

Pitfalls and challenges in the diagnosis and follow-up of hydatid cyst

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Introduction

- The most common site is the **liver** (68.8–80%) followed in frequency by **lung** (10–22.4%), kidney (3%), bone (1-4%) and brain (1-2%).
- Rare localizations are represented by spleen (0.9–8%), skeleton (0.2–3%), kidney (0.4–3.7%), brain (0.4–1%), cardiac muscle (0.02–1.1%), peritoneum (2–5.2%), subcutis (1.6%).
- Familiarity with the **imaging findings** of HD may be helpful in making an accurate diagnosis and preventing potential complications.
- **Unusual sites** for this disease can cause diagnostic problems.

Table 1: The published cases of the hydatid cyst with unusual locations from Iran (1990-2011)

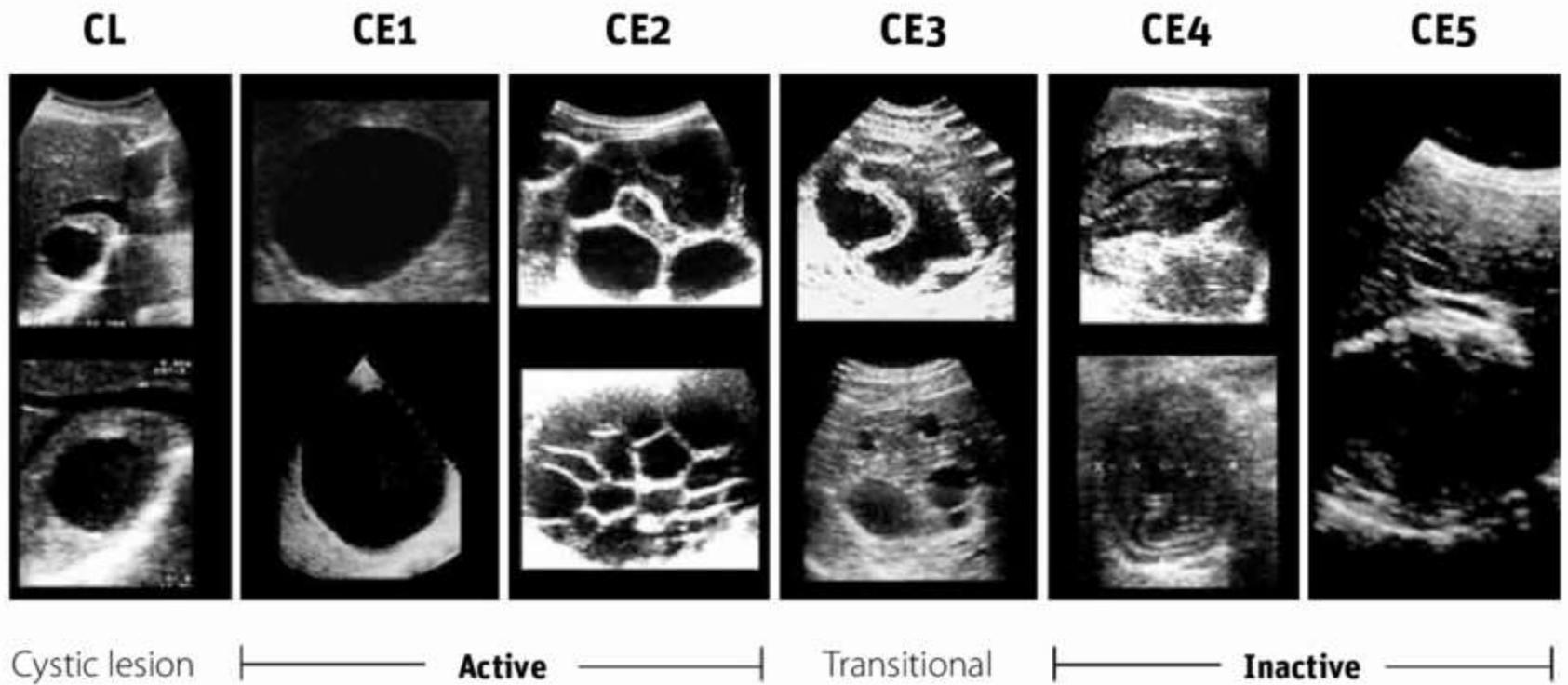
Locations	Numbers	Most common clinical manifestations
Intracranial	256	Headache
Spinal		Low back pain
Orbit		Visual impairment
Musculoskeletal	57	Swelling Pathologic fracture
Cardiovascular	42	Angina, dyspnea and palpitation, pressure effect
Kidney and Urinary Tract	31	Flank pain
Spleen	20	Left upper quadrant pain
Ovary	11	Ovarian mass
Uterus		Lower abdominal pain
Fallopian Tube		
Pancreas	6	Epigastric pain
Salivary Gland	9	Painless swelling
Breast	8	Breast mass
Thyroid	4	Thyroid enlargement
Adrenal	2	Flank pain
Appendix	1	Abdominal pain
Mediastinum	7	Pressure effect on adjacent organs
Omental, Mesenteric, Retroperitoneal	7	Mostly asymptomatic
Parapharyngeal	1	Nonspecific
Nasolabial	1	Nonspecific
Total	463	-

