# REPORT OF THE WHO WORKING GROUP MEETING ON CLINICAL MEDICINE AND CHEMOTHERAPY OF ALVEOLAR AND CYSTIC ECHINOCOCCOSIS

**Besançon, France, 10 October 1992**

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INTRODUCTION

Professor D.A. Vuitton, University of Besançon, France, and host of the meeting, welcomed the group (Annex I). She noted the considerable progress that had been achieved in recent years on diagnosis and treatment of echinococcosis and indicated her wish for the group to reach a consensus on the current states of the art. Professor J. Eckert, University of Zurich, Switzerland, reviewed the historical involvement of WHO in these activities and indicated that the WHO guidelines and protocol for treatment require review and revision.

Dr. T. Fujikura, Veterinary Public Health, WHO, opened the meeting on behalf of the Director-General of WHO and defined its aims which were to:

1. review progress on medical aspects and chemotherapy of echinococcosis since 1990;
2. develop recommendations for further collaborative research on clinical medicine and chemotherapy in echinococcosis.

Professor Eckert was elected Chairman and Professor Pawlowski, Vice-chairman. Dr P. Schantz served as Rapporteur.

Members of the working group reviewed papers contributed to the meeting as well as published data related to indications for treatment, selection of drugs, and methods for monitoring patients and evaluating efficacy.

1. ALVEOLAR ECHINOCOCCOSIS

1.1 General considerations

Alveolar echinococcosis is a very serious disease, which always has a guarded prognosis, but whose management now involves a variety of options, including chemotherapy. Management is complex and requires specific clinical experience. Cases should be referred to national/regional treatment centres with recognized experience in this field.

Early diagnosis significantly improves prognosis of the disease. In highly disease-endemic areas, serological or ultrasound screening for alveolar echinococcosis may be justified based on their value for reducing complications, morbidity and mortality (see also section 3).

1.2 Indications for chemotherapy

The first choice of treatment is surgical resection of the entire parasitic lesion: radical resection provides the best probability for complete cure of the disease. In cases of early diagnosis of isolated small lesions the prognosis for surgery is good, with negligible probability for recurrence. In cases that are inoperable or when resection is incomplete or partial, or in cases where there are metastases to the brain or lungs, surgery should be followed by chemotherapy. In cases of any doubt concerning the possibilities of residual larval tissue, surgery should be followed by chemotherapy to prevent recurrence. In some countries, post-operative chemotherapy for 2 years is routinely carried out after radical resection, with careful monitoring of the patient during a minimum ten years for possible recurrence. Pre-surgical chemotherapy is not indicated in alveolar echinococcosis.
1.3 Selection of drugs

Both mebendazole and albendazole have shown similar efficacy for inhibiting parasite proliferation, prevention of metastases, and prolongation of survival in animal models. In clinical trials with patient follow-up of many years, mebendazole has inhibited progression of alveolar echinococcosis and reduced lesion size in approximately 45 percent of cases. Treatment has enhanced the length and quality of survival in patients. The results of treatment of patients with albendazole have produced similar results; however, the number of patients treated and the length of follow-up has been less than for mebendazole. In most cases, chemotherapy with neither drug was parasiticidal; however, there are some indications that parasite death may occur after treatment of many years. No other drugs have been evaluated yet, and new, proposed drugs must be evaluated for safety and efficacy in recommended animal models.

Praziquantel at oral doses of 40-50 per kg bodyweight per day given for 60 days has shown protoscolicidal activity in animals experimentally infected with larval *Echinococcus multilocularis*; however, germainal membrane proliferation was not significantly inhibited. The latter could only be achieved with excessively high doses (500 mg/kg/day) not applicable in humans. Therefore, praziquantel has no proven value for treatment of alveolar echinococcosis.

1.4 Dosage and duration of chemotherapy

Mebendazole has been administered continuously for more than 10 years at doses of 40-50 mg per kg body weight per day and albendazole has been given for repeated periods of 30 days at doses of 10 mg per kg per day with intervals of 14 days.

Chemotherapy of alveolar echinococcosis is still experimental and, to be able to provide useful data, it is vital that defined protocols be followed and careful monitoring of patients be performed with complete documentation of the results and outcome.

1.5 Monitoring patients

Where possible, serum levels of benzimidazole metabolites should be monitored after one month of chemotherapy and, thereafter, at intervals of 3 months. Dose levels can be adjusted in individual patients to achieve adequate serum levels. Evaluation of hemogram and serum transaminases for possible adverse reactions should be performed at the same time or when indicated for clinical reasons.

