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trophozoites confirming the diagnosis of inva- sive amoebic disease. Other diagnostic methods include (1) dem- onstration of amoebal DNA in faeces/tissues by polymerase chain reaction; (2) serology—but seropositivity does not distinguish current and past tissue invasion. Aside from supportive care, metronidazole for 5 days is usually the first-choice treatment, with the addition of diloxanide to eliminate infection from the bowel and so prevent re- currence of tissue invasion or transmission to others. Uncomplicated invasive intestinal disease (and uncomplicated hepatic amoebiasis) should have mortality less than 1%, but this may reach 40% for amoebic peritonitis with multiple gut perforation. Hepatic amoebiasis—less than 50% of patients give any convincing history of dysentery and few have concurrent dysentery. Presentation is typically with fever, sweating, liver or diaphragmatic pain, weight loss, and tender hepatomegaly. Diagnosis is usually achieved by demon- stration of a (most often solitary) liver abscess on ultrasonography or CT and positive serological testing, with a therapeutic amoebicide trial generally being preferable to diagnostic needling of the liver.

8.8.1 Amoebic infections 1385 Prevention—simple hygienic measures and health education provide considerable protection: boiling water for 5 min kills cysts. Travellers to endemic areas may need a medical check on their re- turn; but chemoprophylaxis is not appropriate. Free-living amoebae Three genera of free-living amoebae, Naegleria, Acanthamoeba, and Balamuthia, cause human disease. Naegleria causes a primary men- ingoencephalitis after bathing or diving or other nasal exposure to fresh water; amphotericin B is an effective drug, but most cases are fatal, partly because of diagnostic delays. Acanthamoeba causes a painful keratitis, mainly in contact lens users, which usually responds to intensive local amoebicides, although corneal grafting may be needed; it also causes a highly fatal granulomatous encephalitis in immunocompromised patients. Balamuthia causes an encephal- itis similar to that of Acanthamoeba in both immunocompromised and immunocompetent individuals; primary skin or facial lesions are common; both genera are potential donor risks in transplantation. Introduction The amoebic species infecting humans belong to two very different groups. The obligate anaerobic gut parasites include the major pathogen Entamoeba histolytica, which ranks second to malaria as the most dangerous parasite in humans; Dientamoeba fragilis, a minor pathogen; and eight nonpathogenic species including the common and important Entamoeba dispar. The second group in- cludes certain aerobic free-living, water and soil amoebae which produce cytopathic changes in cultured cell monolayers and cerebral invasion after intranasal inoculation into mice. They can become facultative tissue parasites in humans after cysts or trophozoites are inhaled, ingested, or enter damaged skin, cornea or mucosae. All motile feeding amoebae are called ‘trophozoites’; they move with pseudopodia and divide by binary fission. The hyaline external cytoplasm, the ‘ectoplasm’, is a contractile gel that surrounds the sol endoplasm containing numerous phagocytic and pinocytic vacu- oles. Noninvasive trophozoites feed on bacteria. All species can form environmentally resistant transmissive cysts by rounding up and se- creting a chitinous cyst wall. The definitive taxonomic separation of E. dispar as a nonpathogenic species separate from E. histolytica was made in 1993. This was based upon genomic and biochemical differences. This distinction is of fundamental importance because their cysts and noninvasive trophozoites are morphologically indistinguishable, but they are now separated by specific antigen and polymerase chain reaction (PCR) assays. All strains of E. histolytica are now regarded as pathogenic, whereas the commoner E. dispar is never pathogenic. Entamoeba histolytica infection Biology and pathogenicity Following ingestion of infective cysts, a population of tropho- zoites becomes established in the caecum and proximal colon. Some degree of tissue invasion occurs in all subjects with at least low-titre

seroconversion. Tissue invasion is frequently mild, self- limiting, and with minimal symptoms, but at the other end of the clinical spectrum it can lead to extensive destruction of the colonic mucosa. Parasite genotype may partly determine clinical outcome. Invasive trophozoites have a characteristic morphology; they may reach 30–40 µm in diameter and are very active with apparently pur- poseful, unidirectional movements during which they become con- siderably elongated. Their most important diagnostic characteristic is the presence of host erythrocytes within the endoplasm, which otherwise appears clear and contains no bacteria. Trophozoites containing red blood cells are described as erythrocytophagous. Progression through tissues is by active movement, facilitated by secreted collagenase; leucocytes are drawn chemotactically towards the amoebae but most are rapidly destroyed on contact. The transmissive cystic form of the parasite is derived entirely from a commensal population within the colonic lumen. Live com- mensal amoebae measure from 10 to 20 µm in diameter, the endo- plasm is granular and contains bacteria, and the pseudopodia are blunt and movement is sluggish. Intestinal hurry from any cause, including the use of laxatives, can lead to the appearance of com- mensal trophozoites in the faeces. Cysts are spherical and measure from 11 to 14 µm in diameter; when mature, they contain four nu- clei, several chromatoid bodies that are ribosome aggregates, and a glycogen vacuole. Host factors may increase susceptibility to overt disease. Steroid therapy given systemically or locally into the rectum carries great risk, as may cytotoxic therapy. Severe amoebic bowel disease is par- ticularly common in late pregnancy and the puerperium. Before pu- berty, both sexes are equally susceptible to hepatic amoebiasis, but in adults this condition is much more common in males. Local dis- ease can also favour tissue invasion; thus, amoebic ulceration may be superimposed upon colonic and rectal cancers, or those of the uterine cervix. Colonic disease is favoured by concurrent Trichuris infection or intestinal schistosomiasis. Infection with HIV ap- pears to have little effect on colonic disease but may facilitate liver involvement. Epidemiology The incidence of disease is particularly high in Mexico, South America, Natal (South Africa), the west coast of Africa, and Southeast Asia. In most temperate countries, E. histolytica is now rare and nearly all amoebic disease seen in such countries will have been acquired elsewhere. Symptomless or convalescent carriers are the main source of infection; patients with dysentery normally pass only trophozoites in their stool and are therefore noninfectious. Cysts remain viable in the environment for up to 2 months. The in- fection is eventually self-limiting and rarely exceeds 4 years. Tissue invasion can occur at any time during an infection but is much more common during the first 4 months; the incubation period may be as short as 7 days. E. histolytica-associated diarrhoea can retard growth in preschool children. The incidence of invasive amoebiasis in a population is best esti- mated from seropositivity surveys. Prevalence of infection is esti- mated by specific faecal antigen or DNA; microscopic surveys for cysts are of no value as their differentiation from E. dispar is impos- sible. Zoonotic sources are uncommon but transient infections do occur in dogs, and molecular methods have confirmed infections in

