

Mini-symposium: Helminths and respiratory health

Paediatric pulmonary echinococcosis: A neglected disease

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Educational aims

The reader will come to appreciate that:

- Pulmonary hydatidosis is the most frequently encountered type of hydatid disease in humans. Due to close contact between sheep and dogs and humans it is endemic to many parts of the world.
- Pulmonary involvement is more common in the paediatric population. The lung parenchyma is the most affected site within the thorax, but echinococcosis may also develop in any extrapulmonary region including the pleural cavity, fissures, mediastinum, heart, vascular structures, chest wall, and diaphragm.
- Pulmonary cysts are typically first seen on chest X-ray, either as an incidental finding or following respiratory symptoms after cyst rupture or secondary infection of the cyst.
- Computed tomography (CT) is of value in determining the presence of cysts in areas difficult to visualise with chest radiography, such as the anterior and posterior costophrenic angles, characterising the cystic nature of the lesion and determining wall thickness and complications.
- Treatment of pulmonary cystic echinococcosis (CE) is a combination of medical therapy and surgery.
- Increased awareness of the infection may expedite diagnosis and prevent undesirable complications which includes unnecessary surgery.

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ABSTRACT

Echinococcosis is a worldwide public health problem causing considerable paediatric morbidity and mortality in endemic areas. The presentation of cystic echinococcosis (CE) varies by age. Unlike adults, where hepatic involvement is common, pulmonary CE is the dominant site in the paediatric population.

Pulmonary cysts are typically first seen on chest X-ray, either as an incidental finding or following respiratory symptoms after cyst rupture or secondary infection of the cyst. In children, pulmonary cysts have a broad differential diagnosis, and a definitive diagnosis relies on the combination of imaging, serology, and histology. In countries with high infectious burdens from diseases such as acquired immunodeficiency syndrome (AIDS) and tuberculosis (TB), the diagnosis is additionally challenging, as atypical infections are more common than in developed countries. Pulmonary CE is treated with a combination of surgery and chemotherapy.

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INTRODUCTION

Echinococcus granulosus (class Cestoda, family Taeniidae) was the first described of the *Echinococcus* species [1]. The larval form (hydatid cyst) was mentioned by Hippocrates (–460 BC to –370 BC) [1].

Hydatidosis or echinococcosis are the general terms used to describe four disease forms caused by the larval stage of *Echinococcus* tapeworms, the smallest tapeworms in the Taeniidae family. Human echinococcosis is a zoonotic disease that occurs in four clinically well-described forms:

- Cystic echinococcosis (CE), also called hydatid disease or hydatidosis, is caused by infection with *Echinococcus granulosus* (*E. granulosus*).
- Alveolar echinococcosis (AE), also called alveolar hydatid echinococcosis is caused by infection with *E. multilocularis*.
- Polycystic echinococcosis is caused by infection with *E. vogeli*.
- Unicystic echinococcosis is caused by infection with *E. oligarthrus*.

Cystic echinococcosis and AE are the key forms of echinococcosis in humans [2].

Pulmonary hydatidosis is the most frequently encountered type of hydatid disease in humans. Due to close contact between sheep and dogs and humans it is endemic to many parts of the world, particularly the Mediterranean countries including Turkey, the Middle East, South America, Africa, New Zealand, Russian Federation, Central Asia, and Australia [3–7]. Very few studies outside of North Africa and the Middle East have reported paediatric pulmonary CE [8,9].

The hydatid cyst of the lung has three layers: pericyst, ectocyst, and endocyst [3,10]. Multiple protoscolices develop on the inner surface of the germinal layer, differentiate into secondary cysts when a cyst ruptures, and form freely floating daughter cysts within the mother cyst [11].

Despite a well-known lifecycle, the presentation, accuracy of diagnostic methods and treatment outcomes of paediatric echinococcal disease remain unclear [8,9].

Echinococcal disease presents differently in all age groups. Hepatic involvement is the most common presentation in adults compared with pulmonary involvement in the paediatric population. The lung parenchyma is the most affected site within the thorax, but echinococcosis may also develop in any extrapulmonary region including the pleural cavity, fissures, mediastinum, heart, vascular structures, chest wall, and diaphragm [12].

Clinically, while small hydatid cysts in the lung often cause no symptoms, large cysts may cause symptoms such as chest pain, coughing, dyspnoea, and haemoptysis as well as allergic reactions including anaphylaxis [13–15].

Pulmonary cysts are typically first seen on chest X-ray, either as an incidental finding or following respiratory symptoms after cyst rupture or secondary infection of the cyst [13]. Pulmonary cysts in children have a broad differential diagnosis which includes congenital, acquired, benign and malignant aetiology. In children, a definitive diagnosis relies on the combination of history, imaging, serology, and histology. In countries with high infectious burdens from diseases such as acquired immunodeficiency syndrome (AIDS) and tuberculosis (TB), other rare infectious causes should be considered [8,9,16,17]. In children, the sensitivity of serology for echinococcal disease is not well described, and the factors predicting a positive result are not well established. There is currently no available standard, highly sensitive and specific test for detecting antibodies in CE [18].

The incidence of complications in paediatric pulmonary CE, including mass effect, cyst rupture, chemical pneumonitis, anaphylaxis, and death, remains unclear [19]. Whilst a few published adult studies have evaluated cyst size, cyst rupture, and surgical management as prognostic factors for postoperative complications, there is a paucity of data on prognostic factors in the paediatric population. There is also limited data to guide treatment type, duration of medical therapy and the optimal timing of surgery in the paediatric population [20–23].

PARASITES AND THEIR LIFECYCLE

Echinococcus species belong to the Taeniidae family of the Cestoda class in the phylum Platyhelminthes. To date, four medically important species have been identified to cause disease in humans. *E. granulosus* is by far the most common and causes cystic echinococcosis. *E. multilocularis*, which causes alveolar echinococcosis, is less common and mostly associated with sylvatic cycles of disease. *E. vogeli* and *E. oligarthrus* have only rarely been isolated from human hosts [19,24].

Mature tapeworms of *Echinococcus* species live in the small intestine of carnivorous mammals, like dogs, wolves, and foxes, usually without causing any notable disease. They are between 2–7 mm in length and consist of a head (scolex), a neck and a tail (strobila). The scolex has a rostellum on its apex, which contains two rows of up to 36 hooklets, and four laterally placed, cup-shaped suckers which allow it to attach to the mucosa of the host's intestine. The strobila is segmented and consists of three interconnected hermaphroditic reproductive units known as proglottids. The terminal proglottid contains the gravid uterus which is filled with thousands to millions of eggs [25–27].

Eggs are intermittently released into the environment either through the faeces of the definitive host following the disintegration of proglottids, or when whole gravid proglottids pass through the host's intestine. Eggs can survive in relatively harsh environments for up to a year but are not resistant to desiccation [28].

Herbivorous and omnivorous mammals, like sheep, cattle, and pigs (or small rodents in the case of *E. multilocularis*), act as intermediate hosts by ingesting the parasite's eggs while grazing. Similarly, humans can be infected via the feco-oral route following contact with the contaminated faeces of domestic dogs or after ingestion of contaminated food and water. Humans are referred to as accidental hosts since they don't participate in perpetuating the parasite's life cycle [28,29].

Once ingested, enzymes in the stomach and duodenum allow eggs to hatch while intestinal bile assists in activating the released oncospheres. Oncospheres are equipped with hooklets allowing them to penetrate the duodenal mucosa, invade the venous circulation and passively migrate through the host's circulatory system to eventually settle in the host's viscera. Here, the oncospheres develop into metacestodes which slowly enlarge to form fluid-filled cysts [30,31].

Mature cysts are composed of three layers with the innermost being a germinal layer. From this layer, brood capsules or daughter cysts develop by means of asexual budding. Daughter cysts can produce thousands of protoscolices which in turn may form further daughter cysts or develop into adult worms. Following ingestion of cyst-infected tissue by a carnivore, the released protoscolices evaginate in the lumen of the new definitive host's gut and attach to the mucosa of its duodenum. After reaching maturity 4–6 weeks later, the adult worm completes its lifecycle by commencing its intermittent shedding of eggs [19,30].

PULMONARY AND EXTRA-PULMONARY PATHOLOGY

The localisation of echinococcal lesions shows that the number of children and adolescents having cysts in the lungs exceeds the number of those having cysts in the liver. This is different to adults, where most cysts are in the liver and cysts are relatively scarce in the lungs [32,33].