Specific antibody levels generally decline following successful radical resection, and serological monitoring, especially with Ee2-ELISA, is useful for assessing possible recurrence. Testing at 6-monthly intervals appears adequate. Serological monitoring has not been useful for predicting prognosis of inoperable or partially resected patients on chemotherapy.

Radiological imaging of affected organs with ultrasound, computer-assisted tomography, or magnetic resonance is the most sensitive practical method for monitoring the response of parasitic lesions to chemotherapy. In most patients, prolonged chemotherapy (>12 months) has been necessary to achieve regression of lesion size.
In patients with residual parasitic tissue, the possibility for recurrence is significant and monitoring must be continued indefinitely. Recurrence has been observed for as long as 11 years following termination of chemotherapy.

1.6 Complementary therapy

Alveolar echinococcosis often involves medical and surgical complications, such as secondary infection and biliary compression or obstruction, requiring special medical and surgical procedures. Optimal handling of these complications requires experience; therefore, patients with alveolar echinococcosis should be treated at recognized centres of competence.

2. CYSTIC ECHINOCOCCOSIS

2.1 General considerations

A proportion of inoperable cystic echinococcosis patients treated with benzimidazole drugs have been cured of their diseases (e.g. complete and permanent disappearance of cysts) and an even higher proportion have responded with significant regression of cyst size and alleviation of symptoms. Response of patients to chemotherapy is variable, however, and the prognosis cannot be accurately predicted. In general, small (<7 cm diameter) isolated cysts surrounded by minimal adventitial reaction respond best, while complicated cysts, with multiple compartments or daughter cysts, or with thick or calcified surrounding adventitial reactions, are relatively refractory to treatment. Each patient must be evaluated individually and the details of treatment, such as dosage, duration, and length of follow-up, be determined in each case.

2.2 Indications for chemotherapy

Surgical removal of intact cysts remains the treatment with fewest complications and best prognosis. Surgery should always be considered the first line of treatment for patients whose symptoms require alleviation by cyst removal. Chemotherapy should be reserved for patients whose cysts are inoperable or only partially resectable. Chemotherapy is also indicated to prevent secondary recurrence in patients following spontaneous or iatrogenic rupture of cysts.

Very young or very old age, in itself, is not a contra-indication for chemotherapy; however, treatment of children under 8 years of age or adults older than 65 should be undertaken with caution and given careful monitoring because of limited experience in these groups.

Another possible indication for primary chemotherapy is the patient with small, non-complicated cysts with few or no symptoms. Some clinicians, in consultation with these patients, may elect to treat such patients with several months of therapy to assess the initial response before considering surgical intervention. The group believed this was a valid alternative that needs further evaluation. The need for any treatment at all in this type of patient needs to be clarified by further studies on the natural history of asymptomatic cystic echinococcosis.
A number of clinical centres report the practice of administering benzimidazoles to patients prior to surgery for the purpose of inactivating protoscolices, altering the integrity of cyst membranes, and reducing the turgidity of the cysts. This is believed to reduce the possibilities of secondary recurrence and facilitate the safe surgical manipulation of the cyst(s). The group acknowledged the possible efficacy of this approach but cautioned that further evaluation of this management alternative must be undertaken before it can be recommended.

2.3 Selection of drugs

Both albendazole and mebendazole have demonstrated efficacy for treatment of cases of cystic echinococcosis. The experience of clinical centres that have used both drugs is that slightly greater efficacy, in terms of rates of complete cure and improvement, has been obtained with albendazole. Similar adverse reactions (neutropenia, liver toxicity, alopecia, and others) have been noted in a minority of patients treated with both drugs, although with greater frequency in patients treated with albendazole.

Certain asymptomatic patients with Echinococcus cysts determined to be inactive may not require surgical or chemotherapeutic intervention. However, periodic monitoring of these patients is recommended when doubt exists concerning the inactive condition of the cyst.

In vitro and in vivo experiments have demonstrated high activity of praziquantel against protoscolices of E. granulosus; however, no lethal effect on established echinococcal cysts has yet been documented. Thus, a role for praziquantel in primary chemotherapy has not been defined. However, it should be further evaluated for prevention of secondary echinococcosis after spillage of protoscolices and as a protoscolicidal agent in the PAIR procedure (see section 2.7).

