Hydatid Liver Disease

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Introduction:

Hydatid disease or Echinococcosis is a zoonotic, parasitic disease transmitted to human beings by larval (metacestode) forms of tapeworms (Echinococcosis) inhabited in the small gut of carnivore animals. The main culprit parasites responsible for human infections are E. granulosus and E. multilocularis causing cystic echinococcosis (CE) and alveolar echinococcosis (AE) correspondingly. The minimum presumed worldwide human burden of cystic echinococcosis measures about 280,000 disability-adjusted life years or approximately per annum loss of US 190,000,000 US dollars (1). If untreated or inadequately treated, alveolar echinococcosis is documenting mortality of >90% within 10–15 years of diagnosis in the international literature (2). The mortality rate from cystic echinococcosis (approximately 2–4%) is inferior to alveolar echinococcosis but it may show upsurge substantially if medical management are scarce (3).

Cystic echinococcosis (CE):

A single organ involvement is documented in 80% patients, where liver is the predominant organ involved having a solitary cyst (80%) followed by lungs (20%) (4). The germinal layer of E. granulosus creates brood capsules and proto-scolecies into a central cavity occupying clear hydatid fluid. This hydatid fluid is bounded immediately by an acellular laminated film followed by host response (5). There may be “daughter” vesicles of variable dimensions in the vicinity of “mother” or initial hydatid cyst (6).

Pathogenesis:

Radiologic based Reviews documented that cysts may grow in size from 1–50 mm yearly or may remain static for decades (7). During course of time, these cysts may also tend to rupture instantly, collapse or even vanish (8-11).

These cysts usually are asymptomatic till they avail a specific size and mostly these cysts induce pressure symptoms. Abrupt clinical presentation is mostly the result of instant rupture of these cysts. Liver cysts are documented to grow at a slower pace as compared to lung cysts(12).

Diagnostic tools:

1. Ultrasound (U/S) examination and World Health Organization (WHO) classification:

   Ultrasound is the modality of choice for the diagnosis of CE involving abdominal organs for the individual as well as community screening and diagnostic purposes (13).

   In 1995, the WHO in collaboration with Informal Working Group on Echinococciosis (IWGE) devised a classification system for CE. This classification comprises of: Active
CE(CE1, CE2), Transitional CE(CE3) and Inactive CE (CE4, CE5) respectively (14). This classification system proceeds from early to late stages of CE (CE1, CE2 are initial while CE4 /CE5 are late stages of CE infections) (Fig 1).

WHO-IWGE classification is currently widely used classification for CE infections worldwide. This classification is different from that of Gharbi’s classification (1981) in following perspectives: (a) addition of undifferentiated stage or cystic lesion (CL), (b) reversing the sequence of CE2 and CE3 and (c) further subclassifying CE3 into CE3a (having cysts with detached endocysts) and CE3b (having compact cysts with daughter vesicles) (Fig 2) (15).

![Figure No.1: WHO-IWGE classification of CE](image1)

![Figure No.2: Comparison of Gharbi’s and WHO-IWGE ultrasound classification](image2)
2. Other imaging modalities:

Conventional radiography is valuable in the diagnosis of thoracic and bony involvement of CE. MRCP is advised in (i) sub-diaphragmatic setting (ii) disseminated ailment (iii) extra-abdominal position (iv) complicated cysts (e.g; abscess, cysto-biliary fistulae), and (v) pre-op assessment (16).

3. Direct assessment of E. granulosus and its viability:

Antigen detection of this parasite contributes no effective clue to viability of CE. Similarly calcification per se is not a valid criterion of non-viable cyst (especially CE4/CE5), however, it may be demonstrable in all phases of CE (17). MR spectroscopy has also been assessed to evaluate viability of cysts in fluid samples obtained either through surgical or percutaneous approach (16).

4. Serologic modalities:

The sensitivity of serologic tests to detect serum antibody for CE (either by indirect hem-agglutination, ELISA, or latex agglutination tests) along with antigen assays in hydatid fluid sample ranks from 85–98% for hepatic hydatosis, 50–60% for pulmonary and 90–100% for multi-organ hydatosis (18-20).

However, confirmatory tests (like Antigen B, 8 kDa/12 kDa subunits or EgAgB8/1 immunoblotting or Arc-5 test etc) must be performed for doubtful scenarios (18, 19).

Treatment of CE:

Management recommendations for CE are multifaceted and depends on hydatid cyst’s characteristics, existing medical and surgical competence/equipment and compliance of patients to follow-up during course of this disease (21). These treatment options are then graded on the basis of grading system of recommendation and evidence by Infectious Diseases Society of America (IDSA). (Table 1)

Table 1: Infectious Diseases Society of America grading system

<table>
<thead>
<tr>
<th>Strength of recommendation</th>
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<tbody>
<tr>
<td>A</td>
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<tr>
<td>B</td>
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<tr>
<td>C</td>
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<tr>
<td>D</td>
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<td>E</td>
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<tr>
<td>Quality of evidence</td>
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<tr>
<td>---------------------</td>
</tr>
<tr>
<td>I</td>
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<td>II</td>
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</tbody>
</table>

A. Surgical approach for CE:

Surgical intervention options for CE include conservative, radical, and laparoscopic modalities (22).

a) **Conservative approaches:** it involves: (i) simple tube drainage, (ii) marsupialization, (iii) capitonnage, (iv) de-roofing, (v) partial simple cystectomy and, (vi) open/closed total cystectomy with/without omentoplasty (4, 23).

b) **Radical approaches:** Radical approaches comprises of: (i) total pericystectomy, (ii) partial hepatectomy, and (iii) lobectomy (24).

c) **Laparoscopic drainage:** This is a least invasive, safe and effective approach. (25-27).

