



**WHO/CDS/CSR/APH/2001.6**

**PAIR: Puncture, Aspiration, Injection, Re-Aspiration**

An option for the treatment of Cystic Echinococcosis

**World Health Organization**

Department of Communicable Disease,  
Surveillance and Response

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# WHAT IS PAIR?

**PAIR** (*Puncture, Aspiration, Injection, Re-aspiration*), was proposed in 1986 by the Tunisian team that first used it in a prospective study. The technique was developed in the middle of 1980s for the treatment of intra-abdominal localizations of Cystic Echinococcosis (CE) infection by the larval cestode, *Echinococcus granulosus*, commonly called “hydatid disease”.

PAIR is a relatively recent and minimally invasive therapeutic option, that complements or replaces surgery which was long considered as the only treatment for CE. PAIR also complements chemotherapy with benzimidazoles, (albendazole and mebendazole) which have been developed since the beginning of the 1980s for the treatment of CE.

The safety and effectiveness of PAIR have been demonstrated in more than 2000 cases published in medical literature and from a worldwide collection of data presented at the Meeting of the WHO-Informal Working Group on Echinococcosis (WHO-IWGE) held during the XVIII International Congress of Hydatidology, Lisbon, November 1997; additional evidence has been presented by a number of teams at the XIX International Congress of Hydatidology, in San Carlos de Bariloche, Argentina, in September 1999 and in published international literature.

Basically, PAIR is percutaneous drainage of echinococcal cysts located in the abdomen. However, reports exist about the use of this treatment for cysts in the lung and extra-abdominal or extra-thoracic localizations. The drainage is performed with a fine needle or a catheter, followed by the killing of the protoscolices remaining in the cyst cavity by a protoscolicide agent. If a catheter is temporarily left in the cyst after the procedure for drainage (D), the acronym PAIRD should be preferred. If numerous and large daughter cysts are present, an alternative percutaneous technique “Percutaneous Puncture with Drainage and Curettage” (PPDC) may be used; however this latter technique should only be performed in surgical settings, using specified materials. PPDC is not described in this booklet.

PAIR is performed under ultrasound (US), sometimes Computer Assisted Tomography (CT) guidance. It is feasible

in types CE1, CE2 and CE3 of the **WHO classification of Cystic Echinococcus cysts.**<sup>1</sup> This proposed imaging classification scheme has evolved from a consensus between specialists in CE, after extended exchanges and discussion within a specific network on the “classification of CE cysts at US examination” of the WHO-IWGE. Its wide use should favour a better standardization of treatment indications and evaluation in the future.

<sup>1</sup> See Annex 1

## THE USE OF PAIR IN THE TREATMENT OF CYSTIC ECHINOCOCCOSIS

PAIR IS CONSIDERED AN EFFECTIVE ALTERNATIVE TO SURGERY AND CHEMOTHERAPY.

Clinical experience including controlled trials confirms that PAIR is now a part of the expanded options for the treatment of CE. However, the use of PAIR as treatment must be discussed on a case by case basis whatever the setting and/or the country.

**Guidelines for the treatment of CE including PAIR, have been proposed by the WHO-IWGE, and published in the Bulletin of the WHO, 1996, 74:213-242.** Experience with PAIR by multiple groups in different countries has given more confidence in the efficacy and safety of the procedure, while it has also brought more insight into the precautions necessary to ensure the highest level of efficacy and safety. Consequently amendments to the recommendations published in the 1996 Guidelines have been included in this booklet.

Like any other therapeutic procedure PAIR requires clinical experience and technical skills. **It should be performed only by teams experienced in liver punctures under ultrasound (US) guidance, after specific training in this field.**

Contributors to the development of this document are available for consultation on the technique and/or for specific training; names and addresses are given in Annex 3 - Contributors.

