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Brice Autier, Bruno Gottstein, Laurence Millon, Michael Ramharter, Beate Gruener, Solange Bresson Hadni, Sarah Dion, Florence Robert-Gangneux

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1 **Narrative review**

2 **Alveolar echinococcosis in immunocompromised hosts**

3 Brice Autier^{a#}, Bruno Gottstein^b, Laurence Millon^{c,d,e}, Michael Ramharter^{e,f}, Beate Gruener^g, Solange
4 Bresson-Hadni^{c,h}, Sarah Dionⁱ, Florence Robert-Gangneux^{a,e}

5 ^a Univ Rennes, CHU Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et
6 travail), UMR_S 1085, F-35000 Rennes, France

7 ^b Institute of Infectious Diseases, Faculty of Medicine, University of Bern, CH-3012 Bern, Switzerland

8 ^c Department of Parasitology-Myology, National Reference Centre for Echinococcoses, University
9 Hospital of Besançon, France

10 ^d UMR CNRS 6249 Laboratoire Chrono-environnement, Université Bourgogne-Franche-Comté,
11 Besançon, France

12 ^e European Study Group of Clinical Parasitology, ESCMID, Basel, Switzerland

13 ^f Center for Tropical Medicine; Bernhard Nocht Institute for Tropical Medicine & I Dept. of Medicine
14 University Medical Center Hamburg-Eppendorf, D-20359 Hamburg, Germany

15 ^g Division of Infectious Diseases, Department of Internal Medicine III, University Hospital of Ulm, D-
16 89081 Ulm, Germany

17 ^h Division of Tropical and Humanitarian Medicine and Gastroenterology and Hepatology Unit, Faculty
18 of Medicine, University Hospitals of Geneva, Switzerland

19 ⁱ Univ Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) -
20 UMR_S 1085, F-35000 Rennes, France

- 21 # brice.autier@univ-rennes1.fr ; Université Rennes 1, Inserm U1085 et Centre Hospitalier
- 22 Universitaire de Rennes, Service de Parasitologie-Mycologie, 2 Avenue du Pr Léon Bernard ; 35043
- 23 RENNES CEDEX, France ; Tel : +33299284268

24 **ABSTRACT**

25 **Background.** Alveolar echinococcosis (AE) results of an infection with the larval stage of *Echinococcus*
26 *multilocularis*, one of the most lethal helminthic diseases. It has been described increasingly in
27 individuals with situation of immune deficiency. So far, recommendations made for the management
28 of these patients have not been specifically adapted to the type of immune background of these
29 patients.

30 **Objectives.** This narrative review aims at describing the presentation of AE according to the type of
31 immunodeficiency, based on retrospective cohorts and case reports. Implications for patient
32 management and future research are proposed accordingly.

33 **Sources.** Targeted search was conducted in PubMed using ((alveolar echinococcosis) OR
34 (multilocularis)) AND ((immunosuppressive) OR (immunodeficiency) OR (AIDS) OR (solid organ
35 transplant) OR (autoimmunity) OR (primary immune deficiency)). Only publications in English were
36 considered.

37 **Content.** Seventeen publications were found, including 13 reports of 55 AE in immunocompromised
38 patients (AE/IS) and 4 retrospective studies of 755 AE immunocompetent patients (AE/IC) and 115
39 AE/IS (13%). The cohorts included 9 (1%) solid organ transplantation (SOT) recipients, 2 (0.2%) HIV
40 patients, 41 (4.7%) with chronic inflammatory/autoimmune diseases (I/AID) and 72 (8.3%) with
41 malignancies. SOT, I/AID and malignancies, but not HIV infection, were significantly associated with
42 AE (odds ratios of 10.8, 1.6, 5.9 and 1.3, respectively). AE/IS was associated with earlier diagnosis,
43 higher rate of atypical imaging and lower sensitivity of serology, compared to AE/IC. Unusually
44 extensive or disseminated infections were described in SOT and I/AID patients.

45 **Implications.** Patients who live in endemic areas should benefit from serology before onset of a long-
46 term immunosuppressive therapy, even if the cost-benefit ratio has to be evaluated. Physicians
47 should explain to immunocompromised patients about prevention measures to avoid AE and think
48 about AE when finding a liver lesion. Further research should address gaps in knowledge of AE/IS.

49 Especially, extensive and accurate records of AE cases have to be collected by multinational
50 registries.

51 **KEYWORDS**

52 *Echinococcus multilocularis*, alveolar echinococcosis, immunosuppressive therapy, transplantation,
53 HIV, cancer, malignant haemopathy, primary immune deficiency

54 INTRODUCTION

55 Alveolar echinococcosis (AE) is a parasitic disease due to the development the larval stage of
56 *Echinococcus multilocularis*, a tapeworm of canids (especially foxes) [1]. Only a few proportion of
57 infected humans will actually develop viable parasitic lesions [2]. Host and pathogen factors that
58 might explain such variability remain to be unravelled, but there is cumulative evidence that host
59 innate and acquired immune response is important in the clinical outcome. After a short description
60 of the immunological events involved in the antiparasitic response, this review will analyse clinical
61 cases reported in each category of immune suppression backgrounds, and discuss implications for
62 the management of these patients and perspectives for research.