2.4 Dosage and duration of chemotherapy

Albendazole is given at doses of 10 mg per kg body weight per day for periods of 4 weeks with intervals of 14 days. Repeated courses are needed in most cases depending on the characteristics of the cysts. Mebendazole is given at doses of 40-50 mg per kg body weight per day continuously for at least 3-6 months but usually longer.

As with alveolar echinococcosis dose rates of both benzimidazoles can be adjusted to obtain adequate serum metabolite levels. This may be especially necessary in unresponsive patients.

For prevention of secondary echinococcosis following spontaneous cyst rupture or accidental spillage of cyst contents, patients should be immediately treated with therapeutic doses of mebendazole or albendazole. The necessary duration of treatment has not been adequately determined. Current recommendations are 1-3 months continuously for mebendazole and 1-3 courses for albendazole.
2.5 Monitoring patients

Methods and parameters for monitoring patients are similar to those described for alveolar echinococcosis. With adequate monitoring, the period within which a definitive assessment of prognosis can be made is shorter for cystic echinococcosis (<5 years) than for alveolar echinococcosis.

2.6 Use of protoscolicidal agents at surgery

Traditional surgical management of cystic echinococcosis involves injection of protoscolicidal chemical solutions into cyst(s), followed by evacuation, prior to further manipulations and extirpation of cysts. The efficacy of this procedure for achieving its purpose, i.e. reducing incidence of secondary recurrence, has never been adequately evaluated. In addition, the use of formalin is no longer acceptable for intracystic injection because of the danger of sclerosing cholangitis. Most of the other compounds, including ethyl alcohol, cetrimide, and hypertonic saline, have been reported to cause some complications. Few of these compounds are registered for parenteral or intraoperative use, and it is often difficult to accurately estimate the volume of cysts or determine if an intrabiliary communication exists. Given these considerations, and the present alternative of pre- and/or post-operative chemotherapy with benzimidazoles, the practice of pre-operative injection of protoscolicidal drugs cannot be recommended as a routine procedure.

2.7 Alternative treatments

Several clinical centres have reported on preliminary results in small numbers of patients treated by percutaneous puncture of cysts, aspiration of cystic fluid, introduction of a protoscolicidal agent (e.g. 95% ethyl alcohol), and re-aspiration (PAIR). The immediate effects of this procedure and the reported results of follow-up of patients for 2-3 years have been favourable, comparable to those obtained with benzimidazole chemotherapy. Although there are a number of theoretical concerns about the safety of this procedure, the group hopes that increased numbers of cases, with longer follow-up, will confirm the safety and efficacy of this form of treatment. One potential risk of this treatment is sclerosing cholangitis resulting from undetected intrabiliary communications; special precautions are required to assess this possibility when evaluating a patient for the procedure.

PAIR and other proposed alternative forms of therapy (e.g. new anthelmintics, immunotherapy, Chinese traditional therapies, and others) should be tested in animal models, following international standards of animal experimentation and humane care. Candidate compounds and procedures should be further evaluated in recommended experimental models and clinical protocols.

3. VALUE OF SCREENING

In alveolar echinococcosis it has been demonstrated, especially in the Japanese experience, that screening of populations at risk with specific immunodiagnostic techniques, followed by imaging studies (ultrasound and computer-assisted tomography), is effective for early detection of cases with consequent improvement of the prognosis following surgical therapy. Routine immunodiagnostic screening of laboratory and field workers potentially
exposed to infection is recommended as a security measure. When possible, screening should be applied to other groups considered at risk (e.g. fox hunters, trappers, veterinarians and others). After initial examination one follow-up sero-examination per year is considered adequate.

For cystic echinococcosis, the most sensitive and specific screening method for detection of abdominal infection is ultrasound examination that can be carried out with portable equipment. Complementary immunodiagnostic examination may be of value in the differential diagnosis of echinococcal cysts and cysts due to other causes. Cases detected by screening procedures should be examined clinically to determine the need for treatment or conservative monitoring.

4. PREVENTION

The principles and practice of control of echinococcosis were presented in detail in the FAO/UNEP/WHO Guidelines on Surveillance, Prevention and Control of Echinococcosis/Hydatidosis (WHO, 1981). Since publication of the Guidelines, considerable experience has been obtained in the application of these principles to control of cystic echinococcosis. Although gaps continue to exist in our knowledge of this disease, and control technology can still be improved, it is generally believed that cystic echinococcosis can be effectively controlled if the principles are adequately applied and sustained for sufficient time. In contrast, much less experience exists with active control and prevention of alveolar echinococcosis. Since some new information is available the group has made recommendations specifically for prevention of alveolar echinococcosis that can be applied for the general public or persons in special high-risk groups.

