

Efficacy and Safety of PAIR for Cystic Echinococcosis: Experience on a Large Series of Patients from Bulgaria

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Abstract. We report our experience with puncture, aspiration, injection, and reaspiration (PAIR) for the treatment of cystic echinococcosis in Bulgaria. PAIR was performed in 230 patients with 348 echinococcal cysts. At 12-month follow-up, 77.6% of the cysts, all cystic echinococcosis (CE) 1 and CE3a cysts according to the World Health Organization Informal Working Group classification, showed various degrees of obliteration. In 11.5% of cysts, all of which were > 10 cm-type CE1, a significant amount of fluid persisted, and they were punctured again. Of those, 16 (4.6%) contained protoscolices and were treated by a second PAIR. The remaining 24 (6.9%) cysts were treated by simple aspiration or drainage. No significant reduction in size and no changes in the structure were observed in 10.9% of cysts, all of which were classified as CE2 or CE3b. Complications developed in 25.2% of patients, including severe anaphylactic reaction in two (0.9%) patients. Our experience confirms that PAIR is a successful first-choice treatment when a stage-specific approach is taken.

INTRODUCTION

Cystic echinococcosis (CE), or cystic hydatidosis, is a complex, chronic disease with a cosmopolitan distribution. It is caused by the larval stage (metacestode) of *Echinococcus granulosus*, and it is endemic in sheep-raising areas.

The adult of *E. granulosus*, a small tapeworm 3–6 mm long, resides in the small intestine of the definitive canine host, whereas cysts occur in intermediate hosts (sheep, cattle, goats, or humans). *Echinococcus* eggs are shed in the feces of an infected dog and may be ingested by grazing ruminants or by humans through fecal–oral contact (ingestion of contaminated vegetables, water, or soil). In the small intestine, eggs hatch into embryos, penetrate the mucosa, and are carried by the circulation to major filtering organs, liver and lungs, where they develop into cysts that contain small tapeworm heads named protoscolices. These are infective to the definitive host on ingestion of the intermediate host's infected viscera, completing the cycle.¹ This is particularly common in endemic countries where it is customary to feed dogs with the viscera of home-slaughtered livestock.

In humans, the clinical spectrum of CE ranges from the most common asymptomatic infection to severe, which is rarely fatal. Diagnosis and staging of hepatic CE is mostly carried out by ultrasound (US). The US appearance of the cyst may change over time, either spontaneously or in response to treatment, and proceeds from an unilocular fluid-filled stage (CE1) through the detachment of the endocyst (CE3a) to either complete solidification (CE4 and CE5) or growth of daughter cysts in its cavity (CE2 and CE3b). CE1 and CE2 are classified as active cysts, and CE4 and CE5 are inactive cysts. CE3 cysts are classified as transitional, although recent studies suggest that CE3b should be reclassified as active.² Four therapeutic approaches are available for hepatic CE: surgery, percutaneous techniques and drug treatment of active and transitional cysts, and the so-called watch and wait approach for inac-

tive and selected cases of transitional CE3b cysts. Allocation of patients to a particular treatment should be based on cyst stage, size, location, comorbidities, and available clinical expertise.³ Puncture, aspiration, injection, and reaspiration (PAIR) with a scolicalidal agent such as 95% ethanol is the most widely used percutaneous technique for echinococcal cysts, and many reports highlight its efficacy and safety in selected cases.^{4,5}

MATERIALS AND METHODS

Patients and cysts classification. Patients with abdominal CE accessing the Clinical Center of Gastroenterology of the University Hospital Queen Joanna—Institute for Specialization and Improvement of Medical Doctors in Sofia, Bulgaria, between 2000 and 2006 were included in the study. All patients were Bulgarian natives from different regions of the country, both urban and rural. Diagnosis was obtained by US (ALOKA SSD2000 and ALOKA SSD5500; ALOKA, Tokyo, Japan) equipped with 3.5-MHz convex probes, and cysts were classified according to the World Health Organization Informal Working Group (WHO-IGWE) standardized classification.⁶ CE3 cysts were further classified into CE3a (detached endocyst) and CE3b (predominantly solid with single or several daughter cysts).^{3,4} All patients were serologically tested (indirect hemagglutination [IHA] and enzyme-linked immunosorbent assay [ELISA] immunoglobulin G [IgG]; BulBio-National Centre of Infectious and Parasitic Diseases, Sofia, Bulgaria) before PAIR. Patients with uncomplicated active (CE1 and CE2) and transitional (CE3a and CE3b) echinococcal cysts located in the abdomen and the retroperitoneum were included in the study and treated with PAIR.

