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Review

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Clinical aspects and treatment of alveolar echinococcosis: the current state of knowledge and difficulties in the diagnosis and management of cases in Poland

Rozpoznanie i leczenie bąblowicy wielojamowej – aktualny stan wiedzy oraz problemy w codziennej praktyce w Polsce

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Summary

The aim of the study is to summarize the current state of knowlege in the diagnosis and monitoring of patients with alveolar echinococcosis (AE), using serological tests and imaging techniques, and to present the most recent therapeutic guidelines based on a literature review. The paper discusses the challenges in diagnosing and treating AE encountered in clinical practice in Poland, based on the analysis of medical records of 86 patients with AE, who were hospitalized in the University Centre for Maritime and Tropical Medicine (UCMTM) between 2000 and 2018. In Poland, AE is usually diagnosed at the advanced stage, when optimal, radical surgery is not an option. Diagnosis of AE is often preceded by invasive diagnostic methods, such as biopsy or exploratory laparotomy, which may result in the infection spreading. Pharmacological treatment is associated with potential adverse effects and is a significant financial burden for the patient due to the lack of reimbursement. There is a need to raise the awareness of AE among physicians performing imaging studies and to facilitate access to modern techniques enabling the assessment of the parasitic process.

Keywords: **alveolar echinococcosis • imaging • serology • treatment**

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INTRODUCTION

Alveolar echinococcosis (AE) is a helminthic zoonotic disease caused by infection with the larval stage of small tapeworm *Echinococcus multilocularis* [38]. AE occurs in the northern hemisphere, in the endemic areas of Western and Central Europe, as well as in Central and Eastern Asia, especially in China [50]. In recent years a significant increase in the incidence of AE in Central and Eastern Europe, including Poland [41], has been noted. In Poland, the Warmia-Masuria and Podlasie Provinces are considered as endemic areas [22, 41]. *E. multilocularis* is commonly maintained in a wildlife life cycle involving two mammalian hosts. The definitive hosts of the sylvatic cycle are feral carnivores, mainly foxes [17, 22].

Humans become infected by ingesting tapeworm eggs [14, 17]. The most frequent site of primary parasitic lesions is the liver [45]. Clinically, the parasitic invasion is characterized by a long-lasting asymptomatic phase (of average duration of 5–15 years) [17]. Often, at the onset of symptoms, an imaging examination reveals the presence of a large tumour-like mass in the liver, suggestive of a proliferative process [15, 39]. In some cases, intercurrent extrahepatic lesions are present; this is due to spread by continuity to adjacent structures or metastasizing via the haematogenic route to remote locations, e.g. the lungs (7–20% of cases) or the brain (1–3% of cases) [10, 30].

Early diagnosis and initiation of appropriate treatment are very important. In untreated patients, mortality reaches 90% within 10 years from diagnosis [3, 17]. However, in recent years in developed countries, thanks to access to modern diagnostic techniques and treatment, the prognosis of AE patients has improved [49]. Radical resection of the lesion at the initial stage of its development, combined with temporary pharmacological treatment with benzimidazoles (BMZ) is the most effective management. Patients with advanced disease, who are not eligible for surgery, require treatment with benzimidazoles for many years, sometimes for the rest of their lives. In some cases, liver transplantation (LTx) remains the only therapeutic option and a chance for survival [8, 9, 42]. Serological blood tests are, next to imaging studies, important tools in diagnosing and monitoring the effectiveness of the treatment [11], as well as in follow-ups after the termination of pharmacotherapy, which is connected to the risk of recurrence, especially in the group of patients receiving immunosuppression. Histopathological and molecular tests (i.e. polymerase chain reaction, PCR) of the collected material confirm the diagnosis [11, 40].

In most cases of AE, the lesions are located in the liver, but the clinical picture varies depending on the location of the lesions and the accompanying complications resulting from the progression of the disease, such as cholestasis, cholangitis, formation of an abscess, or secondary biliary cirrhosis and portal hypertension. During the last 18 years, 86 patients with AE were treated in University Centre of Maritime and Tropical Medicine (UCMTM). Analysis of the clinical material of UCMTM shows that the diagnosis of AE is often made at the advanced stage of the disease and the treatment is problematic and requires the involvement of a multidisciplinary team.