## INDICATIONS FOR PAIR

Patients with:

- Non-echoic lesion  $\geq 5$  cm in diameter (CE1m and l)
- Cysts with daughter cysts (CE2), and/or with detachment of membranes (CE3)
- Multiple cysts if accessible to puncture
- Infected cysts

Also

- Pregnant women
- Children  $>3$  years old
- Patients who fail to respond to chemotherapy alone
- Patients in whom surgery is contraindicated
- Patient who refuse surgery
- Patients who relapse after surgery

## CONTRAINDICATIONS FOR PAIR

- Non-cooperative patients and inaccessible or risky location of the cyst in the liver
- Cyst in spine, brain and/or heart
- Inactive or calcified lesion
- Cysts communicating with the biliary tree
- Cysts open into the abdominal cavity, bronchi and urinary tract



## **BENEFITS OF PAIR**

- Minimal invasiveness
- Reduced risk compared with surgery
- Confirmation of diagnosis
- Removal of large numbers of protoscolices with the aspirated cyst fluid
- Improved efficacy of chemotherapy given before and after puncture (probably because of an increased penetration of antihelminthic drugs into cysts re-filling with hydatid fluid )
- Reduced hospitalization time
- Cost of the puncture and chemotherapy usually less than that of surgery or chemotherapy alone

## **RISKS OF PAIR PROCEDURE**

- Same risks as any puncture ( haemorrhage, mechanical lesions of other tissues, infections )
- Anaphylactic shock or other allergic reactions
- Secondary echinococcosis caused by spillage
- Chemical ( sclerosing ) cholangitis if cysts communicate with the biliary tree
- Sudden intracystic decompression, thus leading to biliary fistulas
- Persistence of satellite daughter cysts
- Systemic toxicity of alcohol or hypertonic saline in case of large cysts (total volume injected must be carefully calculated)

## RISKS OF CHEMOTHERAPY

- Adverse effects of benzimidazoles
- Potential risk of embryotoxicity and teratogenicity (observed in early stage of pregnancy in some laboratory animals). (Contraceptive measures are thus indicated in women, and PAIR should be performed without chemotherapy during early pregnancy)
- Hepatotoxicity (transient increase of aminotransferases), neutropenia, thrombocytopenia, alopecia

# HOW TO PERFORM PAIR

## BASIC REQUIREMENTS

Only personnel trained in interventional ultrasound should perform this procedure, supported by a person trained in resuscitation procedures

## EQUIPMENT, SUPPLIES, DRUGS (MINIMUM REQUIREMENTS) :

- Ultrasound equipment (portable apparatus) with a 3.5 - 5 MHz probe
- Needles (lumbar puncture needles, “fine needles”, especially for multiple daughter cysts)
- Catheters for large cysts (> 5 cm)
- 95 % alcohol or hypertonic (at least 15 %) saline as protoscolicide agent
- “Fast test” for checking the presence of bilirubin in the cystic fluid and thus rule out possible connections with biliary tree
- Optic microscope
- Drugs to be used in case of allergic reactions-anaphylaxis (epinephrine, hydrocortisone); basic resuscitation equipment
- Blood pressure measurement and intravenous catheter must be left in the forearm during the procedure, so that resuscitation can take place immediately, should the need arise

## **ADDITIONAL EQUIPMENT, SUPPLIES, DRUGS FOR OPTIMAL SITUATION**

- CT, ERCP (Endoscopic Retrograde Cholangiopancreatography), fluoroscopy
- Contrast medium to be injected in the cystic cavity to exclude possible connections with the biliary tree after the first aspiration of fluid
- Radiologic equipment for cystography using contrast medium
- Parasite examination kit
- Serologic/Antigen detection kit (ELISA, IHA)
- Biochemistry equipment for measurement of glucose and electrolytes in the fluid

## **ADDITIONAL PERSONNEL**

- Anesthesiologist
- Surgeon available for possible complications during the procedure

# PAIR STEP BY STEP

## PAIR PROTOCOL :

### (MINIMUM REQUIREMENTS)

1. Serological control
2. Prophylaxis with albendazole
3. Puncture and parasitological examination (if possible) or fast test for antigen detection in cyst fluid
4. Aspiration of cystic fluid (10-15 cc)
5. Test for bilirubin in cyst fluid
6.
  - a. If bilirubin present: → stop procedure
  - b. If no bilirubin present: → aspirate all cystic fluid
7. Injection of 95 % ethanol solution or hypertonic saline (1/3 of the amount of aspirated fluid)
8. Reaspiration of protoscolicide solution after 5 minutes
9. New parasitological control if possible

