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Review: Modern Management of Liver Abscess

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Abstract

An encapsulated collection of suppurated material within the liver is termed a liver abscess, which may be caused due to bacterial, parasitic, or fungal infection. Liver abscesses can be divided into infectious, iatrogenic, and malignant. Infection spreading through the biliary tract is the most common cause now. *Escherichia coli*, the most common organism causing liver abscess two decades ago, is replaced by *Klebsiella pneumonia*, accounting for 50 to 70% of cases in the Asian subcontinent; however, liver abscesses due to *Entameba histolytica* are also found quiet often in day to day clinical practice. Risk factors associated with the development of liver abscess are increasing age, male sex, presence of underlying diabetes mellitus, liver cirrhosis, continuous use of proton pump inhibitors, and immunocompromised state. Fever and abdominal pain are the typical clinical symptoms of a liver abscess. Other common symptoms include nausea, vomiting, malaise, and chills. Tachycardia, right upper quadrant tenderness, and hepatomegaly are common examination findings. USG of the abdomen is performed in all suspected cases of liver abscess and has a sensitivity of 85%. Small abscesses, less than 3 to 4 cm, can be managed with antibiotics. Percutaneous drainage can be done either by single-time needle aspiration or catheter drainage.

Keywords

- amoebic liver abscess
- gastrointestinal infection
- liver abscess
- pyogenic liver abscess
- single time aspiration

Introduction

An encapsulated collection of suppurated material within the liver is termed a liver abscess, which maybe caused due to bacterial, parasitic, or fungal infection. Most liver abscesses are due to bacterial infections, which can be gram-positive cocci, gram-negative bacilli, or anaerobic organisms, and are known as pyogenic liver abscesses.[1] Various fungi can also lead to abscess formation in immunocompromised patients. According to classification, there are three types of liver abscess: infectious, malignant, and iatrogenic. The incidence of liver abscess varies between different regions. Its incidence is the highest in eastern countries, especially in Taiwan.[2] It is 275 per 1,00,000 hospital admissions in Taiwan compared with 2.3 per 1,00,000 cases in the USA. Antibiotics are sufficient to manage patients with a size of abscess less than 3 to 4 cm. Metronidazole should be part of the regimen prescribed initially for anaerobic cover and cover amoebic organisms. Abscess more than 5 cm requires pigtail catheter drainage in most cases. It is a better procedure with a higher success rate than a single-time aspiration, especially in abscess $>$ 5 cm.

Etiopathophysiology

Initially, appendicitis was the most common cause three decades ago; however, it has recently been replaced by

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Table 1 Etiology and mechanism related to liver abscess

Etiological organisms				Mechanism related
Gram negative aerobes	Gram-positive aerobes	Anaerobes	Miscellaneous	Portal pyemia
Klebsiella pneumoniae	*Enterococcus* sp.	*Bacteroides* sp.	*Actinomyces*	Ascending cholangitis
E. coli	*Staphylococcus aureus*	*Fusobacterium*	Tubercular	Malignant abscess
Pseudomonas sp.	*Streptococcus* sp.		*Candida albicans*	Iatrogenic (TACE, RFA)
Proteus sp.				Diverticulitis