In adults, echinococcal cysts grow very slowly and take several years to reach a large size, but in children cysts may grow more quickly. The growth may be faster in richly vascularised organs, such as the lungs [34].

In children, the lungs appear to have less physical resistance to the growth rate of echinococcal cysts compared to the dense liver parenchyma. The paediatric lung is more compressible and this facilitates cyst growth. The growth rate of cysts in the lungs is estimated to be at least five-fold higher than in the liver [35].

The size of pulmonary cysts may vary from 1 to 20 cm. Pulmonary cysts are classified as giant cysts when the largest diameter is more than 10 cm. Giant cysts are more commonly reported in children than in adults due to the immature immune system and the greater elasticity of the lung tissue. The pulmonary cyst can be in any lobe but is more commonly found in the lower lobes (55–70%). Cysts can also be bilateral (20%) and multiple (30%) [10,36–41].

The local complications of pulmonary hydatidosis can be classified as rupture (perforation), secondary infection, reactions of the adjacent tissue, and the complications associated with space occupation [11].

Pulmonary cysts can be classified as complicated and uncomplicated. Complicated pulmonary CE was defined as a cyst with a complete or a contained rupture or superinfection. Uncomplicated pulmonary CE was defined as well-defined, homogeneous lesions with low density and smooth, variable-thickness wall, irrespective of the number or lobar location [12]. Centrally located cysts are mostly round, while peripheral cysts are oval or polycyclic [37,42].

A ruptured cyst can occur in up to 47.5% of cases. Several factors may be responsible for cyst rupture which include age, anti-helminthic therapy, chemical reactions, the size of the cyst and the immune system of the host. These factors can lead to rupture via degeneration of the cyst membranes [12,13,37,38].

Ruptured cysts frequently occur in both the lungs and liver. Lung cysts contain fragments of larval tissue and protoscolices which can spill from the ruptured cyst and may flow into the pleural cavity, the bronchus and the blood vessels in the lung. The cyst material may lead to secondary lesions by producing granulation tissue [27,43].

A contained rupture is defined as detachment of the pericyst from the endocyst, rupture of the endocyst, but intact pericyst [10]. A contained rupture is unlikely to result in an allergic reaction or infection as the cyst contents are surrounded by the pericyst. Imaging features of contained rupture include air crescent sign, inverse crescent sign, and air bubble sign.

A complete rupture occurs when both the pericyst and endocyst rupture. Features of complete rupture are any of the following: combo, dry cyst, rising sun, waterlily, whirl, mass within the cavity signs. Complete rupture occurs more frequently in lesions located in the periphery of the lung, due to the facts that the anatomical location provides less protection to the cyst, there is little host tissue to offer support and the pericyst may be deficient [3]. In complete rupture, the cyst empties and may become smaller and less spherical [3].

CE can also rupture directly into the parenchyma, main bronchus, and pleural cavity. Rupture of a hydatid cyst into a bronchus, due to degeneration of the membranes, manifests as vigorous coughing and expectoration of a large amount of salty spu-

tum consisting of mucus, hydatid fluid, and, occasionally, fragments of the laminated membrane [13]. In these cases, solid remnants of the collapsed parasitic membrane are left in the cavity as a source of recurrent infection [44]. When a cyst ruptures into the parenchyma consolidation can develop around the cyst. Centrilobular opacities may be seen due to endobronchial extensions of CEs. Rupture into the pleural cavity can lead to hydrothorax or hydropneumothorax, tension pneumothorax or empyema [13,44,45]. In patients with hydatidosis, the documented rates of pneumothorax range from 2.4% to 6.2%, while empyema is reported to occur in 6.0 to 7.6% of the patients [13,44]. Secondary pleural hydatid disease occurs when the pleura is infested by a live scolex from a ruptured intrapulmonary cyst seeding into the pleural cavity [47]. Acute allergic reactions can develop when the cyst ruptures, but fatal anaphylaxis is rare [10,42].

Superinfection is a common complication of a ruptured CE [44]. Infection in CE occurs only after rupture of both the pericyst and endocyst, allowing bacteria to pass easily into the cystic lesion [3].

The radiological signs of cyst infection are ring enhancement sign, air bubble sign, and an air-fluid level.

Other thoracic pathology includes atelectasis, bronchiectasis, mediastinal lymphadenopathy, and pleural thickening or effusion. Atelectasis develops due to compression by a cyst and may lead to the development of pneumonia. Bronchiectasis can be due to bronchial obstruction and parenchymal destruction [48]. Mediastinal lymphadenopathy may also be seen but is uncommon and associated with superinfection [46].

Intrathoracic but extrapulmonary cysts are rare but can occur secondary to haematogenous spread or extension of hepatic, pulmonary, or splenic cysts. Extrapulmonary cysts may be seen in the chest wall, pleural cavity, fissures, diaphragm, mediastinum, heart chambers, and vascular structures. Transdiaphragmatic migration (0.6–16%) of hepatic hydatid disease can occur in the posterior segment of the right hepatic lobe due to its close location to the diaphragm [10,49]. Transdiaphragmatic migration imaging findings include elevation of the diaphragm, pleural effusion, consolidation and atelectasis at the lung base, and an hourglass-shaped lesion or a loculated pleural effusion in the posterior thorax [10].

A bronchobiliary fistula can develop when there is a rupture of a hydatid cyst, which is located at the upper surface of the liver, into the bronchial tree leading to a communication between the biliary and bronchial tree [50]. The presence of bile in sputum is a pathognomonic finding [50].

CARDIOVASCULAR PATHOLOGY

Cardiac echinococcosis is very rare (0.02–2% of cases) and may be due to haematogenous spread or rupture of a lung cyst. The most affected cardiac chambers (in decreasing order of frequency) are the left ventricle (50–60% of cases) as it has an abundant blood supply, interventricular septum (10–20%), right ventricle (5–15%), pericardium (10–15%), and right or left atrium (5–8%) [51].

Clinical symptoms depend on the size and location of the cyst, and most patients are asymptomatic. Compression effects of the cyst may result in arrhythmias in the case of atrioventricular conduction pathway obstruction. Cysts located in the right or left ventricular outflow tract clinically present with arrhythmia, angina, pulmonary or systemic embolism, and valvular dysfunction [52].

CLINICAL PRESENTATION

The incidence of hydatid disease is not well documented but the reported incidence in Turkey is 1:2000 children with a higher inci-

dence in the rural areas [53]. The most affected age group is 7–10 years but cases as young as 2 years have been reported [2]. No difference in the distribution between boys and girls has been reported in different series but Anadol et al. observed that more boys (59%) were affected [32]. Contact with animals was identified in 27% of cases, with 58% of affected individuals living in rural areas [32].

Children with echinococcosis often remain asymptomatic for many years. The incubation period can last many years until a cyst has grown to a size that causes clinical signs or symptoms [54]. Asymptomatic children are often diagnosed after a chest X-ray for other indications. Asymptomatic children mostly have a small intact cyst. Children become symptomatic when the cyst ruptures and causes anaphylactic shock or if a bacterial infection develops. Secondary symptoms can develop due to a mass effect of a slow-growing hydatid cyst in the lungs. The rupture of pulmonary cysts is followed by expectoration of cyst fluid and can lead to coughing, chest pain and abdominal pain [35]. Expectoration of cyst fluid and membranes is rarely reported, in less than 3% of cases [32].

The presenting symptoms in children depend on the size and the position of the cyst and whether the cyst has ruptured. Cough, fever, purulent sputum, chest pain and abdominal pain are the most common symptoms [14,32]. The presenting symptoms may also be related to extrapulmonary involvement including the liver with coincidental findings on the chest X-ray. The lower lobes are the most common location for CE and may be visible on abdominal X-rays. Physical findings include decreased breath sounds, crackles and hepatomegaly but can be very non-specific. The findings are also dependent on the size, location (unilateral or bilateral), and whether complications (rupture and or secondary infection) have occurred.

Table 1
Imaging findings in paediatric pulmonary/thoracic echinococcal disease.

