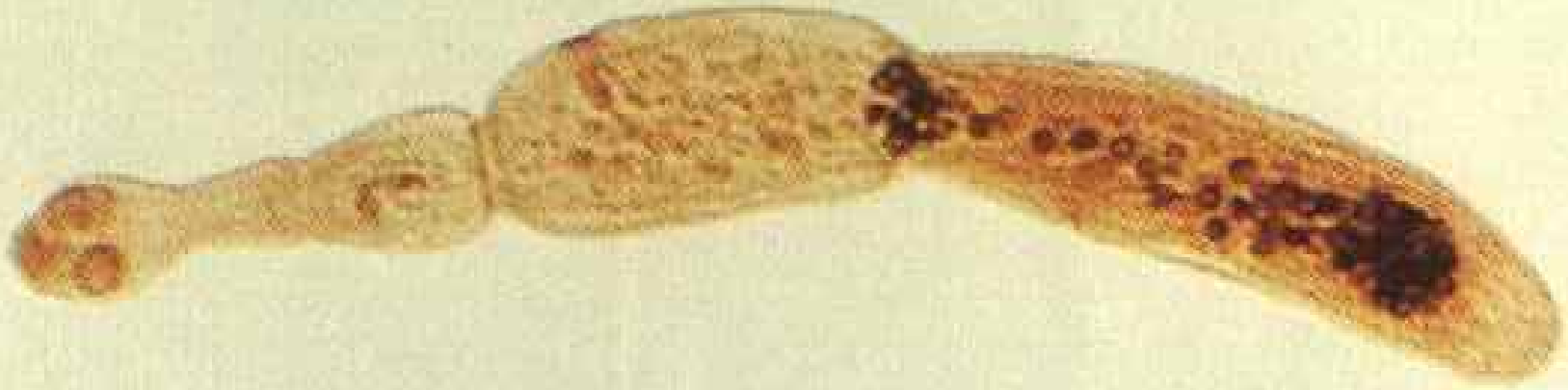
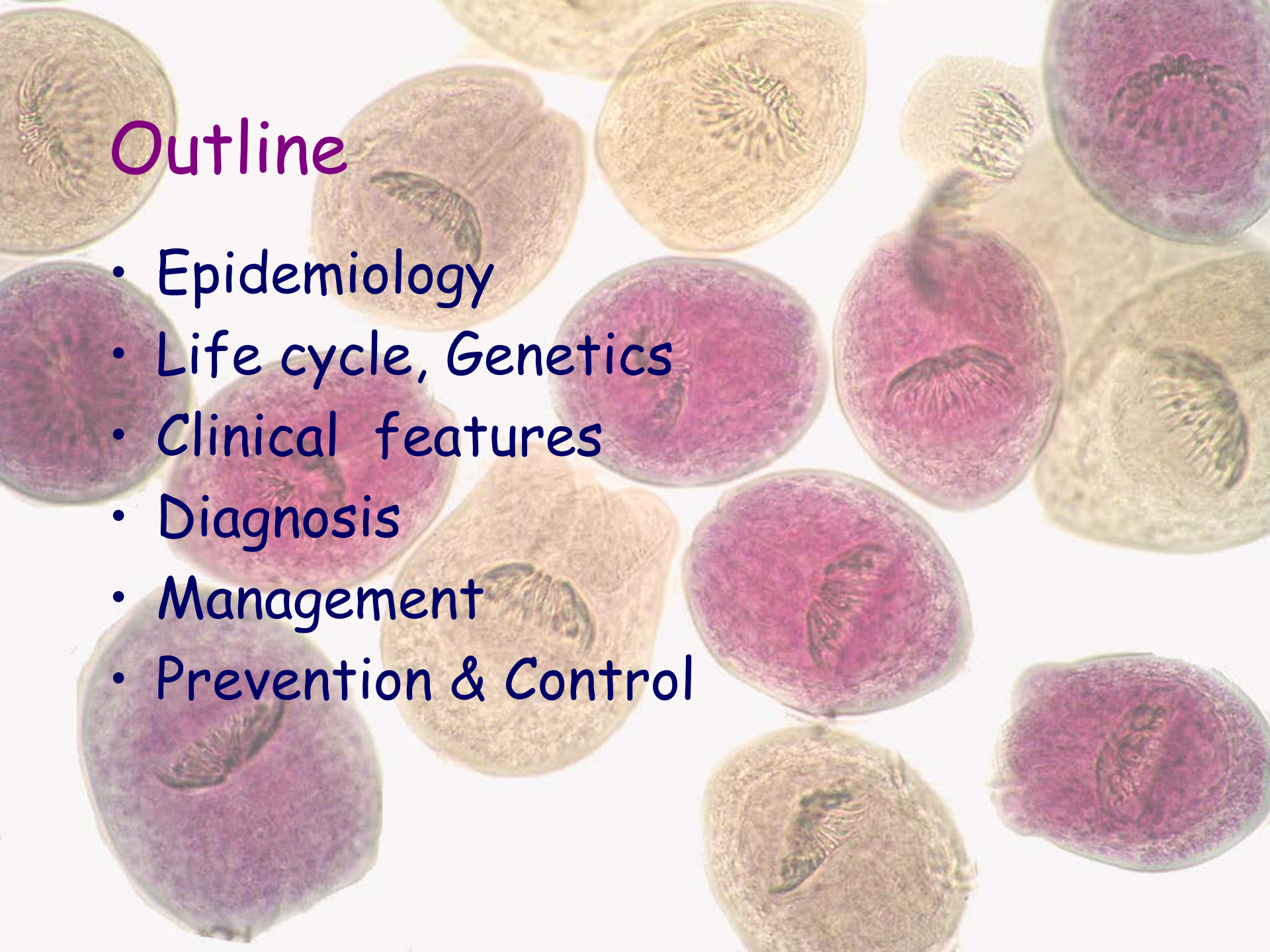
Echinococcosis: a neglected zoonotic infection



E. T. Piperaki MD, PhD, DTM&H



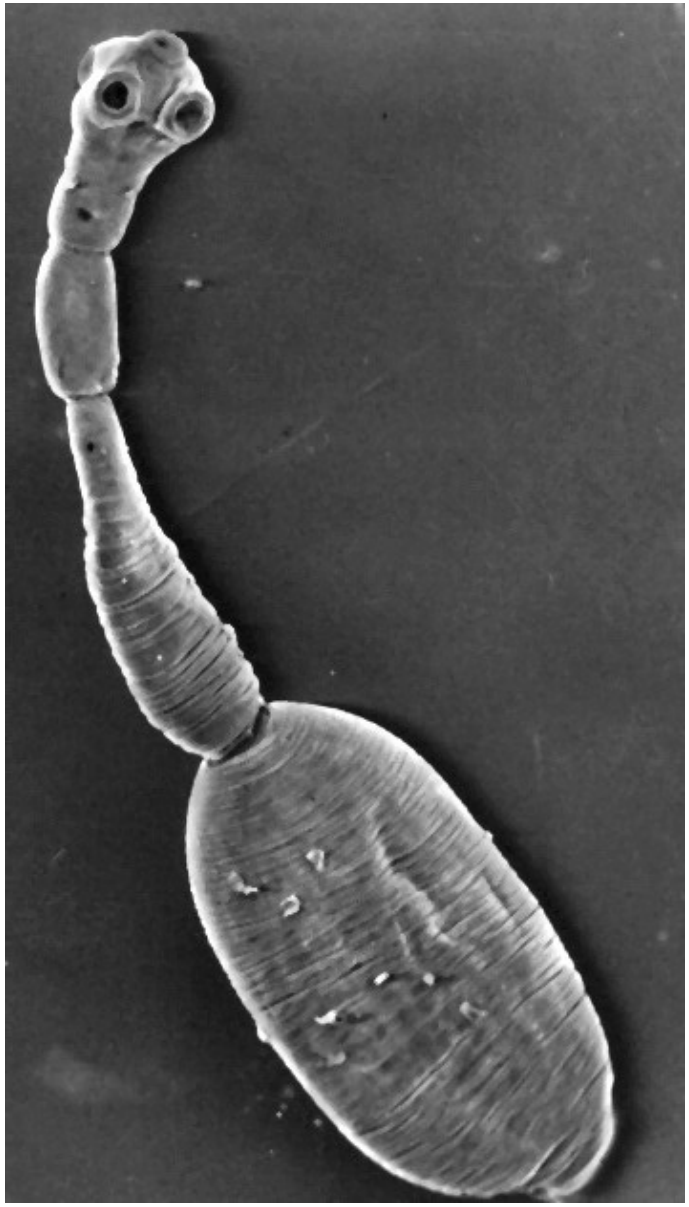
Outline

- Epidemiology
- Life cycle, Genetics
- Clinical features
- Diagnosis
- Management
- Prevention & Control

Echinococcosis

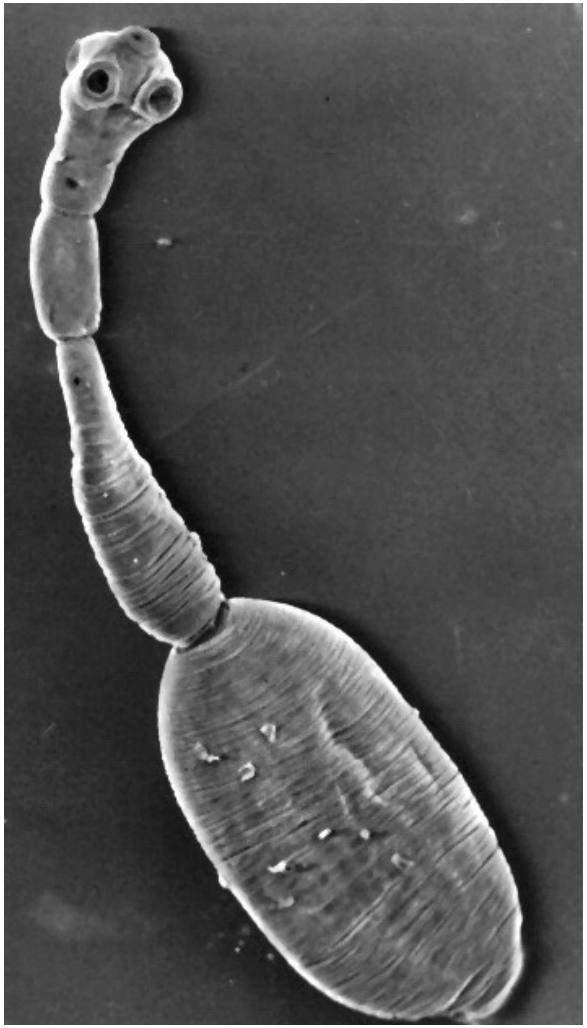
- zoonotic tapeworm diseases
- cystic echinococcosis (CE)
  Echinococcus granulosus sensu lato
  - Cosmopolitan, more common
- alveolar echinococcosis (AE)
  Echinococcus multilocularis

- > 1 million people estimated infected worldwide, >1 million disability adjusted life-years (accounting for under-reporting) lost annually
- Global costs of CE /yr estimated
  - > US$750 million for human
  - > US$2 billion for livestock infection.



Echinococcosis

- annual CE incidence 1 - 200 / 100,000
- annual AE incidence 0.03 - 1.2 / 100,000
- Mortality rate
- AE untreated /inadequately treated 90% (within 10 -15 yrs)
- CE 2% - 4% may (more with inadequate management).
- WHO: echinococcosis 1 of 17 neglected diseases targeted for control or elimination by 2050



McManus et al 2012. BMJ 344:e3866. https://doi.org/10.1136/bmj.e3866.

Schweiger et al. 2007. Emerg Infect Dis 13:878–882. https://doi.org/10.3201/eid1306.061074.

(http://whqlibdoc.who.int/hq/2012/WHO_HTM_NTD_2012.1_eng.pdf).

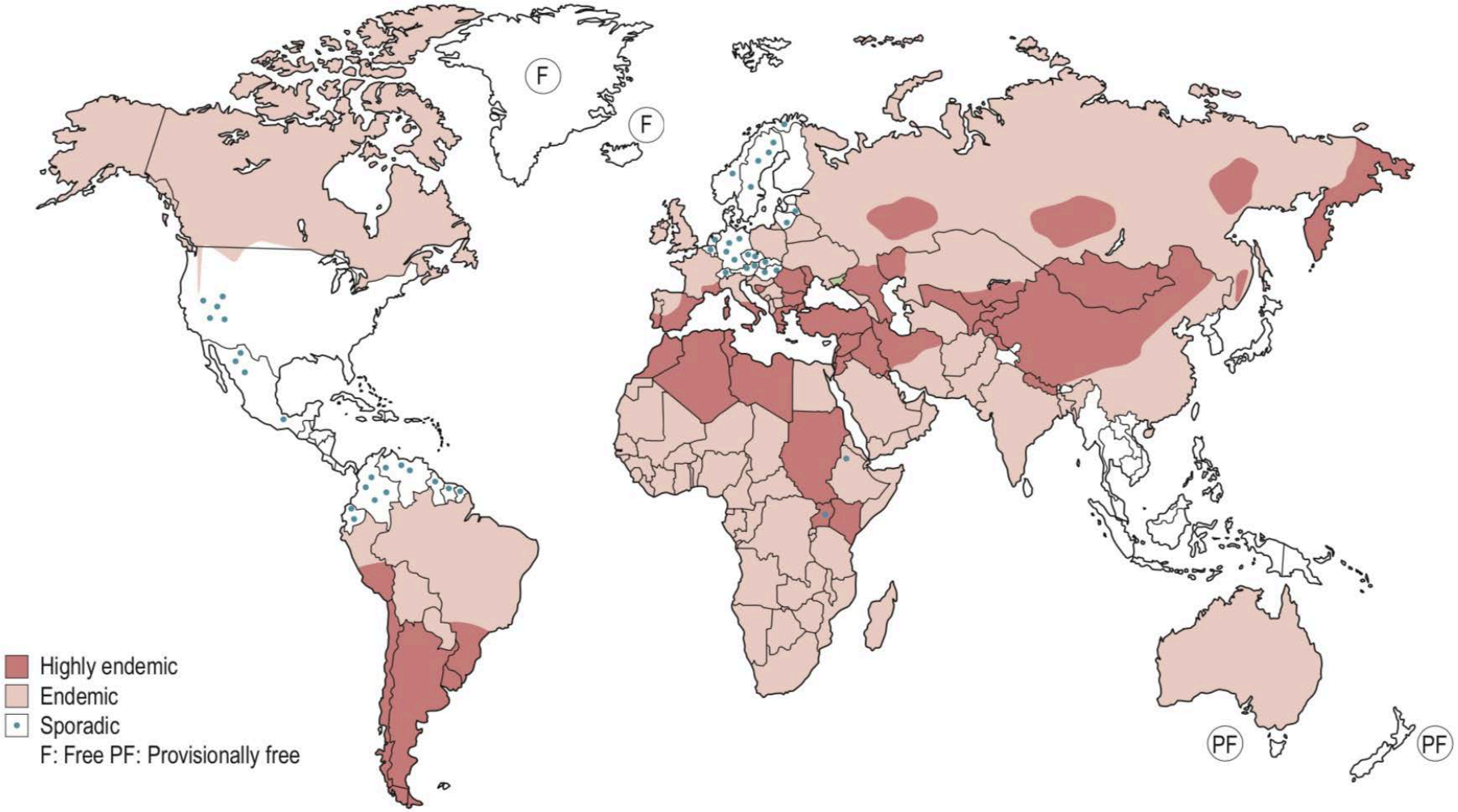


Figure 56.1 Global distribution of *Echinococcus granulosus*. (Copyright © WHO.)