## PAIR PROTOCOL :

### OPTIMUM SITUATION - ALL FACILITIES AVAILABLE

1. Patient's informed consent, if treated by beta-blocking agents: stop the treatment at least one week before the procedure, replace it by another drug, depending on the nature of the treated disease, if necessary
2. Serological tests (IHA , ELISA), controls (US, CT, ERCP), MRI for research purpose only
3. Treatment with albendazole at least 4 hours before procedure (one week for some teams) and during the following 1st month (length of treatment depends on cyst size and US appearance, more or less solid), optimal duration of treatment has not yet been fully evaluated

4. Presence of a professional trained in resuscitation procedures - patient has an intravenous line
5. Puncture under US guidance with or without catheter
6. Aspiration of cyst fluid (10-15 cc)
  - a. If protoscolices are absent and/or antigen detection negative: →
    - i. if clinical and epidemiological data, and biochemical fluid data are negative → stop procedure  
(probably non-parasitic cyst) (non-parasitic cysts are treated with alcohol injection only when symptomatic)
    - ii. if clinical and epidemiological data, and biochemical fluid data are positive → proceed to next steps
  - b. If protoscolices are present: → continue PAIR procedure
7. Intracystic injection of contrast medium and cystography
8.
  - a. if communication with bile ducts: → stop the procedure; contrast medium may be left in the cyst as substitute of protoscolicide
  - b. If no communication with bile ducts: → inject 95% ethanol solution or hypertonic saline (1/3 of the amount of aspirated fluid)
9. Reaspiration of alcohol solution after 5 minutes
10. New parasitological control (to check protoscolex viability; eosin or methyl blue staining)
11. Parasitological, biochemical, serological, immunological and US monitoring every week for the 1st month and every other month for the 1st year, every year over 10 years
12. Chest x-ray one year after PAIR and then every other year, CT (total body) after 5 and 10 years

## MANAGEMENT OF THE PATIENT IN CASE OF ALLERGIC/ANAPHYLACTIC REACTION

- Skin reaction (urticaria [hives], oedema) without arterial blood pressure (ABP) changes (ABP>115-70 mm HG):
  - Inject hydrocortisone and/or anti-histamine drug
  - Careful monitoring of ABP
- Moderate decrease in ABP (115-70>ABP>95-50 mm Hg)
  - Temporarily stop the procedure
  - Careful monitoring of ABP
- Marked decrease in ABP (ABP<90-50 mm Hg)
  - Stop the procedure
  - Inject 1/3 mL of epinephrine (1mg/mL) IM or (3mL of a saline solution of epinephrine-1mL/10mL-through the IV catheter)
  - Careful monitoring of ABP
- If ABP<95-50:
  - new injection of epinephrine up to 1mL (IM) or 10mL of the saline solution of epinephrine (IV)

# SUMMARY OF THE CRITICAL POINTS IN THE PAIR PROTOCOL

CRITICAL POINTS	OPTIMUM SITUATION	MINIMUM REQUIREMENTS
Prophylaxis pre- & post procedure	albendazole To be administered 24 to 4 hours before intervention and 15 days to 30 days after intervention according to cyst size no treatment if pregnant	albendazole To be administered 24 to 4 hours before intervention and 15 days to 30 days after intervention according to cyst size no treatment if pregnant
Communication with biliary tree	ERCP + cystography or cystography alone	Search for bile in the fluid with fast test
Electrolytes in the fluid	Not mandatory; may help for assessing the nature of the cyst	No
Scolicidal agent to be used	Hypertonic saline (at least 15 % final concentration in cyst) or 95 % alcohol	Hypertonic saline (at least 15 % final concentration in cyst) or 95 % alcohol
Quantity of scolicide injected	At least 1/3 of the aspirated quantity	At least 1/3 of the aspirated quantity
Evaluation of viability	Microscopic examination Staining with methylene blue/eosin red	Microscopic examination if possible



**CRITICAL POINTS****OPTIMUM SITUATION****MINIMUM REQUIREMENTS**

Needle vs catheter

Needle for cysts < 5 cm  
or in multiloculated cysts  
Catheter for cyst > 5 cm (PAIRD)

