Pulmonary Echinococcosis or Lung Hydatidosis: A Narrative Review

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Abstract

Background

Lung hydatidosis is a zoonosis related to infection by the Echinococcus tapeworm species. Lung involvement in this condition is second only to the liver Echinococcosis. Diagnosis commonly results from an incidental finding in a routine X-ray evaluation because of the delayed growth of the cysts. Moreover, a uniform treatment regimen or approach may not be feasible because of the variability of pulmonary echinococcosis. In this narrative review we aimed to summarize the main features of lung hydatidosis with a perspective on medical and surgical treatment.

Methods

A literature search was performed using the PubMed database and the Cochrane library. Search terms included “pulmonary echinococcosis” and “lung hydatidosis”. The MeSH terms were “lung” [All Fields] AND {“echinococcosis” [MeSH Terms] OR (“hydatidosis” [All Fields] OR “pulmonary” [All Fields] AND “echinococcosis” [All fields] OR “hydatidosis”. A search period of September 1980 to May 2020 was selected to compare studies from different decades, given the changes in pulmonary echinococcosis management.

Results

A uniform treatment regimen or approach may not be feasible because of the variability of pulmonary echinococcosis. No clinical trials have compared all the different treatment modalities. Cyst size, characteristics, position in the lung and clinical presentation and the availability of medical/surgical expertise and equipment are the mainstays of echinococcosis management. When feasible, surgery is still the main therapeutic option to remove the cysts; antiparasitic drugs may minimize complications during high-risk surgery or be used as a definitive therapy in certain cases with major contraindications to surgery.

Conclusions

Lung hydatidosis management must become less heterogeneous. We support treatment targeted to the individual on the basis of the clinical situation, host factors and surgical risk. Strict cooperation in this process between infectious disease specialists and surgeons may optimise best practices to help create shared practical guidelines to simplify clinicians’ decision-making.

Introduction

Human pulmonary echinococcosis is a zoonotic disease related to infection by the Echinococcus tapeworm species [1]. Lung involvement in this condition is epidemiologically secondary only to liver disease and has been found in about 20% of infected patients [2]. Most cases of echinococcosis are related to *Echinococcus granulosus* [3], and human infection is widespread and considered a significant public health issue in countries where dogs, the main definitive hosts, live in close contact with humans and livestock [4]. Diagnosis commonly results from an incidental finding in a routine X-ray evaluation because of the delayed growth of the cysts, becoming symptomatic with the rupture of the cysts and occasionally with the development of immune-mediated reactions against *Echinococcus* spp. [1-2, 4]. A uniform treatment regimen or approach may not be feasible because of the variability of pulmonary echinococcosis [4-5]. Notwithstanding its frequency and widespread endemicity, the knowledge of and literature on lung hydatidosis must be expanded. Furthermore, a standard of care has not been widely endorsed or implemented outside referral centres [1-2, 4-5]. We aimed to summarize the main features of and evidence on lung hydatidosis from the perspective of medical and surgical treatment.

Methods

A literature search was performed using the PubMed database and the Cochrane library. Search terms included “pulmonary echinococcosis” and “lung hydatidosis”. The MeSH terms were “lung” [All Fields] AND {“echinococcosis” [MeSH Terms] OR (“hydatidosis” [All Fields] OR “pulmonary” [All Fields] AND “echinococcosis” [All fields] OR “hydatidosis”. A search period of 1 September 1980 to 1 April 2020 was selected to narratively review studies from different decades, given the changes in pulmonary echinococcosis management.

Epidemiology

Human echinococcosis is widespread throughout the world and has some peculiarity between cystic and alveolar echinococcosis (CE and AE, respectively) [6-7]. *E. vogeli* and *E. oligarthra*, belonging to the so-called neotropical type of echinococcosis, are limited to South America, and new cases are rarely reported [8-10]. Thompson and Lymbery (1988) suggested the presence of intraspecific variants of CE and introduced the concept of *E. granulosus sensu lato* complex [11]. The latter includes genotypes from G1 to G10 (with the uncertain existence of G9), subdivided according to mitochondrial DNA sequences (mtDNA). Its taxonomy merges the genotypes into five species: *E. granulosus* sensu stricto (G1, G2 and G3), *Echinococcus equinus* (G4), *Echinococcus ortleppi* (G5), *Echinococcus canadensis* (G6, G7, G8 and G10) and *Echinococcus felidis* [2]. According to a recent

summary of 1,661 genotyped cases published worldwide, the majority are caused by *E. granulosus* sensu stricto [2]. Molecular identification of human CE cases is strongly recommended for a better understanding of the epidemiology, pathology and natural history of infection, particularly in areas of sympatry, where multiple etiological agents of CE exist [2]