5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Recommendations for prevention of alveolar echinococcosis

(1) In areas where enzootic cycles of *E. multilocularis* occur in foxes and rodents, berries, mushrooms, salad greens, and other fruits and vegetables possibly contaminated by *E. multilocularis* eggs should be thoroughly washed to reduce infection risk or heated to at least 70°C for 10 minutes to exclude risk.

(2) Due to the cold resistance of *E. multilocularis* eggs, freezing to -20°C does not inactivate the eggs; inactivation requires freezing at -70°C for 4 days or -80°C for 2 days.

(3) The eggs are relatively vulnerable to drying, especially at high temperatures. They are inactivated in 3 hours at 45°C and a relative humidity of 85%-90%, and in 48 hours at +25°C and relative humidity of 27%. It is anticipated that a temperature higher than 45°C and a low humidity will reliably decontaminate rooms.

(4) Carcasses or unprocessed skins of foxes, dogs, other canids, or cats, potentially infected with *E. multilocularis* should not be touched without plastic gloves.

(5) Hand washing after gardening or other field work or after handling pet dogs or cats should be strictly practised.
(6) Persons at special risk of alveolar echinococcosis infection (e.g., hunters, trappers, skinners, veterinarians) should be advised of the availability of serological screening.

(7) Special safety precautions should be observed in laboratories handling foxes or other infected definitive hosts. Such precautions include (a) wearing of protective gloves and face masks (b) deep freezing of foxes to \(-80^\circ\text{C}\) for one week prior to autopsy and (c) periodic monitoring of personnel potentially exposed to *E. multilocularis* eggs.

(8) When pet dogs and/or cats feed on potentially infected rodents, excretion of eggs may be prevented by regular prophylactic treatments with a specific anthelmintic drug (praziquantel) at intervals not exceeding 28 days.

5.2 General recommendations

(1) The existing WHO protocol for chemotherapy of human echinococcosis should be revised on the basis of the considerations discussed at this group meeting. It was recommended that WHO appoint a small expert group for this purpose. It would be desirable to publish the revised protocol to make it available to a wide international audience.

(2) New knowledge on prevention and early diagnosis is now available. This information should be synthesized as recommendations for general prevention and biosafety and published to make it widely available.

(3) An urgent need exists for identification of new candidate drugs for chemotherapy of echinococcosis. WHO should be responsible for and promote this type of research.

(4) The two benzimidazole compounds currently used for chemotherapy of larval echinococcosis are not currently available in all countries where they are needed. Therefore, WHO should encourage countries to explore ways in which these drugs can be made available for these specific indications, compatible with the needs of local physicians, manufacturers of the drugs, and national drug regulations.

(5) Echinococcosis is often not ranked among national public health priorities, even in countries where significant regional problems exist, thus inhibiting research and control activities. It is recommended that national health authorities in such countries designate centres of competence in this field with the responsibility of collecting local surveillance data, providing diagnostic reference services, consultation on treatment, and other services as necessary.

(6) The group agreed that this meeting on medical aspects was useful and productive and recommended that WHO continue to organize future such group meetings for the purpose of reviewing current progress. The next clinical working group meetings, together with other working groups, should be organized in conjunction with the International Congress on Hydatidosis in Beijing, People's Republic of China, in October 1993.
ANNEX I

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ANNEX II

LIST OF WORKING PAPERS

VPH/ECR.CLM/WP/92.1 Recent development of clinical medicine and chemotherapy in alveolar echinococcosis (by Prof R. Ammann)

VPH/ECR.CLM/WP/92.2 False negative and false positive serological reactions in human cystic echinococcosis (by Prof T. Todorov)

VPH/ECR.CLM/WP/92.3 Chemotherapy in human cystic echinococcosis (by Prof T. Todorov)

VPH/ECR.CLM/WP/92.4 Recent developments in clinical medicine and chemotherapy in alveolar hydatid disease of the liver (AHDCL) in Japan (by Prof J. Uchino)

VPH/ECR.CLM/WP/92.5 Echinococcosis control in China (by Prof Jiang Ci-Pang)

VPH/ECR.CLM/WP/92.6 Plans for collaborative work 1992-1994 (by J. Eckert)