DEPARTAMENTO DE BIOLOGIA ANIMAL, PARASITOLOGIA, ECOLOGÍA, EDAFOLOGÍA Y QUÍMICA AGRÍCOLA

Tesis Doctoral

Tratamiento de la equinococosis quística

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DEPARTAMENTO DE BIOLOGIA ANIMAL, PARASITOLOGIA, ECOLOGÍA, EDAFOLOGÍA Y QUÍMICA AGRÍCOLA

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CERTIFICA:

Que **Dª. VIRGINIA VELASCO TIRADO**, Licenciada en Medicina y Cirugía, ha realizado bajo mi dirección la *Tesis Doctoral* titulada **"Tratamiento de la equinococosis quística",** y que dicho trabajo reúne, a mi juicio, originalidad, contenidos, evidencias científicas, calidad y méritos académicos suficientes para ser presentado en la modalidad de *Tesis por compendio de publicaciones* ante el Tribunal correspondiente para optar al **GRADO DE DOCTOR POR LA UNIVERSIDAD DE SALAMANCA.**

Y para que conste, firmo el presente certificado en Salamanca, a 26 de Febrero de 2018.

Fdo.: M. Belhassen García

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DEPARTAMENTO DE BIOLOGIA ANIMAL, PARASITOLOGIA, ECOLOGÍA, EDAFOLOGÍA Y QUÍMICA AGRÍCOLA

Se presenta este documento a modo de *Tesis Doctoral* para optar al Título de "Doctor en Medicina" por la Universidad de Salamanca. Se ha elaborado en base al contenido de cinco trabajos publicados en revistas científicas indexadas en el *Journal of Citation Reports* y dos trabajos en revisión para publicación en revistas científicas. Los trabajos se detallan a continuación:

ARTÍCULO PRIMERO

Medical treatment of cystic echinococcosis: systematic review and meta-analysis. BMC Infectious Diseases. En revisión.

AUTORES: Velasco Tirado V[1,2], Alonso Sardón M[2,3], López Bernús A[2,4], Romero Alegría A[2,4], Burguillo FJ[5], Muro A[2] , Carpio Pérez A[2,4], Muñoz Bellido JL[2,6], Pardo Lledías J[7] y Belhassen García M[2,4].

ARTÍCULO SEGUNDO

Safety of the Combined Use of Praziquantel and Albendazole in the Treatment of Human Hydatid Disease. Am J Trop Med Hyg. 2014 May;90(5):819-22. doi: 10.4269/ajtmh.13-0059.

AUTORES: Alvela Suarez L[4], Velasco Tirado V[1,2], Belhassen García M[2,4], Novo-Veleiro I[4], Pardo Lledias J[7], Romero Alegría A[2,4], Pérez del Villar L[2], Valverde-Merino MP[8] y Cordero-Sanchez M[2,4].

ARTÍCULO TERCERO

Dysgeusia as an adverse reaction to praziquantel. Drug Chem Toxicol. 2012 Jan;35(1):116-7. doi: 10.3109/01480545.2011.584065.

AUTORES: Alvela Suarez L[4], Novo-Veleiro I[4], Belhassen García M[2,4], Velasco Tirado V[1,2], Jimenez-Cabrera S[8], Iglesias-Gomez A[2,4] y Cordero-Sanchez M[2,4].

ARTÍCULO CUARTO

Management of cystic echinococcosis in the last two decades: what have we learned? Transactions of the Royal Society of Tropical Medicine and Hygiene. En revisión.

AUTORES: Velasco Tirado V[1,2], Romero Alegría A[2,4], Pardo-Lledías J[7] , Alonso Sardón M[2,3], López Bernús A[2,4], Quiñones Sampedro J[9], Muñoz-Bellvis L[9] , Iglesias Gómez A[2,4], Muro A[2], Muñoz Bellido JL[2,6], Iglesias-Iglesias M[9], Jiménez López MF[10] y Belhassen García M[2,4]

ARTÍCULO QUINTO

Cutaneous Disease as the First Manifestation of Cystic Echinococcosis. Am J Trop Med Hyg. 2016 Aug 3;95(2): 257-9. doi: 10.4269/ajtmh.15-0855.

AUTORES: Velasco Tirado V[1,2], Yuste-Chaves M[1] y Belhassen García M[2,4].

ARTÍCULO SEXTO

Recurrence of cystic echinococcosis in an endemic area: a retrospective study. BMC Infectious Diseases (2017) 17 (1):455. doi: 10.1186/s12879-017-2556-9.

AUTORES: Velasco Tirado V[1,2], Romero Alegría A[2,4], Belhassen García M[2,4], Alonso Sardón M[2,3], Esteban-Velasco C[9], López Bernús A[2,4], Carpio Pérez A[2,4], Jiménez López MF[10], Muñoz Bellido JL[2,6], Muro A[2], Cordero Sánchez M[2,4] y Pardo-Lledías J[7] y Muñoz-Bellvis L[9].

ARTÍCULO SÉPTIMO

Recurrent spinal Echinococcosis. Int J Infect Dis. 2011 Jun;15(6): e435-6. doi: 10.1016/j.ijid.2011.03.002.

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A mis padres y hermanas, por su amor y apoyo constantes

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ABREVIATURAS

ARF: Ablación térmica por radiofrecuencia.

CAUSA: Complejo Asistencial Universitario Salamanca.

CDC: Centers for Diseases Control and Prevention (Centros para el Control y la Prevención de Enfermedades). Atlanta, USA.

CC.AA: Comunidades Autónomas.

cm: Centímetros.

DALYs: Disability adjusted life years (años perdidos por incapacidad).

E: Especificidad.

ELISA: Enzimoinmunoanálisis.

E. granulosus: *Echinococcus granulosus.*

E. multilocularis: *Echinococcus multilocularis.*

EQ: Equinococosis quística.

E. oligarthrus: *Echinococcus oligarthrus.*

E. vogeli: *Echinococcus vogeli.*

ERCE: European Register of Cystic Echinococcosis (Registro Europeo de Equinocococosis quística).

ETD: Enfermedades Tropicales Desatendidas

HAI: Hemaglutinación indirecta.

HPS: Hipersensibilidad.

IC: Intervalo de confianza

IgE: Inmunoglobulina E.

INE: Instituto Nacional de Estadística.

LHD: Lóbulo hepático derecho.

LID: Lóbulo inferior derecho (pulmón).

LSI: Lóbulo superior izquierdo (pulmón).

mm: Milímetros.

MoCaT: Técnica de cateterización modificada.

Nº: Número.

OMS: Organización Mundial de la Salud.

PAIR: Punción, aspiración, inyección y reaspiración.

PEVAC: evacuación percutánea modificada

RM: Resonancia magnética.

Rx: Radiografía.

S: Sensibilidad.

$: Dólares

SACYL: Salud de Castilla y León.

TC: Tomografía computarizada.

ÍNDICE

INTRODUCCIÓN

La hidatidosis humana o equinococosis quística (EQ) es una zoonosis causada por el *Echinococcus granulosus*, un céstodo cuyo hospedador definitivo es el perro, y en la que el hombre constituye un hospedador intermediario accidental. Debido al impacto en términos de morbilidad, la especial afectación en áreas desfavorecidas y la escasa inversión en investigación, esta enfermedad está incluida en el listado de "*Enfermedades Tropicales Desatendidas*" de la Organización Mundial de la Salud (OMS).

Aunque la hidatidosis es una infección de distribución cosmopolita, el mayor número de casos humanos están concentrados en América del Sur, Norte y Este de África, Oriente Medio y países de Asia Central y del Oeste. En Europa, la equinococosis quística es especialmente prevalente en los países de la cuenca Mediterránea como Grecia, Italia, y Portugal. En España el índice de transmisión continúa siendo alto y se considera un área de alta endemicidad. Las Comunidades Autónomas (CC.AA) del Centro, Noreste y Oeste de España son las más afectadas, por ser las regiones con la cabaña ganadera (sobre todo ovina) más importante a nivel nacional. De forma particular, Salamanca presenta una alta incidencia de EQ comparada con otras provincias.

Cuando la infección se produce en el ser humano da lugar a la formación de quistes en casi cualquier órgano, siendo el hígado y los pulmones las ubicaciones más frecuentes. Los quistes pueden evolucionar de forma variable: un 14% muere y se calcifica; un 20% no crece; en el 66% restante se produce un crecimiento lento de aproximadamente 1 milímetro al mes, por lo que la mayoría de los quistes cursan asintomáticos hasta alcanzar los 10 cm. Cuando producen síntomas lo hacen mediante tres tipos de complicaciones: mecánicas, infecciosas e inmunológicas (o combinadas). Ninguna de ellas es específica y todas son potencialmente mortales.

El diagnóstico de EQ debe cumplir los criterios diagnósticos de la OMS: *i*) un cuadro clínico sugerente; *ii*) una técnica de imagen compatible, fundamentalmente ecografía y/o tomografía computerizada (TC); *iii*) una serología positiva y/o un hallazgo directo

microbiológico o una anatomía patológica compatible.

A pesar de la recomendación de la OMS, no existe un consenso en el tratamiento de la hidatidosis en este momento, de forma que su manejo es enormemente complejo. A modo de resumen, existen fundamentalmente tres tipos de tratamientos, en muchas ocasiones complementarios entre sí: *i)* la cirugía, *ii)* las técnicas percutáneas y, *iii)* los antiparasitarios. Además, existen enormes diferencias en el manejo según medios disponibles, centro sanitario, características del paciente y del quiste.

El abordaje quirúrgico es actualmente el tratamiento de elección, pero existen varias técnicas alternativas disponibles. La PAIR (*Punción, Aspiración, Inyección y Reaspiración*) es una práctica que se ha introducido recientemente y que posiblemente pueda reemplazar la cirugía en casos específicos. La utilidad de otros métodos como la técnica de cateterización modificada (MoCaT), la evacuación percutánea modificada (PEVAC), las terapias inmunológicas o quimio-radioisotópicas y la ablación térmica por radiofrecuencia (ARF) debe ser contrastada en un futuro.

Los antihelmínticos, principalmente benzimidazoles solos o en combinación con otros fármacos como praziquantel, se han reservado hasta ahora para pacientes no candidatos a la cirugía, y han tenido un papel secundario en la reducción del riesgo de anafilaxis, diseminación y/o recidiva posoperatoria. En los últimos años la actitud expectante de "*Watch & Wait* " está siendo analizada en pacientes seleccionados.

Por lo descrito, el tratamiento de la EQ es un problema vigente y sustancial, condicionando un intenso debate parar decidir cual es el tratamiento óptimo. El objetivo de esta tesis doctoral es el estudio del tratamiento de la EQ.

Los artículos originales de los que consta esta tesis doctoral, para responder a los diferentes objetivos planteados son los siguientes:

Artículo primero: "*Medical treatment of Cystic Echinococcosis: systematic review and meta-*

analysis".

Artículo segundo: "*Safety of the Combined Use of Praziquantel and Albendazole in the Treatment of Human Hydatid Disease*".

Artículo tercero: "*Dysgeusia as an adverse reaction to praziquantel*".

Artículo cuarto: "*Management of Cystic Echinococcosis in the last two decades: what have we learned?*".

Artículo quinto: "*Cutaneous Disease as the First Manifestation of Cystic Echinococcosis*".

Artículo sexto: "*Recurrence of Cystic Echinococcosis in an Endemic Area: A Retrospective Study*".

Artículo séptimo: "*Recurrent spinal echinococcosis*".

OBJETIVOS

OBJETIVO GENERAL

Evaluación del tratamiento actual frente a la equinococosis quística.

OBJETIVOS ESPECÍFICOS

1. Valoración de la eficacia y seguridad del tratamiento con antihelmínticos en la equinococosis quística.

1.1 Valoración de la eficacia de los benzimidazoles en el tratamiento de la equinococosis quística.

1.2. Evaluación de la eficacia del tratamiento con albendazol y praziquantel en la equinococosis quística.

1.3. Análisis de la seguridad del tratamiento combinado con albendazol y praziquantel frente a la equinococosis quística.

2. **Evaluación del tratamiento aplicado a los pacientes con equinococosis quística atendidos en el Complejo Asistencial Universitario de Salamanca (CAUSA) durante el periodo de 1998 al 2015.**

2.1. Valoración de las diferentes modalidades de tratamientos seleccionados y las complicaciones secundarias en los pacientes con equinococosis quística atendidos en el CAUSA.

2.2. Análisis de los factores condicionantes de las diferentes estrategias terapéuticas empleadas.

3. **Evaluación de las recurrencias postquirúrgicas en los pacientes atendidos en el CAUSA con equinococosis quística desde 1998 al 2015.**

3.1. Valoración de la frecuencia, retraso diagnóstico y presentación clínica.

3.2. Análisis de los factores de riesgo asociados a las recurrencias.

4. **Valoración de la mortalidad en la equinococosis quística en la cohorte CAUSA.**

4.1. Análisis de la mortalidad global y atribuible.

4.2. Evaluación de los factores asociados a la mortalidad.

DISCUSIÓN

La equinococosis quística (EQ) constituye una de las *Enfermedades Tropicales Desatendidas* por la OMS y como, sucede en estas entidades, existe escaso interés y se destinan recursos económicos insuficientes para su investigación[1-4].

Hace 15 años el grupo de estudio de la EQ del Centro de Investigación de Enfermedades Tropicales de la Universidad de Salamanca (CIETUS) comenzó una línea de investigación que inicialmente se centró en describir la epidemiología de la EQ en Salamanca y en Castilla y León. Para ello se utilizaron herramientas epidemiológicas que posteriormente se han demostrado útiles en el estudio de la realidad de esta parasitosis en otros lugares de España[5,6]. Estas aportaciones han posibilitado la invitación de nuestro centro a participar en el programa Human Cystic Echinococcosis ReseArch in CentraL and Eastern Societies (HERACLES), bajo el auspicio de la Unión Europea[7,8]. En la misma línea, el grupo ha realizado en los últimos años otras aportaciones en el estudio de la EQ, definiendo formas de presentación clínica, complicaciones derivadas de esta parasitosis, etc. Nuestra investigación ha sido recopilada en numerosos trabajos científicos en revistas internacionales de prestigio.

A pesar de estas aportaciones realizadas, tanto nuestro grupo como otros equipos internacionales siguen señalando que el tratamiento de la EQ debe ser el principal objetivo en la investigación de esta parasitosis. Así, continua siendo fuente de debate entre los expertos elegir qué pacientes y cómo tratarlos. El origen de esta controversia se basa en que la EQ humana es tremendamente heterogénea por presentar diferentes:

i) Formas de presentación (EQ complicado o EQ incidental).

ii) Localizaciones (torácica, hepática, etc.).

iii) Estadios (OMS 1-5).

iv) Comorbilidades de los pacientes.

v) Recursos sanitarios y experiencia por parte del equipo médico.

A todo ello hay que añadir la ausencia de una sólida evidencia científica en relación a la eficacia del tratamiento, por la complejidad intrínseca del propio tratamiento (frecuentemente quirúrgico), por las complicaciones postquirúrgicas, y finalmente por el potencial recurrencia de esta infección[9,10]. Finalmente, está la dificultad de investigar una ETD con escasos recursos económicos, que es crónica (de muy lenta evolución), paucisintomática, y en la que existe una carencia de marcadores biológicos validados que permitan definir la curación. Como consecuencia de todo ello, el manejo clínico y las guías de práctica asistencial a lo largo de estas últimas décadas se basan, en gran medida, en opinión de expertos[4,10-12].

El presente trabajo doctoral se centra en resolver algunos aspectos importantes en el tratamiento de la EQ, como son la eficacia y la seguridad de los antiparasitarios, la definición de los factores que influyen en la modalidad del tratamiento, sus complicaciones, el estudio de las recurrencias postquirúrgicas y finalmente como intervienen todos estos aspectos en la mortalidad de la enfermedad.

La presente tesis doctoral evalúa, en una primera parte, la **eficacia** del tratamiento con benzimidazoles y praziquantel (reflejada en el primer artículo original). Para esta evaluación se optó por la realización de un metaanálisis, utilizando como guía el sistema llamado Preferred Reporting Items for Systematic Reviews and Meta-Analyses, conocido como PRISMA[13,14]. Así, sobre una búsqueda sistemática inicial en pubmed (https://www.ncbi.nlm.nih.gov/pubmed/) con mas de 800 trabajos referenciados, se seleccionaron sólo 11 estudios controlados y aleatorizados, que se incluyeron finalmente en el metaanálisis. La escasez de estudios, con un bajo número de pacientes, la falta de homogeneidad entre los estudios, los diferentes tratamientos aplicados y la falta de seguimiento a largo plazo fueron las principales limitaciones de los resultados del metaanálisis y causa de la debilidad de las conclusiones obtenidas.

En este trabajo formulamos como preguntas: *i)* si el tratamiento con antiparasitarios mejoraba los resultados de intervenciones quirúrgicas; *ii)* si el tratamiento con albendazol es más eficaz que el tratamiento con mebendazol y *iii)* si el tratamiento con albendazol y praziquantel es superior al tratamiento con albendazol en monoterapia.

Este primer trabajo permite comprobar como el tratamiento antiparasitario con benzimidazoles mejora la eficacia de la cirugía/PAIR aislados[15-17]. Sin embargo, no hay suficientes datos para establecer cuál es el momento idóneo del inicio del tratamiento antihelmíntico, la dosis adecuada ni la duración. Las pautas de tratamiento más utilizadas con albendazol preoperatorio van desde un día a tres meses antes de la intervención quirúrgica, y continúan tras la cirugía durante 1-3 meses. No son concluyentes los resultados en cuanto a que si tratamientos más prolongados (más de 3 meses) son más eficaces que tratamientos más cortos[2,18]. El beneficio adicional de tratamientos muy prolongados (más de 6 meses) es marginal para la mayoría de los pacientes, aunque es un proceder habitual en la práctica clínica de pacientes con EQ múltiple e inoperable.

Se evaluó también en el metaanálisis cual era el benzimidazol más eficaz, encontrando mejores resultados del albendazol frente al mebendazol. Las dosis más utilizadas en el caso del mebendazol, fueron las de 40-50 mg/kg/día divididas en tres tomas. La dosis normal de albendazol por vía oral es de 10-15 mg/kg/día dividida en dos tomas, o una dosis estándar de 400 mg dos veces al día. El albendazol presenta mejor biodisponibilidad, alcanzando concentraciones séricas elevadas (con concentración pico en cuatro horas aproximadamente, y una semivida de eliminación de 6-15 horas)[19]. Sin embargo, el principal problema del albendazol es la penetración algo irregular en el interior del quiste.

El praziquantel es otro antiparasitario empleado en el tratamiento de la EQ. En algunas series se han descrito tasas de curación del 43% en quistes hepáticos, con recidivas de hasta del 22%, mientras que las tasas de curación de los quistes pulmonares alcanzan el

73%. Los regímenes de tratamiento más empleados consisten en dosis de 10-40 mg/kg/día durante 2-4 meses. Además, como profilaxis precirugía el praziquantel junto al albendazol permiten una reducción de las recidivas[20,21]. Sin embargo, no hay estudios aleatorizados que exploren el tratamiento con albendazol en monoterapia frente a la terapia combinada con albendazol más praziquantel en pacientes sin cirugía[22-27]. Parece que el uso de praziquantel pre y postcirugía en combinación con mebendazol o albendazol es más efectivo y posiblemente más rápido que el tratamiento con benzimidazoles en monoterapia en modelos experimentales y series de casos[22,24,27]. El tratamiento combinado prequirúrgico, podría disminuir las tasas de recidivas en comparación con la monoterapia con albendazol[24]. No hay datos suficientes en la actualidad que respalden el uso habitual del praziquantel en la quimioterapia prolongada para la EQ en la enfermedad diseminada, o cuando no se indica cirugía. El resultado del metaanálisis apoya la superioridad del tratamiento combinado con albendazol más praziquantel frente a la monoterapia con albendazol en pacientes que van a ser intervenidos quirúrgicamente[22-24,27].

Un segundo aspecto del tratamiento antiparasitario es la **seguridad**. Este análisis se planteó porque existen en la literatura muy pocos estudios publicados, en los que se evalúe el tratamiento combinado, estando centrados en el tratamiento de otras parasitosis[28-30], con pautas habitualmente más cortas[31-33].

Tanto el mebendazol como el albendazol pueden presentar toxicidad hepática y hematológica como efectos adversos graves más frecuentes, por lo que se recomienda controles de función hepática y hemograma cada dos semanas durante el tratamiento[34]. No se conocían bien los efectos secundarios del praziquantel con tratamientos prolongados, dado que la mayoría de pautas son en ciclos cortos. En este sentido, se presenta un segundo estudio retrospectivo en el que se evalúa la seguridad del tratamiento combinado con albendazol y praziquantel en pacientes con EQ. Los mayoría de los

tratamientos fueron largos (casi dos terceras partes realizaron tratamientos durante más de un año).

En nuestra cohorte, los efectos adversos detectados fueron infrecuentes, leves y reversibles, una vez que se retiraron los fármacos. Las reacciones adversas afectaron principalmente al aparato digestivo e incluyeron náuseas, vómitos y diarrea, ya descritas por otros autores en los que se utilizó el praziquantel[31,32]. Dos de nuestros pacientes presentaron una disgeusia y disosmia, efectos secundarios no incluidos en la ficha técnica de praziquantel, y según nuestro conocimiento es la primera vez que se han observado como un efecto relacionado con el praziquantel[35]. A pesar del sesgo de selección en nuestra serie, al incluir exclusivamente pacientes hospitalarios, y no pacientes ambulatorios ni con quistes asintomáticos, con una mayor representación de los casos graves, éste no afectaría a nuestras conclusiones sobre la tolerancia y la aparición de efectos postratamiento. Por lo tanto, el uso de esta terapia combinada en el tratamiento de la EQ no sólo parece más eficaz, sino también segura, aunque se necesitarán más estudios prospectivos para confirmar estas observaciones.

Otro de los objetivos de este trabajo doctoral era **evaluar los diferentes tratamiento frente a la EQ en la practica real**. En nuestro hospital el manejo durante los últimos 20 años no tiene un protocolo bien establecido, dada la ausencia de una guía validada internacionalmente. La cirugía ha sido el tratamiento habitual durante este periodo. Muy ocasionalmente se han venido empleando otras modalidades de tratamiento como la PAIR, tratamiento exclusivo con antiparasitarios o la estrategia expectante conocida como *"Wach & Wait"*. Así, en el tercer trabajo original de esta tesis, evaluamos los tratamientos más utilizados en nuestro hospital, analizando los factores implicados en su elegibilidad, y establecimos las complicaciones más frecuentes de los tratamiento empleados. Detectamos que la mayor edad en los pacientes infectados, la existencia de co-

morbilidad o la presentación clínica incidental, eran los factores mas importantes en la selección del tratamiento basado en la estrategia "*Wach & Wait".*

Asimismo describimos qué factores dependientes del propio quiste, como localización, tamaño y número, influyen en la decisión sobre la realización o no de una intervención quirúrgica. Así, mostramos una mayor proporción de cirugías en la EQ torácica respecto de la hepática. Estas diferencias se podrían explicar porque la EQ torácica suele ser más sintomática que en otras localizaciones. Sin embargo, posiblemente exista un sesgo de selección, debido a que el Servicio de Cirugía Torácica de nuestro hospital es unidad de referencia, y pacientes de otras áreas de salud fueron derivados para someterse a diferentes técnicas quirúrgicas. En cuanto al tamaño, los quistes más grandes suelen ser quistes activos con una mayor capacidad de crecimiento y, en consecuencia, una mayor posibilidad de complicación por lo que suelen ser más frecuentemente quirúrgicos. Además, los quistes múltiples en diferentes localizaciones habitualmente no se intervienen debido a la alta tasa de fracaso quirúrgico para la curación de la enfermedad.

Aproximadamente el 20% de los pacientes tratados con cirugía tuvo complicaciones, con una mortalidad similar a la observada en otros estudios[36]. La mortalidad postoperatoria se asoció claramente con la edad del paciente y la comorbilidad. En este sentido, definir los criterios de exclusión de los pacientes quirúrgicos es importante para disminuir la tasa de mortalidad. Por último, respecto al tratamiento médico, los antihelmínticos se usaron principalmente como tratamiento complementario a la cirugía, con un bajo riesgo de complicaciones como previamente se ha referido.

Además de las complicaciones postoperatorias, la principal complicación después del acto quirúrgico es la **recurrencia**. Las recurrencias siguen siendo uno de los principales problemas en el manejo de la EQ, y a pesar de ello, grupos como el WHO-IWGE Expert Consensus (Organización Mundial de la Salud- Grupo Informal de Trabajo Sobre

Echinococcosis) no diferencian claramente entre conceptos como recaída, recurrencia y reinfección[37].

En la literatura existen pocos estudios que analicen, específicamente, las recidivas de la EQ , los factores de riesgo para ésta, la presentación clínica o su tratamiento[9,21,37-43]. Además, la tasa de recidivas presenta entre los diferentes estudios un amplio rango, desde 0 a 22%, lo que refleja una gran variabilidad y escasa homogeneidad entre los pacientes y metodología empleada, especialmente en lo concerniente a la duración del seguimiento[9,38,39,43-45].

Así, en este trabajo doctoral se incluye como cuarto trabajo original un estudio que evalúa en una cohorte de pacientes intervenidos, las recidivas de todos los pacientes con una cirugía con intención curativa. Dada la historia natural de la infección, se realizó un estudio retrospectivo en el que sólo incluimos pacientes que habían sido revisados en nuestro hospital en al menos una ocasión después de la cirugía. La mayoría de pacientes fueron seguidos más de un año.

En nuestro estudio nosotros detectamos un 11% de recurrencias entre los pacientes intervenidos. Más de la mitad de nuestros enfermos estaban asintomáticos en el momento del diagnóstico de la recidiva aunque también detectamos pacientes con EQ complicada. Estos resultados son similares a los descritos por otros autores[9,21,37-43].Hay para resaltar que ningún paciente murió como consecuencia de estas complicaciones HIDATIDOSIS ESPINAL.

En cuanto a los factores de riesgo encontramos que no se asociaban con las recurrencias variables como las actividades ocupacionales, por lo que es más frecuente que la diseminación durante o después de la cirugía sea la causa de la recurrencia, más que una nueva reinfección.