Surgery for abdominal cysts:

**Indications:**

To manage complicated cysts, surgery is the first option. The main indications are:

i. To remove large CE2 and CE3b cysts having numerous daughter vesicles.

ii. Isolated hydatid cyst, located superficially, rupturing either instantly or due to trauma when percutaneous techniques are not available.

iii. Infective hydatid cysts when percutaneous techniques (PT) are non-available.

iv. Hydatid cysts in-communication with the biliary tract (as an alternate to PT) and

v. Hydatid cysts having pressure effects on nearby vital structures (3).

**Contraindications:**

This option is contraindicated for CE in following situations:

i. General contra-indications for surgery, i.e.,

   1. Refusal of surgery by Patient
   2. Extreme geriatric group
(3) Pregnant ladies

(4) Patients having severe co-morbid diseases (i.e., DM/HTN, renal, cardiac or hepatic disorders)

ii. Patients having multiple hydatid cysts

iii. Difficult to approach these cysts by surgery

iv. Dead cysts

v. Calcified cysts (either partially or totally), and

vi. Small cysts without pressure symptoms (28).

Preferred surgical option:

The basic concept of surgical technique is to remove maximally possible parasitic material. However, this aggressive approach increases the operative risk at the cost of lower relapse rate and vice versa (22).

Pericystectomy: it may be open or closed technique. Closed total pericystectomy carts off these cysts without opening while open total pericystectomy first sanitizes these metacestodes with protoscolicidal agents, expels cystic contents and then eradicates these pericystic tissues. The partial cystectomy differs by that contents of the cysts are sterilized, removed after opening while the pericyst is only partially resected. Partial cystectomy is appropriate for CE patients living in endemic areas where specialized hepatobiliary surgeons are scarce and surgeries for CE are performed by general surgeons (29).

Protoscolicidal measures:

Every possible step should be taken to prevent spillage of cystic fluid. These steps include protection of peritoneal structures with surgical drapes soaked in protoscolicidal agents and protoscolicidal injection inside cyst before opening. A solution of 20% hypertonic saline is usually recommended for this purpose (30). This saline solution is recommended to be in contact with the germinal layer of the cyst for a minimum 15 minutes and should be eluded when there is biliary fistula to prevent chemically induced sclerosing cholangitis (31).

Concomitant drug treatment:

Preoperative treatment is recommended to minimize the hazard of secondary echinococcal infections and should commence at least 4 days prior to surgery and should continue for 4 weeks in case of albendazole (ABZ) or 12 weeks in case of mebendazole (MBZ) therapy. This approach reduces CE intracystic pressure, making it much more convenient for the surgeon to remove these endocysts (32, 33).
Table No.2: Stage specific classification of Cystic Echinococcosis

<table>
<thead>
<tr>
<th>WHO-IWGE classification</th>
<th>Surgery</th>
<th>Percutaneous treatment (PT)</th>
<th>Drug therapy</th>
<th>Suggested</th>
<th>Resources setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>CE1</td>
<td></td>
<td></td>
<td>&lt;5 cm ABZ</td>
<td>Optimal</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>PAIR approach</td>
<td>Minimal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>+</td>
<td>&gt;5 cm PAIR + ABZ</td>
<td>Optimal</td>
<td></td>
</tr>
<tr>
<td>CE2</td>
<td></td>
<td></td>
<td>PAIR approach</td>
<td>Minimal</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other PT + ABZ</td>
<td>Optimal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>+</td>
<td>Other PT</td>
<td>Minimal</td>
<td></td>
</tr>
<tr>
<td>CE3a</td>
<td></td>
<td></td>
<td>&lt;5 cm ABZ</td>
<td>Optimal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>+</td>
<td>PAIR approach</td>
<td>Minimal</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;5 cm PAIR + ABZ</td>
<td>Optimal</td>
<td></td>
</tr>
<tr>
<td>CE3b</td>
<td></td>
<td></td>
<td>Non-PAIR PT + ABZ</td>
<td>Optimal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>+</td>
<td>Non-PAIR PT</td>
<td>Minimal</td>
<td></td>
</tr>
<tr>
<td>CE4</td>
<td></td>
<td></td>
<td>Wait and watch approach</td>
<td>Optimal</td>
<td></td>
</tr>
<tr>
<td>CE5</td>
<td></td>
<td></td>
<td>Wait and watch approach</td>
<td>Optimal</td>
<td></td>
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</tbody>
</table>

**Benefits of Surgical approach:**

This approach can cure the disease entirely but the risk of relapse is a possibility. The level of evidence on the basis of meta-analytic reviews is low for the surgical management of complicated hepatic and disseminated cystic echinococcosis (34).

