Treatment of Hepatic Cystic Echinococcosis in Patients from the Southeastern Rhodope Region of Bulgaria in 2004–2013: Comparison of Current Practices with Expert Recommendations

Marin Muhtarov,* Iskra Rainova, and Francesca Tamarozzi

Gastroenterology Ward, Multi-Profile Hospital for Active Treatment “Kardzhali,” Kardzhali, Bulgaria; Department of Parasitology and Tropical Medicine, National Centre of Infectious and Parasitic Diseases, Sofia, Bulgaria; Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, World Health Organization Collaborating Centre for Clinical Management of Cystic Echinococcosis, Pavia, Italy

Abstract. Cystic echinococcosis (CE) is a clinically complex chronic parasitic disease, management options for which include surgery, percutaneous treatments, and treatment with albendazole (ABZ) for active cysts, and the “Watch-and-Wait” approach for uncomplicated, inactive cysts. We examined, retrospectively, the clinical management of 334 patients with hepatic CE from the southeastern Rhodope region of Bulgaria between 2004 and 2013. Cysts were reclassified according to the World Health Organization Informal Working Group on Echinococcosis (WHO-IWGE) on the basis of ultrasound reports and images. The majority (62.3%) of uncomplicated cysts were CE1, 66% of which were treated surgically. Of all interventions, 5% were performed on inactive uncomplicated CE4–CE5 cysts. About half (47.6%) of these cysts were therefore treated inappropriately, exposing patients to unnecessary treatment-related risks and the health system to unnecessary costs. No management change was observed after the publication of the WHO-IWGE Expert Consensus recommendations in 2010. In Bulgaria, ABZ is still used in interrupted cycles as this is reimbursed, and peri-interventional chemoprophylaxis was not administered in the majority of surgical patients. Efforts are needed to introduce the WHO-IWGE classification and management recommendations and to encourage reception of state-of-the-art practices by public health regulatory bodies to improve patient quality of care and optimization of health resources.

INTRODUCTION

Cystic echinococcosis (CE) in humans is caused by the larval stage (hydatid cyst) of the dog tapeworm *Echinococcus granulosus*. Although initially asymptomatic, it may become a serious disabling illness with frequent relapses and may even be fatal. According to official surveillance data from the Bulgarian Ministry of Health and the National Center of Infectious and Parasitic Diseases,¹ during the period 2004–2013, the average CE incidence in Bulgaria was 4.98/100,000 inhabitants, whereas according to the official surveillance data in the southeastern Rhodope region (Kardzhali, Haskovo, and Smolyan districts; Figure 1), it was 5.33/100,000 inhabitants. The clinical management of hydatid cysts includes surgery, percutaneous treatments, and treatment with chemotherapeutic agents for active cysts, while the “Watch-and-Wait” approach is used for uncomplicated inactive cysts.² There is no “best” treatment option for CE, and no clinical trial has compared all the different management modalities, including Watch-and-Wait approach. Treatment indications are complex and are based on cyst characteristics, available medical/surgical expertise and equipment, and compliance of patients with long-term monitoring. Because treatment involves a variety of options and requires specific clinical experience, it is recommended that patients should be referred to recognized, reference national/regional CE treatment centers, whenever available.²

Gharbi and others³ published an ultrasound (US) classification of the hydatid cysts comprising five stages closely related to the natural parasite evolution. In 1995, the World Health Organization Informal Working Group on Echinococcosis (WHO-IWGE) proposed the standardization of the

