Pyogenic and Amebic Liver Abscesses

Jayde E. Kurland, MD and Oscar S. Brann, MD

Address
Department of Gastroenterology, Naval Medical Center San Diego, 34800 Bob Wilson Drive, San Diego, CA 92134, USA.
E-mail: jekurland@NMCSD.med.navy.mil

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Pyogenic and amebic liver abscesses are the two most common hepatic abscesses. Amebic abscesses are more common in areas where *Entamoeba histolytica* is endemic, whereas pyogenic abscesses are more common in developed countries. Pyogenic abscess severity is dependent on the bacterial source and the underlying condition of the patient. Amebic liver abscess is more prevalent in individuals with suppressed cell-mediated immunity, men, and younger people. The right lobe of the liver is the most likely site of infection in both types of hepatic abscess. Patients usually present with a combination of fever, right-upper-quadrant abdominal pain, and hepatomegaly. Jaundice is more common in the pyogenic abscess. The diagnosis is often delayed and is usually made through a combination of radiologic imaging and microbiologic, serologic, and percutaneous techniques. Treatment involves antibiotics along with percutaneous drainage or surgery.

Introduction

Hepatic abscesses are infectious, space-occupying lesions in the liver. The two most common hepatic abscesses are pyogenic and amebic. Most hepatic abscesses in developed countries are pyogenic. Hepatic abscesses can be elusive in their clinical presentation but can be fatal if not diagnosed and treated promptly. This article provides an overview of the epidemiology, pathophysiology, clinical and imaging features, and treatment of pyogenic and amebic hepatic abscesses.

Pyogenic Abscess

Historical background and epidemiology

Historically, pylephlebitis, due to appendicitis and diverticulitis, was the most common cause of pyogenic abscess and carried a mortality rate approaching 80%. The diagnosis was made by clinical impression and plain film until the 1960s. Most of these patients had multiple abscesses. With the advent of improved imaging techniques and procedures, the diagnosis, treatment, and survival of patients with pyogenic abscesses have markedly improved. Over time, the incidence has increased from 13 to 20 cases per 100,000 hospital admissions [1•], whereas the mortality rate now ranges between 10% and 26% [2]. In the past, abscesses were located in both lobes of the liver 49% of the time. Today, they are located in the right lobe of the liver 75% of the time. Male and female patients are equally affected. The average age at presentation is between 50 and 60 years.

Differential diagnosis

The differential diagnosis of a hepatic pyogenic abscess includes solid tumor, lymphoma, hemangioma, alcoholic or viral hepatitis, liver cyst, mycobacterial infection, hepatosplenic candidiasis, amebic liver abscess, echinococcal infection, ascending cholangitis, cholecystitis, and appendicitis.

Pathophysiology

Abscesses can be divided into six categories based on the route of hepatic infection. These include 1) biliary source (60%); 2) portal vein seeding (7%); 3) direct extension (3%); 4) hepatic artery seeding (10%); 5) cryptogenic (17%); and 6) penetrating trauma (5%) [1•]. Abscesses that stem from the biliary tract can be divided into malignant and nonmalignant causes. Concerning malignant causes, pancreatic adenocarcinoma has been surpassed in recent decades by cholangiocarcinoma. Liver metastasis has also increased as a malignant biliary cause of pyogenic abscess. Nonmalignant sources include biliary stones, biliary strictures, and Caroli's disease. Portal vein seeding can be from a pelvic abscess, diverticulitis, postoperative infection, inflammatory bowel disease, or appendicitis. Direct extension causing pyogenic abscess can occur from the gallbladder, subphrenic space, or perinephric space. Pyogenic abscesses may be iatrogenic. Biliary-enteric anastomosis, biliary diversion, tumor ablation, and liver transplantation are examples of iatrogenic causes. Hepatic artery seeding can be caused by hepatic artery thrombosis, bacteremia, line sepsis, or endocarditis. Bloodborne infections go through the hepatic artery to create multiple hepatic abscesses. Seeding from the hepatic artery has increased because of the increased prevalence of immunosuppressed patients and the use of hepatic artery chemoembolization.

Symptoms and signs

The most common presenting symptoms are fever (78%–89%), right-upper-quadrant abdominal pain (27%–48%), nausea and vomiting (43%), malaise (11%–47%), chills (46%–49%), and weight loss (13%–43%) [1•,3,4]. Pyogenic liver abscesses should be considered in the differential diagnosis in elderly patients with fever of unknown origin. Common physical signs are right-upper-quadrant abdominal tenderness (43%–70%), jaundice (22%–55%), and hepatomegaly (28%–48%) [1•,5,6].