**Risks of Surgical approach for CE:**

The risks of surgical approach include general hazards conferred to any surgery (like anesthesia, infections, anaphylaxis, blood-borne and IV transmissible diseases, spillage of active parasitic...
contents causing secondary echinococcosis (2-25%) and potential risk of relapse if some cysts are left during surgery. Although operative mortality is low (0.5- 4 %) but it is reported to be higher than this in countries with inadequate surgical and medical care facilities (4, 30).

**Medical requirements for CE management:**

The medical personnel must have good competency in treating CE. These patients need admission in hospital having well-equipped surgical units. The economic costs of interventions and post-op health care should be in affording range of affected community (35).

**B. Percutaneous treatment approach for CE:**

Percutaneous approach is broadly classified into:

a) Annihilation of the germinal layer (PAIR approach),

b) Drainage of the entire endo-cyst (a.k.a. Modified Catheterization Technique)(36).

**a) PAIR (Puncture/Aspiration/Injection/Reaspiration) Approach:**

PAIR approach for CE treatment comprises these steps: puncture of hydatid cyst percutaneously under ultrasound supervision, maximal aspiration of hydatid cyst fluid, protoscolicidal agent injection (like 20% NaCl or 95% ethanol solution) for a minimum period of 15 minutes and then again re-aspirate the fluid contents of the cyst (37).

**Indications for PAIR approach:**

This approach is indicated in following situations:

i. Non-operable situations like patients having contraindications or refusal for surgery

ii. An-echoic cysts larger than 5 cm in diameter

iii. Gharbi’s type 1 and type II hydatid cysts (38)

iv. Hydatid cysts laminated with a regular double layer

v. Gharbi’s type III cysts larger than 5 cm in diameter having multiple septation except cysts having honeycomb like characteristics (38)

vi. Gharbi’s type I, II and III multiple cysts having 5 cm diameter and occupying various segments of liver (38)

vii. Post-surgical relapse or response-failure to chemotherapy

viii. Pregnant ladies having symptomatic cysts and

ix. Children less than 3 years old. (37, 39).

**Contraindications of PAIR approach:**
i. Unapproachable or hepatic hydatid cysts located superficially due to hazards of leakage of cystic contents in the abdomen

ii. Cysts having multiple septations (honeycomb-like cysts)

iii. Echogenic cysts

iv. Calcified or inactive hydatid cysts

v. Communicating hydatid cysts

vi. Pulmonary hydatid cysts (40, 41).

**Protoscolicidal agents in PAIR approach:**

Hypertonic saline solution (5-30% concentration) exhibits scolicidal effect by generating a robust osmotic gradient across the outer layers of protoscolices resulting in their lysis. One of the benefits of this hypertonic saline solution is that it makes CT imaging of hydatid cyst denser and attenuated which clarifies the radiologic assessment of these cysts and making it more elaborative for the physician and radiologist. Few articles are recommending absolute alcohol if cysts are > 6 cm in diameter or Type III multi-septated cysts, due to its potent sclerosing, scolicidal and obliterating effects on cyst’s cavity (38, 42-46). Before initiating PAIR, a four day course of benzimidazoles is obligatory and should be continued for at least 4 weeks in case of albendazole or 12 weeks in case of mebendazole after the procedure (47, 48).

**Advantages of PAIR approach:**

PAIR is slightly invasive and having minimal risk as compared to surgical approach. PAIR endorses CE diagnosis and eradicates significant amount of protoscolices during the process of aspiration of cystic fluid. This approach is economically cost effective in comparison to surgery with minimal hospital stay (49).

**Risks of PAIR approach:**

The risks are:

i. Just like any other aspiration related procedure (hemorrhage, mechanical trauma to nearby structures, infections),

ii. Anaphylaxis or allergic response due to leakage/spillage of cystic contents and secondary EC. Trans-hepatic puncture of cyst is recommended as puncture of superficial cysts carries a substantial hazard of leakage and spillage.

iii. Chemical induced sclerosing cholangitis,

iv. Abrupt decompression of cysts can result in biliary fistula formation,

v. Perseverance of satellite daughter cysts.
However, complications pertinent to PAIR at the hands of expertise are infrequent as compared to surgery (50, 51).

**Medical requisites of PAIR:**

The requisites are well-trained PAIR physicians and a proper well-qualified surgical standby team ready to cope with complications (52).

**Follow Up for PAIR:**

Serial ultra-sonographic follow-ups following PAIR and ABZ therapy can detect a series of changes in the echopatern of hydatid cysts. Immediately after injecting and aspirating the scolicidal agent, there is dispersion of the germinal layer from the pericyst followed by decline in cyst size, reduction in cyst contents, hardening of inner cyst structure (Pseudo-tumor formation) and in several scenarios, there is ultimate radiographic resolution of these cysts (53). Microscopic analysis detects simultaneous perpetual impairment to the germinal membrane enabling to differentiate viable protoscolices from non-viable protoscolices. Both for uni-vesicular and multi-vesicular hydatid cysts, PAIR can be applied by a single needle puncture (54).

b) **Other Percutaneous modalities:**

These techniques tend to be applied for those cysts difficult to aspirate or relapse after PAIR. A good example is CE2/CE3b cysts (4).