Areas of high endemicity: western China, Central Asia, South America, Mediterranean countries, eastern Europe and eastern Africa

Main risk factors: contact with dogs and raising livestock

Manson's Tropical Infectious Diseases-Saunders (2013)

Epidemiology

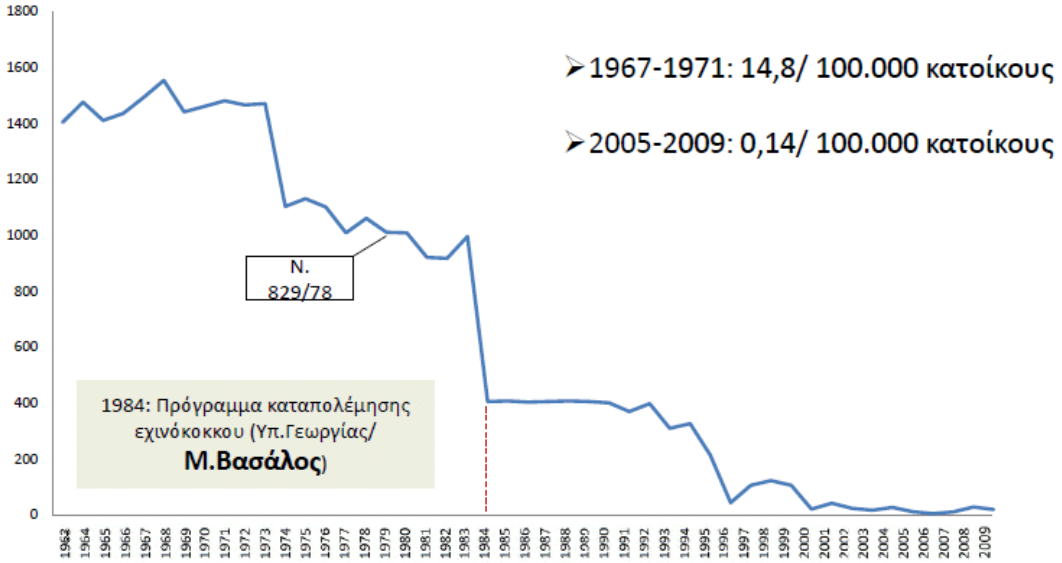
- Western Europe and North America, most human cases imported
- autochthonous cycle of various genotypes within the species group *E. granulosus sensu lato* lack of accurate case recording
- European Registry of CE: Human cystic Echinococcosis ReseArch in CentraL and Eastern Societies (HERACLES) project was launched & funded by the European Commission in 2013.
- around 151 000 people living in rural Bulgaria, Romania, and Turkey might be infected with abdominal cystic echinococcosis.

Tamarozzi F, et al *Lancet Infect Dis 2018; ://dx.doi.org/10.1016/*S1473-3099(18)30221-4.

Epidemiology

- Greece: endemic region
- 0.17-9.1% of dogs infected (depending on area and occupation of the dog)
  - 2000-2009 annual incidence 0.04 -0.37 /100,000
  - 2005-2009 annual mean no of cases: 16 (5 year total : 79 cases)
  - 36% raising livestock
- Risk factors
  - Contact with animals
  - Contact with soil
  - Suboptimal hygiene

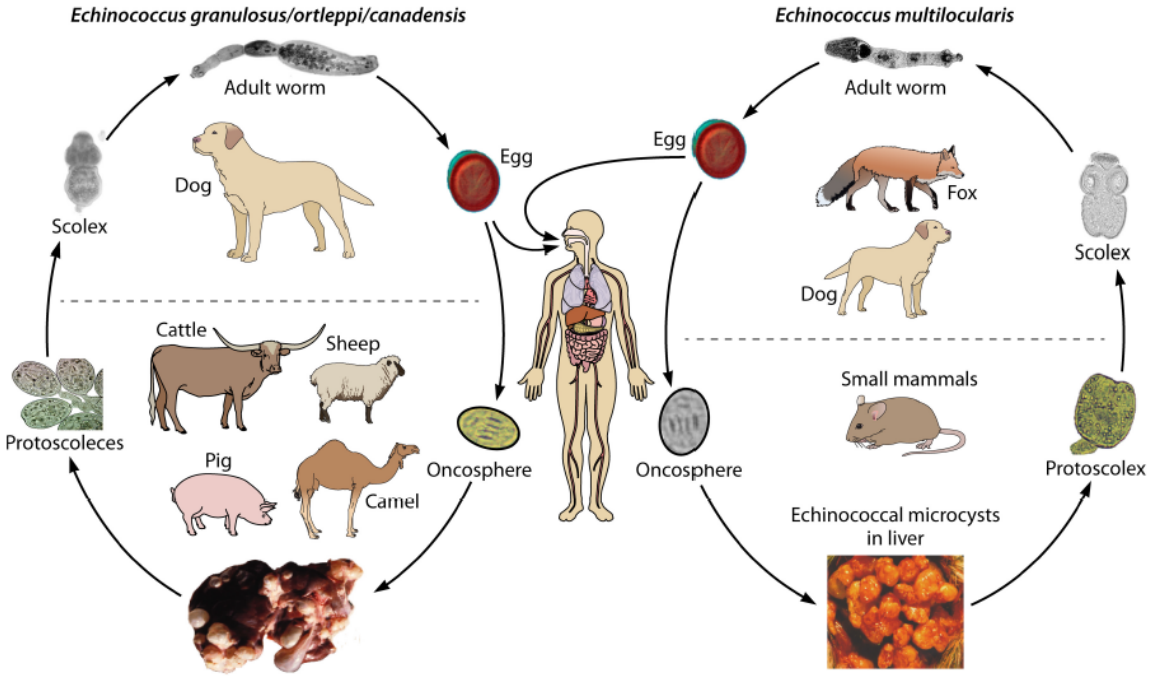
Κρούσματα υδατίδωσης στην Ελλάδα 1963-2009

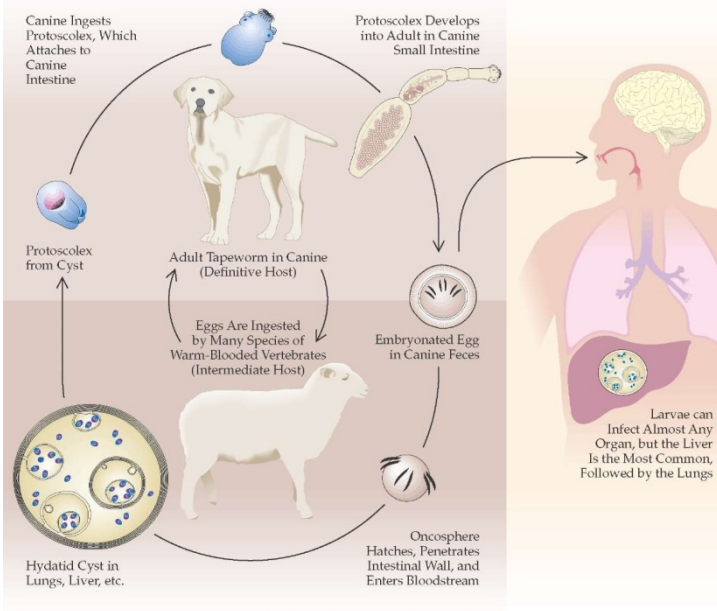


https://keelpno.gr/epidimiologika-statistika-dedomena/etisies-epidimiologikes-ektheseis/

Life cycle

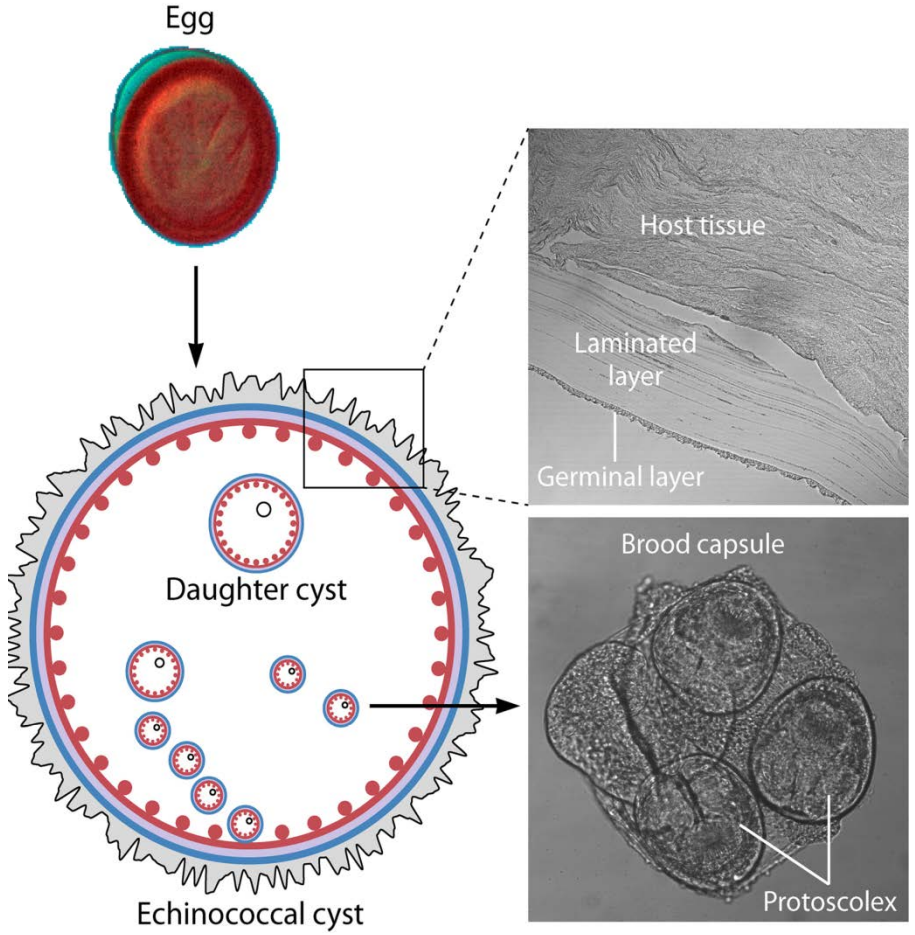
- predator-prey associations involving two mammalian hosts
  - Carnivores (canids and felids) definitive hosts for the adult tapeworms
  - herbivorous prey (ungulates, rodents, and lagomorphs) intermediate hosts for the metacestodes





E.granulosus

- In definitive host
- 1-7 mm
- 3 proglottids
- Matures in 40-60d of infection
- Lifespan 5-29 months
- 200-2.000 eggs/ proglottid/ 2 weeks



- Daughter cysts : 40 protoscoleces (0.1 mm) graddaughter cysts +/- protoscoleces («fertile» / «infertile» hydatids).
- Protoscoleces & debris of destroyed daughter/ granddaughter cysts = hydatid sand
- Hydatid 5 cm may contain 40.000.000 protoscoleces
- Ideal intermediate host for *E.granulosus* = sheep (51% of hydatid fertile)
- Cattle 7.5%, goat 1.9%, swine 1.5% less in other species and humans.