Cystic Echinococcosis (CE)

Attempts to map the incidence and prevalence of CE in humans have found a lack of accurate case records [3]. For example, the European registry of CE (ERCE) was recently launched [12], born of the Human cystic Echinococcosis ReseArch in CentraL and Eastern Societies (HERACLES) project [13]. Most of the available data concerned cases transmitted by domestic intermediate hosts [3]. Nevertheless, with the above limits, CE's epidemiology seems to be stable in the last 20 years, and the latest estimate of the global burden of CE is 188,000 new cases per annum [3]. Eastern China, Central Asia, South America, the Mediterranean and eastern Africa are endemic areas [3, 14-19]. CE has been declared eliminated from New Zealand, and some regions of Australia, such as Tasmania, have been provisionally declared free of the disease in humans [1, 20] although it is still found in Tasmanian wild and rural dogs [20]. In Western Europe [21] and North America [22], CE is not considered a significant cause of morbidity or mortality, and most human cases are imported, although an autochthonous cycle with low prevalence is present. Sporadic cases in the USA were reported by Moro et al. [22] in Alaska, California and Utah. In northern Europe, the United Kingdom is endemic for *E. granulosus* with the highest incidence in the western isles, Shetland and Highlands, while Ireland is believed to be nonendemic for CE [21]. In southern Europe, which includes Portugal, Spain, France, Greece and Italy, CE is the most critical helminth zoonosis, with a life cycle involving dogs and farm livestock as definitive and intermediate hosts, respectively [21].

Alveolar Echinococcosis (AE)

Although AE is generally considered a parasite of the northern hemisphere, the criteria for designation of a region as endemic for *E. multilocularis* have not been consistently defined, largely due to marked global differences in surveillance efforts and sensibility of diagnostic tools, as well as variability in host assemblages and host prevalence [23]. The global annual incidence of AE is estimated to be 18,200 cases, 91% of which occur in China, notably on the Tibetan plateau [24]. AE is also endemic in Central Asia, and both *E. multilocularis* and *E. granulosus* are highly represented in Kazakhstan and Kyrgyzstan [24-25]. Human cases of *E. multilocularis* have recently been found in European countries previously considered to be free of AE,for example, in the previously unrecognized areas of endemicity of France, Switzerland, Germany, and Austria [26-29]. Currently, approximately 1600 new cases of AE have been reported in Europe up to 2019 [24]. AE had not been considered a major

human health issue in North America, except in Alaska, until recently, and *E. multilocularis* has not been reported in Mexico or the southern United States [24, 30].

Life Cycle

Hosts for the cestodes tapeworm may be subdivided into three categories: definitive, intermediate and accidental [31]. The definitive hosts are carnivores, notably dogs, cats and wild canids, in which adult tapeworms (2.0–7.0 mm length for *E. granulosus* and 1.2–4.5 mm for *E. multilocularis*) inhabit the small intestine [31-33]. Domestic animals and other warm-blooded vertebrates, such as sheep, goats, cattle, horses, camels and pigs, act as intermediate hosts, ingesting eggs released by carnivores; they carry predominantly *Echinococcus granulosus*. Rodents, deer, moose, reindeer and bison are intermediate hosts of *E. multilocularis* [34-37]. Humans may accidentally act an intermediate host although they do not have a clear role in the biological cycle [34-37] **(Figure 1)**.

A complete life cycle takes four to seven weeks. In the small intestine of definitive hosts, cestodes scolex present a double row of hooklets, which play a pivotal role in the attachment to the intestinal mucosa. Cestodes scolex have at least two proglottids (the number of proglottids changes between causative agents, from three to six in *E. granulosus* and from two to six in *E. multilocularis*), which contain numerous eggs. The eggs are passed out through the host's faeces and released into the environment [31].

