Multimodal Treatment of Cystic Echinococcosis

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ABSTRACT

Cystic echinococcosis is a zoonotic disease that is caused by the larval stages of cestodes species and belongs to the genus Echinococcus. Echinococcus granulosus (E. granulosus) causes cystic echinococcosis which is global and wider in its distribution than alveolar echinococcosis. Endemic areas of E. granulosus are Russia, Eastern Europe, the Middle East, China, and South America based on data from the World Health Organization (WHO). Incidence rates are 50 per 100,000 person-years. The life cycle of E. granulosus requires both an intermediate host and a definitive host. A human accidentally becomes an intermediate host. Upon infection, cyst formation mostly occurs in the liver (70%). At the first, the infection is usually asymptomatic. Diagnosis of cystic echinococcosis can be done by imaging techniques (ultrasound or CT/MRI), serum serologic testing for antibodies against hydatid antigens, and immunologic testing. In general, there are four different management modalities for cystic echinococcosis, such as surgery, percutaneous therapy surgery, chemotherapy, and watchful waiting.

Keywords: *echinococcosis, granulosus, hydatid, cyst*

ABSTRAK

Kista echinococcosis adalah penyakit zoonosis yang disebabkan oleh stadium larva dari spesies cestoda dan termasuk dalam genus Echinococcus. Echinococcus granulosus (E. granulosus) menyebabkan kista echinococcosis yang bersifat global dan penyebarannya lebih luas dibandingkan echinococcosis alveolar. Berdasarkan data dari World Health Organization (WHO), daerah endemik E. granulosus adalah Rusia, Eropa Timur, Timur Tengah, China, dan Amerika Selatan. Tingkat insidennya adalah 50 per 100.000 orang-tahun. Siklus hidup E. granulosus membutuhkan hospes perantara dan hospes definitif. Manusia secara tidak sengaja menjadi hospes perantara. Ketika terjadi infeksi, pembentukan kista sebagian besar terjadi di hati (70%). Pada awalnya, infeksi biasanya bersifat asimptomatis. Diagnosis kista echinococcosis dapat dilakukan dengan teknik pencitraan (USG atau CT/MRI), uji serologi serum untuk antibodi terhadap antigen hidatid, dan uji imunologi. Secara umum terdapat empat modalitas manajemen yang berbeda untuk kista echinococcosis, yakni pembedahan, terapi perkutaneus, kemoterapi, dan observasi tanpa intervensi.

Kata kunci: *echinococcosis, granulosus, hidatid, kista*

INTRODUCTION

Echinococcosis or hydatid cyst is one of the 17 neglected tropical diseases according to data from the World Health Organization (WHO).[1–3] This disease costs more than 3 billion US dollars annually, while the number of infected cases is increasing worldwide every year.[2,4] Cystic echinococcosis is classified as a zoonotic disease that is caused by the larval stage of cestode species belonging to the genus Echinococcus.[1–3]

There are six species of Echinococcus have been found recently, but only four species can cause serious diseases in humans. All four species are *Echinococcus granulosus* (*E. granulosus*), *Echinococcus multilocularis* (*E. multilocularis*), *Echinococcus vogeli* (*E. vogeli*), and *Echinococcus oligarthrus* (*E. oligarthrus*). Additional two new non-pathogenic species for humans have been described in recent studies as, *Echinococcus felidis* (*E. felidis*) and *Echinococcus shiquicus* (*E. shiquicus*).[5–7] Cystic echinococcosis and alveolar echinococcosis are two forms of human infection that are life-threatening and have the highest mortality rate. However, cystic echinococcosis has a wider distribution than alveolar echinococcosis.[2]

Approximately 70% of the cysts mainly occur in the liver and 30% in the lungs. Based on the results of a study by Kaman et al regarding characteristics, diagnosis, and treatment modality of pediatric patients in Ankara, Turkey, symptomatic cyst infections have been reported in the liver in 100 (76.9%) patients, lungs in 48 (36.9%) patients, both liver and lung in 21 (16.1%) patients, spleen in 8 (6.2%) patients, pelvic region in 5 (3.8%) patients, and kidney in 3 (2.3%) patients. The percentage of liver cysts in the right lobe, left lobe, and both lobes were 57%, 21%, and 22%, respectively. The percentage of lung cysts in the right lung, left lung, and both lungs were 58%, 25%, and 17%, respectively.[8]

The current estimate of the global burden of cystic echinococcosis is approximately 188,000 new cases per annum leading to 184,000 disability-adjusted life years (DALYs), out of which 40% DALYs were in China. According to the World Health Organization (WHO), the global burden of controlling the disease exceeds three billion US dollars annually.[1] Because of that, it's very important to understand the therapy algorithm for cystic echinococcosis to prevent the complication and mortality of the patient.