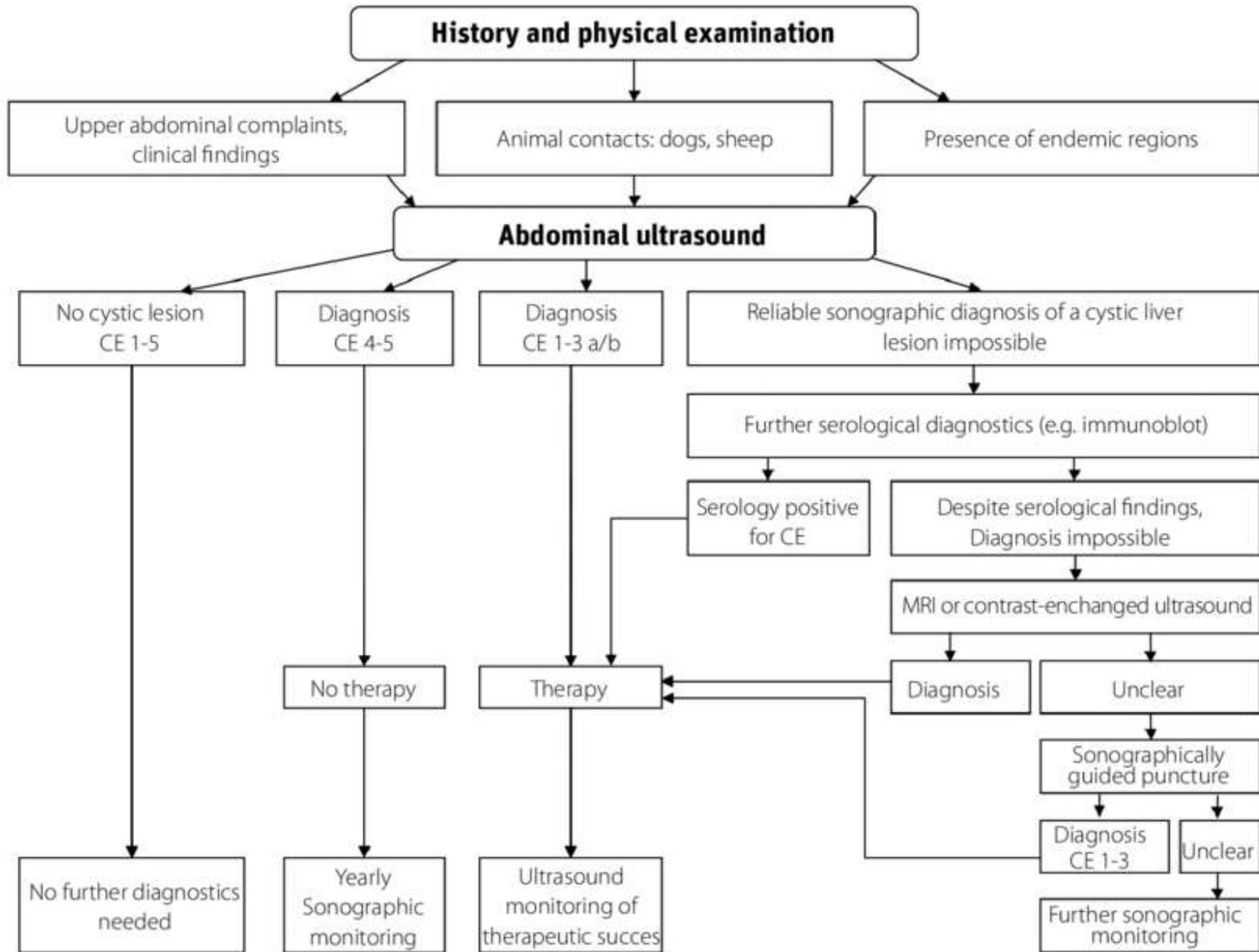
Lab Findings

- Routine **haematological** tests may reveal eosinophilia.
- **Casoni's intradermal test** – due to its **low sensitivity** and **specificity** and because of risk of **causing anaphylactic reactions**, it is obsolete now.
- **Serological tests** detect specific antibodies to the parasite and are the **most commonly** employed tools to diagnose past and recent infection with *E. granulosus*.
- **Ab detection**(IgG) implies exposure to the parasite, while in active infection high titers of specific IgM and IgA antibodies are observed.
- **Ag detection** (circulating hydatid antigen) in the serum is of use in monitoring after **surgery and pharmacotherapy** and in **prognosis**.
- **Gold standard Dx:** Pathology(FNA/H&E)