da Silva AM. Gastroenterol Res Pract. 2010;2010. pii: 583297

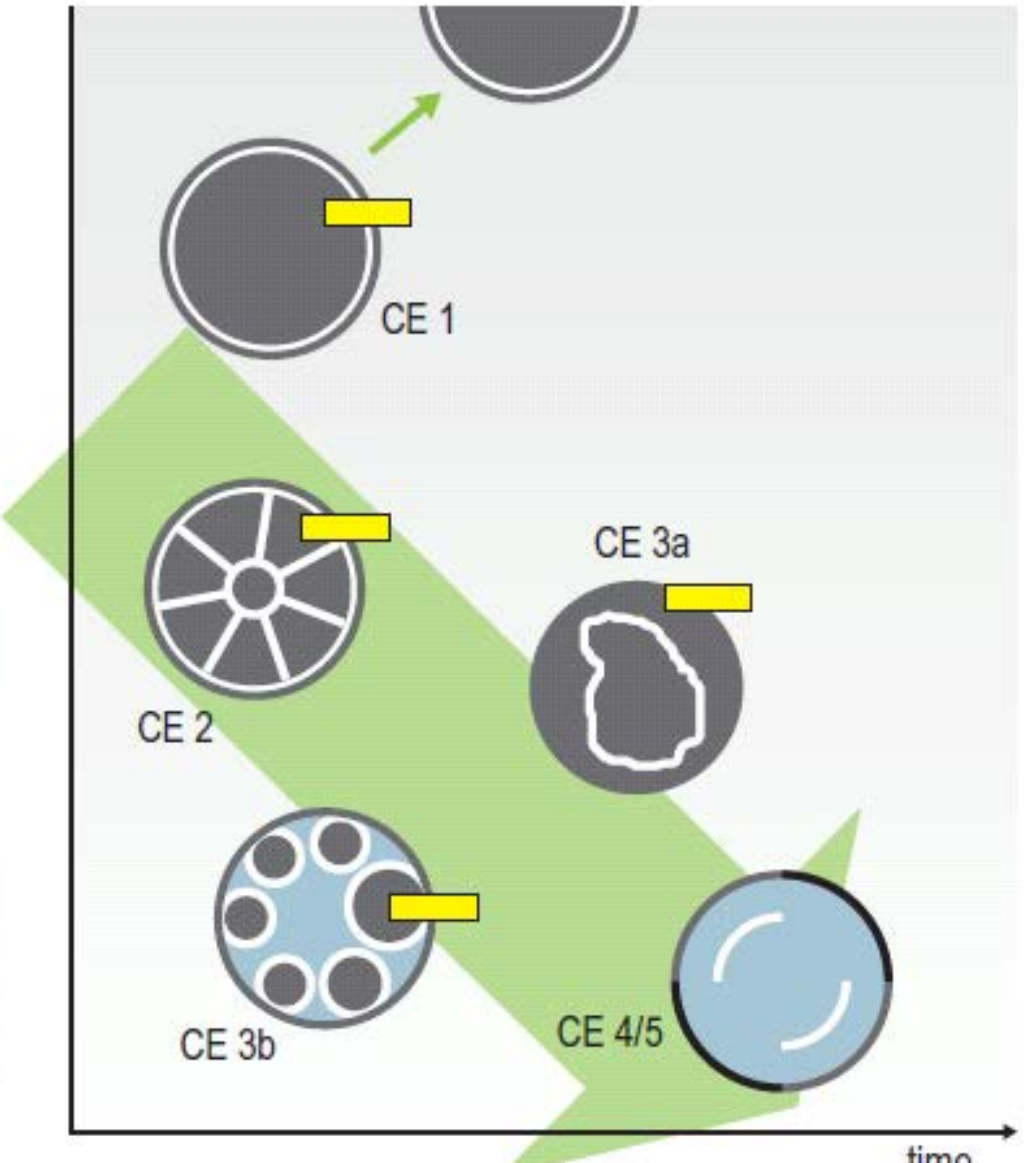
Sequence of CE cyst evolution and involution

CE 1

CE 2

CE 3b

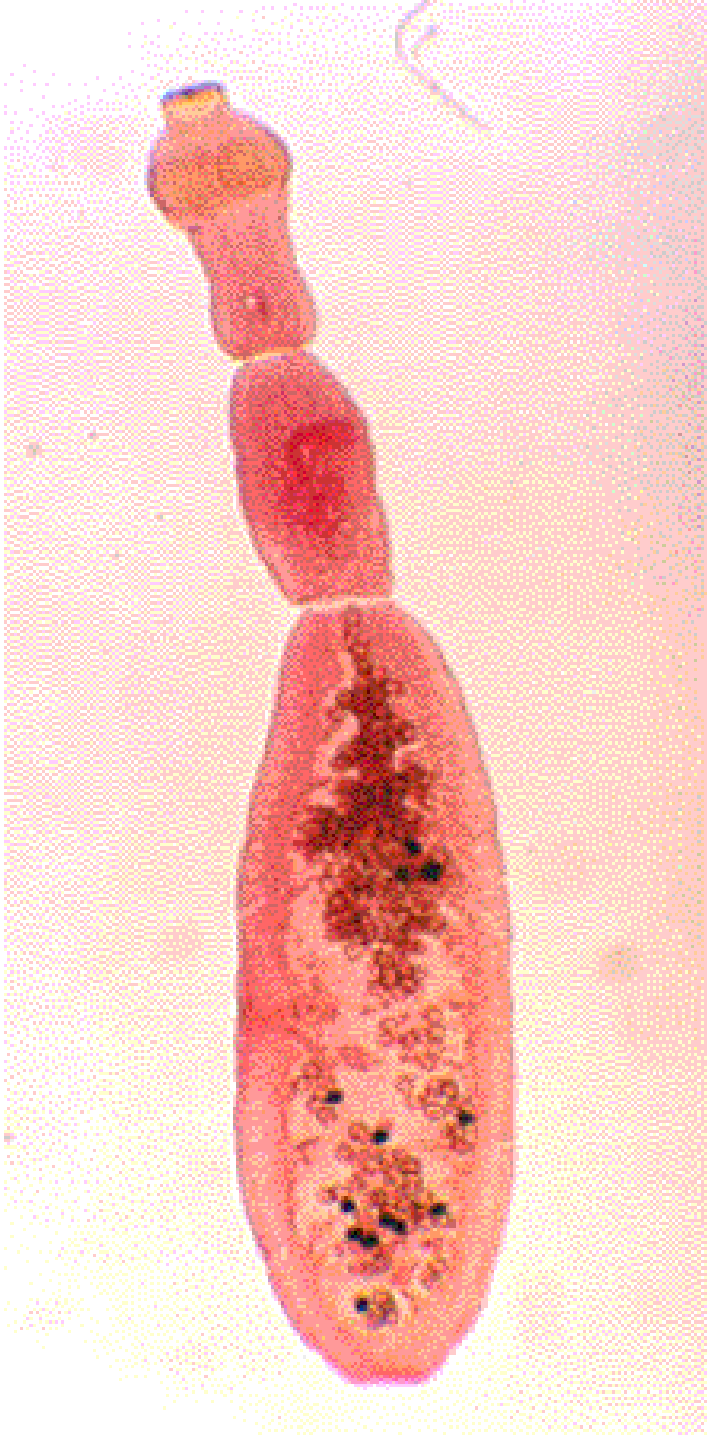
CE 3a



Genetics

- Major change in CE epidemiological picture → redefinition of the *Echinococcus* spp.

- Until recently, *E.granulosus* considered a single species
- now recognized as having distinct strains/genotypes →
- differences in
  - Pathology
  - Responses to drugs
  - Response the defined recombinant vaccine EG95



E. granulosus - strains / genotypes

- the 10 strains/genotypes of *E. granulosus sensu lato* demarcated into 5 species
  - *E. granulosus sensu stricto* (the former "sheep strain," G1 -G3)
  - *Echinococcus equinus* (horse strain, G4)
  - *Echinococcus ortleppi* (cattle strain, G5)
  - *Echinococcus canadensis* (camel strain, G6; pig strain, G7; G9, probably a variant of the pig strain; cervid (deer, elk, caribou, moose) strains, G8 & G10)
  - *Echinococcus felidis* ("lion strain")

9 species

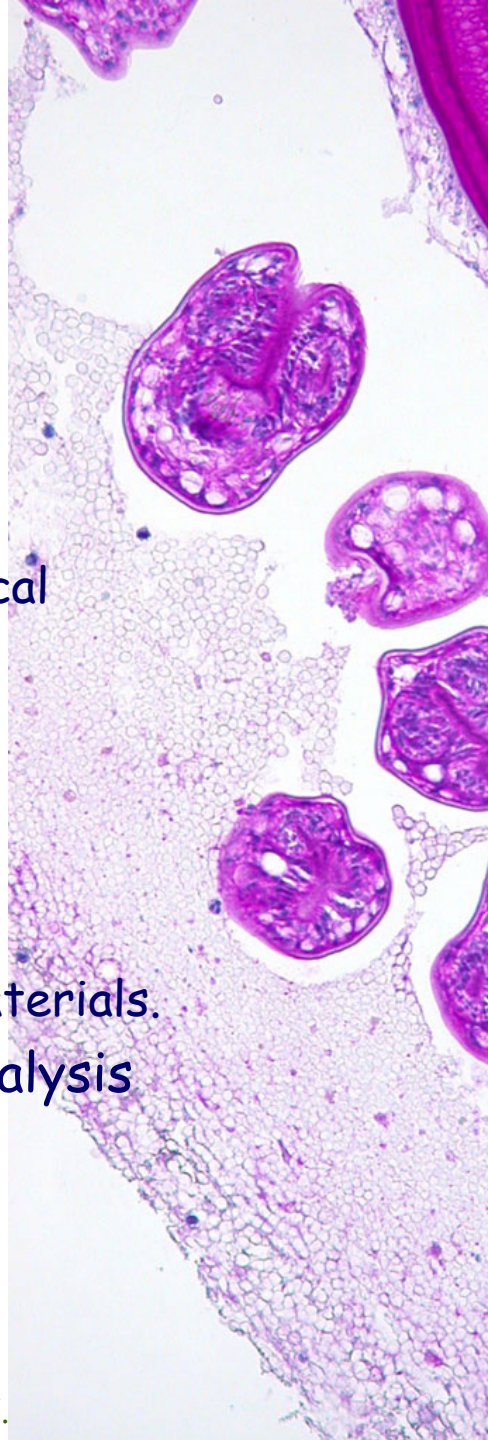
TABLE 1 Current recognized species within the genus *Echinococcus* and their preferential hosts and geographic distribution

Species	Definitive host(s)	Intermediate host(s)	Human cases	Distribution
Echinococcus granulosus sensu stricto	Domestic dog, wolf, dingo, jackal, other canids	Sheep, goat, cattle, pig, camel, buffalo, horse, wild ungulates, marsupials, etc.	Yes	Cosmopolitan
Echinococcus canadensis	Domestic dog, wolf	Pig, camel, cervids	Yes	Eurasia, Africa, North and South America
Echinococcus ortleppi	Domestic dog	Cattle	Yes	Eurasia, Africa
Echinococcus felidis	Lion	Hyena, warthog, zebra, wildebeest, bush pig, buffalo, various antelopes, giraffe, hippopotamus	Not reported	Africa
Echinococcus equinus	Domestic dog	Horse, other equids, cervids	Not reported	Eurasia, Africa
Echinococcus multilocularis	All fox species, wolf, raccoon dog, domestic dog, cat	Arvicoline and microtine rodents and small herbivorous mammals, including lagomorphs (e.g., pika); pigs, boars, horses, cattle, nutrias, nonhuman primates, and dogs are accidental hosts	Yes	Eurasia, North America
Echinococcus oligarthra	Wild felids (e.g., *Puma concolor* [puma])	*Dasyprocta azarae* (agouti), *Didelphis marsupialis* (opossum)	Yes	Central and South America
Echinococcus vogeli	Bush dog, domestic dog	*Cuniculus paca* Linnaeus, 1766 (paca)	Yes	Central and South America
Echinococcus shiquicus	Tibetan fox	*Ochotona curzoniae* (Tibetan plateau pika)	Not reported	Tibetan Plateau