Cysts >10 cm (Giant cysts) are managed effectively by continuous catheter drainage till their output reaches below10mL/ day (50).

The basic aim of these percutaneous procedures is to eradicate the whole endocyst and their daughter cysts from cystic cavity (36). This goal can be accomplished by large-bore catheters, cutting and aspiration devices specifically designed for this purpose (54, 55). In one study analyzing more than 1000 cases of CE, short/medium-term success rates of these modalities were satisfactory with negligible complication rate (47, 56). These treatment options can be effectively utilized for extra-abdominal CE2 cysts (57). The Strength of recommendation and quality of evidence as per IDSA guidelines is B and III respectively.

**C. Anti-parasitic drug treatment:**

The main indications for drug treatment of CE are:

i. Non-operable cases having primary hepatic or pulmonary echinococcosis.

ii. Multiple cysts affecting two or more viscera and peritoneal structures.

iii. Prevention of relapses after surgery or PAIR (32).

iv. Pre-surgical use can diminish the hazard of relapse of CE and can make the surgery easier by reducing the intracystic pressure (58).
The main contra-indications of chemotherapy are:

i. Big cysts have the tendency to rupture. This risk maximizes if cysts are superficial and infected. Only Benzimidazole (BMZ) therapy is ineffective in hydatid cysts > 10 cm diameter as BMZ is having low potency in cysts having significant fluid collection.

ii. Calcified and inactive hydatid cysts.

iii. Medical disorders significantly compromising liver and bone marrow functions as these medications are hepatotoxic and myelotoxic.

iv. First trimester of pregnancy is a contraindication and chemotherapy in 2nd or 3rd trimester is rarely recommended in the literature. Although literature failed to document any abnormal birth outcome with albendazole in pregnant ladies, usage of ABZ in gravid or potentially gravid women should be very cautious keeping in mind the benefit versus risk ratio (59).

**Medications: Benzimidazoles (BMZ):**

The drug of first choice to treat CE at the moment is albendazole (ABZ) either alone or in combination with PT. It is recommended in a dose of 10–15 mg/kg.body weight daily in two divided doses along with high fat diet to maximize its bioavailability (60). Albendazole has documented better in-vitro activity, improved pharmacokinetics and better clinical trials in comparison to MBZ. Albendazole after oral administration underwent first-pass metabolism to albendazole sulfoxide (active metabolite), avails variable levels in blood, bile, hepatic tissues, hydatid fluid, and walls of the cysts and then passes through blood-brain barrier. The current concept is to administer ABZ uninterruptedly in contrast to treatment interruptions on monthly basis advocated in 1980’s (60). The previous concept of treatment interruptions was based on the scarcity of long-term data availability regarding toxic effects of ABZ during that era; however, current literature is not favoring treatment interruptions for CE anymore (4, 61).

**Important Drug interactions:**

Medications that increase the level of ABZ are: dexamethasone, praziquantel, cimetidine and antiepileptic drugs (carbamazepine, phenytoin, and phenobarbital). All these drugs enhance bioavailability of ABZ with increased levels of its active metabolite (62).

Antifungal drug clotrimazole diminishes in-vitro activity of sulfonase in microsomes inhibiting the formation of active and inactive metabolites of ABZ. In case of non-availability or intolerability of ABZ, mebendazole (MBZ) may be used as an alternative, in 3 divided daily doses of 40–50 mg/kg along with high fat food (47, 60).

**Other drugs:**

Praziquantel (PZQ), another antiparasitic agent, has restricted use in the treatment of hepatic hydatosis. This drug enhances the entry of calcium ions into the cell membrane of parasite, initiating robust muscular contractions and paralysis resulting in detachment of cyst from host.
tissues. It is an effective scolicidal agent both in-vitro and experimental animals. In human beings, it has satisfactory drug levels when taken at a dosage of 50 mg/kg.body weight either at every week or every two weeks interval. Various studies have documented the efficacy of combination of PZQ/MBZ or ABZ as compared to BMZ alone (63). Marchiondo A has reported non-viable cysts during surgery when patients are treated pre-operatively with combination of ABZ+PZQ therapy (64). Even few studies have documented the supremacy of combination of PZQ/ABZ over ABZ alone as an effective protoscolicidal agents, however, the effectiveness of PZQ to prevent relapses needs further research (58).

**Advantages of Chemotherapy:**

Chemotherapy is a noninvasive option for patients of all ages, even though limited data is available for children < 6 years age and chemotherapy is least compromised by patient's well-being with the exception of pregnancy in comparison to surgery. Chemotherapy is an outpatient treatment option. Albendazole is more effective in young person having small CE1/CE3a hydatid cysts. However, BMZ are less effective in the management of CE2/CE3b hydatid cysts (60, 65). Systematic reviews have confirmed the significance of cyst’s stage and size in defining the response to treatment (66).