The intermediate hosts ingest the eggs while feeding, which settle in their gut and release oncospheres that are subsequently transported through the blood or lymph to primary target organs. Lymph enters the portal circulation via the intestinal wall and travels to the visceral organs' capillary bed (primarily the liver, secondarily the lungs) [36-37]. In the organs, oncospheres become vesicles (metacestodes) and grow concentrically into a fluid-filled cyst. Hydatic cysts for *E. granulosus* are initially fluid filled, unilocular and rich with hundreds to thousands of protoscolices; the morphology of *E. multilocularis* cysts differs, with masses of numerous small cysts interconnected by dense connective tissue [32-33]. The cysts consist of an inner germinal and nucleated syncytial layer supported externally by a carbohydrate-rich acellular laminated layer of variable thickness, which is surrounded by a host-produced fibrous adventitial layer [31, 38-39]. Daughter cysts may develop within larger primary cysts. Protoscolices (or protoscolex in *E. multilocularis*) are the preceding step before the adult worm when reuniting with the definitive host's intestine [38-39].

Clinical Features and Diagnosis

Pulmonary echinococcosis has been described in about 20% of infected patients, and the lungs are the second target organ after the liver, which is affected in about 70% of cases reported [4]. Most of

the infections in both lungs and liver are due to *Echinococcus granulosus sensu lato* complex, unlike *E. multilocularis,* in which almost all primary lesions are found in the liver [37]. Most patients have single-organ involvement with solitary cysts (cysts range from 1 to more than 20 cm in diameter), but 10% to 15% of patients have two or more involved organs [5]. Lungs are affected by multiple cysts in 20% to 30% of patients and are frequently located in the lower lobes, more often posteriorly than anteriorly and more often in the right lobes (approximately 50% have occurred in the right lung) [4-5, 40]. Subjects with pulmonary echinococcosis are usually children or young adults (20 to 40 years old): in these high-risk groups, lungs may be involved in 50% of *Echinococcus* spp. infections [41-42].

Pulmonary disease may be classified into three main clinical scenarios: asymptomatic early phase, symptomatic stage and complicated late phase.

Asymptomatic early phase

The early stages of CE and AE usually do not cause symptoms, and CE cysts and AE lesions can remain undetected for 10 to 15 years [4-5]. Children and young adults are often asymptomatic despite the presence of large lesions, probably because of anatomical features such as higher elasticity of the lung parenchyma and the rib cage and weaker immune response against parasites [41-43]. Subclinical or late-presenting symptoms are typical for most AE and CE patients because of the slow annually growth of cysts (ranging from 1 to 5 cm per year), especially in immunocompetent patients [4-5, 40]. The faster growth of cysts in CE patients with AIDS suggests that immune suppression may play a role in CE progression [30]. Genetic variation of the human leukocyte antigen (HLA) system is associated with the occurrence or progression of AE lesions in humans; patients with the HLA-DR3 DQ2 haplotype were shown to have more severe disease and a more pronounced Th2-type immune response, associated with a more profound tolerance status [30].

Symptomatic Stage

Various symptoms are loco-regional and may be due to compression or damage to bronchia, vessels, rib cage or mediastinal organs: most symptoms of pulmonary CE are caused by mass effect exerted by the cysts on nearby tissues [44-45]. Cough, chest pain, dyspnea and hemoptysis are the most common symptoms reported [4-5, 46-47]. Less frequent are malaise, nausea, vomiting and thoracic deformations [4-5, 46-47]. Most pulmonary cysts are located in the lower lobes, more often posteriorly than anteriorly [48]. Approximately 50% of cysts are localized in the right lung, 40% in the left lung, and 10% bilaterally [48-49].

Late Complicated Stage

The presence of any complications changes the clinical presentation, either causing new symptoms or increasing the severity of existing symptoms.

