Update/Le point

Guidelines for treatment of cystic and alveolar echinococcosis in humans*

WHO Informal Working Group on Echinococcosis[1]

Summarized in this article are recent experiences in the treatment of human cystic echinococcosis (CE) and alveolar echinococcosis (AE) of the liver caused by the metacestode stages of Echinococcus granulosus *and* E. multilocularis*, respectively. For CE, surgery remains the first choice for treatment with the potential to remove totally the parasite and completely cure the patient. However, chemotherapy with benzimidazole compounds (albendazole or mebendazole) and the recently developed PAIR procedure (puncture–aspiration–injection–re-aspiration) with concomitant chemotherapy offer further options for treatment of CE cases. Chemotherapy is not yet satisfactory; cure can be expected in about 30% of patients and improvement in 30–50%, after 12 months' follow-up.*

AE is generally a severe disease, with over 90% mortality in untreated patients. Radical surgery is recommended in all operable cases but has to be followed by chemotherapy for at least 2 years. Inoperable cases and patients who have undergone nonradical resection or liver transplantation require continuous chemotherapy for many years. Long-term chemotherapy may significantly prolong survival, even for inoperable patients with severe AE. Liver transplantation may be indicated as a life-saving measure for patients with severe liver dysfunction, but is associated with a relatively high risk of proliferation of intraoperatively undetected parasite remnants. Details of indications, contraindications, treatment schedules and other aspects are discussed.

Introduction

Human echinococcosis is a zoonotic infection caused by larval forms (metacestodes) of tapeworms of the genus *Echinococcus* found in the small intestine of carnivores. The eggs of these tapeworms excreted by carnivores may infect various species of natural intermediate host animals and humans. Among the four recognized species of *Echinococcus* (*20*), two are of special medical importance, — *E. granulosus* and *E. multilocularis* — causing cystic echinococcosis (CE) and alveolar echinococcosis (AE) in humans, respectively.

The annual incidence of AE is generally low in most of the endemic areas (0.03–1.2 per 100000 inhabitants) but in untreated or in inadequately treated patients mortality is >90% within 10–15 years of diagnosis (*1*, *2*, *17*). The annual incidence of CE can range from <1 to 220 per 100000 inhabitants in various endemic areas (*16*, *17*). The mortality rate (about 2–4%) from CE is lower than that from AE but it may increase considerably if medical treatment and care are inadequate (*1*, *2*).

* This article is based on the findings of two meetings of the WHO Informal Working Group on Echinococcosis, held in Besançon, 10 October 1992 (unpublished document WHO/CDS/VPH/93.118), and Al-Ain, United Arab Emirates, October 1994. The activities of the Working Group are coordinated by Dr Vuitton, Besançon, France, and Dr F.-X. Meslin, Division of Emerging Diseases, World Health Organization, Geneva, Switzerland. The participants at the meetings are listed below.

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Reprint No. **5696**

In view of the public health significance of CE and AE in many countries (*16, 17*), WHO initiated in 1981 a multicentre clinical study on the chemotherapy of human echinococcosis, because individual studies undertaken since 1977 had produced inconsistent results (*6, 7*).[a] Progress and problems in the treatment of human echinococcosis were discussed at two meetings by the WHO Informal Working Group on Echinococcosis (*9*).[b] The results of these discussions are presented here but it should be borne in mind that the efficacy and safety of some of the methods are not yet clearly defined and require further evaluation. Readers are referred for detailed information and scientific discussion to various published reviews and WHO reports (*1, 2, 8, 14–18, 20–24*).[a]

Cystic echinococcosis

In primary echinococcosis, metacestode cysts develop in various sites from oncospheres after ingestion of *E. granulosus* eggs. In secondary echinococcosis, larval tissue spreads from the primary site and proliferates after spontaneous or trauma-induced cyst rupture or after release of viable parasite material during invasive treatment procedures.

Organ localization

In primary echinococcosis, the metacestodes may develop in almost any organ. Most patients (up to 80%) have a single organ involved and harbour a solitary cyst, localized in approximately two-thirds of cases in the liver and in about 20% in the lungs. In each site cysts are surrounded by the host tissue (pericyst), encompassing the endocyst of metacestode origin. The endocyst consists of an outer acellular "laminated" layer, which is covered on its inner side by a multipotential germinal layer giving rise to the production of brood capsules and protoscolices. The central cavity of *E. granulosus* cysts is typically filled with clear fluid, which in "fertile" cysts contains brood capsules and protoscolices. In addition, "daughter" cysts of variable size are often present inside or outside the "mother" cysts.

[a] *Treatment of human echinococcosis. Report of an Informal WHO Meeting, 29 June–1 July 1981.* WHO unpublished document PDP/82.1, 1981.

[b] *Report of the WHO Working Group meeting on clinical medicine and chemotherapy of alveolar and cystic echinococcosis, Besançon, France, 10 October 1992.* Unpublished document WHO/CDS/VPH/93.118, 1992.

Course of infection

During the natural course of infection, the fate of *E. granulosus* cysts is variable. Some cysts may grow (average increase: 1–30 mm per year) and then persist without a noticeable change for many years; others may spontaneously rupture or collapse and can completely disappear. Spillage of viable protoscolices after spontaneous or traumatic cyst rupture or during interventional procedures, may result in secondary echinococcosis. Calcified cysts are not uncommon.