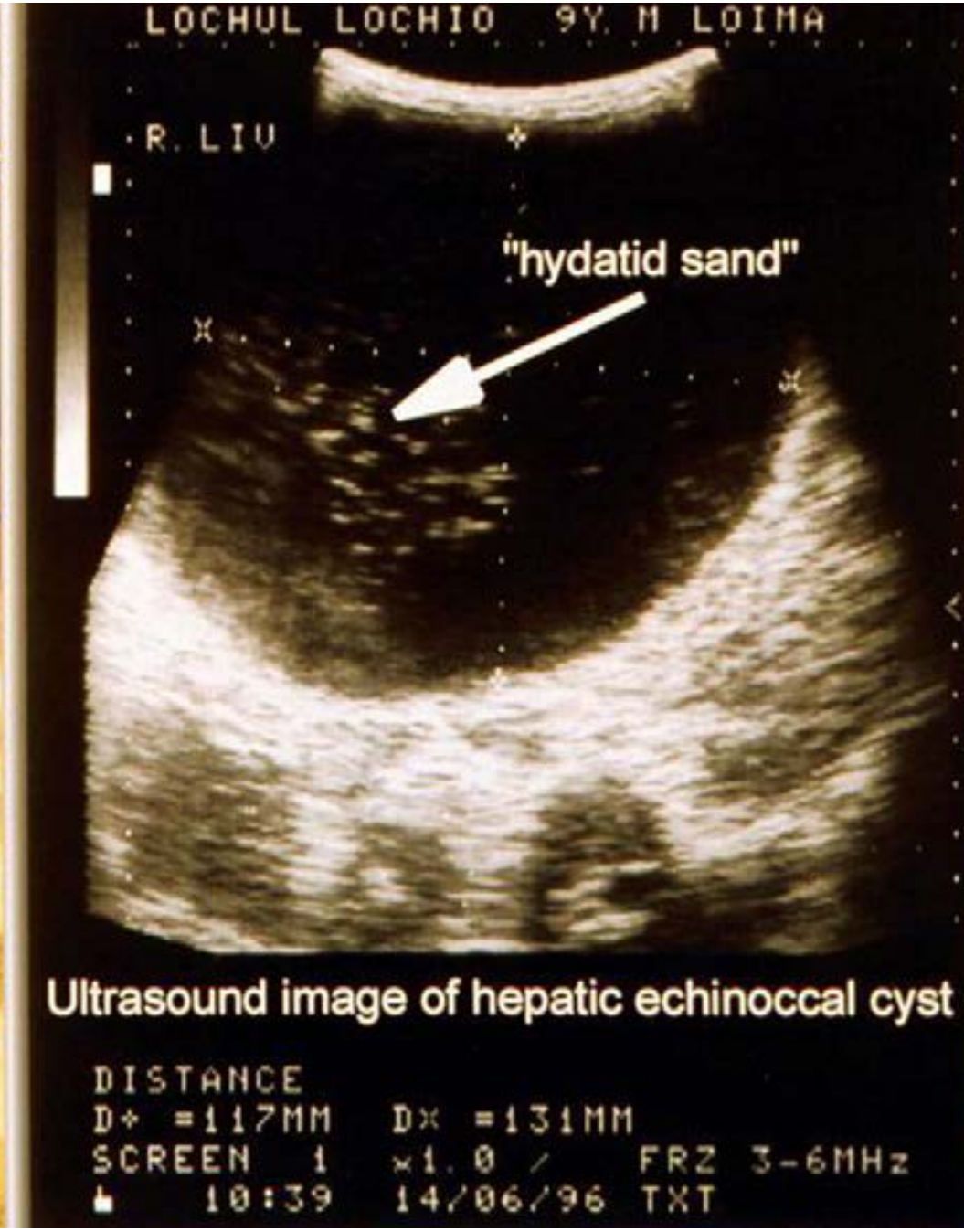
E.granulosus sensu lato : 5 spp

Clinical features

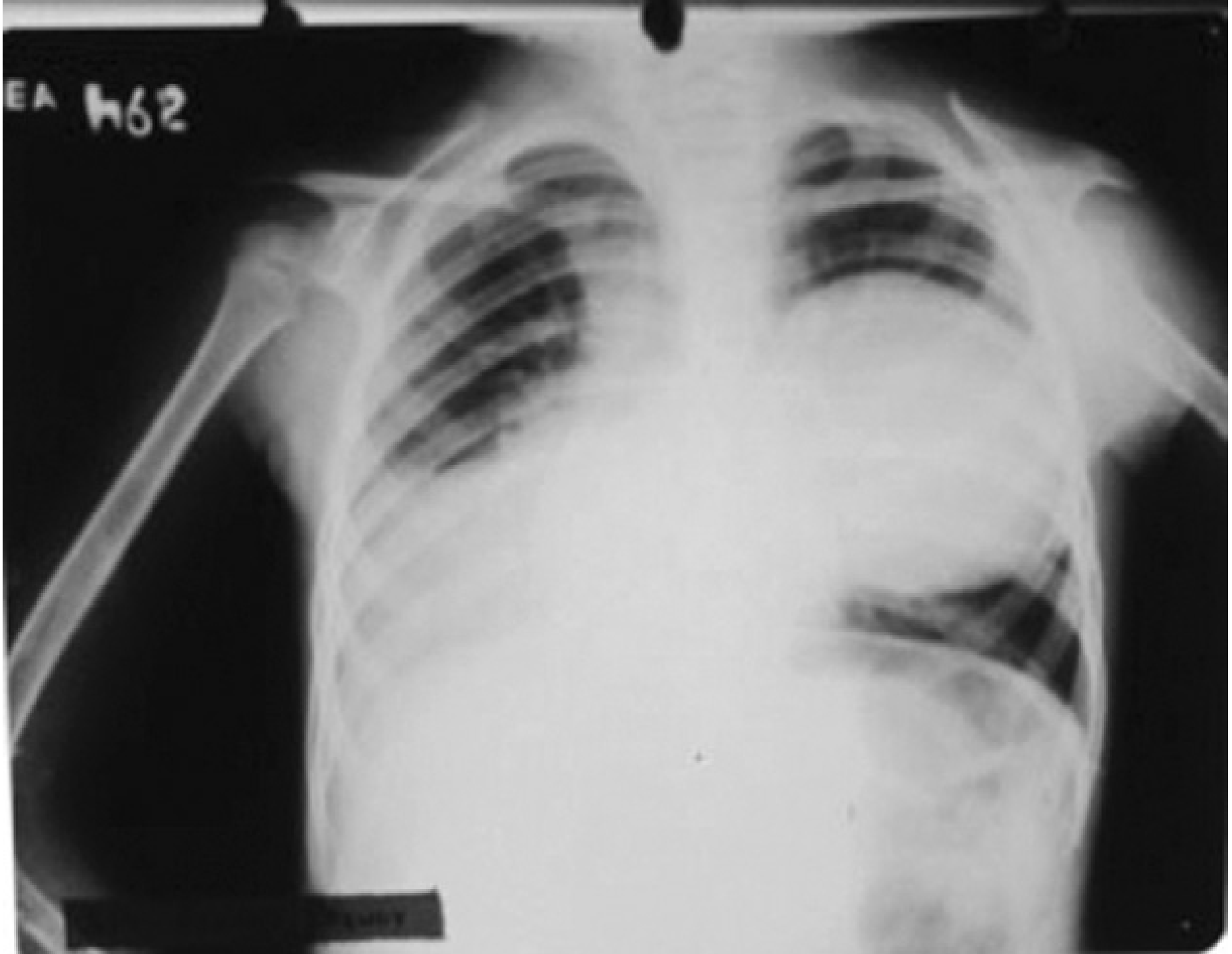
- Incubation: months to >10 yrs
- Commonly asymptomatic
  - Patients present late at clinics or hospitals.
- Clinical symptoms usually
  - when cyst >10 cm (liver) or
  - when >70% of organ volume occupied by cyst(s) → physical compression / damage
- Liver : 70% Abdominal discomfort and poor appetite / jaundice.
  - tumor-like mass, hepatomegaly, abdominal distension
- Lungs 15-30% Chest pain, cough, hemoptysis
  - cyst rupture into the bronchi → expulsion of hydatid materials.
- Brain: signs of intracranial hypertension, epilepsy, paralysis
- Any organ (rupture): fever, urticaria, eosinophilia, anaphylactic shock
- Faster cyst growth in CE patients with AIDS



Frider B et al 1999. J Hepatol 30:228 –231. https://doi.org/10.1016/S0168-8278(99)80066-X.



Ultrasound image of hepatic echinoccal cyst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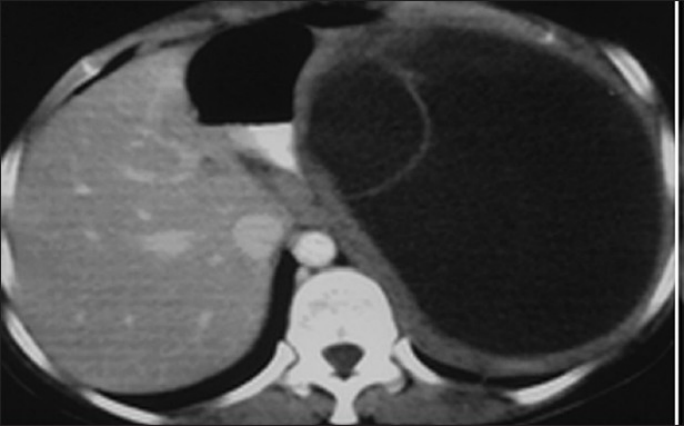

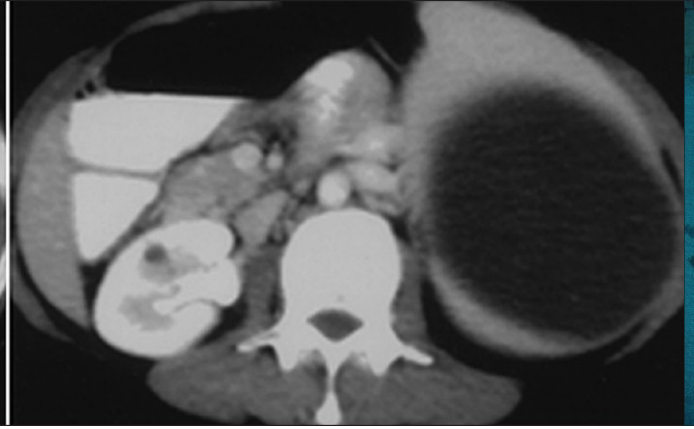

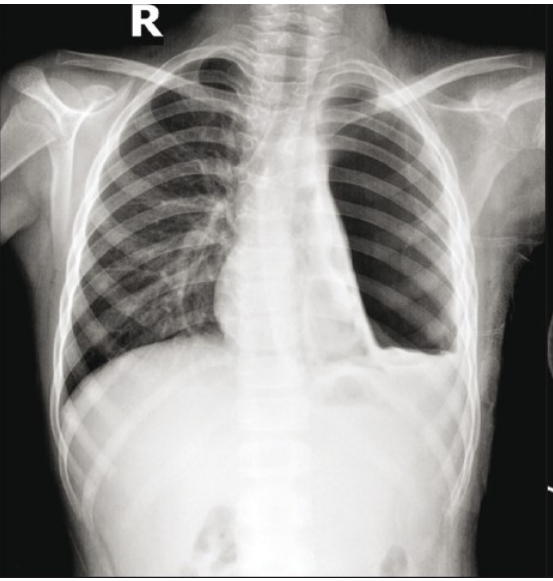
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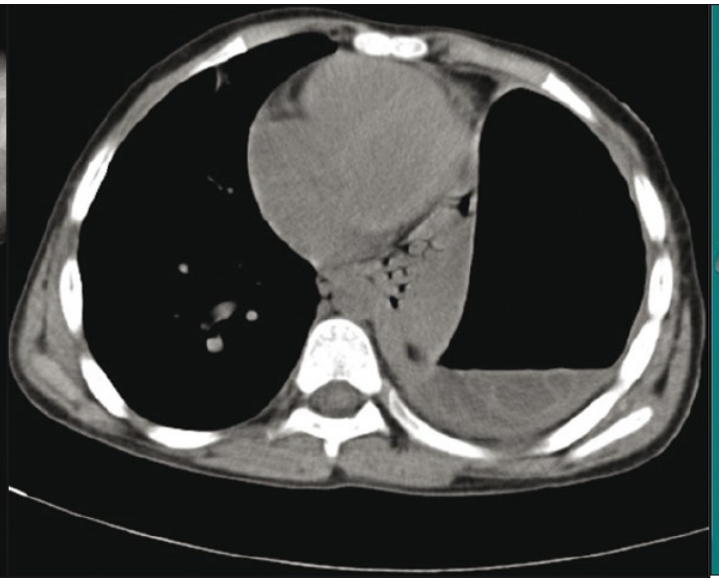


HÔPITAL
SAINTE-JUSTINE
1
2
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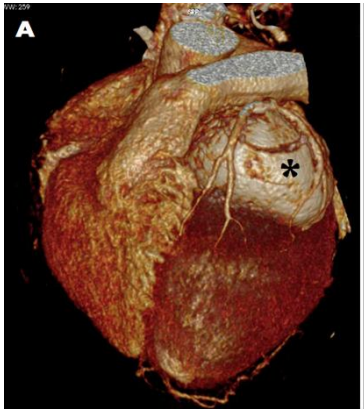
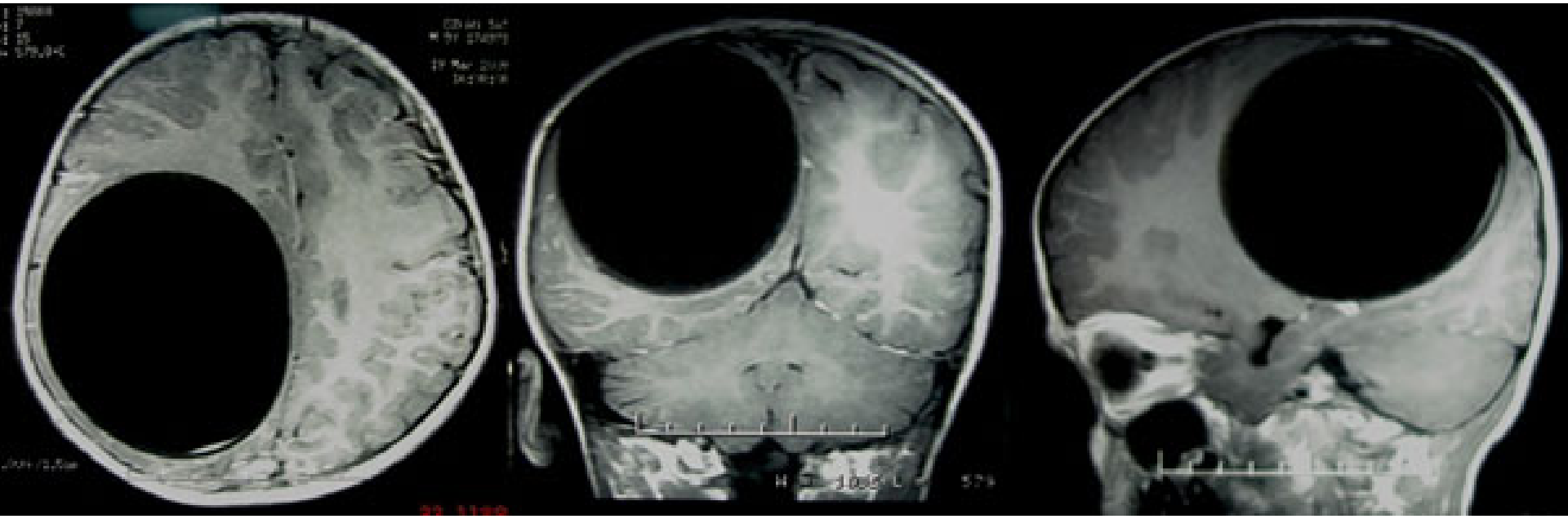
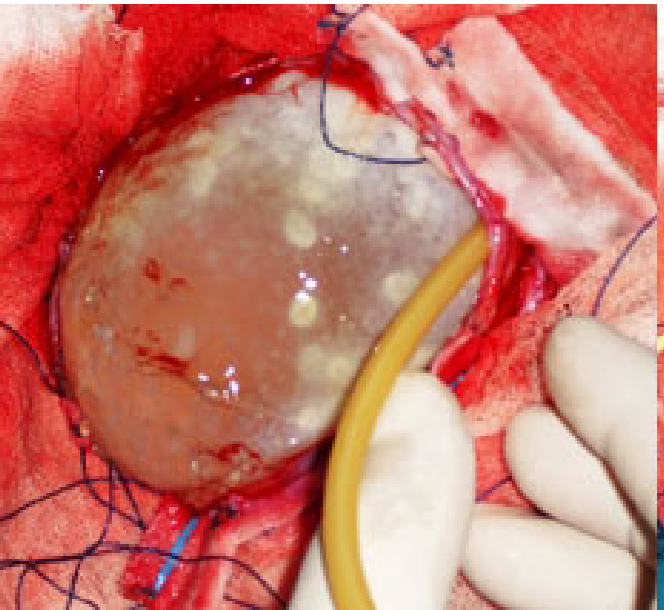
cm