Standardized classification of stage-specific cystic images (WHO-IWGE)

- Effective serological tests for cystic echinococcosis(CE) diagnosis would be of great help to define and support cyst status and their evolution:
- **Active**: CE1, CE2, and CE3b
- **Transitional**: CE3a
- **Inactive**: CE4 and CE5





Main pitfalls

- A number of pitfalls have been detected for immunoDx of HD , including
 1. low sensitivity/specificity (Se/Sp)
 2. a poor prognostic value for follow-up due to the long-lasting persistence of antibodies
 3. Some antigens are differentially expressed in different cyst stages and post treatment outcome (cyst activity based antigens)
 4. Various genotypes that potentially express different antigenic sets (Cyst genotype based antigens)
 5. cyst location other than the liver particularly lung
 6. cyst size (small)
 7. Cyst number (single)
- These pitfalls lead clinicians to consider serology against HF as an approach of little value, with doubtful benefit for the clinical management of CE.

Available antigens in the diagnosis of CE

- Hydatid fluid , AgB , Ag 5 ,
- **Hydatid Fluid**
- Se reported in these studies varied from **64.8% to 100%**.
- Reasons for **false negative** results depend on several factors comprising **cyst location** other than the liver , early (**CE1**) and inactive (**CE4 and CE5**) cyst stages , **single** and **small cysts**.
- A second problem using HF is the percentage of **false positive** results detected.
- **Antigen 5**
- It is predominant and recognized by antibodies (particularly **IgG4**) from patients with early cyst(**CE1**) stages, while **antigen B** is the most scarce in CE1 cyst stage and mainly detected in patients with **CE2** and **CE3** cyst stages.

Antigen B: (mostly 8 kDa subunit)

- **Five recombinant Ag B** : EgAgB1, EgAgB2, EgAgB3, EgAgB4, and EgAgB5
- Reasons for **false negative** results depend on several factors comprising:
 - cyst location other than the liver (**cyst location**)
 - early (CE1) and inactive (CE4 and CE5) (**cyst stage**)
 - Single (**cyst number**)
 - Small cysts (**cyst size**)
- EgAgB recombinant antigen, in ELISA test, showed a Se : CE1(74%), CE2(**96%**), CE3(**90%**), and CE4/CE5(56%) .

Antigen	Number of patients	Confirmatory test	Technique, antibody	Sensitivity (%)	Negative serology more frequent when	Reference
Purified	21	Surgery	Immunochromatography, IgG	100	Not specified	[42]
			Immunochromatography, IgG4	95		
	23	Surgery		100		
	5	Imaging techniques and serology*	ELISA, IgG	80	Not specified	[46]
	13	Serology*		0		
	32	Imaging techniques	ELISA, IgG	93.8	CE4 and CE5 cyst stages	[16]
	40	Surgery	ELISA, IgG	87.5	Not specified	[30]
			ELISA, IgG4	80		
	108	Surgery	DIGFA, IgG	89.8	Cyst location other than liver; CE1, CE4, and CE5 cyst stages; small cysts	[43]
	113	Imaging techniques	DIGFA, IgG	92.9	Not specified	[44]
35	Imaging techniques	ELISA, IgG	54	CE1, CE4, and CE5 cyst stages	[63]	
56	Surgery	ELISA, all (Protein G)	96.9 ¹ 82.1 ²	Not specified	[37]	
Recombinant B1	31	Surgery	ELISA, all (Protein G)	71	Parasite genotype other than G1	[38]
	124	Surgery ⁵	ELISA, IgG	83	Not specified	[19]
	246	Imaging techniques	ELISA, all (Protein G)	77.6	Not specified	[64]
	113	Imaging techniques	DIGFA, IgG	77.9	Not specified	[44]
	56	Surgery	ELISA, all (Protein G)	94.6	Not specified	[37]
	123	Imaging techniques	ELISA, IgG	73.9	CE4 and CE5 cyst stages, no pretreatment	[15]
Recombinant B2	54 ¹	Surgery	ELISA, IgG	77.8	Single cyst, no pretreatment	[17]
	186 ⁴			79		
	124	Surgery ⁵	ELISA, IgG	62.9	Not specified	[19]
Recombinant 2B2	54 ¹	Surgery	ELISA, IgG	92.6	Single cyst, no pretreatment	[17]
	186 ⁴			87.6		
Recombinant B3	124	Surgery ⁵	ELISA, IgG	29	Not specified	[19]
Recombinant B4	124	Surgery ⁵	ELISA, IgG	75.8	Not specified	[19]
	36	Surgery	ELISA, IgG	91.7	Not specified	[39]
Recombinant B5	124	Surgery ⁵	ELISA, IgG	41.3	Not specified	[19]
PI76 peptide	61	Surgery	ELISA, IgG	78.7	Lung cysts, no complications, single cyst, and small cysts	[48]
	63	Surgery	ELISA, IgG	23.8	Not specified	[50]
Long D8-9 peptide	35	Imaging techniques	ELISA IgG	74.3	Not specified	[41]