The main complication is cyst rupture; in any organ, cyst rupture can induce fever, urticaria, eosinophilia and anaphylactic shock [50]. Lung cysts may break, causing cyst material containing fragments of larval tissue and protoscolices to be spilt and eventually flow either into the bronchial tree, producing cough, chest pain, hemoptysis or vomica [51], or into the pleural cavity, causing simple or tension pneumothorax, pleural effusion or empyema [52]. Mediastinal cysts may erode into adjacent structures, causing bone pain, haemorrhage or airflow limitation [53-54]. Eosinophilia and allergic reactions are very uncommon in AE because of the different structure of the parasitic lesions from CE, with dense fibrosis preventing vesicle fluid leakage; these reactions may be observed in rare cases of dissemination of lesion fragments into the blood [55-57]. Other potential clinical effects of hydatid infection include immune complex–mediated disease, glomerulonephritis leading to nephrotic syndrome [58], and secondary amyloidosis [59]. Another significant complication is the superinfection of the cyst, manifesting as a pulmonary abscess with poorly defined margins. Ruptured cysts may become infected with bacteria or with saprophytic or invasive fungi, which are serious complications [60-63]. Hydatid disease causes recurrent acute pulmonary embolism in rare cases [64]. Transdiaphragmatic migration of hydatid disease from the posterior segments of the right hepatic lobe has been reported to be a common complication and is probably related to their proximity to the diaphragm [65].

Diagnosis

Radiological diagnosis

The first step in assessing lung hydatidosis is taking a chest X-ray [66]. Uncomplicated cysts appear on chest radiographs as a rounded or ovalized masses with smooth borders and uniform density and are surrounded by healthy lung tissue [67]. Indirect signs of lung hydatidosis on close structures (e.g., trachea, bronchi) are visible if the dimensions of cysts are relevant, such as a shift of the mediastinum, pleural reactions or compression of the lung parenchyma causing atelectasis [67-68]. X-rays can easily detect calcification of pulmonary cysts, but it is rare to find calcification in pulmonary echinococcosis [68-69]. Complicated cysts, such as broken cysts, present with typical diagnostic but also different signs [67-69]. Typical signs with variable frequencies between case series are visible in X-rays. The crescent or meniscus sign occurs as a result of air introduced between the pericyst and the exocyst, causing the erosion of bronchioles for cyst growth: some authors consider it as an

alarming sign of impending rupture [30, 67-69]. The ingress of air within the cyst may also appear as parallel arches of air with an appearance like an onion peel, which is called Cumbo's sign. [30, 67-68]. The presence of an air/fluid level may be interpreted as a theoretical communication between the cyst and the tracheobronchial tree [30, 67-68]. The water lily or Camelotte sign follows the collapse of the entire endocyst, in which the crumpled internal layer floats freely in the cyst fluid [30]. The fluid component might be expelled in the tracheobronchial tree, and the remaining solid component of the cyst gives rise to a mass within a cavity, or Monod's sign [67-69].

A CT scan is useful to better identify specific details of the lesions and their surrounding structures, helping to exclude alternative differential diagnoses: in intact cysts, a CT scan may reveal a thin rim defining the perimeter [48]. Small cysts, undetectable by a chest X-ray, may be detected with CT scanning's better imaging definition, which is also valuable in the case of complicated cysts; for example, it can identify a cyst wall defect in a ruptured cyst [70]. Infected cysts show in CT scans as poorly defined masses with increased internal density and contrast enhancement around the cyst wall (the ring enhancement sign) after the injection of a contrast substance. CT scanning can elucidate the cystic nature of the lung mass and provide accurate localization to plan the surgical treatment of complicated cysts [70-71].

Ultrasonography is helpful in most cases, providing excellent images only when the cysts are close to the pleural surface [72]. Most importantly, however, ultrasound examination of the liver may reveal concomitant liver involvement in up to 15% of individuals with lung CE [73]. Contrast-enhanced ultrasonography, based on pulsating blood flow imaging, may be used to detect small AE lesions and differentiate them from abscesses and tumours [72-73].

With magnetic resonance imaging (MRI), cysts show low signal intensity in T1-weighted images and high signal intensity in T2-weighted images: signal characteristics of a hydatid cyst may differ depending on the developmental phase [67-68]. FDG-positron emission tomography (FDG-PET) has become the favoured reference tool to evaluate their metabolic activity [74]. In CE, MRI appears to be of better diagnostic value than CT scanning, and both procedures are complementary to AE and should be performed to provide sufficient information for therapeutic decision-making [67-68].

Serological diagnosis

Major antigens for immunodiagnosis are contained in the hydatid fluid [75]. In the past, the Casoni intradermal test has exhibited low specificity and sensitivity; furthermore, poor standardization and ethical issues regarding the injection of reagents of animal origin into humans have considerably limited the use of skin tests for echinococcosis diagnosis [76]. Reported sensitivities of serological

methods for testing CE patients, confirmed by surgical resection, vary from 60% to 90% [75, 77-78]. The encystment of the metacestode prevents the stimulation of antibody-producing cells, which could induce false-negative results of serology tests [75, 77-78].