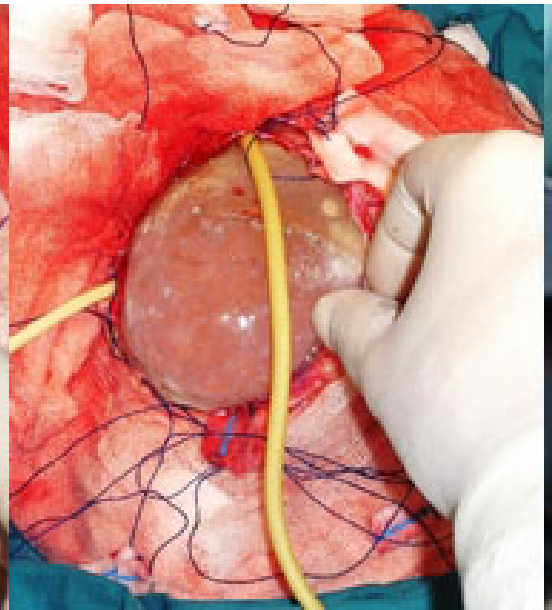

A


B

ΚΝΣ







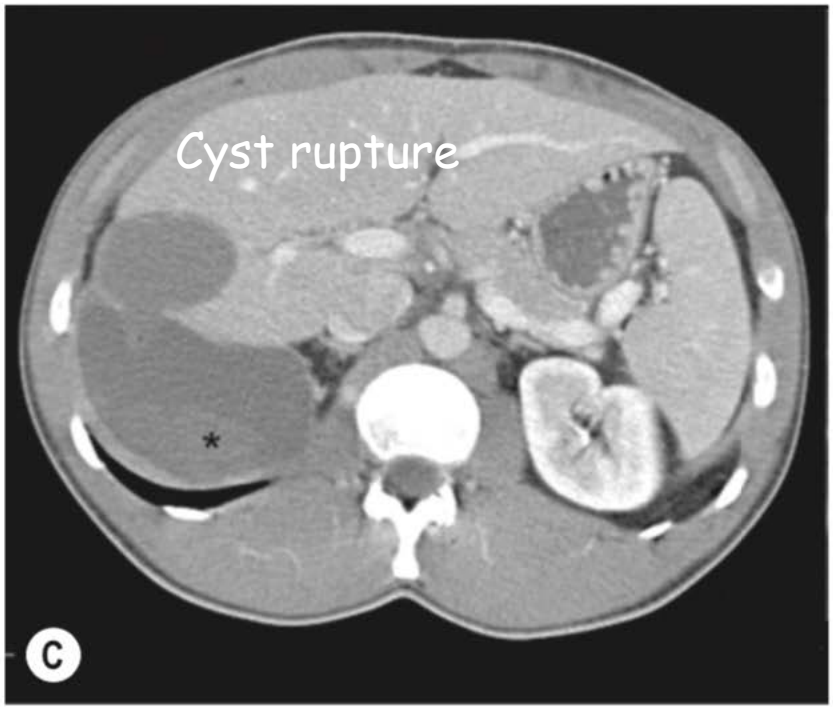

a
b
c
d
e

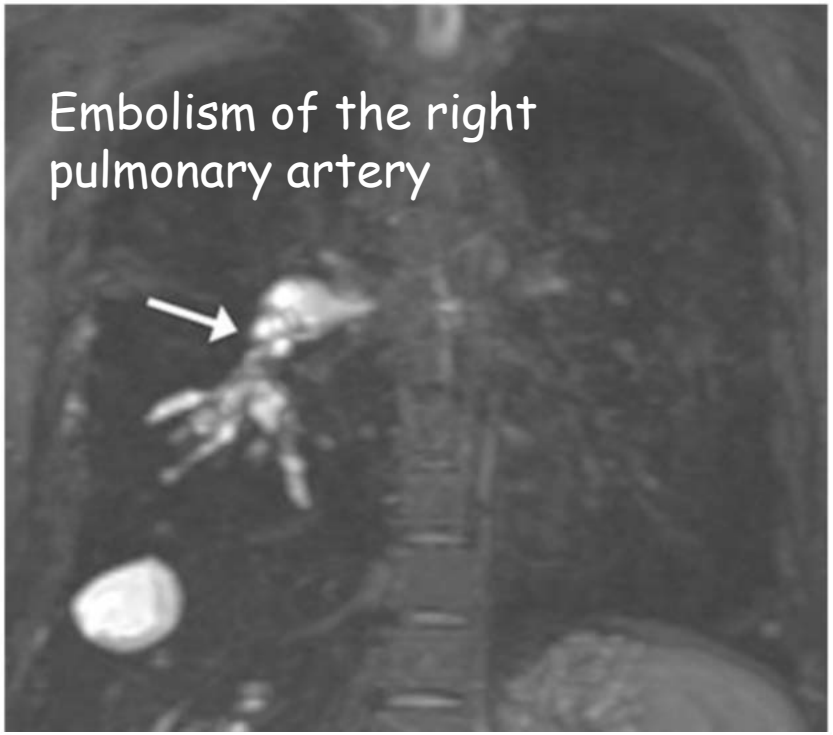
Complications

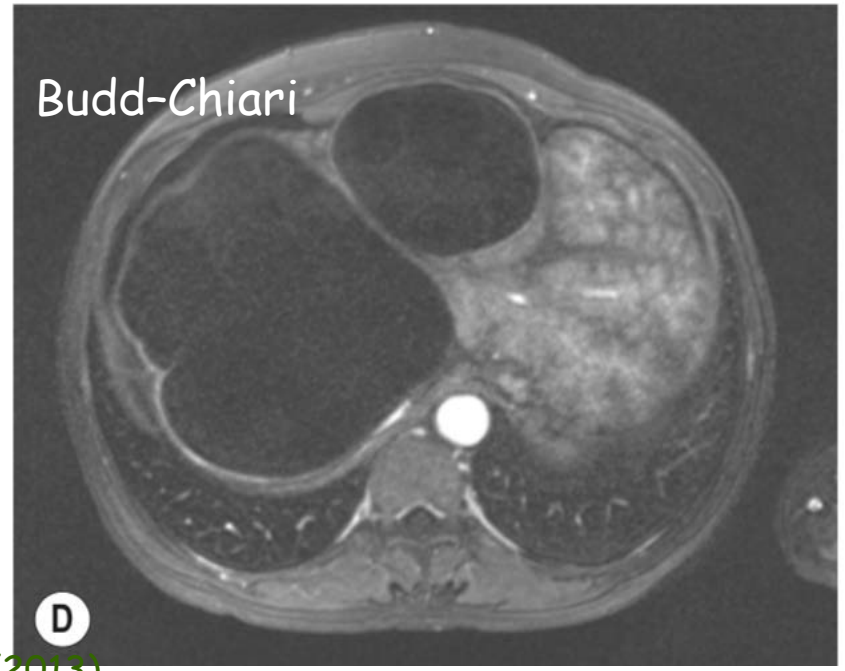
BOX 56.1 CE CYST COMPLICATIONS

- Cysts with fistulas
- Biliary/bronchial obstruction (due to spillage of cyst content via cysto-biliary/cysto-bronchial fistulas)
- Bacterial infection
- Compression syndromes
  - Blood vessels (leading to thrombosis, Budd–Chiari syndrome)
  - Biliary ducts
  - Bronchi
  - Parenchyma/muscles, nerves (leading to atrophy)
- Cyst rupture
- Venous/arterial embolism

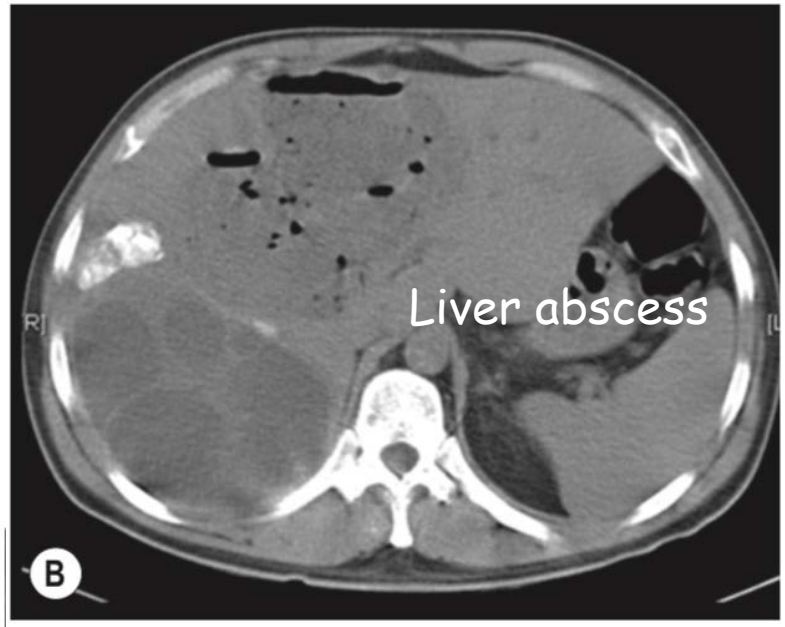
Manson's Tropical Infectious Diseases-Saunders (2013)

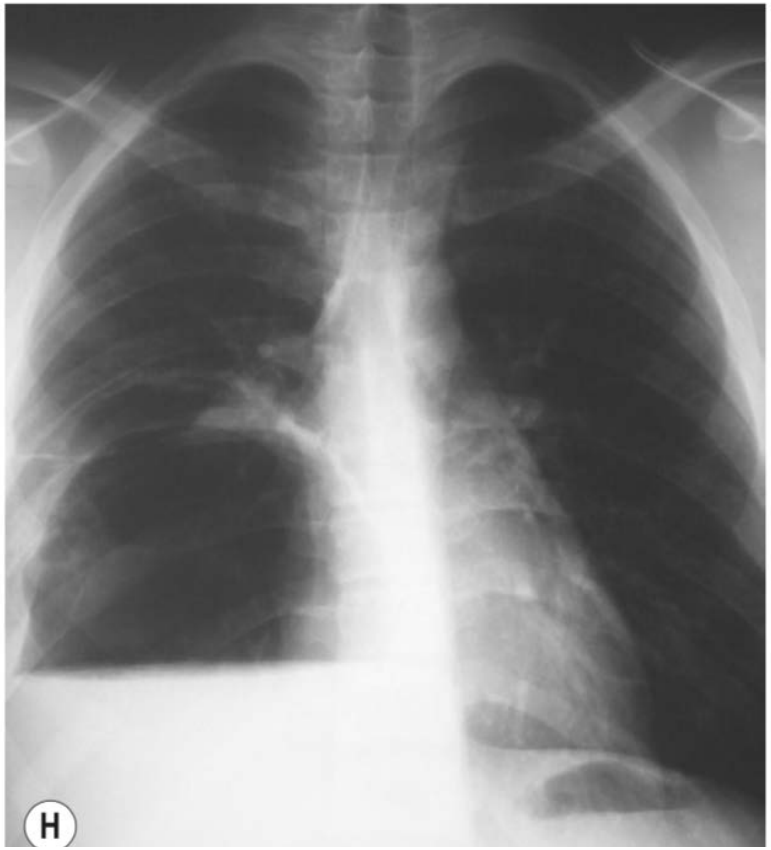


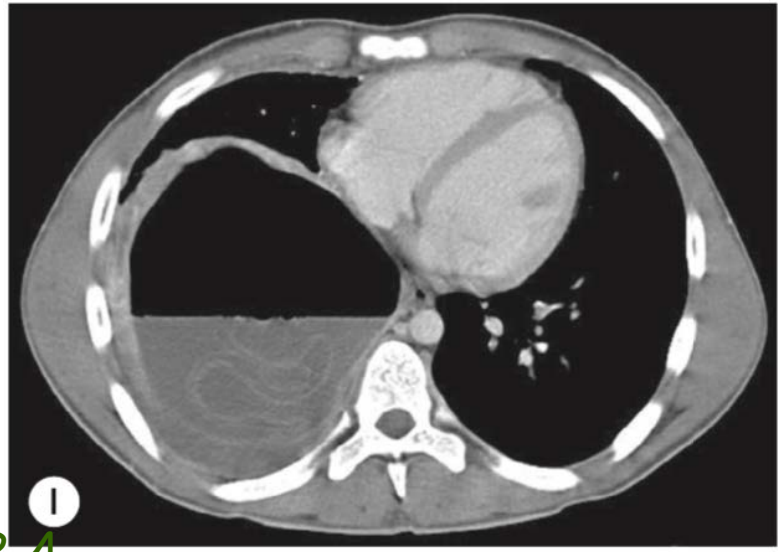




Manson's Tropical Infectious Diseases-Saunders (2013)