After an undefined and variable incubation period, infections may become symptomatic if active cysts exert pressure on adjacent tissue and induce other pathologic events. Usually, cysts do not induce clinical symptoms until they have reached a particular size; sudden onset of symptoms may be due to cyst rupture.

Diagnosis

The diagnosis of CE is based on clinical findings, morphological features detected by imaging techniques, and immunological as well as other laboratory tests.

Treatment

The following comments concern liver echinococcosis; only certain aspects of the treatment of cysts in other organs are mentioned. Currently, surgery remains the treatment that has the potential to remove cysts and lead to complete cure. However, the introduction of chemotherapy and of puncture–aspiration–injection–re-aspiration (PAIR) offers alternatives for treatment, especially for inoperable cysts and for cases with a high surgical risk. In order to make a rational decision, the risks and benefits, indications and contraindications must be considered for each case, based on the following principles and observations.

- Surgery

— *Indications.* Surgery is indicated for removal of large liver cysts with multiple daughter cysts; single liver cysts, situated superficially that may rupture spontaneously or as a result of trauma; cysts that are infected; cysts communicating with the biliary tree and/or exerting pressure on adjacent vital organs; and cysts in the lung, brain, kidney, bones, and other organs.

— *Contraindications.* Surgery is contraindicated, as defined for surgical procedures in general, i.e., patient refusing surgery, patient at the extremes of age, pregnant woman, patient with concomitant severe diseases (i.e., cardiac, renal or hepatic

diseases, diabetes, or hypertension). In addition, surgery is contraindicated in patients with multiple cysts, cysts that are difficult to access, dead cysts, either partly or totally calcified cysts, and in patients with very small cysts.

— *Choice of surgical technique.* Surgical procedures include radical surgery (total pericystectomy or partial hepatectomy); conservative surgery (open cystectomy with or without omentoplasty); or palliative surgery (simple tube drainage of infected cysts or communicating cysts). The more radical the intervention, the higher the operative risk but with the likelihood of fewer relapses, and *vice versa*. With the inclusion of chemotherapy (see below), before or after surgery, it is possible to be less aggressive.

— *Choice of protoscolicides.* For intraoperative killing of protoscolices, there is no ideal protoscolicidal agent that is both effective and safe. The lethal action observed *in vitro* may be hampered *in vivo* by the instability of the substance used, e.g., hydrogen peroxide, or by an unpredictable dilution by hydatid fluid, and difficulties in penetrating daughter cysts. Potential communication between the hydatid cyst and the biliary tree substantially increases the safety requirements for using protoscolicides, which can cause chemical cholangitis leading to sclerosing cholangitis; formalin should therefore not be used. At present, the following protoscolicides are effective and have a relatively low risk of toxicity: 70–95% ethanol, 15–20% hypertonic saline, or 0.5% cetrimide solution. For optimal efficacy the substances have to be left in contact with the cysts for at least 15 minutes. More experimental studies and clinical observations are urgently needed to evaluate the efficacy and safety of individual protoscolicides.

— *Concomitant drug treatment.* Preoperative treatment with benzimidazoles has been reported to soften the cysts, thus reducing intracystic pressure, enabling the surgeon to remove the endocyst more easily. However, neither the required duration of such treatment nor its efficacy has been adequately determined. Preoperative chemotherapy with albendazole (ABZ) or mebendazole (MBZ) (for dosages, see below) may be indicated to reduce the risk of secondary echinococcosis and should begin at least 4 days before surgery and last for 1 month (ABZ) or 3 months (MBZ).

— *Benefits.* Radical surgery has the potential to cure completely the patient, but involves some perioperative risks.

— *Risks.* The risks include those associated with any surgical intervention (anaesthesia, stress, and infections, including those transmitted by blood transfusion, e.g., hepatitis, human immunodeficiency virus (HIV)); anaphylactic reactions; secondary echinococcosis owing to spillage of viable parasite material (2–25% of cases); and possible recurrence, if other cysts are present. Operative mortality varies from 0.5% to 4%, but may be higher if surgical and medical facilities are inadequate.

— *Medical requirements.* The medical staff must have experience in treating cystic echinococcosis. Hospitalization of patients is needed as well as an adequately equipped surgical ward. The costs of intervention and postoperative medical care may be considerable.

• PAIR

Ultrasound-guided cyst puncture, which was introduced in 1986 (*3*, *10*, *11*), has diagnostic and therapeutic potential; however, diagnostic puncture should only be used if other diagnostic methods have failed.

PAIR for treatment of CE includes the following: percutaneous puncture of cysts using ultrasonic guidance; aspiration of substantial amounts of cyst fluid; injection of protoscolicidal substances (20% sodium chloride solution or, better, 95% ethanol) for at least 15 minutes; and re-aspiration of the fluid cyst content. Favourable results have been reported from more than 500 PAIR interventions over a follow-up period of up to 5 years (*3*, *10*, *11*, *23*). However, the efficacy and potential risks of PAIR have not yet been fully evaluated and require further properly controlled long-term studies. PAIR should be accompanied by chemotherapeutic coverage to minimize risks of recurrence (see below).