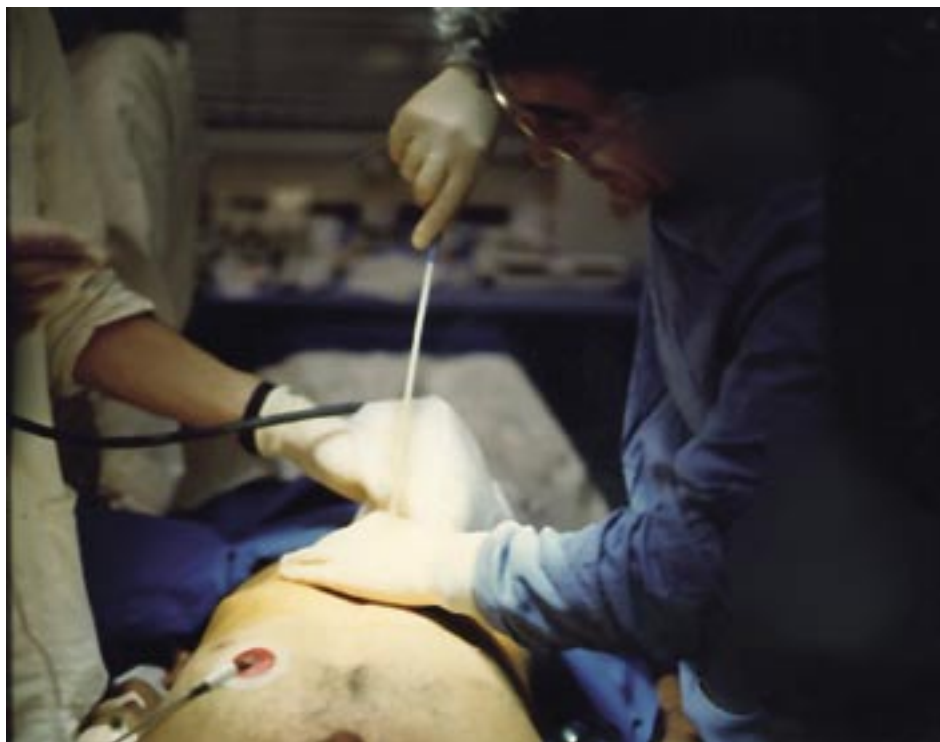
Needle ,Catheter

Follow-up

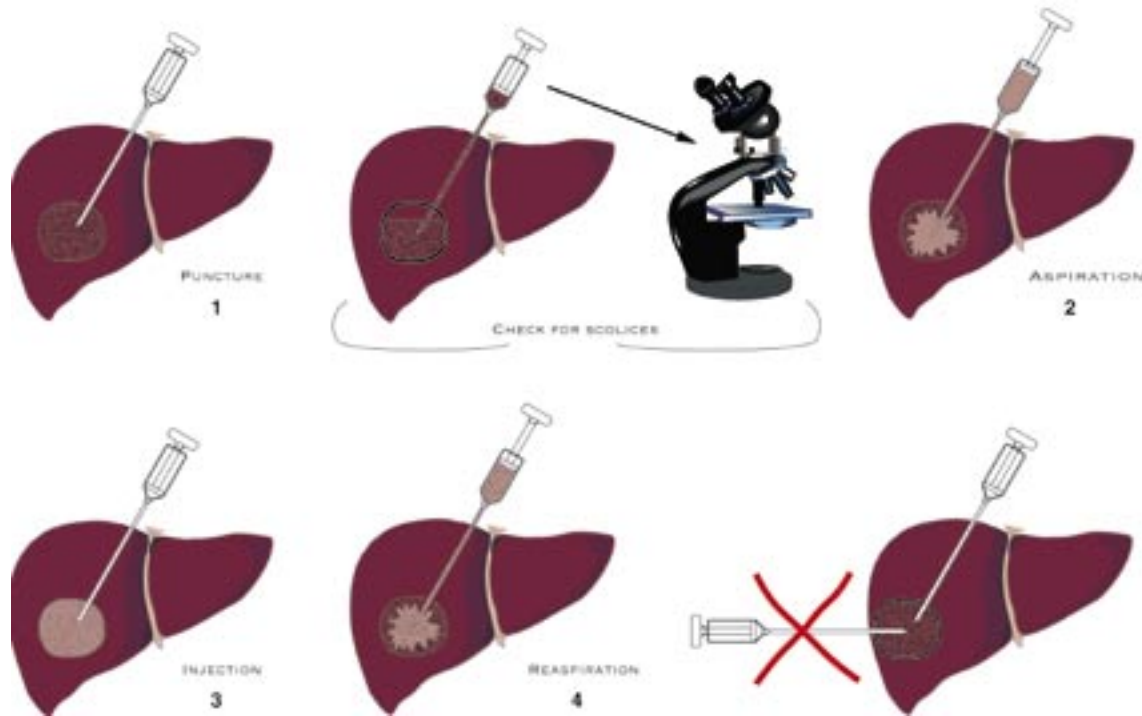
Every week for the 1st month,  
then every other month for the 1st  
year, then every year for 10 years