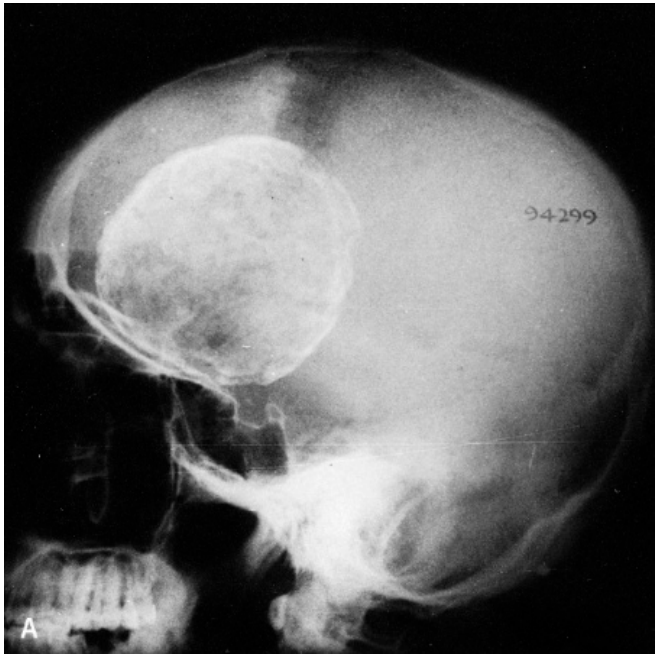


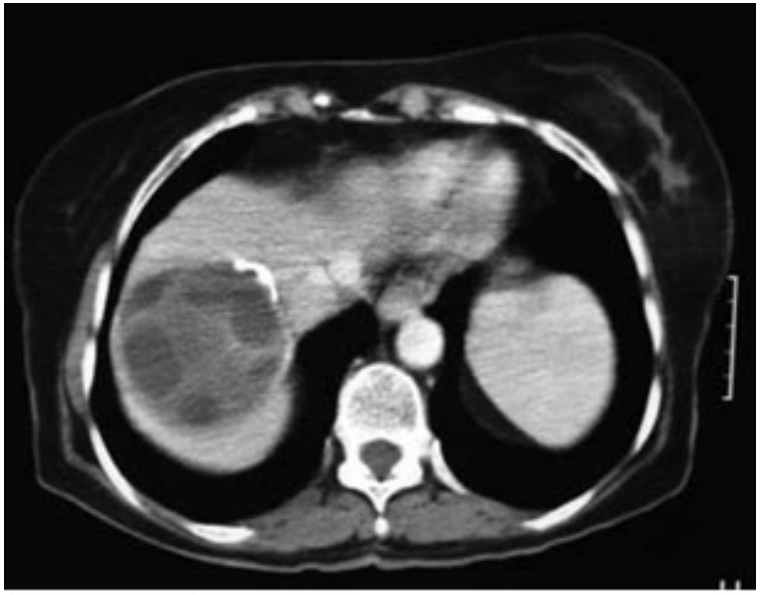


Hosch et al Chest. 2004 Dec;126(6):1982-4.

Diagnosis

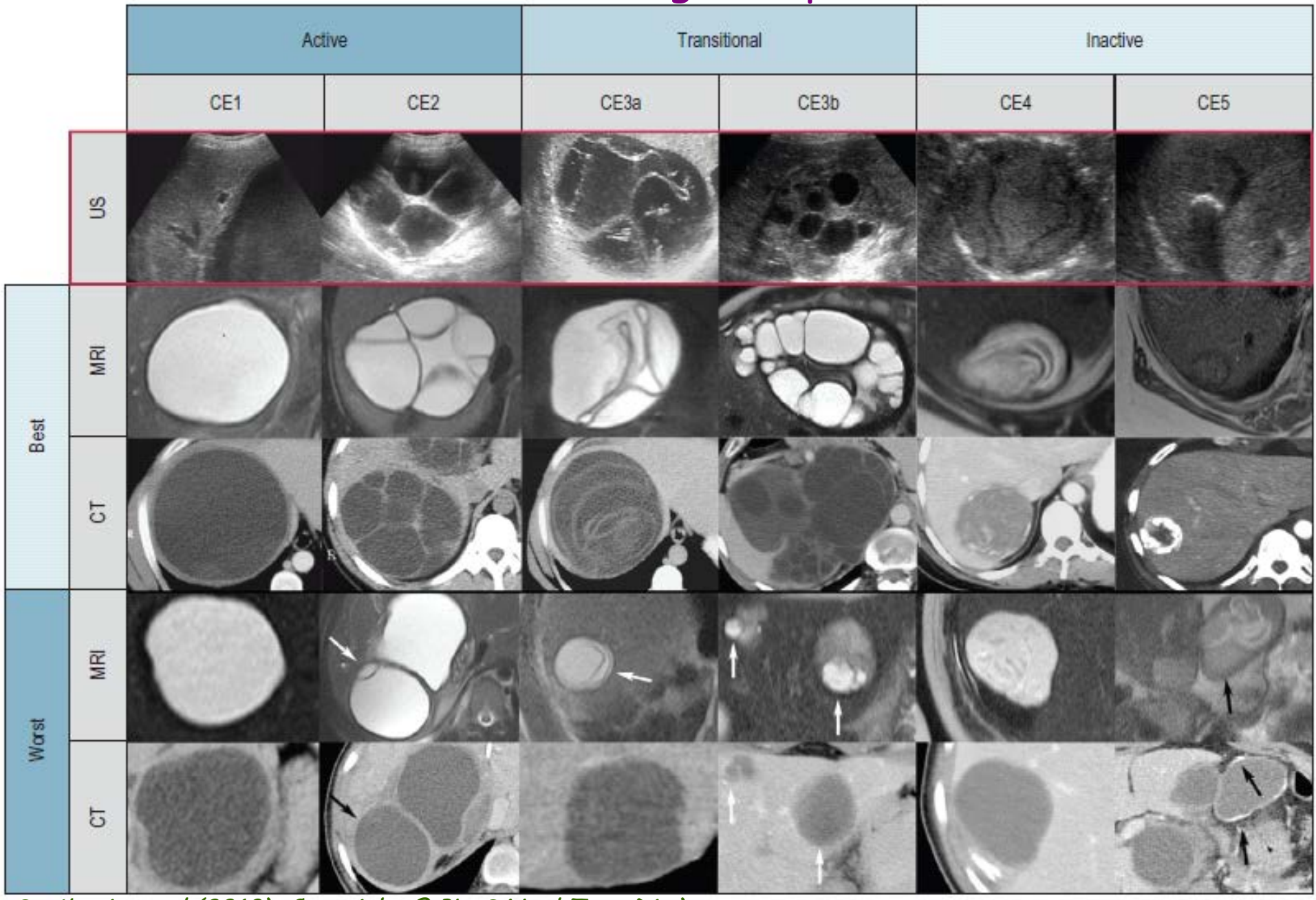
- Imaging : (X-ray **U/S**, CT, MRIT2)
  - Incidental finding
  - Mass population screening w US - best method for early diagnosis
- Serology
- DNA detection
- Diagnostic Puncture
  - Microscopic examination of cyst contents (daughter cysts, protoscoleces, hooklets)
  - Danger of metastatic disease
  - Danger of anaphylactic shock
- Peripheral eosinophilia (20-25%)



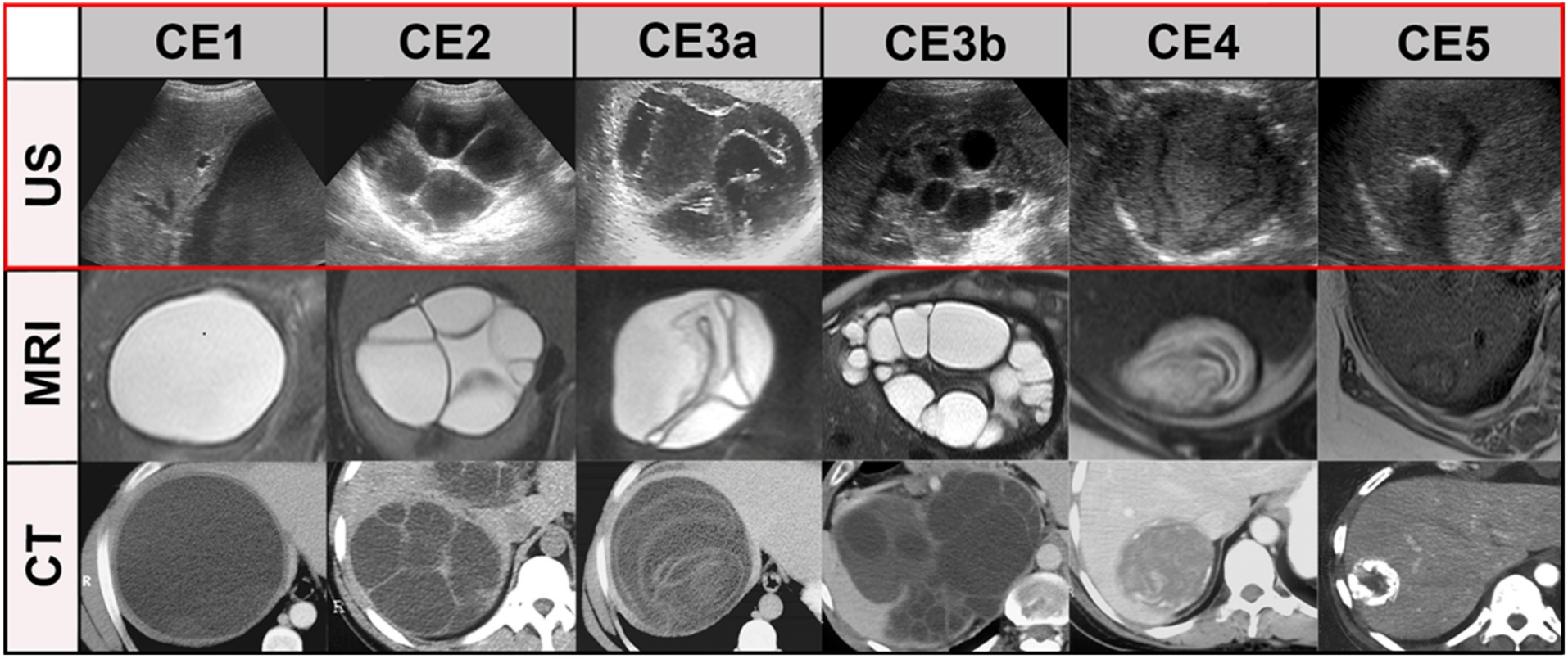


Echinococcal (Hydatid) Cyst

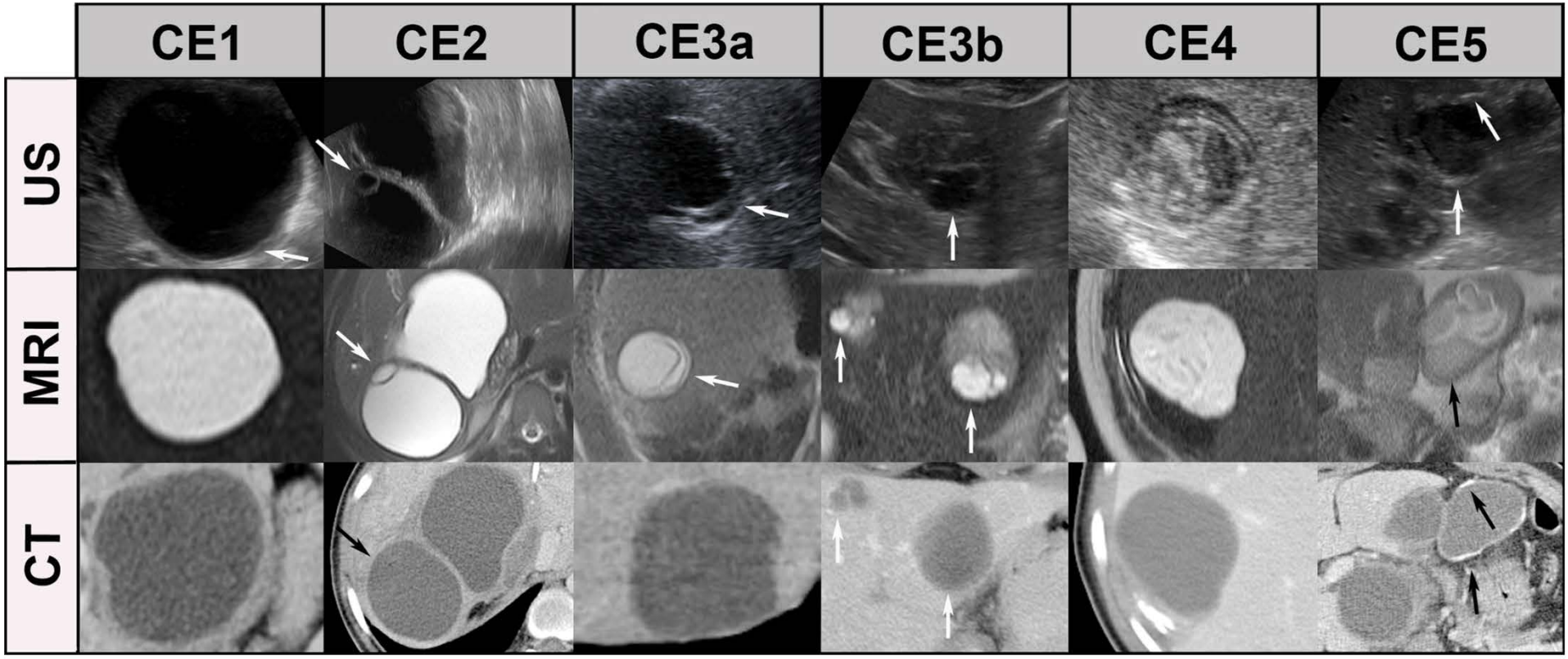
WHO Informal Working Group classification



Stojkovic et al (2012); Copyright © PLoS Negl Trop Dis.)



- **"Best case" of CT/MR imaging.**
- CE1: unilocular, simple cysts with liquid content and often with the CE1-specific "double line sign",
- CE2: multivesicular, multiseptated cysts,
- CE3a: cysts with liquid content and the CE3a-specific detached endocyst, CE3b: unilocular cysts with daughter cysts inside a mucinous or solid cyst matrix,
- CE4: heterogenous solid cysts with degenerative, CE4-specific canalicular structure of the cyst content, and
- CE5: cysts with degenerative content and heavily calcified wall.