— *Indications.* PAIR is indicated for inoperable patients (see contraindications for surgery) and those who refuse surgery. It has been used in the treatment of *Echinococcus* cysts in the liver and of cysts in the abdominal cavity, spleen, kidney and bones, but should not be used for lung cysts (*11*). The following types of liver cysts may be selected for PAIR: anechoic lesions >5-cm diameter; cysts of types I and II, as classified by Gharbi et al. (*12*); cysts with a regular double laminated layer; cysts of >5-cm diameter with multiple septal division (Gharbi type III) except honeycomb-like cysts; multiple cysts 5-cm diameter in different liver segments (Gharbi types I, II and III) (*12*). PAIR can also be used in cases of relapse after surgery or in failure to respond to chemotherapy. Experience using

the technique on pregnant women and children aged <3 years is still limited; it might be indicated for pregnant women with symptomatic cysts but the risk associated with peri-interventional benzimidazole treatment has to be carefully assessed since benzimidazoles are contraindicated during pregnancy, notably during the first 3 months.

— *Contraindications.* PAIR is contraindicated for inaccessible or superficially located liver cysts (in the latter there is a risk of spillage of cyst content into the abdominal cavity); in multiple septal divisions of cysts (honeycomb-like cysts); for cysts with echogenic lesions; inactive cysts or calcified lesions; communicating cysts; and lung cysts. In order to avoid the induction of chemical cholangitis, aspirates from the cysts should be analysed for traces of bilirubin prior to injection of protoscolicides. If the cyst content is contaminated with bile, which indicates that there is direct communication with the biliary ducts, there is a high risk of sclerosing cholangitis after injection of protoscolicidal substances.

— *Concomitant drug treatment.* Four days of treatment with benzimidazoles before PAIR is mandatory and should last for 1 month (albendazole) or 3 months (mebendazole) after the procedure.

— *Benefits.* PAIR is minimally invasive and less risky than surgery. It confirms the diagnosis and removes a large number of protoscolices and antigens with the aspirated cyst fluid. The cost of puncture and chemotherapy may be less than that of surgery (fewer days of hospitalization are needed).

— *Risks.* The risks include those associated with any puncture (haemorrhage, mechanical damage of other tissues, infections); anaphylactic shock or allergic reactions caused by leakage of cyst fluid; and secondary echinococcosis due to spillage. Transhepatic cyst puncture is strongly advised since puncture of superficially located cysts involves a higher risk of spillage. Other potential risks are chemical sclerosing cholangitis, sudden intracystic decompression leading to biliary fistulas, and persistence of satellite daughter cysts.

— *Medical requirements.* PAIR should only be performed by experienced physicians and a surgical back-up team well-prepared to deal with complications.

• Chemotherapy

Over 1000 well-documented cases of cystic echinococcosis have been treated with benzimidazoles, to date. When evaluated up to 12 months, 30% of patients show cyst disappearance (cure), 30–50% show degeneration of cysts and/or significant size reductions (improvement), but 20–40% exhibit no morphological changes of cysts (i.e., failure). Chemotherapy is apparently more effective among young rather than older patients. Small cysts that have a thin wall without infection or communication, as well as secondary cysts (even when multiple) are mostly susceptible to chemotherapy; chemotherapy may, however, be less effective for thin-walled daughter cysts within a mother cyst. Some of the treated patients exhibit relapses but these are sensitive to retreatment in a high proportion of cases (up to 90%).

— *Indications.* Chemotherapy is indicated for inoperable patients with primary liver or lung echinococcosis and for patients with multiple cysts in two or more organs and peritoneal cysts. Cysts localized in bones are less susceptible to chemotherapy. Another important indication for chemotherapy is the prevention of secondary echinococcosis. The pre-surgical use of benzimidazoles (ABZ or MBZ) can reduce the risk of re-occurrence of CE and/or facilitate the operation by reduction of intracystic pressure. Concomitant chemotherapy is also recommended for PAIR.

— *Contraindications.* Chemotherapy is contraindicated for large cysts that have a risk of rupture (notably those superficially situated, infected cysts) and for inactive or calcified cysts. Patients with chronic hepatic diseases and with bone marrow depression should not be treated. Early pregnancy is a contraindication, and chemotherapy during the later stages of pregnancy is rarely strongly indicated.

— *Choice of anthelmintics* (see also, alveolar echinococcosis and Annex). Two benzimidazoles (albendazole (ABZ) (Eskazole®, SmithKline Beecham, England) and mebendazole (MBZ) (Vermox®, 500 mg, Janssen Pharmaceutica, Belgium) have been evaluated using animal models and used on over 1000 patients. These drugs show (mostly partial) efficacy against CE and AE, and are generally well tolerated.

For treatment of CE the usual oral dosage of albendazole is 10–15 $mg.kg^{-1}.day^{-1}$ in several 1-month courses separated by 14-day intervals. Three courses are routinely suggested, and more than six are usually not necessary. Cyclic treatment with intervals of 14 days was originally recommended, but new data on continuous treatment from China, Japan, and Italy show that this approach has better efficacy over

3–6 months or longer with no increase in adverse effects. The usual oral dosage of mebendazole is 40–50 mg per kg per day for at least 3–6 months. Animal experiments have shown that the efficacy of mebendazole against *Echinococcus* metacestodes is positively correlated with serum drug concentration and the duration of treatment. In humans the serum drug levels of MBZ and ABZ may vary widely in individual patients, and correlation with efficacy is inconsistent. Drug dosing in conjunction with a fat-rich meal improves intestinal absorption.