For both CE and AE, serology is now used only to confirm imaging results; it may also provide some insight into the infection pressure on a given population (e.g., children) in a particular geographic area [77-78]. The Expert Consensus of the WHO-IWGE also uses serology results to determine "possible" and "probable" cases [79].

Treatment

A uniform treatment regimen or approach may not be feasible because of the variability of pulmonary echinococcosis. No clinical trials have compared all the different treatment modalities. Cyst size, characteristics, position in the lung and clinical presentation and the availability of medical/surgical expertise and equipment are the mainstays of echinococcosis management . Many patients with lung lesions were admitted to hospital because of complications, mainly infection.

Surgical approach

The aim of surgical treatment of hydatid cysts is the complete evacuation of the cyst, the removal of the endocyst to avoid intraoperative contamination, the closure of the pericystic cavity to prevent prolonged air leak and empyema and the preservation of healthy lung parenchyma [80-82]. All the abovementioned precautions should be taken perioperatively to avoid accidental rupture of the cyst. If anaphylactic shock occurs as a result of cyst rupture, steroids and octreotide infusion must be administered [80-81].

For the removal of the cyst, different surgical techniques may be considered. The Ugon enucleation technique was proposed in 1952 and is suitable for a relatively small cyst. The surrounding area is fixed with packs soaked in a scolicidal agent (povidone iodine or hypertonic saline). An incision is made over the adventitia layer of the cyst to observe the underlying white-coloured laminated membrane [81-83]. The anaesthetist is then asked to apply positive pressure ventilation to the ipsilateral lung. This manoeuvre should cause the cyst to be expelled intact from the cavity. The remaining cyst cavity is irrigated with an isotonic saline solution, and air leaks are obliterated using non-absorbable stitches [81].

Cystotomy with capitonnage (Barrett's method) was proposed in 1952. The enucleation step involves careful incision of the lung parenchyma, avoiding rupture of the cyst. The cyst is carefully dissected with blunt dissection and positive pressure ventilation, which assists the enucleation process. The cavity walls are approximated with either interrupted non-absorbable purse-string

sutures or the walls of the cyst. Finally, the healthy parenchymal ends are approximated with non-absorbable sutures [80-82].

Posadas' method is a modification of Barrett's procedure and consists of the closure of the airway openings before capitonnage. The Perez-Fontana method of pericystectomy was proposed in 1953, and it involves excising the hydatid cyst along with the pericyst, which is adhered to the normal lung parenchyma [82]. There is now a consensus that the host tissue generates the pericyst in response to the cyst, and there is no need to remove it, mainly because its excision leads to a more prolonged air leak.

The needle aspiration method (the Figuera technique) entails no risk of cyst rupture or contamination of the pleura [80-81]. To prevent contamination, a few towels soaked in povidone-iodine solution are placed around the cyst. The syringe and catheters are outside the chest cavity. Then the pericyst is incised with scissors, and the fluid within the cyst is aspirated. When the cyst is decompressed, the surrounding parenchyma is incised, and the endocyst is removed [81-83]. The air leaks are obliterated with absorbable sutures. Although parenchyma-sparing procedures are preferred, sometimes segmentectomy, lobectomy and even pneumonectomy are required. Lung resections for the treatment of hydatid cyst disease of the lung may be required in rare cases. In the literature, the rate of lobectomy ranges from 0.5% to 45% [80]. Indications for lobectomy are a large cyst involving more than 50% of the lung, a cyst complicated by suppurative pulmonary infection not responding to medical treatment, multiple unilobar cysts and parenchymal destruction and fibrosis of lung tissue in chronic cases [80-83].

The best surgical approach depends on the size of the cyst and whether the cyst is single or multiple, unilateral or bilateral, intact or ruptured and associated with a liver dome cyst or with destroyed lung parenchyma [81-83]. Commonly, thoracotomy is the selected approach for the resection of hydatid cysts of the lung. Besides, Median sternotomy is useful for the treatment of bilateral anterior hydatid cysts [80-82]. Moreover, the preferred surgical approach to liver cysts penetrating the diaphragm into the right lower or middle lobe is a standard thoraco-laparotomy. Nevertheless, in last years minimally invasive thoracoscopic approaches, named video-assisted thoracic surgery (VATS) (either, uniportal or multiportal), demonstrated to be a feasible and safe treatment strategy, especially for the treatment of small and peripheral cysts. [80-84]. Reported advantages of VATS

were shorter surgical time, decreased length of hospital stay, lower experienced pain, and reduced surgical morbidity. [85-87] Almost Certainly, in the next future, those minimal invasive approaches, and probably also robotic-assisted surgery, will be more diffusively adopted for surgical treatment of lung hydatidosis, similarly as it occurs in lung cancer disease [88]. .