Every 6 months for the 1st year,  
then every year for 10 years





Percutaneous puncture under US guidance: insertion of a catheter into a large hepatic cyst (PAIRD).  
The insertion is guided by US (see the US probe wrapped in a plastic sheet behind the catheter).

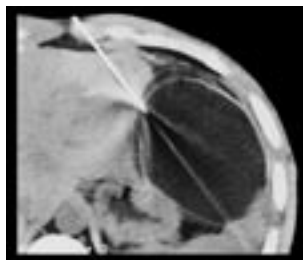


### PAIR SEQUENCE

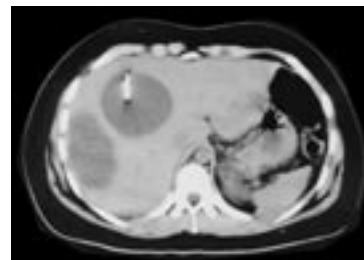
The steps of the puncture procedure (cartoon): the critical point is the angle of puncture: normal liver parenchyma must be present between the puncture point and the surface of the cyst to avoid leakage of cyst fluid (prevention of anaphylactic reactions) and protoscolex spillage (prevention of recurrences). Direct puncture of a cyst close to the abdominal wall must be avoided.



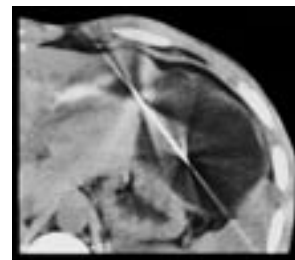
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2



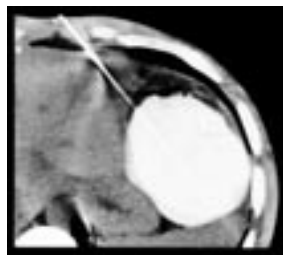
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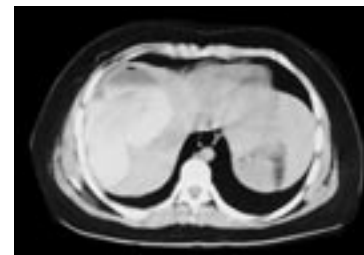
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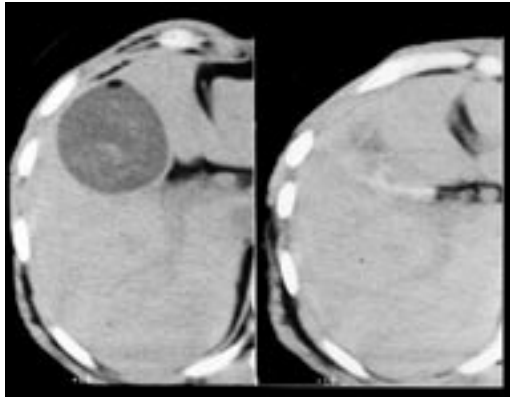


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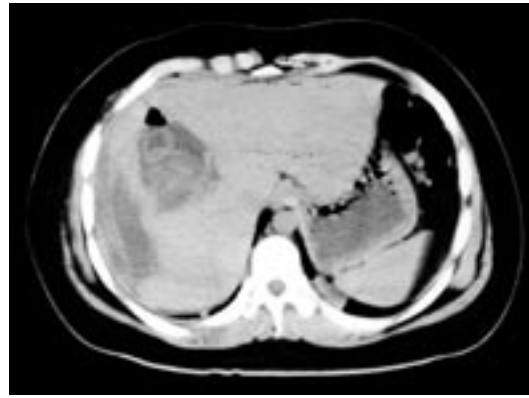


8

The steps of the puncture procedure (CT images) in three patients with CE1 cysts: see the angle of puncture (figures 1, 2 and 3), the aspiration of cyst fluid (figure 4), the appearance of the cyst after injection of contrast medium (figures 5, 6 and 7), and after reaspiration of the protoscolicide agent (figure 8).