**Adverse events of chemotherapy:**

The adverse events of BMZ are hepatotoxicity (transient rise in aminotransferase levels), neutropenia, thrombocytopenia and alopecia (67).

**Monitoring of patients with CE:**

Regular follow-ups along with ultrasonography should be performed initially after every 3–6 months and then on yearly basis once the condition is stable. Serial WBC’s and ALT/AST levels monitoring are mandatory at monthly basis to determine adverse events. The dosage of oral medications can be adjusted on individual basis to achieve optimum serum drug levels but only limited labs have competence to measure ABZ/MBZ plasma drug level (47). The medical and lab assessments of these patients for adverse events are mandatory initially every 2 weeks and then on monthly basis. The WBC counts need monitoring at 2 weekly intervals during the first 12 weeks of therapy as in exceptional scenarios catastrophic and even irreversible myelosuppression has been documented during the initial phase of treatment.

Ideally serum drug levels of ABZ or MBZ should be monitored at 2 and 4 weeks of chemotherapy in order to determine toxic/ineffective drug levels. In case of MBZ, serum drug levels should be monitored 4 hours after the morning dosage. However, this practice is very difficult in poor and developing countries due to higher cost and limited lab facilities to determine drug concentration level. The management of CE requires long-term chemotherapy and evaluation after every 3 months is required to determine efficacy of this chemotherapy (68). Radiographic imaging should be performed during each follow up (69).

**Management of asymptomatic CE detected during screening:**
Mass screening is not recommended on ethical grounds without the consent of community under study and elaborative concept regarding medical care should be offered to individuals having suspicion of CE. If willing, they can undergo specific serologic and clinical assessments for confirmation of diagnosis and selection of those requiring treatment. Infected individuals who are not candidate of urgent treatment needs careful monitoring on regular basis (70).

**Alveolar echinococcosis:**

Alveolar echinococcosis (AE) is a dreadful disease due to larvae of E. multilocularis and manifested as infiltrative growth mimicking tumor like conditions. Its management evolves around different options including chemotherapy and entails specialized clinical expertise (71). All patients with suspicion of AE needs timely referral to a nearby well- experienced AE treatment center. Prompt diagnosis is of prime significance for proper managements as AE community screening programs in endemic zones of the world have clearly displayed the significance of early diagnosis to minimize morbidity and mortality of this disease (72).

**Organ involvement in AE:**

Primarily, liver is the first organ to be infected by the metacestodes. The right hepatic lobe shows predominance, however, hepatic hilum along with one or two lobes may also be affected. These hepatic lesions may vary in size from few mm to > 15 cm in diameter. Primary extra-hepatic involvement of these metacestodes is extremely uncommon (73). These metacestodes of E. multilocularis then disseminate from liver to other structures by infiltration or metastasis.

**Pathogenesis of AE:**

AE infection comprises of initial incubation period of asymptomatic phase lasting from 5-15 years to be followed by chronic course of this disease. The clinical features are usually of cholestatic jaundice and epigastric pain (in approximately 1/3 of cases each) while the remaining (1/3 of cases) AE patients are diagnosed incidentally during medical check-up for lethargy, weight loss, visceromegaly or abnormal lab reports (74). Literature is reporting high mortality rate amongst non-treated/inadequately treated patients. A clinical report from Germany documented 5 year mortality of 70% and 10 year mortality of 94% (75). Another study from Alaska reported average survival rate of 5.3 yrs and 100 % mortality within 14 yrs of diagnosis. However, host immune system has capability to degenerate and even kill the larva of AE and these dead calcified lesions can be recognized during mass screening programs (71, 76, 77).

**Diagnosis of AE:**

AE is diagnosed on the following parameters: interpretation of clinical manifestations, epidemiological data and morphology of lesions under imaging modalities in combination with immunological and other lab investigations.
1. Ultrasound examination:

U/S examination requires competence level. The U/S findings in 70% of cases are:

i. Correlation of hyper and hypo-echogenic foci in pseudo-tumor having asymmetrical margins and scattered calcification and

ii. Pseudo-cystic morphology comprising of central necrosis bounded by irregular hyper-echogenic rim.

In the remainder 30% scenarios, it may be either

i. Hyperechoic lesion nodule like hemangioma or

ii. Calcified focus of dead or tiny parasites (78, 79).

2. CT and other Imaging techniques:

CT imaging gives good results in determining the anatomical and morphological characteristic of the lesion and its calcification. MR modality may elicit the multi-vesicular appearance of these foci, thus favoring AE diagnosis (79). MRCP has substituted percutaneous cholangiography to evaluate the correlation of AE lesion and hepatobiliary tract (79).

3. Assessment of E. multilocularis and its viability:

Histopathology confirms these vesicles to be demarcated by a laminated layer of Periodic Acid Schiff. PCR of biopsy tissues can detect Echinococcus specific nucleic acids while RT-PCR may evaluate even viability of these lesions (80, 81). FDG-PET scan may indirectly delineate active foci of parasites. When patients are asymptomatic and there is high suspicion of relapse despite normal conventional imaging, these modern imaging modalities in combination with CT (PET/CT) or MRI (PET/MRI) may be helpful to detect active disease (82, 83).