EPIDEMIOLOGY

The Mediterranean region (Bulgaria, Cyprus, France, Greece, Italy, Portugal, Spain, Yugoslavia, and Southern Russia), North Africa (Algeria, Morocco, and Tunisia), Southern and Eastern Europe, South America (Argentina, Brazil, Chile, Peru, and Uruguay), Southwest Asia (Iraq, Turkey, and Iran), China, and Australia are endemic areas for *E. granulosus* based on the data from WHO. The incidence rate is 50 per 100,000 person per year.[9,10] In South America, the prevalence rate of this disease varies from 20–95%, especially in areas where there is a lot of slaughter of livestock.[9] In Africa, the prevalence of this disease is 3%.[11] In Australia, 80–100 cases of cystic echinococcosis are diagnosed every years (0.4 per 100,000 population).[12] In Indonesia, the incidence of cystic echinococcosis has been found in people aged more than 10 years who live around Lake Lindu, Central Sulawesi. There were 903 blood serums examined and 17 of them tested positive for *Echinococcus* species antibodies.[9]

The intermediate hosts include sheep, goats, geese, horses, camels, pigs, cattle or cows. Human cystic echinococcosis was frequently caused by sheep.[10] The prevalence of human cystic echinococcosis increases with age. Women are more frequently affected than men. This is probably due to the fact that women are more likely to carry out activities such as feeding, herding, or milking livestock.[3] The mortality rate is 0.2 per 100,000 population.[12]

LIFE CYCLE

The life cycle of *E. granulosus* requires two hosts, namely an intermediate and a definitive host (dog, wolf, and cat). Humans are accidentally intermediate hosts. They get infected by food, water, and soil contaminated with egg-bearing feces of the sheep or dogs.[14] *Echinococcus granulosus* life cycle starts from adult worms (2–7 mm) living in the small intestine of the definitive host. The mature (gravid) proglottid releases the egg and is excreted with the definitive host feces. There are hundreds of eggs within each proglottid. These eggs can be ingested by intermediate hosts and then will release oncosphere (larvae) into the duodenum.[4,9,10,12,13]

The larvae migrate through the penetration of the intestinal mucosa and circulate to the mesenteric vessels which will carry them to the liver.[9] Cystic echinococcosis develops up to 70% in the liver. Larvae that escape from the hepatic filtration system are carried to the lungs, which are the second most

common site for the disease (30%). From the lungs, the larvae can spread to all parts of the body. After ingestion by a suitable intermediate host, eggs hatch in the small intestine and release six-hooked oncospheres that penetrate the intestinal wall and migrate through the circulatory system into various organs, especially the liver and lungs. In these organs, the oncosphere develops into a thick-walled hydatid cyst that enlarges gradually, producing protoscolices and daughter cysts that fill the cyst interior.[13] These cysts grow at a rate of 1–3 cm/year and remain undetected for years. An inner germinal layer and an outer chitinous layer will form the cyst wall. The germinal layer will develop internal protrusions and eventually form daughter cysts within the original cyst.[4,14]

In the intestine, the protoscolices evagination by attaching to the intestinal wall to become adult worms (32–80 days). The same life cycle also occurs in *E. multilocularis* (adult worm size 1.2–2.7 mm), *E. oligarthrus* (adult worm size 2.9 mm), and *E. vogeli* (adult worm size 5.6 mm), but with different definitive and intermediate hosts.[9] The primary cyst structure consists of 3 layers: (1) Adventitia (pericyst): condensed liver parenchyma consisting of fibrous tissue which induces expansion of the cyst; (2) Laminated membrane (ectocyst): elastic white membrane that can easily be separated from the adventitia; (3) Germinal epithelium (endocyst): a single layer of cells lining inside of the cyst and contains hydatid fluid. In some primary cysts, laminated membranes will form protrusions and grow into daughter cysts within the primary cyst space.[14]