 Malaysian rats. All modes of faeco-oral transmission occur in amoeb- iasis. Of special importance are the food handler and contaminated vegetables; transmission by flies and drinking-water is less common. Drinking-water can be contaminated in the home or at surface-water sources. Direct spread can produce outbreaks; it occurs within insti- tutions for children, people with learning difficulties, and with con- taminated colonic irrigation equipment. Household clustering is common; hand-fed infants are frequently infected from the fingers of their mother. Contamination of piped water supplies can lead to ser- ious disease outbreaks, as happened in the Chicago hotels epidemic in 1933. Interruption of piped water

supplies probably caused the re- cent outbreak in Georgia. Entamoeba infections are common among male homosexuals, but most are due to E. dispar; oro-anal contact is probably responsible. However, invasive amoebiasis in HIV-positive homosexual men is an emerging problem in Japan. Pathology The basic lesion is cell lysis and tissue necrosis, which, by creating lo- cally anoxic and acidic conditions, favours further penetration of the parasite. Most amoebae are seen at the advancing edge of the lesion with little inflammatory cell response. In tissue sections, amoebae stain indistinctly with haematoxylin and eosin but appear bright red with periodic acid–Schiff stain; iron haematoxylin is necessary to show nuclear detail. Cysts of E. histolytica are never seen in tissue. Amoebic lesions of the gut are most common in the rectosigmoid and caecum but can occur anywhere in the large bowel; involve- ment may be patchy or continuous. Less commonly, the appendix or terminal ileum are affected. The initial lesions are either small, discrete erosions of the mucosa or minute crypt lesions Fig. 8.8.1.1). Unrestrained, the lesions extend through the mucosa, across the muscularis mucosa and into the submucosa, where they expand laterally to produce lesions that are typically flask shaped in cross- section Fig. 8.8.1.2). Further lateral spread of the submucosal lesions leads to their coalescence and, later, to denudation of over- lying mucosa. The bowel wall may become appreciably thickened. Blood vessels involved in the disease may thrombose, bleed into the gut lumen, or, in the case of portal-vein radicles, enable dissemin- ation of amoebae to the liver. In very severe lesions, and usually in association with toxic megacolon, there is an irreversible coagulative necrosis of the bowel wall. Amoebomas are tumour-like lesions of the colonic wall measuring up to several centimetres in length; they are most common in the caecum and may be multiple. Histologically there is tissue oedema, with a mixed picture of healing and new areas of epithelial loss and tissue destruction; round-cell infiltration is patchy. Lesions may be annular and rarely an amoeboma initiates an intussusception; narrow, stricture-like amoebomas may occur in the anorectal region. Amoebae reach the liver in the portal vein. Once initiated, the amoebic lesion extends progressively in all directions to produce the liver-cell necrosis and liquefaction that constitute an amoebic liver abscess. The lesions are well demarcated from surrounding liver tissue; untreated nearly all will eventually extend into adjacent structures. Secondary bacterial infection is rare and usually follows rupture or aspiration. Clinical manifestations Invasive intestinal amoebiasis The clinical features show a wide spectrum from minimal changes in bowel habit to severe dysentery. Lesions may be limited to a small part of the large bowel or extend throughout its length. A relapsing course is common. Amoebic colitis with dysentery Dysentery, the passage of loose or diarrhoeal stools containing fresh blood, occurs when there is generalized colonic ulceration or when more localized lesions occur in the rectum or rectosigmoid. Onset may be gradual, intermittent, or, much less commonly, acute. Typically, constitutional upset is initially mild and the patient remains ambulant; mild or moderate abdominal pain is common, often col- icky and maximal over affected parts of the gut. Tenesmus can occur but is rarely severe. Stools vary in consistency from semiformed to watery. They are foul smelling and always contain visible or occult blood; even when they are watery, faecal matter is nearly always pre- sent. Symptoms frequently wax and wane over a period of weeks or even months and such patients can become debilitated and wasted. Fig. 8.8.1.1 Amoebic colitis. Crypt abscess. Periodic acid–Schiff stains amoebae red. Copyright Viqar Zaman. Fig. 8.8.1.2 Amoebic colitis. Superficial ulcer breaching the muscularis mucosae. Copyright Viqar Zaman.