	Sign	CXR	CT	MRI
Uncomplicated cyst		Homogeneous fluid density intra-parenchymal mass [Fig. 1 a,c]	Water intra-pulmonary mass of varying sizes [Fig. 1 b,d]	Simple fluid [Fig. 3b] T2W↑ T1W↓
Complicated cyst				
- Early separation of ectocyst from pericyst.	Meniscus CXR Crescent CT	Peripheral air separating ecto and pericyst [Fig. 5 a]	Peripheral air, separating ecto and pericyst [Fig. 5b]	
- Wide separation of ectocyst from pericyst	Cumbo/ Onion peel	Peripheral air with air-fluid internally [Fig. 6 a]	Peripheral air separating ecto and pericyst, with endocyst air-fluid level [Fig. 6b]	
- Disruption of integrity of the endocyst	Whirl/ serpent	Erect or decubitus air fluid level with undulating membranes [Fig. 6 c, Fig. 7 a and d]	Dependent detached membranes [Fig. 6 d Fig. 7 b]	
		Solid appearance (not shown)		
			Cyst with “solid” membrane content	
- Complete loss of fluid content	Mass in cavity Empty cyst	Sequential progression to lung cyst, devoid of internal content [Fig. 7 f]	Small cyst-devoid of internal content	

Imaging spectrum of hydatid cysts. () indicates figures in text.

Table 2
Imaging pearls.

Always look for associated liver hydatids, cerebral hydatids (Fig. 8). Fluid level does not always have to be “floating lily” and may in fact appear completely regular. NB decubitus view (Fig. 7). The detached membranes in the cyst fluid may be obscured on lung settings. Best to manipulate CT window width and level to show the serpiginous membranes. Small air locules can be trapped beneath the serpiginous membranes below the surface, alerting to the presence of membranes (Fig. 5c). Ultrasound may be better at demonstrating the three layers and the detached membranes (Fig. 4) Duplication cyst has only two layers, which aids in differentiation. Daughter cysts are less common in pulmonary hydatids.

Large airway compression is not often reported but can be significant if a cyst is very large or located close to the mediastinum. Both the trachea and the main bronchi may be affected.

Children may also present with symptoms and signs of lung abscess including fever and purulent sputa. Once infected, CE will result in similar imaging findings as a lung abscess or an infected bronchogenic cyst.

As described above, rupture into the pleural cavity can lead to pleural effusion or hydropneumothorax, pneumothorax, or empyema with the relevant clinical findings. Although cardiac involvement is rare, children can present with unexplained arrhythmia, angina, pulmonary or systemic embolism and valvular dysfunction [55]. Bronchiectasis can develop in children with untreated CE or complicated disease. This will lead to lobar bronchiectasis, mostly in the lower lobes.

IMAGING FINDINGS IN PAEDIATRIC PULMONARY/THORACIC ECHINOCOCCAL DISEASE (TABLES 1 AND 2)

Plain radiography

Chest X-ray is the initial modality on patient presentation, also helpful for follow-up evaluation of response to treatment.

Computed tomography (CT)

CT is of value in determining the presence of cysts in areas difficult to visualise with chest radiography, such as the anterior and

posterior costophrenic angles, characterising the cystic nature of the lesion and determining wall thickness.

Ultrasonography

Ultrasonography is particularly useful if the cyst abuts on the chest wall. Demonstration of laminated membranes within the involved area may be a guide to the correct diagnosis.

Magnetic resonance imaging (MRI)

MRI is useful in selected cases to evaluate soft tissue involvement, e.g., chest wall imaging or central nervous system involvement. There is the distinct advantage of avoidance of ionizing radiation.

IMAGING FEATURES OF PULMONARY DISEASE

A. Intact cyst

a) Chest radiography

On a chest X-ray, the typical intact pulmonary hydatid cyst presents as a well-defined, solitary, round or oval, homogeneous opacity ranging in size from 1 to 15 cm in diameter. (Fig. 1a and c) Giant cysts (greater than 15 cm) are prevalent in children (Fig. 2). Multiple opacities are also relatively common (30%) (Fig. 3a) [10,12,38,40].

A well-defined, homogeneous, rounded pulmonary opacity in a country with endemic hydatid disease is highly suggestive of the condition [12].

Large cysts may cause atelectasis of the adjacent lung and shift of the mediastinum, and peripheral cysts can elicit a pleural reaction [10,12,38,40]. An intact cyst may simulate a bronchogenic cyst (typically middle mediastinal in origin, or perihilar lower lobe if intra-parenchymal), round pneumonia, haematoma, arteriovenous malformation, granuloma of a different aetiology, or benign tumours [12]. Cysts abutting on the mediastinum simulate a mediastinal mass, while those attached to the thoracic wall may resemble a cold abscess or loculated pleural effusion. Multiple cysts can be confused with pulmonary metastases. Calcification of pulmonary cysts is extremely rare [12,38,40,57].

b) Computed tomography (CT)

CT shows simple (intact) cysts to have smooth walls and homogenous contents of water or near-water density (Fig. 1b and d) The three layers in an intact cyst are seen as a single wall.

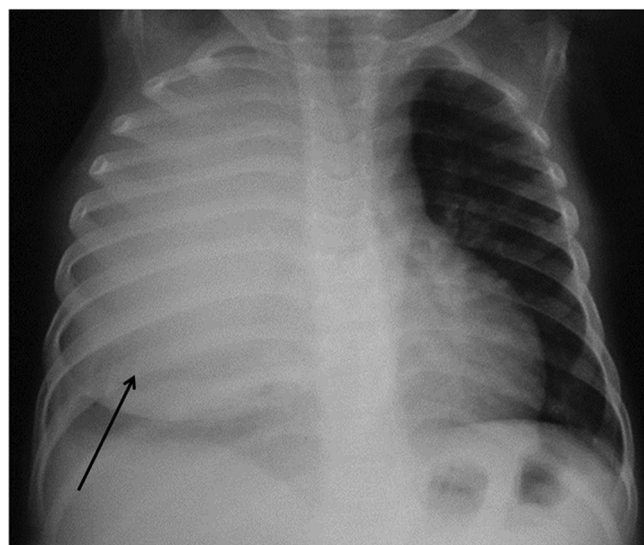


Fig. 2. Chest X-ray demonstrating a giant homogenous cyst in the right lung (black arrow).

Intact hydatid cysts cannot be differentiated from water-density lung cysts of different aetiology through CT appearance alone. The intact cyst wall typically does not enhance. However, in endemic regions the CT demonstration of the cystic nature of a lung mass provides collaborative evidence in clinically suspected cases [12].

c) Ultrasound

Imaging features depend on the proximity to the chest wall. Simple cysts containing hydatid sand are seen as echogenic foci/snowstorm [38]. The membranous nature of cysts may be demonstrated as concentric regions of hypo-/hyper-echoic signals. (Fig. 4)

d) Magnetic resonance imaging (MRI)

Simple cysts demonstrate a typical simple fluid intensity signal, with a T2-weighted hyperintense (Fig. 3b) and T1-weighted hypointense signal (not shown) [12,38,40].

B. The earliest separation of the ectocyst from the pericyst

Loss of integrity of the pericyst allows air from the bronchial tree or alveoli to become interposed between the pericyst and

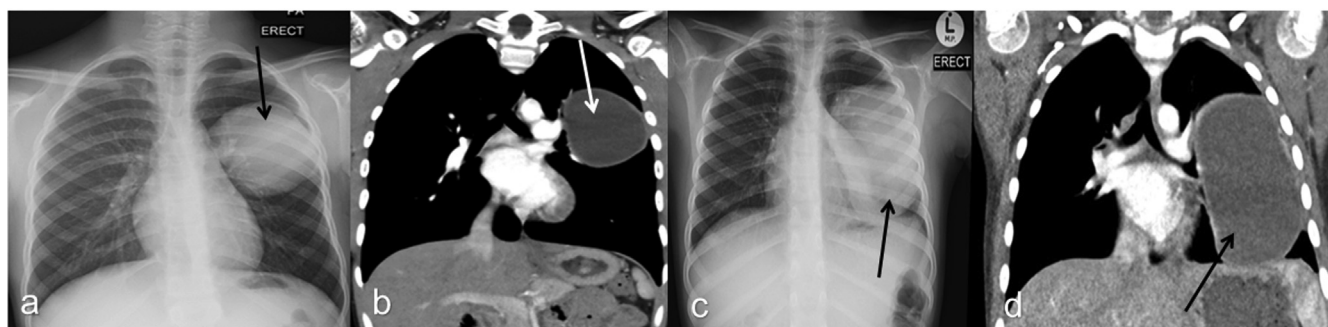


Fig. 1. a: Chest X-ray demonstrating a homogenous intra-pulmonary mass in the left upper lobe (black arrow). b: Coronal chest CT soft tissue window demonstrating a simple cyst in the left upper lobe (white arrow). c: Chest X-ray demonstrating a homogenous mass in the left lower zone (black arrow). No effacement of cardiac/mediastinal borders. d: Coronal chest CT soft tissue window demonstrating a simple cyst in the left lower lobe (black arrow).