PAIR procedure. Ninety-five percent absolute alcohol or 25% sterile hypertonic saline was used as a scolicalidal agent, the latter in cases of difficult approach such as in proximity to large vessels. All aspirates were analyzed for presence of protoscolices before and after the injection of the scolicalidal agent. The aspirates were tested for the presence of bilirubin by fast dipstick test urine dipstick (CombiScreen10SL; Analyticon Biotechnologies AG, Lichtenfels, Germany). Because of the absence of bilirubin in all of the aspirates, no

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contrast investigation of the biliary tree was carried out. PAIR was performed as follows: (1) percutaneous puncture of the cyst under US control, (2) aspiration of the maximum quantity of the cystic content, (3) injection of a scolical agent, and (4) reaspiration of the agent after 15 minutes. Chiba needles (18 G) were used with an intercostal and/or transabdominal approach, depending on size and location of the cyst.

Follow-up. Although a longer follow-up is generally recommended for CE,¹ we evaluated changes on US only at 6 and 12 months, because many patients, residing in distant rural areas, found it difficult to return for a longer follow-up. For the same reason, no serological follow-up was carried out. Percutaneous drainage of some of the residual cavities (i.e., totally or partially fluid-filled cysts without protoscolices at the microscopic examination) between 6 and 12 months after PAIR was performed with 5- to 8-F pigtail catheters in selected cases (cysts > 10 cm in diameter, also called giant cysts, persisting clinical complaints, liquid persistently filling more than 75% of the cyst, and/or bacterial superinfection of the cyst). Chemoprophylaxis with albendazole (Zentel, GlaxoSmithKline, Mayenne, France) (10–15 mg/kg per day from 4 days before until 1–2 months after the procedure) was carried out in all patients without contraindications such as drug intolerance, active hepatitis B virus (HBV) infection with elevated liver enzymes, or jaundice because of compression of the cyst on the biliary tree.

RESULTS

Patients and pre-treatment characteristics. Two hundred thirty patients (104 males and 126 females, mean age = 44.8 years, range = 18–75 years) underwent PAIR from 2000 to 2006. Three hundred forty-eight cysts were treated (mean size = 7.2 cm, range = 4–20 cm). Two hundred seventy-four (78.7%) cysts were located in the liver, and 74 (21.3%) were extra-hepatic. Of the latter, 67 (19.3%) were in the abdominal cavity, 4 (1.1%) were in one of the kidneys, and 3 (0.9%) were in the spleen. Two hundred ninety-six (85.1%) cysts were CE1 (226 located in the liver, 63 located in the abdominal cavity, 4 located in one of the kidneys, and 3 located in the spleen), 12 (3.4%) cysts were CE2 (all hepatic), 14 (4%) cysts were CE3a (10 hepatic and 4 in the abdominal cavity), and 26 (7.5%) cysts were CE3b (all hepatic). As for size, 76 (21.9%) were smaller than 5 cm, 180 (51.7%) were between 5 and 10 cm, and 92 (26.4%) were larger than 10 cm in diameter. Before the procedure, 98 (42.6%) patients had cyst-related signs or symptoms, such as abdominal pain or discomfort, palpable abdominal mass, itching, and rash. Abnormalities of laboratory tests (leucocytosis, eosinophilia and elevated aspartate aminotransferase [AST], alanine

aminotransferase [ALT], alkaline phosphatase [AP], gamma glutamil transpeptidase [GGT], and serum bilirubin) were observed in 30 (13%) patients. Forty-two (18.3%) patients were serologically negative before PAIR. Chemoprophylaxis of secondary echinococcosis with albendazole was carried out in 220 (95.7%) patients.