biliary tract abnormality.[1] In immunocompromised patients, atypical organisms such as *Candida* and Cytomegalovirus can be causative organisms.(►**Table 1**). Mortality has significantly reduced over the past three decades and is estimated to be 10 to 20% of all cases.[3] We can divide liver abscesses into infectious, iatrogenic, and malignant categories.[4,5] Infections gain access either through hematogenous spread or through continuous spread by blunt or penetrating trauma.[4] Intra-abdominal infections are prone to spread to the liver, as in appendicitis and diverticulitis. Organisms are seeded via the portal vessels, and the liver is the first organ encountered by these organisms.[6,7] About 40 to 50% of liver abscess in today's world is due to biliary infections that develop in the setting of obstruction due to calculi, strictures, or malignancy.[8,9] Infection spreads to the liver parenchyma following the development of ascending cholangitis. *Escherichia coli*, the most common organism causing liver abscess two decades ago, is replaced by *Klebsiella pneumonia*, accounting for 50 to 70% of cases in the Asian subcontinent.[1,2] This organism is also consistent with the cases of liver abscesses in the western world. Other organisms that cause liver abscess are *Streptococcus* species, *Enterococcus*, anaerobes such as *Bacteroides* and *Peptostreptococcus*, and other gram-negative organisms.[2] Around two or more organisms are responsible for causing liver abscess in 24% of the patients.[5] In extraintestinal amoebiasis, trophozoites breach the mucosa of the colon and reach the liver via the portal circulation. The majority of patients with amoebic liver abscesses have no gastrointestinal symptoms. Stool microscopy for cysts and trophozoites is also negative in most cases.[10] Biliary procedures such as sphincterotomy and biliary stenting are rarely associated with iatrogenic liver abscess when the drainage is inadequate or stents are blocked. However, transarterial embolization (TACE), and radiowave frequency ablation (RFA), leads to necrosis of the parenchyma, thus leading to increased risk of abscess formation.[11] Surgical procedures that lead to disruption of the liver's blood supply carry a risk of ischemic parenchyma necrosis, which gets superinfected and causes abscess formation.[9] Malignant abscesses have been seen in three settings: secondary infection in the case of hepatocellular carcinoma and secondary infection in a metastatic lesion. Primary HCC can lead to central necrosis, which predisposes it to infection of that area, leading to an abscess. HCC can also obstruct the biliary tract, leading to ascending cholangitis and abscess. Abscess formation over metastatic lesions is, however, rare.

Risk Factors

Risk factors associated with the development of liver abscess are increasing age, male sex, presence of underlying diabetes mellitus, liver cirrhosis, continuous use of proton pump inhibitors, and immunocompromised state.[12–16] Roughly, two-thirds of all patients with liver abscesses are males in their fourth to fifth decades of life. Various studies did point toward diabetes mellitus being one of the significant risk factors for developing a liver abscess. Diabetes mellitus leads to altered neutrophilic function, including chemotaxis and phagocytosis. About 30 to 40% of patients presenting with liver abscess have an underlying diabetes mellitus.[16–18] Patients with cirrhosis of the liver are at 15.4 times higher risk of liver abscess development.[16] Prolonged and continuous use of proton pump inhibitors (PPIs) increases the gastric pH and weakens the hosts' natural defenses, making them more prone to developing a liver abscess. However, the dose–response relationship is still not well established.[14] Similarly, patients on immunosuppression and chemotherapy are at a higher risk of developing a liver abscess.

Clinical Features

Fever and abdominal pain are the typical clinical symptoms of a liver abscess. The classical clinical triad of symptoms, fever, pain abdomen, and malaise, is only present in one-third of the cases. Fever is the most commonly reported clinical symptom in most patients with a liver abscess.[19] Fever is high grade and associated with chills in cases of pyogenic liver abscess. Abdominal pain is commonly localized to the right upper quadrant. It may result from the inflammation of the liver capsule due to sub-capsular abscess, the stretch of the capsule due to hepatomegaly, or gall bladder wall edema. However, the absence of abdominal pain does not exclude the diagnosis. Other common symptoms include nausea, vomiting, malaise, and chills.[20–23] About one-fourth of the patients with a liver abscess develop jaundice and loss of weight, and 10% present with diarrheal illness.[4,14,24] Necrosis in liver parenchyma leads to bile duct damage, forming biliovascular fistulae, and jaundice.[9,25] Due to non-specific symptoms, the diagnosis can be delayed by 4 to 5 days. Tachycardia, right upper quadrant tenderness, and hepatomegaly are common examination findings associated with a liver abscess.[9] Around 50 to 60% of the patients present either with tenderness or hepatomegaly. However, right-sided pleural effusion, jaundice, ascites, Murphy's sign,

or hypotension are less common examination findings.[4] An elevated total leucocyte count (TLC), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and C-reactive protein (CRP) are some common laboratory findings seen in a liver abscess. Low hemoglobin and albumin are also observed frequently. Elevated ALP is seen in ~85% of the cases, with 50% of patients showing elevated ALT and bilirubin levels. Deranged international normalizing ratio (INR) is found in 13% of the cases.[4] However, most laboratory findings are non-specific and do not point toward a particular diagnosis.