En la literatura, se han descrito numerosos factores de riesgo derivados del quiste como la localización, gran tamaño (más de 7 cm), estadio, acceso quirúrgico difícil, quistes

abdominales múltiples, con discordancias entre los estudios[9,37,40,42,43]. En nuestro estudio también evaluamos factores asociados al quiste y encontramos que en pulmón era menos frecuentes las recidivas, seguidas de hígado y del resto de localizaciones. Otros factores, como el tamaño de los quistes (más de 7–10 cm) o los estadio I-II WHO presentaban mayor frecuencia de recurrencias, aunque no llegaron a ser estadísticamente significativas.

La técnica quirúrgica y la experiencia del cirujano pueden ser también factores que influyan en la recurrencia[9,21,40-42,46,47]. Con respecto a las técnicas quirúrgicas utilizadas, la tasa de recidivas fue mayor con la cirugía laparoscópica, que con las intervenciones abiertas (8,89% frente a 3,15%)[40]. Otras variables asociadas con un mayor riesgo o recurrencias incluyen: dejar material durante la cirugía[40], una escisión incompleta del quiste, o la rotura de los quistes pre o intraoperatoriamente[21,41,42,47]. Sin embargo, no hay datos que muestren una relación entre el tipo de incisión y la cifra de recurrencias[40]. Dos factores importantes son la práctica y la experiencia del cirujano[42,46]. En nuestra serie, todos los pacientes fueron sometidos a cirugía abierta y no detectamos otros factores asociados al riesgo de recidiva. Asimismo, en muchos de nuestros pacientes se han usado diferentes pautas pre y postquirúrgicas con antihelmínticos (albendazol con o sin praziquantel) para disminuir el riesgo de recidiva.

No hay consenso en la literatura respecto a cómo se debe tratar una recurrencia. Parece razonable que, si es posible, el manejo debería ser similar al de la enfermedad inicial [41,48], aunque algunos autores abogan por un manejo más conservador con antihelmínticos debido al lento progreso de la enfermedad. Hay autores que sugieren que en caso de fracaso primario al albendazol, el tratamiento de la recurrencia también fallaría. Otros autores sugieren que, aunque sean técnicamente más difíciles y pueden tener tasas de morbimortalidad más altas, se debe intentar una cirugía radical [37,40]. Por lo tanto, la elección entre un manejo conservador y radical depende de factores, como la localización, tamaño, estadio de los quistes, y disponibilidad de las distintas opciones terapéuticas en

cada centro sanitario. En nuestro trabajo, todos los pacientes con recurrencias fueron sometidos a cirugía y la mortalidad fue nula, incluidos los casos complicados, apoyando la idea de que con una buena selección de casos el tratamiento quirúrgico se asocia a buenos resultados.

No está bien establecido al tiempo de seguimiento de los pacientes con EQ, ni cómo debe hacerse. Dado que los títulos de anticuerpos pueden persistir años tras la cirugía, la recurrencia debería ser confirmada por técnicas de imagen (la recurrencia generalmente se produce en la misma área de la primaria EQ)[9]. Algunos autores han sugerido que se debería seguir al paciente tanto como sea posible y no menos de 3 años, ya que en ese periodo se producirían recurrencias asintomáticas. A los 3-4 años postcirugía es cuando aparecen la mayoría de los cuadros sintomáticos[9,10]. La eficiencia de un programa de detección en relación con el riesgo y el costo no ha sido establecida.

Finalmente, el último objetivo fue examinar la **mortalidad global y atribuible a la EQ.** Nuestro grupo con anterioridad publicó un estudio que analizó la mortalidad intrahospitalaria en pacientes con EQ durante el periodo 1998 al 2011[49]. Se analizaron las causas finales de muerte y se estableció que la propia EQ y sus complicaciones constituían una de las principales causas de mortalidad. Sin embargo, en ese trabajo, debido a la metodología utilizada, no pudimos establecer los factores de riesgo asociados de mortandad atribuible. Por eso, en el tercer trabajo original de esta tesis doctoral nosotros planteamos como objetivo definir de nuevo cual era la mortalidad atribuible de la EQ y los factores de riesgo asociados.

En este sentido realizamos un estudio en toda nuestra cohorte de pacientes que al menos tenían dos evaluaciones en nuestro hospital. De igual manera a lo publicado previamente, encontramos que la EQ es una de las causas más importantes de mortalidad global, tras el cáncer y las enfermedades cardiovasculares. En cuanto a los factores relacionados con la mortalidad, en la EQ encontramos que factores relacionados con el quiste como un mayor número de quistes, un gran tamaño al diagnóstico o la localización torácica eran factores asociados a una mayor mortalidad. Asimismo, encontramos que variables dependientes del huésped como la edad y la comorbilidad se asociaban a una mayor mortalidad. Finalmente, estudiamos si el tipo de tratamiento podría estar relacionado con la mortalidad. Observamos que la estrategia "*Watch & Wait*" se asoció con una mayor mortalidad. Las variables que más influyen en la mortalidad causada por EQ en esta cohorte fueron la presencia de comorbilidad y complicaciones en el tratamiento. Hasta

donde sabemos, no hay otros estudios que evalúen los factores implicados con la mortalidad en pacientes con EQ. Aunque nuestro trabajo presenta evidentes sesgos, especialmente de selección, y limitaciones debido a su naturaleza retrospectiva, creemos que este trabajo puede contribuir a optimizar la elección del tratamiento para pacientes con esta parasitosis.

En resumen, este trabajo doctoral establece un punto de partida en la investigación del tratamiento de la EQ, estableciendo la utilidad y la seguridad del tratamiento antiparasitario; se determinaron en nuestra cohorte los factores dependientes del quiste, del hospedador y del tratamiento que pueden influir en cada una de las posibles líneas de tratamiento. Asimismo, se valoraron las complicaciones secundarias y las recurrencias. Finalmente, hay que entender que la EQ es una infección potencialmente mortal y establecer sus factores determinantes nos permitirá seleccionar el mejor de los tratamientos de forma individualizada. No obstante, es fundamental seguir insistiendo que el mejor tratamiento de la EQ es el preventivo, con una eficacia epidemiológica demostrada, pero que exige por parte de las autoridades una gran implicación en medidas de salud pública, siendo necesario destinar gran cantidad de recursos y mantenerlos en el tiempo.

CONCLUSIONES

Primera. El tratamiento con antiparasitarios de la equinococosis quística mejora los resultados en pacientes que van a ser intervenidos. El tratamiento combinado con albendazol junto con praziquantel frente a la monoterapia con albendazol presenta una mayor actividad escolicida.

Segunda. Los efectos secundarios a la quimioterapia antihelmíntica con albendazol y praziquantel suelen ser infrecuentes, leves y reversibles, lo que sugiere que el tratamiento combinado es seguro.

Tercero. Los principales factores implicados en la selección de la estrategia terapéutica son las características de los pacientes y de los quistes .

Cuarta. Las recurrencias son un problema frecuente en la equinococosis quística. Pueden ocurrir décadas después del tratamiento y la localización del quiste primario es el principal factor asociado.

Quinta. Una de las principales causas de mortalidad entre los pacientes con equinococosis quística son las complicaciones del quiste. El tamaño, la localización el número de quistes y la estrategia expectante de tratamiento "*Watch & Wait*" son los principales factores implicados.

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TRABAJOS ORIGINALES

Los resultados de este trabajo doctoral vienen estructurados como artículos originales, que dan respuesta a cada uno de los diferentes objetivos previamente referidos. Así, los artículos de los que consta esta tesis doctoral son:

Objetivo 1.

i) "Medical treatment of Cystic Echinococcosis: systematic review and meta-analysis".

ii) "Safety of the Combined Use of Praziquantel and Albendazole in the Treatment of Human Hydatid Disease".

iii) "Dysgeusia as an adverse reaction to praziquantel".

Objetivos 2 y 4.

iv) "Management of Cystic Echinococcosis in the last two decades: what have we learned?"

v) "Cutaneous Disease as the First Manifestation of Cystic Echinococcosis".

Objetivos 3 y 4.

vi) "Recurrence of Cystic Echinococcosis in an Endemic Area: A Retrospective Study.

vii) "Recurrent spinal echinococcosis".

ARTÍCULO PRIMERO

Medical treatment of Cystic Echinococcosis: systematic review and meta-analysis.

Antecedentes: El tratamiento médico de la EQ es controvertido y la evidencia que apoya las modalidades terapéuticas es débil. El objetivo de este trabajo es realizar una revisión sistemática y un metaanálisis de la bibliografía del tratamiento médico de la EQ.

Métodos: Búsqueda electrónica sistemática de la literatura relevante sin restricciones de idioma. Se utilizó PubMed (Medline), el Registro Cochrane Central de ensayos controlados, BioMed, la base de datos de *Abstract of Reviews of Effects* y Cochrane Plus hasta el 1 de febrero de 2017. Se valoraron para el análisis cualitativo todos los estudios descriptivos publicados. Los ensayos controlados aleatorizados fueron incluidos en un metaanálisis cuantitativo usando el procedimiento metodológico PRISMA.

Resultados: Se incluyeron 33 estudios relacionados con el tratamiento farmacológico para la equinococosis quística. De éstos, 22 estudios fueron analizados cualitativamente y 11 se analizaron cuantitativamente mediante un metaanálisis.

Conclusiones: Los resultados del tratamiento quirúrgico o mediante PAIR son mejores cuando se combinan con benzimidazoles administrados antes y/o después de la cirugía. El albendazol es el antihelmíntico de elección en la hidatidosis. El tratamiento combinado con albendazol más praziquantel resultó ser más escolicida y con mayor actividad frente a quistes y es más probable que produzca curación o mejoría que el albendazol solo.

BMC Infectious Diseases

Medical treatment of Cystic Echinococcosis: systematic review and meta-analysis

--Manuscript Draft--

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Full Title:	Medical treatment of Cystic Echinococcosis: systematic review and meta-analysis
Article Type:	Research article
Section/Category:	Parasitological diseases
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Abstract:	Background: Cystic echinococcosis (CE) is a well-known neglected parasitic disease. However, evidence supporting the four current treatment modalities is inadequate, and treatment options remains controversial. The aim of this work is to analyse the available data to answer clinical questions regarding medical treatment of CE. Methods: A thorough electronic search of the relevant literature without language restrictions was carried out using PubMed (Medline), Cochrane Central Register of Controlled Trials, BioMed, Database of Abstracts of Reviews of Effects, and Cochrane Plus databases up to February 1, 2017. All descriptive studies reporting an assessment of CE treatment and published in a peer-reviewed journal with available full-text were considered for a qualitative analysis. Randomized controlled trials were included in a quantitative meta-analysis. We used the standard methodological procedures established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Results: We included 33 studies related to the pharmacological treatment of CE in humans. Of these, 22 studies with levels of evidence 2 to 4 were qualitatively analysed, and 11 randomized controlled trials were quantitatively analysed by meta-analysis. Conclusions: Treatment outcomes are better when surgery or PAIR (Puncture, Aspiration, Injection of protoscolicidal agent and Reaspiration) is combined with benzimidazole drugs given pre- and/or post-operation. Albendazole chemotherapy was found to be the primary pharmacological treatment to consider in the medical management of CE. Nevertheless, combined treatment with albendazole plus praziquantel resulted in higher scolicidal and anti-cyst activity and was more likely to result in cure or improvement relative to albendazole alone.
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Title

Medical treatment of Cystic Echinococcosis: systematic review and meta-analysis

Short title

Medical treatment of Cystic Echinococcosis

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Abstract

Background: Cystic echinococcosis (CE) is a well-known neglected parasitic disease. However, evidence supporting the four current treatment modalities is inadequate, and treatment options remains controversial. The aim of this work is to analyse the available data to answer clinical questions regarding medical treatment of CE.

Methods: A thorough electronic search of the relevant literature without language restrictions was carried out using PubMed (Medline), Cochrane Central Register of Controlled Trials, BioMed, Database of Abstracts of Reviews of Effects, and Cochrane Plus databases up to February 1, 2017. All descriptive studies reporting an assessment of CE treatment and published in a peer-reviewed journal with available full-text were considered for a qualitative analysis. Randomized controlled trials were included in a quantitative meta-analysis. We used the standard methodological procedures established by the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* statement.

Results: We included 33 studies related to the pharmacological treatment of CE in humans. Of these, 22 studies with levels of evidence 2 to 4 were qualitatively analysed, and 11 randomized controlled trials were quantitatively analysed by meta-analysis.

Conclusions: Treatment outcomes are better when surgery or PAIR (*Puncture, Aspiration, Injection of protoscolicidal agent and Reaspiration*) is combined with benzimidazole drugs given pre- and/or post-operation. Albendazole chemotherapy was found to be the primary pharmacological treatment to consider in the medical management of CE. Nevertheless, combined treatment with albendazole plus praziquantel resulted in higher scolicidal and anti-cyst activity and was more likely to result in cure or improvement relative to albendazole alone.

Keywords

Echinococcus granulosus; Cystic Echinococcosis; Albendazole; Mebendazole; Praziquantel.

Background

Cystic echinococcosis (CE) is a zoonosis caused by cestode worms of the genus *Echinococcus* spp. *Echinococcus granulosus* is the most important *Echinococcus* species that parasitizes humans. The significance of this neglected parasitic disease is recognised; CE has a greater socio-economic impact than American trypanosomiasis or leprosy [1,2]. CE has a worldwide geographical distribution, and the Mediterranean basin is considered an important endemic area[3]. Four treatment options are currently available: i) surgery, ii) PAIR, iii) chemotherapy with albendazole, mebendazole or other anthelmintic drugs, and iv)watch and wait for inactive or silent cysts. There is lack of evidence that supports treatment options [4]. This may be a result of the complexity of this neglected disease and limitations related to health-care facilities[5]. Drugs are usually indicated before surgery to diminish the size of hydatid cysts, to sterilize them, and to avoid relapses. In addition, medical treatment is the sole therapeutic option in inoperable and disseminated CE. To date, the medical treatment of CE is based on drugs of the benzimidazole family, usually albendazole [6,7]. Over the last few years, praziquantel has been associated with albendazole [8,9]. In addition, other drugs like nitazoxanide have also been used in disseminated CE[10]. Despite World Health Organization (WHO) recommendations, there is no standard for the medical management of CE, and variability exists in the timing of treatment initiation, dose and duration, which remain undefined.

The aim of this study is to analyse available data to answer the following clinical questions regarding the medical treatment of CE: i) Could pharmacological treatment improve the results of surgical interventions? ii) Is albendazole more effective than mebendazole? iii) Should albendazole be administered alone or in combination with praziquantel?

Methods

Search strategy and criteria for study selection

A systematic search of PubMed (Medline), Cochrane Central Register of Controlled Trials (CENTRAL), BioMed, DARE (Database of Abstracts of Reviews of Effects), and Cochrane Plus databases was conducted without language restrictions to identify

studies that assessed the efficacy of medical treatment of CE and had been published up to February 1, 2017.

The following search key words and Boolean operators were entered: (*"cystic echinococosis"* OR *"hydatid disease"*, OR *"Echinococcus granulosus"*) AND (*"medical treatment"* OR *"albendazole"* OR *"mebendazole"* OR *"praziquantel"*) AND (*"randomized controlled trials"*) AND *"humans"* [AND NOT *"animals"*]. Additional records were also identified through other sources (UpToDate).

All relevant studies that reported the assessment of one modality of treatment or a comparison of two or several therapeutic methods to treat CE in humans and were published in a peer-reviewed journal with full text available were considered for analysis and classified according to levels of evidence and grades of recommendation proposed by the *Oxford Centre for Evidence-Based Medicine (OCEBM)*[11]. Data from editorials, letters to editors, reports of expert committees, and opinions of respected authorities based on clinical experience were excluded from the analysis because these designs do not have the same value, impact or power to make decisions or make recommendations. The results from non-randomized controlled trials, cohort or case-control analytic studies, prospective or retrospective case series, and literature reviews were qualitatively analysed but excluded from our quantitative meta-analysis. We included in the meta-analysis only studies from randomized controlled trials [Level of Evidence 1, Grade of recommendation A].

Data extraction and quality assessment

After the relevant studies had been identified and selected, a systematic method was applied to data collection from each included study. The data collected were the first author's name, year of publication, country of origin, study objective, study design, trial time period, number of patients, population characteristics, number of cysts, cyst location, mean cyst size, treatment, endpoint, main quantitative findings and conclusions. All relevant texts, tables and figures were reviewed for data extraction. A quality evaluation of each study was done, and conclusions were based on levels of evidence and grades of recommendation according to OCEBM[11].

The PRISMA *(Preferred Reporting Items for Systematic Reviews and Meta-Analyses)* statement [12] was used as a guide. Prespecified outcome-specific quality criteria were used to judge the admission of each qualitative and quantitative outcome into the

appropriate analysis. Two investigators independently reviewed each eligible study and extracted the information and data necessary to carry out the qualitative analysis and the meta-analysis. Disagreements were resolved by consensus among all authors. The authors evaluated all randomized trials included in the meta-analysis to determine whether they were in accordance with the CONsolidated Standards Of Reporting Trials-CONSORT 2010 statement[12].

Meta-analysis methods

Meta-analysis was performed utilizing the *Cochrane Review Manager (RevMan 5.3)* software. Statistical significance was defined at the level of 0.05. Recommendations of the PRISMA statement were considered as the outcome measure is dichotomic odds ratio was used as effect size. To combine studies to find a summary effect, we have resorted to the Mantel-Haenselz statistical weights. Heterogeneity across studies was followed with the *Cochrane Q-statistic* (whereby $p \leq 0.05$ was considered statistically significant), and homogenicity of studies was rejected. The I^2-*statistic* was also used to describe the percentage of total heterogenicity across studies. The following suggested cut-off points were used: I^2=0–25%, no heterogeneity; I^2=25–50%, moderate heterogeneity; I^2=50–75%, large heterogeneity; I^2=75–100%, extreme heterogeneity. A *fixed-effect model* was used if the p-value for Q was >0.05 and I^2 was <50%. However, if both statistics rejected the homogeneity hypothesis, a *random-effect model* was used. The significance of the pooled odds ratio was evaluated with the Z test and its two-tailed p-value. Forest plots with odds ratios and their 95% confidence intervals were used to visualize all results. Unfortunately, the small amount of combinative data published to date did not allow any analysis of publication bias or validation, but the reported values in the present work can be considered consistent.

Results

Literature search

A PRISMA Flow diagram of the literature search is shown in **Figure 1**.

By searching the electronic database, we identified 826 records related to the medical treatment of CE. Additionally, 10 records were identified through other sources. Six publications were removed because they were duplicate records. We screened 830 records, 741 of them were excluded for not meeting the inclusion criteria or full-text were not available. Eighty-nine full text articles were read in entirety. Fifty-six full-text articles were excluded for reasons including diagnosis (7), animal studies (4), studies of *Alveolar echinococcosis* (1), surgery treatment and PAIR without chemotherapy (42) and case reports/expert opinion [Level of Evidence 5] (2).

Thirty-three articles[6,8-10,13-41] related to medical treatment of CE in humans that met the inclusion criteria of CE treatment in humans were selected and classified by type of study design. Of them, 22 studies[6,10,13-32] non-randomized controlled trials, prospective or retrospective case series and literature reviews [Levels of Evidence 2 to 4] were qualitatively analysed, and 11 randomized controlled trials[8,9,33-41] [Level of Evidence 1] were quantitatively analysed by meta-analysis.

Qualitative synthesis

This analysis included 22 studies[6,10,13-32] with levels of evidence below 1 (2 to 4): non-randomized controlled trial, one paper[13]; cohort study, one paper[21]; prospective descriptive study, six papers[15,17,22,24,25,29]; retrospective study, six papers[16,18,23,26,28,32]; and case series, two papers[10,30] (**table 1** summarizes the main data of these studies in alphabetical order).
We also included four papers corresponding to literature reviews[14,20,27,31] and two systematic reviews[6,19] in this qualitative analysis (**table 2**).
Chronologically, the oldest publication dates back to 1992 from Todorov *et al*.[29], while the most current was published in 2012 by Ghoshal *et al*.[18].

The geographic location of studies is varied: England (UK)[14,19], Germany[6,20], Italy[15], Spain[10], Greece[27], Yugoslavia[23,25], Romania[28], Bulgaria[29], Turkey[13,16,32], Israel[24], Saudi Arabia[30,31], Libya[17], India[18], China[22], Argentina[21] and Peru[26].

In relation to the study population, ten papers correspond to studies in adult patients[10,13,15,17,18,22,24-26,30], three papers are studies in pediatric patients[16,21,28], seven studies are in both adults and pediatric

patients[6,19,20,23,27,29,32], and two literature reviews covered both animal and human studies[14,31]. The sample sizes of the studies were very different; 5745 school-age children participated in a study cohort[21], 3760 adult and pediatric patients were included in a systematic review[19], and 7[10] and 4[30] adult patients were included in the case series. Other sample sizes were 711, 372, 119, 111, 106, 95, 82, 73, 70, 68, 51, 49, 40 and 27 patients.

Relative to cyst location, the studies principally analysed multi-organ/abdominal cysts[6,10,14,17,19-22,24,27-32], liver[13,15,23,25,26] and lungs[16,18].

The drug used in most antihelmintic therapies is albendazole[6,10,13,16-24,26-32], alone or combined with mebendazole[6,15,16,20,27,29] or praziquantel[10,14,20,25,30,32]. All studies are coincident in terms of their results.

From a qualitative assessment of the 22 studies, treatment outcomes are better when surgery or PAIR is combined with pharmacological therapy of benzimidazole drugs given pre- and/or post-operation. Based on a qualitative synthesis, there was a positive and statistically significant association between cyst size and treatment results. In all studies comparing albendazole to mebendazole or praziquantel, more cysts showed statistical improvement with albendazole than with praziquantel. Albendazole combined with mebendazole or praziquantel performed better than albendazole alone.

Quantitative synthesis using meta-analysis

The meta-analysis included 11 randomized controlled trials[8,9,33-41] [Level of Evidence 1, Grade of recommendation A]. The main methodological characteristics of these studies are presented in **Table 3**, and therapeutic findings are shown in **Table 4.** Chronologically, the oldest publication dates back to 1986 (Davis *et al*.[34]), while the most current was published in 2011 (Shams-UI-Bari *et al*.[41]). The geographic location varies, including Turkey[33], Spain[9,37], Switzerland[34,35], Italy[36], Iran[38,39], India[40,41] and Saudi Arabia[8].

Most of the participants in the clinical trials were adult patients. The mean age (range age) of the participants was 36.7 (16-64) years in the Shams-UI-Bari *et al*. [41] study, and the maximum age was 52 (4-84) in the work of Franchi *et al*. [36]. The sample size of the studies varies, from 448 patients[36] to 15[17] [others samples sizes were 121, 112, 84, 72, 55, 47, 41, 30 and 21 patients]. The number of cysts varied from 33

reported by Khuroo *et al*.[40] to 929 in Franchi *et al*.[35]. Most of the studies analysed multi-organ/abdominal cyts[8,34-37,39], liver[9,33,40,41] and lung[38].

Several studies analysed albendazole alone[33,37-41] or in combination with mebendazole[34-36] or praziquantel[8,9]. Endpoints were protoscolex and cyst viability (viable/non-viable or intact/dead), and/or response to treatment (cured, improved, no changed, worsened). Due to differences among articles, we could only extract data for statistical treatment from 4 out of 11 papers. In the study by Franchi *et al*.[35], cysts treated with albendazole relapsed in 134/640 (20.9%) cases, while the rate for mebendazole treatment was 37/289 (12.8%). In the case series by Keshmiri *et al*. 1999[38] and 2001[39], only one case relapsed following albendazole treatment (1/11; 9.1%), and 1/17 (5.8%) relapsed following mebendazole treatment. According to Shams-UI-Bari *et al*.[41], patients who did not receive albendazole therapy reported a recurrence rate of 6/36 (16.6%), while no recurrence was reported in patients who received albendazole therapy ($p<0.01$). Albendazole therapy was associated with fewer recurrences than mebendazole therapy.

These seven studies were examined in three meta-analyses, as described below.

i) Albendazole plus surgery versus surgery alone. Blidik *et al*.[33], Gil-Grande *et al*.[37], Khuroo *et al*.[40], and Shams-UI-Bari *et al*.[41] address this issue. These studies compare albendazole plus surgery to surgery alone and analyse the viability of the scolex as a common point. In all 3 studies, the number of non-viable scolex in the experimental group (albendazole plus surgery) is higher than the control group (surgery alone) (**tables 3 and 4**). These three studies were significantly heterogeneous ($p=0.01$ for Q test and 78% for I^2), so a random-effects model was used. The results are shown as a forest plot in **Figure 2**.

The summary odds ratio was 48, which is clearly significant in favor of albendazole plus surgery, with a p-value of 0.002 according to the Z test.

Davis *et al*. 1986[34], Davis *et al*. 1989[35], Keshmiri *et al*. 1999[38] and Keshmiri *et al*. 2001[39] answer the second clinical question that we considered in this meta-analysis*:*

ii) Albendazole versus mebendazole. These studies compare albendazole to mebendazole (**Figure 3**) and analyse the response to treatment (cured, improved, no

changed, worsened) as a common point. In all studies, the proportion of cysts cured/success or improvement in the experimental group (albendazole) is higher than that in the control group (mebendazole or placebo) (**table 4**).

Figure 3 (forest plot) shows the results[34,35]. The Q test of heterogeneity was not significant (p=0.73), indicating excellent homogeneity (I^2= 0%) of these studies.

(iii) Albendazole versus placebo. **Figure 4** shows the results obtained from comparing albendazole to placebo[38,39].

The test of heterogeneity was not significant (p=0.89), indicating excellent homogeneity (I^2=0%).

Cobo *et al*.[9], answer the third clinical question that we considered in this meta-analysis.

iv) Albendazole versus albendazole plus praziquantel. It was not possible to statistically combine the data comparing albendazole plus praziquantel treatment to albendazole alone. However, an answer is given in Mohamed *et al*.[8] and Cobo *et al*.[9]. In the latter paper[9], the number of non-viable scoleces in the albendazole plus praziquantel group was higher than in the albendazole alone group. According to Mohamed *et al*.[8], the reduction in the number of cysts and cases cured or improved in the albendazole plus praziquantel group was higher than it was in albendazole alone group (**table 4**). It was not possible to generate a forest plot.