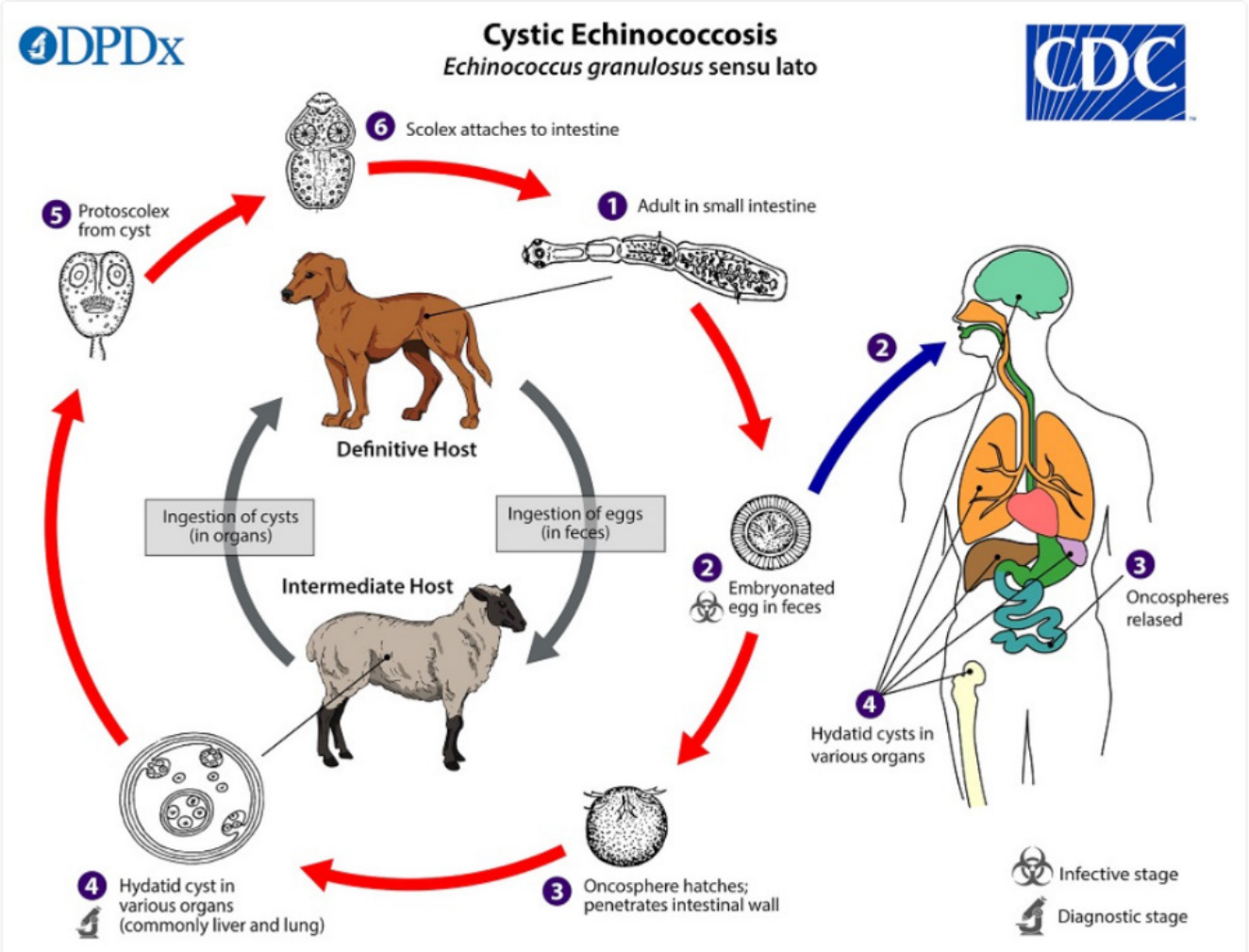

Figure 1. The life cycle of *Echinococcus granulosus*[13]

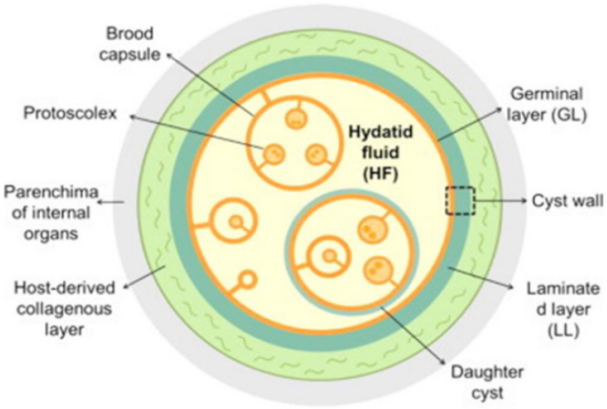

Figure 2. Three layer structure of Echinococcosis[15]

CLINICAL MANIFESTATION

In the early phase, echinococcosis infections are always asymptomatic. This is because of the very slow development of cysts (1–3 cm/year) and the immune system's response from the host so that symptoms begin to appear in adults. Symptoms are usually occurred because of the suppression effect on the surrounding organs. The cyst in the liver can compress the bile duct which manifests as obstructive jaundice, upper right abdominal pain, anorexia, and itching. If the cyst grows in the lungs, the clinical symptoms are chronic cough, shortness of breath, pleuritic chest pain, and hemoptysis. A ruptured or leaking cyst can cause immunological symptoms such as acute hypersensitivity reaction characterized by urticaria and mucosal edema. When a big cyst ruptures, it can cause a life-threatening anaphylactic reaction.[9,10] Anaphylaxis is a frequent complication in 10% of cases of cystic echinococcosis found in the peritoneum space. When the cysts rupture, all contents come out including the protoscolices resulting formation of secondary cystic echinococcosis. Therefore, the clinical manifestation is sepsis, either due to primary or secondary infection from leakage into a biliary tree (cholangitis).[16]

There 7.3% (37/503) of patients diagnosed with cystic echinococcosis had bacterial superinfection in one study. Four of these patients had severe sepsis and two of them died. *Enterococcus*, *Escherichia coli*, and *Streptococcus viridans* are bacteria that are often found in hepatic cyst infections.[10] Other complications are hepatitis, blockage of the bile ducts, formation of intracystic or subphrenic abscess, rupture of cysts in the bronchial tree that cause the formation of bronchobiliary fistulas, and embolism. Therefore, in patients with hepatitis, colic pain, portal hypertension, Budd-Chiari syndrome, liver cysts, hepatic hemangioma, adenomas, liver abscess, hepatoma, and any mass formation in the liver, hepatic echinococcosis should be considered as differential diagnosis.[16]

DIAGNOSIS

The diagnosis of cystic echinococcosis in the liver is often incidental. The appearance of symptoms leading to infection with cystic echinococcosis with a history of exposure to sheep or dogs supports the diagnosis of cystic echinococcosis in endemic areas. A combination of serologic, immunologic, and imaging examination is required for a definitive diagnosis of cystic echinococcosis. Routine laboratory tests rarely show abnormal results, except for eosinophilia which can occur in cases of leakage cysts. Serum alkaline phosphatase level is sometimes elevated in one-third of cases.[5,14,16]

The serologic examination can detect antibodies to parasites and it is a diagnostic tool that can be used to detect new or past infections of *E. granulosus*. IgG antibodies indicate chronic infection, while high titers of IgM and IgA indicate new and active infections. Apart from detection of parasitic antibodies, detection of circulating antigens should also be performed as a post-surgical monitor or pharmacotherapy to determine patient's prognosis.[11] Some modalities for examining parasite antibodies include immunoelectrophoresis (IEP), enzyme-linked immunosorbent assay (ELISA), and immunoblots (IB). Immunoblots reportedly have the highest sensitivity (80%), followed by ELISA (72%), and immunoelectrophoresis (31%). However, the results of the above examinations highly depend on cyst activity, number and size of cysts, and duration of treatment before the serum is taken (≤ 12 months). Secondary antibody testing is needed, for example, testing for antibodies to the antigen "arc 5" contained in cystic echinococcosis fluid, IgG4-ELISA, or immunoblots in patients with positive test results and imaging findings. Secondary tests are used to rule out cross-reactivities or false-positive results.[10] Although seropositive is usually found in patients with multiple cysts, seronegativity is found in 20% of patients. Patients with seronegativity are usually in CE1, CE4, and CE5 stages.[16]