4. Multilocularis serology:

The diagnostic sensitivity and specificity of E. multilocularis antigens produced either by purified/recombinant or in-vitro technique ranges from 90–100% and 95–100% respectively (81).

W.H.O. classification of AE:

AE is classified by WHO-IWGE PNM classification system. PNM classification system represents hepatic involvement by the parasitic lesion (P), extension to nearby structures (N) and metastases (M) (84).

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<table>
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<tbody>
<tr>
<td>P</td>
<td>Hepatic involvement of AE</td>
</tr>
<tr>
<td>PX</td>
<td>Primary lesion can’t be evaluated</td>
</tr>
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Table No.3: W.H.O. classification of Alveolar echinococcosis
<table>
<thead>
<tr>
<th>No</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>P0</td>
<td>No detectable hepatic lesion</td>
</tr>
<tr>
<td>P1</td>
<td>Peripheral lesions without involving proximal vasculature and/or biliary tract</td>
</tr>
<tr>
<td>P2</td>
<td>Central lesions with proximal vascular and/or biliary tract involvement of one lobe</td>
</tr>
<tr>
<td>P3</td>
<td>Central lesions with hilar vascular or biliary tract involvement of both lobes and/or with involvement of two hepatic veins</td>
</tr>
<tr>
<td>P4</td>
<td>Any hepatic lesion with involvement of the vessels and the biliary tract</td>
</tr>
<tr>
<td>N</td>
<td>Extra-hepatic involvement of nearby structures (pleura, lung, diaphragm, heart, pericardium, peritoneum, gastric and duodenal wall, adrenal glands, retroperitoneum, parietal walls of muscles/bone/skin, pancreas, regional lymph nodes, liver ligaments and kidney etc;</td>
</tr>
<tr>
<td>NX</td>
<td>Non-evaluable</td>
</tr>
<tr>
<td>N0</td>
<td>No regional involvement</td>
</tr>
<tr>
<td>N1</td>
<td>Regional involvement of neighboring structures</td>
</tr>
<tr>
<td>M</td>
<td>The absence or presence of distant metastasis (spleen, lung, distant lymph nodes, CNS, orbital, bone, skin, muscle, kidney, distant peritoneum and retroperitoneum)</td>
</tr>
<tr>
<td>MX</td>
<td>Not completely evaluated</td>
</tr>
<tr>
<td>M0</td>
<td>No metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Metastasis</td>
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</tbody>
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**Diagnostic criteria of AE:**

At least one of the following four diagnostic criteria is required to diagnose AE:

i. Distinctive organ lesions identified by imaging techniques (abdominal U/S, CT, MRI)

ii. Detection of Echinococcus species specific serum antibodies by high sensitivity serological tests and confirmed by a high specificity serological test

iii. Histopathologic findings compatible with AE

iv. Detection of E. multilocularis nucleic acid sequence in a clinical scenario (84).
Possible versus probable versus confirmed case of AE:

Possible case: A patient having clinical, epidemiologic and imaging features or serologic evidence of AE.

Probable case: A patient having clinical, epidemiologic, imaging features and serologic evidence of AE with two positive tests.

Confirmed case: All the above features and (1) histopathologic findings compatible with AE and/or (2) detection of E. multilocularis nucleic acid sequence(s) in a clinical acumen (84).

Treatment of AE:

The following concepts are generally considered in the management of AE:

i. Radical surgery of the whole lesion is first option in all operable patients.

ii. Chemotherapy after radical resection is indicated for a limited time.

iii. Chemotherapy of prolonged duration is compulsory if: lesion is incompletely resected, non-operable conditions including post-interventional procedures and post-liver transplant AE patients. Referral to a recognized nearby AE treatment center is advisable and if this is not feasible, treatment should be initiated under the supervision of such center (85).

Table No.4: Stage-specific approach to AE
<table>
<thead>
<tr>
<th>WHO classification</th>
<th>Surgery</th>
<th>Interventional treatment</th>
<th>Drug therapy</th>
<th>Recommended</th>
<th>Resources setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1N₀M₀</td>
<td>+</td>
<td>+</td>
<td>BMZ</td>
<td>Radical resection (R₀)</td>
<td>Optimal</td>
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<td></td>
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<td>BMZ for 2 years</td>
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<td>PET/CT controls</td>
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<td>Radical resection (R₀)</td>
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<td>BMZ for 3 months</td>
<td>Minimal</td>
</tr>
<tr>
<td>P2N₀M₀</td>
<td>+</td>
<td>+</td>
<td>BMZ</td>
<td>Radical resection (R₀)</td>
<td>Optimal</td>
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<td></td>
<td>BMZ for 2 years</td>
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<td></td>
<td></td>
<td>BMZ for 3 months</td>
<td>Minimal</td>
</tr>
<tr>
<td>P3N₀M₀</td>
<td>+</td>
<td></td>
<td>BMZ</td>
<td>Radical resection (R₀)</td>
<td>Optimal</td>
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<td>P3N₁M₀</td>
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<td>P4N₀M₀</td>
<td>+</td>
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</tbody>
</table>

**Surgery for AE:**

The excision of these lesions is conducted by the principle of radical tumor resection. Radical or non-radical resections and liver transplantation needs adjuvant chemotherapy. Radical resection
of lesion is the main aim of management. Excision of the whole lesion follows the basics of tumor resection and is classified on the basis of quality of resection: R₀: without residue; R₁: microscopic residue; R₂: macroscopic residue.