 In a few patients the disease runs a fulminating course. The most frequent physical sign is abdominal tenderness in one or both iliac fossae, but tenderness may be generalized. The affected gut may be palpably thickened. A low fever is common, but dehydration

is un- common. Abdominal distension occurs in the more severely ill pa- tients, who sometimes pass relatively small amounts of stool. A careful proctoscopy or sigmoidoscopy should be done. The endoscopic appearances may be nonspecific in early, acute, or very severe colitis; the findings are hyperaemia, contact bleeding, or con- fluent ulceration. In more chronic cases, the presence of normal- looking intervening mucosa is highly suggestive of amoebiasis. Early lesions are often elevated, with a pouting opening only 1 to 2 mm in diameter; later, ulcers may reach 1 cm or more in diameter, with an irregular outline, and often a loosely adherent, yellowish, or grey ex- udate. Mucosal scrapings or superficial biopsies taken at endoscopy should be examined immediately by wet-preparation microscopy. Special forms of amoebic colitis Fulminant colitis—This may arise de novo, for example, in preg- nant women or during steroid therapy, or it may evolve during a dysenteric illness. Patients show progressive abdominal distension, vomiting, and watery diarrhoea. Bowel sounds are absent and there may be little or no abdominal tenderness, guarding, or rigidity. Plain radiographs may reveal free peritoneal gas, together with acute gas- eous dilatation of the colon; affected segments of bowel may ap- pear relatively narrow and show visible mucosal pathology. Barium enema and full sigmoidoscopy are contraindicated. Stools contain erythrocytophagous trophozoites. Amoebic colitis without dysentery—When ulceration is limited to the caecum or ascending colon, or when early, mild, or localized le- sions occur elsewhere in the colon, there may be no dysenteric symp- toms. Patients complain of change in bowel habit, blood-staining of the stool, flatulence, and colicky pain. Often the only physical sign is tenderness in the right iliac fossa or elsewhere along the course of the colon. Some patients eventually go into complete remission; others progress to a dysenteric illness. The most important diagnostic measure is repeated stool exam- ination for erythrocytophagous amoebae; the finding of cysts or commensal trophozoites is of little diagnostic value, especially in endemic areas, unless E. histolytica specific methods are used. Sigmoidoscopy is often normal when the distal bowel is not involved but colonoscopy may reveal typical lesions. Amoeboma This presents as an abdominal mass, most frequently in the right iliac fossa. The lesion may be painful, tender, and associated with fever. Bowel habit is altered and some patients have intermittent dys- entery, especially if lesions are multiple or distal. Evidence of partial or intermittent bowel obstruction may be present, particularly when lesions are distal and annular. Localized perforation and amoebic appendicitis Sudden perforation with peritonitis can occur from any deep amoebic ulcer; alternatively, leakage may lead to a pericolic abscess or retroperitoneal cellulitis. Amoebic appendicitis is an uncommon but important condition that occurs when amoebic lesions are con- fined to the appendix and caecum. The clinical presentation can re- semble that of simple appendicitis, often with some clinical evidence of dysentery. If it is unrecognized at appendicectomy the outcome can be disastrous, with gut perforation; fresh smears should be made from the resected appendix and examined immediately. Rectal bleeding Some patients with amoebiasis present with rectal bleeding, with or without tenesmus; this occurs particularly in children. Massive bleeding into the gut lumen can occur in any form of amoebic colitis but is rare. Differential diagnosis Amoebic colitis must be differentiated from other causes of in- fective colitis. High-volume diarrhoea, copious mucus, and severe tenesmus are all uncommon in amoebiasis. In temperate countries, nonspecific ulcerative colitis, Clostridium difficile colitis, and colo- rectal carcinoma create the greatest diagnostic problems. Parasitic conditions to be considered are intestinal schistosomiasis, heavy Trichuris infection, and balantidiasis. More chronic amoebic path- ology may clinically resemble Crohn’s disease, ileocaecal tubercu- losis, diverticulitis, or anorectal lymphogranuloma venereum. Hepatic amoebiasis Less than half of all patients give any convincing history of dysen- tery and few have concurrent dysentery. In those with no dysenteric history, the interval between presumed

infection and presentation may be as short as 3 weeks or as long as 22 years; for most, it is between 8 weeks and 1 year. The dominant symptoms are fever and sweating, liver or diaphragmatic pain, and weight loss. Onset of constitutional symp- toms is often insidious, but pain may begin abruptly. Most patients seek medical help between 1 and 4 weeks. Fever is typically remit- tent, with a prominent evening rise, brief rigors, and very profuse sweating. Liver pain may be poorly localized initially and later be- come pleuritic, referred to the right shoulder tip or localized to the abdominal wall. Within a few weeks, patients lose much weight and often become anaemic; a painful dry cough is common. The most important clinical finding is liver enlargement Fig. 8.8.1.3) with localized tenderness, which should be searched for in the right hypochondrium, the epigastrium, and along all the intercostal spaces overlying the liver. Liver pain, on compression or heavy digital percussion, is a less useful sign. Left-lobe lesions can present as an epigastric mass. Hepatomegaly may be difficult to de- tect by abdominal palpation when enlargement is mainly upwards, but bulging of the right chest wall may be noted, together with a raised upper level of liver dullness on percussion. Reduced breath sounds or crepitations may be heard at the right lung base. Important radiological findings are a raised or locally upward- bulging right diaphragm Fig. 8.8.1.4) with immobility on screening, areas of lung collapse or consolidation, and sometimes a pleural ef- fusion. A neutrophil leukocytosis is almost invariable, the erythro- cyte sedimentation rate is raised, and normochromic normocytic anaemia is common. Liver function tests are frequently completely normal or there may be a raised alkaline phosphatase; less commonly the serum transaminase or bilirubin is elevated. Liver scanning to demonstrate a filling defect is of great value; about 70% of lesions are solitary, but multiple lesions are common in children and those with concurrent dysentery. Ultrasonographic and CT scans are the most useful. Lesions appear round or oval and are usually between 4 and 10 cm in diameter at the time of presentation. On ultrasonography