An imaging examination is also performed. Plain radiographs of the chest and abdomen can sometimes reveal cystic echinococcosis that has calcified. Calcification can be seen in 30% of cases of cystic echinococcosis and usually manifests as a ring-like formation indicating calcification of the pericyst. It indicates the natural process of healing. Solid calcification usually occurs in all parts of the

cyst. Parasitic death was not indicated only from calcification that occurred at the pericyst side, but also from calcification from all cyst components (complete calcification).[16]

Ultrasound examination is a diagnostic method that is often used as the main choice and has an accuracy of 90%. However, this examination is very dependent on the experience and skill of the operator.[10,14] The radiological features that are often found are solitary cysts with a single (univesicular) sac, an anechoic image with a clear border, and appears hyperechoic with posterior acoustic shadowing. The specific characteristics that lead to the diagnosis of cystic echinococcosis are the presence of debris (hydatid sand) that moves freely depending on the patient's position and the presence of calcification of the cyst wall or local thickening associated with the daughter cyst. The hydatid sand contains cyst fluid mixed with protoscolices that comes out due to the rupture of a daughter cyst in the primary cyst. An endocyst can also separate from the pericyst. This may appear as a well-defined cystic lesion with a localized split in the wall and "floating membranes" within the cystic cavity. The water lily sign can be seen as a complete detachment observed by ultrasound examination.[10]

Daughter cysts are pathognomonic for cystic echinococcosis when found on ultrasound examination. It looks like a honeycomb cyst with multiple septa that represent the daughter cyst wall which appears as a cyst within the cyst.[14] Daughter cysts separated by the hydatid matrix can produce a "wheel-spoke pattern". The content of the matrix is detached membranes, which may appear as serpentine linear structures, scolices, broken daughter vesicles, and hydatid sand. Ultrasound examination has the highest sensitivity for the detection of these components. The cyst will appear as a solid mass when the matrix fills the cyst space. Calcification of the cyst usually occurs within the cyst wall and appears as a hyperechoic lesion with acoustic shadowing. Only the anterior portion of the cyst can be seen if there is severe calcification because it limits ultrasound penetration.[10]

WHO developed a standard classification system for the diagnosis of hepatic cystic echinococcosis using ultrasonography. This system was first developed by Gharbi and colleagues in 1981, but has been revised by the WHO-Informal Working Group classification on echinococcus (IWGE) and is currently used for classification and early detection.

In general, there are 3 categories of cysts, active (CE1 and CE2), transitional (CE3), and inactive (CE4 and CE5) cysts. Cystic lesion (CL) is a cyst stage consisting of unilocular cyst lesions without pathognomonic images on ultrasonography so parasitic infection must be proven by other tests. The CE3 cyst is further divided into CE3a (characterized by detach of the endocyst) and CE3b (characterized by a solid structure filled with daughter cyst sacs). CE3a cysts are true transitional cysts because they can be active or inactive, while CE3b cysts are always active.[3] All of these cysts categories will determine the type of therapy to be performed. In addition to diagnostics, ultrasonography is also used for monitoring therapy every 3–6 months until 1 year for.[16]

Computed tomographic scan (CT-scan) has the highest sensitivity (100%) in the detection of cysts. This is the best method for detecting the size, number, and location of cysts. This tool can also provide clues to the presence or absence of complications such as infection and rupture of a cyst to the biliary tree. In addition, this imaging technique can also estimate the volume of the cysts and detect exogenous cysts. CT-scan is often used when the results of the ultrasound examination are inconclusive, when surgery is being performed, or when the disease recurs.[14]

Cyst fluid looks like water on a CT scan with a density of ± 0 Hounsfield units (HU). The wall calcification of the cyst or inner septa appears as hyperdense on CT without contrast. The membrane separated from the pericyst can be visualized as a linear and hyperdense area within the cyst. Daughter cysts are characterized by a round structure located peripherally in the primary cyst and the cyst fluid appears thinner than the primary cyst.[14]

Table 1. WHO-Informal Working Group classification on echinococcus (IWGE)[15–17]

Classification type		Classification characteristics	Stage
Gharbi	WHO-IWGE		
I	CE1	Single vesicular fluid collection/simple cyst	Active
III	CE2	Multiple vesicular fluid collections with multiple daughter cysts or septae (honeycomb)	Active
II	CE3 A	Fluid collection with membrane detached (water lily sign)	Transitional
III	CE3 B	Daughter cysts in a solid matrix	Transitional
IV	CE4	Cysts with heterogeneous matrix,no daughter cysts	Inactive /degenerative
V	CE5	Solid cystic wall	Inactive /degenerative