Diagnosis

Imaging is the preferred modality to diagnose liver abscesses and helps find the underlying cause. It also identifies a possible predisposing risk factor such as cirrhosis or biliary tree disease. Imaging is also helpful for aspiration of content from abscess to look for an etiological agent, and it also has therapeutic roles when percutaneous drainage is warranted. Commonly used methods include ultrasonography (USG) (►**Fig. 1 A,B**) and computed tomography (CT) (►**Fig. 2A–D**). USG of the abdomen is performed in all suspected cases of liver abscess and has a sensitivity of 85%.[26] In current clinical practice, contrast-enhanced computed tomography (CECT) abdomen is performed in cases of high clinical suspicion if the initial sonography is not showing any abscess or the findings are equivocal. Hepatic abscesses are typically hypoechoic on the ultrasonography but can have varying degrees of echoes due to debris, gas, or septations.[27] CECT has higher sensitivity as compared with USG, 95 to 97%, according to various studies.[28] Usually, a well-defined round lesion with central hypoattenuation signifies a common liver abscess-enhancement of the rim and internal septa due to increased vascularity in these parts. The appearance of a liver abscess is variable and evolves. In the pre-suppurative phase, the abscess can simulate a tumor, looking heterogeneous with poorly marginated borders and irregular contours. Later on, it becomes a delineated hypodense lesion with a thick capsule during the suppurative phase.[29] This picture of peripheral hyperattenuation with central hypoattenuation is characteristically known as the 'Ring sign.'[30] Less commonly, this peripherally enhancing border is surrounded by a non-enhancing hypodense ring consisting of perilesional edema, known as the 'target sign.'[31] The presence of air is a pathognomonic sign, though it is present only in 15 to 20% of the cases. Abscesses are solid in 58% of cases and cystic in 48% of cases.[28] Contrast-enhanced USG (CEUS) is another modality that is now increasingly used. It is performed by injecting a contrast medium through the peripheral line, and views are seen in different phases. These are the arterial phase (10–30 s post-injection), portal phase (30–120 s post-injection), and late phase (>120 s post-injection).[32] In the arterial phase, a rim enhancement or septa with a honeycomb appearance is seen. In the late phase, a washout of contrast is seen.[33] It has been established that CEUS has better sensitivity, confirming the diagnosis in 93% of cases.[32] It has been shown that rim enhancement on CEUS can be seen in 20% of infected granulomas and 50% of cases having pseudotumor.[34] All cases of infective granulomas and pseudotumor demonstrate late washout, making it a non-specific finding.[35] For these reasons, the diagnostic ability of CEUS is questioned, but it allows better visualization of abscess contents and internal septa.[36] MRI is a modality used only when results are equivocal or not diagnostic of an abscess with high clinical suspicion. On T1-weighted imaging, low signal intensity is usually seen, whereas hyperintense signals are observed on T2-weighted imaging.[37] Perilesional edema gives a hyperintense signal on T2W imaging and is seen in one-third of cases.[38]

Management

Medical Management

In the case of liver abscess, blood cultures should be drawn upfront before starting antibiotics.

Antibiotics should be started promptly to reduce septicemia and systemic complications.[39,40]