METHODS

We have reviewed available serological tests and imaging techniques in diagnosis, monitoring and current therapeutic guidelines in patients with AE. Medical records of 86 patients with AE, hospitalized in UCMTM between 2000 and 2018, were analysed. Study participants were patients with probable and confirmed diagnosis of AE.

According to WHO Informal Working Group on Echinococcosis (WHO-IWGE), the probable diagnosis was based on the positive results of serological tests and a typical pattern of lesions in imaging examinations. The diagnosis was considered as certain in patients in whom the disease was additionally confirmed by histopathological or molecular (PCR) examination. The usefulness of imaging and serological examinations in the diagnosis of AE, assessment of its clinical stage, and planning and monitoring of the treatment was evaluated. The administered treatment and treatment-related problems were analysed.

ETHICAL ISSUES

The study has been approved by the Independent Bioethics Committee for Scientific Research at Medical University of Gdansk on June 25, 2003 as part of the research project of the State Committee for Scientific *Research/ the* Ministry of Science and Higher Education (KBN/ MNiSW). Approval number: NKEBN/457/2003; project numbers: 4PO5D04212 and 3PO5B10625.

Imaging examinations in the diagnosis and monitoring of treatment in patients with AE. Among imaging examinations, ultrasound remains the first-choice modality in both the diagnosis and monitoring of treatment of patients with AE [12]. It is also used as a screening tool in endemic areas, in addition to serological tests [41]. To date, there has been no generally accepted ultrasound classification of hepatic lesions observed in AE [33]. So

far ultrasound classification based on the number and size of lesions and presence of central necrotic fluid has been used in field studies in China, evaluating the usefulness of serological tests depending on the type of liver lesion of AE [21, 35, 48]. Alternative ultrasound classification, considering the type of lesion, has been developed by researchers from the University Hospital in Ulm (Germany) [33]. This classification is based on 5 types of lesions:

- Type 1 – a hailstorm pattern appearing as heterogeneously echogenic areas with irregular contours and visible scattered hyperechoic areas, in some cases calcifications can be seen;
- Type 2 – a pseudocystic pattern with an irregular hyperechoic rim that is not vascularized on power Doppler;
- Type 3 – a metastasis-like pattern;
- Type 4 – haemangioma-like pattern;
- Type 5 – ossification pattern with features of calcifications;

According to expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans [11], typical findings observed in 70% of cases correspond to hailstorm and pseudocystic patterns. Pseudocystic pattern of the lesion can be first observed at the time of diagnosis or during the treatment, when it reflects the lesion's evolution and central necrosis formation. Suspicion of AE based on an ultrasound examination allows us to properly plan further diagnostics, including serological testing and extended imaging techniques also aimed at excluding pulmonary and cerebral AE [11]. Computed tomography (CT) allows for a precise assessment of the location and extent of parasitic infiltration in the liver, along with the evaluation of the vascular system and bile ducts at the time of diagnosis [12, 45]. CT is a sensitive tool in the assessment of calcifications [12, 37]. The presence of calcification plays an important role in the assessment of echinococcal lesions. Their number and localization within the parasitic infiltration changes during the natural course of the disease and is also modified by pharmacological treatment. But the presence of calcifications does not exclude the metabolic activity of AE lesions on 18F-FDG-PET-CT [5, 18]. Calcifications only suggest indirectly the duration of the inflammatory process. To facilitate the diagnosis and improve the comparability of CT findings in the context of scientific studies the Echinococcosis Multilocularis Ulm Classification-CT (EMUC-CT) has been suggested [25]. The classification of liver lesions distinguishes five main types of lesions depending on their size and the dominant cystoid, solid or mainly calcified component in correlation to the calcification pattern. Compared with CT and ultrasound examination, magnetic resonance imaging (MRI) allows for a more accurate assessment of alveolar structures which are characteristic of AE [5, 6, 7] as well as showing the invasion of the vascular and biliary structures [12]. Magnetic resonance cholangiopancreatography plays a significant role in the evaluation of biliary tract invasion and connection between the biliary tracts and necrotic pseudocystic cavities [37].

Kodama et al. [32] proposed an MRI morphological classification for liver AE lesions with five types:

- Type 1 – multiple small round cysts without a solid component,
- Type 2 – multiple small round cyst with a solid component,
- Type 3 – a solid component surrounding a large and/or irregular pseudocyst with multiple small round cyst,
- Type 4 – a solid component without cysts,
- Type 5 – a large cyst without a solid component.