- **"Worst case" of CT/MR imaging.**
- The "double line sign", typical for CE1 is often seen in US (CE1/US, arrow), less reliably in MRI and CT. Daughter cysts and detached endocyst ("water-lily-sign") is often missed by CTs, but clearly visible in US and MRI (see CE2, CE3a, arrows). Daughter cysts inside a solid cyst matrix are often not recognized by CT (CE3b, arrows).
- The CE4-specific canalicular structure is often not visible on CT images. These cysts may be misinterpreted as type CE1 cysts, i.e. staged "active" instead of "inactive". The identification of calcifications is the domain of CT imaging. MRI does not differentiate well between thick hyaline walls and calcifications. US picks up calcifications only when a dorsal echo shadow is produced (see CE5, arrows). MRI: HASTE sequence, CT: post contrast enhanced images.

Serological diagnosis

- responses : stage-specific & depend on cyst location
- Early cysts(CE1, CE2): antigenic components sequestered from the host's immune system by the parasite-derived multilaminated layer
- → may remain seronegative as long as intact.

- Endocyst rupture (natural involution or intervention) → serology positive.
- Cyst involution (consolidation, calcification) → serology negative again over years (CE4 and CE5).

- included in definition of "possible" and "probable" cases by the Expert Consensus of the WHO-IWGE

Serology

- Major Ag source for immunodiagnosis - Hydatid fluid
  - HF lipoproteins : antigen B (AgB) & antigen 5 (CE)
  - Reported sensitivities and specificities of serological methods for CE 60% - 90%.
  - enriched / recombinant → increased diagnostic value (sensitivity 92.2% specificity of 95.4%)
- Casoni intradermal test - low specificity and sensitivity
  - Poor standardization / ethical issues (reagents from animal origin injected into humans) →limited use
- Major issue : lack of appropriate antigens for serological detection of small CE cysts in liver and cysts any size cysts in lungs.

Table 14.4 Antibody detection tests for human cystic and alveolar echinococcosis[a]

Type of echinococcosis test	Antigen	Sensitivity (%)	Specificity (%)	Cross-reactions
Cystic echinococcosis				
IgG ELISA	Crude *E. granulosus* cyst fluid	80–>99	61.7	Cestodes (89%), trematodes (30%), nematodes (39%)
	Antigen B (native or synthetic peptide)	63–92	85–93	Alveolar echinococcosis
IgG4 ELISA	Crude cyst fluid	61–67	>99	Alveolar echinococcosis only
EITB	Crude cyst fluid	71	>98[b]	*T. solium* cysticercosis only
	Antigen B fraction	92	100	None
	Antigen B subunit	34–36	>90	

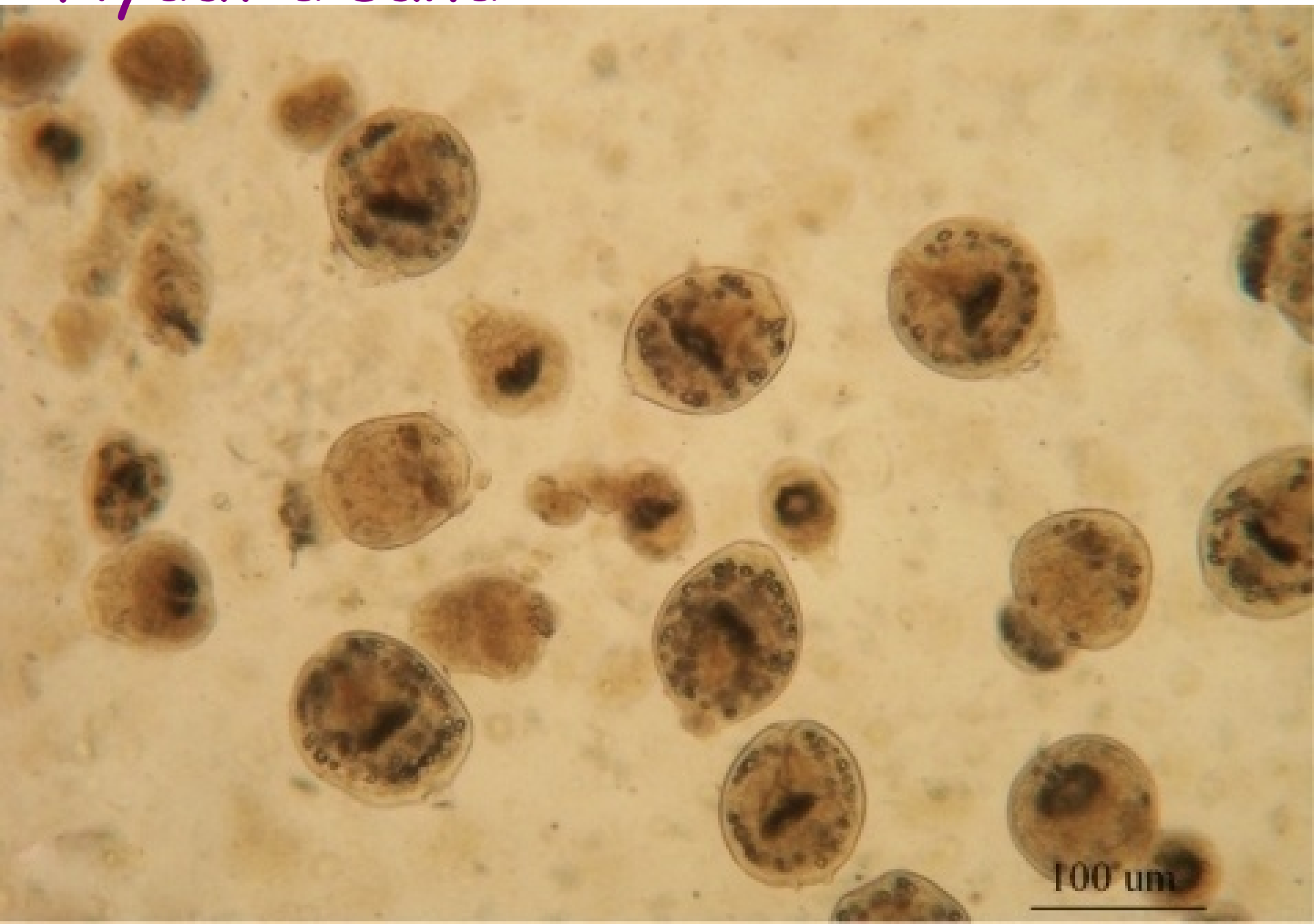
LS Garcia -Diagnostic medical parasitology-ASM Press (2007)

DNA detection

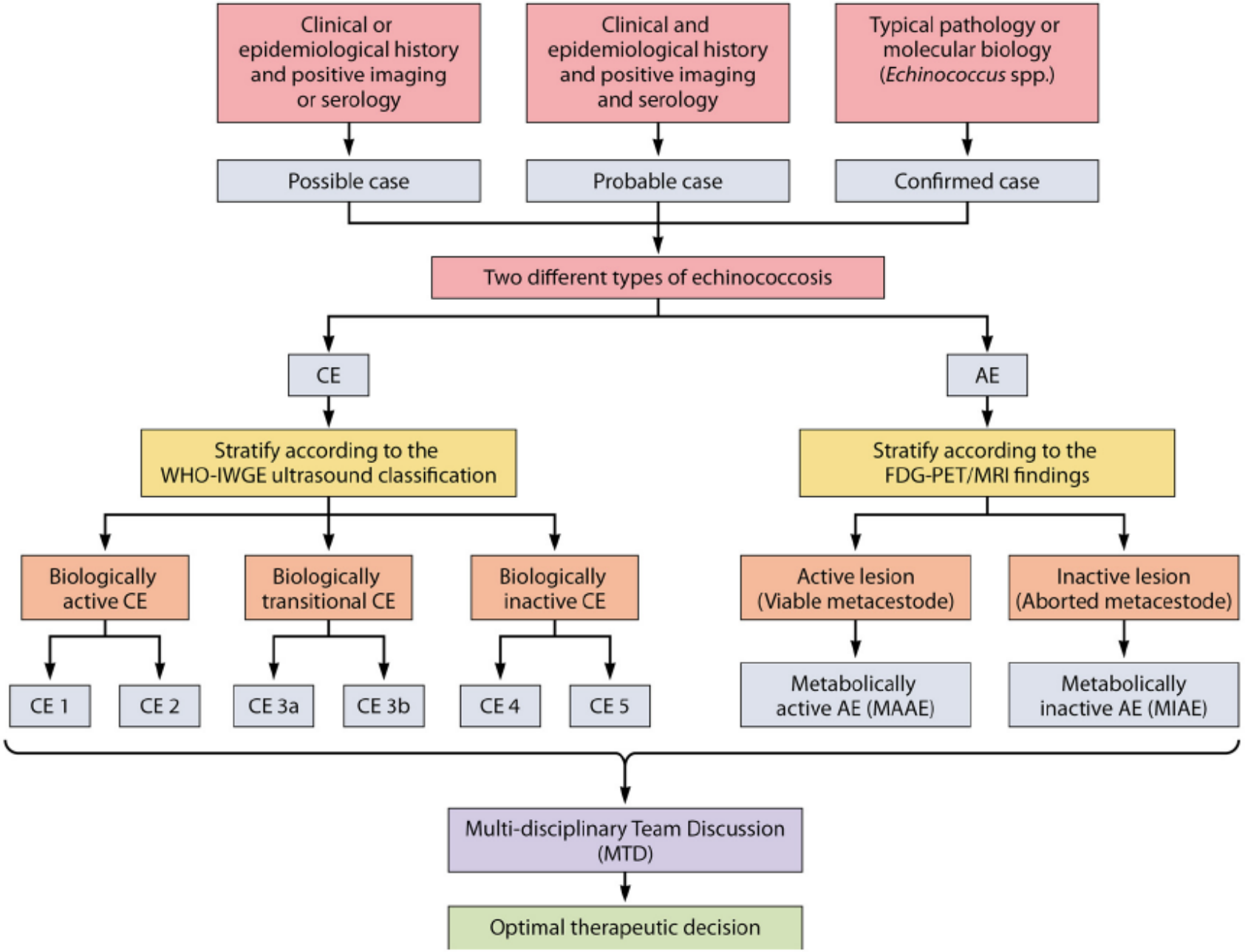
- qPCR, nested PCR, LAMP
- sensitive, specific
- distinguish *Echinococcus* species
  - from other cestodes, from each other, discriminate *E. granulosus* genotypes
- part of the definition of "confirmed cases" of the WHO-IWGE Expert Consensus

- first-line screen in the field
- detect egg DNA in environmental samples
  - identifying high-risk contaminated areas
  - defining routes of human infection

Hydatid sand



Hooklets

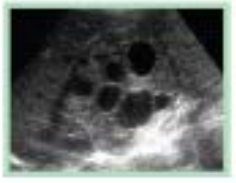
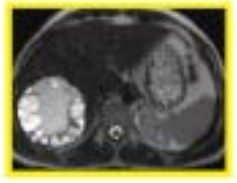
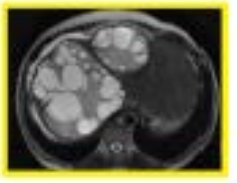


Wen H, et al. Clin Microbiol Rev. 2019 Feb 13;32(2). doi: 10.1128/CMR.00075-18.

Management

- Based on
  - cyst type (WHO-IWGE US classification)
  - size, location
  - presence/absence of complications
  - available medical expertise /equipment
- Four treatment options
  1. Drug treatment with benzimidazoles
  2. Percutaneous sterilization techniques
  3. Surgery
  4. 'Watch and wait'.
- Management includes
  - interdisciplinary team consultations
  - combination of surgical and drug treatments
  - long-term follow-up
  - international recommendations establishment /reference centers creation

Brunetti E, et al 2010. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. Acta Trop 114:1–16. https://doi.org/10.1016/j.actatropica.2009.11.001.

Active cysts	Early Rx	Late Rx	Very late Rx	No Rx	Inactive cysts
	Risk of complications				
	5–6 cm	>5–6 cm <10 cm	10 cm		
CE1					
CE3a					
CE2					
CE3b					
	Benzimidazoles (possibly higher efficacy) **Benzimidazoles** (possibly lower efficacy) **PAIR** **Surgery**/(continuous catheter drainage [CE1, CE3a], large-bore catheter [CE3a, CE3b, CE2]) **Watch & wait**			 	CE4 CE5

Drug treatment

- Albendazole 10–15 mg/kg / day in two divided doses
  - Preferable, better bioavailability
- Mebendazole 40–50 mg/kg / day in three divided doses
- with a fat-rich meal (2-5x better absorption)
- Duration: At least 3 months (possibly 6)
  - Allow 6mo for visible effect in imaging
- Works best on small (<6cm) active cysts
  - CE3b cysts respond initially convert into CE4 cysts, but frequently relapse after albendazole stopped.
- Overall effectiveness across all cyst stages 40–60% in small (≤6 cm) cysts.
- Prevention of secondary CE
  - WHO-IWGE currently recommends to start 4 hours before the intervention until 1 month after the intervention

Manson's Tropical Infectious Diseases-Saunders (2013)

Puncture – Aspiration – Injection – ReAspiration, PAIR

- US-guided percutaneous sterilization of cyst content
- CE1 and CE3a cysts of 5–6 cm to <10 cm in diameter, in which cysto-biliary fistulas are reliably excluded
  - sclerosing cholangitis and liver failure
- Prophylaxis of secondary echinococcosis with albendazole
- Percutaneous puncture of the cyst under US (or CT) guidance
- Aspiration of cyst fluid
- Testing for bilirubin and injection of contrast medium (verification of absence of cysto-biliary communications).
- Aspiration of contrast medium
- If fistulas are reliably ruled out: injection of protoscolicidal (parasitocidal) agent – 95% ethanol or 20% sodium chloride to remain in the cyst for 10–15 minutes
- Re-aspiration of the fluid
- Follow-up for a minimum of 5 years to detect relapses and secondary CE.