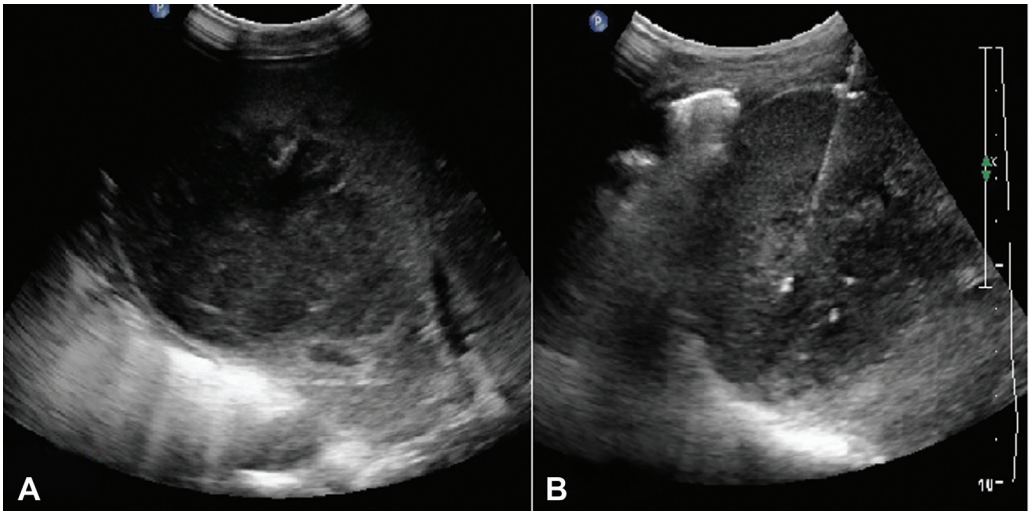

Fig. 1 Well-defined heterogeneously hypoechoic collection in the right lobe of liver suggestive of liver abscess (**A**) with pigtail in situ (**B**).