Use of praziquantel (PZQ), an isoquinoline derivative, has been proposed at a dose of 40 mg/kg once a week concomitantly with benzimidazoles. PZQ might also be useful in cases of operative spillage; however, the rationale for such treatment needs confirmation since available data are very limited.

— *Benefits.* Chemotherapy is a noninvasive treatment that can be used on patients of any age (although there is little experience with under-6-year-olds) and is less limited by the patient's status (except pregnancy) than surgery.

— *Risks.* The adverse effects of benzimidazoles include hepatotoxicity (transient increase of aminotransferases) (*19*, and Annex), neutropenia, thrombocytopenia and alopecia. The potential risks of benzimidazoles include embryotoxicity and teratogenicity, which, however, have only been observed in some laboratory animals during the early stages of pregnancy.

— *Medical requirements.* Hospitalization is not necessary, but regular follow-up examinations are required. The costs of anthelmintics and repeated medical examinations may be considerable.

— *Monitoring of patients.* Medical and laboratory examinations for adverse reactions are necessary initially every 2 weeks then monthly. Leukocyte counts should be checked at 2-week intervals during the first 3 months because in rare instances severe and not always reversible leukopenia has been observed in the early phases of chemotherapy. Serum drug concentrations (ABZ-sulfoxide or MBZ parent compound) should be monitored after 2 weeks and 4 weeks of chemotherapy, respectively, in order to identify levels that are too high (possibly toxic) or too low (ineffective). For MBZ it has been recommended that serum or plasma levels be determined 4 hours after the morning dose. Oral drug doses can be adapted to individual patients in order to achieve adequate serum levels (see Annex), but such attempts are frequently unsuccessful. Only a few laboratories have the capability to determine ABZ-sulfoxide or MBZ serum drug levels (see also section on alveolar echinococcosis). Chemotherapy has to be applied over a prolonged period of time and its efficacy requires evaluation every 3 months. Each follow-up visit should include an imaging examination.

— *Treatment of CE cases detected at screening.* For ethical reasons mass screening should not be undertaken without the consent of the population involved and a clear idea of the medical attention to be offered to persons with a suspected diagnosis of echinococcosis. These persons should be offered further clinical and serological examinations to confirm the diagnosis and to select those who may need treatment. Those infected who do not qualify for immediate treatment should be carefully monitored.

Alveolar echinococcosis

Alveolar echinococcosis is a very serious disease caused by the metacestode of *E. multilocularis* and is characterized by a tumour-like, infiltrative growth. Treatment of AE involves a variety of options, including chemotherapy, and requires specific clinical experience. Therefore, patients should be referred to recognized national/regional AE treatment centres. Early diagnosis is of special importance for successful treatment since population screening programmes for AE in endemic areas of Japan and elsewhere have clearly shown that early diagnosis reduces morbidity and mortality.

Organ localization

Initially, metacestodes of *E. multilocularis* develop almost exclusively in the liver. The right lobe is predominantly infected, but the liver hilus together with one or two lobes may also be involved. Parasitic lesions in the liver can vary from small foci of a few mm in diameter to large areas of infiltration (15–20 cm or more in diameter). Primary extrahepatic localizations of *E. multilocularis* metacestodes are extremely rare. From the liver, the metacestode tends to spread to other organs by infiltration or metastasis formation. Until recently it was believed that the metacestode of *E. multilocularis* usually retains an unlimited proliferative capacity until the death of the patient; however, under the influence of the host's defence mechanisms, the metacestode can degenerate, calcify, and finally die. Therefore, spontaneous cure of AE is possible but its frequency is not known.

Course of infection

Cases of AE are characterized by an inital asymptomatic incubation period of at least 5–15 years and a subsequent chronic course. The symptoms are primarily cholestatic jaundice (about a third of cases) and/or epigastric pain (about a third of cases). AE is detected in the remaining third of patients incidentally during medical examination for symptoms such as fatigue, weight loss, hepatomegaly, or abnormal routine laboratory findings. Mortality among untreated or inadequately treated persons is high. In a series of 66 individuals with AE in the Federal Republic of Germany (period, 1960–1972), 70% died within 5 years and 94% within 10 years of being diagnosed. According to recent data from Alaska, in 21 untreated persons the average survival time after diagnosis was 5.3 years, and all patients died within 14 years (*1*, *2*, *25*).

Diagnosis

Diagnosis of AE is based on the following: clinical findings and epidemiological data; lesion morphology reviewed by imaging techniques; and immunological and other laboratory tests.

Treatment

The following principles are now commonly accepted for the treatment of AE.

— The first choice in all operable cases is radical surgical resection of the entire parasitic lesion from the liver and other affected organs.

— Chemotherapy for a limited period of time is indicated after radical surgery.

— Long-term chemotherapy is mandatory after incomplete resection of the lesions, in inoperable patients (including cases after interventional procedures) and in AE patients after liver transplantation (for further details see below).

• Surgery

Excision of the parasitic lesion has been carried out using the procedures of radical tumour surgery. Radical or nonradical surgery and liver transplantation require concomitant chemotherapy, as discussed.

— *Indications*. Resectability of the parasitic lesion in the liver is a prerequisite for radical surgery and must be assessed by imaging techniques before the operation.

— *Contraindications*. Inoperable lesions, extensive lesions, and lesions not confined to the liver and involving other organs must be managed using alternative therapies following interdisciplinary consultation.