Laboratory findings

Laboratory evaluation often reveals elevated alkaline phosphatase (70%), aspartate aminotransferase (64%), alanine aminotransferase (67%), and total bilirubin (49%) levels. Aspartate aminotransferase, lactate dehydrogenase, and bilirubin are more elevated than in amebic liver abscess (ALA). Also observed are anemia (77%), leukocytosis (75%–85%), prolonged prothrombin time (62%), and hypoalbuminemia (71%). An elevated globulin level greater than 3 g/dL has been reported.

Risk factors

Variables that predict a complicated course include decreased hemoglobin (<10 g/dL), bacteremia, polymicrobial infection, hypoalbuminemia (<2 g/dL), elevated prothrombin time, and septic shock on presentation. One study noted an increased risk of mortality with the following factors: biliary source, underlying malignancy, shock, multiple abscesses, low hemoglobin level (<10 g/dL), old age, and high blood urea nitrogen [7].

Diagnosis

Imaging

Imaging is necessary to document the number, location, and possible source of the pyogenic abscess. CT scanning is 93% to 96% accurate in diagnosing pyogenic liver abscess, compared with ultrasound (83%). CT scanning with intravenous contrast is preferred because it can also detect the source of the abscess, such as malignancy. Abscesses appear as hypodense lesions that do not enhance with intravenous contrast on CT scan (Fig. 1). Abscesses appear either as unilocular with smooth outer margins or multilocular with irregular margins. Rim enhancement, which indicates inflammation, is a hallmark finding but is only found in 6% of patients [8]. A halo (edema) around the abscess is rare but supports the diagnosis of pyogenic abscess.

The sonographic appearance of pyogenic abscesses can be hypoechoic or hyperechoic with internal debris. Hepatic neoplasms may have a similar sonographic appearance, with septations and internal debris. The location of the abscess is not usually contiguous with the liver capsule. Abscesses caused by hepatic artery thrombosis after liver transplantation are best assessed by Doppler ultrasound or angiography. Abscesses appear hypointense on T1-weighted magnetic resonance imaging (MRI) and hyperintense on T2-weighted MRI. Abdominal radiography reveals gas within the abscess 40% to 50% of the time. When imaging and clinical evidence do not reveal biliary tract disease or pylephlebitis, aggressive evaluation of the intestinal tract is not necessary [5].

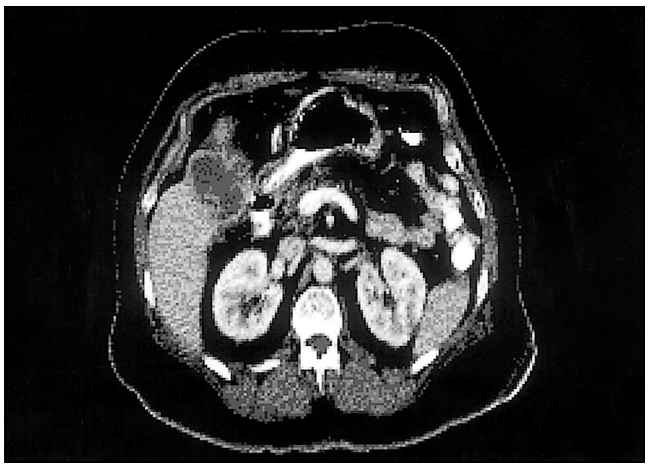

Figure 1. CT scan revealing a right-lobe pyogenic hepatic abscess with septations.

Microbiology

Bile cultures are positive 95% of the time, and blood cultures are positive 52% of the time [1•,5]. Twenty-five percent of pyogenic abscesses have resistant organisms due to exposure to broad-spectrum antibiotics, biliary stents, and immunocompromised status of patients. The most common organism in North America is *Escherichia coli*, followed by *Klebsiella* and *Streptococcus* species. *K. pneumoniae* is surpassing *E. coli* as the most common organism in the Far East [9]. Enterococci and *S. viridans* are commonly found in polymicrobial abscesses. Nearly half of pyogenic abscesses are polymicrobial. Enterococci and enteric Gram-negative organisms are commonly isolated when the abscess is caused by biliary disease. Coliforms and anaerobes (*eg, Bacteroides fragilis*) are more common when there is portal seeding. With a history of penetrating trauma, *Staphylococcus aureus* and *S. pyogenes* are usually the bacteria isolated from the abscess.