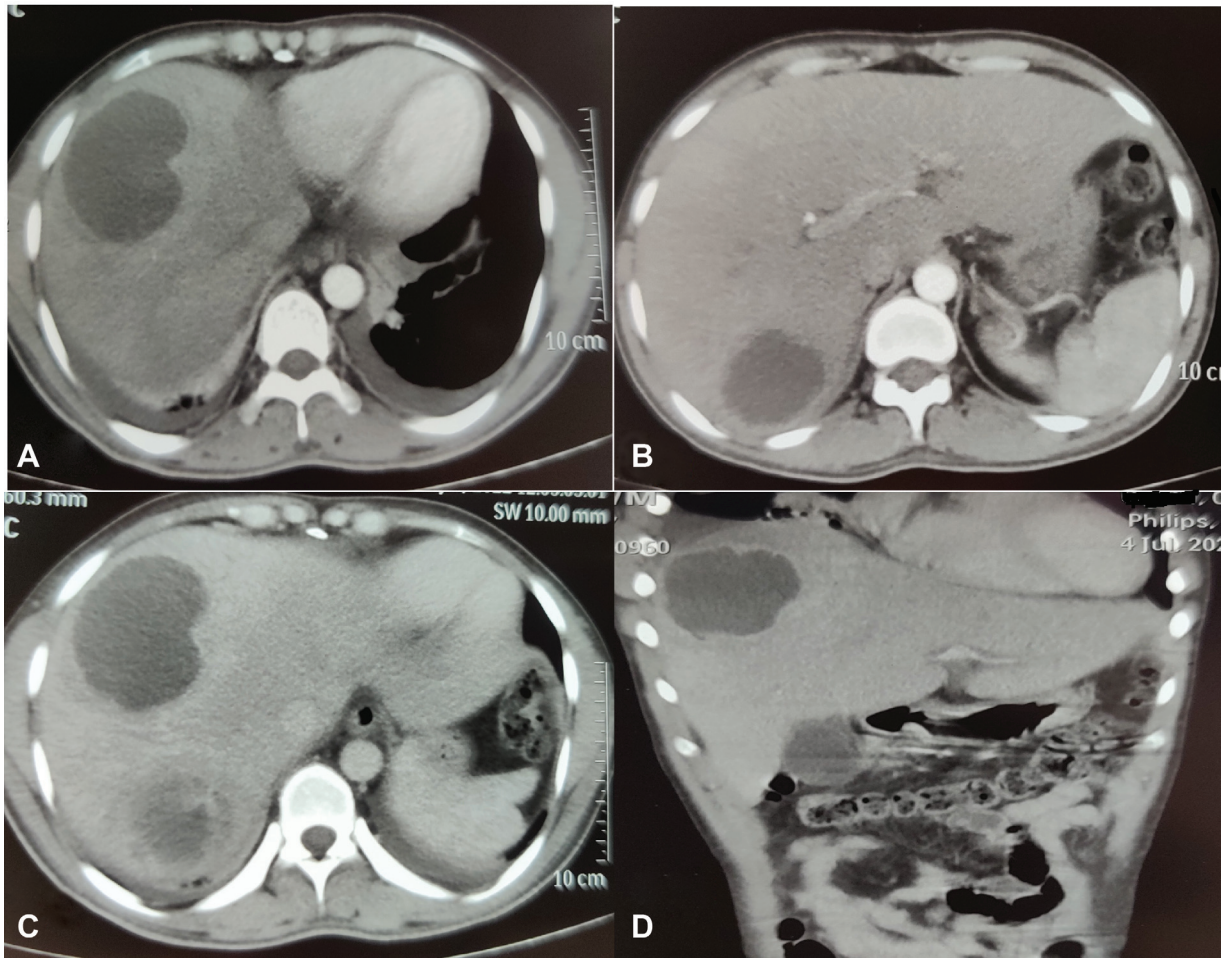

Fig. 2 Contrast-enhanced computed tomography of the abdomen showing peripherally enhancing hypodense lesions with shaggy margins and perilesional edema in the right lobe of the liver in the subcapsular region (**A, C, D**) suggestive of a liver abscess (**B**).

Small abscesses, less than 3 to 4 cm, can be managed with antibiotics alone as the success rate is close to 100% in managing small (less than 3 cm) unilocular abscesses with antibiotics.[41] Initially, intravenous antibiotics should be administered for 2 to 3 weeks to attain appropriate serum concentrations, which oral antibiotics can follow for another 4 to 8 weeks.[40–43] However, a shorter course of 2 weeks of oral antibiotics than a 6 to 8 weeks course is sufficient in treating the liver abscess.[44] Treatment duration is determined by clinical as well as radiological response. Early conversion to oral antibiotics has been studied for *Klebsiella*-related liver abscesses and has been found equally efficacious.[44,45] Empiric antibiotics should be directed against organisms typically responsible for causing liver abscess, covering gram-positive cocci, aerobic gram-negative bacilli, and anaerobes. Metronidazole should be considered if the antibiotic regime does not cover anaerobic organisms. Commonly used antibiotics include piperacillin and tazobactam, third-generation cephalosporins (ceftriaxone and cefotaxime), and carbapenems.[46,47] The use of regimens containing ampicillin, amoxicillin, and fluoroquinolones has significantly decreased due to emerging resistance against these agents. Previous intake of amoxicillin has been described as a risk factor for *Klebsiella pneumoniae*.[48] The empirical antibiotics regimen should also cover *Entamoeba histolytica* unless clinical suspicion for this infection is very low.[5] Empiric coverage for this organism should be continued until another causative organism has been found or amoebic serology testing is negative. Commonly used antibiotic regimens include intravenous ceftriaxone (2 g once daily) plus metronidazole (500 mg thrice daily), intravenous piperacillin and tazobactam (4.5 gram every 6 h) plus metronidazole, intravenous ampicillin (2-g i.v. every 4–6 h) + gentamicin (5–7 mg/kg) + metronidazole, intravenous carbapenem (imipenem–cilastatin or meropenem) + metronidazole.[44,48] If suspicion of *Staphylococcus aureus* is high (in patients with an indwelling catheter), vancomycin (15–20 mg/kg) should be added to the regimen. Metronidazole is added to piperacillin and tazobactam to cover only E. *histolytica*. Carbapenems are reserved for patients where third-generation cephalosporins, piperacillin, and tazobactam cannot be used or if the isolated organism is resistant to first-line agents.[49] Carbapenems are the drug of choice in extended-spectrum beta lactamases (ESBL) producing *E. coli* or *K. pneumoniae*. New strains of *K. pneumonia*, such as New Delhi metallo β-lactamase 1 (NDM 1), are of serious concern as they are