Medical treatment

Antiparasitic drug treatment may be a first definitive option or an adjunctive therapy following surgery [79]. Albendazole has proven to be the first choice for *Echinococcus spp.* infections, but an alternative option is mebendazole. Praziquantel is less effective but has been studied in combination with benzimidazoles.

Historically, variable periods (from two to four weeks) of anti-helminth chemotherapeutic agents are prescribed preoperatively to prevent disease recurrence due to spillage at the time after surgical treatment of liver hydatidosis, and albendazole plus praziquantel has been found to be superior in its scolicidal activity when compared with albendazole alone [89-90]. However, at this time, the efficacy of preoperative or post-operative therapy has not been clearly studied in pulmonary hydatidosis. As a convention, by translating evidence from liver hydatidosis studies, preoperative albendazole for two to four weeks is prescribed for preventing the post-operative regrowth ensuing on intra-operative spillage [89-91]. Despite that, the optimal duration of preoperative anti-helminths treatment in pulmonary echinococcosis remains unclear.

Benzimidazoles

Benzimidazoles may be the first option in small, uncomplicated lung cysts. The cut-off size for the diameter of lung lesions is not standardized, unlike for liver cysts, for which Albendazole (or Mebendazole) is suggested for diameters < 5 cm (CE1, WHO classification). Brunetti et al. [79], in an expert consensus, suggested that benzimidazoles should be avoided pre-operatively in larger lung cysts. A study [84] on the clinical experience of surgical therapy for thoracic hydatidosis reported an antiparasitic role of albendazole for multiple intrathoracic cysts (with or without liver lesions). Medical treatment is the preferred choice when surgery is not available or when complete removal is not feasible.

Albendazole

Albendazole **(Table 1)** is an anthelmintic benzimidazole carbamate given orally but poorly absorbed via this route of administration (< 5%) and, because of its insolubility, has not been administered parenterally [92]. In contrast with intestinal helminth species, for which drug absorption is not necessary, systemic parasites require an extended treatment to produce a sufficiently therapeutic drug [92-93]. Albendazole sulfoxide, the main metabolite of albendazole, is the main agent in systemic infections, with an elimination half-life of 8–12 hours, and it is moderately bound to plasma proteins (70%) [92-93]. Albendazole acts first through the inhibition of parasite beta-tubulin polymerization and, second, through downstream effects, such as fumarate reductase inhibition and the interruption of energy pathways that result in parasite death [92].

Culture and in-vitro tests of the susceptibility of helminths to albendazole are often impossible, and anti-parasitic activities have been extrapolated by empirical testing in vivo in humans or by extrapolation from the doses used for domestic animal species [93].

In humans, definitive evidence of clinical resistance is lacking, but for *Echinococcus spp*., prolonged infections and intermittent treatment with anti-helminthic drugs might provide ideal circumstances for the development of resistance. On the other hand, transmission to other individuals would not occur as human infection represents a dead end for the parasite life cycle [93].

Albendazole presents a hepatic metabolism, but there is a lack of information about dose adjustment in liver impairment. [93-94]. Cotting et al. [95] presented five patients with echinococcosis and significant extrahepatic biliary obstruction, for whom the absorption and clearance of albendazole were significantly delayed and C_{max} was doubled. Albendazole diffuses well in various tissues and has been detected in urine, bile, liver, cyst walls, cyst fluid and cerebrospinal fluid and is highly correlated with drug's concentrations in plasm [93-94].

Mebendazole

Mebendazole **(Table 1)** belong to the same anthelmintic class as albendazole, which has now largely replaced albendazole for Echinococcus infections. Its oral bioavailability is near 5–10%, but with tracer doses of [3H]-mebendazole administered orally and intravenously, the absolute bioavailability was estimated to be 22% [96].