Treatment

Antibiotics should be started as soon as a pyogenic abscess is suspected. Delaying therapy until percutaneous aspiration is not recommended because of the high mortality. Parenteral broad-spectrum antibiotics are recommended to cover enteric Gram-negative rods, anaerobes, and enterococci (Tables 1 and 2) [11••]. The combination of ampicillin, gentamicin, and metronidazole is cost-effective antibiotic coverage. Ampicillin covers enterococci and metronidazole covers anaerobes as well as *Entamoeba* species. However, *Klebsiella* species are highly resistant to ampicillin, and β-lactamase inhibitor should be considered [12]. Cefoxitin can be substituted for ampicillin but will not cover enterococci. Anaer-

Table 1. Antibiotic therapy for biliary source of pyogenic abscess

Medication	Special consideration
Ampicillin and gentamicin	—
Cefoxitin and metronidazole	If renal insufficiency; does not cover *Enterococcus*
Imipenem or meropenem	May not cover *Enterococcus* [10]
Third-generation cephalosporin and gentamicin, metronidazole	If allergic to penicillin
Vancomycin, gentamicin, and metronidazole	If allergic to penicillin

Table 2. Antibiotic therapy for nonbiliary source of pyogenic abscess

Third-generation cephalosporin and metronidazole
Imipenem or meropenem or antipseudomonal penicillin with β-lactamase inhibitor and metronidazole
Fluoroquinolone, metronidazole ± aminoglycoside (quinolones are more costly)

Adapted from Johannsen *et al.* [11••]

obes, particularly *B. fragilis*, are resistant to clindamycin, and its use should be limited [13].

Antibiotics are usually necessary for 4 to 6 weeks and should be tailored to the specific microbiologic diagnosis. Oral antibiotics can be started once the abscess has been drained and the patient is stable.

Percutaneous abscess drainage is considered the gold standard procedure. Success rates range from 80% to 87%. Catheter displacement can be prevented by suturing the catheter to the skin or using a securing disk. The catheter should be irrigated with saline solution every 8 hours with an amount sufficient to fill up to one third of the cavity. The catheter is usually removed when the patient is afebrile, the leukocyte count has normalized, and catheter drainage is less than 10 mL over 24 hours. Catheters can usually be removed between 5 and 7 days after placement [14•]. In general, an imaging study of the cavity is used to confirm adequate drainage. The risks of percutaneous abscess drainage include empyema, pneumothorax, catheter dislodgement, hemorrhage, sepsis, intraperitoneal leakage, broncho-pleural-hepatic fistulae, and subphrenic abscess. Cultures should not be taken from preexisting drains because they are not accurate.

Percutaneous aspiration with antibiotics but without drainage is controversial. The aspirate is purulent, thick, and foul smelling. One study using this method reported a 98% success rate with no deaths or recurrence [15]. In this study, an average of 2.2 aspirations per patient was reported in 115 patients with pyogenic liver abscesses. The authors used saline irrigation and intracavitary antibiotics in this study, but only in carefully selected patients. The best candidates for this treatment are patients with a solitary cryptogenic abscess of 1 to 3 cm in size. There must be a low threshold to drain the abscess if the patient does not respond to aspiration (persistent fever, pain, tenderness in the right upper quadrant, and leukocytosis). The risks of percutaneous aspiration include bile peritonitis, biliocutaneous fistulae, and abscess recurrence. Percutaneous aspiration is relatively contraindicated in patients with multiloculated abscesses [16].

Endoscopic and interventional biliary ductal drainage is necessary for diffuse microabscesses caused by biliary obstruction. A percutaneous drain alone is unlikely to cure a pyogenic abscess from a biliary source without endoscopic treatment of the biliary source first.

Open surgical drainage is reserved for patients who fail percutaneous drainage, require surgical management of the underlying problem (*eg*, biliary tract disease), or have an intra-abdominal abscess, and in some patients with multiple abscesses, multi-septated lesions, or lesions that are inaccessible by the percutaneous route. Surgical drainage entails aspiration, core biopsy, irrigation, and catheter placement. A transperitoneal approach is usually employed to inspect the peritoneal cavity. Patients with large intrahepatic stones or abscesses in segments II or III of the liver, or those who fail drainage, should undergo hepatic resection.

Percutaneous needle aspiration has a success rate of 73% to 98% [15,17,18]. Percutaneous catheter drainage has a success rate of 70% to 93% [2,19,20]. The mortality rate ranges between 5% and 6% with the percutaneous approach [5]. The mortality rate for surgical management ranges between 12% and 26% [21– 23].