63 PATHOPHYSIOLOGY AND DIAGNOSIS OF ALVEOLAR ECHINOCOCCOSIS

64 Human infection occurs after accidental ingestion of eggs through contaminated food or water, or
65 hand-to-mouth route. In the digestive tract, eggs release an oncosphere, which accedes to the blood
66 circulation by passing through the intestinal mucosa, then establishes in any vascularized organ, with
67 a preferential location in the liver as it filters the blood from the portal vein. There, it develops into
68 the larval stage, also called metacestode (Fig 1) [3]. In accidental hosts, such as humans, the
69 metacestode is a heterogeneous multicystic structure that actively proliferates at its periphery. The
70 parasite is surrounded by a strong infiltration of immune cells associated with dense fibrotic tissue,
71 neovessels and epithelioid cells, and containing central caseous necrosis and calcifications [4].

72 Host-parasite interactions in human tissues are highly complex and lead to various clinical
73 presentations. In most contaminated individuals (detected upon species-specific serology), no
74 parasitic lesion is observed, suggesting that the parasite has been killed early, in the intestinal
75 mucosa or in the liver parenchyma [2]. In about 20% of cases, the metacestode aborts spontaneously
76 at a later stage, forming a calcified non-viable parasite lesion, etiologically diagnosed on the basis of
77 a positive serology, or upon histology and PCR [5]. These are called aborted or died-out lesions [2,3].

78 Finally, the evolutive form of AE, consisting of a viable parasite which continuously develops until its
 79 host dies, affects only a small percentage of contaminated individuals [2].

80 Dendritic cells and macrophages initiate a pro-inflammatory Th1/Th17 immune response, which is
 81 considered to be putatively efficient against the parasite (Table 1) [6]. In susceptible hosts, the
 82 response progressively turns into a mixed Th1/Th2 response, with contribution of regulatory T
 83 CD4⁺FoxP3⁺ lymphocytes (Treg) and IL-10 secretion, allowing parasite survival [6]. Humoral immunity,
 84 although present, is not effective in the control of AE.

85 **Table 1. Summary of research findings about immunity in alveolar echinococcosis**

Factor	Associated with parasite control	Associated with parasite development	References
Cell populations	M1 macrophages, polymorphonuclear, NK, Th1 and Th17 cells	M2 macrophages, Th2 and Treg cells	[4,6–13]
Cytokines	IFN- α , IL-12, TNF- α , IFN- γ , IL-17	IL-4, IL-5, IL-9, IL-10, IL-13, TGF- β 1, FGL-2	[4,6,10,14,15]
Drugs	Albendazole, mebendazole	Cyclosporine, methotrexate, steroids	[6,16]
Tissue response	Type IV hypersensitivity, fibrosis	Angiogenesis	[4,17]

86 Diagnosis relies on usual imaging techniques (ultrasonography (US), Magnetic Resonance Imaging
 87 (MRI), Computed Tomography (CT-scan)) and detection of anti-Em2 or anti-Em2+ antibodies by
 88 ELISA, and/or with anti-*Echinococcus* IgG immunoblot [19,21]. Discrimination between evolutive and
 89 aborted lesions in humans is often difficult. Currently, the best marker to assess viability of the
 90 parasite is the detection of anti-recEm18 antibodies, which can be detected by ELISA (45-80%
 91 sensitivity and 99-100% specificity for evolutive AE) [18–20], and/or PET-scan [21].

92 Medical imaging allows staging of the disease using the PNM classification proposed in 2006 [22].
 93 This system is based on three parameters similarly to the TNM system for tumours: P for the location
 94 and extension of the parasite within the liver (P0 to P4), N for the involvement of neighbouring
 95 organs (N0 or N1), and M for the metastasis (M0 or M1). Depending on the PNM classification, AE
 96 cases are then staged from I to IV, i.e. the less and the most severe, respectively.

97 **OVERALL FINDINGS REGARDING IMMUNOCOMPROMISED PATIENTS**

98 A total of 170 AE patients with immunosuppressive conditions (AE/IS) were mentioned in the
 99 literature, including 57 SOT recipients, 4 HIV-positive patients, 45 patients with inflammatory or
 100 auto-immune disorder (I/AID), 72 with cancer and 2 with a primary immune disorder (PID) (Table 2).
 101 Of note, 8 patients had both cancer and I/AID, and 1 SOT recipient had an haematological
 102 malignancy. Four retrospective cohort studies were published, one from France (1982-2012) [23],
 103 two others from Switzerland (late 90's-2020) [24,25], and one from Canada (2013-2020). Altogether,
 104 these studies described 115 AE/IS cases with previously mentioned backgrounds vs 755 AE cases in
 105 immunocompetent individuals (AE/IC). An increasing number of AE/IS cases was highlighted (6/166
 106 AE cases (3.6%) in 1992-2002, vs 42/229 AE cases (18.3%) in 2002-2012 in the French cohort, $p < 0.01$)
 107 [23]. By comparing the prevalence of each immunosuppressive condition between AE patients and
 108 the general population, SOT, I/AID and malignancies, but not HIV infection, were overrepresented
 109 among AE patients (odds ratios of 10.8, 1.6, 5.9 and 1.3, respectively) (Table 3).