resistant to carbapenems. Colistin and tigecycline can cover these organisms.[50–52] If enterococcus is a clinical possibility (in cases with a history of biliary procedure), piperacillin, and tazobactam are better than third- generation cephalosporins.[53] The choice of regimen is based on many factors such as previous antibiotic exposure, contraindications, history of any allergic reaction to an antibiotic, and following local antimicrobial stewardship rules.[19] Even if a gram-negative bacillus or streptococcus is isolated on either aspirated specimen or blood culture, a polymicrobial coverage is given rather than a single antibiotic based on the sensitivity pattern obtained.[54] Regimens having gentamicin should not be given for more than 48 hours. Amoebic liver abscess shows an excellent response to metronidazole. Most patients show a clinical response in 3 to 4 days of therapy. Oral therapy with metronidazole for 7 to 10 days is sufficient. The recommended dose is 500 to 750 mg, taken three times daily. A 2-g tablet of tinidazole can also be used once a day for 5 days. Tinidazole is associated with early clinical response in the form of resolution of fever and abdominal pain.[55,56] The cure rate with these agents is more than 90%.[10] In addition to these drugs, luminal agents are required to eliminate luminal cysts. Commonly used agents are diloxanidefuroate (500 mg TDS for 10 days) and paromomycin (25–30 mg/kg orally) in three divided doses for 7 days). Large abscesses can be successfully managed without any drainage procedure.[55] In uncomplicated cases, there is no advantage observed with drainage in addition to antimicrobials.[57]

Drainage

Percutaneous catheter drainage is required in cases with no clinical response after 5 to 6 days of metronidazole therapy. Mortality in cases with amoebic liver abscess is $< 1\%$ if treated early with antimicrobials.[10] Percutaneous drainage is a commonly used modality in centers where intervention radiologists are available. It can be done either by single-time needle aspiration or catheter drainage. Both procedures are image-guided and are done under ultrasonographic or computed tomographic guidance. In single-time aspiration, a 16- or 18-gauge needle is inserted into the cavity, and its contents are aspirated until it is properly emptied and evacuated.[58,59] In catheter drainage, an 8 to 14 F pigtail is inserted into the cavity, and the contents are emptied over a few days with gravity's help. Percutaneous catheter drainage is a better procedure with a higher success rate.[60–62] It is a minimally invasive procedure, requiring only local anesthesia. This procedure may be unsuccessful in 10 to 15% of cases with multiloculated abscess or if the viscosity of contents is high, leading to catheter block. According to a recently published meta-analysis, the success rate of catheter drainage is significantly higher than percutaneous aspiration (100% vs. 68%), in cases with the abscess size being > 5 cm.[18] It also revealed shorter hospital stays (4 days vs. 9 days) and 50% lesser abscess resolution time with catheter drainage.[18] So, catheter drainage is preferred over percutaneous aspiration for large abscesses. Rare complications of the procedure include hemorrhage and the formation of biliary fistulae. In patients with a single unilocular abscess less than 5 cm in size, needle aspiration results are comparable to catheter drainage.[63,64] The choice between two procedures depends on the preference of the operator. Repeated aspirations are needed in ~50% of patients. If the abscess is less than 3 cm or not aspirable, it should only be managed with antimicrobials. If the size of the unilocular abscess is > 5 cm, catheter drainage is superior to needle aspiration, given success rates.[58] A pigtail should remain in situ until drainage is minimal. The mean duration is close to 7 days. Giant abscesses, defined as size > 10 cm, should also undergo percutaneous catheter drainage, though the proportion of failures is significantly high in these cases.[65] In a study by Ahmed et al, 39 patients with abscess size > 10 cm went for catheter drainage, and 25% of patients experienced either a complication due to abscess or required repeated percutaneous drainage.[66] We prefer to drain abscesses which are multiple (for culture and microbiological tests), left lobe, large with impending rupture-like thinned out parenchyma at the periphery.

Surgical Management

It is observed that treatment failure is more common in patients undergoing percutaneous drainage than surgery in cases with abscesses > 5 cm. Still, the two groups have no differences in complication rates or mortality.[67,68] In cases with multiple or multiloculated abscesses, the decision regarding percutaneous drainage versus surgery can be taken individually, considering the number, size, and accessibility of abscesses.[69] Surgical drainage is indicated in cases with peritonitis, abscess rupture, large abscess at a difficult anatomical site, or if the patient requires surgery for some other indication.[70] Laparoscopic surgery is a safe and viable alternative for patients requiring surgical drainage following failed medical or percutaneous treatment.[71] Various studies have shown that large multiloculated abscesses of more than 5 cm have better outcomes with surgical drainage than percutaneous drainage[20,41,72] (►**Fig. 3**).