1



2

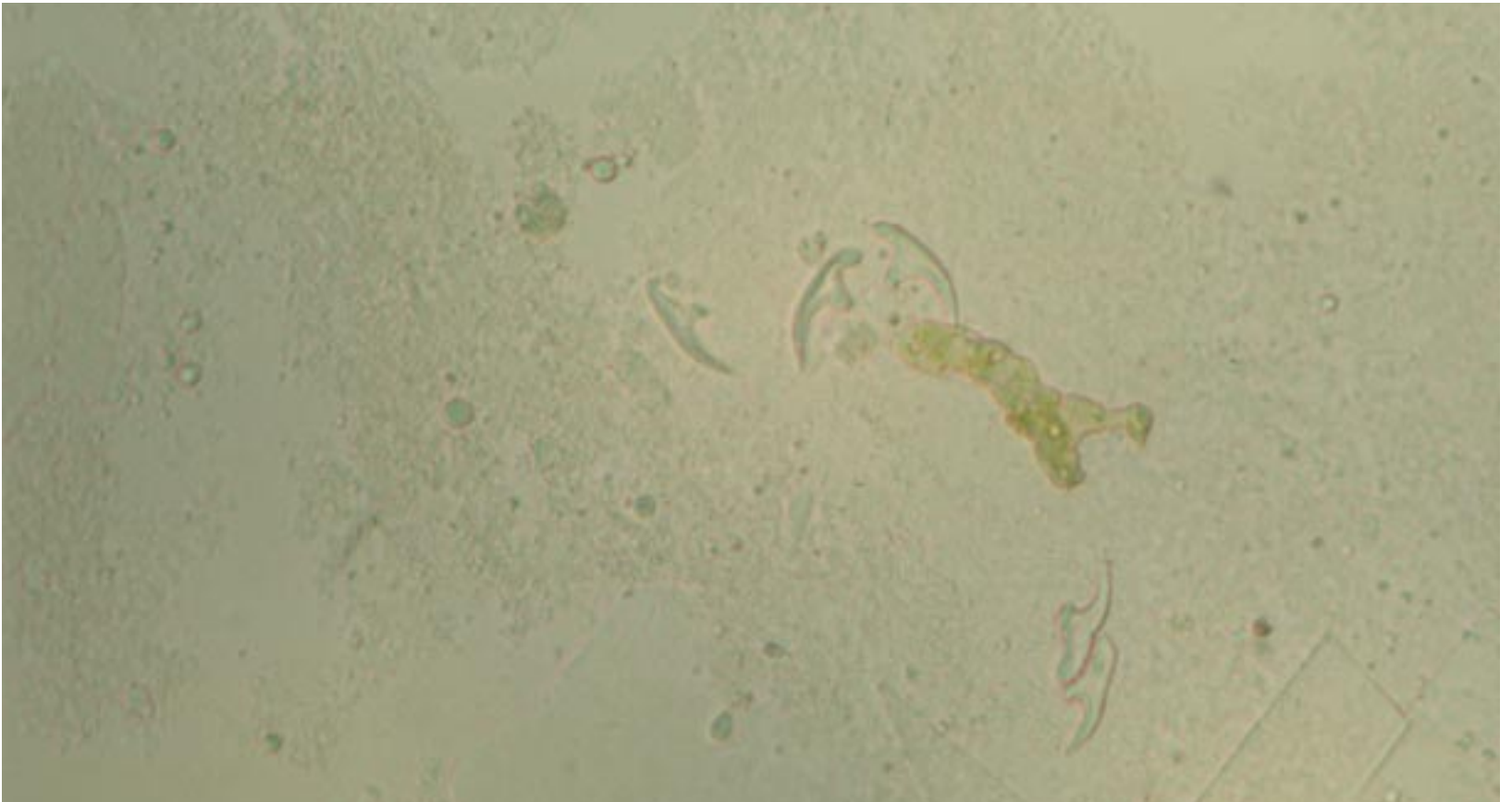


3

Patients' follow-up: comparison of CT images before and 6 months after PAIR in one patient (figure 1); CT images on J+1 after PAIR (figure 2), and 6 months after PAIR in another patient (figure 3).