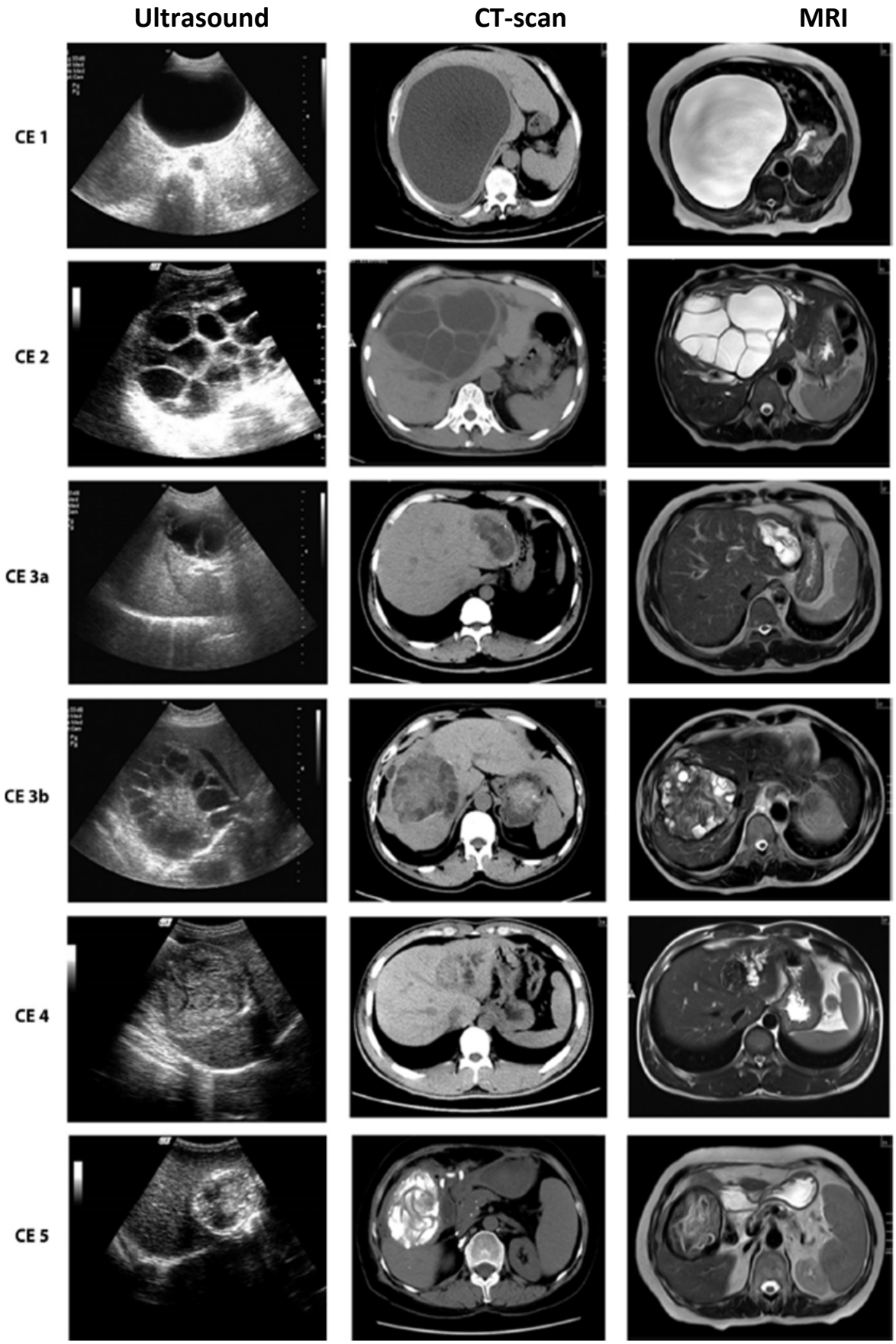

Figure 3. Imaging of cystic echinococcosis[6]
CT: computed tomography; MRI: magnetic resonance imaging