— *Benefits*. Radical surgery may eliminate the parasites and cure the patient. An early diagnosis of AE can improve prospects for complete cure. Nonradical surgery is regarded as beneficial for reducing the parasite mass and for increasing the chances of effective chemotherapy.

— *Risks*. Lesions cannot always be clearly defined by imaging techniques; incomplete resection leaves invisible remnants of parasitic tissue with a potential of regrowth and dissemination into other organs, even after years. General risks may be associated with surgical intervention (anaesthesia, stress, etc.), immunosuppression, infections (including those transmitted by blood transfusion) or other factors.

— *Medical requirements*. Hospitalization in a surgical ward is mandatory. The surgical team should be experienced in major liver surgery and in treating AE.

• Chemotherapy

Extensive studies in animals have demonstrated the significant parasitostatic efficacy of benzimidazoles against the metacestode stage of *E. multilocularis*, and based on this, chemotherapy of AE in human patients has been practised since 1975. Comparison of the survival of patients on chemotherapy with that of untreated historical controls shows that the 10-year survival rate of the treated group has increased from <10% to 85–90% (*1*, *2*, *8*, *25*). Increased survival rates might not only be associated with chemotherapy but also with early diagnosis, improved surgery, and medical care of the patients (*26*).

— *Indications*. There are several indications for chemotherapy. 1) Chemotherapy is indicated for a limited time after radical surgery. Since residual parasite tissue may remain undetected at radical surgery, post-operative chemotherapy for at least 2 years should be carried out and patients should be monitored for a minimum of 10 years for possible recurrence. 2) Long-term chemotherapy for several years is mandatory in inoperable AE patients, following incomplete surgical resection of the parasite lesions and after liver transplantation. 3) Presurgical chemotherapy is not indicated for AE. However, in cases for whom surgery was contraindicated at the time of diagnosis, surgery can be carried out after a prolonged course of chemotherapy.

— *Contraindications.* In view of the severity of AE and the relatively low toxicity of the drugs currently used (mebendazole or albendazole), there are only a few contraindications for chemotherapy. In some instances (e.g., pregnant women) certain precautions and limitations or modifications of drug administration are necessary (see Annex).

— *Choice of anthelminthics.* Two benzimidazoles (mebendazole and albendazole) are preferentially used for chemotherapy of AE (see Annex).

Mebendazole (Vermox®, 500 mg, Janssen, Belgium) is given as 500-mg tablets in daily doses of 40–50 mg/kg body weight (in three divided doses postprandially). After an initial continuous treatment of 4 weeks it is advisable to adjust the oral doses in order to obtain plasma drug levels of >250 nmol/l (74 ng/ml). In special situations the dose may be higher than the recommended amount, but a daily dose >6 g per adult patient should not be given. The duration of treatment is at least 2 years after radical surgery, or continuously for many years in inoperable cases, as well as for patients who have undergone incomplete resection or liver transplantation. For some patients, mebendazole has been administered for more than 11 years (*1*).

Albendazole (Eskazole®, SmithKline Beecham, England) is given as 500-mg tablets in daily doses of 10–15 mg/kg (in two divided doses). Repeated cycles of 28 days should be followed by a "wash out" phase of 14 days as recommended by the manufacturer. The number of necessary cycles has not yet been determined, and it is not known whether this drug can be given over periods of several years. Data from 11 Chinese patients indicate that continuous treatment with 20 mg/kg body weight per day (divided into two doses) for 1–5 years is well tolerated (*13*).

Praziquantel has been used for the treatment of human AE, but experimental data obtained from animal models indicate that its efficacy against the metacestode stage of *E. multilocularis* is far less pronounced than that of albendazole or mebendazole, even if it is given in very high doses.

— *Benefits of benzimidazole treatment.* This is a noninvasive treatment with a relatively low toxicity. However, in most patients, benzimidazoles are only parasitostatic.

— *Risks of benzimidazole treatment.* The main risks are neutropenia, alopecia, and liver dysfunction. Because of the potential embryotoxicity and teratogenicity (only observed in laboratory animals), such treatment should not be used in women of child-bearing age, unless contraceptive measures are taken, and during the early stages of pregnancy (see Annex).

— *Medical requirements.* Hospitalization is not needed but regular medical and laboratory checks for adverse reactions and efficacy are necessary. The costs of anthelmintics and of repeated medical examinations are high.

— *Monitoring of patients.* In the initial phase, monitoring of AE patients is similar to that of CE patients. Subsequently, routine haemograms, serum transaminase determinations, other laboratory tests, and ultrasound imaging of the liver should be performed at intervals of 3 months. At intervals of 6–12 months the patients should be examined in a clinical reference centre where special imaging techniques, e.g., computer-assisted tomography, can be used to monitor parasitic lesions and their response to chemotherapy. A long-term follow-up of more than 10 years is recommended.

• Interventional procedures

With AE patients for whom surgery is contraindicated, a number of local complications may occur for which interventional procedures have to be considered. Dilatation and stent implantation in vessels, drainage of necrotic liver lesions and/or bile, and endoscopical sclerosing of oesophageal varices are the main interventional ultrasound or endoscopically guided procedures performed in AE. In conjunction with chemotherapy, these procedures can be beneficial for patients.