However, contrast enhancement and the presence of calcifications are not included in Kodama's classification system. The authors stated that type 1 lesion represents the earliest stage of the disease. An Positron emission tomography with Fluorine-18fluorodeoxyglucose (18F-FDG-PET-CT) is an advanced sensitive imaging technique that is useful in suspected AE, in disease staging, planning therapy treatment and monitoring the treatment of AE patients. There is a correlation between the presence of microcysts and metabolic activity around parasitic lesions on 18F-FDG-PET-CT. The absence of microcysts on MRI (Type 4 and 5 in Kodama's classification) is strongly correlated to a metabolically inactive disease [5].

Nevertheless, 18F-FDG-PET-CT negativity does notnecessarily indicate a lack of vitality of the parasite [47]. Contrast-enhanced ultrasound (CEUS), which is less expensive and more available than 18F-FDG-PET-CT, could be an alternative diagnostic technique for the assessment of the extent and activity of echinococcal lesions in the liver [18]. However, CEUS has not to date been accepted as a diagnostic standard in hepatic AE [34].

SEROLOGICAL TESTS IN THE DIAGNOSIS AND MONITORING OF TREATMENT IN PATIENTS WITH AE

Serological diagnosis is usually based on commercially available immunoenzymatic (ELISA) and immunoblot assays containing recombinant and purified *Echinococcus* antigens. As screening tests usually serve ELISA tests comprising antigens from native purified *Echinococcus multilocularis* vesicle fluid or *Echinococcus granulosus* hydatid fluid. The assay used to confirm the results obtained is the immunoblot, which is also used in the differentiation between cystic echinococcosis (CE) and AE. The recombinant antigen Em18 used both in ELISA and immunoblot assays is currently considered the most useful in the differentiation between AE and CE [27, 28, 29, 31] as well as in the assessment of the activity of parasitic lesions [20, 26].

Purified and recombinant antigen Em2 is also useful in differenting between *Echinococcus* species [27]. Commercially available serological ELISA tests that are currently

in use contain a combination of recombinant antigens Em2-Em18, which results in high sensitivity and specificity. When interpreting the results of serological tests, the possibility of cross-reactions should be additionally considered. False-positive results may occur in other parasitic infections with *Ascaris lumbricoides* or *Anisakis simplex*. Cross-reactivity may also occur when performing tests in the group of patients diagnosed with neurocysticercosis and schistosomiasis [23, 36]. Many studies emphasize the necessity of conducting serological diagnostics of AE using simultaneously several assays with different level of sensitivity and specificity in relation to *Echinococcus* antigens [31].

TREATMENT

Treatment plan depends on the pre-operative AE staging according to WHO- IWGE PNM classification [11]. This classification describing the anatomical extent of AE at the time of diagnosis is based on the assessment of three components: hepatic localization of the parasitic lesion (P), extrahepatic involvement of neighbouring organs (N) and absence or presence of distant metastasis (M). Radical hepatic resection with a safety margin in combination with pharmacological therapy is the best treatment option [11] with low recurrence rate. Currently available drugs against AE in clinical settings are mainly limited to benzimidazoles (BMZ), principally to albendazole (ABZ). In cases when ABZ is not well tolerated, mebendazole (MBZ) remains an alternative therapeutic option. BMZ exert a parasitostatic rather than a parasitocidal effect against *E. multilocularis* [39]. BMZ are generally well tolerated, although their safety profile is limited because of hepatotoxicity, alopecia, gastrointestinal disturbances or severe leukopenia. ABZ and MBZ may also induce embryotoxic or teratogenic effects [46] and have not been fully evaluated in children younger than six years of age. No alternative treatment is now available for patients who have experienced severe side effects and have contraindications for BMZ treatment. ABZ is poorly absorbed in the gastrointestinal tract after oral administration [46]. No proper pharmacokinetics studies have been conducted to conclusively validate the optimal time course and ABZ dosage for the treatment of human AE [46]. The currently recommended dosage is 10–15 mg/kg/day in two divided doses taken during a fatty meal. Continuous therapy is recommended. Recommended dosage of MBZ for the chemotherapeutical treatment of AE is 40–50mg/kg/day orally with three divided doses taken during a fatty meal [11]. In recent years, some research has been carried out on developing new liposomal formulations or nanoparticles as a liver-targeting delivery system, to enhance the solubility and bioavailability of BMZ. However, clinical data on the efficiency of these new therapies are very limited [46]. Therapies based on the combination of ABZ and other agents, such as artesunate or the natural biocide compound thymol, acting synergistically against AE are also under investigation. However, ABZ and praziquantel combined therapy, despite several previous reports on its usefulness in treatment of AE, is no longer recommended.