 most are hypoechoic with well-defined walls without enhanced echoes. Even when concurrent dysentery is absent, the stools are frequently, but not always, positive for E. histolytica. Colonoscopy may reveal unsuspected lesions. Complications Most complications involve extension of hepatic lesions into adja- cent structures: usually the right chest, the peritoneum, and the peri- cardium. Upward extension usually produces adhesions between the liver, the diaphragm, and the lung; in consequence, subphrenic rupture and amoebic empyema are rare, although a right serous pleural effusion is not uncommon. Untreated, the disease process advances upwards through lung tissue leading to hepatobronchial fistula and expectoration of brownish, necrotic liver tissue, the so- called ‘anchovy sauce’ sputum. Rupture into the peritoneum can occur at any time; it is sometimes the mode of presentation of an amoebic liver abscess, the cause of peritonitis being discovered only at laparotomy. Amoebic pericarditis usually results from upward ex- tension of a left-lobe liver lesion. Initially patients have retrosternal pain and a pericardial friction rub; later rupture or large serous ef- fusion produces cardiac tamponade. The diagnosis is most difficult when an underlying liver abscess was not suspected. Less commonly the lesion extends through the skin, producing a sinus and cutaneous lesion. The gut, stomach, vena cava, spleen, and kidney are occasionally involved by direct spread. Blood- borne spread to the lung produces a lesion resembling an isolated pyo- genic lung abscess. Amoebic brain abscesses due to E. histolytica are rare; most are discovered postmortem Fig. 8.8.1.5). Jaundice occurs when a large lesion compresses the common bile duct or when multiple lesions compress several intrahepatic bile ducts. Rupture into a major bile duct can cause haemobilia. Portal-vein compression occasionally produces portal hypertension and con- gestive

splenomegaly. Differential diagnosis Amoebic serology and scanning have now greatly simplified diag- nosis. However, a few patients (generally less than 5%) are initially seronegative; scanning patterns may be atypical before lesions have liquefied. Pyogenic abscess, especially when cryptogenic, may be clinically indistinguishable and this condition is quite common in some Asian countries. Other conditions to be distinguished are pri- mary and secondary carcinoma of the liver, lesions of the right lung base and right pleura, subphrenic abscess, cholecystitis, septic chol- angitis including that resulting from aberrant Ascaris worms, and liver hydatid cysts. Fig. 8.8.1.3 Amoebic liver abscess. Hepatic enlargement with focal tenderness in a Thai woman. Courtesy of the late Professor Sornchai Looareesuwan. (c) (b) (a) Fig. 8.8.1.4 Amoebic liver abscess. Radiographic changes showing (a) elevated right diaphragm; (b) enormous abscess in the right lobe of the liver outlined with air (fluid level) and contrast medium introduced during the aspiration of more than 1 litre of pus; and (c) same patient as (b), lateral view. Courtesy of the late Professor Sornchai Looareesuwan.

 Needle aspiration of the liver Fig. 8.8.1.6) may be necessary for diagnostic or therapeutic purposes (see next). Suspected pyo- genic abscess is the main indication for the former; blood cultures should also be taken. Typically, the aspirate in hepatic amoebiasis is pinkish-brown, odourless, and bacteriologically sterile Fig. 8.8.1.7); a thinner, malodorous, or frothy aspirate suggests bacterial infec- tion. A therapeutic amoebicide trial is generally preferable to diag- nostic needling of the liver. Cutaneous and genital amoebiasis Skin ulceration due to *E. histolytica* produces deep, painful, and foul-smelling lesions that spread rapidly. Secondary bacterial in- fection is common and may mask the amoebic pathology. Lesions are most frequent in the perianal area, but also occur at colostomy stomas, laparotomy scars, and at the site of skin rupture by a hep- atic lesion. Female genital involvement results from faecal contamination, the extension of perianal lesions, or by the formation of internal fis- tulae from the gut, which can involve the bladder. Lesions of the vulva and uterine cervix may resemble carcinoma. Male genital le- sions follow rectal coitus, the lesion beginning as a balanoposthitis and progressing rapidly. Laboratory diagnosis Microscopy and culture The identification of live erythrocytophagous trophozoites in tem- porary wet mounts is of prime importance because it confirms the diagnosis of invasive amoebic disease. Amoebae should be sought in dysenteric bowel-wall scrapings, the last portion of aspirate from a liver abscess Fig. 8.8.1.8), sputum, and tissue scrapings from skin lesions. In nondysenteric stools, flecks of pus, blood, or mucus should be looked for and examined. The amoebae re- main active for about 30 min at room temperature. Other micro- scopical features of faeces in amoebic colitis are scanty or absent leucocytes, clumped or degenerating red cells, and, sometimes, Charcot–Leyden crystals. If wet preparations are not made or are negative, a portion of the specimen should be preserved in poly- vinyl alcohol or sodium acetate–acetic acid–formalin fixative for later smear preparation; alternatively, drying faecal smears should be fixed in Schaudinn’s solution. In either case, fixed smears Fig. 8.8.1.5 Metastatic brain abscess in a patient with an amoebic liver abscess. Courtesy of the late Professor Sornchai Looareesuwan. Fig. 8.8.1.6 Diagnostic/therapeutic aspiration of ‘anchovy sauce’ pus from a patient with amoebic liver abscess. Contrast medium is being injected after aspiration of the abscess. Copyright D. A. Warrell. Fig. 8.8.1.7 ‘Anchovy sauce’ pus drained from and amoebic liver abscess. Copyright Viqar Zaman. Fig. 8.8.1.8 Aspirate from amoebic liver abscess showing margin of hepatocytes and erythrocytophagous trophozoites of E. histolytica. Copyright Viqar Zaman.