— *Indications.* Interventional procedures are indicated if surgery is inadvisable because of disturbances of essential organ functions, i.e., hyperbilirubinaemia due to cholestasis, vena cava, or portal vein thrombosis, colliquative liver necrosis with risk of rupture into the abdomen, and bleeding of oesophageal varices secondary to portal hypertension.

— *Contraindications.* Interventional procedures have the potential to spread parasite material and are not indicated if post-interventional chemotherapy is not possible.

— *Benefits.* Inclusion of interventional procedures together with chemotherapy as options for treatment can improve the life expectancy and quality of life of patients with AE.

• Liver transplantation

Liver transplantation has been carried out in approximately 20 patients with inoperable AE and chronic liver failure (*4*). Recent experience shows that regrowth of metacestode remnants and for-

mation of distant metastases may occur under immunosuppression (*5*).

— *Indications*. Liver transplantation may be indicated, following interdisciplinary consultation, in severe AE with chronic liver failure; it requires long-term post-operative chemotherapy.

— *Contraindications*. Liver transplantation is not indicated in extensive AE that is not confined to the liver or for patients with contraindications for prolonged immunosuppressive treatment and/or concomitant benzimidazole treatment.

— *Benefits*. Liver transplantation can be a lifesaving procedure for patients with severe liver dysfunction.

— *Risks*. These include general surgical risks, specific risks of long-term immunosuppressive treatment, and induction of proliferation of metacestode remnants and metastases formation (particularily in the brain) under immunsuppression.

— *Medical requirements*. Liver transplantation requires a highly specialized team and equipment. Supportive medical care includes post-transplantation clinical observation, adaptation of immunosuppressive drugs, and diagnosis and management of complications of immunosuppressive treatment under continuous chemotherapy with benzimidazoles.

Acknowledgements

We are grateful to many colleagues in various countries who have supported experimental and clinical studies on the treatment of echinococcosis and to WHO for coordination activities. Janssen Pharmaceutica, Beerse, Belgium, and SmithKline Beecham, Brentford, Middlesex, England, are thanked for providing considerable amounts of drugs free of charge.

Résumé

Directives pour le traitement de l'échinococcose cystique et alvéolaire chez l'homme

L'échinococcose humaine est une zoonose due aux formes larvaires (métacestodes) de ténias appartenant au genre *Echinococcus*, qui parasitent l'intestin grêle des carnivores. Les oeufs de ces vers, excrétés par les carnivores, peuvent infester diverses espèces d'hôtes intermédiaires naturels, dont l'homme. Deux espèces d'importance médicale particulière, *E. granulosus* et *E. multilocularis*, provoquent respectivement l'échinococcose cystique et l'échinococcose alvéolaire chez l'homme. Etant donné l'importance de ces maladies en santé publique dans un grand nombre de pays, deux réunions du groupe de travail informel OMS sur l'échinococcose ont fait le point sur leur traitement. On en trouvera ci-dessous les principales conclusions.

Echinococcose cystique

Dans l'échinococcose primaire, les métacestodes peuvent se développer dans pratiquement n'importe quel organe. La plupart des malades (jusqu'à 80%) n'ont qu'un organe touché et hébergent un kyste unique, localisé dans le foie dans environ les deux tiers des cas, et dans les poumons chez environ 20% des cas.

Traitement chirurgical. Ce traitement permet l'exérèse des kystes et la guérison totale. Il existe toutefois des solutions alternatives, telles que la chimiothérapie et la technique PAIR (ponction-aspiration-injection-réaspiration) notamment pour les kystes inopérables et les cas à haut risque chirurgical. Le traitement chirurgical est indiqué dans les cas suivants: kystes hépatiques de grande taille avec nombreuses vésicules filles; kystes hépatiques uniques, de localisation superficielle et susceptibles de se rompre spontanément ou à la suite d'un traumatisme; kystes infectés; kystes communiquant avec l'arbre biliaire et/ou exerçant une pression sur les organes vitaux voisins; kystes situés dans les poumons, le cerveau, les reins, les os et autres organes. Le traitement chirurgical est contre-indiqué chez les malades porteurs de kystes multiples, de kystes difficiles d'accès, de kystes morts, de kystes partiellement ou entièrement calcifiés, et de kystes de très petite taille.

Plus l'intervention chirugicale est radicale, plus le risque opératoire est élevé, mais plus le risque de rechute est faible. Pour la destruction intra-opératoire des protoscolex, il n'existe pas de protoscolicides à la fois efficaces et sans danger, mais des produits comme l'éthanol à 70–95%, le soluté hypertonique à 15–20% ou une solution de cétrimide à 0,5% sont efficaces et relativement peu toxiques. Le traitement préopératoire par des benzimidazoles ramollit les kystes, ce qui entraîne une baisse de la pression intrakystique et facilite l'évacuation chirurgicale de l'endokyste.