A follow-up CT scan is recommended 1 to 2 months after treatment with antibiotics. The associated medical conditions (*ie*, cancer or biliary tract obstruction) will influence the patient's outcome.

Complications

Rupture of a pyogenic abscess occurs infrequently into the pericardial or peritoneal space. Other reported complications include pleural effusion, empyema, and broncho-pleural-hepatic fistulae.

Amebic Abscess

Historical background and epidemiology

Amebic liver abscess is the most common extraintestinal site of infection but occurs in less than 1% of *E. histolytica* infections. It has a high endemic prevalence in Mexico, the Indian subcontinent, Indonesia, sub-Saharan and tropical regions of Africa, and parts of Central and South America. ALA are three to 10 times more common in men [24], and patients most commonly affected are aged between 20 and 40 years [25]. Usually patients with ALA have recently traveled to or emigrated from an endemic area.

Pathophysiology

The *E. histolytica* cyst is ingested via contaminated water or food. It then travels to the small bowel, where excystation takes place. The trophozoite migrates to the colon, where it penetrates the mucosa. Trophozoites are then carried through the portal venous system to form a hepatic abscess. Five mechanisms of virulence are known in which *E. histolytica* is pathogenic to humans. Galactose-inhibitable lectin adhesin (Gal/GalNAc) on the parasite surface allows attachment to the colonic mucosa and invasion of the colon. In addition, the lectin prevents the membrane attack complex C5b-C9 from forming, making the ameba resistant to complement-mediated lysis. Cysteine proteinases lyse host cells, facilitating penetration through the extracellular matrix of the colon. Cysteine proteinases also activate complement but inactivate C3a and C5a anaphylatoxins, causing further resistance to lysis of the trophozoites. Pore-forming peptide and phospholipases cause tissue lysis and necrosis [26•]. Finally, the ameba is able to resist the respiratory burst, antigen presentation by class II major-histocompatibility-complex, tumor necrosis factor production, and hydrogen peroxide release by macrophages.

The three stages of abscess formation are 1) acute inflammation; 2) granuloma formation; and 3) necrosis with necrotic abscess or periportal fibrosis.

Symptoms and signs

Amebic liver abscesses usually appear 8 to 20 weeks (median, 12 weeks) after the patient has left an endemic area. However, ALA can occur as early as 4 days after exposure [27].

Patients with an amebic liver abscess are often more acutely ill than those with pyogenic abscesses. Diarrhea occurs in up to one third of patients with ALA. Concurrent ALA and amebic dysentery are unusual. Patients with ALA present with high fever more frequently than in pyogenic abscess. They also have a higher prevalence of septic shock. ALA patients are more likely to have a history of recent travel from an endemic area. Common clinical symptoms include fever (69%–87%), right-upper-quadrant abdominal pain (54%–67%), weight loss (45%), and nausea (85%) [28]. Jaundice is uncommon (10%) and is a sign of severe disease. The most common sign is liver tenderness, which occurs in 92% of patients.

Amebic infection can be acute or chronic based on the duration of symptoms, with acute defined as less than 10 days of symptoms and chronic as more than 2 weeks. Acute infection occurs infrequently and is more aggressive. Symptoms and signs include high fever, tender liver, elevated aspartate aminotransferase, and normal alkaline phosphatase level. Acute amebic abscess presents with a single lesion in the right lobe of the liver 50% of the time. Chronic infection presents with low-grade fever, a mildly tender liver, anemia (hemoglobin <10 g/dL), and elevated alkaline phosphatase; elevated aspartate aminotransferase is seen in 25% of patients. More than 80% of chronic infection is presented with a large solitary right-lobe abscess. Seventy-five percent of amebic abscesses are found in the right lobe of the liver. Response to amebicidal therapy is similar in the acute and chronic forms of infection [29].

Laboratory findings

Laboratory evaluation reveals leukocytosis and elevated alkaline phosphatase (>75% of the time), erythrocyte sedimentation rate, and C-reactive protein [30]. Significant elevation of bilirubin is uncommon. Eosinophilia is not present and if noted should prompt a search for another parasitic source.

Risk factors

Susceptible hosts include patients with HIV infection, hypoalbuminemia, chronic infection, tuberculosis, syphilis, or splenectomy. Any condition that affects cell-mediated immunity makes a patient more susceptible to amebic abscess. Malignancy, corticosteroid use, malnutrition, institutionalization, pregnancy, extremes of age, and homosexual activity are known risk factors for developing severe disease [31].