Discussion

The clinical handling of CE involves four therapeutic alternatives: surgery, percutaneous intervention, drugs, and the "watch and wait" approach for quiescent cysts. The evidence supporting pharmacological treatment is weak. This lack in quality is due to i) small number of patients forming an homogeneous clinical group, even in referral hospitals in endemic countries; ii) the different applied methodology prevents comparison between studies; iii) CE is a chronic disease, which requires long-term monitoring to determinate the effectiveness of an intervention [42]. There are no gold standard methods to determinate biological status and response to treatment [37]. Drug-induced echographic changes can be compare with viability studies of protoscoleces

developed on surgically removed cysts, which would generate parasitological data to correlate with clinical effects. These objectives were used by Gil Grande *et al*. [37] in their randomized controlled trial of the efficacy of albendazole, but data collection has not been posible for praziquantel, despite its clinical use in last 20 years. Furthermore, hydatid cysts may spontaneously regress with shedding of membranes, solidifying and calcification in their natural history, without any chemotherapeutic assistance [43].

Despite attempts by the WHO, the management of CE disease remains a major problem [44]. There is no consensus on disease management [1,45]. Thereby, studies to establish the efficacy of medical treatment, the dosing and the minimal effective dose have not been yet determined by sufficient evidence. Case definitions, diagnostic proceedings and defined monitoring methods for long-term follow-up need to be standardised, and comparative efficacy surveys need to be performed. Future progress in chemotherapy may be attained by identifying drugs with higher anti-echinococcal activity.

Clinical question 1. Does chemotherapy treatment improve the results of surgical treatment?

Our data show that treatment outcomes are better when surgery or PAIR is combined with chemotherapy of benzimidazole drugs given pre- and/or post-surgery. The summary odds ratio found in the meta-analysis shows a value of 48 (95% CI: 4-586), which is far greater than the value of 1 that would indicate equality of the treatments.

Chemotherapy is applied in many scenarios, so it is very difficult to standardize the results. Anthelmintics are usually indicated before and after surgery to reduce the size of cysts, to sterilise them, and to prevent relapses. Furthermore, medical treatment is the only therapeutic option in scattered CE and/or inoperable CE. To date, there are insufficient data to establish the optimal duration of treatment or frequency of dose. Recommendations on the timing of the start of chemotherapy before surgery or PAIR are varied. Preoperative treatment with albendazole begins at least 3 months to 1 day before surgery and/or PAIR and continues for 1-3 months post-treatment, and there is no clear recommendation on praziquantel dosage schedules. In terms of cyst viability and radiological efficacy, the data are not conclusive as to whether longer courses of treatment (3 months) are more efficacious than shorter courses of treatment[19,37].

The additional benefit from very long treatment (more than 6 months) is marginal for most patients, and although it is performed in clinical practice with patients with multiple or inoperable CE, it has never been well evaluated. There is a suggestion that lesions in organs other than the liver, lung and peritoneum may benefit from more prolonged therapy, but the numbers are small.

Clinical question 2. *Albendazole vs. mebendazole*.

Our data show in all of the studies that the odds ratio of cure/success or improvement in the albendazole group is greater than those in the other groups (mebendazole or placebo). To be exact, the summary odds ratio for albendazole versus mebendazole was 2.4 (95% CI: 1.3, 4.4) with a p-value of 0.006. There is some evidence that albendazole should be chosen over mebendazole, at least until more trials are reported. As expected, the comparison of albendazole and placebo is in favor of the drug treatment, with a p-value of 0.002 for the Z test of significance.

Mebendazole is a broad-spectrum antihelminthic agent of the benzimidazole type with in vivo activity in CE. Nevertheless, albendazole is more active in vitro than mebendazole and has better gastrointestinal uptake and bioavailability. It has been published better clinical outcomes with albendazole. [46]. Flubendazole is not used for CE. Liver and haematological toxicities are the most frequent serious adverse effects of albendazole and mebendazole. Thus, patients receiving drug therapy are generally recommended to have hepatic enzymes and complete blood counts monitored every two weeks during treatment[47]. Although it is orally administered, albendazole results in high serum concentrations but penetration into cyst contents is irregular. Both drugs may reduce the size of hydatid cysts and may lead to the sterilization of cyst contents in some cases[46]. However, less than half treated patients achieve clinical and radiological resolution without concomitant drainage. [46]. The normal dose of orally dispensed albendazole, with or without PAIR, is 10–15 mg/kg/day in two divided doses, or a standard dose of 400 mg bid. If mebendazole is used, the daily dose is 40–50 mg/kg in three divided doses. Treatment is usually administered in 1–6 monthly cycles separated by 10–14 day intervals. Clinical and radiographic improvement (in most studies defined as >25% reduction in cyst size, membrane separation, or cyst calcification is seen frequently, but complete cure (i.e., cyst disappearance) generally occurs in less than half of patients treated with anti-parasitic monotherapy[48]. Our data show that the efficacy of albendazole was superior to that of mebendazole, with a p-

value of 0.009. Although there are works that show that the rate of relapse was similar for patients treated with albendazole or mebendazole, it is necessary to carry out prospective studies over long periods to generate robust data.

Clinical question 3. *Albendazole vs albendazole plus praziquantel*.

Our data show that combined treatment with albendazole plus praziquantel is superior to treatment with albendazole alone.

Praziquantel, an isoquinolone derivative, has had limited use in the treatment of CE[46]. Praziquantel is an effective scolicide in vitro and in animal models; in humans, it has positive pharmacokinetics when given in a dose of 50 mg/kg either once weekly or every two weeks[46]. There are few clinical studies documenting the efficacy of praziquantel in humans[8,9,30,49]; however, several of these have suggested that the use of praziquantel in combination with mebendazole[49] or albendazole[8,9] is more effective and possibly more rapid than treatment with the benzimidazoles alone. The earliest report of a trial of combination praziquantel and albendazole in the treatment of human hydatid disease was made by Yasawy *et al*.[30]. Main disadvantages of these studies are the use of different praziquantel regimens: various treatment groups are too small for meaningful analysis and, given the heterogeneity of appearances in CE diseases, failure to use contemporaneous matching controls[8,30]. There is evidence to suggest some benefit from the use of praziquantel in combination with albendazole in pre- and post-intervention chemotherapy for CE[8,9]. Praziquantel might be useful in cases where spillage occurs during surgery. Combined treatment reduces potentially the risk of disease recurrence and intraperitoneal seeding of infection that may develop via cyst rupture and spillage. Additionally, praziquantel may prevent the vesicular development of protoscoleces and inhibit the formation of secondary cysts. Combination therapy increases levels of albendazole sulphoxide (the active metabolite of albendazole) both in serum and in cyst fluid compared with levels in patients received only albendazole. Praziquantel has been given at a dose of 40 mg/kg in different regimens for each patient (daily, weekly, fortnightly or monthly) with standard courses of albendazole for between 2 and 3 months. At present, there is scarce evidence supportting a recommendation for the routine use of praziquantel in prolonged chemotherapy for established CE where surgery is not indicated or in severe disseminated disease. This treatment and its dosage regimen require evaluation. Further randomized controlled studies are required to determine whether there are significant

benefits of combination therapy with albendazole and praziquantel over monotherapy with albendazole so that treatment recommendations for its use can be clarified. Finally, as with every neglected disease, there are very few drugs available to treat CE. As there is evidence to suggest some benefit from the use of praziquantel in this condition, its potential should no longer be neglected.

Limitations

One of the limitations of this study was the calculation of *overall effects* in the meta-analysis sections due to the scarcity of data. Some authors argue that, since clinical and methodological diversity always occurs in meta-analyses, a good statistical combination of studies is always difficult[50,51]. Nevertheless, a qualitative review and a meta-analysis are better than a lack of information. The authors used *forest plots* to interpret the results of the meta-analyses, which is an accepted methodology. However, when there are few studies, these plots and their associated tests of significance are not very robust, and more studies are necessary to obtain conclusive evidence.

Risks of bias (methodological and clinical) may have a bearing on the results of our qualitative review and meta-analysis. The overall effect of meta-analysis may be affected by *publication bias*, overestimating the efficacy of treatment, since studies with statistically significant results are more likely to be published than those with non-significant differences. Funnel plots visually check the possible existence of publication bias, but unfortunately, this type of analysis cannot be used when the number of included studies is scarce, as it was the case here.

Despite these limitations, this systematic review and meta-analysis seeks to synthesize the large volume of information available up to date related to medical treatment of CE to help make decisions on evidence-based medicine in daily clinical practice.

Conclusions

Does our study provide sufficient evidence to influence decisions for the treatment of CE?

We think that our data are strong enough to claim the following: i) pharmacological treatment improves results in patients with CE who will undergo surgical treatment; ii) for now, albendazole chemotherapy is the primary medical treatment to consider in the

medical management of CE; and iii) treatment with albendazole plus praziquantel shows higher scolicidal activity and a greater number of cysts cured or improved compared to albendazole alone.

List of abbreviations

CE: Cystic Echinococcosis

CONSORT: Consolidated Standards Of Reporting Trials

OCEBM: Oxford Centre for Evidence-Based Medicine

PAIR: Puncture, Aspiration, Injection of protoscolicidal agent and Reaspiration

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

WHO: World Health Organization

Declarations

Ethical approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

All authors declare no potential conflicts of interest.

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Authors´ contributions

VVT, MAS, MBG, AM, JPL: study design and mayor contributiong to writting; MAS, ALB, ARA, FJB: analysis and interpretation of data. ACP, JLMB, MC: Study implementation and writting. All authors read and approved final versión.

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Table legends

Table 1. Main characteristics of non-randomized controlled trials, prospective or retrospective case series included in the qualitative analysis.

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Table 3. Main methodological characteristics of randomized controlled trials included in the quantitative analysis *(meta-analysis)*.

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Figure legends

Figure 1. Flowchart of information through the different phases of the systematic review following the PRISMA recommendations

Figure 2. Forest plot of comparison: intervention (albendazole plus surgery) *vs* control (surgery alone), outcome: Viability of scolex (Event=non-viable or dead).

Figure 3. Forest plot of comparison: intervention (albendazole) *vs* control (mebendazole), outcome: Response to treatment (Event = cure/success plus improvement).

Figure 4. Forest plot of comparison: intervention (albendazole) *vs* control (placebo), outcome: Response to treatment (Event = cure/success plus improvement).

Additional files list

Additional file 1: Supplementary methods. Search strategy.

Additional file 2: PRISMA checklist.

Table 1. Main characteristics of non-randomized controlled trials, prospective or retrospective case series included in the qualitative analysis.

Author/s Year(Ref.no.)	Location, Country	Study design (follow-up period)	Participants	Sample size(N)	No. cysts	Cyst location	Objective	Anthelminthic drugs	Results/Conclusions
Aktan AO, *et al*. 1996[13]	Istanbul, Turkey	A non-randomized controlled trial	Adult patients	70	89	Liver	To evaluate the effect of preoperative ABZ treatment (3-weeks) in two groups: **1st group** *(experimental group)* ABZ 3 weeks before surgery, **2nd group** *(control group)* surgery (no preoperative treatment).	ABZ	The ICP values of viable cysts in the 1st group were significantly lower ($p<0.05$). The number of non-viable cysts was also significantly higher in the 1st group ($p<0.05$). ABZ has proved to be effective in decreasing the viability of liver hydatid cysts when given for 3 weeks preoperatively.
Di Matteo G, *et al*. 1996[15]	Rome, Italy	A prospective, descriptive, non-comparative study (1985-1992)	Adult patients (mean age, 42)	95	No data	Liver	To show that radical surgery is most effective when it is associated with medical therapy of benzoimidazole drugs (MBZ) pre- and post-operatively.	MBZ	The most effective treatment for echinococcus cystic disease of the liver is radical surgery. Results are best when surgery is combined with medical therapy of benzoimidazole drugs (MBZ) given pre- and post-operatively.
Doğru D, *et al*. 2005[16]	Ankara, Turkey	A retrospective study	Pediatric patients	82	102	Lung	To demonstrate the safety and efficacy of medical treatment.	MBZ *vs* ABZ	The cure and the failure rates were statistically insignificant in cysts treated with MBZ and ABZ; however statistically significantly more cysts were improved with ABZ. The results were statistically insignificant between continuous and cyclic ABZ treatment. There was a positive, weak and statistically significant correlation between the cyst size and treatment results. These results cannot recommend a standard treatment regimen as the duration of treatment should be individualized for each patient.
el-Mufti M, *et al*. 1993[17]	Benghazi, Libya	A prospective, descriptive, non-comparative study	Adult patients	40	63	Multi-organ	To assess the effectiveness of ABZ before surgery.	ABZ	It is suggested that patients suffering from uncomplicated hydatid disease should be given the benefit of a trial course of ABZ therapy before surgery.
Ghoshal AG, *et al*. 2012[18]	Kolkata, India	A retrospective study (5 years)	Adult patients	106	No data	Lung	To determine the presentation, treatment (ABZ and surgery) and outcome of hydatid disease of lung.	ABZ	Surgery is a safe and effective way of treatment for thoracic hydatid cyst along with perioperative ABZ therapy. There is a scope for chemotherapy with ABZ in inoperable cases.
Larrieu E, *et al*. 2004[21]	Río Negro, Argentina	A prospective cohort study (5-6 years)	Pediatric patients	5745 *Exposed cohort*=4644 *Unexposed cohort*=1101	No data	Abdominal	To evaluate the results of a program carried out in endemic areas of the Province of Río Negro, Argentina, during the years 1997-2002 in asymptomatic children, screening.	ABZ	Treatment with ABZ confirmed its action in modifying the prognosis of CE, presenting positive effects in 76% of patients receiving the drug. None of the treated cases required surgery. The combination of ultrasonographic screening and ABZ treatment showed promising results.
Li T, *et al*. 2011[22]	Sichuan, China	A prospective, descriptive, non-comparative study	Adult patients	49	No data	Abdominal	A post-treatment follow-up study was carried out to assess the effectiveness of community based use of cyclic ABZ treatment in Tibetan CE cases.	ABZ	Cyclic ABZ treatment proved to be effective in the great majority of CE, but periodic abdominal ultrasound examination was necessary to guide appropriate treatment. Serology with recombinant antigen B could provide additional limited information about the effectiveness of ABZ in CE cases. Oral ABZ for over 18 months was more likely to result in CE cure.
Mikić D, *et al*. 1998[23]	Republic of Serbia	A retrospective study	Adult and pediatric patients (female age range, 9-83; males age range, 6-72)	119	No data	Liver	To value the efficacy of ABZ and surgery.	ABZ	Surgical removal of the cyst takes a leading place in the treatment of hepatic echinococcosis. However, in well-selected cases and in the patients with high surgical risk, anthelminthic therapy and PD of echinococcus cyst are of more significance.
Nahmias J, *et al*. 1994[24]	Moztkin, Israel	A prospective, descriptive, non-comparative study (3-7 years)	Adult patients	68	No data	Multi-organ	To assess long-term efficacy of ABZ.	ABZ	Follow-up for 3-7 years showed that this treatment alone eradicated the cysts in many patients; in most of the remainder, disease progression stopped. No patient worsened but a recurrence occurred in two patients at about 56 months.
Perez Molina	Madrid,	A case series	Adult patients	7	No data	Multi-organ	To describe the clinical	ABZ *vs*	Nitazoxanide combination therapy seems to be active for

JA, *et al*. 2011[10]	Spain		(age range, 27-68)				effectiveness and tolerability of nitazoxanide, combined with ABZ, with or without PZQ, in patients affected by disseminated chronic CE.	ABZ+PZQ	disseminated CE affecting soft tissues, muscles, or viscera, and apparently it has no role in chronic and extensive bony lesions.
Redzić B, *et al*. 1995[24]	Republic of Serbia	A prospective, descriptive non-comparative study (from 1989 to 1993)	Adult patients	73	No data	Liver	To value the efficacy of PZQ.	PZQ	The drug treatment was the therapy of choice in patients with *Echinococcus granulosus*. It should be given prophylactically, preoperatively, to sterilize the cyst and also as a curative treatment.
Salinas JL, *et al*. 2011[26]	Lima, Perú	A retrospective study (from January 1997 to December 2007)	Adult patients (mean age at diagnosis, 51±14)	27	No data	Liver	To ascertain factors associated with the success of ABZ in the treatment of non-complicated hepatic CE, and to establish the frequency of long-term worsening and recurrence of disease after treatment completion in Peru.	ABZ	Long-term hepatic CE treatment outcomes and the success rate of ABZ were modest (3 cycles are few and needed treatment 6-12 months). It´s necessary to investigate into alternate therapeutic strategies for this neglected disease.
Tarnovetchi C, *et al*. 2010[28]	Romania	A retrospective study (2004-2009 and 2000-2009)	Pediatric patients (age range, 2-17)	111	No data	Abdominal	To value the efficacy of ABZ and surgery (Lagrot partial pericystectomy).	ABZ	The treatment includes both surgical and medical means. There is a relatively high rate of postoperative complications (although some of them being minor) in 31 patients.
Todorov T, *et al*. 1992[29]	Sofia, Bulgaria	A prospective descriptive study	Adult and pediatric patients (age range, 6-70)	51 (28 MBZ, 23 ABZ)	No data	Multi-organ	To test the efficacy of MBZ and ABZ.	MBZ or ABZ	Treatment with MBZ was successful in 8 (28.6%), partially successful in 8 (28.6%) and unsuccessful in 12 (42.8%). Treatment with ABZ was successful in 10 (43.5%), partially successful in 10 (43.5%) and unsuccessful in 3 (13.0%).
Yasawy MI, *et al*. 1993[30]	Riyah, Saudi Arabia	A case series	Adult patients	4	No data	Pelvic, abdominal and thoracic	To value the response to combined medical treatment (ABZ and PZQ).	ABZ plus PZQ *vs* ABZ	This preliminary report shows that the response to combined treatment is better and much quicker compared to ABZ alone.
Yilmaz Y, *et al*. 2006[32]	Van, Turkey	A retrospective study (10 years)	Adult and pediatric patients	372 (of them, 8 urinary hydatid disease)	No data	Liver, spleen, brain and kidneys(7)-retrovesical area(1)	To discuss therapeutic options and treatment results according to current literature.	ABZ	Treated surgically (271 cases) and drained percutaneously (99 cases). Kidneys were removed totally (4 cases), cystectomy and omentoplasty was performed in one case. ABZ was administered to 192 patients.

*ABZ, Albendazole; PZQ, Praziquantel; MBZ, Mebendazol.

Table 2. Main characteristics of the reviews included in the qualitative analysis.

Author/s, Year(Ref.no.)	Location, Country	Study design	Participants	Sample size(N)	No. cysts	Cyst location	Objective	Anthelminthic drugs	Results/Conclusions
Bygott JM, *et al*. 2009[14]	London, England	A literature review	In vitro/vivo animal studies, human studies	No data	No data	Liver, lung, intra-abdominal	To review the evidence on the use of PZQ in treatment of cystic hydatid disease from in vitro and in vivo animal studies, human clinical studies and human case reports.	PZQ	Insufficient published evidence to support a clear recommendation for the use of PZQ in prolonged chemotherapy for established hydatid disease for which surgery is not indicated or in severe disseminated disease and further work is necessary.
Horton RJ. 1997[19]	Brentford, UK	A systematic review	Adult and pediatric patients (age range, 6-83)	3760	No data	Principally in the liver, with lung infection being the second most common	To review the efficacy and safety of ABZ obtained in the last 12 years.	ABZ	ABZ has been shown to be a useful advance in the management of CE both when used as sole treatment or as an adjunct to surgery or other treatments. Efficacy seems to increase with exposure up to 3 months in the commoner cyst sites.
Kern P, *et al*. 2003[20]	Ulm, Germany	A literature review	Adult and pediatric patients	No data	No data	Liver, lung, kidney, spleen, muscles, abdominal and pelvic cavity,…	To review clinical presentation and medical treatment *vs* conservative treatment and outcome *Echinococcus granulosus* infection.	ABZ or MBZ or PZQ	Of major importance in the management of CE is long-term observation and longitudinal monitoring. Liver cysts relapse more frequently than do cysts at other sites, presumably because of greater proliferative potential of the metacestode tissue remaining in the hepatic environment. Further cycles of benzimidazole treatment of patients with recurrences were again well tolerated and effective. It was suggested that the higher metabolic activity of relapsed cysts makes them more susceptible to the action of benzimidazole carbamates.
Stamatakos M, *et al*. 2009[27]	Athens, Greece	A literature review	Adult and pediatric patients	No data	No data	Liver, lung, and peritoneal cysts	To clarify anthelminthic treatment as an alternative hydatic cyst therapy, its indications and contraindications.	ABZ or MBZ	ABZ and MBZ have a favourable effect in patients suffering from multiorgan and multicystic disease, in inoperable primary liver or lung echinococcosis, and they can also prevent secondary echinococcosis. Chemotherapy is contraindicated for large cysts that are at risk to rupture and for inactive or calcified cysts. The main adverse events are related to changes in liver enzyme levels. The best efficacy is observed with liver, lung, and peritoneal cysts. Certain various factors influence the therapeutic results of medical treatment. The vast majority of the recurring cysts show good susceptibility to re-treatment.
Stojkovic M, *et al*. 2009[6]	Heidelberg, Germany (6 Centers: Rome, Bulgaria, Romania, Palermo, Greece, Turkey)	A systematic review	Adult and pediatric patients	711	1159	Liver and peritoneal cysts	To describe cyst outcome after initiation of benzimidazole treatment, with outcome defined by cyst stage determined by ultrasound following the WHO classification of 2001.	ABZ or MBZ	The overall efficacy of benzimidazoles has been overstated in the past. There is an urgent need for a pragmatic randomised controlled trial. The clarification of the efficacy of benzimidazoles in CE treatment is of paramount importance since benzimidazoles are the only drugs currently available to treat this neglected disease.
Yasawy MI 2001[31]	Saudi Arabia	A literature review	Clinical cases and animal studies	No data	No data	Multi-organ	To review the efficiency of benzimidazole (ABZ) and isoquineline (PZQ).	ABZ or PZQ	Combination therapy is more effective and requires a shorter period of treatment than ABZ alone. Pre- and postoperative prophylactic therapy reduce risk of spillage and dissemination during surgery and percutaneous aspiration.

*ABZ, Albendazole; PZQ, Praziquantel; MBZ, Mebendazol.

Table 3. Main methodological characteristics of randomized controlled trials included in the quantitative analysis *(meta-analysis)*.

Author/s. Year[Ref.no.]	Location Country	Objective*	Study design	Trial time period	Participants	Sample size(N)**	No. Cysts	Patients characteristics***
Bildik N, *et al*. 2007[33]	Kartal-Istanbul, Turkey	To evaluate the efficacy of preoperative ABZ therapy	A randomized controlled trial	1998-2003	Patients with isolated hydatid cysts of the liver	84	84	Sex (M/F), 36/48 Range age (*yr*), (14-67) **Group I** n=21 No.cyst=21 | **Group II** n=21 No.cyst=21 | **Group III** n=21 No.cyst=21 | **Group IV-control group** n=21 No.cyst=21
Cobo F, *et al*. 1998[9]	Pamplona-Navarra, Spain	To compare the effects of a combined medication of ABZ plus PZQ *vs* ABZ alone in the preoperative treatment	A randomized controlled trial	1990-1997	Patients with intra-abdominal hydatidosis	62→47	No data	n: **Group I** 19→12 | **Group II** 17→14 | **Group III** 26→21 Sex (M/F): 6/6 | 11/3 | 9/12 Age (*yr*, mean±SD[range]): 47.9(19-67) | 51.1(31-70) | 46.9(18-75) Cyst/patient (mean[range]): 1.17(1-3) | 1.57(1-4) | 1.43(1-5)
Davis A, *et al*. 1986[34]	WHO, Geneva, Switzerland	*First phase:* Studies coordinated by the WHO were conducted in seven clinical centers on the chemotherapy of human echinococcosis with MBZ, ABZ and FBZ.	A multicenter randomized clinical trials (5 clinical centers, Beirut, Paris, Rome, Sofia and Zurich)	1982-1984	Adults patients, mainly, only 7% below 15 years	121	121	n=121 Sex (M/F)=63/58 No.cyst=402 **MBZ** 85 38/47 348 | **FBZ** 6 3/3 18 | **ABZ** 30 22/8 36
Davis A, *et al*. 1989[35]	WHO, Geneva, Switzerland	*Second phase:* To value the efficacy of ABZ and MBZ in human CE coordinated by WHO.	A multicenter randomized clinical trials (4 clinical centers, Beirut, Paris, Rome and Sofia)	1985-1987	Adults patients, mainly, only 4% below 15 years	176→112	106	n=112 Sex (M/F)=47/65 Follow-up <12 months=44 Follow-up >12 months=68 No.cyst patients >12 months=106 **ABZ** 67 27/40 21 46 76 | **MBZ** 45 20/25 23 22 30
Franchi C, *et al*. 1999[36]	Rome, Italy	To evaluate the results obtained during long-term follow-up of a series of patients treated with benzimidazole carbamate	A randomized controlled trial	1982-1997	Patients with hydatidosis located in various body organs	448	929	Sex (M/F), 191/257 Age (*yr*, mean[range]), 52 (4-86) Follow-up (months, mean[range]), 22 (12-170) n: **MBZ** 125 | **ABZ** 323 No.cyst: 289 | 640
Gil-Grande LA, *et al*. 1993[37]	Madrid, Spain	To assess the efficacy and safety of ABZ in a medical treatment	A randomized controlled trial	1987-1991	Patients with intra-abdominal hydatid disease	66→55	55	n: **Group A** 18 | **Group B** 19 | **Control gr.** 18 Sex (M/F): 10/8 | 12/7 | 9/9 Age (*yr*, mean±SD): 41.7±14.2 | 47.3±13.9 | 41.2±17.3 No.cyst: 18 | 19 | 18
Keshmiri M, *et al*. 1999[38]	Mashhad, Iran	To compare the effects of ABZ *vs* placebo in the treatment of hydatid cysts	A triple-blind parallel randomized clinical trial	1994-1995	Patients with hydatid cysts of the lung/pulmonary echinococcosis	20[All p.] 15[Treat.]	179[All p.] 150[Treat.]	**Treatment group**: **All p.**[+] 14 8/6 41±15 137 12.2±13.4 | **Treat.**[+] 11 5/6 40±17 124 16.3±13.9 **Placebo group**: **All p.**[+] 6 3/3 39±17 42 10.8±13.7 | **Treat.**[+] 4 3/1 45±17 26 8.8±7.6 n / Sex (M/F) / Age (*yr*, mean±SD) / No.cyst / Cyst/patient
Keshmiri M, *et al*. 2001[39]	Mashhad, Iran	To evaluate the effect of ABZ on hydatid disease	A double-blind parallel-group randomized clinical trial	1994-1995	Patients with hydatid cysts of the lung and abdomen (including liver)	29[All p.] 21[Treat.]	240[All p.] 203[Treat.]	**Treatment group**: **All p.**[+] 22 11/11 41.4±15.9 | **Treat.**[+] 17 7/10 40.5±17.3 **Placebo group**: **All p.**[+] 7 4/3 35.4±18.3 | **Treat.**[+] 4 3/1 45.5±17.4 n / Sex (M/F) / Age (*yr*, mean±SD)
								No.cyst: 191 | 172 | 49 | 31 Cyst/patient: 8.6±9.0 | 9.8±9.9 | 7.1±6.5 | 7.8±6.1
Khuroo MS, *et al*. 1993[40]	Srinagar, Kashmir, India	To compare the safety and efficacy of percutaneous drainage (PD) with ABZ therapy	A randomized controlled trial	1989-1992	Patients with hepatic hydatid cysts	30	33	**PD** | **ABZ-PD** | **ABZ** n: 10 | 10 | 10 Sex (M/F): 4/6 | 3/7 | 4/6 Age (*yr*, mean±SD): 36.7±12.3 | 41.3±14.9 | 39.5±14.4 (Range age): (12-55) | (12-64) | (18-60) No.cyst: 10 | 12 | 11 Size Ø (*cm*, mean±SD): 9.2±4.4 | 10.8±3.0 | 8.8±4.5 Volume (cm^3, mean±SD): 686±651 | 835±528 | 642±717
Mohamed AE, *et al*. 1998[8]	Riyadh, Saudi Arabia	To evaluate the effect of different regimens of medical treatment	Two prospective randomized intervention studies	1st study, 1985-1990 2nd study, 1990-1998	Adult Saudi patients with hydatid disease at the Armed Forces Hospital	1st, 22 2nd, 19, Total,41	No data	**1st, ALB** n=22 | **2nd, ABZ+PZQ** n=19
Shams-Ul-Bari, *et al*. 2011[41]	Srinagar, Kashmir, India	To assess the effect of preoperative ABZ therapy on the viability of protoscoleces at the time of surgery	A randomized controlled trial	2002-2003 + follow-up 5 years	Patients with diagnosis of hydatid liver disease	72	72	Sex (M/F), 39/33 Range age (*yr*), (17-66) n: **Group A-Surgery** 36 | **Group B-ABZ+surg+ABZ** 36 Sex (M/F): 19/17 | 20/16 Age (*yr*, mean±SD[range]): 36.75±11.34(16-64) | 36.78±11.79(17-62) No.cyst: 36 | 36

*ABZ, Albendazole; PZQ, Praziquantel; MBZ, Mebendazol; FBZ, Flubendazole.