Bilirubin assessment using a fast dipstick test (urine dipstick): if there is a communication with the biliary tree, bilirubin is present and the dipstick turns a purple blue roughly equivalent to that of the colorimetric scale on the bottle.



Typical hooks in the cyst fluid





Viable protoscolices (microscope examination of the cyst fluid)



1

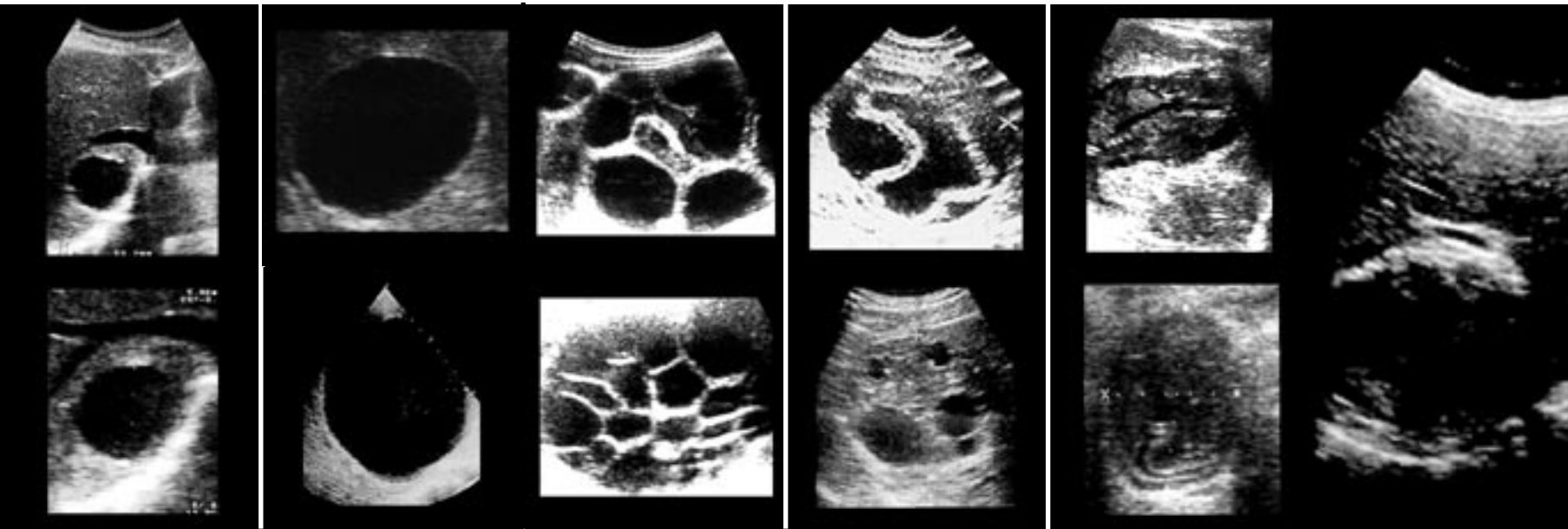


2

US images of a treated CE2 cyst, before (figure 1) and 10 months after (figure 2) the PAIR procedure

# ANNEX 1

## WHO-IWGE CLASSIFICATION OF ULTRASOUND IMAGES OF CYSTIC ECHINOCOCCOSIS CYSTS



CYSTIC LESION

ACTIVE

TRANSITIONAL

INACTIVE

**TYPES OF CYSTIC LESIONS AND CE CYSTS THAT MAY BE FOUND ON US EXAMINATION AND A BRIEF DESCRIPTION OF EACH LESION AND CE TYPE.**

**CL**



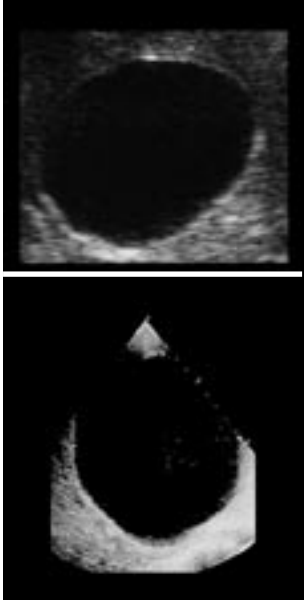
**IMAGING FEATURES AND REMARKS**

- Unilocular, cystic lesion (s) (CL) with uniform anechoic content, not clearly delimited by an hyperechoic rim (= cyst wall not visible).
- Normally round but may be oval.
- Size: variable but usually small. CLs (< 5.0 cm), CLm (5 - 10 cm), CLl (> 10cm).
- Status: If CE - active.