Poor prognostic factors predicting increased morbidity and mortality include multiple abscesses, volume greater than 500 mL, elevated right hemidiaphragm or pleural effusion on chest radiography, encephalopathy, bilirubin greater than 3.5 mg/dL, anemia (hemoglobin <10 g/dL), albumin less than 2 g/dL, and diabetes [32].

Diagnosis

Serology

Amebic serology usually confirms or excludes the diagnosis of ALA. However, a negative serology does not completely exclude the diagnosis. Indirect hemagglutination (IHA) is the most sensitive test (90%) and is positive in 90% to 100% of patients with hepatic abscesses. However, the antibody may be negative early in infection. If initial studies are negative and clinical suspicion is high, serology should be repeated 7 days later. IHA can remain positive for up to 20 years and can represent a previous infection; however, IHA is being replaced by EIA (enzyme immunoassay) [24]. IgG-EIA has a sensitivity of 99% and a specificity of 90% with ALA [33]. Polymerase chain reaction studies using the amebic 16S ribosomal RNA on aspirated material from the liver abscess can be helpful if the IHA titer is not significantly elevated. Serologic tests are more useful in detection of ALA than are stool antigen or stool microscopy.

Imaging

It is difficult to differentiate pyogenic from amebic abscess by imaging alone. Therefore, needle aspiration may be necessary to exclude pyogenic abscess. The fluid from an ALA is odorless unless secondarily infected. The reddish-brown anchovy paste appearance of the aspirate, which is pathognomonic, indicates that the abscess has been present for weeks and is not found in the majority of patients. Amebic

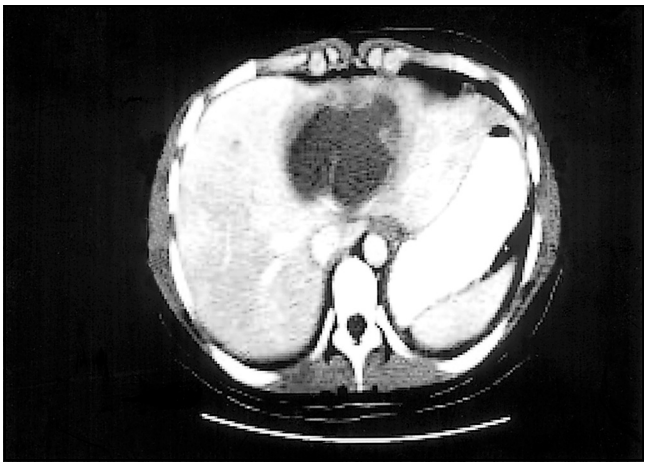

Figure 2. CT scan showing a large left-lobe amebic liver abscess.

trophozoites are located only in the wall of the abscess. The rest of the abscess is composed of lysed leukocytes. A negative Gram stain and culture increase the likelihood of an amebic abscess.

Sonographic features of amebic abscesses include absence of significant wall echoes (abrupt transition between liver and abscess); oval or round shape; hypoechoic lesion that is homogeneous; location near the liver capsule; and enhanced through transmission of sound deep to the lesion [34].

The contrast CT appearance is usually rounded and well defined. There is hypodense attenuation between 10 and 20 Hounsfield units (Fig. 2) [35]. An enhancing wall of edema around the abscess is common. Septations within the cavity can be observed. T1-weighted MRI reveals well-defined margins. Fifty percent of these patients have an elevated right hemidiaphragm on chest radiography.

Technetium sulfur colloid nuclear scanning was used in the past for differentiating ALA from pyogenic abscess. The amebic abscess appeared cold with a "hot" halo or rim (leukocytosis) surrounding the abscess. Contrast CT and ultrasound have largely replaced this modality.

Both ultrasound and CT are used to guide percutaneous aspiration and drainage. Percutaneous aspiration of the abscess is indicated if there is concern for pyogenic abscess because one is not likely to aspirate trophozoites in ALA. Aspiration was once avoided based on the concern that, if the abscess were actually an echinococcal cyst, spillage could cause anaphylaxis. However, imaging-guided aspiration has been reported to be safe and effective [36]. Anti-helminthic coverage prior to aspiration is recommended if echinococcal infection is a concern.

Treatment

Metronidazole is the treatment of choice for ALA (Table 3). Treatment for 5 to 10 days is appropriate. Side effects of metronidazole include psychosis, seizures, disulfiram effect with alcohol, peripheral neuropathy, and a metallic taste. Chloroquine can be used as an alternative or adjuvant to metronidazole in extraintestinal disease. Side effects of chloroquine include diarrhea, abdominal cramps, cardiotoxicity, seizures, and hypotension. Tinidazole is preferable to chloroquine but is not available in the United States.