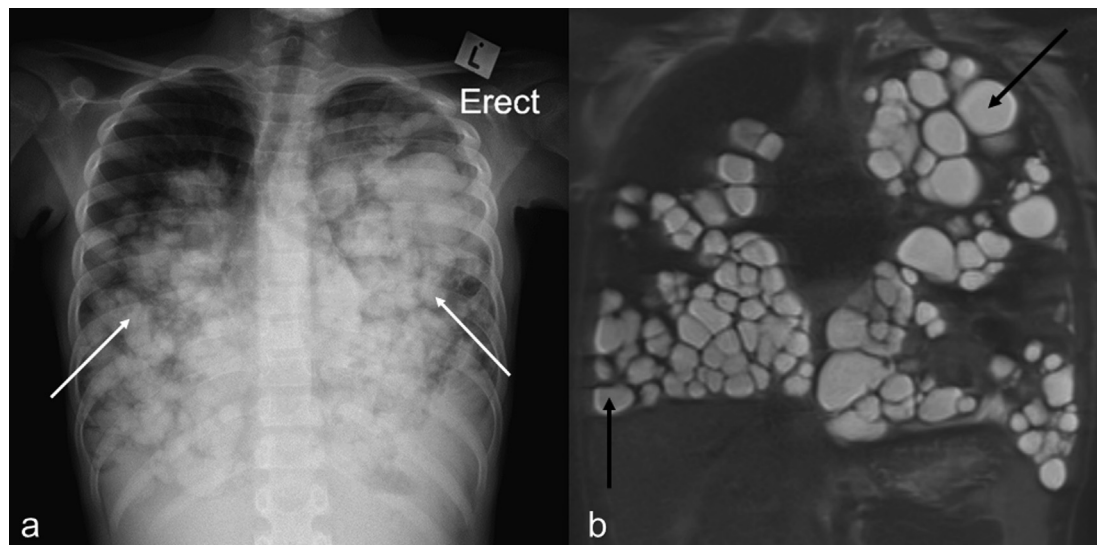


Fig. 3. a: Chest X-ray demonstrating numerous bilateral homogenous opacities (white arrows). b: Coronal heavily T2-weighter MRI demonstrating numerous bilateral simple cysts, with internal hyperintense signal, compared to skeletal muscle (black arrows).

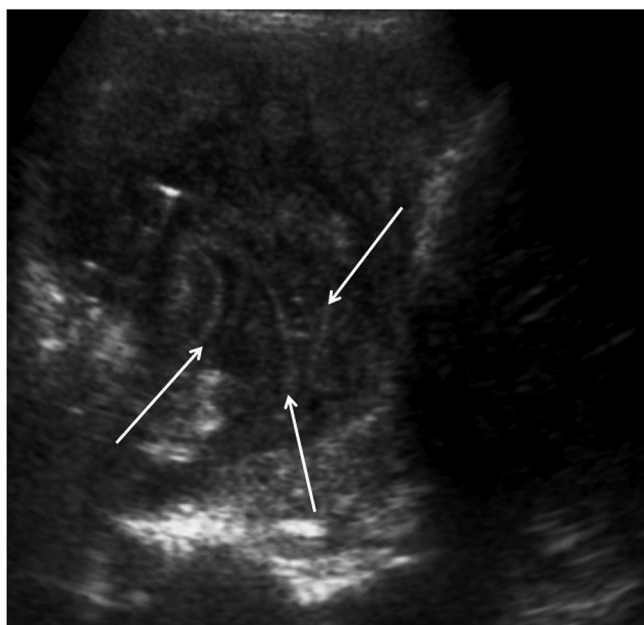


Fig. 4. Transverse ultrasound of the right lower lobe demonstrating alternating hyper- and hypo-echoic membranes (white arrows).

ectocyst. This is seen radiographically as an air crescent in the upper part of the cyst, known as the meniscus sign on chest X-ray (Fig. 5a) and the crescent sign on CT (Fig. 5b). This sign is highly reliable for hydatid disease but not pathognomonic [10,12,38,40,56,58]. Intracystic air blebs at the periphery of the cyst between the pericyst and endocyst, known as the air bubble/signet ring sign, are best appreciated on CT (Fig. 5c) and often a helpful clue to the correct diagnosis.

C. Wide separation of the ectocyst from the pericyst

Further air entry leads to internal air-fluid levels within the endocyst and a peripheral air crescent, collectively known as the combo/onion peel sign. An air-fluid level is seen on both chest X-

ray and CT, with a meniscus/crescent of peripheral air on chest X-ray (Fig. 6a) and CT (Fig. 6b), respectively [10,12,38,40,56,58].

D. Disruption of the integrity of the cyst

Following fluid expectoration, collapsed membranes may be seen within the cyst cavity, called the whirl/serpent sign (Fig. 6c and d). Further cyst collapse is seen as detached membranes appearing to float on dependent water, called the water lily sign. This is seen as an undulating surface in the inferior aspect of the cyst on chest X-ray (Fig. 7a, c and d) with CT accurately demonstrating the detached membranes lying inferiorly (Fig. 7b) [10,12,38,40,56,58].

E. Complete loss of fluid content of cyst

Chest X-ray and CT show an empty thin-walled cyst after complete evacuation of the hydatid membranes, called the empty cyst sign (Fig. 7e and f) [10,12,38,40,56,58].

F. Complications

a) Secondary infection

An infected hydatid cyst may cause hydatid lung abscess. Disintegration of membranes and the purulent cystic content may produce an air-fluid level with no demonstrable floating membranes [14]. A hydatid cyst with such an appearance cannot be differentiated from an ordinary pyogenic abscess by CT even in endemic regions. Complicated pulmonary hydatid cysts, either ruptured or infected, may have higher CT attenuation numbers than that of water due to mucus, haemorrhagic content or infection. These lesions are also difficult to differentiate from other cavitory lesions [12].

b) Pleural spread

Rupture into the pleural cavity can lead to hydrothorax or hydro-pneumothorax. (Fig. 8a) Secondary infection with empyema formation may also occur. Tension pneumothorax may rarely occur. The differential diagnosis of pleural involvement is bacterial empyema, bronchogenic cyst, lymphoma, sarcoma or pleural metastases [12].

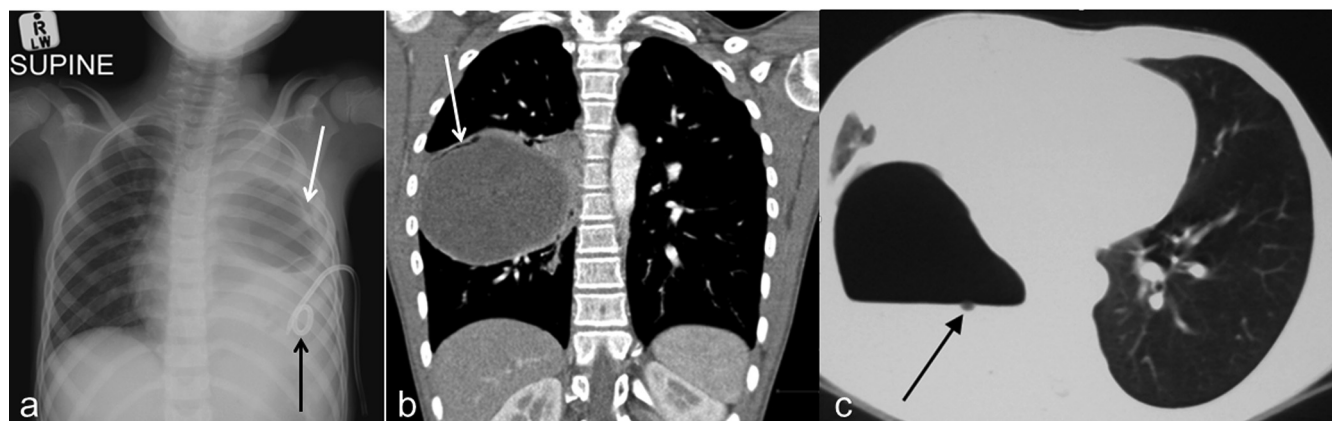


Fig. 5. a: Chest X-ray demonstrating an air filled left upper lobe mass, with peripheral air (white arrow), called the meniscus sign. Left sided intercostal drain present (black arrow). b: Coronal chest CT soft tissue window demonstrating a simple right lower lobe cyst with a peripheral air crescent (white arrow), called the crescent sign. c: Axial chest CT lung window demonstrating a large air-fluid level with air loculi trapped between membranes (black arrow), called the air bubble sign.