As mentioned above, radical surgery is the first choice treatment in patients with AE and should be combined with prolonged anti-parasite drug treatment for at least 2 years. Total resection is possible in stages 1 and 2 according to the WHO-IWGE PNM classification, i.e. in the absence of distant metastasis and extrahepatic involvement of neighbouring organs, and without hilar vascular and biliary involvement of both lobes. Excision of the entire parasitic lesion should follow the rules of tumour surgery, classified according to the quality of resection: R0 – no residue, R1 – microscopic residue, R2 – macroscopic residue [11]. Non-radical liver surgery is not routinely recommended but might be in some cases beneficial for the advanced hepatic AE patients [13, 43] in the management of liver abscess due to a bacterial infection of necrotic fraction of the lesion, if percutaneous or endoscopic drainage are not effective [11]. Liver transplantation (LTx) is regarded as a salvage therapy in advanced hepatic AE. Reports from Turkey show more frequently performed living donor LTx in comparison to deceased donor LTx [4, 16]. Results from hepatobiliary/transplant centre in China suggest *ex vivo* liver resection auto transplantation as an effective alternative to allotransplantation for end-stage hepatic AE [1]. Indications for LTx include severe liver insufficiency, most often due to recurring cholangitis, secondary biliary cirrhosis, chronic Budd-Chiari syndrome or bleeding caused by portal hypertension. LTx is possible in the absence of extra-hepatic AE lesions [11].Cases with residual AE in lung or abdominal cavity should be qualified for LTx after a rigorous evaluation of the pros and cons, only among patients without contraindications for long-term BMZ treatment [11]. Brain involvement remains an absolute contraindication for LTx [11]. Late biliary complications requiring treatment are observed in advanced non-resectable hepatic AE in about 10 up to 30% of cases [19, 24] and may predict a poor prognostic outcome [19]. Previous surgery is considered as a potential risk factor [19]. Endoscopic interventions are the therapeutic options for patients not qualified to radical resection alleviating the late biliary complications and improving prognosis [2]. The main preventive measure to reduce the risk of cholangitis is an intensive biliary duct lavage during the procedure with full removal of stones and parasitic debris in combination with antibiotics [2]. Systematic numerous stent placement and early stent exchange to prevent plastic stent dysfunction is recommended [2]. Insertion of multiple plastic stents prolongs the time intervals before stent occlusion and leads to effective and prolonged patency of obstructed bile ducts [2]. Usefulness of ursodeoxycholic acid treatment in AE in biliary complications has not been yet defined in controlled trials [2]. AE patients demand careful attention during treatment and after it is over. This involves BMZ treatment safety assessment, evaluation of AE progression and onset of potential complications during treatment. According to expert consensus [11] stage-specific approach to AE, long-term BMZ treatment for several years (even life-long) is mandatory in all inoperable AE patients. Patients after LTx

are at risk of invisible or unrecognized extra-hepatic AE lesions regrowing and disseminating during the course of immunosuppressive therapy. The decision to terminate BMZ treatment shall be taken individually for each patient on the basis of medical history, negative results in serologic tests and 18F-FDG-PET-CT.

CLINICAL EXPERIENCE OF UCMMT IN DIAGNOSING AND TREATING PATIENTS WITH AE

Between 2000 and 2018, 86 patients with confirmed or probable diagnosis of AE were hospitalized in UCMTM. The characteristics of the analysed group are presented in Table 1. The patients' clinical stages of AE at diagnosis are shown in Figure 1. Imaging diagnostics of AE was based on ultrasound, CT and MRI. The assessment of lesions was descriptive, taking into account the presence of liquid necrotic fraction or calcification, but none of the proposed classifications of AE lesions was systematically used. CT and MRI were found to be more useful in assessing the stage of AE and qualifying patients for surgical treatment, especially in the case of expansion of the infiltration beyond the liver hilum or retroperitoneal space involvement. None of the patients underwent 18F-FDG-PET-CT or evaluation of liver lesions in the CEUS, because these procedures are