Initially considered to be a beneficial option in reduction of parasitic load, non-radical hepatic surgery confers no advantage over conservative management (72, 85).

Parasitic foci not restrained to liver are not considered to be contraindication for surgery but they must fulfill R₀ resection criteria, otherwise, these lesions must be managed by alternative approaches following interdisciplinary integration. Lesions affecting other organs (brain etc.) may undergo either surgery or alternative interventions. All these treatment modalities must be accompanied with adjuvant BMZ chemotherapy for 2 years at least (86).

**Indications of Surgery for AE:**

Radiologic assessment of these lesions before surgery is mandatory as lesion’s resectability in liver is a prerequisite for radical surgery. These pre-op assessments will determine potential for resection and possibility of dissemination of disease too (85).

**Contraindications of Surgery for AE:**

a) Non-operable disease

b) Disseminated lesions (85).

**Choice of the surgical techniques for AE:**

Radical resection (R₀ resection) is the first choice of treatment. Surgical techniques and modalities adopted in oncology with a concept of 2 cm clear margins are practiced during resection of these parasitic lesions (64, 87, 88). All Post-op patients must undergo chemotherapy with BMZ and long-term follow-up. Palliative surgery is not recommended but the diverse characteristics of AE in some instances may pursue this approach. If PT approach fails for a septic focus, then R₀/ R₁ or even R₂ surgical resection is advised. To treat skin lesions, a combination of palliative resection with adjuvant BMZ is also beneficial (85). The Strength of recommendation and quality of evidence as per IDSA guidelines is B and III respectively (85).

**Benefits of surgery:**

Radical surgery may eradicate these parasites and cure the disease. A timely diagnosis markedly enhances the perspective of cure for AE. Non-radical surgery may be helpful to minimize the parasite load and augment the efficacy of chemotherapy (89).

**Liver transplantation for incurable AE:**

Liver transplantation as a treatment option was utilized in 45 cases having incurable AE across 65 hepatic transplant centers in European countries (90). However, literature is reporting relapse of disease under the influence of immunosuppression (47).

The main criteria to qualify AE patients for liver transplant (LT) are:
i. Decompensated liver failure (like secondary biliary cirrhosis/hepatic vein thrombosis) or recurrent episodes of severe cholangitis and

ii. Non-operable radical resection of liver.

**Indications for LT in AE infections:**

Interdisciplinary integration is mandatory for LT in patients having severe AE with decompensated liver disease and it necessitates long-term postop chemotherapy (90).

**Contraindications for LT:**

LT is contra-indicated in: disseminated AE, AE patients having contraindications for long-term immunosuppression/or adjuvant BMZ (90).

**Benefits of LT:**

LT may be a lifesaving approach in patients having severe hepatic compromises.

The survival rate of 5 years with and without relapse is reported in few studies of approximately 71% and 58% respectively which is encouraging in comparison to HCC (91). Long-term cure is a possibility in AE patients having residual or recurrent disease with adjuvant BMZ therapy (90, 92).

**Risks of LT in AE:**

Risks are same as for general surgery/anesthesia, risks associated with immunosuppression, regrowth and relapse of disease and metastases specifically to CNS during immunosuppressive therapy (91). The Strength of recommendation and quality of evidence as per IDSA guidelines is C and II respectively (91).

**Medical requirements for LT:**

LT needs state of the art center and well trained highly experienced staff along with back-up medical team having ample experience in post-transplant management (93).

**Chemotherapy for AE:**

Meta-analysis in animals has documented the significance of parasito-static efficacy of BMZ against metacestodes of E. multilocularis and on this basis; chemotherapy in humans for AE is being practiced as early as 1975. Survival rate comparison between patients treated with BMZ and untreated historical cohorts is documenting that 10 year survival rate of treated cohort has augmented from <10 % to 85-90%. This improvement in survival is the contribution of chemotherapy together with timely diagnosis, improvisation of surgical and medical care of AE patients (93).

**Indications of Chemotherapy for AE:**

Prolong yearly therapy with BMZ is compulsory for all AE patients having non-operable disease and those having post-resection of the lesions. As the remnants of AE residues after radical
surgery/LT may persist undetected, so BMZ therapy is recommended for a minimum 2 years and these cases needs monitoring for at least a decade for potential relapse (86). Pre-surgical chemotherapy is not recommended for AE except in patients having contra-indications for surgery, however, surgery can be pursued after long-term chemotherapy (93).

**Contraindications of Chemotherapy:**

There are few contraindications of chemotherapy and include life-threatening side effects. Pregnant ladies need specific precautions as already discussed (93).