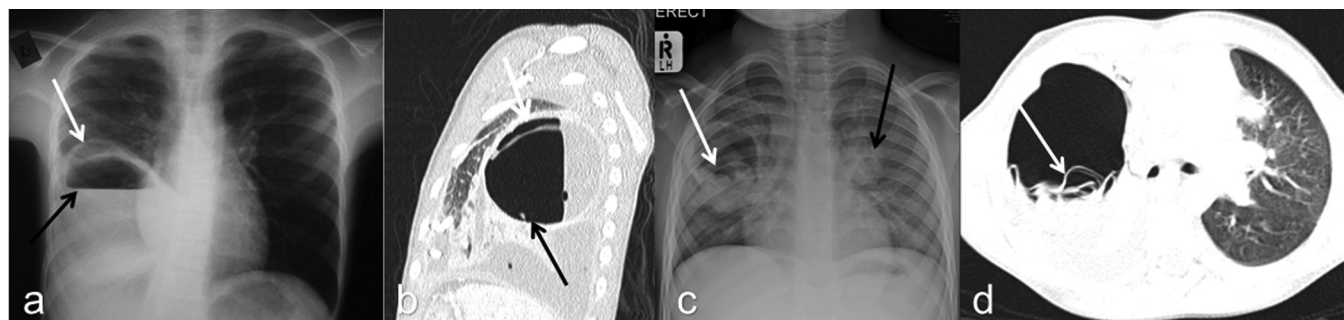


Fig. 6. a: Chest X-ray demonstrating a right lower lobe intra-pulmonary mass with peripheral air (white arrow) and air-fluid level (black arrow). The combination of peripheral air crescent and central air-fluid level is called the cumbo sign. b: Sagittal chest CT lung window demonstrating the peripheral air crescent (white arrow) and central air-fluid level (black arrow). The combination of peripheral air crescent and central air-fluid level is called the cumbo sign. c: Chest X-ray demonstrating a right lower zone cavity with internal air and dependent membranes (white arrow), called the serpent sign. Additional left hilar mass (black arrow). d: Axial chest CT lung window demonstrating a large air-filled cavity with dependent membranes (white arrow), called the serpent sign.

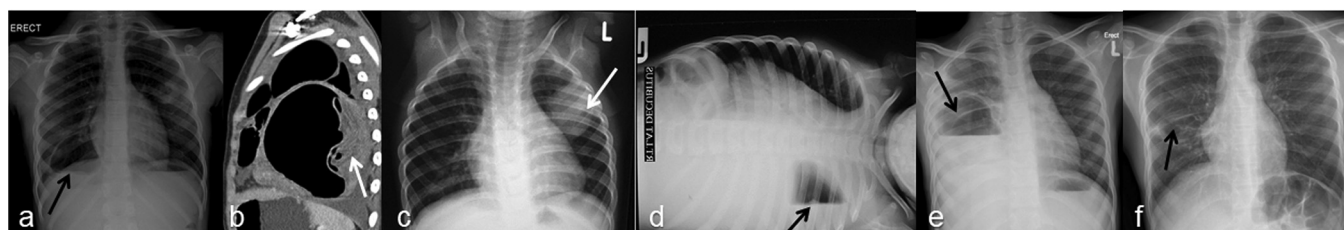


Fig. 7. a: Chest X-ray demonstrating a right lower lobe cavity, with dependent undulating content (black arrow), called the water lily sign. b: Sagittal chest CT soft tissue window demonstrating dependent membranes (white arrow), called the water lily sign. c: Chest X-ray demonstrating a homogenous opacity in the left upper lobe (white arrow). d: Decubitus chest X-ray demonstrating an air fluid level with a small undulating membrane (black arrow), favouring hydatid disease. e: Chest X-ray demonstrating a right lower zone mass (black arrow) with internal air-fluid level and peripheral air crescent. f: Chest X-ray following expectoration demonstrating an empty thin-walled cystic mass (black arrow), called the empty cyst sign.

c) Chest wall invasion

Direct extension of pulmonary disease into the chest wall is a rare complication. Clinical presentation is with fluctuant chest wall swelling/inflammation [12].

d) Vascular invasion

Inferior vena cava or hepatic vein invasion from hepatic disease is a rare cause of hydatid pulmonary embolism and carries a significant risk of sudden death, by way of massive embolism or anaphylactic shock [59–61].

e) Primary pleural, cardiac, or chest wall disease

i) Primary pleural disease

Pleural involvement occurs via haematogenous dissemination after ingestion of ova. Uni- or multilocular cystic involvement may be seen, attached to the visceral pleura. Subpleural or perifissural locations are recognized [12,38].

ii) Primary cardiac disease

The heart is typically involved via haematogenous spread following ova ingestion. Involvement of the left ventricle, inter-ventricular septum, right ventricle, pericardium and atriums occur in decreasing frequency.

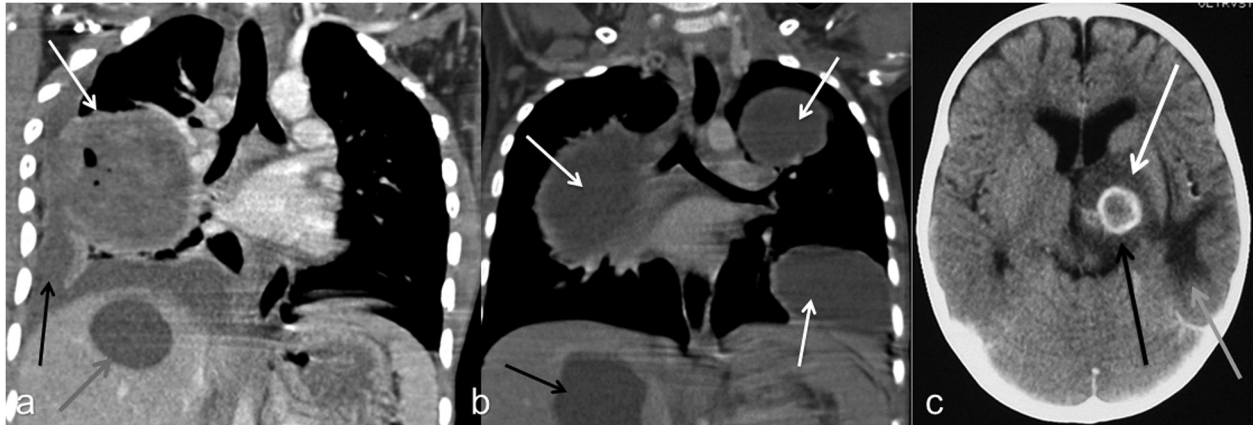


Fig. 8. a: Coronal chest CT soft tissue window demonstrating right upper zone cyst with fluid content and air loculi (white arrow). Right sided pleural effusion (black arrow) and concomitant superior segment simple hepatic cyst (grey arrow). b: Coronal chest CT demonstrating multiple simple intrapulmonary cysts (black arrows) and a simple hepatic cyst (white arrow). c: Axial post contrast brain CT soft tissue window demonstrating a rim enhancing lesion in left thalamus (black arrow), with surrounding oedema, seen as hypodensity surrounding the thalamic mass (white arrow) and vasogenic oedema of the left parietal lobe (grey arrow).

Rupture into cardiac chambers may lead to embolisation into the pulmonary arteries and systemic hydatidosis. Chronic/sub-acute recurrent pulmonary embolism may occur. Cardiac disease fatality is related to compression of vital vascular structures. Diagnosis is via transthoracic echocardiography, cardiac CT or MRI [12,38].

iii) Primary chest wall disease

Bone involvement

Although the spine is the most common site of osseous involvement, rib and sternal involvement is recognized. Multiloculated lytic expansile lesions with cortical destruction are seen. The absence of the pericyst in osseous disease leads to the absence of the typical spherical shape. The differential diagnosis of osseous involvement includes tuberculosis, metastasis, giant cell tumor, bone cyst and neurofibroma [12,38].

Soft tissue involvement

Isolated muscular involvement is very rare, and disease typically occurs via extension from adjacent organs. Subcutaneous soft tissue involvement may range from uni- to multilocular or complex cystic lesions which may calcify. The differential diagnosis includes haematoma, abscess, necrotic soft tissue tumours, lymphangioma or necrotic lymphadenopathy [12,38].