section 8 Infectious diseases 1390 should be stained with Gomori trichrome or Heidenhain's iron haematoxylin. Cysts and commensal trophozoites of E. histolytica found in wet faecal mounts are indistinguishable from those of E. dispar. The cysts of both species are four-nucleated and can be differenti- ated from the smaller E. hartmanni using an eyepiece micrometer. Direct mounts are made by emulsifying a small portion of stool in 1% eosin and in Lugol's iodine; however, the diagnostic sensitivity, per specimen, is only about 30%. Concentration methods for cysts such as formol-ether sedimentation give a 70% sensitivity per spe- cimen. Cultivation of intestinal amoebae from faeces in Robinson's medium is relatively easy. Species identification requires immuno- fluorescent staining. Amoebae are often difficult to find microscop- ically in liver aspirates. Positive cultures from extraintestinal sites do confirm invasive E. histolytica. DNA and immunological tests PCR methods can now be used for both E. histolytica and E. dis par using either faecal or tissue material. E. histolytica antigen can be detected in faecal specimens, and assays for antigen in serum have also been used in extraintestinal disease. These new methodologies have excellent sensitivity and specificity. Where they are available, they greatly simplify diagnosis in both amoebic disease and in carriers. They are already revolutionizing our ideas on epidemiology.
E. histolytica DNA can now be detected in the blood, urine, and saliva of patients with invasive disease using real-time PCR assay. Many serodiagnostic methods have been applied to amoeb- iasis. The most detectable antibody is IgG, with some IgM in ac- tive disease. However, seropositivity does not distinguish current and past tissue invasion. The more sensitive methods are indirect haemagglutination, enzyme immunoassay, and indirect immuno- fluorescence. Latex agglutination and gel-diffusion precipitation are also used, the former being commercially available as a slide test, taking only minutes to perform. Using sensitive tests, over 95% of patients with liver abscess are seropositive, as are about 60% of those with invasive bowel disease; patients with amoeboma are nearly all seropositive. All patients with tissue invasion eventually become seropositive. Titres decline after therapy but may remain positive for 2 years or more with the most sensitive tests. Patient management Chemotherapy Metronidazole for 5 days will be the first choice in most patients. The usual adult dose of metronidazole is 800 mg thrice daily for 5 or 8 days; the daily paediatric dose is 35 to 50 mg/kg in three div- ided doses. The alternative is tinidazole, which has the advantage of a single daily dose, 2 g in adults and 50 to 60 mg/kg in children. A 5- or even a 3-day course may be sufficient for tissue amoebae but rates of parasite elimination from the intestine are low. When nitroimidazoles are contraindicated, or not available, erythromycin is useful in non-severe colitis. The synthetic derivative dehydroemetine is a potent tissue amoebicide. It has less cumulative cardiotoxicity than the alkaloid emetine and is more rapidly excreted in the urine. Where appro- priate nitroimidazoles are unavailable, as continues to be the case in some tropical contexts, this drug will continue to be lifesaving, especially when a parenteral drug is needed.
A daily intramuscular dose of dehydroemetine of 1.25 mg/kg (maximum 90 mg) is given for 5 days. Cutaneous and genital amoebiasis responds well to metronida- zole, partly perhaps because the lesions often contain anaerobic bacteria. Amoebiasis at other sites is nearly always secondary to hepatic lesions and the chemotherapy will be the same. Metronidazole crosses the blood–brain barrier and should be used in the desperate situation of amoebic brain abscess due to E. histolytica. All patients with E. histolytica infection treated with a tissue amoebicide should also be given diloxanide to eliminate infection from the bowel and so prevent recurrence of tissue invasion or transmission to others. The dosage of diloxanide for adults is 500 mg thrice daily for 10 days; the daily dose in children is 20 mg/kg daily in three divided doses. Alternatives to diloxanide when it is not avail- able are paromomycin 30 mg/kg daily for 5 to 10 days or iodoquinol 650 mg thrice daily for 20 days, but iodoquinol may cause optic or peripheral neuropathy if the dose is

exceeded. Early re-infection with E. histolyica after diloxanide is reported to be a problem among male homosexuals in Japan. Convalescent carriers, and also infected family contacts, should always be treated. Persons entering temperate countries from the tropics or new residents from such countries should be screened if there is a significant risk of infection; those with E. his tolytica faecal antigen, or who are seropositive and have four-nu- cleated Entamoeba cysts in their stools, should be treated. In these contexts, diloxanide is the drug of choice. Metronidazole is less effective even using an 8-day course and side-effects are trouble- some. Unfortunately cure rates with tinidazole are very low when followed up at 1 month. Supportive and surgical management Intestinal amoebiasis Supportive management plays a major role in patients with com- plicated amoebic colitis, with emphasis on fluid and electrolyte re- placement, gastric suction, and blood transfusion as necessary. Gut perforation complicating extensive colitis carries a very poor prog- nosis; management may have to be medical. Parenteral metronida- zole is invaluable in these situations because of its activity against anaerobic bacteria in the peritoneum and blood stream. A cephalo- sporin plus gentamicin will normally be given as well. Amoebomas respond well to metronidazole; a slow response should arouse suspicion that the amoebic lesion is superimposed upon other pathology, particularly a carcinoma. Surgical manage- ment is important in several situations. Acute colonic perforation in the absence of diffuse colitis or ruptured amoebic appendicitis may be amenable to local repair. In the case of diffuse colitis, local repair, or end-to-end anastomosis, may not be possible because of the poor condition of the gut wall: temporary exteriorization with an ileos- tomy may be necessary. In fulminant colitis with multiple perfor- ation the viability of the gut wall is uncertain and the only definitive option is total colectomy. Hepatic amoebiasis A favourable response to medical treatment alone can be expected in about 85% of patients. Liver abscesses may rupture before, during, or after oral chemotherapy; this requires parenteral metronidazole or dehydroemetine. Intra-abdominal rupture will always require