**N start of the study→N the end of the study

***M/F, Male/Female ratio.

+All patients, Completed treatment.

Table 4. Main therapeutic findings and conclusions of randomized controlled trials included in the quantitative analysis *(meta-analysis)*.

Author/s. Year[Ref.no.]	Cyst location	Mean cyst size(cm)	Treatment*	Endpoint	Main quantitative findings**		
Bildik N, *et al.* 2007[33]	Liver	Non-registered information	**G-I:** ABZ (10 mg/kg/day 1 month before surgery) **G-II:** ABZ (10 mg/kg/day 2 months before surgery) **G-III:** ABZ (10 mg/kg/day 3 months before surgery) **G-IV (control gr.):** surgery (no preoperative therapy)	Viability of the scoleces		**Intact**	**Dead**
					G-I	10	11
					G-II	7	14
					G-III	2	19
					G-IV	17	4
Cobo F, *et al.* 1998[9]	Liver	Non-registered information	**G-I:** ABZ (10 mg/kg/day 1 month before surgery) **G-II:** ABZ (20 mg/kg/day 1 months before surgery) **G-III:** ABZ (10 mg/kg/day) + PZQ (25 mg/kg/day 1 month before surgery)	Protoscolex viability. ABZ sulphoxide levels in serum and cyst fluid	**Protoscoleces viability**		
					G-III and **G-I**		p=0.004
					G-III and **G-II**		p=0.030
					ABZ sulphoxide levels		
					G-III and **G-I**		p=0.016
					G-III and **G-II**		p=0.034
Davis A, *et al.* 1986[34]	Liver, lung, other organs	Non-registered information	**MBZ** (13 to 136.4 mg/kg/day) **FBZ** (37.5 to 54.5 mg/kg/day) **ABZ** (9.8 to 15.4 mg/kg/day)	Results: -success -partial success -improvement -no success	**MBZ**	**FBZ**	**ABZ**
					8 (9.4)	1	5 (16.7)
					4 (4.7)	-	4 (13.3)
					40 (47.1)	-	14 (46.7)
					33 (38.8)	5	7 (23.3)
Davis A, *et al.* 1989[35]	Liver, lung, other organs	Non-registered information	**ABZ** (10 mg/kg/day 1 month) **MBZ** (1.5 to 4.5 gr/kg/day, children half of the adult dose)	Results: -success -favourable effect -no success	Follow-up	**ABZ**	**MBZ**
					<12 months:	**21 (100)**	**23 (100)**
					-success	-	-
					-favourable effect	13 (62)	6 (26)
					-no success	5 (24)	13 (57)
					no evaluation	3 (14)	4 (17)
					>12 months:	**46 (100)**	**22 (100)**
					-success	18 (39)	3 (14)
					-favourable effect	18 (39)	14 (64)
					-no success	10 (22)	5 (23)
Franchi C, *et al.* 1999[36]	Liver, abdomen, lung	Non-registered information	**G-I:** MBZ (50 mg/kg/day) **G-II:** ABZ (10-12 mg/kg/day) Both drugs in continuous 3- to 6-months cycles	Chest radiographic, ultrasonography, morphological changes and sonographic classification by *Caremani et al*	**Cysts**	**G-I**	**G-II**
					Treated	289	640
					Evaluated	271	611
					Changed	152	502
					Further deg.	34	110
					Relapse	37	134
Gil-Grande LA, *et al.* 1993[37]	Liver or abdominal	**G-A:** 10.4±4.1 **G-B:** 8.9±4.3 **G-C:** 10.5±5.1	**G-A:** ABZ (10 mg/kg/day 1 month before surgery) **G-B:** ABZ (10 mg/kg/day 3 months before surgery) **G-C (control group):** surgery (no ABZ treatment)	Protoscolex and cyst viability (patients/mice). Echographic changes			**p-value**
					Viability of protoscolices		0.041
					Intraperitoneal inoculation		0.167
					Membrane disruption		<0.001
					Echographic changes		0.038
Keshmiri M, *et al.* 1999[38]	Lung	**E.gr:** cm^3±SD, 29.6±50.5[All] 27.1±45.8[Treat.] **C.gr:** cm^3±SD, 18.3±49.5[All] 25.1±63.3[Treat.]	**Experimental group:** ABZ (10-15 mg/kg/day 6 months) **Control group:** placebo	Radiological or ultrasonic findings. Response to treatment was classified: -Cured -Improved -No change -Worsened (*Caremani et al)*		**ABZ**	**Placebo**
					No. cysts	124	26
					Worse	9 (7)	10 (39)
					No change	32 (26)	13 (50)
					Decreased		
					>25% (p<0.001)	83 (67)	3 (12)
					>50% (p<0.001)	60 (48)	1 (4)
					>75% (p=0.067)	36 (29)	1 (4)
					Disappeared(p=0.075)	16 (13)	0 (0)
Keshmiri M, *et al.* 2001[39]	Lung, abdomen (including liver)	**E.gr:** cm^3±SD, Lung, 29.6±50.5[All] 27.1±45.8[Treat.] Abdomen (liver), 198.1±403.7[All] 212.7±426.2[Treat.] **C.gr:** cm^3±SD, Lung, 18.3±49.5[All] 25.1±63.3[Treat.] Abdomen (liver), 74.0±130.8[All] 91.9±155.4[Treat.]	**Experimental group:** ABZ (400 mg twice a day, in 3 cycles of 6 weeks with 2 weeks between cycles) **Control group:** placebo	Volume. Ultrasonography and Computed tomography changes: 7 types,T1-T7. Response to treatment was classified: -Cured -Improved -No change -Worsened (*Caremani et al*)		**ABZ**	**Placebo**
					No. cysts	172	31
					Worse (p<0.001)	15 (8.7)	11 (35.5)
					No change	23 (13.4)	16 (51.6)
					Improved (p<0.001)	117 (68)	4 (12.9)
					Cure (p=0.081)	17 (9.9)	0 (0.0)
Khuroo MS, *et al.* 1993[40]	Liver	cm / cm^3, mean±SD At entry into the study *vs* the end of study **PD,** 9.2±4.4 *vs* 5.1±3.9 686±651 *vs* 297±515 **ALB-PD,** 10.8±3.0 *vs* 4.8±3.4 835±528 *vs* 260±389 **ALB,** 8.8±4.5 *vs* 8.0±5.0 642±717 *vs* 606±741	**G-I:** PD **G-II:** ABZ (10 mg.kg-1.day-1 for 8 weeks) plus PD **G-III:** ABZ alone	At entry into the study *vs* the end of study: -Clinical response -Cyst size -Cyst echopattern -Hydatid serology -Complications			**p-value**
					Clinical response		<0.001
							<0.005
					Cyst diameter		<0.05
					Cyst volume		<0.01
					Cyst echopattern		<0.01
					Hydatid serology		NS
Mohamed AE, *et al.* 1998[8]	**1st,** Liver(18), lung(1), multiple cyst(3). **2nd,** Liver(13), lung(2), others:pelvis, mediastinum, kidney, spinal(4)	Non-registered information	**1st, ABZ** (400 mg twice day four weeks/two-week drug free period) **2nd, ABZ** (400 mg twice a day) + **PZQ** (50 mg/kg)	Ultrasound and computed tomography changes, magnetic resonance, hydatid serology and chest-X-ray. Complete cure rates		**ABZ**	**ABZ+PZQ**
					No. patients	22	19
					Disappearance	8 (36.4)	9 (47.4)
					Liver		7/13
					Lung		2/2
					Reduction	5 (22.7)	9 (47.4)
					Liver		5/13
					Others		4/4
					No change	2 (9.1)	1 (5.2)
					Increase	0	0
Shams-Ul-Bari, *et al.* 2011[41]	Liver	Non-registered information	**Group A:** surgery. **Group B:** ABZ (10 mg/kg/day 12 weeks) + surgery + ABZ (10 mg/kg/day 12 weeks)	Viability, motility of the scolices and their ability to exclude 5% eosin, under immediate microscopy. Recurrence.		**G-A**	**G-B**
					Type I	12 (33.3)	11 (30.5)
					Type II	10 (27.2)	11 (30.5)
					Type III	8 (22.2)	10 (27.7)
					Type IV	6 (16.6)	4 (11.1)
					Viable	36 (100)	2 (5.5)
					Non-viable, p<0.01	0 (0)	34 (94.5)
					Recurrence, p<0.05	6 (16.6)	0 (0)

*ABZ, Albendazole; PZQ, Praziquantel; MBZ, Mebendazol; FBZ, Flubendazole.

**Statistical significance level of 5% (p <0.05)

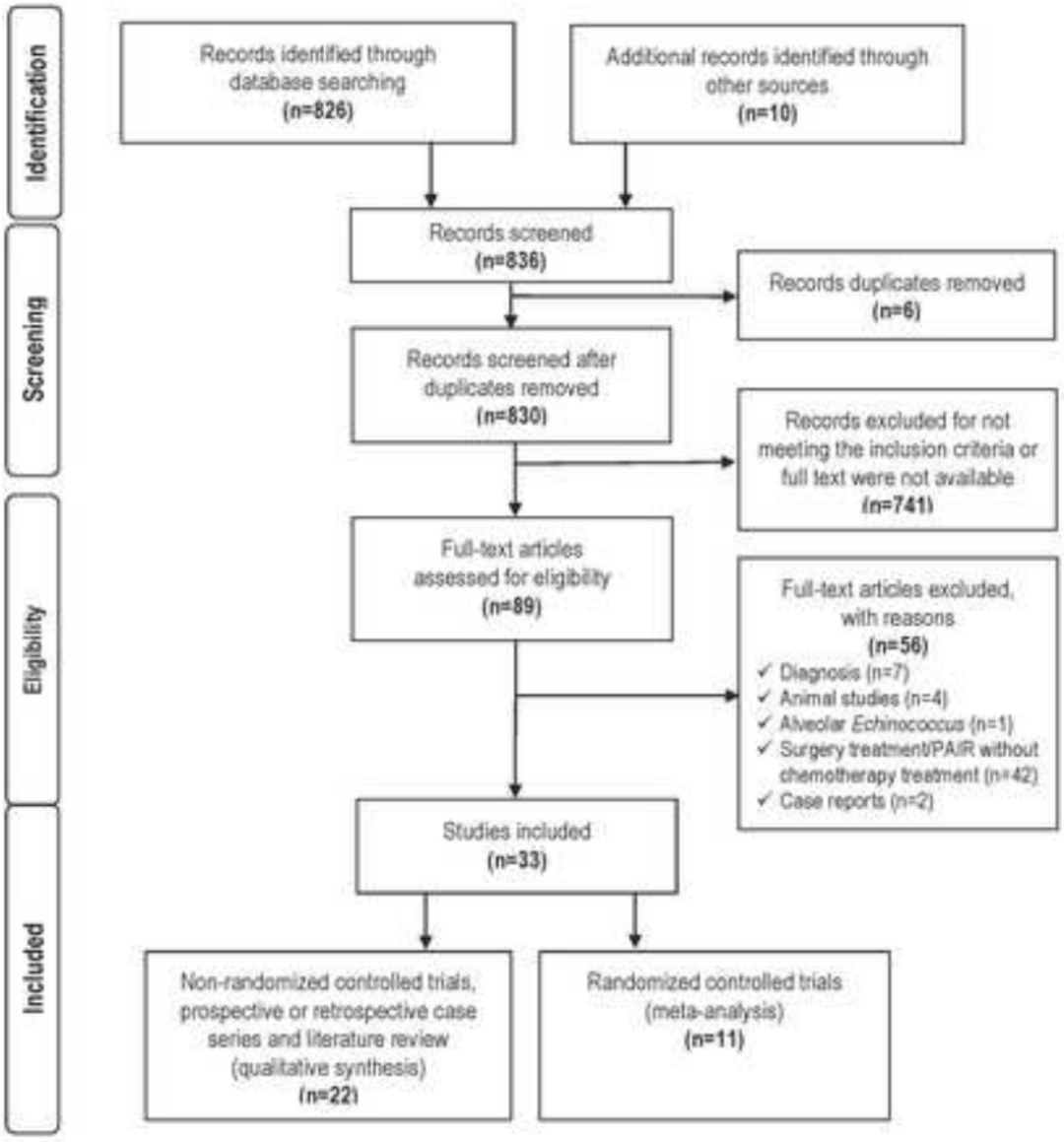
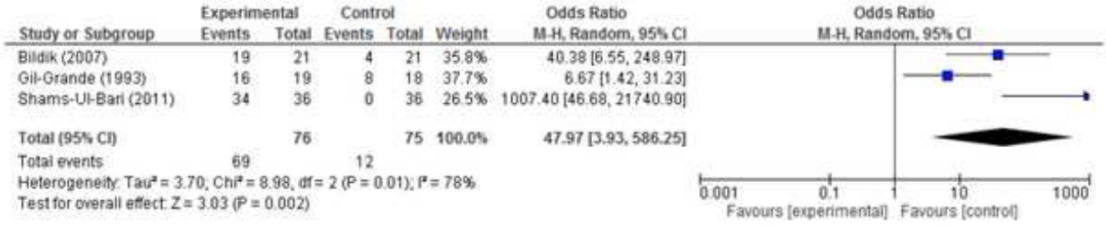
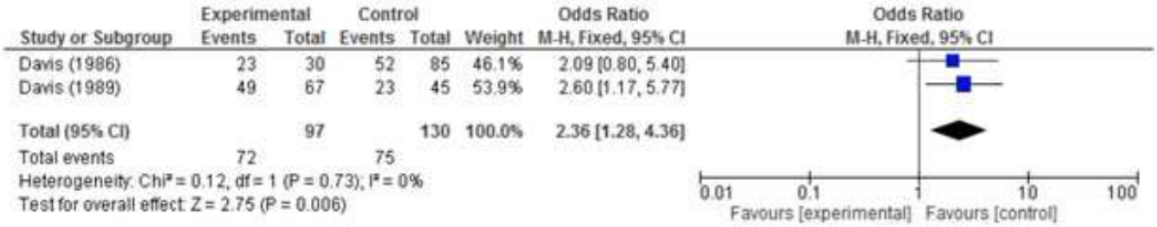


Figure 1. Flowchart of information through the different phases of the systematic review following the PRISMA recommendations



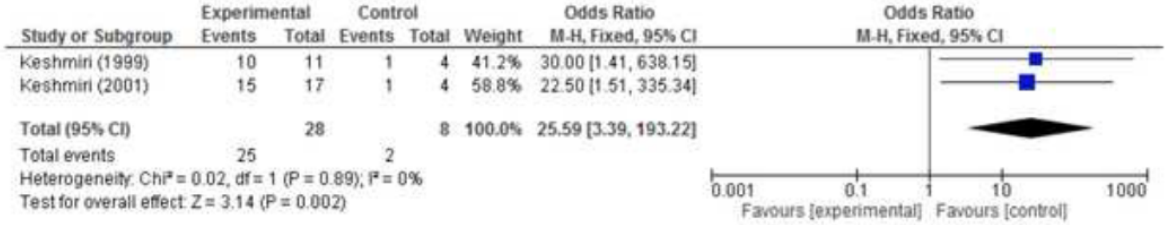
*Statistical method, Mantel-Haenszel. Analysis model, Random Effects. Effect measure, Odds Ratio. 95% Confidence Interval.

Figure 2. Forest plot of comparison: intervention (albendazole plus surgery) vs control (surgery alone), outcome: **Viability of scolex** (Event=non-viable or dead).



*Statistical method, Mantel-Haenszel. Analysis model, Fixed Effect. Effect measure, Odds Ratio. 95% Confidence Interval.

Figure 3. Forest plot of comparison: intervention (albendazole) vs control (mebendazole), outcome: **Response to treatment** (Event = cure/success plus improvement).



*Statistical method, Mantel-Haenszel. Analysis model, Fixed Effect. Effect measure, Odds Ratio. 95% Confidence Interval.

Figure 4. Forest plot of comparison: intervention (albendazole) vs control (placebo), outcome: **Response to treatment** (Event = cure/success plus improvement).

SUPPLEMENTARY METHODS

The search strategy was as follows:

1) "hydatid disease"[All Fields] OR "cystic echinococosis"[All Fields]
2) "*Echinococcus granulosus*"[All Fields]
3) #1 AND #2
4) "medical treatment"[All Fields]
5) "albendazole"[All Fields] OR "mebendazole"[All Fields] OR "praziquantel"[All Fields]
6) #4 OR #5
7) #3 AND #6
8) #7 AND "randomized controlled trials"[All Fields]
9) #8 AND "humans"[MeSH Terms]

The filter *Etiology/Broad* was applied through the *Clinical Queries* tool.

ARTÍCULO SEGUNDO

Safety of the Combined Use of Praziquantel and Albendazole in the Treatment of Human Hydatid Disease.

Antecedentes: No existe un consenso establecido sobre el manejo de la hidatidosis. La cirugía sigue siendo la primera opción terapéutica, aunque el tratamiento con antiparasitarios se aplica como adyuvante a la cirugía y en aquellos casos que la cirugía no es posible. Habitualmente el albendazol se usa en monoterapia como tratamiento estándar. Sin embargo, la terapia combinada de albendazol más praziquantel parece mejorar la eficacia antiparasitaria. La bibliografía respecto a la seguridad de la terapia combinada de albendazol y praziquantel para el tratamiento de la hidatidosis es escasa.

Métodos: Estudio observacional retrospectivo. Se realizó una revisión de las historias clínicas de los pacientes atendidos en el Hospital Universitario de Salamanca con diagnóstico de equinococosis quística y tratados con albendazol y praziquantel desde enero de 2006 a julio de 2010.

Resultados: 57 pacientes con hidatidosis fueron tratados con praziquantel más albendazol. 8 (14%) pacientes presentaron efectos secundarios, ninguno grave.

Conclusiones: Los efectos adversos relacionados con la terapia combinada de praziquantel y albendazol son leves e infrecuentes. Todos los efectos fueron reversibles tras la retirada del tratamiento. Por lo tanto, el uso de esta terapia combinada parece ser factible y segura para tratar a pacientes con equinococosis quística.

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Safety of the Combined Use of Praziquantel and Albendazole in the Treatment of Human Hydatid Disease

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Abstract. There is still no well-established consensus about the clinical management of hydatidosis. Currently, surgery continues to be the first therapeutic option, although treatment with anti-parasitic drugs is indicated as an adjuvant to surgery to decrease the number of relapses and hydatid cyst size. When surgery is not possible, medical treatment is indicated. Traditionally, albendazole was used in monotherapy as the standard treatment. However, combined therapy with albendazole plus praziquantel appears to improve anti-parasitic effectiveness. To date, no safety studies focusing on such combined therapy have been published for the treatment of hydatidosis. In this work, we analyze the adverse effects seen in 57 patients diagnosed with hydatidosis who were treated with praziquantel plus albendazole combined therapy between 2006 and 2010.

INTRODUCTION

Hydatidosis is a zoonosis caused by cestode worms of the genus *Echinococcus* spp. Among them, *Echinococcus granulosus* is the most important species that parasitizes humans. The relevance of this neglected parasitic disease is well known; in fact, human hydatidosis has a greater socio-economic impact than Chagas or Hansen's diseases.[1,2] *Echinococcus granulosus* has a worldwide geographical distribution and the Mediterranean basin is considered an important endemic area.[3–6] In this sense, a recent epidemiological study performed in our area (Salamanca, Spain) between 1996 and 2003 established the human incidence of hydatid disease at 10.8 per 100.000 habitants per year.[7]

Despite World Health Organization (WHO) recommendations, there is no optimal standard for the treatment of hydatidosis. This lack of consensus is possibly a result of the complexity of this neglected disease and limitations related to health care facilities.[8,9] There are basically three treatment options: surgical, percutaneous treatment, and the use of anti-parasitic drugs.[10–12] Surgery continues to be the first choice for the treatment of hydatidosis. Nevertheless, it is not the optimal therapeutic option for all patients, mainly limited by poor clinical conditions and the location of the hydatid cysts. Thus, other techniques such as PAIR (Puncture, Aspiration, Injection, and Reaspiration) have gained international recognition[13–15]; nevertheless, PAIR has several contraindications, among them the possibility of breakage or fistulation of the cysts. In addition, the location of the cyst in organs such as heart or brain means that PAIR is not always feasible. Accordingly, because of the contraindications and complications of invasive procedures, in recent years medical therapy has gained ground over the other choices.[16–18]

Medical treatment is usually indicated before surgery to diminish the size of hydatid cysts, to sterilize them, and to avoid relapses. In addition, medical treatment is the sole therapeutic option in disseminated hydatidosis. To date, the medical treatment of hydatidosis has relied on compounds belonging to the benzimidazoles family (albendazole or mebendazole); in particular, albendazole currently represents the best pharmacological option for the treatment of hydatidosis.[19–22] Over the past few decades, other anthelmintic chemotherapies such as praziquantel and nitazoxanide have also been tested against *Echinococcus* spp., but their efficacies are inferior to those of benzimidazoles.[16,23,24] Despite this, the combination of albendazole with praziquantel has shown synergistic activity against *Echinococcus* spp. In fact, observational studies suggest that the combined therapy could improve the cure rates obtained with albendazole alone[23–26]; regarding the safety of medical therapy, an increase in transaminases levels is the most frequent adverse reaction related to albendazole treatment,[27] whereas digestive symptoms are the most frequent adverse effects associated with praziquantel in monotherapy. Anaphylactic reactions related to praziquantel have also been described.[28,29] Some safety studies have focused on the co-administration of albendazole plus praziquantel in other parasitic diseases,[30–33] but no randomized clinical trials have been conducted to determine the safety of combined therapy in human echinococcosis. Therefore, the main objective of this study is to evaluate the safety and tolerability of combined treatment with praziquantel and albendazole in a group of 57 patients diagnosed with hydatidosis.

MATERIAL AND METHODS

This was a retrospective observational study. The epidemiological data and those regarding the clinical evolution of the disease were collected after a review of the medical records collected from patients diagnosed with echinococcosis. The diagnosis of hydatid disease was based on the combination of clinical assessment, serological tests, and imaging techniques (computed tomography, ultrasonography, or magnetic resonance imaging, depending on the location of the hydatid cyst and the patient's characteristics). The criteria for eligibility included patients treated with the combined treatment of albendazole and praziquantel. The study was conducted between January 2006 and July 2010 in the University Hospital of Salamanca, located in Western Spain. This center is a tertiary care hospital attending a population of 350,000 individuals. A descriptive statistical analysis was carried out using the SPSS Statistical Package (SPSS Inc., Chicago, IL). The

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TABLE 1
Clinical and epidemiological data of patients infected with *Echinococcus granulosus*

Patients ($N = 57$)	
Age (mean ± SD)	52.7 ± 16.7
Percentage of women patients (%)	35 (61.4)
Location of cyst	
Liver	42 (73.7%)
Lung	3 (5.3%)
Various locations	12 (21.1%)
Complications of hydatid cysts	46 (80.7%)
Fistulization	21 (36.8%)
Compression of structures*	16 (28.1%)
Superinfection†	8 (14%)
Anaphylactic shock	1 (1.7%)
Treatment ABZ+PZQ‡	
Before surgery	5 (8.8%)
After surgery	20 (50.9%)
Before and after surgery	16 (28.1%)
Only chemotherapy	7 (12.2%)

*Cyst complicated with obstruction biliary, obstruction bronchial, etc.
†Cyst complicated with other microorganism mainly bacterial and fungal.
‡Albendazol and praziquantel.

data were described as means ± SD or frequency and percentage when appropriate.