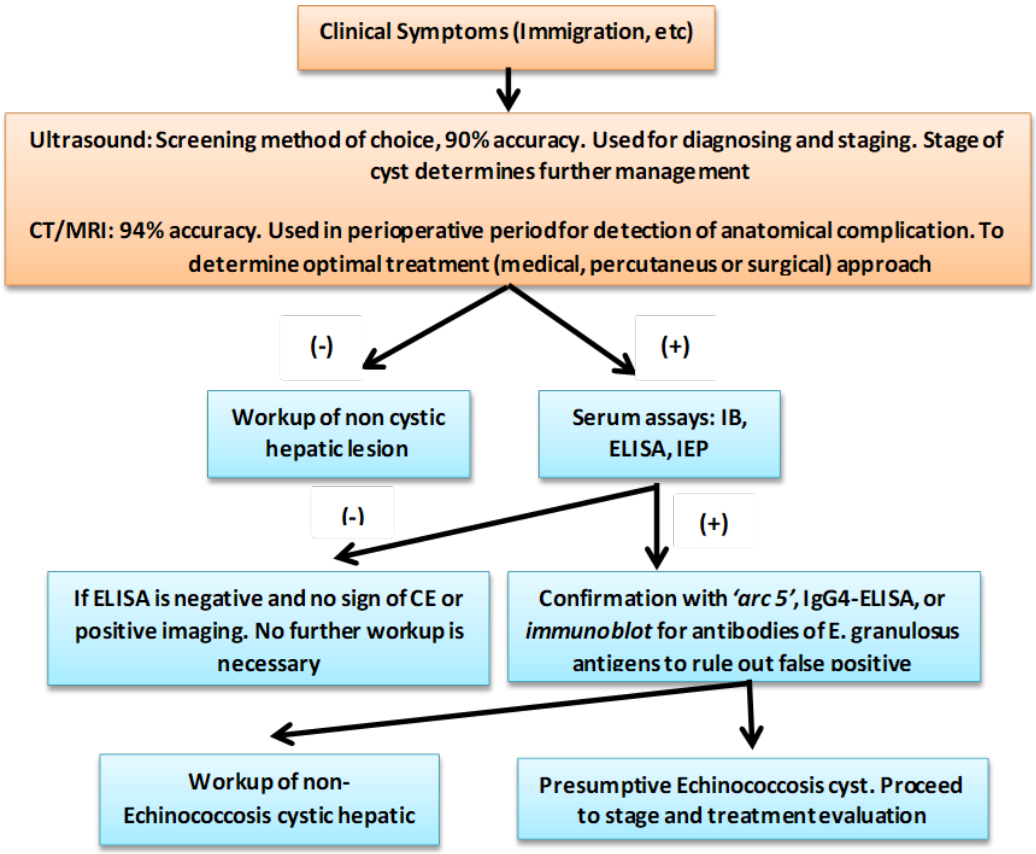

Figure 4. Diagnostic algorithm of cystic echinococcosis[10]

Magnetic resonance imaging (MRI) scan shows the cyst capsule better than CT scans even though it's not done regularly. Cysts are hyperintense at T2- weighted with characteristic low signal intensity rim. This probably indicates a collagen-rich outer layer (pericyst) of cystic echinococcosis. Daughter cysts demonstrate a hypointense appearance on T1- weighted. The collapsed and separated membrane appears as a twisted linear line in the same way as on a CT scan. Although calcification is very clearly described by a CT scan, MRI can detect the initial irregularity of the cyst membrane leading to the detachment of the pericyst membrane.[10,14]

MANAGEMENT

There are 4 treatment modalities for Echinococcosis hepatic cysts such as surgery, percutaneous therapy, chemotherapy, and observation (watchful waiting).[3,6] The gold standard therapy for cystic echinococcosis is surgery.[13,16] The goals of surgery are to inactivate the parasite, evacuate the cyst until the germ layer, prevent the breaking of cyst scolex into the peritoneum, and clean the remaining cyst pocket. Surgery can be performed at a high success rate if the location of the cyst growth is not difficult or risky. However, surgery cannot be performed in a patient with multiple cysts spread across multiple organs and when surgical facilities are inadequate. The basic principles of surgery for cystic echinococcosis are: (1) Complete removal of all infectious components of the cysts; (2) Prevent of spillage of cyst contents at the time of surgery; (3) Management of communication between cysts and surrounding organ structures; (4) Management of the remaining cavity.[14]

The indication for surgery is a large, active, symptomatic, and complex size of the disease. CE2–CE3b cysts > 5 cm in diameter, with multiple daughter cysts, superficial sites, or infected cysts, cysts associated with the biliary tree, and causing a compression effect to the surrounding organs are some indications for surgery.

The entire surgical procedure can be divided into two groups, conservative or radical techniques. Conservative techniques are usually safer, and simpler, and are best used in cases of uncomplicated cysts. Conservative surgery involves cleaning the contents of the cyst but still leaving the pericyst.[16] Marsupilation is the most commonly used technique because it is relatively safe and fast. Meanwhile, the main weakness is the high risk of postoperative complications such

as leakage of bile from the bile and cyst connection, peritonitis, and bilomas (4–28%).[14]

RADICAL SURGERY PROCEDURE

Cystectomy, pericystectomy, lobectomy, and hepatectomy are radical surgical procedures. They have a lower risk of recurrence and complications, but the intraoperative risk during surgery is very high.[14]

Cystectomy

The procedure includes cleaning the cyst (lamina membrane, daughter cyst, and capsule). This simple procedure has a low recurrence rate. Management of the remaining cavity is the greatest challenge, especially in patients with very large cysts. A variety of techniques have been found for treating remaining cavities, such as capitonnage, external drainage, and omentoplasty.[14]

Pericystectomy

This procedure includes resection of the cyst and all components that compress the liver tissue around the cyst regardless of the anatomical structure of the surrounding organs. This surgical technique is more difficult than cystectomy and often results in large amounts of blood loss. This technique is also quite dangerous if used in complicated cysts that caused changes in important anatomical structures such as the hepatic vein or biliary duct.[14]

Hepatic Resection

This technique was initially used as the main modality in the management of hepatic cystic echinococcosis. However, it is starting to be abandoned because it also can cause damage to the healthy liver tissue. Besides, the distortion of the anatomy makes surgery harder.[14]

LAPAROSCOPY

This technique is a surgical technique with a minimally invasive method. It has several advantages over conventional surgery. It causes lower disease morbidity and shorter hospital stay. In addition, it provides better visual control of the cyst cavity under magnification which allows better detection of the biliary fistula. However, the laparoscopic technique can only be used in certain cases.

Some of the criteria that exclude the choice of this treatment modality are cyst rupture in the biliary tree, central localization of the cyst, cyst diameter > 15 cm, number of cysts > 3, thickening or calcification of the cyst wall, bile duct surgery must be performed because of bile leakage. In addition, allergic reactions often occur due to the leakage of fluid and daughter cysts into the peritoneal cavity. This leakage can also cause echinococcosis peritoneal cysts.[14]

PERCUTANEOUS INJECTION THERAPY

Percutaneous treatment is divided into two groups. The first is puncture, aspiration, injection, and re-aspiration (PAIR) and the second is catheterization into the cyst using a wider tube to clear all the contents of the cyst including daughter cysts.[16] PAIR is cystic Echinococcosis therapy with a percutaneous injection technique. This technique was first introduced by a team of surgeons from Tunisia in 1986. The goal of this therapy is the destruction of the germinal layer or the evacuation of the entire endocyst. PAIR consists of four steps; (1) Percutaneous puncture of the cyst with ultrasound guidance; (2) Aspiration of the cyst fluid; (3) Injection of a protoscolicidal agent (e.g., 95% ethanol or 20% NaCl) for at least 15 minutes; (4) Re-aspiration fluid. PAIR is indicated in Echinococcosis CE1 and CE3a cysts > 5 cm in diameter.[11]

WHO recommends PAIR as an alternative therapy to surgery with the following indications and contraindications.