 laparotomy. Extension into the pleural or pericardial cavities neces- sitates drainage of these structures, together with aspiration of the liver lesion; pericardial drainage is most urgent when tamponade is present. Hepatopulmonary lesions generally require drainage of the liver lesion but medical treatment alone has been successful in some cases. Antibiotics will always be needed when the abscess ruptures into the peritoneum or lung. The most common management problem is slow response to the amoebicide. Patients whose pain and fever do not subside by 72 h are at significantly greater risk of rupture or therapeutic failure, and aspiration is generally to be recommended. A likely explanation of poor initial response is a tense lesion that restricts drug entry. Regular ultrasonographic monitoring is of great value as it will in- dicate the risk of rupture and guide the aspiration procedure. No change in lesion size on ultrasound can be expected during the first 2 weeks, although its outline may become clearer. Percutaneous as- piration with a wide-bore needle will be possible in most patients; if unsuccessful or anatomically contraindicated, then surgical help should be sought. Catheter drainage is a better alternative to re- peated needle aspiration with large abscesses. Resolution times for small or moderate lesions are unaffected by aspiration. All patients with hepatic amoebiasis should be given diloxanide to eliminate bowel infection. Prognosis Uncomplicated invasive intestinal disease and uncomplicated hepatic amoebiasis should normally have a mortality rate of less than 1%. In complicated disease, the mortality is much greater and may reach 40% for amoebic peritonitis with multiple gut perfor- ation. Prognosis is usually better in centres where the disease is common and more likely to be recognized early. Late diagnosis increases the probability of complicated disease and mortality rises accordingly. Unless parasitological cure is achieved and the gut completely

freed of E. histolytica, clinical relapse is quite common, although probably limited by immunological responses. There is, so far, no evidence of naturally occurring strains of E. histolytica being resistant to normally used drugs. Hepatic scans show that nearly all liver abscesses completely disappear within 2 years; the median reso- lution time is 8 months. In secondarily infected lesions, bizarre hep- atic calcification may be seen years afterwards. Healing of the bowel is remarkably rapid and complete; occasionally fibrous strictures persist after severe dysentery. Prevention Chlorination of water supplies does not destroy amoebic cysts, but adequate filtration will remove them. Regular stool screening by microscopy of food handlers and domestic staff is of no value, but health education is important with encouragement to have a med- ical check if diarrhoea occurs. Visitors to the tropics should not attempt chemoprophylaxis; in particular, long-term unsupervised use of hydroxyquinoline drugs must be strongly deprecated. Simple hygienic measures provide considerable protection. Boiling water for 5 min kills cysts. Routine examinations in temperate countries for returning visitors from the tropics or for new residents coming from such countries is of no value unless E. histolytica can be differentiated from E. dispar. Amoebic serology is useful in those with gut symptoms or a history of dysentery. Other parasitic gut amoebae including Dientamoeba fragilis The nuclei of Entamoeba species have a fine ring of peripheral chro- matin and a small central endosome. Six cyst forming Entamoeba species are nonpathogenic colonic commensals. Entamoeba coli has eight-nucleated cysts and is the commonest species in most surveys. E. dispar and E. hartmanni both have cysts with four nu- clei; the former was previously known as ‘nonpathogenic E. his tolytica’ and the latter as ‘small race E. histolytica’. Size is the only microscopic diagnostic criterion for E. hartmanni; its cysts are less than 10 μm in diameter. The relative prevalence of E. dispar and E. histolytica varies greatly, but the former is usually much more common, especially where sanitation and water supplies are better. E. chattoni is primarily a pig and primate parasite; the cyst has one nucleus and an ‘inclusion body’. Human infections are common in highland Papua New Guinea where humans and pigs may share a peridomestic environment; elsewhere it is rare. Recently an- other species E. bangladeshi has been found to be quite common in Bangladesh infants. Lastly there is E. moshkovskii, which nor- mally lives in soil and sewage; it infects and can be transmitted between humans. It was previously incorrectly referred to a low- temperature variant of E. histolytica. It should be mentioned that the complete nonpathogenicity of E. dispar, at least in experimental animals, has been challenged. E. gingivalis has no cystic stage and lives in the mouth within gin- gival pockets and tonsillar crypts. It is spread by kissing or more indirect oral contact. Its possible role in periodontal disease was for- merly dismissed but there is now renewed interest following recog- nition of its high prevalence in individual lesions in people with this condition; it may act as a bacterial vector within the lesions. It has been found on intrauterine devices, sometimes causing symptoms. Both in the uterus and in the mouth, this amoeba occurs in associ- ation with the bacterium Actinomyces israelii. Endolimax nana and Iodamoeba bütchlii both have nuclei with large endosomes and no visible peripheral chromatin. Cysts of the former are oval in shape with four nuclei; those of the latter are somewhat irregular in shape with a single nucleus and a large glycogen vacuole that stains prominently with iodine. Neither spe- cies is pathogenic. Dientamoeba fragilis is overlooked in most parasitological labora- tories and most reports are from developed countries. There is good evidence that it can cause colonic inflammation; however, this is not severe and there is no ulceration or systemic spread. No cystic stage is found using standard methods and, unless this organism is specif- ically looked for, it will be missed. In fixed stained smears, about 60% of trophozoites have two nuclei; the endosome is large and lobulated and there is no peripheral chromatin. Using special techniques, however, both cysts and precysts have recently been demonstrated in stools. Infected

patients may shed the parasite intermittently. Alternatively, D. fragilis may be identified in faeces or cultures using immunofluorescence with specific antibody or of parasite DNA by PCR; some patients are seropositive. Transmission is direct but