Six-month follow-up. At the 6-month follow-up, a significant decrease in size, followed by a gradual obliteration and solidification of the cyst or even its disappearance in some cases, was obtained in cysts < 10 cm³ (Table 1).

In detail, 212 (60.9%) cysts showed a significant reduction in size or complete/substantial obliteration of the cyst cavity. Cyst disappearance and complete or > 75% obliteration was observed in 115 (33.1%) cysts. Ninety-seven (27.9%) cysts showed partial (50–75%) obliteration. Folding of the endocyst (the so-called water lily sign) with significant reduction in size was observed in 98 (28.2%) cysts (93.9% of them with initial size over 10 cm). No significant reduction in size or change of the structure was observed in any of the CE2 and CE3b cysts.

Twelve-month follow-up. As summarized in Table 2, 1 year after the procedure, 270 (77.6%) cysts either disappeared or showed complete, > 75%, or 50–75% obliteration. In 40 (11.5%) cysts, all > 10 cm-type CE1, a significant amount of fluid persisted. All the CE2 and CE3b cysts remained structurally unchanged over the follow-up period.

Forty (11.5%) cysts, all > 10 cm-type CE1, needed a second puncture (PAIR or simple aspiration) or drainage during the follow-up period. Of those, 16 (4.6%) cysts contained protoscolices and were treated again by second PAIR. The remaining 24 (6.9%) cysts, classified as residual cavities, were treated by simple aspiration and lavage with saline (0.9% NaCl) and povidone iodinated solution (7.5 g povidone iodine [10% available iodine] per 100 g solution, Braunol; B. Braun Melsungen AG, Melsungen, Germany) or by percutaneous drainage, daily lavage, and continuous aspiration according to size.

Complications. Post-procedure complications were observed in 58 (25.2%) patients. The major complications of PAIR are anaphylactic shock, secondary echinococcosis caused by spillage of cystic fluid, and chemical cholangitis caused by contact of the scolical agent with the biliary tree.¹ Severe anaphylactic reactions with rash, bronchial/laryngeal spasm, and hyperpnea were observed in only two patients (0.9%) and were managed successfully with steroids and intensive care. Other major complications were not observed. Minor complications were observed in 56 (24.3%) patients. These were biliary fistula during the second puncture of cysts > 10 cm (8.9%), transitory leukocyte elevation (7%), high temperature (6.1%), urticaria (5.2%), local pain in the site of needle insertion

TABLE 1
Post-treatment changes of the cysts at the 6-month follow-up

Outcome	Number of cysts according to stage, size, and location											
	CE1			CE2			CE3a			CE3b		
	< 5 cm	5–10 cm	> 10 cm	< 5 cm	5–10 cm	> 10 cm	< 5 cm	5–10 cm	> 10 cm	< 5 cm	5–10 cm	> 10 cm
Disappearance	32L											
Complete obliteration	30L	8L, 2K, 2S					2L					
> 75% obliteration	14L	20L, 2K, 1S					2L					
50–75% obliteration		74L, 18A					4L, 1A					
Persistent liquid content		6L	42L, 45A						2L, 3A			
No change in structure					12L							26L
Subtotal		296			12			14				26
Total						348						

L = liver; K = kidney; S = spleen; A = abdominal cavity.

TABLE 2
Post-treatment changes of the cysts at the 12-month follow-up

Outcome	Number of cysts according to outcome and interventions needed at 12-month follow-up			
	Success	Second PAIR	Single aspiration or drainage of residual cavity	No change in structure
Disappearance	32 (CE1 < 5 cm)			
Complete obliteration	44 (CE1 and CE3a < 10 cm)			
> 75% obliteration	92 (CE1 and CE3a)			
50–75% obliteration	102 (CE1 and CE3a)			
Persistent liquid content		16 (hepatic CE1 > 10 cm)	24 (hepatic CE1 > 10 cm)	
No change in structure				38 (hepatic CE2 and CE3b)
Subtotal	270	16	24	38
Total			348	

(4.8%), mild transitory pleural effusion after treatment of cysts in liver segments located beneath the diaphragm and reached with an intercostal approach (2.2%), bacterial superinfection with *Escherichia coli* and *Staphylococcus aureus* (1.3%), and intracystic hemorrhage (0.4%). Some of the patients had two or more mild complications at the same time.