Table 2. Indication and contraindication of puncture, aspiration, injection, re-aspiration (PAIR)[9]

Number	Indication	Contraindication
1	Non-echoic lesion (≥ 5 cm in diameter). Cysts with daughter cysts and/or with membrane detachment	Non-cooperative patients
2	Accessible multiple cysts to puncture	Risky or inaccessible location of the cysts
3	Infected cysts	Cysts in the spine, brain, and/or heart
4	Patient refuses surgery	Inactive or calcified lesion
5	Recurrence case after surgery	Cyst connecting with the biliary tree
6	Patients who have contraindications in surgery	
7	Patients who fail to respond to chemotherapy alone	
8	Children over > 3 years	
9	Pregnant woman	

A recent improvement in PAIR is the "modified catheterization technique" (MoCAT). This technique, which can be used for cysts measuring 10 cm in diameter, includes aspiration of the parasitic membranes as well as aspiration of the contents of the cyst leaving a catheter for postoperative drainage. This technique can be used as an alternative to noncomplicated CE2 and CE3 cyst surgery.[6]

ENDOSCOPY

Endoscopic retrograde cholangiopancreatography (ERCP) can be used to evaluate the involvement of the biliary tract due to infection with cystic echinococcosis. Endoscopic techniques are very useful in cases of ruptured cysts in the bile duct that requires exploration and drainage. Besides, it can be done if, after surgery, there is residual cyst material (membrane and daughter cysts) in the biliary tract. During exploration, the bile ducts are cleaned using a balloon catheter or dormia basket. Endoscopic sphincterotomy is also performed to facilitate drainage through the common bile duct.[14]

CHEMOTHERAPY

Benzimidazole carbamates such as mebendazole and albendazole, are medical therapy for cystic echinococcosis. This drug has been used since 1970.[16] This class of drug can provide clinical improvement by eradicating the cyst because of the ability to penetrate the cyst wall. These drugs interfere with glucose absorption in the parasite wall, causing glycogen depletion and degenerative changes in the mitochondria and echinococcus endoplasmic reticulum.[11] These drugs are used in cases of disseminated liver cystic echinococcosis, inoperable cases, or combined with surgery to prevent a recurrence. Side effects of albendazole are nausea, mild stomach pain, vomiting, itching, dizziness, redness, headache, and alopecia. Sometimes leucopenia, eosinophilia, jaundice, and transaminitis can also be found.[14]

Albendazole is said to be more effective because it has better penetration and absorption abilities. The dose of albendazole is 10–15 mg/kg BW/day in 2 divided doses for 3–6 months. Therapy using mebendazole requires a larger dose and a longer duration. The dose of mebendazole is 40–50 mg/kg BW/day, in 3 divided doses, for 3–6 months.[6.11,16] The administration of this therapy should not be interrupted, especially in Cystic echinococcosis class CE1 < 5 cm in diameter.[16]

According to WHO recommendations, medical therapy should be started 4–30 days before surgery and continued up to 1 month by using albendazole and at least 3 months by using mebendazole.[5,16] Praziquantel at a dose of 40 mg/kg BW, once per week, can be combined with albendazole.[11,16] This combination therapy is said to be more effective than albendazole administration alone. For uncomplicated cases (CE4 and CE5 cysts), it is recommended to do observation alone without specific therapy.[11]

Clinical and radiographical improvement, in most studies, was demonstrated by a reduction in cyst size by 25%, separation of the cyst membrane, or cyst calcification. This is greatly influenced by the duration of the cyst. However, complete recovery (loss of cyst) occurs mostly in 1/3 of patients treated with chemotherapy alone.[11] Another study also shows that 28.5–58% of patients who receive chemotherapy are declared cured, but the cure rate does not increase although the duration of therapy is extended.[16]

OBSERVATION

Another therapeutic modality is observation and watchful waiting. The hypothesis underlying this therapy is that CE4 and CE5 cysts are predominantly calcified and therefore inactive. Besides, this modality is also recommended for asymptomatic CE1 cysts.[6,10] Close monitoring using ultrasound is recommended for this type of cyst. Regular and close observation should be done for up to 10 years.[10]