RESULTS

Five hundred and fifty-two patients were newly diagnosed with hydatidosis between January 2006 and July 2010. Of them, 57 (37.5%) were treated with albendazole plus praziquantel; the clinical–epidemiological data of these 57 patients are shown in Table 1. Average age was 52.7 ± 16.7 years and 35 (61.4%) patients were female. The liver was the organ most frequently affected in 42 cases (73.7%), followed by the lung in 3 cases (5.3%). In addition, 31 patients (54.4%) had more than one cyst. Of importance, a high number of patients 46 (80.7%) had a complication related to hydatid cysts: 21 (36.8%) cases showed fistulation (17 biliary, 2 bronchial, 1 vascular, and 1 subcutaneous), 16 cases (28.1%) had compression of structures, 8 (14%) cases had a superinfection of the hydatid cysts, and 1 (1.7%) patient underwent an anaphylactic reaction, with shock.

Treatment with albendazol plus praziquantel was associated with surgery in 50 (87.7%) of the cases: specifically, 5 (8.8%) patients received the combined therapy before surgery, 29 (50.9%) patients received the combined therapy after surgery, and 16 (28.1%) patients received the medical treatment both before and after surgery. The remaining 7 (12.2%) patients were excluded for intervention because of their age, their underlying pathology, or the presence of multiple hydatid cysts. The drug administration schedule was 400 mg q12h for albendazole, whereas the dosage for praziquantel was 20–75 mg/kg/day, depending on the patient's weight, as shown in Table 2. The average duration of treatment was 68 weeks (range 1–436 weeks) and 37 (64.9%) patients received combined treatment of more than 1 year. Four (7%) patients were lost to follow-up; 2 (3.5%) patients died because of primary complications of their hydatid cyst; 17(29.8%) patients continued the medical therapy with albendazol plus praziquantel, and 3 (5.3%) patients continued the treatment with albendazol alone.

TABLE 3
Adverse effects related with the combined treatment (praziquantel and albendazole)

Adverse effects	Number of patients
Digestive effects	6 (10.5%)
Diarrhea	3 (5.2%)
Vomiting and abdominal pain	2 (3.5%)
Hypertransaminasemia	1 (1.7%)
Neurological effects	2 (3.5%)
Migraine	1 (1.7%)
Dysgeusia and dysosmia	1 (1.7%)

The safety analysis included self-reporting of adverse events, hemograms, and biochemistry before and after treatment. Only 8 (14%) patients reported some mild adverse effects (Table 3). The most frequent were digestive; specifically 3 (5.2%) patients developed diarrhea, 2 (3.5%) cases reported vomiting, and 1 (1.7%) patient presented a mild hypertransaminasemia (alanine aspartate aminotransferase maximum 74 U/L and alanine aminotransferase maximum 154 U/L), followed by neurological problems such as headaches in 1 (1.7%) and dysgeusia in 1 (1.7%) patient. No clinically relevant changes in the hematological results were detected along the treatment period. The adverse events tended to occur within the first 2 weeks after start of treatment. In these cases, the adverse effects disappeared after the withdrawal of albendazole plus praziquantel or praziquantel; in these medical therapy was continued, maintaining albendazole alone.

DISCUSSION

Despite the efforts made by the WHO to define a new classification of patients to homogenize and optimize studies addressing human hydatidosis,[34] the results expected have

TABLE 2
Outcome measures of patients infected with *Echinococcus* spp. included in the combined treatment protocol

No. of cases	Praziquantel	Albendazole	Treatment time in weeks median and range	Side effects no. of cases (%)	Clinical evolution
20	1,200 mg q12h* 2,400	400 mg bid	68 R = 437 (9–436)	3 (15.0%)	Improvement 8 (40%) Equal 8 (40%) Worsening 1 (5.0%)
16	600 mg q8h** 1,800	400 mg bid	62 R = 427 (9–436)	1 (6.3%)	Improvement 9 (56.3%) Equal 6 (37.5%) Worsening 1 (6.3%)
4	600 mg q12h 1,200	400 mg bid	60 R = 68 (26–94)	0	Improvement 2 (50.0%) Equal 2 (50.0%)
3	1,200 mg q8h 3,600	400 mg bid	216 R = 204 (66–270)	0	Equal 3 (100%)
1	1,200 mg-600 mg-1,200 mg 3,000	400 mg bid	162 R = 0	0	Improvement 1 (100%)
13	Unknown dose	400 mg bid	58 R = (1–108)	4 (30.8%)	Improvement 6 (46.2%) Equal 5 (38.5%)

not emerged. Presently, there are no common clinical guidelines or an established consensus for the clinical management of hydatidosis. Among other reasons, this lack of consensus could be caused by the considerable difficulty involved in dealing with this cestode in terms of its slow evolution and clinical variability. This strong heterogeneity in the medical management of the disease prompted us to evaluate a treatment protocol combining albendazole and praziquantel. The medical treatment was initiated before surgery, and was held for up to 1 year. If the clinical, analytical, and radiological controls were negative, the medical therapy was suspended 1 year after the start of the combined therapy.

The drugs classically used against *E. granulosus* are the benzimidazoles. This family of compounds began to be used at the beginning of the 70s.The first drug used for hydatidosis treatment was mebendazole. However, in the 80s this drug was replaced by albendazole because of its better bioavailability.[8,19–21] The mechanism of anti-parasitic action of the benzimidazoles is based on a decrease in the recapture of glucose and their union to β-tubulin, which generates metabolic and structural alterations in the parasite, leading to its death.[19] Hydatid cysts not affordable by surgery require a plasma concentration of 100 ng/mL of albendazole for months or years for the necessary anthelmintic effect to be achieved.[35] Medical treatment implemented at doses between 800 and 1,200 mg/day (10–20 mg/kg day) for 3–4 months achieves cure rates of hepatic cysts that vary from 28.5% to 43%, with a rate of relapse between 3% and 22%, whereas the cure rates of pulmonary hydatid cysts reach 73%. In addition, as previously indicated medical treatment with albendazole before surgery allows relapses to be reduced.[36,37]

Other anti-parasitic drugs have been tested in combination with benzimidazoles with a synergic action. Although there are no comparative randomized studies exploring treatment with albendazole in monotherapy versus combined therapy with albendazole plus praziquantel in patients without surgery, it appears that the combined therapy could improve the results obtained with albendazole alone.[17,18,23–26,38] In addition, treatment with praziquantel plus albendazole before surgery could be more efficient as regards reducing relapse rates in comparison with albendazole monotherapy.[23] To date, there are no published randomized clinical trials comparing both therapeutic strategies. Moreover, only a few studies in the literature report the use of the combined therapy for the treatment of hydatidosis, and these are based on small series. Only one randomized assay performed in sheep with natural echinococcosis infection showed that the benzimidazoles with or without praziquantel had greater efficacy than placebo administration. However, no differences were observed between the monotherapy and combined treatment groups and evidently no adverse effects were described.[39] Furthermore, it is possible that medical treatment alone, when surgery is not feasible, could reduce and even disappear the hydatid cysts; in fact, some series suggest that prolonged medical treatment could be more advantageous than surgery.[40]

Some safety studies have focused on the co-administration of albendazole and praziquantel in other parasitic diseases[30–33]; however, there are no safety studies for combined treatment with these drugs in human echinococcosis. Thus, experience related to the safety of praziquantel is based on its use in other pathologies requiring treatment of much shorter times.[41–43] By contrast, the medical treatment of hydatidosis is more prolonged and in this sense our series of cases even surpassed 1 year of treatment. It is interesting to note that the long-term side effects observed in this work were mild and disappeared after the withdrawal of praziquantel. The most frequent adverse reactions affected the digestive system and included nausea, vomiting, and diarrhea, as previously described by other authors reporting studies in which praziquantel was used in other parasitic diseases.[29,44] Interestingly, one of our patients developed dysgeusia and dysosmia; this side effect is not included in the technical record of praziquantel, and to our knowledge this is the first time it has been observed as a side effect related to praziquantel.[45] New drugs are also being tested, in particular in disseminated hydatidosis with multiple cysts or bone affectation, which makes surgery impossible. The use of nitazoxanide in combination with albendazole, with or without praziquantel, appears to be useful in this type of case.[16,46] In our series there was an obvious selection bias, because all patients were hospitalized and no outpatients were included (who generally present a less aggressive hydatidosis), and of course without bearing in mind carriers of asymptomatic of hydatid cysts, which have not even been diagnosed. This would suggest the existence of an over dimension of severe cases in our series. In any case, this would not affect our conclusions regarding tolerance and the appearance of possible side effects with this medication.

CONCLUSIONS

According to our experience, the adverse effects related to praziquantel plus albendazole combined therapy are mild and infrequent, being reversible after treatment has been withdrawn. Thus, the use of this combined therapy seems to be feasible and safe for the treatment of patients with hydatidosis, although further clinical studies are necessary to confirm these observations.

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ARTÍCULO TERCERO

Dysgeusia as an adverse reaction to praziquantel.

Antecedentes: El Praziquantel es un antiparasitario derivado de la pirazinoisoquinolina que se usa frente a tremátodos y céstodos. En los últimos años, el praziquantel se ha usado junto a albendazol en el tratamiento de la equinococosis quística. Presentamos dos casos de disgeusia asociados al praziquantel.

Métodos: Descripción de casos clínicos.

Conclusiones: Los efectos secundarios de praziquantel descritos son escasos, probablemente debido a que los tratamiento no suelen ser prolongados. Entre ellos se incluyen dolor abdominal, náuseas, cefalea, malestar y somnolencia. En nuestros pacientes, la relación causal entre praziquantel y la disgeusia se sospechó cuando los síntomas aparecieron tras el inicio de la medicación y desaparecieron inmediatamente después de la retirada del fármaco.

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CASE REPORT

Dysgeusia as an adverse reaction to praziquantel

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Keywords: Echinococcus granulosus, Praziquantel, adverse reaction

Introduction

Praziquantel is an antiparasitic drug derived from pyrazinoisoquinoline that is used against trematodes and cestodes. Over the last few years, praziquantel has been combined with albendazole in the medical treatment of hydatidosis, in spite of the lack of controlled assays. We present two cases of dysgeusia associated with praziquantel. Dysgeusia is an unpleasant alteration of taste sensation, often with a metallic taste.

Case 1

The patient was a 63-year-old woman with a personal record of diet-controlled hypertension and ulcerative colitis. She did not receive any drug. After an episode of right-upper quadrant pain, two hydatid cysts of World Health Organization stage CE 3–4 (WHO, 2003), measuring 5.3 × 3.1 cm on hepatic segment I and 5.2 × 4.3 cm on segments VII–VIII, were found in addition to cholelithiasis. Cholecystectomy and cystopericystectomy were performed. Postoperatively, treatment with albendazole (400 mg b.i.d.) and praziquantel (1,200 mg b.i.d.) was begun. After 3 weeks, the patient reported a metallic taste 30 minutes after the praziquantel dose, which intensified over the subsequent weeks, together with dysosmia, malaise, and diarrhea. All symptoms disappeared when praziquantel was removed.

Case 2

A 28-year-old woman presented with a 6-month history of episodes with pruritus in the palms and soles, facial edema, and troncal wheals. Having been diagnosed with chronic urticaria, she received anti-H1 drugs. While pregnant, an ecographic control revealed hydatid cysts in hepatic segments VI (6.2 × 8.5 cm) and VII (6 × 4.4 cm), with stage CE 2. Eosinophilia (up to 19.4%; 1,120 × 10^3/μL) and hemagglutination against *Echinococcus granulosus* (1:2,560) were prominent findings. Six months after delivery, cholecystectomy and parcial cystopericystectomy were performed. Treatment with albendazol (400 mg b.i.d.) and praziquantel (1,200 mg b.i.d.) was begun; 1 month later, she abandoned antiparasitic drugs because of an intense metallic taste (i.e., dysgeusia). When she resumed monotherapy with albendazol, treatment was well tolerated.

Discussion and conclusion

The treatment of choice for hydatidosis is still an invasive intervention (i.e., either surgery or puncture-aspiration-injection-reaspiration). Throughout the 1970s, the use of antiparasitic drugs against the disease started. First, there was high-dose mebendazole, which was replaced by albendazole in the 1980s because of better bioavailability. Praziquantel has been the last drug included in the therapeutic approach against *E. granulosus*. To date, the comparison between different pharmacological combinations has been based on case series (with a reduced number of patients), without randomized essays between them (Mohamed, A. et al, 1998) (Haralabidis, S. et al, 2008). This lack of studies means that there are factors, such as a better combination of drugs, doses, time of intake, or duration of treatment, that still need to be clarified. Continuous medical

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treatment is the recommended approach in inoperable cases or whenever the clinical situation of the patient rules out surgery (Cobo, F. et al, 1998) (Jamshidi, M. et al, 2008). Generally speaking, tolerance to praziquantel is very good because of the fact that it is usually taken in monodoses or during short periods. There are few described adverse effects, because long-term treatments with praziquantel are seldom applied. Adverse reactions are rare and mild, including abdominal pain, nausea, cephalalgia, malaise, and sleepiness (Shen, C. et al, 2007) (Bagheri, H. et al, 2004) (Dayan, A. et al, 2003) (El Hawey, A. et al, 1990) (Berhe, N. et al, 1999). Exceptionally, idiosyncratic or serious allergic reactions have been described. To the best of our knowledge, there have been no cases described with dysgeusia or dysosmia as an adverse effect of praziquantel or its production mechanism. In our patients, the causal relationship between praziquantel and dysgeusia was suspected symptoms that disappeared immediately after removal of the drug.

Declaration of interest

The authors report no financial conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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ARTÍCULO CUARTO

Management of cystic echinococcosis in the last two decades: what have we learned?.

Antecedentes: Las opciones terapéuticas frente a la equinococosis quística incluyen cirugía, PAIR, antiparasitarios y la opción de "*Watch & Wait*". El primer objetivo de este estudio fue examinar la modalidad terapéutica aplicada en una cohorte de pacientes con equinococosis quística, los factores implicados en la selección del tratamiento y las complicaciones del tratamiento. El segundo objetivo fue evaluar la tasa de mortalidad y los factores causales.

Métodos: Realizamos un estudio descriptivo retrospectivo de los pacientes diagnosticados con EQ entre 1998 y 2015 según los criterios ICD-9 (código 122 · 0 a 122 · 9) en el Complejo Asistencial Universitario de Salamanca, España.

Resultados: De los 491 pacientes diagnosticados de EQ, 342 (69.7%) recibieron cirugía: solo cirugía 166 (33.8%) pacientes y cirugía y antihelmínticos 176 (35.8%) pacientes. 193 (39.4%) pacientes fueron tratados únicamente con fármacos: 123 (63,7%) pacientes solo albendazol y 70 (36,3%) pacientes con una combinación de albendazol y praziquantel. La estrategia de "*Watch & Wait*" se realizó en 131 (26,7%) pacientes. Durante el período de estudio, 80 (16.3%) pacientes murieron, 14 (2.9%) de ellos debido a la EQ.

Conclusiones: Las complicaciones de la EQ son una de las causas más comunes de mortalidad en los pacientes con EQ. El tamaño, la localización, el número de quistes y la estrategia de tratamiento "Watch & Wait" son los principales factores asociados con la mortalidad.

TRSTMH

Management of cystic echinococcosis in the last two decades: what have we learned?

--Manuscript Draft--

Article Type:	Full Length Article
Full Title:	Management of cystic echinococcosis in the last two decades: what have we learned?
Abstract:	Background: Management options for Cystic Echinococcosis (CE) remain a great problem. The first aim of this study was to examine the selection and complications of treatment applied in patients with CE. The second aim was to evaluate the mortality rate and causative factors. Methods: We conducted a retrospective descriptive study of patients diagnosed with CE between 1998 and 2015 according to ICD-9 (code 122·0 to 122·9) criteria in the Complejo Asistencial Universitario of Salamanca, Spain. Results: Of the 491 patients diagnosed with CE disease, 342 received surgery: 166 (33.8%) patients received only surgery and 176 (35.8%) received a combination of surgery and drugs. A total of 193 (39.4%) patients were medically treated:123 (63,7%) patients used albendazole alone, and 70 (36,3%) patients used a combination of albendazole & praziquantel. 65 patients (19.0%) had complications after surgery and 7 of them (2%) died. Only 15 (7.8%) cases had side effects of anthelmintics. The strategy of Watch & Wait was conducted in 131 (26.7%) patients. Throughout the study period, 80 (16.3%) patients died, 14 (2.9%) of them due to CE disease. Conclusions: Complications of CE are one of the most common causes of mortality in CE patients, with size, location, and number of cyst and the "Watch & Wait" treatment strategy being the main factors associated with mortality.
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Management of cystic echinococcosis in the last two decades: what have we learned?

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Abstract

Background: Management options for Cystic Echinococcosis (CE) include surgery, percutaneous management, drug therapy, and the *Watch & Wait* option. Therefore, the lack of advances in the management of CE remains one of the major problems. The first aim of this study was to examine the treatment applied in a cohort of patients with CE, the factors involved in the treatment selection and the treatment complications. The second aim was to evaluate the mortality rate and causative factors. **Methods:** We conducted a retrospective descriptive study of patients diagnosed with CE between 1998 and 2015 according to ICD-9 (code 122·0 to 122·9) criteria in the Complejo Asistencial Universitario of Salamanca, Spain. **Results:** Of the 491 patients diagnosed with CE disease, 342 received surgery: 166 (33.8%) patients received only surgery and 176 (35.8%) received a combination of surgery and drugs. A total of 193 (39.4%) patients were medically treated:123 (63,7%) patients used albendazole alone, and 70 (36,3%) patients used a combination of albendazole & praziquantel. 65 patients (19.0%) had complications after surgery and 7 of them (2%) died. Only 15 (7.8%) cases had side effects of anthelmintics. The strategy of *Watch & Wait* was conducted in 131 (26.7%) patients. Throughout the study period, 80 (16.3%) patients died, 14 (2.9%) of them due to CE disease. **Conclusions:** Complications of CE are one of the most common causes of mortality in CE patients, with size, location, and number of cyst and the "Watch & Wait" treatment strategy being the main factors associated with mortality.

Key words

Cystic echinococcosis; *Echinococcus granulosus*; Hydatidosis; Albendazole; Praziquantel; Treatment; Chronic diseases; Survival

Introduction

Cystic echinococcosis (CE) is a chronic, complex and neglected zoonotic disease caused by the larval stage (metacestode) of *Echinococcus granulosus*. CE occurs worldwide but it is endemic in central Asia, northern and eastern Africa, Australia, South America and the Mediterranean Basin.[1-3] In humans it may result in a wide spectrum of clinical manifestations, ranging from asymptomatic infection to fatal disease.[4] The clinical management of CE is complex and fundamentally based on three pillars: surgical, pharmacological and percutaneous treatment, which are sometimes administered as complementary treatments.[5,6] Surgical treatment is currently the technique of choice; however, there are several alternative techniques available. For example, PAIR (*puncture-aspiration-injection-reaspiration*) is one such technique that has recently been introduced and that may possibly replace surgery in specific cases[7-9] Other techniques such as modified catheterization technique (MoCaT), modified percutaneous evacuation (PEVAC), immunological or chemo-radioisotope therapies and radiofrequency thermal ablation (RFA) will merit more attention in the future[8]. Anthelmintics, mainly benzimidazoles alone or in combination with other drugs such as praziquantel, have so far been reserved for non-operated patients and have had a secondary role[10,11], in reducing the risk of anaphylaxis, dissemination and/or postoperative recurrence[12] .However, in select patients, the option of "*Watch & Wait*" is being validated[13].

Therefore, despite advances in surgical techniques, the use of chemotherapy and others treatments, and attempts made by WHO, the management of CE disease remains a major problem[14]. Today, there is still no consensus on the management of CE[15], and consequently, the ‘‘best’’ treatment is still a subject of debate[13,16]. As such, it is essential to develop clinical studies comparing treatments in homogeneous groups of patients. However, there are a lot of important difficulties in developing prospective clinical assays for CE, such as the long-term

evolution of this infection, the heterogenicity of patients and cysts, and the absence of clinical tools for detecting infection or relapse in early stages of infection. Thus, based on retrospective work, we must to examine the evolution of CE patients with different types of treatment. The first aim of this study was to examine the treatment applied in a cohort of patients with CE, the factors involved in the treatment selection and the treatment complications. The second aim was to evaluate the mortality rate and the causative factors.

Material and Methods

The design of this study was a descriptive longitudinal-retrospective study that was performed in two phases. First, we describe, in our cohort, the treatment applied and the factors involved in the treatment selection and the treatment complications. We reviewed all patients diagnosed with CE according to the ICD-9 (code 122·0 to 122·9) criteria who were admitted to CAUSA between January 1998 and December 2015. CAUSA is a tertiary care hospital that covers an area of 12 350 km^2, and it accommodated 342.459 inhabitants in 2014 (National Institute of Statistics (INE); http://www.ine.es/)[17] and is located in western Spain. Clinical and epidemiological data were collected after review of medical records. Diagnosis and classification of CE were assessed according to the criteria proposed by the World Health Organization Informal Working Group on Echinococcosis for CE[15]. Surgical complications were defined as any deviation from the normal postoperative course[18]. Hypertransaminasemia was defined as having serum transaminase levels at a value greater than 5 times the upper limit of normal (UI/L). Second, we evaluated the mortality rate in patients who attended follow-up at our hospital and the causative factors. Follow-ups were defined with two or more clinical controls. Patients with duplicate records, without follow-up or with missing data were excluded from the study.

Statistical analysis

The results were expressed as percentages for categorical variables and as the mean and standard deviation (SD) for continuous variables. To perform bivariate analysis, a chi-square test was used to compare the association between categorical variables, such as clinical and demographics variables, and the measured outcome was expressed as the odds ratio (OR) together with the 95% CI for OR. Continuous variables were compared with Student's t-test, analysis of variance (ANOVA) or Mann-Whitney test for two groups, depending on their normal or non-normal distribution, and *Least Significant Difference (LSD)* post hoc test. Additionally, we applied the logistic regression model to perform multivariate analysis of variables that influenced mortality of the cohort, estimating the parameter B, standard error (E.T.), and statistical significance with the Wald test and the estimation of the OR (Exp (B)) with 95% CI. Multi-correspondence analysis was performed to help interpret the relationships between the categories of the variables. Survival rates were analyzed by a Kaplan-Meier method. We considered a p-value <0.05 as a statistically significant difference. All data were analyzed with *SPSS Statistics 23 (Statistical Package for the Social Sciences)*.

Ethics statement

The study was approved by the Ethics Committee of CAUSA. Because this was an epidemiological study, written consent was not obtained and was specifically waived by the approving institutional review board. All data were analyzed anonymously.

Results

A total of 571 patients with new CE-related diagnosis codes 122.0 to 122.9 were registered in CAUSA between January 1998 and December 2015. Of these patients, 80 patients with missing data were excluded from the study. Thus, 491 patients with new CE diagnosis were

included in the study, and the patient data are shown in **Table 1**. A total of 288 patients were male (58.7%), the mean age (±SD) was 59.5±20.4 years, 360 (73.3%) patients received medical and/or surgical treatment and 131 (26.7%) patients decided on the *"Watch & Wait"* option. The temporal evolution of the different strategies implemented in the cohort during the study period is presented in **Figure 1. T**here are significant differences in the percentage distribution over the study period between different treatment groups, and thus, while surgery alone or anthelmintics only were the more common treatment strategies at the start of the cohort study, the combination of both therapies was the most frequent treatment strategy at the end of the cohort study ($p<0.001$).

The mortality rate was analyzed in 247 (50.3%) patients who attended follow-up our hospital.

Surgery treatment

Of all the patients, 342 (69.6%) were treated by any surgical method, and of these, 166 (48.5%) received surgery as the only treatment, and 176 (51.5%) received surgery in combination with anthelmintics.

Variables associated with an indication of surgical intervention of CE were location of CE, which was more frequent in thoracic cyst than hepatic locations (62/69 (89.9%) *vs* 274/410 (66.8%)), (OR=4.46, 95% CI, 1.99-9.99; $p<0.001$). The main surgical techniques are shown in **Table 2**.

After surgery, 65/342 (19.0%) patients had complications, with the most frequent being postoperative fistula (17); these complications are shown in **Figure 2.** Between the variables associated with surgical complications, the location of the cyst was the most prominent. We found less postoperative complications in lung cysts (7/62 (11.3%)) than in the remaining locations (65/321 (20.2%)), which include the liver (56/274 (20.4%)), disseminated or other locations (9/47 (19.1%)); however, these results were not statistically significant (OR=2.05,

95% CI, 0.88-4.74, p=0.087). Between the patients with hepatic CE, there was an increased risk of complications when surgery involved liver segments IV (OR=2.20; 95% CI, 1.12-4.31; p=0.019) and VIII (OR=1.96; 95% CI, 1.05-3.64; p=0.030). In contrast, segments III (OR=0.34; 95% CI, 0.11-0.98; p=0.042) and V (OR=0.31; 95% CI, 0.10-0.91; p=0.026) had three times fewer complications than other segments. Also, there were increases in the risk of complications (OR=1.83, 95%CI 1.05-3.22, p=0.032) when the cyst size was greater than 7 centimeters (23.3% *vs* 14.2%). Patients who underwent interventions for CE complications (superinfections, fistula, etc.) had similar postoperative complications as CE patients with elective surgery (p=0.220). We also did not find differences between the different techniques applied (p=0.404).

Postoperative complications were not associated with age, sex, comorbidity, or any immunodeficiency. Among the surgically treated patients, 7 (2%) patients died from postoperative complications: 6 patients from sepsis and 1 patient from massive hemoptysis. We detected a higher mortality rate depending on the age (7/7 deaths involved patients older than 60 years, OR=2.31; 95% CI, 2.04-2.61; p=0.003) and comorbidity (6/7, OR=10.61; 95% CI, 1.26-89.18; p=0.007).

Medical treatment

A total of 193 (39.3%) patients received medical treatment: 176 (91.2%) combined with surgery, and only 17 (8.8%) patients received anthelmintics treatment only. Regarding the use of anthelmintics, 123 (63.7%) patients received treatment with albendazole alone, and 70 (36.3%) received a combination of albendazole & praziquantel. There were differences in the treatment used; while albendazole was the most common strategy followed at the beginning of the study, the combination of albendazole & praziquantel was the most common treatment strategy at the end of the cohort (p=0.001). With respect to the modes of management, 88

(50.0%) patients received preoperative treatment (mean (±SD): 13.5±20.3 weeks) and 138 (78.4%) patients received postoperative treatment (mean (±SD): 30.9±31.8 weeks). Only 56 (31.8%) patients received both pre- and postoperative medical treatment.