PAIR. L'utilisation de la PAIR pour traiter l'échinococcose cystique comporte les étapes suivantes: ponction des kystes par voie percutanée, sous guidage échographique; aspiration d'une quantité

importante de liquide hydatique; injection de substances protoscolicides (solution de chlorure de sodium à 20% ou mieux d'éthanol à 95%) pendant au moins 15 minutes; réaspiration du contenu du kyste. Cette technique est indiquée pour les malades inopérables et ceux qui refusent l'intervention chirurgicale, et peut être utilisée pour le traitement des kystes localisés dans le foie, la cavité abdominale, la rate, les reins et les os. Elle peut aussi être utilisée en cas de rechute après traitement chirurgical ou en cas d'échec de la chimiothérapie, mais est contre-indiquée lorsque les kystes hépatiques sont inaccessibles ou superficiels et en cas de kystes cloisonnés. Un traitement de quatre jours par les benzimidazoles est obligatoire avant toute PAIR et doit être poursuivi pendant un mois (albendazole) ou 3 mois (mébendazole) après l'intervention. Cette technique est très peu invasive et comporte moins de risques que la chirurgie.

Chimiothérapie

Plus de 1000 cas bien documentés d'échinococcose cystique ont été traités jusqu'à présent par les benzimidazoles. La chimiothérapie est indiquée pour les malades inopérables présentant une échinococcose primaire du foie ou du poumon et pour les porteurs de kystes multiples dans deux ou plusieurs organes, et de kystes péritonéaux. La chimiothérapie est également indiquée dans la prévention de l'échinococcose secondaire. L'utilisation préchirurgicale des benzimidazoles (ABZ et MBZ) peut réduire le risque de rechute de l'échinococcose cystique et/ou faciliter l'intervention en abaissant la pression intracystique. Comme on l'a vu, une chimiothérapie concomitante est également recommandée avec la technique PAIR. La chimiothérapie est contre-indiquée en cas de kystes de grande taille présentant un risque de rupture (principalement les kystes superficiels et infectés) et en cas de kystes inactifs ou calcifiés. Le début de grossesse constitue également une contre-indication.

Pour le traitement de l'échinococcose cystique, la dose habituelle d'albendazole est de 10–15 mg/kg par jour en plusieurs cures d'un mois séparées par un intervalle de 14 jours. Toutefois, le traitement continu est plus efficace lorsqu'il est administré sur trois à six mois ou plus, et n'entraîne pas plus d'effets indésirables. La dose orale habituelle de mébendazole est de 40 à 50 mg/kg par jour.

Les effets indésirables des benzimidazoles consistent en hépatotoxicité, neutropénie, thrombocytopénie et alopécie et leur utilisation comportent des risques potentiels d'embryotoxicité et de tératogénicité. Il est nécessaire de procéder à un examen médical et à des analyses de laboratoire pour rechercher ces effets, toutes les deux semaines en début de traitement puis une fois par mois.

Echinococcose alvéolaire

L'échinococcose alvéolaire est une maladie très grave due aux métacestodes d'*E. multilocularis* et se caractérise par une croissance infiltrante évoquant une tumeur. Le traitement comporte plusieurs options, dont la chimiothérapie, et exige une expérience clinique spécifique. Au début, les métacestodes d'*E. multilocularis* se développent presque exclusivement dans le foie, puis ils tendent à gagner les autres organes par infiltration ou formation de métastases.

Les cas d'échinococcose alvéolaire se caractérisent par une incubation silencieuse durant au moins 5 à 15 ans, puis évoluent sur le mode chronique. Les principaux symptômes consistent en ictère cholestatique et/ou douleurs épigastriques. Non traitée ou insuffisamment traitée, la maladie entraîne une forte mortalité.

Le traitement de l'échinococcose alvéolaire repose actuellement sur les principes généraux suivants:

- La première option, dans tous les cas opérables, est l'exérèse chirurgicale radicale de la lésion parasitaire dans le foie et les autres organes touchés.

- Une chimiothérapie de durée limitée est indiquée après exérèse radicale. En revanche, une chimiothérapie préchirurgicale n'est pas indiquée dans le cas de l'échinococcose alvéolaire.

- Une chimiothérapie de longue durée est obligatoire après exérèse incomplète des lésions, chez les malades inopérables et chez les malades ayant subi une transplantation hépatique.

Chimiothérapie. Le mébendazole est administré en comprimés dosés à 500 mg à raison de doses quotidiennes de 40–50 mg/kg de poids corporel (réparties en 3 prises, après les repas). Après traitement initial continu de quatre semaines, il est conseillé d'ajuster les doses orales afin d'obtenir un taux plasmatique >250 nmol/l (74 ng/ml). Le traitement doit être poursuivi pendant au moins deux ans après exérèse radicale, et en continu pendant un grand nombre d'années dans les cas inopérables.

L'albendazole est administré en comprimés dosés à 500 mg en doses quotidiennes de 10–15 mg/kg (en deux prises). Chaque cycle de traitement de 28 jours sera suivi d'une phase

d'élimination de 14 jours, comme le recommande le fabricant. Le nombre de cycles nécessaires n'a pas encore été déterminé. Au début du traitement, la surveillance des malades est identique à celle des cas d'échinococcose cystique. Tous les six à douze mois, les malades seront examinés dans un centre de référence clinique, au moyen de techniques d'imagerie spécialisées.

Chirurgie. La lésion parasitaire devra être excisée suivant les techniques de l'exérèse radicale des tumeurs. Que l'exérèse soit radicale ou non, une chimiothérapie concomitante est indispensable.

Il n'est pas toujours possible de définir clairement les lésions par les techniques d'imagerie. Une résection incomplète laisse des fragments invisibles de tissus parasitaires susceptibles de se développer à nouveau et de se disséminer dans les autres organes, parfois au bout de plusieurs années.