Luminal agents are used to eradicate intestinal colonization after amebicidal treatment of the liver abscess. Because intestinal infection precedes the amebic abscess, all patients should be treated with a luminal agent. Paromomycin and iodoquinol are available in the United States. One of the side effects of paromomycin is diarrhea. Iodoquinol is contraindicated in patients with hepatic insufficiency or hypersensitivity to iodine. Diloxanide furoate is available from the US Centers for Disease Control and is indicated in patients who fail to respond clinically to iodoquinol or paromomycin. Reinfection after treatment of invasive amebiasis is uncommon.

Aspiration of an amebic abscess is indicated when the cavity is greater than 5 cm or at high risk of rupture; if there is a left-lobe liver abscess (associated with higher mortality and higher frequency of peritoneal leak or rupture into the pericardium); and if the patient fails to respond clinically to an amebicidal agent within 5 to 7 days [37].

Cavities that are 6 cm or larger can be drained or aspirated. Percutaneous catheter drainage, as opposed to aspiration, is indicated in abscesses of the left lobe and large abscesses because of the potential for rupture into the pleural cavity or pericardium. Filice *et al.* [38] reported improved results with intracavitary metronidazole, compared with drainage or antibiotic therapy alone. Percutaneous catheter drainage is rarely necessary in ALA patients. Surgical drainage is indicated in large left-lobe abscesses that cannot be accessed percutaneously.

Timely diagnosis, testing, and treatment for concomitant HIV infection can improve patient outcomes with prompt antiretroviral therapy in addition to amebicidal therapy [39].

Complications

Rupture of an amebic liver abscess into the chest cavity occurs in 10% to 20% of patients, whereas rupture into the peritoneum occurs in only 2% to 7% [40]. Rupture into the chest cavity may lead to broncho-pleural fistulae, hepatobronchial fistulae, or empyema. Patients with rupture into the bronchial tract may develop a cough and complain of the taste of liver. Bacterial superinfection may occur. Left–hepatic lobe abscesses have been reported to rupture into the pericardium, causing tamponade, with a resulting high mortality rate. Rare cases of compression of the inferior vena cava and brain abscess have been reported.

Outcomes

Complete resolution of the cavity occurs in 3 to 9 months. Ten percent of patients have a cavity present for more than 6 months. Follow-up imaging studies are not necessary for

Table 3. Treatment of amebic liver abscess

Medication	Adult dosage	Pediatric dosage
Amebicidal agents		
Metronidazole	750 mg orally three times a day for 5–10 days; 500 mg IV every 6 hours for 5–10 days	30–50 mg/kg/d for 5–10 days orally in three divided doses; 15 mg/kg IV load followed by 7.5 mg/kg every 6 hours (maximum, 2250 mg/d)
Chloroquine (base)	600 mg/d orally for 2 days, then 300 mg/d orally for 14 days	10 mg /kg of chloroquine base
Luminal agents		
Paromomycin	30 mg/kg/d orally for 7 days in three divided doses	25 mg/kg/d orally for 7 days in three divided doses (maximum, 2 g/d)
Iodoquinol	650 mg orally three times a day for 20 days	30–40 mg/kg/d for 20 days in three divided doses (maximum, 2 g/d)
Diloxanide fureate	500 mg orally three times a day for 10 days	20 mg/kg/d in three divided doses

IV—intravenous.

patients who have clinical resolution of symptoms after an uncomplicated amebic abscess.

Conclusions

Pyogenic and amebic liver abscesses have many features in common. Diagnosis can be delayed because of vague clinical symptoms at presentation, and such a delay can adversely affect outcomes. Because of the difficulty in differentiating between these two types of abscesses in early presentation, antiamebic therapy is recommended in addition to broad-spectrum antibiotics.

In the West, pyogenic abscesses are more common. Pyogenic abscess is a disease of middle-aged to elderly patients and is related to underlying illness. Percutaneous aspiration and drainage are recommended early for diagnosis and treatment. However, medical therapy alone is effective for the amebic liver abscess. Mortality is low with amebic abscess compared with pyogenic abscess. Abscesses are slow to resolve. A multidisciplinary approach, including a gastroenterologist, radiologist, surgeon, and laboratory, is crucial for successful treatment of these infections.

Disclaimer

The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.

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