Only 15 (7.8%) patients presented complications secondary to drug treatment (**Figure 2**), which occurred more frequently in patients with albendazole & praziquantel than in patients with albendazole alone (9/70 (12.9%) *vs* 6/123 (4.9%)) [OR=2.87, 95%CI 1.01-8.45, p=0.047]. The most frequently detected complications were digestive intolerance (8) and hypertransaminasemia (6) (**Figure 2**). All cases were resolved after drug discontinuation. These complications were not related to age, sex or comorbidity (p>0.05).

Watch & Wait strategy

A *Watch & Wait* strategy was conducted in 131 (26.7%) patients in the cohort. The main factors associated with *Watch & Wait* included age over 60 years old [117 (89.3%) vs 14 (10.7%); OR 9.76; 95% CI, 5.40-17.65; p<0.001)], any condition causing comorbidity [92 (70.2%) vs 39 (29.8%) (OR=3.75; 95% CI, 2.43-5.76; p<0.001)] and stage 5 of WHO [68 (54.8%) *vs* 56 (45.2%) in other stages; (p<0.001)]. Ninety-nine (75.6%) patients were asymptomatic. Patients who underwent the *Watch & Wait* strategy presented several complications: 19 (14.5%) infections, 10 (7.6%) mechanical, 3 (2.3%) both.

Overall survival & mortality

Of the total cohort, only 247 (50.3%) patients attended follow-up our hospital with two or more revisions, with a mean (±SD) duration of 3.36±3.50 years. The Kaplan-Meier curve of the study period is shown in **Figure 3**, which was associated with age, immunosuppression and comorbidity (p<0.001) and was not associated with gender, clinical diagnosis, complications or recurrences (p>0.05).

Eighty (16.3%) patients died along the study, 14 of them (2.9%) were directly caused by CE disease or other complications (**Table 1**). Other causes of mortality not related to echinococcosis were as follows: cancer (26, 32%), cardiovascular (17, 21%), other non-related infectious diseases (13, 16%) and other non-specified complications. First, we analyzed the overall survival/mortality rate in the cohort (all-cause mortality), 80 *exitus*.

Bivariate analysis showed that the variables significantly ($p<0.05$) associated with higher mortality were age, immunosuppression, comorbidity, number of liver segments and treatment strategy (**Table 4**).

Multivariate logistic regression analysis confirmed that age is a risk factor ($p=0.003$), and the clinical variables that most significantly influenced the overall cohort mortality were the presence of comorbidity [Exp(B)=7.06; 95%CI, 1.56-31.92; p=0.011] associated with the *Watch & Wait* strategy [Exp(B)=3.01; 95%CI, 1.01-9.02; p=0.050]. Later, we analyzed the clinical variables that influenced mortality in CE disease, 14 *exitus*. *Bivariate analysis* showed that the variables significantly ($p<0.05$) associated with higher mortality by CE were comorbidity, clinical symptoms *vs* asymptomatic-casual finding, *Watch & Wait* strategy and treatment complications. *Multivariate logistic regression analysis* confirmed that the clinical variables that most significantly influenced CE disease mortality were the presence of comorbidity [Exp(B)=10.42; CI 95%, 1.22-88.59; p=0.032] associated with surgical treatment complications [Exp(B)=5.85; CI 95%, 1.24-27.52; p=0.025].

DISCUSSION

Over decades the clinical management of echinococcosis has evolved without adequate evaluation of efficacy and the current management and treatment of CE is still largely based on expert opinion and moderate to poor quality of evidence[8,11,15,19]. Despite these limitations, standard of treatment in CE today, is based in the use of different surgical techniques with or

without chemotherapy. Nevertheless, there are a high percentage of patients who are not suitable candidates for surgical treatment, and their treatment consists of other types of therapies such as PAIR, anthelmintics or "*Watch & Wait*" strategy.

During two decades, we have attended to patients with CE without having a previously established treatment protocol in our hospital. The aim of this study was to determine the most frequently applied treatment in our cohort, the factors involved in the treatment selection and the complications regarding each type of treatment applied. Thus, we have attended to more than 500 patients with CE in our hospital, with surgical treatment being the main treatment used. We detected that factors such as age, co-morbidity or clinical setting were involved in selecting the type of treatment applied to the same patient and the highest comorbidity were the collective most frequently directed to an alternative treatment based on "*Watch & Wait*" strategy.

Regarding surgical methods, we found that factors such as the cyst location, size and number were involved. Therefore, we detected a higher proportion of surgical interventions in thoracic CE than in liver CE. These differences could be explained because thoracic CE is more frequently symptomatic than other locations. However, a selection bias is also possible due to the fact that the Service of Thoracic Surgery involves a referral of several areas of health of other regions, from which many patients were referred for surgical procedure.

Other characteristics such as large size or a solitary CE were also factors associated with the use of a surgical procedure. In this sense, larger cysts are usually active cyst with a higher growth capacity and, consequently, a higher possibility of complication. Moreover, because of the high failure rate of treatment, multiples cyst in different locations are a classic factor that results in the patient not being recommended for surgical resection.

In our work, we also detected that the anthelmintics used were somewhat associated with surgical treatment. Although there are studies that showed the utility of benzimidazole only

as a treatment for CE patients with response rates ranging from 28.5% to 73%, there was a high relapse rate after the completion of treatment that limited its use. The use of combined benzimidazoles and praziquantel could be an alternative treatment; however, despite the safety[11] of this combination, their clinical use is not still well characterized. Thus, medical treatment for CE is usually limited to decrease the relapse after of surgical treatment.

Another aim of our work was to evaluate the complications associated with different types of treatment used. Between the patient treated with surgical treatment, approximately 20% had surgical complications, with fistula being more frequent in the liver than in other locations, especially when CE was localized in the IV and VIII segments.

The mortality rate was similar to that observed in a multi-center series study (1-2%), which revealed a lesser postoperative morbidity[20].However, other characteristics of the cysts or the patients characteristics were not associated with an increasing risk of complications. We observed a postoperative mortality rate of 2% that was clearly associated with patient age and comorbidity. In this sense, defining the clinical exclusion criteria of surgical patients is important to decrease this mortality rate.

Regarding medical treatment, anthelmintics were typically used as a complementary treatment to surgical procedure. We detected a low risk of complications, with the most frequent being digestive intolerance and hypertransaminasemia; however, both cases were resolved after drug discontinuation.

Finally, another aim of our study was to examine the global and attributable mortality in our cohort. We previously published a study in which we examined the mortality and main causes of mortality in CE patients. In our previous study, we evaluated only CE patients who died in our hospital (1998-2011), and thus, we concluded that complications of CE were one of the main causes of mortality in patients infected by *Echinococcus granulosus*. However, due the methodology used in our previous work, we could not establish other factors

associated with patient mortality. In order to evaluate these factors, in the present study we included patients with CE (1998-2015) who had at least two evaluations in our hospital. Thus, similar to our previous work, we also detected that complications of CE were one of the most important causes of global mortality after cancer and cardiovascular diseases.

Moreover, another important objective in this study was to evaluate the factors associated with mortality in our cohort. Thus, thoracic CE and CE with large-sized or increased numbers of cysts were factors associated with higher mortality. Also, depending on the host, age and comorbidity were also associated with higher mortality. Finally, we also studied if the type of treatment could be involved with mortality. Therefore, *Watch & Wait* strategy was also associated with a higher mortality. The variables that most influence the mortality caused by CE in this cohort were the presence of comorbidity [Exp(B)=10.42; CI 95%, 1.22-88.59; p=0.032] and

complications in the treatment. To our knowledge, there are no other studies that evaluate the factors involved with mortality in patients with CE.

Although our work has some limitations and bias due to the retrospective nature of the study, we believe that this study can contribute to selecting the best treatment for patients with CE. However, future studies involving other multi-center randomized clinical trials could provide us with insight to develop treatments for this neglected disease.

Conclusions

Characteristics of cysts and patients are factors involved in the selection of different treatments for CE patients. Surgical complications were frequent but were accompanied by a low mortality rate. Complications of CE are one of the most common causes of mortality in CE patients, with size, location, and number of cysts and "*Watch & Wait*" treatment strategy being the main factors associated with mortality.

Authors contribution

MBG and JPL conceived the study;

MBG and MAS designed the study protocol

VVT, ALB and ACP carried out the revision of records

MBG, MII, AIG, JQS, MAS carried out the analysis and interpretation of data

ARA, MBG and JPL drafted the manuscript

JLMB, LMB, AM and MFJL critically revised the manuscript for intellectual content

All authors read and approved the final manuscript

MBG and JPL are guarantors of the paper.

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Competing interests

None declared

Ethical approval

Not required

Legends

Figure 1. Temporal evolution of the different strategies during the study period

Figure 2. Complications associated to medical and surgical treatment

Figure 3. Kaplan-Meier Survival Curve

Table 1. Main epidemiological and clinical data in 491 patients included in the study.

Table 2. Surgical techniques performed in the first intervention.

Table 3. Variables *(risk factors)* that influence mortality of the cohort (*Bivariate analysis*).

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Figure 1

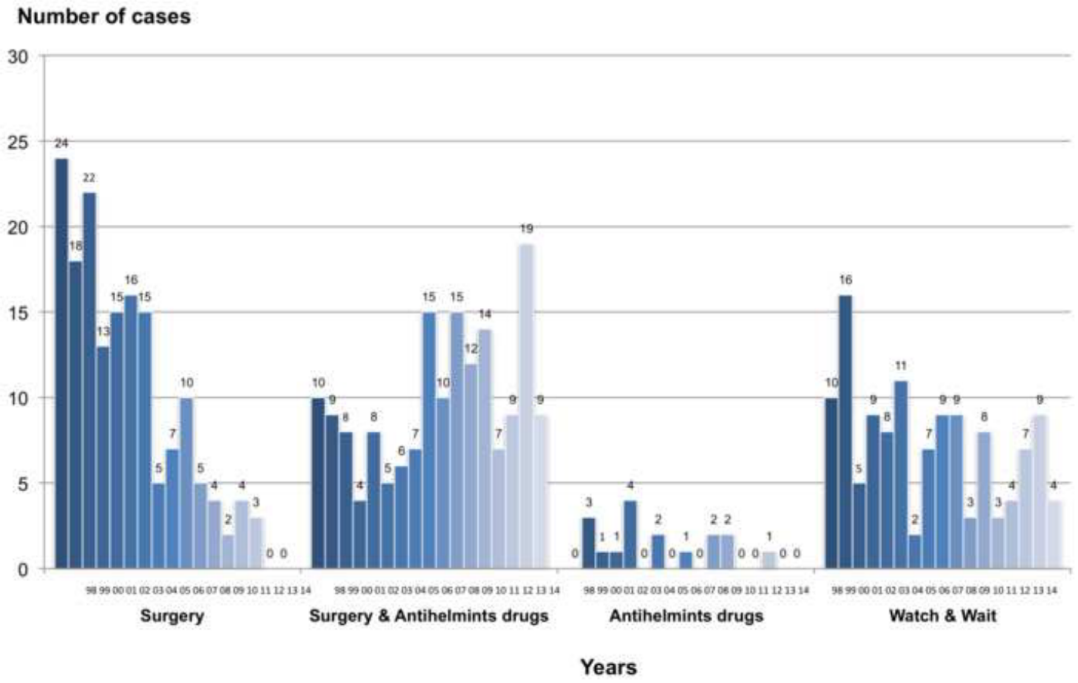
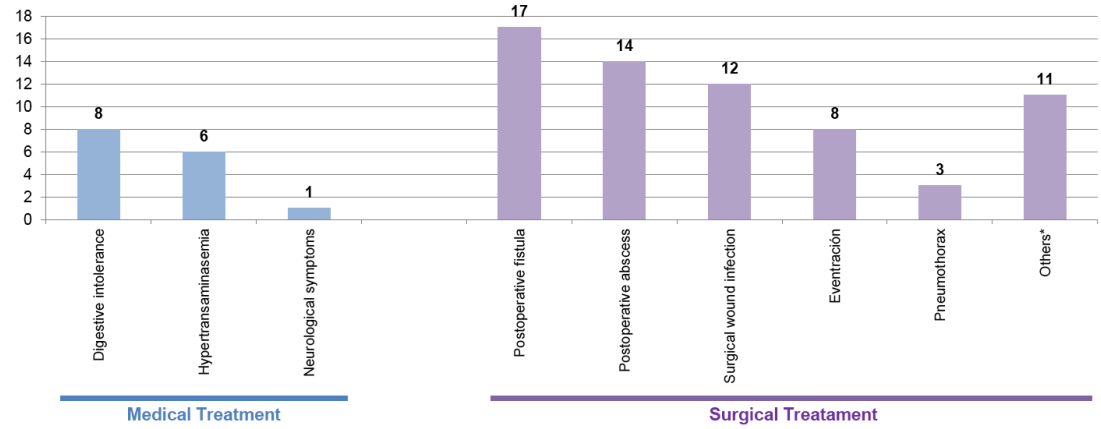


Figure 2: Complications associated to medical and surgical treatment



***Others:** one of each septic shock, intestinal ischemia, hypernatremia, nosocomial pneumonia, acute pulmonary edema, anaemia, hemoperitoneum, hemothorax, splenic bleeding, incisional wound, multiorgan failure.

Figure 3. Kaplan-Meier Survival Curve

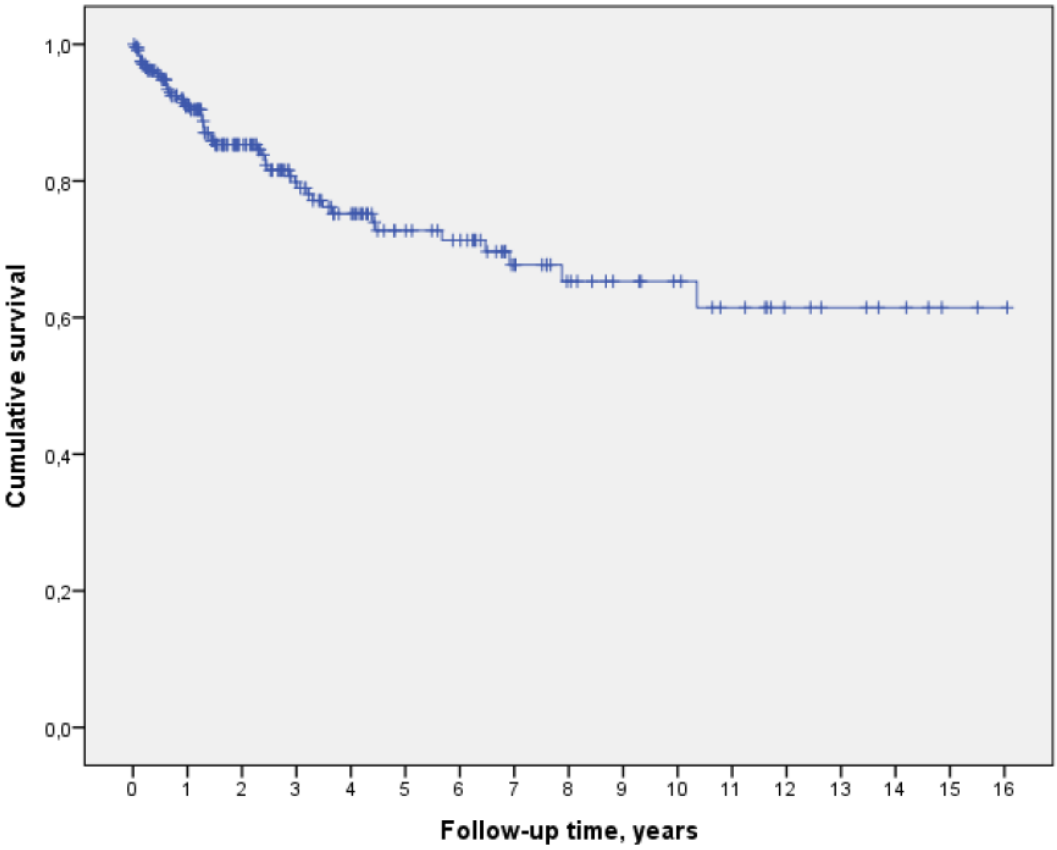


Table 1. Main epidemiological and clinical data in 491 patients included in the study.

	All patients n (%) 491 (100)	Surgery & drugs n (%) 176 (35.8)	Surgery alone n (%) 166 (33.8)	Drugs alone n (%) 17 (3.5)	Wach & Wait n (%) 131 (26.7)	PAIR n (%) 1 (0.2)	p-value
Age							0.000
mean±SD, years	59.5±20.4	50.4±19.7	55.7±17.2	71.2±20.8	75.1±14.7	79.0	
<59 years	208 (42.4)	107 (60.8)	83 (50.0)	4 (23.5)	14 (10.7)	0 (0.0)	
Sex (male)	288 (58.7)	116 (65.9)	93 (56.0)	9 (52.9)	69 (52.7)	1 (100.0)	0.141
Comorbidity	231 (47.0)	56 (31.8)	71 (42.8)	11 (64.7)	92 (70.2)	1 (100.0)	0.000
Number of diseases							0.007
1 disease	136 (58.9)	33 (58.9)	53 (74.6)	4 (36.4)	46 (50.0)	0 (0.0)	
≥ 2 diseases	95 (41.1)	23 (41.1)	18 (25.4)	7 (63.6)	46 (50.0)	1 100.0)	
mean ± SD	1.6±1.1	1.6±0.9	1.3±0.7	1.9±0.8	1.9±1.3	3.0	
Immunosuppression	99 (20.2)	18 (10.2)	28 (16.9)	5 (29.4)	48 (36.6)	0 (0.0)	0.000
Diagnostic							0.000
Asyntomatic	293 (59.7)	93 (52.8)	93 (56.0)	7 (41.2)	99 (75.6)	1 (100.0)	
Mechanical	96 (19.6)	35 (19.9)	47 (28.3)	4 (23.5)	10 (7.6)	0 (0.0)	
Infectious	58 (11.8)	20 (11.4)	14 (8.4)	5 (29.4)	19 (14.5)	0 (0.0)	
Alergic	15 (3.1)	12 (6.8)	3 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	
Mechanical & infectious	27 (5.5)	14 (8.0)	9 (5.4)	1 (5.9)	3 (2.3)	0 (0.0)	
Mechanical &alergic	2 (0.4)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Eosinophilia >450/µL	111 (22.6)	56 (33.3)	40 (26.8)	2 (12.5)	12 (9.2)	1 (100.0)	0.000
EIA *E. granulosus* (>1/80)	162 (33.0)	96 (54.5)	48 (28.9)	6 (35.3)	12 (9.2)	0 (0.0)	0.000
Number of cyts							0.000
1	337 (68.6)	100 (56.8)	127 (76.5)	7 (41.2)	102 (78.5)	1 (100.0)	
≥2	153 (31.2)	76 (43.2)	39 (23.5)	10 (58.8)	28 (21.5)	0 (0.0)	
Size of the largest cyst							0.001
<6.9 cm	262 (53.5)	80 (45.5)	82 (49.4)	12 (70.6)	88 (67.7)	0 (0.0)	
≥7 cm	228 (46.5)	96 (54.5)	84 (50.6)	5 (29.4)	42 (32.3)	1 (100.0)	
mean±SD, cm	7.3±4.2	8.0±4.4	7.8±4.4	6.0±3.6	6.1±3.5	7.0	
Cyst location							0.000
Liver	410 (83.5)	150 (85.2)	124 (74.7)	12 (70.6)	124 (95.4)	0 (0.0)	
Lung	69 (14.1)	25 (14.2)	37 (22.3)	4 (23.5)	3 (2.3)	0 (0.0)	
Other/diseminated	61 (12.4)	24 (13.6)	23 (13.8)	3 (17.6)	10 (7.7)	1 (100.0)	
WHO stages							0.000
1	18 (4.4)	6 (4.0)	8 (6.5)	2 (16.7)	2 (1.6)	-	
2	105 (25.6)	48 (32.0)	35 (28.2)	4 (33.3)	18 (14.5)	-	
3	58 (14.1)	30 (20.0)	13 (10.5)	1 (8.3)	14 (11.3)	-	
4	72 (17.6)	29 (19.3)	21 (16.9)	0 (0.0)	22 (17.7)	-	
5	157 (38.3)	37 (24.7)	47 (37.9)	5 (41.7)	68 (54.8)	-	
Recurrences	51 (10.4)	23 (13.1)	13 (7.8)	3 (17.6)	11 (8.4)	1 (100.0)	0.013
Cohort mortality	80 (16.3)	6 (3.4)	21 (12.7)	5 (29.4)	48 (36.6)	0 (0.0)	0.000
CE disease mortality	14 (2.9)	2 (1.1)	5 (3.0)	0 (0.0)	7 (5.3)	0 (0.0)	0.045
Mean hospital stay (days)	12.8±12.6	11.7±10.1	14.3±16.9	12.0±5.6	12.5±9.8	1.0	0.290
Follow-up	247 (50.3)	141 (80.1)	76 (45.8)	12 (70.6)	18 (13.7)	---	0.000
Follow-up time (mean±SD, years)	3.36±3.50	3.49±3.30	3.29±3.87	2.67±3.67	3.20±3.43	---	0.870

Table 2. Surgical techniques performed in the first intervention.

	Patients n (%) 342 (100.0)
Partial pericystectomy+ cholecystectomy	147 (43.0)
Combined techniques	61 (17.9)
Total pericystectomy+ cholecystectomy	54 (15.8)
Segmentectomy	40 (11.8)
Cystectomy	27 (7.9)
Lobectomia	8 (2.4)
Splenectomy	4 (0.9)
Nephrectomy	1 (0.3)

Table 3. Variables *(risk factors)* that influence mortality of the cohort (*Bivariate analysis*).

Factors	All-cause mortality (N=80)			CE disease mortality (N=14)		
	n (%)	**OR (CI 95%)**	**p-value***	**n (%)**	**OR (CI 95%)**	**p-value***
Host factors						
Elderly (≥60) *vs* young	71(88.8) *vs* 9 (11.3)	7.4 (3.6-15.2)	0.000*	14 (100.0) *vs* 0	-	0.001*
Man *vs* woman	50 (62.5) *vs* 30 (37.5)	-	0,445	7 (50.0) *vs* 7 (50.0)	-	0.505
Rural habitat *vs* urban habitat	52 (65.0) *vs* 28 (35.0)	-	0.322	9 (64.3) *vs* 5 (35.7)	-	0.658
Contacting animals *vs* non-contact	20 (25.0) *vs* 60 (75.0)	-	0.785	4 (28.6) *vs* 10 (71.4)	-	0.828
Immunosuppression, yes *vs* no	31 (38.8) *vs* 49 (61.3)	3.1 (1.8-5.3)	0.000*	3 (21.4) *vs* 11 (78.6)	-	0.905
Comorbidity, yes *vs* no	61 (76.3) *vs* 19 (23.8)	4.5 (2.6-7.8)	0.000*	12 (85.7) *vs* 2 (14.3)	7.0 (1.5-31.9)	0.003*
Clinical setting						
Relapse *vs* first CE	5 (6.3) *vs* 75 (93.8)	-	0.185	1 (7.1) *vs* 13 (92.9)	-	0.686
Clinical symptoms *vs* asymptomatic-casual finding	28 (35.0) *vs* 52 (65.0)	-	0.289	12 (85.7) *vs* 2 (14.3)	9.3 (2.0-42.4)	0.000*
Cyst´s characteristics						
Single *vs* multiple cyst	59(73.8) *vs* 21 (26.3)	-	0.294	8 (57.1) *vs* 6 (42.9)	-	0.341
Pulmonary/lung localization, yes *vs* no	7 (8.8) *vs* 73 (91.2)	-	0.134	3 (21.4) *vs* 11 (78.6)	-	0.423
Hepatic/liver localization, yes *vs* no	72 (90.0) *vs* 8 (10.0)	-	0.094	13 (92.9) *vs* 1 (7.1)	-	0.346
1 segment liver *vs* ≥2 segments	51 (70.8) *vs* 21 (29.2)	1.7 (1,1-3.0);	0.048*	7 (53.8) *vs* 6 (46.2)	-	0.619
Big (>7cm) *vs* small size	31 (38.8) *vs* 49 (61.2)	-	0.127	7 (50.0) *vs* 7 (50.0)	-	0.792
Treatment strategy						
Wait and see *vs* other strategies	48 (60.0) *vs* 32 (40.0)	5.9 (3.5-9.8)	0.000*	7 (50.0) *vs* 7 (50.0)	2.8 (1.1-8.2)	0.045*
Treatment complications, yes *vs* no	7 (21.9) *vs* 25 (78.1)		0.340	4 (57.1) *vs* 3 (42.9)	5.9 (1.3-27.5)	0.009*

*Statistical significance level of 5% ($p < 0.05$).

ARTÍCULO QUINTO

Cutaneous Disease as the First Manifestation of Cystic Echinococcosis.

Antecedentes: La EQ es una enfermedad compleja. Las técnicas de serodiagnóstico tienen un alto porcentaje de falsos negativos y, por lo tanto, el diagnóstico de EQ puede ser difícil. La EQ puede permanecer silente durante un largo periodo. Clínicamente puede presentarse como una infección asintomática hasta una enfermedad grave e incluso mortal. Desde el punto de vista cutáneo puede manifestarse por complicaciones mecánicas, como fístulas cutáneas o bien reacciones anafilactoides, como urticaria aguda y crónica. Se supone que estos síntomas son causados por una ruptura parcial del quiste y un drenaje microscópico.

Métodos: Descripción de un caso clínico de EQ que se presentó clínicamente como eccema generalizado de larga evolución.

Conclusiones: Las manifestaciones cutáneas pueden ser una pista en el diagnóstico de enfermedades infecciosas potencialmente graves como la EQ, y debemos incluir a la EQ en el diagnóstico diferencial del eccema generalizado.

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Images in Clinical Tropical Medicine

Cutaneous Disease as the First Manifestation of Cystic Echinococcosis

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A 61-year-old man from a rural area (Salamanca, Spain), who had contact with dogs, was admitted with generalized itching for 4 years. He was treated with oral antihistamines. A physical examination revealed greyish hyperpigmentation and severe lichenification and infiltration on the face, without mucosal pigmentation. His trunk and limbs showed xerosis, erythematous scaly skin areas with lichenification and hyperpigmentation (Figure 1).

Increased levels of IgE of 2,864 UI/L (0–114 IU/L), but no eosinophilia, were detected. Skin biopsy revealed perivascular spongiotic dermatitis with eosinophilic infiltrate, congruent with eczema (Figure 2). Allergic and photoallergic contact dermatitis and aeroallergen sensitization were ruled out. Bronchial hyperresponsiveness was determined and the patient was treated with salbutamol inhalation.