section 8 Infectious diseases 1392 possibly within eggs of the threadworm Enterobius. It causes a rela- tively mild diarrhoeal illness that may persist for several weeks and sometimes there is a superficial eosinophilic colitis. Irritable bowel syndrome may be suspected. Protein-losing enteropathy is reported and blood eosinophilia is quite common. This infection is frequent in some institutional contexts. It is found within some resected ap- pendices but a causal role is unlikely. Electron micrographs and gen- etic studies indicate that D. fragilis is a trichomonad rather than a true amoeba. The infection responds to metronidazole, but a single dose of ornidazole is also effective. Series of symptomatic patients who improve after treatment continue to be reported, but in a recent placebo-controlled study in Danish children metronidazole treat- ment conferred no benefit. Free-living amoebae A shared feature of these species is the very large central nuclear endosome, quite different from that of E. histolytica, from which dif- ferentiation may be necessary in tissue sections. Under dry condi- tions, trophozoites form resistant cysts that permit survival and also airborne dispersal; cysts can resist chlorination. Many species are thermophilic and they are one of the causes of ‘humidifier fever’, a form of extrinsic allergic alveolitis presenting with fever, cough, and dyspnoea. Some bacteria including Legionella and Parachlamydia acanthamoebae may live symbiotically within these amoebae per- sisting within the phagosome, being resistant to lysosomal enzymes. Surprisingly, Legionella can survive encystment: the amoebae pro- vide a refuge for these bacteria when chlorination or other anti- bacterial measures are applied. Four groups of free-living amoebae cause human infections: 1 Naegleria fowleri is an amoeboflagellate with two trophozoite forms. The amoeba moves rapidly with a single pseudopodium, it can transform into a nonfeeding flagellate in hypotonic media, and these free-swimming forms facilitate dispersal. Cysts are thin walled and spherical. 2 Acanthamoeba has no flagellate form. The small pseudopodia are multiple, thin, and spike-like; they are called acanthopodia Fig. 8.8.1.9). Cysts are thick walled, angulated, and buoyant Fig. 8.8.1.10); their dispersal may be wind borne. Several species are pathogenic but morphological classification is unsatisfac- tory; rRNA sequences differentiate 15 genotypes. Acanthamoeba is sometimes isolated from throat or nasal swabs or from stool specimens. 3 Balamuthia is closely related to Acanthamoeba and not a leptomyxid amoeba; it shows little directional movement and has an irregular or branched shape. Cysts are thick walled and spherical. Human infections formerly attributed to Hartmanella are now all thought to be due to Balamuthia mandrillaris, a species described in 1993 from a mandrill baboon that died of meningoencephalitis in San Diego zoo. Balamuthia can only be cultured on tissue culture monolayers. About 200 cases have been reported worldwide, with many from Latin America. 4 Sappinia pedata has caused at least one case of granulomatous amoebic encephalitis. Its trophozoites contain a double nucleus and when living the ectoplasm has a rippled appearance. Primary amoebic meningoencephalitis due to
Naegleria fowleri Epidemiology and pathology In temperate countries most patients give a history of swimming or diving in warm fresh water or spa water between 2 and 14 days before the illness began, common-source outbreaks occur during warm summer months. Amoebic trophozoites cross the cribriform plate from the nasal mucosa to the olfactory bulbs and subarachnoid space. At autopsy the brain shows cerebral softening and damage to the olfactory bulbs; cysts are never formed in the tissues. The first human case was reported in 1965, at least 450 cases have now been reported from temperate countries, some retrospectively, and many Fig. 8.8.1.9

Acanthamoeba trophozoite showing spike-like acanthopodia. Courtesy of the late Professor Sornchai Looareesuwan. Fig. 8.8.1.10 Acanthamoeba cysts. Copyright Viqar Zaman.

8.8.1 Amoebic infections 1393 from the United States of America. Some are undoubtedly missed clinically and are discovered at autopsy or in preserved pathological material. Specific antisera enable amoebae to be recognized by im- munofluorescence staining. In the tropics this is an emerging problem that is being increas- ingly recognized, for instance in Pakistan. High temperatures and lack of clean water for washing encourage bathing in waters con- taining N. fowleri. In addition, religious practices and ablutions add to the risk. A particular local hazard is nasal irrigation from a spouted pot called a 'neti'. Clinical features and diagnosis Patients are immunocompetant; most are young adults and chil- dren. Initial nasal symptoms and headache are soon followed by fever, neck rigidity, coma, and, later, convulsions; most die within a few days. Cerebrospinal fluid is often turbid and bloodstained with high protein, low glucose, and neutrophils. Amoebae must be urgently looked for in wet specimens using phase-contrast mi- croscopy. Unless amoebae are seen, bacterial meningitis will be sus- pected; on Gram staining amoebae appear as indistinct smudges. Fixed preparations stained with iron haematoxylin will show full details of nuclear structure. Confirmation is by culture at 37°C using a bacterial lawn on nonnutrient agar. Amphotericin B can be an effective drug, it should be given by daily intravenous infusion, and intrathecally; other additional drugs that have been used are intra- venous fluconazole and rifampicin; in mouse models, azithromycin is effective. So far, very few patients have survived but this may partly be due to diagnostic delays. Cadaver organ donation from such pa- tients carries potential risk. Amoebic keratitis due to Acanthamoeba Most patients, but not all, are contact lens users; some are using disposable lenses. Among contact lens users, annual incidence rates of 1.49 and 0.33 per 10 000 are reported from Scotland and Hong Kong, respectively, but most figures are lower. Risk factors include poor hygiene when handling lenses and their cases, use of chlorine-based disinfectants, swimming or washing eyes while wearing lenses, handling lenses after gardening, and too pro- longed use of plastic or unwashed lenses. The most appropriate disinfectants are chlorhexidine and hydrogen peroxide. Corneal lesions are painful with photophobia, and present as indolent and progressive ulcers leading eventually to perforation. Recognition may be in the context of lesions unresponsive to anti- biotics or corticosteroids. Differentiation must be made from commoner causes of microbial keratitis, including Pseudomonas, Staphylococcus, and herpes simplex. Inflammatory cells are mainly neutrophils. Infection may be by wind-borne cysts upon a damaged epithelium or from contact lenses. Solutions used to store or wash lenses can be contaminated by these amoebae, many of which are resistant to some antiseptics, especially as cysts. Amoebae are found in corneal scrapings or histologically in corneal tissue, but can be missed unless stained with special stains or by immunofluorescence. PCR and DNA methods are now available. Cysts may be seen in tissue. Cultures from fresh material, using a bacterial lawn on non- nutrient agar, should be at 30°C. The majority (90%) of cases are due to genotype T4. Early aggressive topical treatment is with chlorhexidine 0.02% with a aromatic diamidine such as 0.1% propamidine or 0.1% hexamidine, plus neomycin. Both trophozoites and cysts must be destroyed. Hourly application is needed for three days and then 3-hourly for 3–4 weeks. Regular surgical debridement may be needed and sometimes corneal grafting. Topical steroids are not recommended. Granulomatous amoebic encephalitis due to Acanthamoeba, Balamuthia, and Sappinia The main route of infection is the lower respiratory tract followed by haematogenous spread to the brain. Other routes of entry are the skin (Fig. 8.8.1.11a), the nasopharynx (Fig. 8.8.1.11b), the lungs and the stomach. Primary lesions have