Large-bore Catheters, Modified Catheterization (MoCat) and Percutaneous Evacuation (PEVAC)

- Evacuation of the entire parasite-derived cyst components (endocyst plus content).
- For large cysts and cysts with solid content which cannot be approached with PAIR (CE2, CE3b)
- Prerequisites:
  - Experienced Interventionalist
  - resuscitation equipment in place to treat severe anaphylactic reactions
  - surgical back-up

The decision to move from drug and minimal invasive treatment to surgery

- Lack of large appropriately designed clinical trials
- Patient and health facility specific factors
- Move to Surgery: CE1 and CE3a cysts which do not respond to benzimidazole and percutaneous sterilizing procedures
- CE2 & CE3b (benzimidazole →disappointing). Alternatives : surgery and large-bore catheter approaches
- If not validated → arbitrary triage
- Concerns
- Uncomplicated small (<5 cm) CE1, CE2, CE3a and CE3b cysts in anatomically non-critical sites which cannot undergo PAIR and do not respond to benzimidazoles
  - CE3b cysts, which progress to CE4 under benzimidazole treatment → increased risk of relapse
- Watch and wait (follow up with US) for 2 years
  - Progression to CE4, CE5
  - Repeated 3 month benzimidazole courses

Manson's Tropical Infectious Diseases-Saunders (2013)

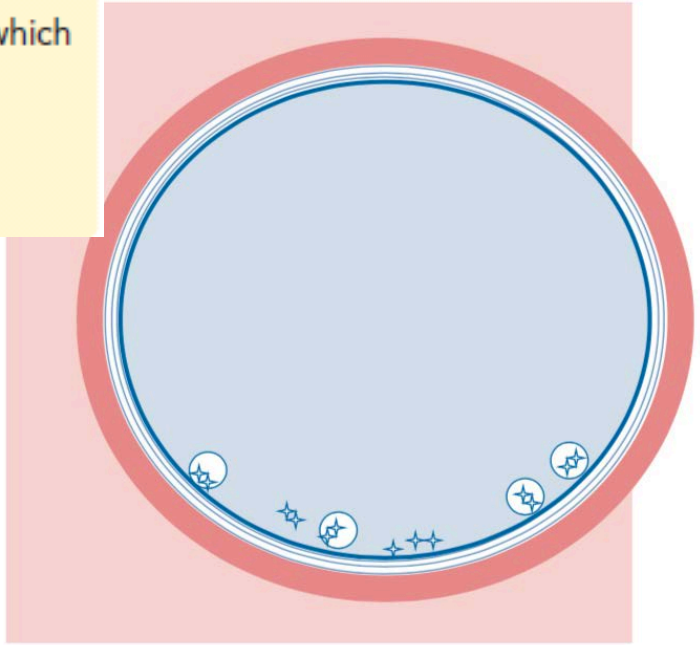
Surgery

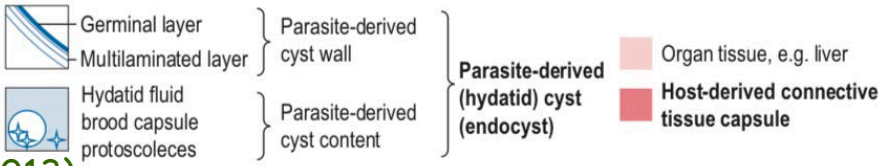
BOX 56.4 THERE ARE TWO MAJOR SURGICAL APPROACHES

1. Partial Cystectomy: Removal of the parasite-derived cyst components (endocyst) and part of the pericyst (host-derived connective tissue capsule).
2. Total cystectomy and Resection
   a. Total cystectomy: Removal of the parasite-derived cyst components (endocyst) and the entire pericyst (host derived connective tissue capsule)
   b. Resection: additional removal of part of the organ in which the CE-cyst is embedded

FOLLOW-UP

All patients should be followed-up for a minimum of 5 years.





Manson's Tropical Infectious Diseases-Saunders (2013)

Surgery

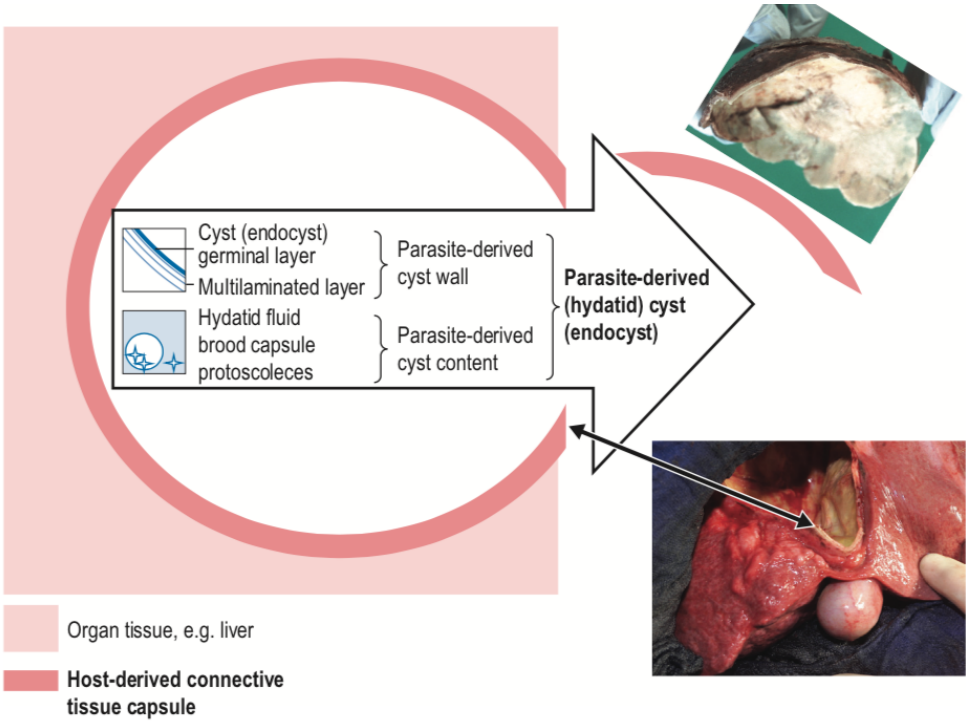


Figure 56.12 Partial cystectomy: Removal of the parasite-derived cyst components (endocyst) and part of the pericyst (host-derived connective tissue capsule). After a trocar has been inserted into the cyst and cyst content aspirated (spillage prophylaxis with cloth soaked with 20% sodium chloride to protect the peritoneum) as much of the host-derived capsule (pericyst) as possible is resected, which allows a good view of the residual cyst cavity. The layer of host-derived connective tissue which is left in place and which is firmly connected to the organ tissues – in this case the liver parenchyma – minimizes the risk of bleeding. *(Copyright © Heidelberg University Hospital.)*

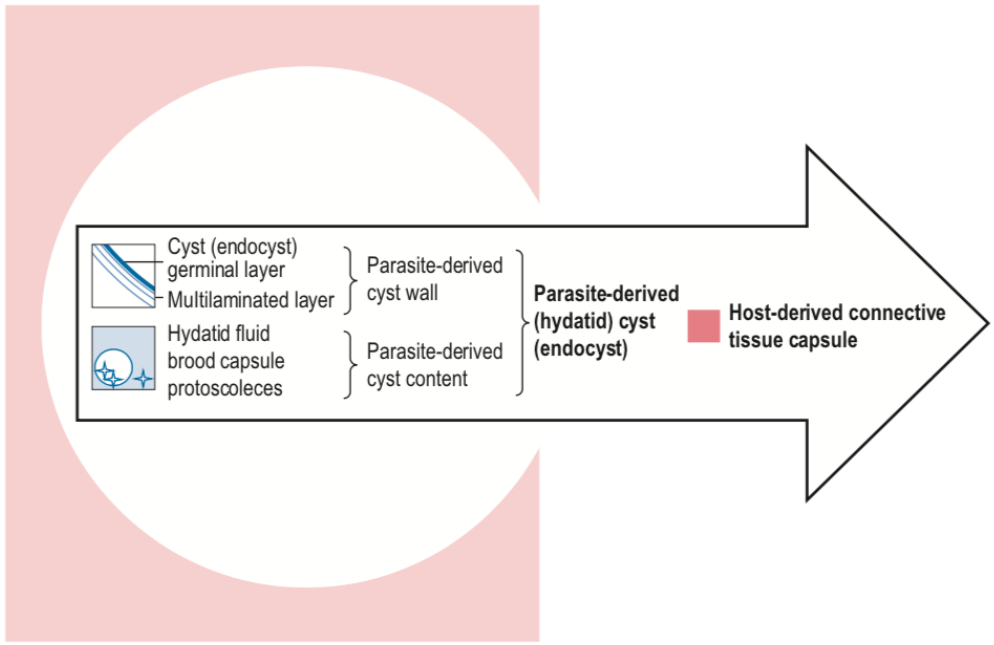


Figure 56.13 Total cystectomy (pericystectomy). The parasite-derived cyst components (endocyst) are removed together with the host-derived connective tissue capsule (pericyst), with the major advantage that the cyst remains closed and there is no exposure to infective cyst content at any time during the procedure. Risks include bleeding

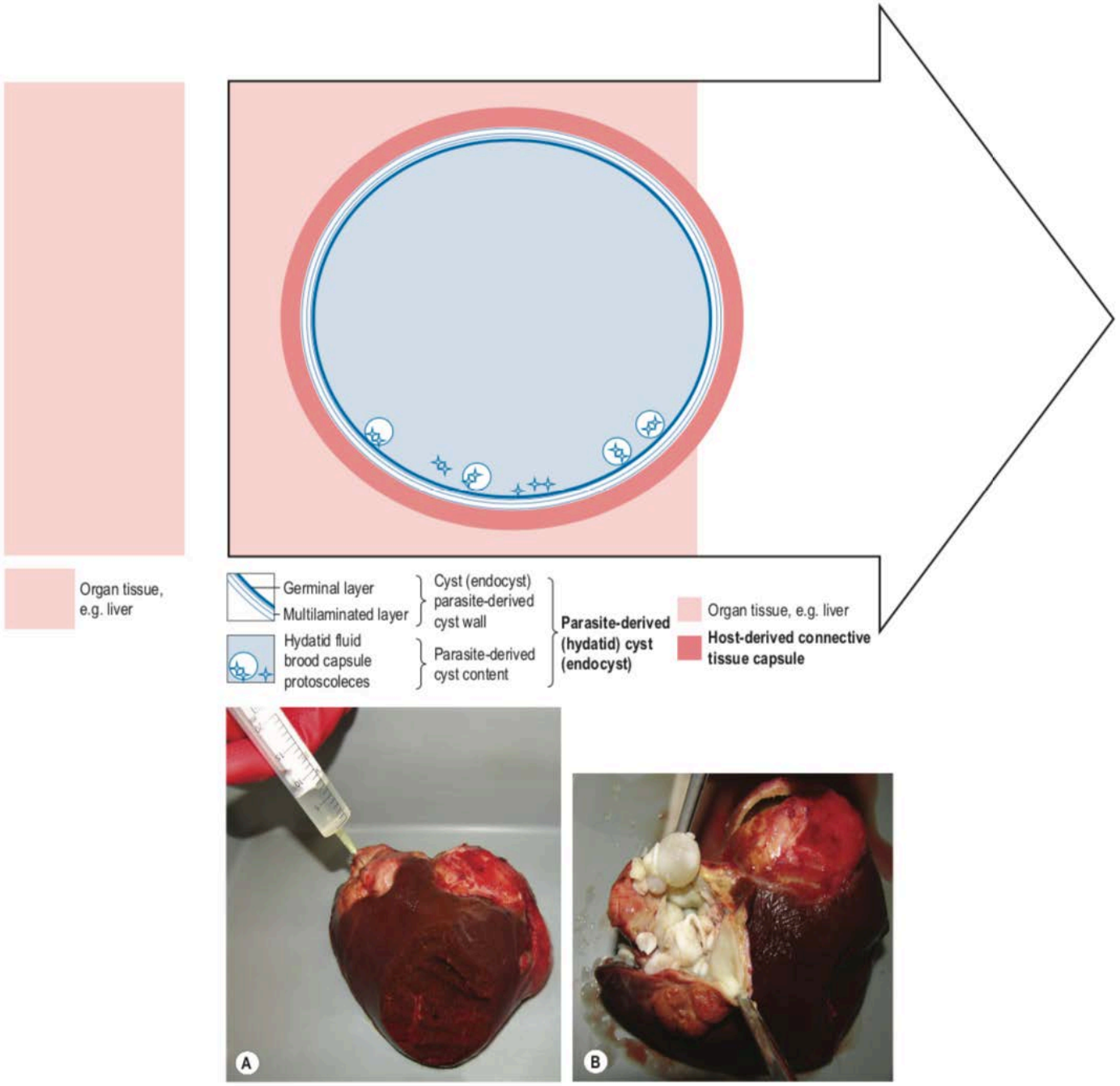


Figure 56.14 Resection: In addition to the parasite-derived cyst (endocyst) and the host-derived connective tissue capsule (pericyst) part of the organ in which the cyst is embedded is resected. Schematic and right liver lobectomy with two large CE cysts: (A) Clear hydatid fluid extracted from an active CE2 cyst; (B) Opened CE2 cyst with multiple daughter cysts. *(Copyright © Heidelberg University Hospital.)*

Follow up

- CE for at least 5 years
  - High relapse rates / uncertainty of complete cure
- Regular blood tests first 6 months ABZ
  - Blood counts
    - Leukopenia
  - Transaminases
    - Hepatic toxicity
  - ABZ / MBZ measurements
- ELISA for Ig
- Alternatively
  - circulating blood / serum *Echinococcus* Ag?
  - Circulating cell-free DNA?

CE - prevention and control

- Safe animal slaughtering conditions
  - offal destruction and preventing dogs from feeding on infected organs of ungulates
- Dosing dogs with praziquantel

- Vaccination
- Sheep EG95
- Dogs EgM9 and EgM123 vaccine candidates

Cvejic D, et al CMR 2016. Parasitol Res 115:1195–1202

Ευχαριστώ

για την προσοχή σας