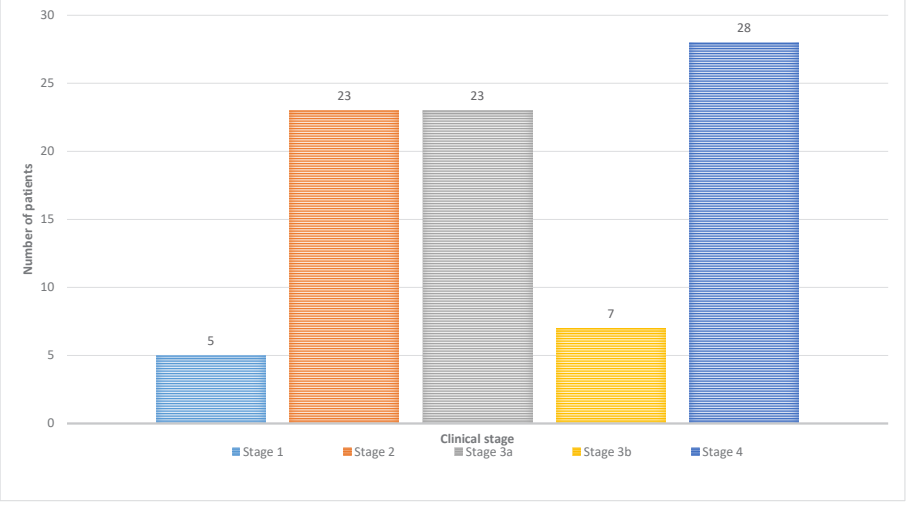

Fig. 1. Clinical stage of AE patients' at the time of diagnosis.
Stage 1 – peripheral liver lesions without proximal vascular and/or biliar involvement. Stage 2 –central liver lesions with proximal vascular and/or biliar involvement of one lobe. Stage 3a – central liver lesions with hilar vascular and biliar involvement of both lobes and /or with involvement of two hepatic veins. Stage 3b – any liver lesion with extension along the vessels and the biliary tree or with regional involvement of contiguous organs or tissues. Stage 4 – any liver lesion with extension along the vessels and the biliary tree with regional involvement of contiguous organs or tissues or any liver lesion with distant metastasis with/without regional involvement of contiguous organs or tissues

Table 1. Characterisation of patients at the time of diagnosis and during the follow-up

Total (number of patients)	86
Sex: female/male (number of patients)	47/39
Age at the time of diagnosis (years)	53.3 (6-82)
Conservative treatment (number of patients)	33
Radical resection (number of patients)	24
Nonradical resection (number of patients)	17
Liver transplantation (number of patients)	12
ERCP at the time of diagnosis (number of patients)	16
Deaths (number of patients)	9
Lost for observation (number of patients)	9
Adverse effects requiring temporary or permanent cessation of albendazole treatment (number of patients)	22

not reimbursed in Poland. The screening test used by the UCMTM between 2000 and 2016 was Echinococcus granulosus ELISA (Bordier Affinity ProductsSA, Crissier, Switzerland). To confirm screening test results, *Echinococcus* Western Blot IgG (LDBIO Diagnostics, Lyon, France) was used. This test indicated AE in 69.7% of cases. The remaining 30.3% of the test did not differentiate between AE and CE. Negativization of *Echinococcus* Western Blot IgG (LDBIO Diagnostics) assay results was observed in some patients who received conservative treatment and those who underwent radical surgery or LTx during the two-year follow-up. Echinococcus multilocularis ELISA test (Bordier Affinity Products SA, Crissier, Switzerland) detecting antibody response against Em2 plus antigen was additionally used, aside from *Echinococcus* Western Blot IgG test, to differentiate between AE and CE. The Echinococcus multilocularis ELISA test has been shown to be useful in monitoring the effectiveness of treatment of patients undergoing radical surgery. The negativization of its results was observed within one month to one year after surgical procedure. No change in test results was observed in the group of 25 unoperated patients. In 2016, serological diagnostics was extended to include commercially available tests EUROIMMUN Anti-*Echinococcus* ELISA (IgG) and ANTI-*Echinococcus* EUROLINE-WB (IgG) EUROIMMUN US Inc. According to the manufacturer's data, sensitivity and specificity of the above mentioned tests are respectively 96% and 96% for ELISA and 93% and 100% for WB tests.