DISCUSSION

Human CE is still a major health and economic problem in Bulgaria. Between 1971 and 1982 and between 1983 and 1995, the average nationwide annual number of surgical cases (new and readmitted) of human CE increased by more than 60% (from 176 to 291), and the corresponding annual incidence rates rose from 2.0 to 3.3 per 100,000. In 1995, the average incidence rate by district showed variations from 1.9 to 15.8 per 100,000.^{8,9} From 1991 to 2000, 5,431 cases were registered, of which 89.6% consisted of primary infections and 10.4% resulted from post-operative relapses. The average incidence rate of the country was 2.4–8.5 per 100,000, with higher morbidity (15–27 per 100 000) in some southern regions of Bulgaria.¹⁰ As a result of the national control program for echinococcosis implemented from 2004 to 2008 and other factors, the average incidence rate in the country decreased to 6.28 for 2006, 6.24 for 2007, and 5.61 for 2008 per 100,000.¹¹ The ideal treatment of this high number of patients should be relatively inexpensive, minimally invasive, and easily repeatable if needed. PAIR meets all these requirements. The advantages of this technique in selected cases of CE have been shown by several reports over the last 20 years.^{3,5,12,13}

Although computed tomography (CT) and magnetic resonance imaging (MRI) are important tools for the diagnosis of hepatic and extra-hepatic CE, we chose US for diagnosis and guiding PAIR, because US scanning is part of our daily clinical practice, allows for better stage definition, and does not use ionizing radiation.

Our results confirm the efficacy of PAIR when a stage-specific approach is used, because the response to the percutaneous treatment is a function of the stage and size of the cyst.⁴ One of the limitations of our study is the short-term nature of follow-up. This is because patients living in remote rural areas, often elderly persons living alone, could not afford to return for a longer time period. Despite these limitations, our results are in accordance with previous reports showing that multivesiculated cysts (CE2 and CE3b) are prone to relapse, not only after albendazole but also after PAIR.^{14,15} Our findings support the idea that CE3b cysts, although transitional from a clinical standpoint, should be considered active from a biological per-

spective.^{2,4} Large cysts tend to have a much slower response to classical PAIR compared with small ones. This may be because of the injection of an inadequate quantity of scolicalid agent and/or a too short time of contact with the parasite, which results in an incomplete killing of the germinal layer. Some preliminary work reported that larger cysts show a better response to continuous catheterization compared with PAIR, but analysis of larger series is needed to confirm this observation.¹⁶ Cysts smaller than 5 cm showed an optimal response to PAIR, with complete obliteration or even disappearance. Although the use of PAIR for small cysts may be debatable when albendazole is available, in low-resource settings like the one presented here, the percutaneous approach can be a valuable alternative to a 3- to 6-month course of albendazole.

The presence of biliary fistulae in large cysts with fluid negative for bilirubin at the first puncture is consistent with the hypothesis that the endocyst, when expanded by the fluid pressure in CE1 cysts, may initially seal these communications.¹² Whether this requires a further search for bilirubin at an interval (e.g., 48 hours) after the first puncture is still unclear. Research addressing this specific risk is needed. Our experience suggests that, even in these cases, the final step of reaspirating the scolicalid agent would prevent the occurrence of sclerosing cholangitis (which was not observed in our series) that could result from its contact with the biliary epithelium. Anaphylactic shock is an uncommon complication and when it occurs, can be managed successfully. Therefore, the concerns of its occurrence should not prevent clinicians from choosing a percutaneous drainage when indicated. The presence of a resuscitation team during the procedure is mandatory as is the peri-procedural administration of albendazole to avoid secondary echinococcosis in case of intraabdominal spillage of cystic fluid.

CONCLUSIONS

Our experience on a large series of patients confirms that PAIR is a safe and effective treatment of CE1 and CE3a cysts located in the liver and selected extra-hepatic sites. PAIR is less invasive and expensive than surgery, and it should not be considered as an alternative but a method of choice for uncomplicated cysts in the context of a stage-specific approach. Very large cysts might not be suitable for PAIR, and modified techniques should be further investigated to make the percutaneous procedure more effective in these cases.

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