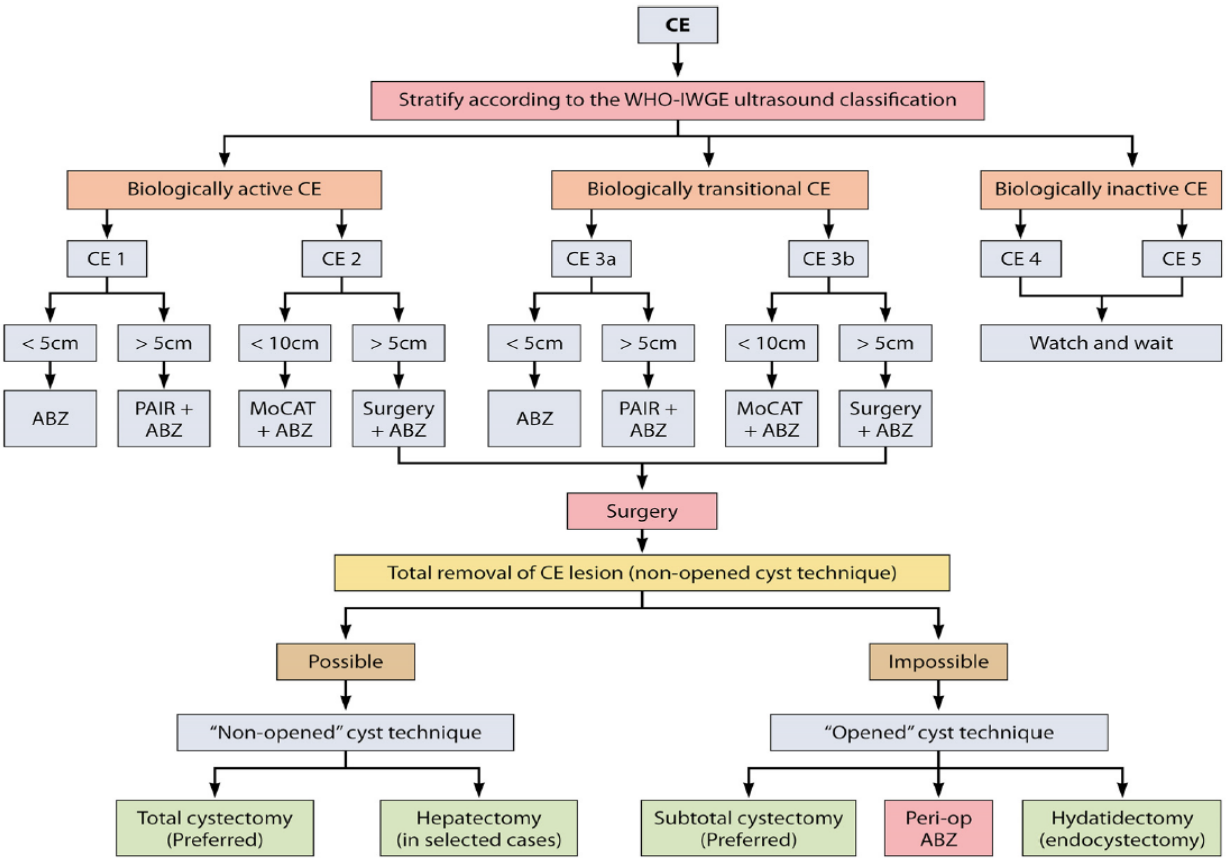

Figure 5. The algorithm therapy for cystic echinococcosis[6]

CE: cystic echinococcosis; ABZ: albendazole; PAIR: puncture-aspiration-injection-reaspiration; MoCAT: modified catheterization technique

These are the following summaries of indications, advantages, and disadvantages of 4 treatment modalities for Echinococcosis hepatic cysts. Sometimes, each modality should be combined with the other.

Table 3. Comparison between therapies[5,6,13,16]

Type of treatment	Indication	Advantages	Disadvantages
Observation and watchful waiting	• Stages CE4 and CE5 cysts (inactive, degenerative, variable size)	Non-invasive	• Long-term follow-up • Noncurative,
Chemotherapy	• Stages CE1, CE 3A (single compartment and < 5 cm in diameter) • Inoperable cases with multiple cysts & peritoneal involvement • Pre-surgical or pre-puncture cases for cyst pressure reduction	Non-invasive	Sometimes noncurative, long duration of therapy, and should be combined with any other treatment
Puncture, aspiration, injection, and re-aspiration (PAIR)	• Stages CE1, CE 3A (single compartment and > 5 cm in diameter) • Large cysts likely to rupture • Early pregnancy • Chronic hepatic condition or bone marrow suppressive disorder • CE 1, CE3a cysts that have not responded well to medical therapy	Minimally invasive	• Potential anaphylactic shock • Post-treatment monitoring using leukocyte count, aminotransferases, and ultrasound should be done every 3 to 6 months initially then once yearly once the patient is stable
Surgical resection	• Stages CE2–CE3b cysts > 5 cm in diameter, with multiple daughter cysts, superficial sites, or infected cysts • Percutaneously inaccessible cyst • Cysts communicating with biliary structure and causing a compression effect on the surrounding organs • Complex multi-separated cyst	Conservative techniques: usually safer, simpler, and are best used in cases of uncomplicated cysts Radical techniques: lower risk of recurrence and complications Laparoscopy: minimally invasive method, lower disease morbidity, and shorter hospital stay	Conservative techniques: high risk of postoperative complications such as leakage of bile from the bile and cyst connection, peritonitis, and bilomas Radical techniques: intraoperative risk during surgery is very high Laparoscopy: laparoscopic technique can only be used in certain cases

CONCLUSION

Cystic echinococcosis is a zoonotic disease caused by infection with cestode worms in the larval stage. Six species of echinococcus have been found, but only four species can cause serious diseases in humans. Cystic echinococcosis have a wider distribution than alveolar echinococcosis. There are 70% of cysts are found in the liver. The life cycle of *E. granulosus* requires two hosts, an intermediate and a definitive host. Humans are intermediate hosts who are accidentally infected. In the early phase, cystic echinococcosis is always asymptomatic. Symptoms usually appear in the form of a suppression effect on the surrounding organs. The definitive diagnosis of cystic echinococcosis requires a combination of imaging, serologic and immunologic examination. In general, there are 4 treatment modalities such as surgery, percutaneous therapy, chemotherapy, and observation (watchful waiting).

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