Diaphragmatic involvement

Diaphragmatic involvement is typically due to direct extension from posterior segments of the right liver lobe, due to proximity to the diaphragm. Extension is via the hepatic bare area and the lack of peritoneal coverage allows unrestricted cyst growth. Involvement may be seen as a cystic lesion with a waist/collar or as a loculated effusion/pulmonary parenchymal involvement. Chest imaging may demonstrate elevated hemidiaphragm, basal atelectasis, parenchymal consolidation or pleural effusion. Multiplanar MRI imaging can demonstrate the diaphragmatic defect and aid in surgical repair [12].

Concurrent pulmonary, hepatic and central nervous system hydatid cysts may occur, necessitating routine abdominal ultrasound and brain CT in select cases (Fig. 8b and c) [12,62].

The primary diagnostic method in pulmonary hydatid disease is the plain radiograph. This method is helpful for the diagnosis of

intact cysts, but it may be inadequate for the assessment of complicated cyst morphology. CT depicts certain details of the lesions and can detect others that are not visible by chest radiography. CT examination can elucidate the cystic nature of the pulmonary lesion and provide accurate localisation for planning of surgical treatment of complicated cysts. Multiplanar and multiparameter imaging features of MRI facilitate comprehensive evaluation of intrathoracic and extrapulmonary hydatid cysts (e.g., chest wall, mediastinal, pericardial, fissural, and pleural).

BRONCHOSCOPIC FINDINGS

Bronchoscopy is not routinely used in the diagnosis or management of pulmonary hydatid disease. Bronchoscopy may be diagnostic in cases of recurrent pneumonia or pneumonia that does not clear. In these cases, parts of the cyst may be visible in the affected airway (Fig. 9).

The cyst must not be removed endoscopically as there is a significant risk for bleeding. Intraoperative bronchoscopy may be

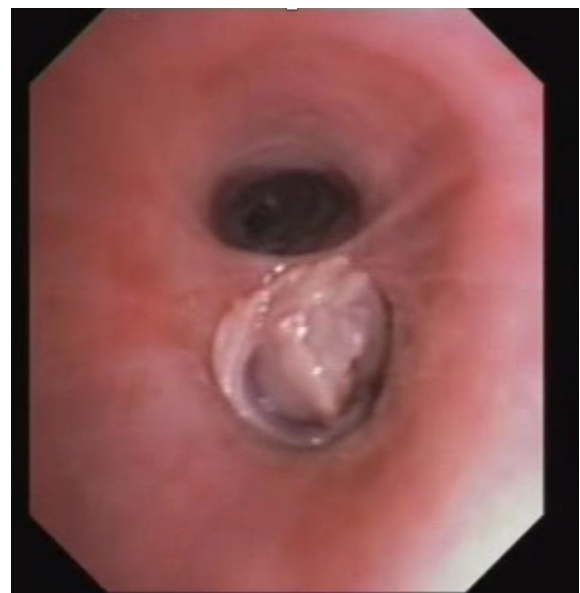


Fig. 9. Hydatid cyst presenting in a segmental bronchus of the left lower lobe.

needed in the management of complicated, infected, or very large cysts.

Bronchial blockers are used in younger children instead of double-lumen tubes to block the selected main bronchus during surgery [63]. The bronchial blocker is a rounded balloon catheter threaded on a guidewire that has a loop at its distal tip. The flexible bronchoscope (FB) and catheter are inserted through a multiport adaptor connected to the endotracheal tube. The FB is placed through the wire loop and guides the catheter into the main stem bronchus on the selected side for surgery. The balloon is inflated under vision to confirm that it is in the right position and has not migrated into the trachea. Adequate inflation of the balloon is required for an adequate seal of the airway to cause lung collapse. This is achieved under FB guidance until the bronchial blocker reaches the bronchial wall and requires a variable amount of air depending on the patient's age and weight. During the procedure, the need might arise to deflate and inflate the balloon according to the surgeon's needs. It is important to re-check the position of the balloon and the size of the balloon during these manipulations. Fogarty catheters may be used as a cheaper alternative [64]. An extraluminal blocker on the outside of an endotracheal tube can be used in smaller children.

LABORATORY DIAGNOSIS

The diagnosis of echinococcosis relies heavily on the presence of epidemiological risk factors, clinical signs and symptoms, and the detection of hydatid cysts by means of imaging [29]. Immunodiagnoses and other laboratory parameters can nevertheless assist in the diagnosis of primary disease and the subsequent monitoring of disease progression and resolution. Immunodiagnoses can also be utilised for the differentiation of *Echinococcus* species and the assessment of the host's immune status for the purpose of optimal management [30,65].

Mild eosinophilia and non-specific liver function abnormalities may be present or absent during all stages of infection and are therefore not particularly helpful. In fact, markedly raised eosinophil counts are seen in less than 15% of cases and typically only occur after the leakage of antigenic contents from compromised cysts [19,29].

Several serological assays form part of the immunodiagnostic armamentarium. It is however important to note that the diagnostic sensitivity and specificity of these assays vary greatly and depend on several factors including the sensitivity of the chosen technology, the quality of the antigens used in assays, the anatomical site of infection, and the competency of the host's immune system [65].

Initial screening for echinococcosis, by detection of pathogen-specific antibodies in the host's serum, arguably delivers acceptable results and is also widely accessible. A lack of standardisation and the use of crude antigens in many of these assays however negatively impact their sensitivity. The diagnostic sensitivity of commonly used enzyme-linked immunosorbent assays and indirect haemagglutination tests targeting IgG antibodies typically reach 50% for pulmonary, and up to 90% for hepatic disease. Sensitivity can however be as low as 25% depending on the site of infection which serves as a firm reminder that negative results do not rule out disease [2,11–13,19,66–68].

Cross-reactivity as seen with other tape worm infections, notably *Taenia* species, and unrelated host conditions, like malignancies, cirrhosis and auto-immune diseases, can also lead to false positive results emphasising the importance of using more specific confirmatory tests. The use of techniques like immunoblotting and the utilisation of more specific antigens like antigen 5 and recombinant antigen B in diagnostic assays may help to mitigate these shortcomings [65,66,68].

Cysts of *Echinococcus* species grow slowly and can remain intact and asymptomatic for many years when undisturbed. In such cases where the host fails to launch a proper immune response, the parasitology laboratory can assist with further microbiological confirmation.

Unlike the case for many other parasitic conditions, screening for *Echinococcus* eggs in stool samples is not routinely performed as humans typically act as intermediate hosts. Eggs are also indistinguishable from those of species of the *Taenia* genus from which *Echinococcus* diverged millennia ago [24].

When collecting samples for the diagnostic laboratory, care must be taken to prevent the rupture of cysts as spillage of the highly antigenic content could lead to anaphylactic shock and the formation of numerous secondary cysts [29,65].

Microscopic evaluation of intra-operatively collected 'hydatid sand', cystic fluid or cyst-infected tissue may reveal evaginated and invaginated protoscolices and floating hooklets indicative of *Echinococcus* species. 'Hydatid sand' refers to the macroscopic appearance of remnants of brood capsules, protoscolices, hooklets, and calcareous corpuscles present in primary or daughter cysts (Fig. 10a–c).

PATHOLOGY

The pathology seen in humans (who act as aberrant intermediate hosts) is the cystic hydatid form. Once the oncospheres have penetrated the intestinal wall (post ingestion), they migrate to various organs, most commonly liver and lungs (in *Echinococcus gran-*

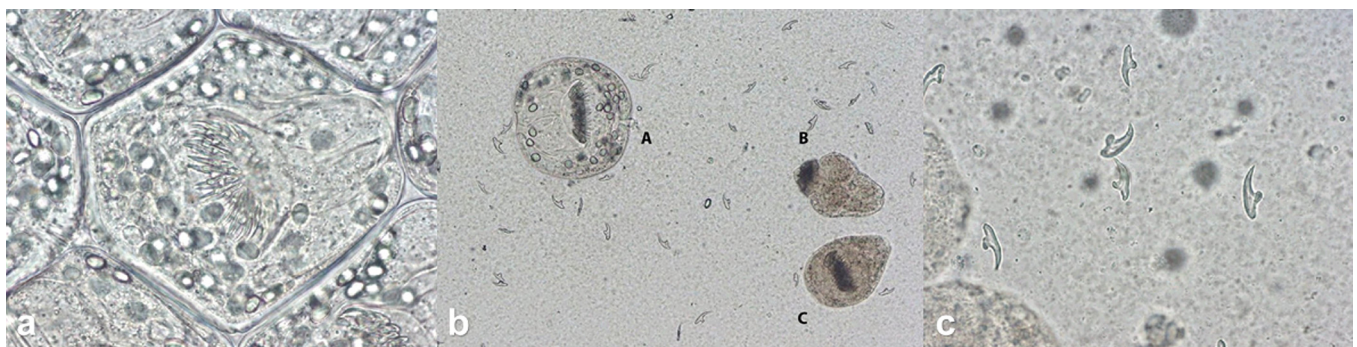


Fig. 10. a: Unstained wet mount of fluid collected from a hydatid cyst: multiple daughter cysts featuring 'hydatid sand' and a prominent evaginated protoscolex (500× magnification). b: Unstained wet mount of fluid collected from a hydatid cyst: (A) a daughter cyst with 'hydatid sand' (B) an evaginated, and (C) invaginated protoscolex (500× magnification). c: Unstained wet mount of fluid collected from a hydatid cyst: floating hooklets (500× magnification). Photo credit: Jeremy Goodway (NHLS Tygerberg Hospital, Cape Town, South Africa).