Transplantation hépatique. La transplantation hépatique peut être indiquée dans les cas graves d'échinococcose alvéolaire avec insuffisance hépatique chronique. Elle exige une chimiothérapie postopératoire de longue durée. Elle n'est pas indiquée en cas d'échinococcose alvéolaire étendue, non limitée au foie, et chez les malades pour lesquels un traitement immunodépresseur prolongé et/ou un traitement concomitant par le benzimidazole sont contre-indiqués. La transplantation hépatique exige une équipe chirurgicale et un matériel hautement spécialisés.

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Annex

Characteristics of benzimidazoles

• Mebendazole is poorly absorbed (<10%) after oral administration. The rate of absorption is increased (up to 8-fold) if the drug is taken during a meal, especially one with a high fat content. After oral administration of standard doses, serum drug levels are highly variable among individuals and are not correlated with the doses given. In blood plasma >90% of the drug is protein-bound. Based on data from animal experiments, the serum drug concentrations required for effective chemotherapy are estimated to be >250 nmol/l (74 ng/l). However, several studies have shown that such serum levels may not be attained by more than 30% of patients and that lower (as yet undetermined) levels may be sufficient for long-term therapy. Mebendazole is rapidly metabolized in the liver and excreted via urine and bile. The elimination half-life times are short (2.5–5.0 h) and may be increased in patients with cholestasis and other disturbances of liver function. Serum mebendazole concentrations 4 h after the morning dose have a high degree of predictability for the 24-h average serum concentrations, and the 4-h value has therefore been proposed for monitoring serum drug levels.

• Albendazole has similar pharmacokinetic properties to mebendazole with low absorption rates and high interindividual variability of serum drug levels that may lie in the range 200–6000 nmol/l; average values are 1000–2000 nmol/l (albendazole sulfoxide). Serum drug levels are higher in patients with cholestasis and other liver dysfunctions, and intestinal absorption rates are increased by fatty substances. The mean half-life elimination time in 14 persons was 8.5 h (SD, 6.0). The effective serum drug levels are not well defined; based on data from animal experiments, they are estimated to be 650–3000 nmol/l.

• Drug efficacy. MBZ and the main metabolite of ABZ, albendazole sulfoxide, have antiparasitic properties.

Animal experiments have shown that long-term treatment with benzimidazoles has the following effects against *E. multilocularis* metacestodes: inhibition of metacestode proliferation, resulting in reduction of parasite masses; destruction of protoscolices and partial destruction of the germinal layer and of the cystic structure of the metacestode; prevention or suppression of metastasis formation; calcifications; and prolongation of host animal survival.

Long-term animal studies have shown that *E. multilocularis* metacestodes are normally not killed by drug treatment but that their proliferation is inhibited. The effect of the drugs in animals is therefore not parasiticidal but parasitostatic. On the other hand, *E. granulosus* cysts may be killed by long-term benzimidazole treatment.

• Adverse reactions. MBZ and ABZ are generally well tolerated and adverse reactions are relatively mild. Examples of such reactions from two larger series are presented below.

— Adverse reactions in 70 patients with alveolar echinococcosis under long-term chemotherapy (mean duration, 6.5 years. No. of patients treated: MBZ: 61, ABZ: 4, MBZ/ABZ: 5) (*1*): elevation of transaminases (27%); proteinuria (21%); loss of hair (18%); gastrointestinal disturbances (16%); neurological symptoms (e.g., vertigo) (11%); and leukopenia (6%).

— Adverse reactions associated with albendazole treatment of 780 patients with cystic echinococcosis. (The duration of treatment is generally shorter than that for alveolar echinococcosis (J. Horton, personal communication, 1994): elevation of transaminases (14.7%); abdominal pain (5.7%); loss of hair (2.8%); headache (2.1%); abnormal liver biopsy (1.7%); vertigo/dizziness (1.3%); nausea (1.3%); fever (1.2%); reversible leukopenia (1.2%); abdominal distension (0.6%); urticaria (0.5%); jaundice (0.5%); thrombocytopenia (0.3%); allergic shock (0.3%); bone marrow toxicity (0.1%); and cyst pain (0.1%).

Two-thirds of the patients experienced one or more side-effects, but they were mostly of minor importance and reversible. Only in rare instances was permanent discontinuation of chemotherapy indicated. Allergic reactions may also occur. Monitoring of serum drug levels is mandatory to avoid severe adverse reactions.

• Precautions. Patients with CE or AE under chemotherapy should be carefully monitored.

• Pregnancy and nursing. Under certain conditions MBZ and ABZ may induce embryotoxic or teratogenic effects in animals. Although such effects have not been observed in humans, it is recommended that use of these drugs be avoided for pregnant women, to postpone chemotherapy until after delivery, or to use the drugs only in urgent cases in the second or third trimester after a careful risk analysis. For women of child-bearing age, contraceptive measures are indicated during treatment. Experience with MBZ or ABZ treatment during breast-feeding does not appear to put the infant at risk of side-effects.

• Liver disturbances. For patients with cholestasis or hepatocellular disturbances, the drug doses may have to be reduced. Such patients require frequent monitoring of liver function parameters and of serum drug levels, especially those with chronic cholestasis and portal hypertension.

• Diabetes. Mebendazole may reduce insulin requirements; therefore, the serum glucose bood levels of diabetics receiving this drug must be carefully monitored.