Mortality Predictors

In a case of a liver abscess, higher mortality may be associated with particular risk factors. Male sex, cirrhosis of liver, diabetes mellitus, sepsis with multi-organ dysfunction, infection with mixed organisms, extra-hepatic involvement, size of abscess greater than 5 cm and respiratory distress are causes of high mortality in patients with liver abscess.

Conclusion

Initially, the liver abscess was predominantly treated by surgical intervention, but lately, medical management with antibiotics and the availability of intervention radiology have drastically changed the management paradigm. A liver abscess can usually be managed relatively efficiently with antibiotics and percutaneous drainage.

Ethical Statement
Not applicable.

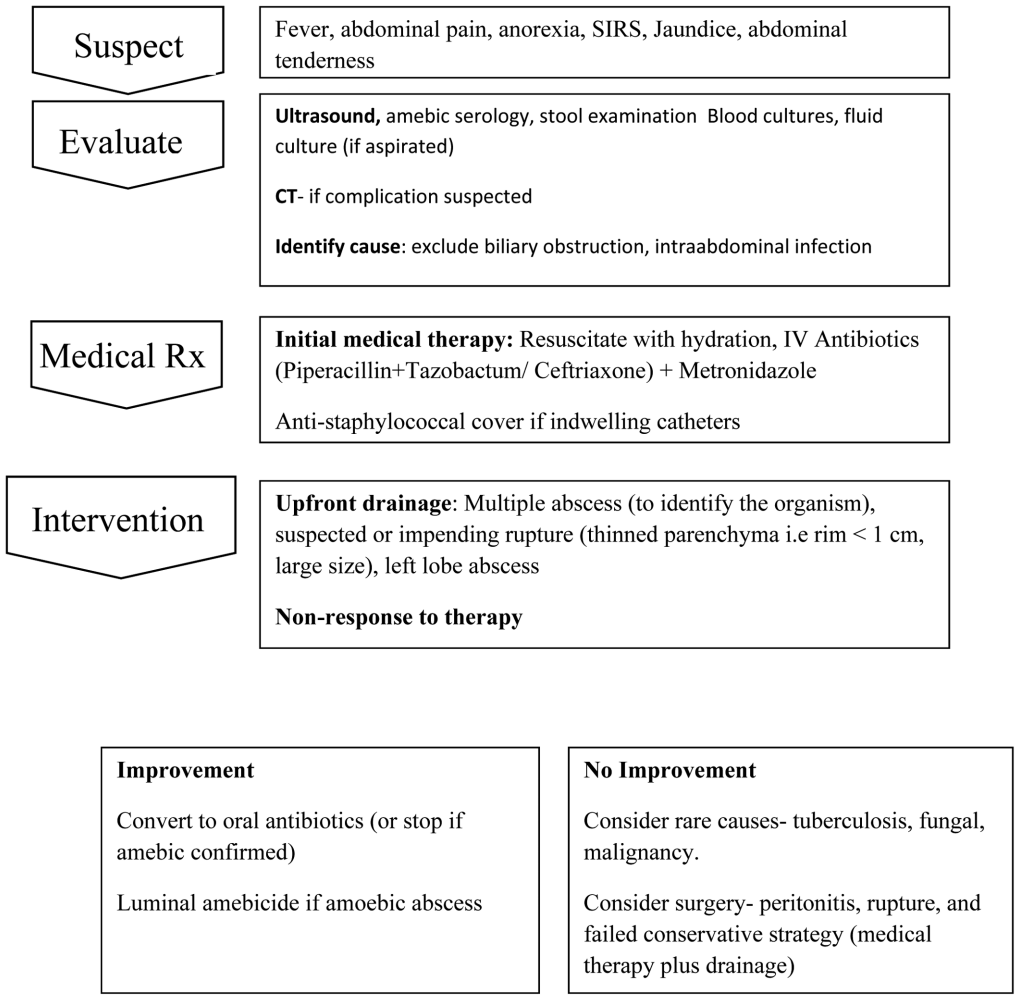

Fig. 3 Management of liver abscess

Author Contributions

S.W.: Data collection and drafted the manuscript; N.A.: Drafted the manuscript, edited the rough draft; D.P.D: Manuscript correction and expert guidance.

Data Availability Statement

There is no data associated with this work.

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Conflict of Interest

None declared.

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