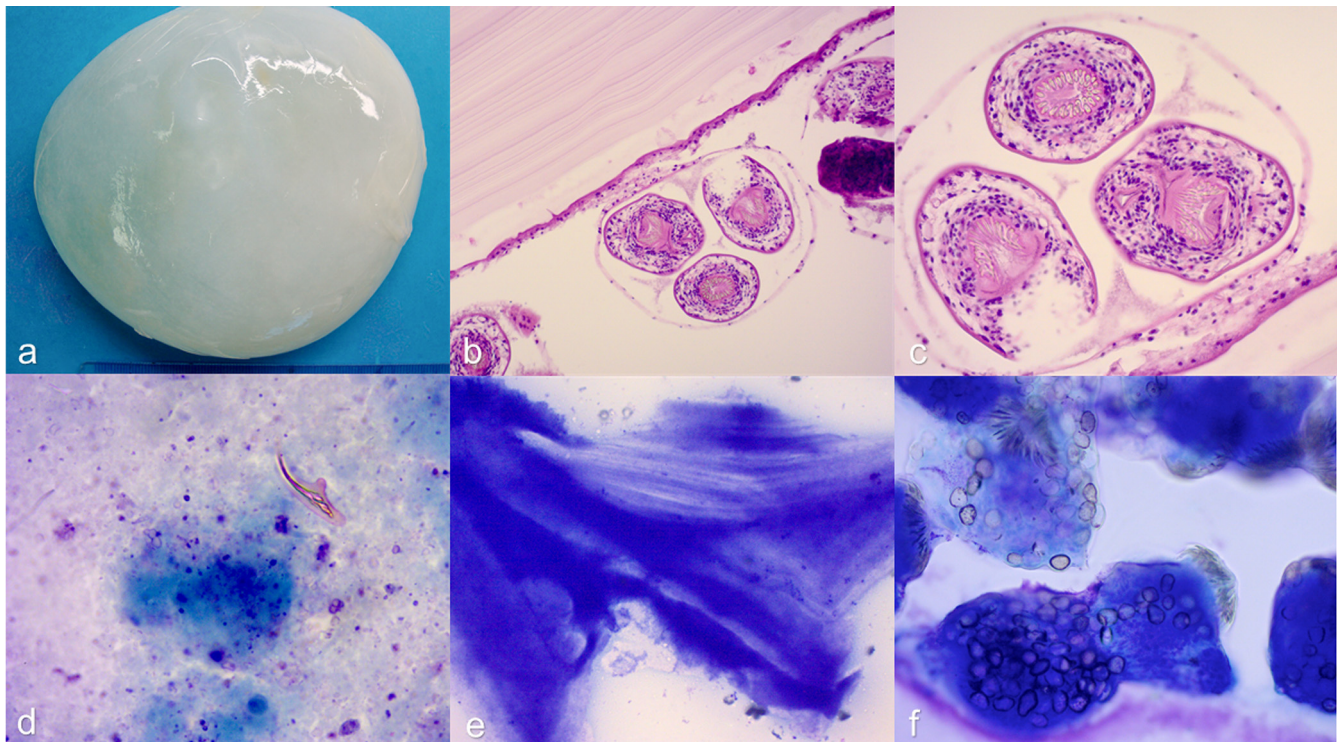


Fig. 11. a: Macroscopic appearance of the *Echinococcus* endocyst that was removed without accompanying pericyst tissue. b: Histological image of the laminated chitinous wall (top left) with an eosinophilic inner germinal layer and brood cysts which contain the protoscoleces (bottom right). (Haematoxylin and eosin stain, 20×). c: High magnification of three brood capsules which contain protoscoleces each consisting of 2 rows of chitinous hooklets. (Haematoxylin and eosin stain, 40×). d: Cytological image showing a single hooklet lying on a granular background representing the hydatid sand. (Papanicolaou stain, 100×). e: Fine needle aspiration of a liver *Echinococcus* cyst demonstrating the laminated layer of the endocyst. (Giemsa stain, 40×). f: Fine needle aspiration demonstrating the brood capsules with the refractile chitinous hooklets forming the protoscoleces. (Giemsa stain 40×).

ulosus). There they develop into a thick-walled hydatid cyst which is white in color and can range in size from few millimeters to multiple centimeters (Fig. 11a) [65]. The cyst consists of 2 layers: the outer host layer (pericyst), and the endocyst which consists of a middle-laminated layer and an inner germinal layer [66,67]. The pericyst is the paraparasitic host response, consisting of fibrous tissue with fibroblasts and inflammatory response with neutrophils, eosinophils, macrophages, multinucleated giant cells and even a granulomatous inflammatory response [67]. The endocyst has a thick, laminated, acellular, chitinous outer layer, which can be accentuated with a PAS stain, and an inner germinal layer, which is a thin cellular layer giving rise to the brood capsules which contain the protoscoleces (Fig. 11b) [66,67]. The protoscoleces contain two circular rows of hooklets and a sucker (Fig. 11c). The hooklets have a curved, shark tooth appearance.

The remainder of the cyst is filled with clear fluid [67]. In fertile cysts, numerous daughter cysts are seen floating freely (brood capsules with protoscolex). In degenerating cysts, the brood capsules break up and the chitinous hooklets are found free floating in a somewhat granular background giving the so-called appearance of 'hydatid sand' (Fig. 11d) [67].

On aspiration cytology of the hydatid cyst one can find fragments of the laminated chitinous layer, brood capsules and loose lying hooklets (Fig. 11e and f) [68].

TREATMENT

Surgery is the main therapeutic approach to pulmonary hydatid disease. Surgical treatment has two goals: to remove the parasite, prevent intraoperative dissemination and treat the bronchipericycst pathology and other associated lesions [69,70].

Surgery may involve excision of the cyst or resection of the cyst and the immediate surrounding parenchyma. The most accepted surgical treatment for pulmonary CE is complete excision using parenchyma-preserving methods, such as cystostomy, intact cyst enucleation or removal after needle aspiration preserving as much lung parenchyma as possible [71,72].

Various factors need to be considered when deciding to utilise antihelminthic therapy for the treatment of CE. The World Health Organisation and World Organisation for Animal Health's Manual on Echinococcosis in Humans and Animals list several indications for medical treatment including inoperable patients with primary liver cysts, patients with cysts in more than one organ, and the prevention of secondary echinococcosis. Contra-indications to chemotherapy alone include cysts at risk of rupture, inactive cysts, and early and late pregnancy [73].

The benzimidazoles albendazole (ABZ) and mebendazole are regarded as the most effective drugs for treating uncomplicated cysts and may be an alternative to surgery. Mebendazole was the drug of choice in the 1970s and 1980s, but ABZ is now widely used. Mebendazole has been reported to be less effective than ABZ due to ABZ's improved oral bioavailability and increased plasma levels [69,74,75]. There is however still no consensus on the optimal drug and duration of therapy, mainly due to a lack of well-designed clinical trials [26,76].

The studies carried out with both drugs have been small, with heterogeneity in methodology [69]. Stojkovic et al. have reported on pooled data that the overall efficacy of these drugs may have been overstated [77]. Hydatid cysts may be at different stages of development, and this seems to influence their response to therapy. Benzimidazoles are not effective against large cysts (>10 cm) as the drugs may get diluted by the volume of fluid present [69].

WHO guidelines for hydatid disease state that chemotherapy using benzimidazoles is the preferred treatment when surgery is not available, or complete removal is not feasible.