US classification.⁴ This resulted in a new classification, known as the WHO-IWGE US classification (Figure 2)⁵, which was published in 2003 and addressed some ambiguities present in previous classifications.^{4,6} CE3 transitional cysts were subsequently differentiated into CE3a (with detached endocyst) and CE3b (predominantly solid with daughter vesicles).⁷ CE3a are the “true” transitional cysts, because they are inactive in 50% of cases and still active in the other 50% of cases, while CE3b are placed in the active group.⁸ Depending on the size of the cysts, each stage is divided into three subgroups: small (S) ≤ 5 cm, medium (M) = 5–10 cm, and large (L) ≥ 10 cm. The WHO-IWGE Expert Consensus on diagnosis and treatment of human echinococcosis based on this classification was published in 2010.² It recommends a stage-specific approach for uncomplicated liver CE, according to the US characteristics of the cysts (Figure 2). Cyst stage, size, location, and presence/absence of complications are the basis of decision making.² According to WHO-IWGE Expert Consensus, surgery should be performed only on CE2 and CE3b cysts, which are prone to relapse if treated with medical or standard percutaneous treatment, and on complicated cysts of other stages, always in association with medical treatment with benzimidazoles to prevent relapses and secondary echinococcosis from spillage of the cystic fluid.^{2,9–11} Antiparasitic treatment with benzimidazoles either alone or associated with percutaneous treatment should be preferably used for active uncomplicated unilocular cysts. Percutaneous treatments include PAIR (puncture, aspiration, injection of scolicidal agent, reaspiration) for unilocular cysts and other percutaneous techniques, such as modified catheterization, for multivesiculated complex cysts.^{12,13} Uncomplicated inactive CE4 and CE5 cysts do not have to be treated but only followed over time with US.^{2,14}

Despite the availability of the WHO-IWGE classification as a guidance for treatment, allowing a rational, comparable, and safe approach to CE, an online survey conducted in 2014 on the treatment options that clinicians around the world would choose in five clinical cases of CE found not only extremely heterogeneous managements of the same cases but also a

*Address correspondence to Marin Muhtarov, Gastroenterology Ward, Multi-Profile Hospital for Active Treatment “Kardzhali,” 19 Trakya Boulevard, 6600 Kardzhali, Bulgaria. E-mail: mukhtarov@abv.bg

FIGURE 1. The southeastern Rhodope region of Bulgaria comprising Kardzhali, Haskovo, and Smolyan districts.

worrying number of practices that are either unsafe or not recommended.¹⁵ Furthermore, a systematic review of the literature published since the introduction of the WHO-IWGE classification and the Expert Consensus guidance found that more than 70% of published works do not include CE stage in the description of their cases or cohorts, and thus probably also ignore it in the clinical decision making.¹⁶

The aim of this work was to investigate the clinical approach for the treatment of uncomplicated hepatic CE in the southeastern Rhodope region of Bulgaria, which includes

Kardzhali, Haskovo, and Smolyan districts, between 2004 and 2013.

MATERIALS AND METHODS

We performed a retrospective study of medical records from patients with isolated hepatic localization of CE treated during the 2004–2013 period. All patients lived and were diagnosed in the Rhodope region (Kardzhali, Haskovo, and Smolyan districts) and were treated for CE either in the

FIGURE 2. Schematic representation of the natural history of hepatic cystic echinococcosis (CE) and suggested clinical approaches according to the World Health Organization Informal Working Group on Echinococcosis (WHO-IWGE). Solid black arrow indicates natural evolution toward inactivation; black dashed arrows indicate evolution of therapy-unresponsive chronic stages. Ultrasound (US) images: cyst US classifications according to WHO-IWGE and Gharbi. Gray boxes suggested stage-specific approach to uncomplicated hepatic CE according to the WHO Expert Consensus. ABZ = albendazole; PAIR = puncture, aspiration, injection of scolecidal agent, reaspiration. (Modified from Ref. 5.)

region or in other centers in the country. Data source were the following: Diagnostic and Consultation Center 1, Medical Center "Avicenna," and hospitals "Atanas Dafovski" and "Kardzhali" in Kardzhali, as well as data from the National Health Insurance Fund (NHIF) and the Regional Health Inspectorates. Retrieved data included abdominal US results from hospital discharge records and outpatient data and were collected according to the Bulgarian law on Access to Public Information. When available, US images typical of CE were reclassified (by MM) according to WHO-IWGE US classification and divided into size groups: $S \leq 5$ cm, $M = 5-10$ cm, and $L \geq 10$ cm. When images were not available, reclassification was based on the description of the cyst as provided in US clinical report. All images and reports used for the analysis were collected before the beginning of the treatment.

RESULTS

Data of 334 individuals with isolated hepatic localization of CE were retrieved and analyzed. Of these patients, 139 were males and 195 females, aged 4–84 years, including 31 children (< 19 years). Patients were treated as follows: 241 (72.2%) with surgical treatment, 43 (12.9%) with PAIR, and 29 (8.7%) with chemotherapy with albendazole (ABZ) alone. The Watch-and-Wait approach was applied in 21 (6.3%) patients. Among the 241 operated patients, 36 (14.9%) had complicated liver CE while 205 (85.1%) presented uncomplicated hepatic CE. The complicated liver CE group comprised 15 patients with extrahepatic cholestasis, 12 with superinfection of the cyst, seven with cyst rupture, and two with "other complications" of unspecified nature. Complicated cases were not considered for further analysis.

In Bulgaria, the Gharbi classification is still in use, and 64 (19.2%) of our patients were classified according to this classification; however, the majority of US reports ($N = 270$ [80.8%]) did not mention any classification of CE cysts. No report used the WHO-IWGE classification.

After reclassification according to the WHO-IWGE classification, the 406 uncomplicated hepatic CE cysts were as follows: 252 CE1, 99 CE2, four CE3a, nine CE3b, 20 CE4, and 22 CE5. The distribution of the different management options by cyst stage is summarized in Table 1. For 58 (53.9%) patients, US reports concerned relapsed cysts: 35 were relapses after previous surgery, four after PAIR, four after ABZ treatment, and 15 after unspecified previous treatment.

As the Expert Consensus was published at the beginning of 2010, we investigated whether the management of CE changed after the publication of this document. As shown in Table 1, a significantly lower percentage of surgical procedures was performed in the period 2010–2013 ($P = 0.004$, χ^2 test).

Surgical treatment. Of the 205 patients with uncomplicated hepatic CE, 156 had one cyst, 39 had two cysts, and 10 had more than or equal to three cysts. The total number of uncomplicated cysts treated surgically was 270. The majority of operated cysts were type CE1 ($N = 167$ [61.8%]), the majority being ≥ 5 cm diameter ($N = 139$ [83.2%]). All cysts were confirmed as *E. granulosus* after the surgical procedure. Only 100 (41.5%) patients who were treated by surgery received ABZ chemoprophylaxis against relapse. The details of operated cysts are summarized in Table 2. Of patients having more than one cyst, only one receiving surgery for CE1 cysts had the presence at the same time of a cyst in a stage (CE2) requiring surgery according to the WHO-IWGE Expert Consensus. Regarding operated inactive cysts, two patients (with total $N = 5$ CE4–CE5 cysts) operated in the

TABLE 1

Distribution of management approaches by cyst stage (WHO-IWGE) implemented in patients with uncomplicated hepatic hydatid disease between 2004 and 2013

Cyst stage	Surgery		PAIR		ABZ		Watch-and-Wait approach		Any active treatment	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
2004–2013										
CE1	167	66.27	51	20.23	33	13.10	1	0.40	251	99.60
CE2	87	87.88	5	5.05	7	7.07	0	0.00	99	100
CE3a	2	50.00	1	25.00	1	25.00	0	0.00	4	100
CE3b	2	22.22	3	33.33	4	44.44	0	0.00	9	100
CE4	7	35.00	1	5.00	6	30.00	6	30.00	14	70
CE5	5	22.73	0	0.00	1	4.55	16	72.73	6	27.27
Any stage	270	66.50	61	15.02	52	12.81	23	5.66	383	94.33
2004–2009										
CE1	119	74.38	30	18.75	10	6.25	1	0.63	159	99.37
CE2	55	88.71	2	3.23	5	8.06	0	0.00	62	100
CE3a	1	33.33	1	33.33	1	33.33	0	0.00	3	100
CE3b	1	16.67	1	16.67	4	66.67	0	0.00	6	100
CE4	5	33.33	1	6.67	6	40.00	3	20.00	12	80.00
CE5	3	27.27	0	0.00	1	9.09	7	63.64	4	36.36
Any stage	184	71.59	35	13.62	27	10.51	11	4.28	246	95.72
2010–2013										
CE1	48	52.17	21	22.83	23	25.00	0	0.00	92	100
CE2	32	86.49	3	8.11	2	5.41	0	0.00	37	100
CE3a	1	100	0	0.00	0	0.00	0	0.00	1	100
CE3b	1	33.33	2	66.67	0	0.00	0	0.00	3	100
CE4	2	40.00	0	0.00	0	0.00	3	60.00	2	40.00
CE5	2	18.18	0	0.00	0	0.00	9	81.82	2	18.18
Any stage	86	57.72	26	17.45	25	16.78	12	8.05	137	91.95

ABZ = albendazole; CE = cystic echinococcosis; PAIR = puncture, aspiration, injection of scolecidal agent, reaspiration; WHO-IWGE = World Health Organization Informal Working Group on Echinococcosis.

*Difference between 2004–2009 and 2010–2013 periods $P = 0.004$ (χ^2 test). Active treatment indicates surgery, PAIR, and medical treatment with ABZ.

TABLE 2

Uncomplicated hepatic CE cysts classified according to WHO-IWGE treated by surgery between 2004 and 2013

Cyst stage	S		M		L		Any size	
	n	%	n	%	n	%	n	%
2004–2013								
CE1	28	10.37	91	33.70	48	17.78	167	61.85
CE2	15	5.56	53	19.63	19	7.04	87	32.22
CE3a	0	0.00	2	0.74	0	0.00	2	0.74
CE3b	0	0.00	1	0.37	1	0.37	2	0.74
CE4	4	1.48	2	0.74	1	0.37	7	2.59
CE5	4	1.48	1	0.37	0	0.00	5	1.85
Any stage	51	18.89	150	55.56	69	25.56	270	100
2004–2009								
CE1*	20	10.87	64	34.78	35	19.02	119	64.67
CE2	14	7.61	32	17.39	9	4.89	55	29.89
CE3a	0	0.00	1	0.54	0	0.00	1	0.54
CE3b	0	0.00	0	0.00	1	0.54	1	0.54
CE4†	4	2.17	0	0.00	1	0.54	5	2.72
CE5†	3	1.63	0	0.00	0	0.00	3	1.63
Any stage	41	22.28	97	52.72	46	25.00	184	100
2010–2013								
CE1	8	9.30	27	31.40	13	15.12	48	55.81
CE2	1	1.16	21	24.42	10	11.63	32	37.21
CE3a	0	0.00	1	1.16	0	0.00	1	1.16
CE3b	0	0.00	1	1.16	0	0.00	1	1.16
CE4†	0	0.00	2	2.33	0	0.00	2	2.33
CE5†	1	1.16	1	1.16	0	0.00	2	2.33
Any stage	10	11.63	53	61.63	23	26.74	86	100

CE = cystic echinococcosis; L = large; M = medium; S = small; WHO-IWGE = World Health Organization Informal Working Group on Echinococcosis.

*N = 2 CE1 cysts of M size were operated in a patient also having a CE2 cyst.

†N = 3 CE4 cyst (N = 2 in 2004–2009 and N = 1 in 2010–2013) and N = 4 CE5 cysts (N = 3 in 2004–2009 and N = 1 in 2010–2013) were operated in patients also having S or M size CE1 cysts.

period 2004–2009 and two patients (with total N = 2 CE4–CE5 cysts) operated in the period 2010–2013 did not harbor at the same time any cyst in a stage requiring surgery according to the WHO-IWGE Expert Consensus. There was no significant difference in the surgical management attitude between the two periods (pre- and postpublication of the WHO-IWGE Expert Consensus). Short-term postsurgical complications occurred in five patients: three required a second surgery due to superinfection (N = 1), pneumothorax (N = 1), and perforation of the diaphragm (N = 1), whereas two died after surgery, one of liver failure and one of “sudden death.”

Treatment with PAIR. Forty-three patients with 61 uncomplicated hepatic CE cysts were treated with PAIR: 28 had only one liver cyst, 12 had two cysts, and three had three cysts. The majority of cysts were CE1 (N = 51 [83.6%]), the majority being ≥ 5 cm diameter (N = 35 [68.6%]). PAIR was also performed on 16 (26.23% of all PAIR-treated cysts; no significant difference between the two periods examined) CE1 < 5 cm, five (8.2%) CE2, three (4.92%) CE3b, and one (1.64%) CE4 cysts. All cysts were confirmed as *E. granulosus* after the microscopical analysis of the cyst fluid. ABZ chemoprophylaxis against relapse was administered in more than two-thirds of the PAIR-treated patients (N = 35 [72.9%]). Short-term post-PAIR complications occurred in three patients: one experienced urticaria and two experienced anaphylactic shock, of which one died.

Treatment with ABZ. In Bulgaria, ABZ is used for the medical treatment of hydatid disease and is reimbursed by NHIF only if given with interruptions between cycles. Treatment with ABZ as the sole approach was performed in

TABLE 3

Uncomplicated hepatic CE cysts classified according to WHO-IWGE treated by ABZ as the sole approach only between 2004 and 2013

Cyst stage	S		M		L		Any size	
	n	%	n	%	n	%	n	%
2004–2013								
CE1	27	51.92	5	9.62	1	1.92	33	63.47
CE2	3	5.77	3	5.77	1	1.92	7	13.46
CE3a	0	0.00	1	1.92	0	0.00	1	1.92
CE3b	3	5.77	0	0.00	1	1.92	4	7.69
CE4	3	5.77	3	5.77	0	0.00	6	11.54
CE5	1	1.92	0	0.00	0	0.00	1	1.92
Any stage	37	71.15	12	23.08	3	5.77	52	100
2004–2009								
CE1	10	37.04	0	0.00	0	0.00	10	37.04
CE2	2	7.41	2	7.41	1	3.70	5	18.52
CE3a	0	0.00	1	3.70	0	0.00	1	3.70
CE3b	3	11.11	0	0.00	1	3.70	4	14.81
CE4*	3	11.11	3	11.11	0	0.00	6	22.22
CE5	1	3.70	0	0.00	0	0.00	1	3.70
Any stage	19	70.37	6	22.22	2	7.41	27	100
2010–2013								
CE1	17	68.00	5	18.52	1	4.00	23	92.00
CE2	1	4.00	1	3.70	0	0.00	2	8.00
CE3a	0	0.00	0	0.00	0	0.00	0	0.00
CE3b	0	0.00	0	0.00	0	0.00	0	0.00
CE4	0	0.00	0	0.00	0	0.00	0	0.00
CE5	0	0.00	0	0.00	0	0.00	0	0.00
Any stage	18	72.00	6	22.22	1	4.00	25	100

ABZ = albendazole; CE = cystic echinococcosis; L = large; M = medium; S = small; WHO-IWGE = World Health Organization Informal Working Group on Echinococcosis.

*N = 1 CE4 cyst was treated with ABZ in a patient also having a CE1 cyst of M size.

29 patients with a total of 52 liver CE cysts. The majority of cysts were CE1 (N = 33 [63.5%]), of which the majority was S size (N = 27 [51.9%]). There was no significant difference in the ABZ use between the two periods (pre- and postpublication of the WHO-IWGE Expert Consensus).

The details of the cysts treated with ABZ only are summarized in Table 3. Treatment side effects occurred in one patient who experienced hepatitis requiring hospitalization.

Watch-and-Wait approach. The Watch-and-Wait approach was performed in 21 patients with 23 uncomplicated hepatic CE cysts. Virtually all of them (N = 22 [95.6%]) had inactive cyst types CE4 and CE5 on abdominal US.

DISCUSSION

We carried out a comprehensive review of the management of uncomplicated hepatic CE in the southeastern Rhodope region of Bulgaria between 2004 and 2013 and compared it with the most up-to-date indications of the WHO Expert Consensus on the diagnosis and treatment of human echinococcosis.² In Bulgaria, detailed description of the visualized hepatic cysts on US report is routinely carried out. However, more than 80% of US reports did not mention any classification of CE cysts, while Gharbi classification was used in the remaining cases. No report referred to the WHO-IWGE classification. Therefore, to analyze the data, we reclassified cysts based on US report descriptions and images according to WHO-IWGE US classification.⁴

The Expert Consensus on the diagnosis and treatment of echinococcosis² was published at the beginning of 2010; therefore, we investigated whether the management of CE

changed after the publication of this document. Overall, no significant differences were found between the management of CE cysts before and after the publication of the recommendations. It is difficult to carry out an analysis on the "appropriateness" of treatment of every patient using retrospective records, which may not contain complete data or details on the types of treatment provided. However, it is possible to comment that CE1, CE2, and possibly CE3a cysts were generally treated in accordance with the logic of the Expert Consensus recommendations, while treatment of CE3b and management of inactive CE4 and CE5 stages were not.

As shown in Table 1, over 10% of surgical procedures were performed for uncomplicated CE1 cysts < 5 cm, which according to the WHO-IWGE Expert Consensus should be treated with benzimidazoles or undergo percutaneous treatment.² In addition, over 4% of surgical procedures were performed on uncomplicated, inactive CE4 and CE5 cysts (Table 1). Similarly, 26% of PAIR procedures were performed on CE1 cysts < 5 cm, in which, treatment with ABZ only is advised. Moreover, over 7% of PAIR procedures were performed on multivesiculated CE2 and CE3b cysts, which have a high rate of relapses after classic PAIR.⁹ Of all cysts treated with ABZ, over 21% were multivesiculated CE2 and CE3b cysts, which are highly prone to relapse after ABZ,^{10,11} and 13.5% were inactive CE4 and CE5 cysts (Table 3). In fact, PAIR and ABZ alone were the treatment modalities mostly used for CE3b cysts (33.3% and 44.4%, respectively). The Watch-and-Wait approach was properly applied to inactive hydatid cysts and not to other stages.¹⁴ However, 5% of all interventions, either invasive or pharmacological, were carried out even though cysts were inactive and asymptomatic. In terms of cysts, about half (47.6%) of uncomplicated inactive CE4–CE5 cysts were therefore treated inappropriately, exposing patients to unnecessary treatment-derived risks and the health system to unnecessary costs.

Treatment with ABZ in Bulgaria is still applied in cycles of 28 days with 2-week breaks between cycles and not continuously as recommended by the most recent scientific consensus.² If administered intermittently, ABZ is reimbursed by NHIF. Unfortunately, this common practice is still supported, as in other European countries, by the lack of updating to the prescribing information, which inhibits the correct administration of the drug if NHIF reimbursement is sought. Furthermore, chemoprophylaxis against relapse was not administered in the majority of surgical patients, whereas it was used in the majority of patients treated with PAIR. This is most likely because in Bulgaria benzimidazoles can be reimbursed by NHIF only if prescribed by a specialist in medical parasitology. There are no such specialists in the Rhodope region and most of the patients who underwent surgery were treated in local hospitals of the region. PAIR, on the contrary, was performed in specialized metropolitan centers, which have facilitated access to parasitology specialists.

To conclude, this retrospective observational study shows that the medical approaches to uncomplicated hepatic CE cysts in CE1 and CE3a stages of patients from the south-eastern Rhodope region in Bulgaria, which represent 63.3% of all uncomplicated cysts in the studied cohort, are treated in overall conformity with the WHO Expert Consensus. However, the treatment of other stages is still suboptimal and more effort is needed to implement internationally accepted

guidance. Knowledge of the US standardized classification and of the stage-specific approach to CE cysts by specialists practicing in endemic areas is key to a correct diagnosis and a rational clinical approach. It would be therefore highly recommended, on the one hand, that endemic countries assess their own situation and determine ways to implement this approach, if it is not been followed, for example through the issue of national recommendations in the local languages and the implementation of training programs for general practitioners and physicians specialized in relevant disciplines. On the other hand, it is extremely important that the WHO-IWGE explore more effective ways to convey the information on the most recent consensus for the clinical management of the infection. Surely, official WHO guidelines on the clinical management of CE are strongly needed. However, at the moment, due to the difficulty in the issue of evidence-based guidelines on CE, a revised, updated, and clear official WHO consensus document would be the best practical approach.

Perioperative use of ABZ for every invasive procedure has to be implemented and access of patients with CE to ABZ has to be facilitated. Finally, drug indications for ABZ treatment should ideally be amended to comply with the most recent international guidance to avoid exposing the patient and physician to a choice between the appropriate but not reimbursable treatment and an expensive reimbursable treatment that is administered in a manner that has ceased to be recommended. However, such a global prescription revision at the level of each country regulator would be extremely difficult. Therefore, again, the most effective approach would likely be the implementation of this change by WHO through directed policy to ensure global understanding that medical treatment of CE is now recommended in a continuous regimen.

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Authors' addresses: Marin Muhtarov, Gastroenterology Ward, Multi-Profile Hospital for Active Treatment "Kardzhali," Kardzhali, Bulgaria, E-mail: mukhtarov@abv.bg. Iskra Rainova, Department of Parasitology and Tropical Medicine, National Centre of Infectious and Parasitic Diseases, Sofia, Bulgaria, E-mail: rainova@ncipd.org. Francesca Tamarozzi, Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, WHO Collaborating Centre for Clinical Management of Cystic Echinococcosis, Pavia, Italy, E-mail: f_tamarozzi@yahoo.com.

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