**Remarks:**

- If these cystic lesions are caused by CE at an early stage of development then usually these cysts are not fertile.
- Ultrasound does not detect any pathognomonic signs.
- Differential diagnosis of these cystic lesions requires further diagnostic techniques.

## CE1



### IMAGING FEATURES AND REMARKS

- Unilocular, simple cyst with uniform anechoic content. Cyst may exhibit fine echoes due to shifting of brood capsules which is often called hydatid sand (“snow flake sign”).
- Cyst wall is visible.
- Normally round or oval.
- Size variable: CE1s (< 5.0 cm), CE1m (5 - 10 cm), CE1l (> 10cm)
- Status: active.

#### Remarks:

- Usually fertile.
- Pathognomonic signs include visible cyst wall and snow flake sign.

## CE2



## IMAGING FEATURES AND REMARKS

- Multivesicular, multiseptated cysts; cysts septations produce “wheel-like” structures, and presence of daughter cysts is indicated by “rosette-like” or “honeycomb-like” structures. Daughter cysts may partly or completely fill the unilocular mother cyst.
- Cyst wall normally visible.
- Normally round or oval.
- Size variable: CE2s (< 5.0 cm), CE2m (5 - 10 cm), CE2l (> 10cm).
- Status: active.

### Remarks:

- Usually fertile.
- Ultrasound features are pathognomonic.

## CE3



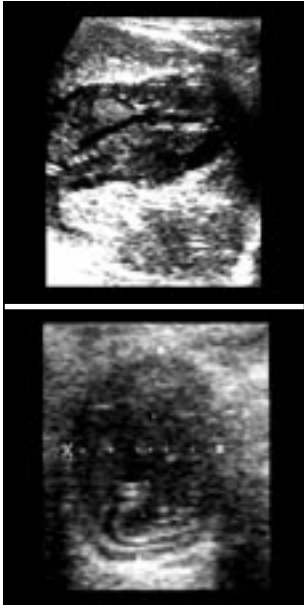
### IMAGING FEATURES AND REMARKS

- Unilocular cyst which may contain daughter cysts.
- Anechoic content with detachment of laminated membrane from the cyst wall visible as floating membrane or as “water-lily sign” which is indicative of wavy membranes floating on top of remaining cyst fluid.
- Cyst form may be less rounded because of decrease of intra-cystic fluid pressure.
- Size variable: CE3s (< 5.0 cm), CE3m (5 - 10 cm), CE3l (> 10cm).
- Status: transitional.

#### Remarks:

- Transitional stage. Cyst which may degenerate further or may give rise to daughter cysts.
- Ultrasound features are pathognomonic.

## CE4



### IMAGING FEATURES AND REMARKS

- Heterogenous hypoechoic or hyperechoic degenerative contents.  
No daughter cysts.
- May show a “ball of wool” sign which is indicative of degenerating membranes.
- Size variable: CE4s (< 5.0 cm), CE4m (5 - 10 cm), CE4l (> 10cm).
- Status: inactive.

#### Remarks:

- Most cysts of this type are not fertile.
- US features are not pathognomonic and further diagnostic tests are required to ascertain a diagnosis.



## CE5



### IMAGING FEATURES AND REMARKS

- Cysts characterized by thick calcified wall that is arch shaped, producing a cone shaped shadow. Degree of calcification varies from partial to complete.
- Size variable: CE5s (< 5.0 cm), CE5m (5 - 10 cm), CE5l (> 10cm).
- Status: inactive.

#### Remarks:

- Cyst not fertile in most cases.
- Diagnosis is uncertain. Features are not pathognomonic but highly suggestive for *E. granulosus*.

# ANNEX 2

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# ANNEX 3

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