximum, 2000 mg) × 3 days

a diameter of more than 5 cm or by the presence of lesions in the left lobe.[103] Because many patients with amebic liver abscess also have anaerobic bacteria in the abscess fluid,[86] addition of antibiotics, drainage, or both to the treatment regimen in the absence of a prompt response to nitroimidazole therapy is reasonable. Image-guided percutaneous treatment (needle aspiration or catheter drainage) has replaced surgical intervention as the procedure of choice for reducing the size of an abscess.[103]

PROGNOSIS

Invasive disease develops in 50 million people each year, and 50,000 to 100,000 deaths result.[81,87,88] The case-fatality ratio is between 1 in 500 and 1 in 1000 diagnosed cases. Among patients with illness severe enough to require hospitalization, the case-fatality ratio is higher. One small study in children reported a 9 percent mortality rate and a 27 percent morbidity rate.[70]

Bowel necrosis or perforation is the cause of death from purely intestinal amebiasis, and early surgical intervention can reduce the mortality rate of these complications from 100 to 28 percent.[104] Amebic liver abscess has a case-fatality rate of 10 to 15 percent in combined figures of adults and children.[56,73,84] The mortality rate when pleural involvement is noted is 14 percent.[49,56] Amebic pericarditis has a case-fatality rate of 40 percent.[34] Cerebral amebiasis is fatal if untreated.[98]

FUTURE CONSIDERATIONS

Amebiasis would be prevented by eradicating fecal contamination of food and water. Providing sanitation and safe food and water for all children in developing countries is an important and achievable goal but will require massive societal changes and monetary investments. An effective amebiasis vaccine is a desirable and feasible goal to help the approximately 1 billion people living in unsanitary conditions. The high incidence of amebiasis in community-based developing country studies of infants, who bear the brunt of morbidity and mortality from diarrhea, suggests that an effective vaccine would improve child health.

The fact that humans naturally acquire partial immunity against intestinal infection indicates that barriers to stimulating an effective acquired immune response should not be insurmountable. Aiding vaccine design is the demonstration that several recombinant antigens, including the Gal/GalNAc-specific lectin, provide protection in animal models of amebiasis and that human immunity is linked to intestinal IgA against the lectin.[33,37,39] The high degree of sequence conservation of the Gal/GalNAc-specific lectin suggests that a vaccine could be broadly protective. Finally, the absence of epidemiologically significant animal reservoirs suggests that herd immunity could interrupt fecal-oral transmission in humans. The challenges will be to design vaccines capable of eliciting durable mucosal immunity, to understand the correlates of acquired immunity, and, most important, to enlist the continued support of industrialized nations to combat diarrheal diseases of children in developing countries.

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