* Positive serology against HF in ELISA IgG, ¹EgAgB purified from a Chinese sheep isolate, ²EgAgB purified from a Iranian sheep isolate, ³patients selected by their positivity in ELISA IgG against HF, ⁴Spanish patients, and ⁵Peruvian patients.

Subisotype antibodies

- Remarkably, it is known that the **subisotype** responses against **CE1, CE2, and CE3** cyst stages are mainly **IgG4** (low cross reactivity)
- while **IgG1, IgG2, and IgG3** responses predominate against **CE4** and **CE5** cysts, although this is still a question of debate .
- **Follow-up** : **IgE** antibodies have been considered as better markers than IgG after **chemotherapy and surgery** .
- Nevertheless, these isotypes are more frequently underdetected in CE patients, similar to different IgG subisotypes .

Available recombinant antigens

- Six recombinant antigens:
 - RecEgAgB1
 - RecEgAgB2
 - RecEgAg5
 - RecEgAgMDH
 - RecEgAgCaBP
 - RecEgAgAFFP
- will be tested for the **serodiagnosis and follow-up** of CE on a wide panel of samples obtained from extended ultrasound surveys in Eastern Europe.

Conclusions: A New Hope for the Future?

- Diagnosis and follow-up of CE patients are mainly based on **imaging techniques**.
- Serological tools supporting imaging techniques would be desirable.
- **ELISA system:**
- Specific **recombinant antigens (Ag B & Ag 5)** have good potential as diagnostic and follow-up tools for CE, but progress in this field is hampered by **lack of standardization**.
- Recent findings revealed that the simultaneous usage of **AgB1** and **AgB 2** could be a suitable approach for the diagnosis of **CE 2-3**. Se **96.7 %**, Sp **93.3%** (Khatami et al.,2020)
- **CE1 : Ag5**
- **Both Dx and follow-up : IgG4** levels could be correlated with cyst activity , and it seems to be useful to diagnosis **active cyst** and define **the success of treatment**.
- **IEP system:**
- Currently available and suggested test in Iran for all CE staging : **CCIEP has high sensitivity (98% - 100%) , but low sp**
- **Rapid Diagnostic Test system (Lateral flow dipstick):** **1. VIRapid™ (purified AgB/Ag5 ; Se: 100% , Sp: 89% , Spain , best Dx performance)**
- **2. Hyd Rapid™ (rAgB + IgG4; Se: 95% Sp:88% ; Malaysia)**
- **Useful for screening , first line**
- Thus, a challenge still exists to develop a reliable world standard based on serology for the diagnosis and monitoring of CE patients.

Data bases

- The database behind the European Register of Cystic Echinococcosis ERCE, <http://www.heracles-fp7.eu/erce.html>, and CYSTRACKdatabase, <http://cystrack.irnasa.csic.es>).
- Hosting of samples and clinical data has been organized in a dedicated biobank (EchinoBiobank).

Primary Characteristics of 24 Published Cases of **Hepatic Alveolar Hydatid Cyst** From Iran (1995 and 2015)

- Twenty-two patients were from the northeast part of the country, i.e., Khorasan Razavi province, one patient was from Ardebil province, and one case was reported from the south, i.e., Khuzestan province.

The most common sign in physical examination was hepatomegaly and liver mass in all 24 patients, which was tender in two of them (8.3%).

Hepatic Alveolar Hydatid Cyst From Iran (1995 and 2015)

F/M	20/4
Age	21 - 74 (42.6 ± 12.20)
Duration of symptoms	20 days to 5 years (35.6 ± 27.5 months)
Clinical presentation	Abdominal (RUQ) pain
Physical examination	Hepatomegaly and liver mass
Location	Khorasan Province
Lobe of involvement	Right lobe
Size	10 - 30cm