There are no clinical data on dose adjustment in renal impairment. Even with renal impairment, mebendazole is largely metabolized in the liver, so dose adjustment is not likely to be required in most cases [97]. Nevertheless, some authorities have advised caution during long-term therapy in patients with hepatic echinococcosis because metabolism may be impaired in such patients, leading to elevated levels of the parent drug and possible toxicity [96]. Moreover, plasma concentrations were

reported to be higher in a patient with cholelithiasis than in normal subjects [97-98]. The metabolites are excreted principally in the urine, and in patients receiving long-term, high-dose of mebendazole, metabolites might accumulate [98-99].

Mebendazole can be measured in a number of tissues, most notably the liver, and in echinococcal cysts, where the concentrations correlated well with the free mebendazole plasma concentrations four hours after dosing [100]. There is significant interindividual variability in the bioavailability and metabolism of mebendazole, and there is little data to directly correlate the clinical activity of mebendazole with its pharmacokinetic and pharmacodynamic parameters [101].

Praziquantel

Praziquantel **(Table 1)** is a pyrazinoisoquinoline derivative found to be active against a wide range of trematode and cestode helminths [102]. Praziquantel is currently the mainstay treatment for schistosomiasis and opisthorchiasis. Its absorption after oral administration is up to 80%, and it has almost total renal excretion. Its short plasma half-life requires administration three times per day [102-103].

Monotherapy with praziquantel has no activity against cystic echinococcosis. A small trial combining praziquantel and albendazole for six months resulted in a superior rate of cyst disappearance (47.4% vs. 36.4%) for up to three years, compared to 22 historical controls, which received albendazole alone [104]. This observation remains to be confirmed. In vitro and in vivo praziquantel theoretically has a role as a protoscolicide in preventing the dissemination of cyst content [105].

It is of note that praziquantel has a well-recognized effect on the pharmacokinetics of albendazole, increasing serum and intracyst concentrations of albendazole sulfoxide by inhibiting hepatic catabolism [106]. The relevance of this observation to clinical efficacy has yet to be established.

Conclusions

There is a growing tendency to manage uncomplicated cysts according to one of the main treatment options (e.g. watch and wait, surgical treatment, medical treatment, or both medical and surgical treatment) notably on the basis of host factors, comorbidities and cyst stage, size and location. Medical treatment (alone or combined) is the preferred choice when surgery is not available or when complete removal is not feasible [107]: in our opinion, antiparasitic drugs may be valuable in three specific instances: 1) in single, small, uncomplicated cysts, 2) in disseminated diseases or 3) patients with poor surgical risk. The cyst may be disrupted by medical therapy, but membranes associated with cysts carry a significant risk of infection. [108-109].

For pulmonary hydatidosis, surgery remains indicated in most cases: operative mortality remains acceptable (1–2%), and morbidity is low [109-110]. The recurrence rate varies from 1.9% to 2.9%, depending on the series [109-111].

A standard of care has not been widely endorsed or implemented outside referral centres because of a lack of well-designed clinical trials to respond to this need and to consolidate the best practices for treating hydatidosis **(Figure 2)**. Complicated cysts require a case-by-case decision for appropriate management [108-110]. In support of surgical management, alongside the removal of the parasite, surgery may also act on associated parenchymal, bronchial, or pleural damage. Nevertheless, surgery must be as conservative as possible; resection is proposed only for severe and irremediable lung damage, and lobectomy is necessary in less than 10% of the patients [111-112]. Proper management of hydatidosis may also be considered from an infection control perspective. Monitoring the transmission of Echinococcus spp. has a pivotal role in public health, and efforts should be focused on strengthening and improving control programs in endemic areas to reduce the incidence and burden of echinococcosis [113-114].

In conclusion, hydatidosis management must become less heterogeneous. We support treatment targeted to the individual on the basis of the clinical situation, host factors and surgical risk. Strict cooperation in this process between infectious disease specialists and surgeons may optimise best practices to help create shared practical guidelines to simplify clinicians' decision-making.

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Figure 1: Lifecycle of *Echinococcus granulosus* between definitive, intermediate and accidental hosts

Figure 2: Tailored approach to lung hydatidosis according to size and number of cysts, features of cysts, host's features and surgical risk

Table 1: Main pharmacokinetics and pharmacodynamics features of Albendazole, Mebendazole and Praziquantel