been described at all these sites. Soil contamination of skin and craniofacial wounds is an important risk factor. Almost all patients infected by Acanthamoeba are immunocom- promised; this is associated with malignancy, collagen disorder, alcoholism, diabetes mellitus, AIDS, and steroid or immunosup- pressant therapy, including that used in transplant patients. More patients with B mandrillaris are now being reported, many immuno- compromised, but in Peru most of the patients are not. These infections are now important in transplantation medi- cine. Acanthamoeba encephalitis has been reported in immunosup- pressed transplant recipients of liver or haematopoietic stem cells. Transplant donors can also be the source of infection. In 2009 two patients with B. mandrillaris were reported who received kidney graft from the same donor. In 2010 four patients received organs from a presumed stroke patient. Two recipients developed B. man drillaris encephalitis and died but two others who received heart and kidney transplants remained asymptomatic; the donor had had a large chronic skin lesion on his back and this was the presumed source of the infections. Pathologically lesions resemble chronic bacterial brain ab- scesses or localized subacute haemorrhagic necrosis; involvement of the meninges is common. Some patients present with head- ache and meningism, others with evidence of a focal brain lesion (Fig. 8.8.1.11c, Fig. 8.8.1.12). Unless these amoebae are found in wet tissue preparations or cerebrospinal fluid, the diagnosis will be usually based on histology, often at autopsy. Cysts may be seen in tissue but trophozoites may be missed unless stained with iron haematoxylin or immunofluores- cence using specific antisera. Cultural diagnosis at 37°C from fresh biopsies or cerebrospinal fluid is sometimes possible. PCR and DNA methods are becoming available. Survival of patients with this condition is still only rarely re- ported. Intracranial pressure can be relieved by mannitol and cerebrospinal fluid drainage, and total excision of cerebral le- sions is occasionally possible. Drug treatment with combinations of miltefosine, fluconazole, pentamidine, and cotrimoxazole, may be successful. Acanthamoeba encephalitis has been success- fully treated with cotrimoxazole plus rifampicin in a liver trans- plant recipient. Amoeba-infected skin lesions, especially following cranio-facial trauma, may precede the encephalitis by several weeks and should be recognized early and treated.

 FURTHER READING Gut amoebae Barwick RS, et al. (2002). Outbreak of amebiasis in Tbilisi, Republic of Georgia, 1998. Am J Trop Med Hyg, 67, 623–31. Diamond LS, Clark CG (1993). A redescription of Entamoeba histo lytica Schaudinn, 1903 (emended Walker 1911) separating it from Entamoeba dispar Brumpt, 1925. J Eukaryot Microbiol, 40, 340–4. Gilchrist CA (2014). Entamoeba bangladeshi: an insight. Trop Parasitol, 4, 96–8. Jha AK, et al. (2015). Clinicopathological study and management of liver abscess in a tertiary care center. J Nat Sci Biol Med, 6, 71–5. Karin IMA, et al. (2003). Entamoeba moshkovskii infection in children in Bangladesh. Emerg Infect Dis, 9, 580–4. Lau YL, et al. (2014). Molecular detection of Entamoeba histolytica and Entamoeba dispar infections among wild rats in Kuala Lumpur, Malaysia. Tropical Biomedicine, 31, 721–7. Marie C, Petri WA Jnr. (2014). Regulation of virulence of Entamoeba histolytica. Ann Rev Microbiol, 68, 493–520. Nagata N, et al. (2012). Risk factors for intestinal invasive amoebiasis in Japan, 2003–2009. Emerg Infect Dis. 18, 717–24. Nespola B, et al. (2015). First case of amoebic liver abscess 22 years after the first occurrence. Parasite, 22, 20. Oliveira FMS, et al. (2015). Entamoeba dispar: could it be pathogenic. Trop Parasitol, 5, 9–14. Panja SK, et al. (2014). Laboratory methods of identification of Entamoeba histolytica and its differentiation from look-alike Entamoeba spp. Trop Parasitol, 4, 90–5. Singh O, et al. (2009). Comparative study of catheter drainage and needle aspiration in management of large liver abscess. Ind J Gastroenterol, 28, 88–92. (a) (b) (c) Fig. 8.8.1.11 Balamuthia mandrillaris infection. Cases at Instituto de Medicina Tropical ‘Alexander von Humboldt’ Universidad Peruana Cayetano Heredia,

Lima, Peru: (a) cutaneous lesion in a 26-year-old man from Ica, (b) perforating lesion of palate in 16-year-old boy from Piura, and (c) encephalitis in a 57-year-old man from Piura showing the skin lesion that was the likely portal of entry. Copyright D. A. Warrell. Fig. 8.8.1.12 Balamuthia mandrillaris infection. MRI scan in same patient as in Fig. 8.8.1.11c. Copyright D. A. Warrell.

Revision #1
Created 2026-01-22 16:46:04 UTC by Omar Ayman
Updated 2026-01-22 16:46:04 UTC by Omar Ayman