Patients with AE were treated with BMZ. The drug of choice was ABZ, initially used in cyclic therapy (28 days treatment/14 days drug-free interval) and then in accordance with the recommendations of the expert consensus [11] – on a continuous basis. Adverse effects requiring temporary or permanent cessation of treatment were observed in 22 cases (25.6%). The most common reason for treatment cessation was the observed increase in transaminase activity (18.6%). Half of the cases were patients with cholestasis and in this group treatment with ABZ could be continued after normalization of transaminase activity due to effective endoscopic interventions. In the remaining 8 cases, in patients with initially normal transaminase levels and enzyme indicators of cholestasis, transaminase levels increased within one to three months after initiating ABZ treatment. This was related to the toxicity of ABZ and was a contraindication to its further use. In these cases, the treatment was continued with MBZ. The second factor resulting in the reduction of ABZ doses was neutropenia (4.7%). It was most frequently observed in patients with portal hypertension and hypersplenism and initially reduced the number of white blood cells. Two patients had transient alopecia. Fifty-three patients underwent surgical treatment – 24 patients radical surgery, and 17 patientsnon-radical surgery. Twelve patients underwent LTx. Main indications for LTx were parasitic disease progression despite pharmacological therapy, recurrent cholangitis and hepatic failure.

DISCUSSION

Diagnosis of AE is based on clinical presentation, epidemiological data, imaging techniques, serology, histopathology and/or nucleic acid detection. The suspicion of AE made on the basis of imaging and serological results allows for avoiding invasive diagnostic procedures, such as a biopsy of lesions or exploratory laparotomy, often performed without prior implementation of antiparasitic treatment, which may cause the spread of infection. Our experience shows that, despite the growing awareness of AE, invasive diagnostic procedures are performed. Of the 16 new cases of AE registered in UCMTM in 2016–2018, in seven cases serological diagnosis and inclusion of BMZ treatment were preceded by a biopsy of the liver lesions, and in four cases by exploratory laparotomy with tissue sampling for histopathological evaluation. In one case, in which a biopsy was performed prior to radical surgical treatment, the patient required prolonged treatment with BMZ due to the peritoneal dissemination of AE found intraoperatively. Analysis of the clinical stage at diagnosis presented in Figure 1 shows that AE is usually diagnosed when the disease is very advanced. Only in 28 patients (32,5%), the clinical stage at diagnosis allowed for the use of radical surgical treatment. This indicates the need to disseminate knowledge among medical personnel as well as conducting screening tests in endemic areas. The results of serological tests should always be evaluated in conjunction with the results of imaging studies and data on the clinical course of AE, including previous surgical treatment. This applies to tests performed in order to confirm *Echinococcus* spp. infection or to differentiate between AE and CE. Although in most cases, the radiological pictures of these two diseases are different, sometimes differentiation can be difficult. In such cases, a serological test can be helpful. However, it should be remembered that effective surgical treatment or pharmacological therapy resulting in reduced parasitic disease activity affects the results of serological tests, making the differentiation between echinococcosis species during treatment less likely. A difficult moment in the treatment of patients with AE is the decision to terminate pharmacological therapy in patients who did not undergo surgical treatment or underwent non-radical surgery, and in those after LTx. The high cost of 18F-FDG-PET-CT is a barrier to its widespread use, whereas CEUS, a less expensive diagnostic method to evaluate the activity of AE lesions in the liver, is not included in the recommendations of expert groups. In Poland, pharmacological treatment of AE is associated with a high financial burden to the patients. In addition, AE is not listed as a specific indication for use in the Summary of Medicinal Product Characteristics of ABZ or MBZ (off label use). Treatment with ABZ is not reimbursed, and MBZ therapy is only reimbursed in the case of enterobiasis, ascariasis, trichuriasis, ancylostomiasis or necatoriasis. In this situation, for many patients the only chance for continuing pharmaco-

logical treatment is to buy medicines abroad or from online sellers, where the origin and composition of medicines are uncertain and may pose a health risk. Our experience shows that treatment of patients with AE requires involvement of a multidisciplinary team, and should be based on sharing experience between centres dealing with echinococcosis.

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