**Choice of anti-helminthics in AE:**

Two BMZ (MBZ and ABZ) are preferentially used for chemotherapy of AE.

The dose of ABZ is same as recommended in CE (10–15 mg/kg, in daily 2 divided doses with high fat diet). In daily clinical practice, a total dose of 800 mg/day is given orally to adults in 2 divided doses. Non-interrupted ABZ therapy for AE is well tolerated and is being in clinical practice for more than 20 years (93).

ABZ has been prescribed in higher doses of 20 mg/kg/day for 4-5 years in occasional scenarios. In case of non-availability or intolerability of ABZ, MBZ can be substituted in a daily oral dose of 40–50 mg/kg divided into three doses with high fat diet (93). The Strength of recommendation and quality of evidence as per IDSA guidelines is B and III respectively (93).

**Other Drugs for AE:**

PZQ can be an alternative option in AE but animal experimental data is not favoring its efficacy even in very high doses (64). Conventional or liposomal Amphotericin B has been utilized as an alternative therapy in few cases who were not tolerating BMZ (94). Nitazoxanide has not documented any efficacy a recent trials (95). New formulations of ABZ may improve bioavailability, however; further randomized trials are needed to draw definite conclusions regarding these new formulations (93).

**Benefits of BMZ therapy:**

BMZ is a noninvasive option having minimal side effect profile. However, this therapy is parasito-static in most cases (93).

**Risks of BMZ therapy:**

The main hazards of BMZ therapy and its use during pregnancy have already been described in detail.

**Medical requirements for Chemotherapy:**

Patients can be managed on out-patient basis but regular clinical and lab surveillance is mandatory (93).
Pharmacovigilance of Chemotherapy:

Regular follow-ups for adverse events are necessary initially every 2 weeks for first 12 weeks, then on monthly basis for first year and later on every 3 months. As BMZ is mandatory for all AE cases, so if ALT/AST values rises more than 5 times ULN, the following precautions should be followed: (a) evaluate these patients for other causes of rise in aminotransferase levels, (b) monitor drug therapeutic level, (c) if there is higher serum drug level of BMZ in comparison to recommended therapeutic level, minimize the parent drug dosage and switch to available alternative BMZ, and (d) if still aminotransferase values remain above 5×ULN, consultation to a reference center becomes mandatory. A reduction in WBC count below 1.0×10^9 /L specifies toxicity of BMZ and necessitates urgent treatment withdrawal (93).

Interventional options for AE:

AE patients having contraindications for surgery may develop a variety of complications. These complications can be effectively managed in combination with chemotherapy by interventional procedures like: dilatation/stent implantation in vessels, drainage of necrotic liver lesions and/or bile, and endoscopic sclerosing of esophageal varices (89).

Indications of Interventional options:

These procedures are indicated if surgical option is impracticable due to involvement and dysfunction of vital structures (i.e. hyper-bilirubinemia due to cholestasis, thrombosis of portal vein/inferior vena cava, liquefactive necrosis of liver with rupture into abdomen and risk of esophageal varix bleeding due to portal hypertension) (89).

Contraindications of interventional procedures:

Interventional procedures have the tendency to metastatise this disease and is not recommended if post-procedure chemotherapy is impracticable (89).

Principles of interventional procedures:

Bile or abscess drainage by percutaneous approach has substituted palliative surgery with jejuno-biliary anastomosis to manage critical cholangitis or hepatic abscess (78, 79). Dilatation of bile duct strictures endoscopically followed by insertion of multiple plastic stents is another alternative to percutaneous interventions as it quickly manages internal bile obstruction (79). Adjuvant therapy with urso-deoxycholic acid (UDCA) is practiced in few centers; however its efficacy in prophylactic stent obstruction needs approval from prospective studies (79).

Benefits of interventional procedures:

Interventional procedures in combination with adjuvant chemotherapy may improve the quality and expectancy of life of AE patients (89).
Risks associated with interventional procedures:

Risks of endoscopic and percutaneous interventions (EPIs) include hemorrhage and internal or prolonged external biliary leakage (89). The Strength of recommendation and quality of evidence as per IDSA guidelines is B and III respectively (89).

Surveillance of AE patients:

All types of treatment modalities require regular long-term follow-up by U/S and CT/or MRI scans at interval of 2–3 years. Progress of disease is manifested as enlargement of lesions with passage of time. Serum drug level of ABZ should be determined 4 hours later to morning dose approximately 3 months after treatment initiation and 2–4 weeks after each dose adjustment. The target therapeutic range is 0.65–3 mol/L. If two serial serum levels of ABZ are > 10 mol/L, then the dose of this drug needs reduction. Similarly, serum MBZ level can also be monitored and it should be > 250 nmol/L (47). The levels of anti-Em2 and anti-Em18 antibodies fall quickly even up-to extent of non-detection after total surgical excision of lesions (93). Serologic tests interpretation in AE patients managed with chemotherapy without radical resection is complex and needs careful interpretation (96). The detection of anti-II/3-10/Em18 antibodies favors viable metacestodes of AE and disappearance of these antibodies indicates dying out of these lesions (97).
References: