

## Shortage of Albendazole and Its Consequences for Patients with Cystic Echinococcosis Treated at a Referral Center in Italy

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**Abstract.** Albendazole (ABZ) is the best drug available to treat cystic echinococcosis (CE), a neglected tropical disease. Cystic echinococcosis patients often receive a continuous course of the drug for 6–12 months. In Italy, ABZ shortages occur almost on a yearly basis. We searched clinical records at the World Health Organization Collaborating Center for the Clinical Management of CE in Pavia, Italy, to estimate the amount of ABZ prescribed to patients between January 2012 and February 2017. The cost of ABZ was estimated at €2.25 per tablet based on the current market price in Italy. Patients to whom ABZ had been prescribed were contacted to determine if they had experienced difficulties in purchasing the drug and to assess how such problems affected their treatment. Of 348 identified CE patients, 127 (36.5%) were treated with ABZ for a total of 20,576 days. This led to an estimated cost of €92,592. Seventy-five patients were available for follow-up, 42 (56%) reported difficulties in obtaining ABZ. Of these patients, four (9.5%) had to search out of their region and 10 (23.8%) had to go out of the country. A total of 27 patients (64%) had to visit more than five pharmacies to locate the drug and 10 patients (23.8%) interrupted treatment because of ABZ nonavailability. Shortages in ABZ distribution can disrupt CE treatment schedules and jeopardize patient health.

### INTRODUCTION

Cystic echinococcosis (CE) is a zoonotic disease caused by the metacestode of a tapeworm from the *Echinococcus granulosus* sensu lato complex.<sup>1</sup> The parasite has a life cycle comprising a definitive host (dogs or other canids) and an intermediate host (sheep or other ungulates).<sup>1</sup> Humans are accidental intermediate hosts, where the parasite larvae develop as cysts mainly in the liver and lungs.<sup>2</sup> Cystic echinococcosis has a high socioeconomic impact. Infection in humans causes estimated mean yearly losses ranging from 193,529,740 to 763,980,979 U.S. dollars and from 88,082 to 1,590,846 disability-adjusted life years, respectively, when underreporting is not assumed or is assumed.<sup>3,4</sup> Nevertheless, CE remains a neglected disease with little attention and funds devoted to research focusing on the clinical management of patients.<sup>5</sup>

Human CE can currently be treated by surgery, percutaneous procedures, and medical therapy with benzimidazole derivatives. For inactive cysts, a watch-and-wait strategy can be adopted (Figure 1). However, the evidence base that should guide the choice of treatment is poor due to lack of prospective, randomized studies.<sup>6,7</sup> Benzimidazole derivatives, especially albendazole (ABZ), are recommended for CE1 and CE3a cysts of the liver. However, unlike the vast majority of other helminthiases for which ABZ is used, long-term administration is needed for CE, ranging from 3 months to over 12 months in particular cases.<sup>5,7,8</sup> Here we report on difficulties in the clinical management of CE patients treated at an Italian referral center due to the current shortage of ABZ.

### MATERIALS AND METHODS

**Patients.** We included in the study recorded in the European Register of CE (ERCE)<sup>9</sup> and seen at the World Health Organization (WHO) Collaborating Center for the Clinical Management of CE in Pavia, Italy, where they were prescribed ABZ, from January 2012 to February 2017. All CE patients were eligible for inclusion regardless of cyst location, cyst stage, or clinical severity. Demographic data and information on ABZ intake, including total duration of therapy and treatment scheme, were extracted from the ERCE.

**Patient interview process.** Eligible patients were contacted by phone or e-mail or filled a questionnaire during follow-up visits to determine if they had experienced difficulties in acquiring ABZ. Interviews and e-mail exchanges with patients were conducted by two investigators (T. M. and A. V.). Each patient was administered a four-item questionnaire as follows, inquiring: 1) whether purchase of the drug was perceived as difficult; 2) whether the patient had to visit more than five pharmacies to obtain the drug; 3) whether the patient had to search for the drug out of his region of residence or outside of Italy, and 4) if the patient had to interrupt treatment because of being unable to acquire the drug. A treatment interruption was defined as having to interrupt drug administration for at least three consecutive days.

**Cost estimation.** The official 2017 cost of ABZ in Italy obtained from the pharmacy of the San Matteo Hospital Foundation, Pavia, is €2.25 per 400 mg tablet. Costs deriving from ABZ use were estimated considering individual patient treatment duration recorded in the ERCE at a standard administration dose of 400 mg ABZ twice a day.

**Ethical approval.** This survey was conducted using patient data from the ERCE. At the time of registry enrollment, all patients provide written informed consent for their information to be used for research purposes. In addition, all patients are asked to provide consent to be contacted at a later date for research purposes. Before completing the questionnaire,

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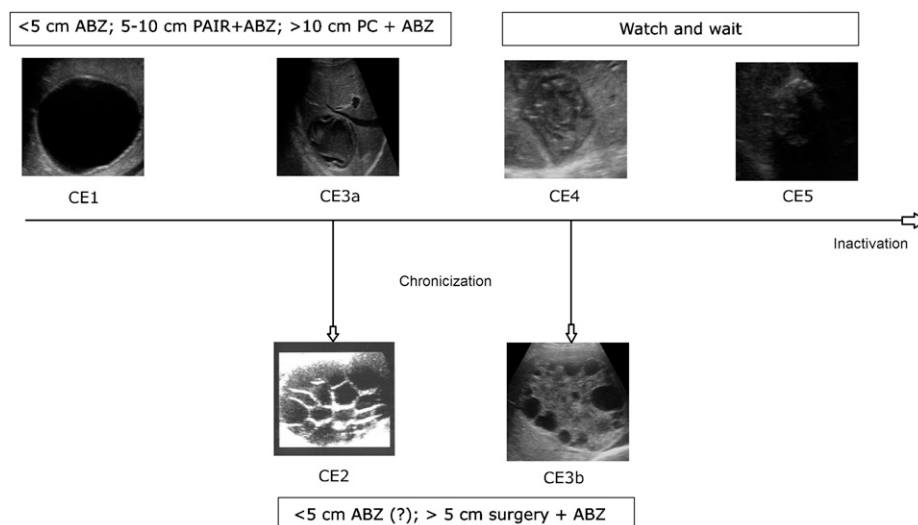


FIGURE 1. Recommended treatment options for uncomplicated cystic echinococcosis (CE) cysts of the liver. Modified from.<sup>13</sup>

patients were again asked for consent to participate. Research-related use of the ERCE has been approved by the IRCCS San Matteo Hospital Foundation Ethical Committee.

## RESULTS

Of the 348 patients with CE registered by our center during the study period, 127 (36.5%) were prescribed ABZ for a total of 20,576 days. Ten patients (7.8%) were treated for extrahepatic localizations, including osteomuscular CE ( $N = 4$ , 3.1%), CE of the lungs ( $N = 5$ , 3.9%), and the spleen ( $N = 2$ , 1.6%). The median duration of treatment was 90 days (range 15–840 days) and the total estimated cost of medical treatment was €92,592. Eighty patients (63%) were treated solely with medical therapy for a median of 180 days (range 15–630 days). Thirty patients (23.6%) were treated surgically and they all received ABZ for a median of 30 days after surgery (range 28–70 days). Fifteen surgical patients also received additional cycles of ABZ for a median of 180 days (range 30–570 days). Seventeen patients (13.4%) were prescribed ABZ after percutaneous procedures and took the drug for a median of 90 days (range 30–240 days). Of these patients, six took an additional course of ABZ for a median of 135 days (range 30–570). In addition, one patient (0.8%) was initially treated with a percutaneous procedure but later required surgery and was also treated with ABZ for 570 days. We attempted to contact all 128 patients who had received ABZ as part of their management strategy. Of 75 patients who were reachable by phone or e-mail and answered the questionnaire, 42 (56%) reported difficulties in obtaining ABZ. Of these patients, four (9.52%) had to look for ABZ out of their region and 10 (23.8%) had to go out of the country. A total of 27 patients (64%) had to visit more than five pharmacies to locate the drug and 10 patients (23.8%) interrupted treatment due to ABZ nonavailability.

## DISCUSSION

Currently, four clinical management options are available for the management of CE, depending on the affected organ and cyst size: medical therapy with benzimidazoles; surgery;

percutaneous techniques, such as catheter-based procedures or the puncture–aspiration–injection–reaspiration technique<sup>10</sup> and its derivatives;<sup>11–13</sup> and watch-and-wait.<sup>7,14</sup> Patients receiving surgery or percutaneous procedures for hepatic CE should receive ABZ from the day of the intervention to 1 month post-intervention to prevent secondary echinococcosis due to the dissemination of parasitic material.<sup>7</sup>

Mebendazole (MBZ) became available for human use in the mid-1980s,<sup>15</sup> with ABZ soon to follow. Since then, no new drugs have been introduced to treat CE. Benzimidazoles appear to act on the parasite by blocking beta tubulin formation<sup>15,16</sup> and are mainly parasitostatic,<sup>17,18</sup> with ABZ showing better efficacy than MBZ.<sup>19</sup> Long-term outcome of medical therapy, however, depends on many variables, including the size and, most importantly, the stage of the cyst. For example, medical therapy is largely ineffective on CE2 or CE3b cysts, whereas better results are achieved with small CE1 and CE3a cysts<sup>7,20,21</sup> (Figure 1).

There are problems associated with the use of ABZ to treat CE. When first introduced for the treatment of CE, ABZ was administered with therapy interruptions, with cycles composed of 28 days of treatment followed by 14 days without treatment. This was because of limited long-term toxicity data available at the time, with early suspicions that long-term ABZ use was linked to tumor formation in animals.<sup>15</sup> However, it has subsequently been established that the drug can safely be used with continuous administration.<sup>15,19,22</sup> The optimal duration of therapy has not been formally assessed, but therapy duration generally varies between 3 and 6 months for abdominal CE,<sup>7,15,19,21,23</sup> and in some cases, lifelong administration has been used in the management of particular cases, such as bone infection.<sup>24,25</sup> Despite expert opinion that this treatment regimen is safe and carries a small risk of side effects,<sup>6,7,15</sup> most countries, including Italy, still mandate a maximum of three treatment cycles of 28 days, separated by 14 days without treatment.<sup>6,15</sup> However, in many centers today, an adult patient is prescribed two 400 mg tablets of ABZ each day, meaning that they will need 60 tablets for 1 month of treatment. At present, this is still considered off-label use of the drug. In the last few years, the situation in Italy has been complicated further by the intermittent availability of ABZ.

Albendazole has been on the official list of drugs, with a shortage in Italy from the end of 2016 to February 2018.<sup>26</sup> Shortages have also been anecdotally reported from several other countries,<sup>6</sup> which has resulted in a WHO initiative to conduct an international survey investigating the drug's use and availability on an international scale.<sup>27</sup> The present study is the first to present data on the impact of ABZ shortages on CE patients. Although less effective, MBZ can also be used for the treatment of CE<sup>17,19,22,28</sup> but it is often not available<sup>6</sup> and its price can be prohibitive.<sup>29</sup> In Italy, ABZ has been only intermittently available over the last 5 years and, since September 2017, availability has been extremely limited. The Italian National Drug Agency (Agenzia Italiana del Farmaco [AIFA]) and the drug's producer (GlaxoSmithKline) have stated that the drug shortage has been caused by problems with the drug production.<sup>26</sup> To make matters worse, although packages containing 60 ABZ tablets are available in many other European countries, only three tablet packages are currently available in Italy. This is because ABZ production is being targeted at the treatment of soil-transmitted helminthiasis. This makes filling prescriptions and complying with the full course of therapy difficult for patients because pharmacies typically only stock a limited number of boxes of each drug.<sup>30</sup>

The nonavailability of drugs is a problem with which health systems throughout the world constantly struggle. This issue is not specific to tropical medicine but can also impact other specialties, ranging from oncology to anesthesiology.<sup>29,31–34</sup> Ideally, health systems should work with the private sector to minimize the impact of drug shortages on patient care but this is not always possible.<sup>32</sup> Moreover, the distribution of drugs between countries can be difficult because permitted uses for each drug vary from one country to another. Because of the intermittent nonavailability of ABZ in Italy during the last 5 years, patients followed up in our center had substantial difficulties in receiving the correct treatment. In the present study, 56% of surveyed patients perceived the process of drug acquisition as being difficult. This difficulty was confirmed by the fact that a comparable proportion of patients had to visit more than five pharmacies to access drug supply and that many patients had to locate the drug outside their home region or the country.

The lack of access to ABZ has been recognized as a key problem by the WHO Informal Working Group on Echinococcosis.<sup>6</sup> Although CE is typically a benign condition and most patients are asymptomatic at the time of diagnosis,<sup>7</sup> medical treatment can be crucial, whether it is carried out as prophylaxis for secondary CE after invasive procedures or as a treatment.<sup>5,8</sup> Patients seen in our center and treated with medical therapy alone are prescribed ABZ for 3–6 months, with continuous administration, whereas patients who undergo surgery or percutaneous procedures receive a 1-month course as prophylaxis of secondary CE, which can be prolonged on the basis of ultrasound characteristics and percutaneous treatment type.<sup>13</sup>

The total cost of medical treatment of patients followed up in our center in the last 5 years was €92,592, using Italian market prices for ABZ. The Italian health system covers most of the costs of treatment, including medication costs, with younger, healthier, and wealthier individuals asked to cover part of their healthcare costs. Although CE is undoubtedly a chronic pathology requiring follow-up, even in the case of inactive cysts,<sup>5,14</sup> only the Piedmont region of Italy exempts patients

from paying all CE-related expenses. Interestingly, Piedmont is not a highly endemic area for CE.

This study is part of a continuing effort to assess the burden of CE on health systems. We have previously reported on the costs of surgery for CE, showing that an intervention has a mean cost of €11,003, with some surgeries resulting in much higher costs.<sup>35</sup> Albendazole can be used to treat patients who do not need surgery (Figure 1). However, overtreatment with surgery is a well-known problem for patients treated in non-referral centers.<sup>36</sup> Albendazole is also used for the prophylaxis of relapses and secondary CE after surgery or percutaneous procedures. The benefit of this practice has been shown in animal models.<sup>37</sup> As secondary CE can be severely disabling,<sup>38</sup> and relapses can require further surgeries, the cost of prophylactic ABZ can be justified by its long-term benefits.

The nonavailability of ABZ in Italy can seriously compromise the patients' treatment, as 23% of our cohort had to interrupt the treatment for this reason. This difficulty is compounded by the fact that ABZ cannot be prescribed in Italy as a continuous treatment without being considered an off-label prescription. When ABZ is not available in Italy, importing the drug can be problematic if prescribed for off-label usage because the AIFA has ruled that imported drugs cannot be prescribed for off-label usage.

In the absence of ABZ, MBZ can be prescribed to patients suffering from CE. However, MBZ has a less favorable bioavailability than ABZ because of its lower solubility in fat and it requires higher doses to achieve the same effect as ABZ. This is known to hamper treatment compliance. Furthermore, MBZ is not officially recognized as an anthelmintic drug in several countries.<sup>6</sup>

Unfortunately, no new drugs have been introduced to treat CE in the last three decades. Other drugs in the benzimidazole family have only been tested in animal models for their effect on *E. granulosus*.<sup>39,40</sup> Nitazoxanide has been used in the treatment of CE but only anecdotally and with unclear results.<sup>24,41</sup> Several other chemotherapeutic compounds, including extracts from plants have been tested in vitro or in vivo in animal models,<sup>42–44</sup> but even phase 1 clinical trials are not on the horizon. Albendazole remains the main drug for the treatment of this disease, and lack of availability poses serious problems to patients and physicians.

## CONCLUSIONS

Our study shows that the lack of access to ABZ disrupts the treatment of CE. This is especially concerning for patients in need of perioperative prophylaxis and those for whom benzimidazole treatment is a bridge to surgery. As a consequence, we believe that policymakers should acknowledge this problem, which impacts CE patients treated in both endemic and nonendemic areas.<sup>9,45</sup> Policymakers also need to officially recognize the continuous use of ABZ as a standard practice.

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