Medical treatment can result in reduction of cyst size but long courses (several months) of ABZ are needed. According to Moro et al., medical treatment is most successful in cases where cysts are small (<7 mm), singular and uncomplicated, with treatment failure and subsequent recurrence of disease being more common in cases where there are multiple, complicated cysts surrounded by thickened calcified tissue layers [30]. Doğru et al. reported success following medical treatment of paediatric cases with uncomplicated pulmonary cysts smaller than 5 cm [78], and Gupta et al. also reported favourable outcomes in the paediatric population [29].

The duration of therapy is not clear but several months of therapy is advisable. The current recommendation is 10–15 mg/kg/day in two divided doses for children with a weight under 60 kg [19,26,30,73]. Treatment should start at least four days, but up to three months before surgery, with a total duration of 1–3 months after surgery depending on the severity of disease, and the clinical and radiological response to treatment [19,73,79]. Some studies have shown superior clinical outcome with albendazole-praziquantel combination therapy, but due to the limited data on the efficacy of this combination, ABZ remains the primary agent of choice [73,79–81].

A newer benzimidazole compound, oxfendazole, has been studied in animal models and preliminary data suggest it may be more effective [82]. The combination of ABZ and oxfendazole may provide synergistic effects and better efficacy.

Therapy with benzimidazoles is not without side effects, including mild hepatotoxicity, leukopenia, hair loss and gastric disturbances.

SURGICAL MANAGEMENT OF PULMONARY HYDATID DISEASE

Surgery is the treatment of choice for hydatid cysts of the lung and can be safely performed with low morbidity. The principles of surgery are: [83–85]

- to enucleate the cyst, intact if possible
- close the bronchial air-leaks in the pericystic cavity
- close the pericystic cavity with imbricating sutures beginning at the base of the cavity
- preserve as much lung parenchyma as possible
- prevent seeding of possible daughter cysts

A muscle sparing posterolateral thoracotomy in the fourth or fifth intercostal space is used to expose the pulmonary cysts. Adhesions around the lung vary from trivial to dense, depending on the size of the cyst and whether it ruptured or not. Bilateral pulmonary cysts (Fig. 8b) are done sequentially with 3–4 weeks between surgeries. Some centres do bilateral cysts through a median sternotomy in one setting [86]. However, other authors believe exposure is better through a posterolateral thoracotomy, especially for posterior cysts at the base of the lung. If a complication such as a prolonged air leak is encountered, it is easier and safer to manage when only one lung has been operated. In bilateral disease, the larger cyst or complicated side should be operated first. In patients with pulmonary and hepatic cysts, the hepatic cysts are treated after the pulmonary cysts.

After identifying the cyst, the area around the cyst should be packed with gauze saturated with 20% hypertonic saline or 1% povidone-iodine solution. This helps to prevent soiling of the surgical wound and pleural space with cystic material and daughter cysts. The pericystic tissue is carefully dissected to expose the smooth germinative layer. Small unruptured cysts can then be safely delivered, with the help of ventilation, by carefully developing the plane between the pericystic tissue and the germinative layer. (Video)

Uncomplicated giant cysts (Fig. 1c and d, Fig. 2) should first be aspirated with a 20-gauge needle to decrease the intracystic pressure and can then be carefully removed. Ruptured cysts are managed by opening the pericystic tissue and removing the ruptured germinative layers. Infected cysts and pleural spaces are drained and the rinsed.

The pericystic cavity is rinsed with hypertonic saline and carefully inspected for bronchial leaks. There may be several bronchial openings in the pericystic cavity, and they should all be closed sep-

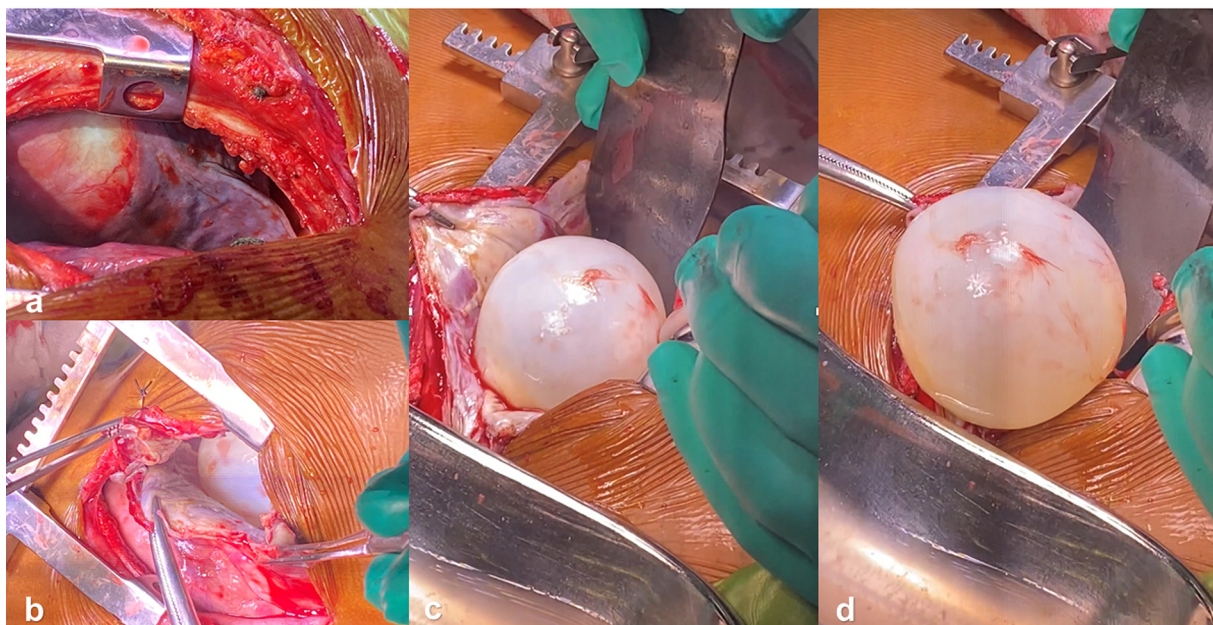


Fig. 12. a: A posterolateral thoracotomy incision exposes the intrapulmonary cyst in the left upper lobe. b: The pericystic tissue is opened, revealing the smooth germinative layer of the cyst. With gentle dissection and ventilation the cyst is delivered intact (c and d).

arately with interrupted sutures. Inflating the lung with normal saline in the cavity helps to identify air leaks. As the larger bronchial openings are sutured, some of the smaller bronchial openings start to leak and are easier to identify. The cystic cavity is then closed with serial imbricating sutures to obliterate the cavity. This is called capitonnage and helps to prevent post-operative air leaks. It can be done with absorbable sutures such as 3-0 polyglactin 910 (Vicryl; Ethicon®), 3-0 polydioxanone (PDS II; Ethicon®) or nonabsorbable sutures such as 3-0 or 4-0 polypropylene (Prolene; Ethicon®) (Fig. 12).

It is seldom necessary to perform lung resections for hydatid cysts and this should be reserved for complicated cysts where most of the surrounding lung tissue is destroyed. One could then consider a wedge resection or lobectomy of the affected lobe [84].

Video assisted thoracoscopic surgery (VATS) for pulmonary hydatid cysts is done in adults but has not gained widespread use in children as single lung ventilation is not always feasible [87]. A concern with VATS is the fact that the cyst must be aspirated before removal, which increases the risk of soiling of the pleural space. Gauze soaked in 1% povidone-iodine solution is packed around the cystic area to avoid intrathoracic contamination.

Morbidity after surgery is low (about 10%) with the main complications being atelectasis, prolonged air leak, residual pleural space, pneumonia and empyema [83,84].

Patients should be treated with albendazole for 1–3 months postoperatively to avoid recurrence of hydatid disease.

CONCLUSION

Pulmonary CE can cause considerable morbidity and even mortality in children. Children rarely present prior to cyst rupture and can remain asymptomatic for years. The diagnosis of pulmonary CE relies on a combination of chest X-ray, CT imaging, and serology. However, serological tests have a limited diagnostic utility. Pulmonary CE is treated with a combination of surgery and chemotherapy.

DIRECTIONS FOR FUTURE RESEARCH

- Development of improved diagnostic methods for hydatid disease including serological markers.
- Research into surgical vs. medical treatment for various types of pulmonary cysts.
- Randomised controlled trials to determine the optimal doses of medication, duration of therapy and side effect profile in children.

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DECLARATIONS OF INTEREST

None.

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