After a diagnosis of generalized eczema, he was managed with topical propionate of clobetasol and topical tacrolimus, oral ebastine, and oral prednisone in a tapering regimen during flares. Skin lesions worsened with bronchial reactivity 4 years later. IgE > 5,000 UI/L and eosinophilia of 900/μL (7.19%) were detected. Chest X-ray was normal. Antibodies against hepatitis B virus, hepatitis C virus, syphilis, *Trichinella* sp., *Toxoplasma gondii*, *Strongyloides* sp., *Fasciola hepatica*, *Taenia solium*, and parasites in stool (three serial samples) were negative. IgG results for hydatic disease were repeatedly negative, but specific *Echinococcus granulosus* IgE was detected (3.13 kUA/L) (negative < 0.35 kUA/L, ImmunoCAP system, Phadia, Uppsala, Sweden). Abdominal computerized tomography showed three focal lesions that were consistent with hepatic hydatid cysts: the first cyst was localized in segment I of 24 × 21 × 18 cm (stage cystic echinococcosis [CE] 5), the second cyst in segment II of 48 × 31 × 36 cm (stage CE3), and the third cyst in segment VII of 45 × 34 × 34 cm (stage CE3) (Figure 3). Albendazole (400 mg twice a day) and praziquantel (1,200 mg twice a day) were administered and surgery was subsequently performed. Removal of cysts in segment I, II, and VII was done. Histopathological examination confirmed infection by *E. granulosus*. Treatment with only albendazole was continued because of digestive intolerance from praziquantel. The patient improved symptomatically and with regard to the skin lesions (Figure 4). All treatments (topical, oral, and inhaled) were stopped after 18 months.

In dermatology, increased levels of IgE and eosinophilia are commonly related to atopy, but other entities with skin manifestations, mainly neoplasms and infectious diseases, should also be considered. CE is a chronic, complex, and neglected zoonotic disease, and it remains an important health problem in many areas of the world.[1] In humans, it may result in a wide spectrum of clinical manifestations, ranging from asymptomatic infection to severe and even fatal disease.[2] CE typically grows slowly and may long remain clinically silent. Common serodiagnotis techniques may produce a high percentage of false-negative results, and thus CE diagnosis can be difficult.[3] *Echinococcus granulosus* infection may produce different cutaneous manifestations, some of which are due to mechanical complication, such as skin fistulae,[4] and others are due to anaphylactoid reactions, such as acute or chronic urticaria and flushing.[5] It is assumed that these former symptoms may be caused by a partial rupture of the cyst with microscopic drainage. We propose that this continuous antigenic trigger and repeated scratching could potentially result in clinical manifestations in our patient, which were resolved using antiparasitic treatment. We have not found any previously described association between the skin alterations in our patient and hydatid disease. In conclusion, we highlight that skin manifestations may be a clue in the diagnosis of potentially severe infectious diseases, and we should include CE in the differential diagnosis of generalized eczema.

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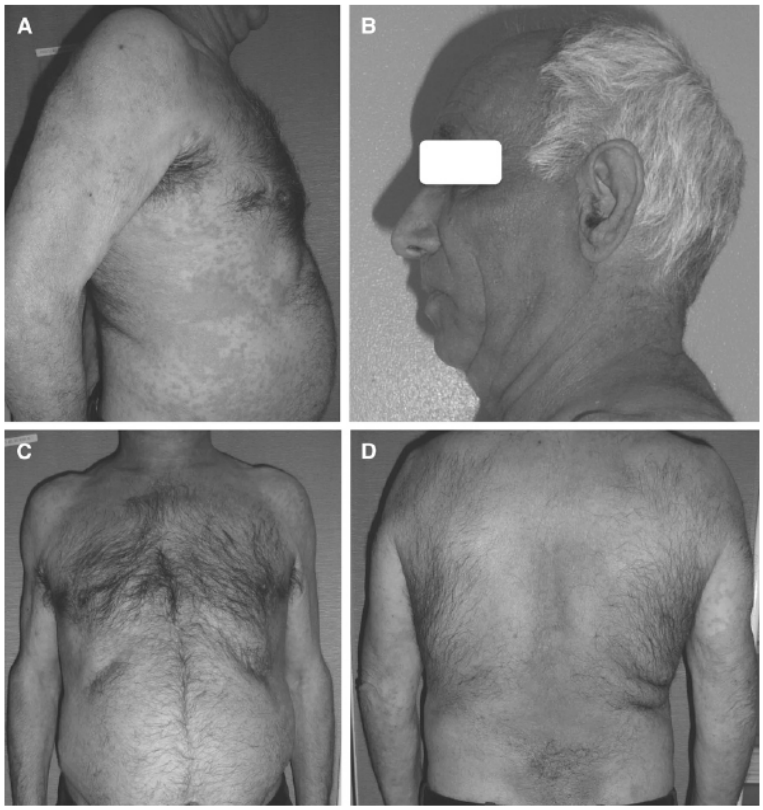

FIGURE 1. **(A, C, D)** Xerosis, erythematous scaly skin areas with lichenification and hyperpigmentation of the trunk and upper limbs. **(B)** Greyish hyperpigmentation and severe lichenification and infiltration on the patient's face. This figure appears in color at www.ajtmh.org.

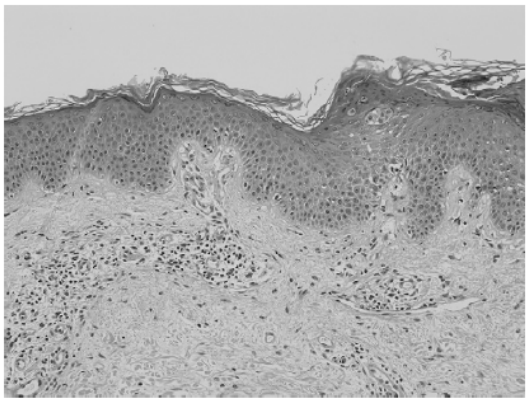

FIGURE 2. Perivascular spongiotic dermatitis with eosinophilic infiltrate in the histopathological examinations of skin biopsy (H-E × 10). This figure appears in color at www.ajtmh.org.

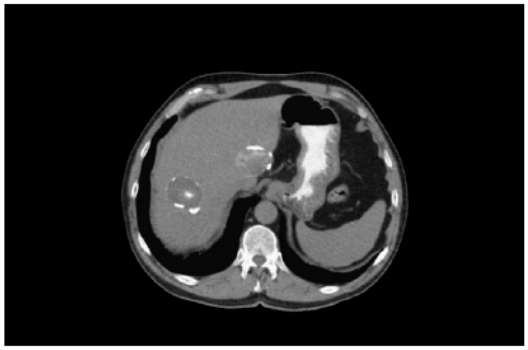

FIGURE 3. Computerized tomography showing hepatic hydatid cysts.

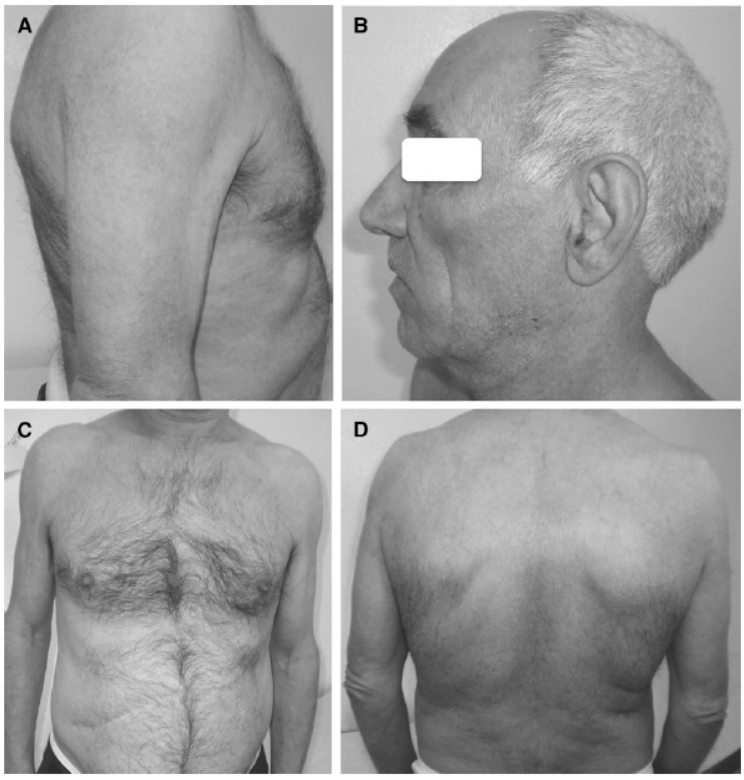

FIGURE 4. (**A–D**) Clear improvement of skin lesions, with (**D**) hyperpigmentation only in the trunk.

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ARTÍCULO SEXTO

Recurrence of cystic echinococcosis in an endemic area: a retrospective study.

Antecedentes: La EQ es una enfermedad zoonótica crónica, y compleja. Da lugar a un amplio espectro de manifestaciones clínicas, que van desde casos asintomáticos a una enfermedad letal. A pesar de los avances en las técnicas quirúrgicas y el uso de la quimioterapia, las recurrencias sigue siendo uno de los problemas importantes en el manejo de la EQ. El objetivo de este estudio fue determinar la frecuencia de las recurrencia y los factores de riesgo implicados.

Métodos: Se diseñó un estudio descriptivo longitudinal-retrospectivo. Revisamos a todos los pacientes diagnosticados con CE según CIE-9 (código 122-0 a 122-9) admitidos y con seguimiento, en el Complejo Asistencial Universitario de Salamanca, entre enero de 1998 y diciembre de 2015.

Resultados: de los 217 pacientes estudiados, 25 (11.5%) presentaron recurrencia tras un tratamiento inicial con intención curativa. La duración media del diagnóstico de recurrencia fue de 12.35 años (DE: ± 9.31). 16 casos estaban asintomáticos en el momento de la recidiva. Las recurrencias se asocian más frecuentemente a localizaciones del quiste primario fuera de hígado y pulmón y el manejo quirúrgico en pacientes seleccionados produce resultados adecuados.

Conclusiones: Las recurrencias siguen siendo uno de los principales problemas en el tratamiento de la enfermedad hidatídica a pesar de los avances en el diagnóstico y las técnicas terapéuticas en la hidatidosis. El manejo actual de las recurrencias se basa todavía en opinión de expertos y la calidad de la evidencia es baja. En consecuencia, se necesitan estudios para proporcionar recomendaciones para su manejo clínico.

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BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Recurrence of cystic echinococcosis in an endemic area: a retrospective study

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Abstract

Background: Cystic echinococcosis (CE) is a chronic, complex and neglected zoonotic disease. CE occurs worldwide. In humans, it may result in a wide spectrum of clinical manifestations, ranging from asymptomatic infection to fatal disease. Clinical management procedures have evolved over decades without adequate evaluation. Despite advances in surgical techniques and the use of chemotherapy, recurrence remains one of the major problems in the management of hydatid disease. The aim of this study was to determine the frequency of CE recurrence and the risk factors involved in recurrence.

Methods: A descriptive longitudinal-retrospective study was designed. We reviewed all patients diagnosed with CE according to ICD-9 (code 122–0 to 122–9) criteria admitted at Complejo Asistencial Universitario de Salamanca, Spain, between January 1998 and December 2015.

Results: Among the 217 patients studied, 25 (11.5%) had a hydatid recurrence after curative intention treatment. Median duration of recurrence's diagnosis was 12.35 years (SD: ±9.31). The likelihood of recurrence was higher [OR = 2.7; 95% CI, 1.1–7.1; $p < 0.05$] when the cyst was located in organs other than liver and lung, 22.6% (7/31) vs 14.2% (31/217) in the cohort. We detected a chance of recurrence [OR = 2.3; 95% CI, 1.4–6.5; $p > 0.05$] that was two times higher in those patients treated with a combination of antihelminthic treatments and surgical intervention (20/141, 14.2%) than in patients treated with surgical intervention alone (5/76, 6.6%).

Conclusions: Despite advances in diagnosis and therapeutic techniques in hydatid disease, recurrence remains one of the major problems in the management of hydatid disease. The current management and treatment of recurrences is still largely based on expert opinion and moderate-to-poor quality of evidence. Consequently, large prospective and multicenter studies will be needed to provide definitive recommendations for its clinical management.

Keywords: Cystic echinococcosis, *Echinococcus granulosus*, Hydatidosis, Recurrence, Treatment

Background

Cystic echinococcosis (CE) is a chronic, complex and neglected zoonotic disease caused by the larval stage (metacestode) of *Echinococcus granulosus*. CE occurs worldwide but is endemic to central Asia, northern and eastern Africa, Australia, South America and the Mediterranean Basin [1–3]. CE has peculiar features that imply difficulties in the evaluation of its magnitude [2]. In humans, it may result in a wide spectrum of clinical manifestations, ranging from asymptomatic infection to fatal disease [4]. Its clinical management is complex, has evolved over decades without adequate evaluation of efficacy, effectiveness, rate of adverse reactions, relapse rate, and cost. The current management and treatment of CE is still largely based on expert opinion and moderate-to-poor quality of evidence [5, 6]. Despite advances in surgical techniques and the use of chemotherapy, recurrence remains one of the major problems in the management of hydatid disease [7]. Overall, CE recurrence rates appear to be highly variable

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(0%–22%) and are seen in intervals ranging from 3 months to 20 years from the first operation [8]. The recurrence of disease may present with major complications including pyogenic infection, intrabiliary rupture, or anaphylaxis. However, it is usually initially asymptomatic, and therefore regular long-term follow-up should be routine after primary treatment [9, 10]. Recurrent disease is the main criteria of failure of treatment [10]. Finally, the absence of protocols and clinical guidelines of the "best" management for echinococcal cysts is also a clear factor underlying recurrent CE [11]. The purpose of this study was to determine the frequency of CE recurrence, the clinical setting and the risk factors involved in recurrence. Moreover, we studied the treatment applied to these patients and their mortality.

Methods

The design was a descriptive longitudinal-retrospective study. We reviewed all patients diagnosed with CE according to ICD-9 (code 122–0 to 122–9) criteria admitted at Complejo Asistencial Universitario de Salamanca (CAUSA) between January 1998 and December 2015. CAUSA is a tertiary care hospital, located in western Spain. It covers an area of 12,350 km^2 with a population of approximately 350,500 individuals [12]. The clinical and epidemiological data were collected after revision of medical records. Diagnosis and classification of CE were assessed according to the criteria proposed by the World Health Organization Informal Working Group on Echinococcosis for CE [6]. Recurrent disease was defined as the appearance of new active cysts after intentional curative therapy, including the reappearance with continuous growth of live cysts at a site of a previously treated cyst or the appearance of new distant disease. To be included in the study, at least one of the following radiological images of the hydatidosis-affected area was to be performed: *i)* abdominal ultrasonography (US) and/or *ii)* computed tomography (CT) in the twelve postoperative months. During follow-up, cysts areas imaged by US and/or CT without a change in size and without evidence of daughter cysts were not considered as recurrence. Patients without follow-up or radiological image, with missing data and who were not recipients of surgery were excluded from the study.

Subsequently, a search was conducted in PubMed from 1966 to January 2016 with *relapses*, *recurrences*, *hydatidosis* and *Echinococcus granulosus* terminus. Clinical cases and non-relevant works were discarded.

The statistical analysis

The results were expressed as percentages for categorical variables and as the mean and standard deviation (SD) for continuous variables. A chi-square test was used to compare the association between categorical variables, such as clinical and demographics variables, and the measured outcome was expressed as the odds ratio (OR) together with the 95% CI for OR. Continuous variables were compared with Student's *t*-test, ANOVA or the Mann–Whitney *U* test for two groups, depending on their normal or non-normal distribution. Additionally, we applied the corresponding regression models for multivariate analysis. Recurrence rates were analyzed by Kaplan–Meier method for patients undergoing surgery and apparently disease-free at discharge from hospital. We considered a statistically significant difference from chance at a p-value <0.05. All data were analyzed with SPSS 23 (*Statistical Package for the Social Sciences*).

Results

A total of 571 patients were diagnosed with CE according to ICD-9 (code 122–0 to 122–9) criteria in CAUSA between January 1998 and December 2015. Of these, 343 (60.0%) patients were treated with curative intention (surgery & PAIR [Puncture, Aspiration, Injection, and Re-aspiration]). After exclusion criteria, the study sample was 217 patients. The main epidemiological and clinical data of these patients were shown in Table 1. The mean (±SD) of follow-up was 3.42 ± 3.50 years. The median (25th and 75th percentiles) value was 2.17 years (0.96 and 4.46, respectively). Among the 217 patients, a total of 423 cysts were detected and the cysts per patient mean (±SD) was 1.95 ± 2.66.

A total of 25 (11.5%) patients had CE recurrences during their follow-up. The mean time until diagnosis of CE recurrence was 12.35 years ±9.31 (interval range: 0.02–41.61 years). Four cases were detected in the five first years after surgical intervention, 7 cases between 5 and 10 years of surgical intervention, and 14 cases after 10 years of surgical intervention (Fig. 1). The time trend of recurrences are shown in Fig. 2. In 23 (92%) cases, recurrence appeared next to the surgical site, and only two (8%) recurrences appeared remote to the surgical site (one patient had recurrent CE in the psoas muscle and other in lumbar paravertebral musculature).

Among patients with recurrent CE, 16 (64.0%) were asymptomatic at the moment of diagnosis, with it usually an incidental diagnosis. Nine (36.0%) recurrent cases had clinical manifestations of complicated CE: 6 cases had mechanical complications; two cases had structural displacements; one case had vomica (caused by bronchial fistula); one case had thoracic pain (associated to bronchial fistula); one case was jaundice (by biliary fistula) and one case presented with sciatica (caused by spinal CE). Two patients with recurrent CE presented secondary super-infections pyogenic with suppurative cholangitis and two cases presented urticarial reactions. No patient with recurrent CE died as a consequence of recurrent complicated cyst. The variables associated with recurrence are shown in Table 2. We did not detect any

Table 1 Main epidemiological and clinical data in 217 patients included in the study

	Patients n/N (%)
Age, mean ± SD (range),years	52.55 ± 18.20 (5–82)
≤ 59 years	124/217 (57.1)
Male sex	133/217 (61.3)
Patients from rural areas	148/217 (68.2)
Professional activity-agriculture/livestock	31/217 (14.3)
Contact with animals	60/217 (27.6)
Immigrants	6/217 (2.8)
Comorbidity	73/217 (33.6)
Asyntomatic/casual finding	129/217 (59.4)
Clinical manifestations	88/217 (40.6)
Mechanics	54/88 (61.3)
Infectious	35/88 (39.7)
Allergic	14/88 (15.9)
Eosinophilia (>0.450 × 10^9 eosinophils/L)	65/217 (29.9)
ELISA (>1/80)	105/217 (48.4)
Cyst location *(multiple response variable)*	
Liver	193/217 (88.9)
Lung	12/217 (5.5)
Others/disseminated	31/217 (14.2)
No. of cysts, mean ± SD (range)	1.95 ± 2.66 (1–20)
1	137/217 (63.1)
≥ 2	80/217 (36.9)
Size of the largest cyst, mean ± SD (range),cm	8.18 ± 4.35 (1–23)
≥ 7 cm	122/217 (56.2)
≤ 6.9 cm	95/217 (43.8)
WHO classification	193/217 (88.9)
CE1	10/193 (5.2)
CE2	59/193 (30.6)
CE3	32/193 (16.6)
CE4	30/193 (15.5)
CE5	62/193 (32.1)
Treatment	
Combined treatment (Antihelminths & surgical)	141/217 (65.0)
Surgical technics	76/217 (35.0)
Surgical treatment complications	38/217 (17.5)
Cohort mortality from all causes	13/217 (6.0)[a]
Mortality attributable to hydatidosis	2/217 (0.9)[b]

[a]Exitus ethiology: cardiovascular 1. Cancer 1. Infectious 5. No data 6
[b]Exitus ethiology for *E. granulosus*: Infectious (sepsis) 1. Hemoptysis 1

epidemiological variables associated with the occurrence of relapses in patients ($p > 0.05$).

In regard to the location of primary CE, recurrence was higher in primary CE located in organs other than the liver or lung [22.6% vs 9.8% vs 0% (OR 2.7 (1.1–7.1) vs 0.3 (0.1–0.9), $p < 0.05$]. Recurrence was higher in patients surgical treated with two or more vs one cyst [13.8% vs 10.2%, OR 1.4 (0.6–3.2)], although these results were not significant ($p > 0.05$) Recurrences were more frequent in primary cysts larger than 7 cm that in smaller cysts, but these differences were not significant [13.1% vs 9.4%, OR 1.4 (95% CI 0.6–3.4), $p > 0.05$]. With respect to WHO classification, relapses were more frequently detected between CE2-CE3 than CE4-CE5 [12/91 (13.2%) vs (7,6%); OR 1.6 (95% CI 0.6–4.3) $p > 0.05$], but these differences were not significant.

We detected the likelihood of recurrence was twice as likely in those patients treated with a combination of anti-helminthic treatments and surgical intervention than patients treated with surgical intervention alone [14.2% vs 6.6%, OR 2.34 (CI 95 0.84–6.52) $p > 0.05$)]. The logistic regression model shows the following clinical pattern: patients with hepatic cysts are treated with surgery alone [Exp (B) = 3.50; 95% CI, 1.20–10.18; $p < 0.05$], whereas patients with localized cysts in organs other than liver or lung receiving combination therapy [Exp (B) = 2.72; 95% CI, 1.03–7.19; $p < 0.05$].

Finally, we evaluated the treatment given to patients with recurrences (Tables 1 and 2). All patients (25, 100%) with recurrences, were treated: 5 (10%) patients with surgical treatment alone, and 20 (80%) patients with a combination of surgical and anti-helminthic treatments (50% with albendazole and 50% albendazole and praziquantel). The mortality in both groups was null.

Discussion

Cyst echinococcosis (CE) is a parasitic disease highly complex, due mainly to involvement of different organs and tissues and its very slow course (usually over decades). During this large time period, CE may pass from stages active to inactive, and its clinical setting may range from an asymptomatic form to several complications, including fatal disease [4].

The lack of large, longitudinal and controlled studies is due to different factors. First, the chronicity of the disease requires a follow-up of several years to evaluate relapse rates. Second, because there are not tools sensitive enough to allow us to arrive at early diagnosis, and consequently, optimal monitoring after treatment. Finally, its status as a neglected disease contributes to scarce funding for investigations of CE [6]. As a consequence, clinical management has evolved over decades based only on poor-to-moderate quality of evidence and recommendation strengths [6, 7]. Accordingly, major constraints of our work are conditioned by retrospective design. Therefore, the "best" management for CE is still a subject of debate [7]. Besides, in the WHO-IWGE Expert Consensus (World Health Organization-Informal Working Group on Echinococcosis) there is no clear definition of relapse, recurrence and reinfection, which reflects difficulties found in clinical practice.

However, factors such as the introduction of the WHO-IWGE classification for CE or the recent European project HERACLES, have allowed the establishment of a framework that may contribute to advances in the treatment of CE [13].

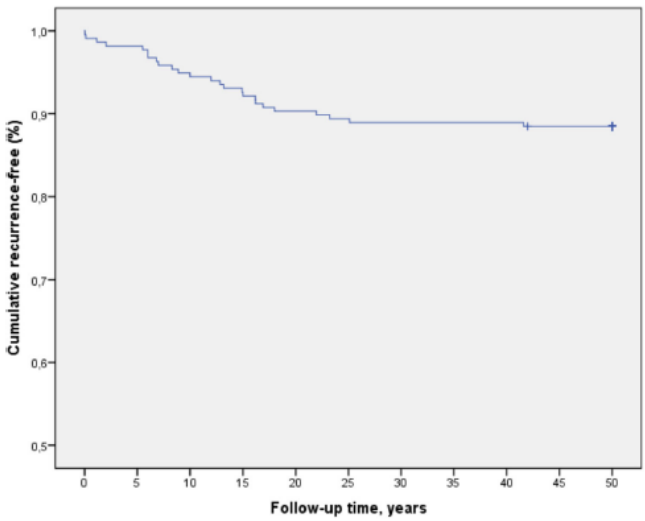

Fig. 1 Kaplan-Meier Curve of recurrence-free time in the cohort

Today, standard of treatment in CE is based in the use of different surgical techniques with or without chemotherapy and recurrence remains one of the major problems in the management of CE [14] as it can occur with any of the therapeutic methods employed [14]. Although, there are many series of patients with CE, only a few studies specifically analyzed the presence of recurrences and assessed its frequency and surrounding circumstances (Table 3) [8, 14–21].

The aim of this work was to determine, in our center, the frequency of recurrence after CE surgery, and the main factors associated with this recurrence. Our work analyzed recurrence using data from clinical records. Therefore, we detected a rate of recurrence above 11%.

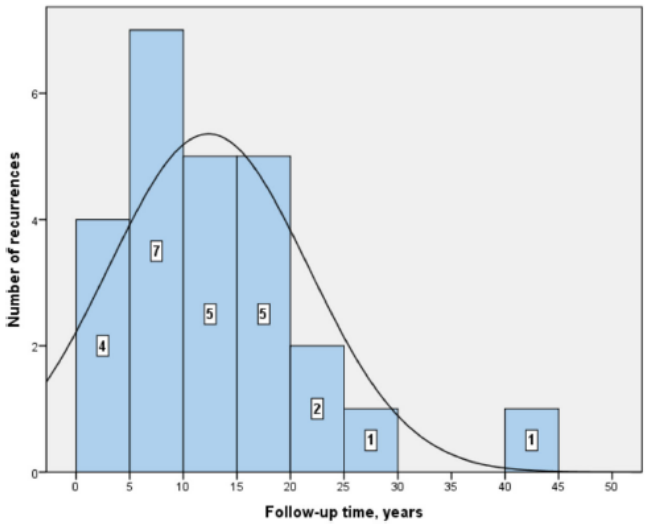

Fig. 2 Number of recurrences during follow-up time

Table 2 Study of factors associated with recurrence. Bi-variable analyses between host factors, primary cyst and treatment used with recurrence

Patients with recurrences	n/N (%)	OR (IC95%)	*p*-value*
Host factors			
Age ≤ 59 years	17/124 (13.7)	1.6 (0.6–4.0)	0.244
Male sex	18/133 (13.5)	1.7 (0.6–4.3)	0.243
Patients from rural areas	17/148 (11.5)	0.9 (0.4–2.4)	0.982
Professional activity-agriculture/livestock	2/31 (6.5)	0.4 (0.1–2.1)	0.340
Contact with animals	4/60 (6.7)	0.4 (0.1–1.4)	0.166
Immigrants	0/6 (0.0)	–	–
Comorbidity	7/73 (9.6)	0.7 (0.2–1.8-)	0.526
Cyst primary factors			
Complicated	9/88 (10.2)	0.8 (0.3–1.9)	0.622
Cyst size (≥7 cm)	16/122 (13.1)	1.4 (0.6–3.4)	0.405
Cyst location			
Liver	19/193 (9.8)	0.3 (0.1–0.9)	0.028*
Lung	0/12 (0.0)	–	–
Others/disseminated	7/31 (22.6)	2.7 (1.1–7.1)	0.037*
No. of cysts (≥2)	11/80 (13.8)	1.4 (0.6–3.2)	0.432
WHO classification	19/193 (9.8)		0.587
CE1	0/10 (0.0)		
CE2	8/59 (13.6)		
CE3	4/32 (12.5)		
CE4	2/30 (6.7)		
CE5	5/62 (8.1)		
Factors associated to treatment			
Combinated treatment (Antihelminths & surgical)	20/141 (14.2)	2.3 (1.4–6.5)	0.094
Surgical technics	5/76 (6.6)		
Surgical treatment complications	7/38 (18.4)	2.0 (0.7–5.2)	0.142

*p-value of the test: Total patients with treatment with curative intention-follow-up & Recurrences. Statistical significance level of 5% ($p < 0.05$)

The rate of recurrence showed by other groups ranged from 0% to 22% in post-surgery [8, 9, 11, 19, 21] and 0%–1.27% in other percutaneous treatments [22]. This wide range reflects several methods employed in these studies, especially with regards to methods used and duration in the follow-up. Despite this, it is probable that all these data on recurrence, including the highest, undervalue the actual incidence.

In regard to the methods used, serological methods did not allow us an optimal follow-up because antibody titers may persist for years after the removal of a cyst. Consequently the relapse must be confirmed by ultrasonography or CT [19]. The differentiation of remaining cavities of effectively treated cysts from locally recurrent disease is difficult, therefore we relied on the accepted imaging marker of the increase in size of the cyst on serial examination, which proved to be effective [19].

Recurrence of CE may be diagnosed after 3 months to 20 years post-surgery, with the mean time ranging 2 and 10 years [9, 10, 17, 18]. In our work, the mean time to detection was lengthy. This is possible because a follow-up prospective after surgery of patients with CE has not been well standardized in our hospital. Therefore, most patients were only prospectively followed-up for one or two years.

In regard to our clinical setting, more than half of our patients were asymptomatic at the moment of diagnosis of relapse. Nevertheless, we also detect patients with CE complications, including pyogenic super-infection, biliary and pleural fistula, or immunological reactions such as a type of urticarial rash. However, there is to highlight that no patient with recurrent CE died as result of these complications. These results are similar to those reported by other authors (Table 3). Consequently, it has been suggested that the postoperative follow-up period should not be shorter than 3 years and should be continued for as long as possible, due the frequently asymptomatic recurrence and the onset of symptoms 3–4 years after surgery [7, 19]. Our results support this strategy, although the efficiency of a screening program in relation to risk and cost has not been established.

Recurrence usually occurs in the same area of the primary CE. Accordingly, in this paper, we detected a local recurrence in more than 90% of cases, and in only two

Table 3 Comparative results of different study of recurrence CE

Reference	Type study/ period	Country	Number of patients of CE n	Localitation	Number of patients with recurrence CE (%)	Treatment with antihelminths first episode	Morbidity (%)	Mortality (%)	Median Time of follow-up (months)	Interval for recurrences (months)	Risk Factor for recurrences
Saidi 1978	Retrospective 1963–1973	Iran	106	159 liver 118 lung 67 others	11.3	ND	ND	8.3	6–36	21.5 ± 14.8	Local spillage
Kapan 2006	Retrospective 1998–2003	Turkey	172	172 liver	4.65	Albendazol pre and postoperatively	5.8	0.58	60.5	23.4 ± 5.3	Multiple cysts
Little 1988	Retrospective 1980–1986	Australia	39	39 liver	22	No	7.6	0	0–60	30	Rupture hydatid cyst
Gollackner 2000	Retrospective 1949–1995	Austria	74	69 liver 3 spleen 2 others	15	50% patients albendazol/ mebendazol pre and postoperative	25.0	2.7	93.6 (24–564)	3–240	ND
El Malki 2010	Retrospective 1990–2004	Morocco	672	672 liver	8.5	No	ND	ND	24 (10–48)	75 (40–119)	Liver hepatic cyst >3 cyst
Prousalidis 2012	Retrospective 1970–2003	Greece	584	436 liver 101 lung 21 peritoneum 12 spleen 13 others	8.7	Albendazol preoperatively and postoperatively	27	ND	58 (48–204)	6–204	Spillage of hydatid cyst missing the cysts pre-intraoperatively incomplete pericystectomy
Bedioui 2012	Retrospective 1996–2006	Tunis	391	391 liver	12	ND	ND	ND	51.6	50	Rural origin cyst > 7 cm unilocular cysts
Akyildiz 2009	Retrospective 1988–2006	Turkey	412	412 liver	9.2	ND	ND	ND	69.6 (12–180)	24–120	ND
Atmatzidis 2005	Retrospective 1982–2001	Greece	109	97 liver 12 others	36	ND	22	2.7	144	84	Chirurgical technique
Meimarakis 2009	Retrospective 1982–2004	Germany	10	10 spleen	0	Albendazol/mebendazol	40	0	105.6	0	ND
Chautems 2005	Retrospective 1980–1999	Swiss	84	84 liver	0	15% Albendazole postoperative	37	0	103.2	0	ND

ND no data

cases was recurrence detected to distance. This fact could be due to the dissemination of the protoscolex from viable CE during surgical procedure by contamination of the surgical bed. However, it is also possible that the dissemination occurs before surgery, especially in complicated CE.

The other objective of our work was to find risk factors associated with recurrence, to implement measure to decrease its risk. In the literature, numerous risk factors have been described, although with important differences between studies [19]. Regarding the factors associated with the host, in our work we found that the epidemiological variables were not associated with recurrences including professional activity–agriculture/livestock or contact with animals. This supports the fact that recurrences are more frequently caused by dissemination before or during surgical procedure than subsequent reinfections.

With respect to primary CE, some characteristics were associated with recurrence. In our study, the location of CE outside of the liver and lung, followed by location in the liver were associated with higher recurrence. Nevertheless, in other series location in the liver [14, 15], in the difficult surgical access [16] or multiple abdominal cysts [14, 15], were variables associated to relapse. Other factors affecting the cyst such as its size, especially in cases larger than 7–10 cm [14, 11] or stages I-II WHO [11] have been associated with recurrence. In our study, we found more frequent relapses in these groups of patients, although these differences were not statistically significant.

In regard to surgery techniques used, the rate of recurrences was higher with laparoscopic surgery, than with open conservative interventions (8.89% vs 3.15%) [16]. Other variables associated with a higher risk or recurrences included: leaving viable material behind during conservative operative interventions [16], incomplete excision of the endocyst, missing the cysts pre- or intraoperatively and incomplete pericystectomy [19] spillage during surgical removal [15, 17, 18, 23]. However, there are no reports showing the association of recurrence and the choice of incision [16]. Two important factors are the surgeon's practice and experience [15, 24].

In our series, all patients were subjected to open surgery and we do not detect factors increasing the risk of relapse.

Finally, anthelminthic drugs as albendazole or mebendazole, with or without praziquantel, have been used for decrease the risk of relapse in patients undergoing surgery for CE. The results in animal models and humans have shown a reduced recurrence in patients operated with these drugs prophylactically. According to a recommendation of the WHO Informal Working Group on Echinococcosis and other studies, antiparasitic chemotherapy is considered today an indication to prevent secondary echinococcosis and reduce the risk of recurrence [14]. In our work, we detected a higher rate of relapse in patients with combined treatment than with surgery alone. This was possibly a selection bias due to the higher use of combined treatment in complicated cyst CE or greater surgical difficulty.

With respect to the treatment of recurrence, there is no consensus in the literature. Not every patient with documented recurrent active hydatid disease needs to be treated with surgical treatment due to the fact that hydatid disease progresses slowly. Therefore, local recurrence, small cysts in asymptomatic patients with advanced age and/or serious co-morbid conditions are best followed and treated only when complications develop [17, 25]. Haddad et al. suggested that in patients with recurrences smaller than 5 cm in diameter, antihelminthic therapy for 3–6 months was the ideal treatment, and the cysts with difficult location for surgery should be drained percutaneously. In the other hand, there are also reports suggesting that in patients, for whom albendazole treatment for the primary disease failed, treatment of recurrence would also fail. Treatment options for local recurrence are similar to those for the primary disease. However, radical interventions are also suggested in patients with recurrence who previously underwent surgery conservatively. Nevertheless, these radical operations are technically more difficult, and reoperations have higher morbidity and mortality rates [14, 16]. Therefore, the choice between conservative vs radical interventions depends on a number of factors, such as location, size and stage of the cysts/lesions, and availability of therapeutic options in each health center. In our work, all patients with recurrent CE were subjected to surgical intervention and the mortality was null, including complicated CE cases. This supports the notion that surgical treatment in well selected cases is associated with good outcomes.

Conclusions

CE recurrence remains one of the major problems in the management of hydatid disease. It can occur decades after surgery, and in the clinical setting is usually diagnosed only incidentally. However, primary cyst can be detected as a complicated cyst. The main risk factor associated with relapse is the location of the primary cyst outside of the liver and lung followed by liver cysts. Mortality in this group of patients was null and surgical intervention of recurrent cyst in well-selected cases is associated with good outcomes.

Abbreviations

CAUSA: Complejo Asistencial Universitario de Salamanca; CE: Cystic echinococcosis; WHO-IWGE: World Health Organization-Informal Working Group on Echinococcosis

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WT, ARA, MBG, AM, JPL: study design and mayor contributiong to writting; MAS, ALB, ACP: analysis and interpretation of data. CEV, MFJL, JLMB, MCS, LMB: Study implementation. All authors have read and approved final versión.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
The study was approved by the Ethics Committee of CAUSA. Due to the fact it was an epidemiological study. All data were analyzed anonymously. Written consent was not obtained and it was specifically waived by the approving IRB.

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ARTÍCULO SÉPTIMO

Recurrent spinal echinococcosis.

Antecedentes: Las recidivas son una complicación frecuente y en ocasiones graves en el manejo de la equinococosis quística.

Métodos: Descripción de un caso clínico.

Conclusiones: La hidatidosis medular puede ser un cuadro fatal.

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Medical Imagery

Recurrent spinal echinococcosis

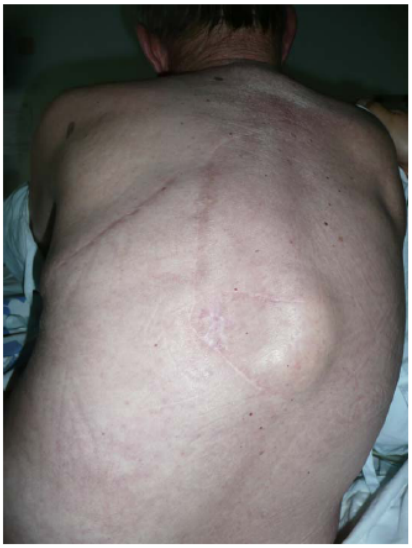

Figure 1. On examination, a fluctuant mass (6 × 6 cm) was observed on the back of the patient.

A 74-year-old man presented with paraparesis and a painful mass on his back of 4 weeks duration. He had been operated on for thoracic and vertebral hydatidosis (T10–L1 levels) 5 years previously, and had been treated with albendazole and praziquantel for 1 year with a full recovery. Physical examination revealed post-surgery scars and a new dorsal mass (6 × 6 cm) (Figure 1), paraplegia, paresthesia with no sensitive level, and decreased anal sphincter tone. Laboratory data showed elevated C-reactive protein (26.1 mg/l). The white cell count was 12.4 × 10^9/l without eosinophilia. Serologic tests for hydatid disease had increased. Magnetic resonance imaging of the dorsal and lumbar spine showed a paravertebral mass with destruction of T11, intraspinal invasion, and medullary compression (Figures 2 and 3). The final diagnosis was recurrent spinal echinococcosis with medullary involvement. He was rejected for surgery due to secondary complications. He received medical treatment (antiparasitic drugs and steroids) with little clinical improvement and finally died due to urinary sepsis.

Conflict of interest: No potential conflict of interest relevant to this article.

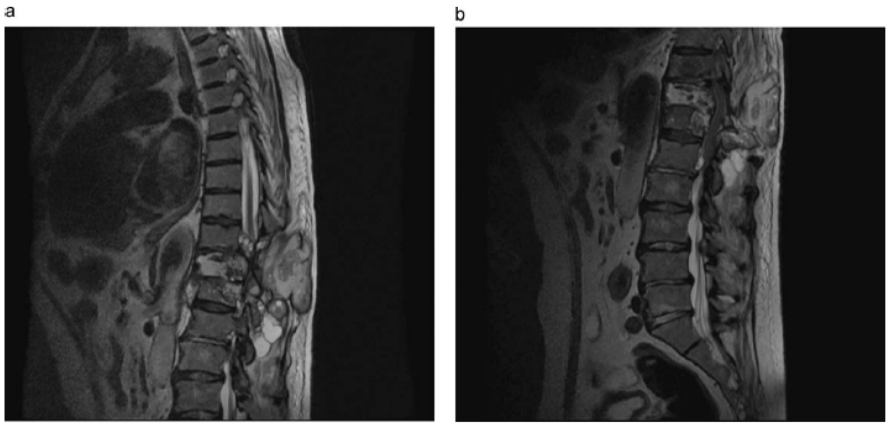

Figure 2. Sagittal section MRI shows a paravertebral mass with destruction of T11, intraspinal invasion, and medullary compression.

1201-9712/$36.00 – see front matter
doi:10.1016/j.ijid.2011.03.002

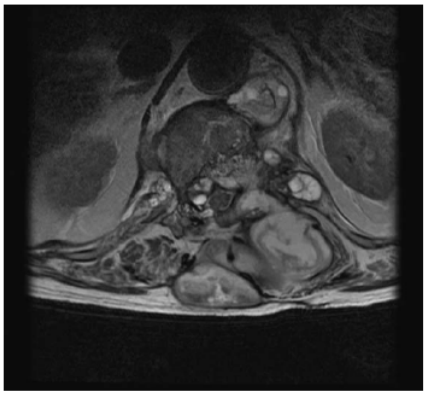

Figure 3. Transverse section MRI shows a paravertebral mass with destruction of T11, intraspinal invasion, and medullary compression.

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ANEXOS

ANEXO METODOLÓGICO

Diseño	Estudio revisión sistemática y metaanálisis.
Ámbito de estudio	Internacional
Población diana	Pacientes con diagnóstico *Echinococcus* sp. CIE-9, códigos 122.0 a 122.9
Tamaño de la muestra	33 artículos: 22 artículos (análisis cualitativo) 11 artículos (análisis cuantitativo = metaanálisis)
Bases de datos	PubMed (Medline) Cochrane Central Register of Controlled Trials (CENTRAL) BioMed DARE (Database of Abstracts of Reviews of Effects) Cochrane Plus
Período de tiempo	Hasta 1 de Febrero de 2017
Software	Cochrane Review Manager (RevMan 5.3)

Diseño	Estudio descriptivo longitudinal retrospectivo
Ámbito de estudio	Provincia de Salamanca
Población diana	Pacientes con diagnóstico *Echinococcus* sp. CIE-9, códigos 122.0 a 122.9
Tamaño de la muestra	491 pacientes
Fuentes de datos	Conjunto Mínimo Básico de Datos Historias clínicas
Período de tiempo	1998-2015
Software	SPSS Statistics 23.0

ÍNDICES DE CALIDAD DE LAS PUBLICACIONES

Aunque no es posible conocer de forma absoluta la calidad de las publicaciones científicas, existen indicadores cuantitativos de la producción científica que permiten valorar de una forma relativa su impacto en la comunidad científica y que son de utilidad para el personal docente e investigador.

Unos indicadores valoran específicamente la producción científica de la REVISTA (como es el caso del *factor de impacto*, *índice de inmediatez* o el *cuartil*), mientras otros la producción científica de un INVESTIGADOR (*índice H de Hirsch* e *índice G*).

Indicadores de la producción científica de una REVISTA

- ✓ **Factor de impacto o índice de impacto:** mide la frecuencia con la que una revista ha sido citada en un año concreto. Es un indicador que permite comparar revistas y evaluar la importancia relativa de una revista dentro de un mismo campo científico.

- ✓ ***Índice de inmediatez:*** *mide la rapidez con la que se citan los artículos de una revista científica y permite identificar revistas punteras en investigaciones de amplia repercusión.*

- ✓ ***Cuartil:*** *es un indicador o medida de posición de una revista en relación con todas las de su área. Si dividimos en 4 partes iguales un listado de revistas ordenadas de mayor a menor factor de impacto, cada una de estas partes será un cuartil. Las revistas con el factor de impacto más alto estarán el primer cuartil, los cuartiles medios serán el segundo y el tercero y el cuartil más bajo será el cuarto.*

ARTÍCULO PRIMERO: *Medical treatment of Cystic Echinococcosis: systematic review and meta-analysis*. En revisión

Título de la revista	**BMC Infectious Diseases**			
ISO Abbrev. Título	BMC Infect. Dis.			
JCR Abbrev. Título	BMC INFECT DIS			
ISSN	1471/2334			
Lengua	Inglés			
País de la revista/Territorio	Reino Unido			
Editorial	BIOMED CENTRAL LTD			
Factor de impacto 5-años	**2016 Factor de impacto**		**2.768**	
	2015 Factor de impacto		2.690	
	2014 Factor de impacto		2.613	
	2013 Factor de impacto		2.561	
	2012 Factor de impacto		3.025	
2016 Índice de inmediatez	0.293			
Categorías temáticas	INFECTIOUS DISEASES			
***2016 Ranking* de la revista**	**Categoría**	**Total revistas en la categoría**	***Ranking* de la revista en la categoría**	***Quartil* en la categoría**
	INFECTIOUS DISEASES	84	37	Q2

ARTÍCULO SEGUNDO: *Safety of the Combined Use of Praziquantel and Albendazole in the Treatment of Human Hydatid Disease.* Am J Trop Med Hyg. 2014 May 7; 90(5): 819–822. doi: 10.4269/ajtmh.13-0059.

Título de la revista	**American Journal of Tropical Medicine and Hygiene**			
ISO Abbrev. Título	Am. J. Trop. Med. Hyg.			
JCR Abbrev. Título	AM J TROP MED HYG			
ISSN:	0002-9637			
Lengua	Inglés			
País de la revista/Territorio	USA			
Editorial	American Society of Tropical Medicine (ASTM)			
Factor de impacto 5-años	2016 Factor de impacto	2.549		
	2015 Factor de impacto	2.453		
	2014 Factor de impacto	**2.699**		
	2013 Factor de impacto	2.736		
	2012 Factor de impacto	2.534		
2014 Índice de inmediatez	0.551			
Categorías temáticas	TROPICAL MEDICINE PUBLIC, ENVIRONMENTAL & OCCUPATIONAL HEALTH			
2014 Ranking de la revista	**Categoría**	**Total revistas en la categoría**	***Ranking* de la revista en la categoría**	***Quartil* en la categoría**
	TROPICAL MEDICINE	20	3	Q1
	PUBLIC, ENVIRONMENTAL & OCCUPATIONAL HEALTH	165	40	Q1

ARTÍCULO TERCERO: *Dysgeusia as an adverse reaction to praziquantel*. Drug Chem Toxicol. 2012 Jan;35(1):116-7. doi: 10.3109/01480545.2011.584065.

Título de la revista	**Drug and Chemical Toxicology**			
ISO Abbrev. Título	Drug Chem. Toxicol.			
JCR Abbrev. Título	DRUG CHEM TOXICOL			
ISSN	0148-0545			
Lengua	Inglés			
País de la revista/Territorio	USA			
Editorial	INFORMA HEALTHCARE			
Factor de impacto 5-años	2016 Factor de impacto		1.732	
	2015 Factor de impacto		1.653	
	2014 Factor de impacto		1.233	
	2013 Factor de impacto		1.098	
	2012 Factor de impacto		**1.293**	
2012 Índice de inmediatez	0.414			
Categorías temáticas	PHARMACOLOGY & PHARMACY TOXICOLOGY			
2012 *Ranking* de la revista	**Categoría**	**Total revistas en la categoría**	***Ranking* de la revista en la categoría**	***Quartil* en la categoría**
	PHARMACOLOGY & PHARMACY	260	190	Q3
	TOXICOLOGY	85	70	Q4

ARTÍCULO CUARTO: *Management of cystic echinococcosis in the last two decades: what have we learned?* En revisión

Título de la revista	**American Journal of Tropical Medicine and Hygiene**			
ISO Abbrev. Título	Am. J. Trop. Med. Hyg.			
JCR Abbrev. Título	AM J TROP MED HYG			
ISSN:	0002-9637			
Lengua	Inglés			
País de la revista/Territorio	USA			
Editorial	American Society of Tropical Medicine (ASTM)			
Factor de impacto 5-años	**2016 Factor de impacto**		**2.549**	
	2015 Factor de impacto		2.453	
	2014 Factor de impacto		2.699	
	2013 Factor de impacto		2.736	
	2012 Factor de impacto		2.534	
2016 Índice de inmediatez	1.986			
Categorías temáticas	TROPICAL MEDICINE PUBLIC, ENVIRONMENTAL & OCCUPATIONAL HEALTH			
2016 Ranking de la revista	**Categoría**	**Total revistas en la categoría**	***Ranking* de la revista en la categoría**	***Quartil* en la categoría**
	TROPICAL MEDICINE	19	5	Q2
	PUBLIC, ENVIRONMENTAL & OCCUPATIONAL HEALTH	176	48	Q2

ARTÍCULO QUINTO: *Cutaneous Disease as the First Manifestation of Cystic Echinococcosis*. Am J Trop Med Hyg. 2016 Aug 3;95(2):257-9. doi: 10.4269/ajtmh.15-0855.

Título de la revista	**American Journal of Tropical Medicine and Hygiene**			
ISO Abbrev. Título	Am. J. Trop. Med. Hyg.			
JCR Abbrev. Título	AM J TROP MED HYG			
ISSN:	0002-9637			
Lengua	Inglés			
País de la revista/Territorio	USA			
Editorial	American Society of Tropical Medicine (ASTM)			
Factor de impacto 5-años	**2016 Factor de impacto**		**2.549**	
	2015 Factor de impacto		2.453	
	2014 Factor de impacto		2.699	
	2013 Factor de impacto		2.736	
	2012 Factor de impacto		2.534	
2016 Índice de inmediatez	1.986			
Categorías temáticas	TROPICAL MEDICINE PUBLIC, ENVIRONMENTAL & OCCUPATIONAL HEALTH			
2016 Ranking de la revista	**Categoría**	**Total revistas en la categoría**	***Ranking* de la revista en la categoría**	***Quartil* en la categoría**
	TROPICAL MEDICINE	19	5	Q2
	PUBLIC, ENVIRONMENTAL & OCCUPATIONAL HEALTH	176	48	Q2

ARTÍCULO SEXTO: *Recurrence of cystic echinococcosis in an endemic area: a retrospective study*. BMC Infect Dis. 2017; 17: 455. doi: 10.1186/s12879-017-2556-9

Título de la revista	**BMC infectious Diseases**			
Título de la revista	BMC Infectious Diseases			
ISO Abbrev. Título	BMC Infect. Dis.			
JCR Abbrev. Título	BMC INFECT DIS			
ISSN	1471/2334			
Lengua	Inglés			
País de la revista/Territorio	Reino Unido			
Editorial	BIOMED CENTRAL LTD			
Factor de impacto 5-años	**2016 Factor de impacto**		**2.768**	
	2015 Factor de impacto		2.690	
	2014 Factor de impacto		2.613	
	2013 Factor de impacto		2.561	
	2012 Factor de impacto		3.025	
2016 Índice de inmediatez	0.293			
Categorías temáticas	INFECTIOUS DISEASES			
***2016 Ranking* de la revista**	**Categoría**	**Total revistas en la categoría**	***Ranking* de la revista en la categoría**	***Quartil* en la categoría**
	INFECTIOUS DISEASES	84	37	Q2

ARTÍCULO SÉPTIMO: *Recurrent spinal Echinococcosis: International Journal of Infectious Diseases* 2011; 15 (6): e434-3436. doi: 10.1016/j.ijid.2011.03.002.

Título de la revista	**International Journal of Infectious Diseases**			
ISO Abbrev. Título	Int. J. Infect. Dis.			
JCR Abbrev. Título	INT J INFECT DIS			
ISSN	1201-9712			
Lengua	Inglés			
País de la revista/Territorio	Reino Unido			
Editorial	ELSEVIER SCI LTD			
Factor de impacto 5-años	2016 Factor de impacto		2.532	
	2015 Factor de impacto		2.229	
	2014 Factor de impacto		1.859	
	2013 Factor de impacto		2.330	
	2012 Factor de impacto		2.357	
	2011 Factor de impacto		**1.938**	
2011 Índice de inmediatez	0.343			
Categorías temáticas	INFECTIOUS DISEASES			
***2011 Ranking* de la revista**	**Categoría**	**Total revistas en la categoría**	***Ranking* de la revista en la categoría**	***Quartil* en la categoría**
	INFECTIOUS DISEASES	70	46	Q3

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EL COMITE ETICO DE INVESTIGACION CLINICA DEL AREA DE SALUD DE SALAMANCA,

I N F O R M A

Que el Proyecto de Investigación presentado por D. MONCEF BELHASSEN GARCÍA,

Titulado:

"ANÁLISIS CLÍNICO-EPIDEMIOLÓGICO DE PACIENTES CON HIDATIDOSIS ATENDIDOS EN EL COMPLEJO ASISTENCIAL UNIVERSITARIO DE SALAMANCA".

Que presenta como Investigador responsable, SE AJUSTA A LAS NORMAS ÉTICAS Y DE BUENA PRÁCTICA CLÍNICA, establecidas para tales estudios.

Y para que conste lo firma en Salamanca con fecha 23 de mayo de 2014

EL SECRETARIO

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