110 **Table 2. Summary of published cases and cohorts of alveolar echinococcosis in**
 111 **immunocompromised patients**

Population	Number of case reports	Number of cases in cohort studies	Progressive AE ¹	References
SOT recipients	48 ²	9 ³	Yes	[23–32]

HIV/AIDS	2	2	Yes	[23,24,33,34]
Chronic I/AID	3	41	Yes	[23–25,32,35–37]
Malignancies	-	72 ⁴	No	[23–25,32]
Primary immune disorder	2	0	Yes	[38,39]

112 SOT Solid organ transplant, I/AID Inflammatory and Autoimmune disorder

113 ¹ Progressive AE: unusually fast-growing or extensive AE

114 ² Including 45 patients who had liver transplantation for incurable AE, and 2 and 1 patients who had
115 kidney and lung transplantation, respectively, for another indication

116 ³ Transplanted organs: 4 kidneys, 2 hearts, 1 liver, 2 not specified

117 ⁴ Includes 44 solid cancers, 12 haematological malignant diseases and 16 “malignancies” (not
118 specified)

119 **Table 3. Prevalence of immunosuppressive conditions in alveolar echinococcosis patients and**
120 **general population**

	Prevalence among AE patients: n/N (%)	Estimation of prevalence in the general population	Odds ratios and significance ⁴
SOT recipients	9/870 (1.0%)	97/100.000 ¹	10.8, p<0.001
HIV/AIDS	2/870 (0.2%)	180/100.000 ²	1.3, p=0.955
Chronic I/AID	41/870 (4.7%)	3.000/100.000 ³	1.6, p<0.01
Malignancies	72/870 (8.3%)	1.500/100.000 ²	5.9, p<0.001
Total	115/870 (13.2%)	4.777/100.000	3.0, p<0.001

121 SOT Solid organ transplant, I/AID Inflammatory and Autoimmune disorder

122 ¹ Estimation based on the whole number of living SOT recipients in France in 2021, from the public
123 “Agence de la Biomédecine” database (<https://rams.agence-biomedecine.fr/bibliotheque-de->
124 [donnees](https://rams.agence-biomedecine.fr/bibliotheque-de-donnees)).

125 ² Estimation based on (i) the whole number of individuals living with HIV in France and Switzerland,
126 and (ii) the prevalence of cancer in France in 2000 and 2008, from the public WHO database
127 (<https://gateway.euro.who.int/en/>).

128 ³ Estimation from Cooper et al. 2003 [40].

129 ⁴ Statistical test: Fisher’s exact test

130

131 Compared to AE/IC, AE/IS cases were diagnosed more often incidentally (66/86 (77%) in AE/IS vs
132 144/341 (42%) in AE/IC, $p < 0.001$) and, consequently, earlier in the parasite development (PNM
133 stages I-II: 49/85 (58%) in AE/IS vs 137/348 (39%) in AE/IC, $p < 0.01$). Clinical presentation of the
134 symptomatic cases was not compared between AE/IS and AE/IC. Importantly, AE/IS was significantly
135 associated with false negative serology compared to AE/IC patients (58/77 (75%) in AE/IS vs 64/329
136 (19%) in AE/IS, $p < 0.001$), but this could be also related to earlier diagnosis [21]. A high frequency of
137 atypical liver ultrasound and CT imaging findings were described in the French cohort (48%, 24/50),
138 suggesting cancer metastasis (36%, 18/50), liver abscess (8%, 4/50), haemangioma (2%, 1/50) or
139 hematoma (2%, 1/50) instead of typical imaging (heterogeneous mass with calcifications and/or
140 clustered microcysts) (Fig 2) [23]. This proportion was significantly higher compared to German and
141 Turkish reports in the whole AE population, showing only 28% (106/375) of atypical imaging findings
142 ($p < 0.01$) [41,42]. Interestingly, the French retrospective study also reported a better treatment
143 efficacy in AE/IS patients compared to AE/IC ((21/41 (51%) vs 50/187 (27%) of lesion regression after
144 1 year of treatment, $p < 0.01$). However, the authors also emphasized the high frequency of side
145 effects (40%), possibly associated with high concentrations of albendazole sulfoxide in plasma, thus
146 encouraging pharmacological monitoring in these patients. However, this proportion was not

147 significantly different from the 20% (7/35) observed in a previous German cohort of AE patients [43].
 148 Mortality was significantly higher in AE/IS compared to AE/IC patients (16/80 (20%) vs 13/313 (4%),
 149 $p < 0.001$), but was not clearly imputed to AE. The main conclusions of these studies are summarized
 150 in Table 4.

151 **Table 4. Main facts regarding alveolar echinococcosis and immune suppression**

Item	AE/IS	AE/IC	Significance (Fisher's exact test)	Interpretation for AE/IS compared to AE/IC	References
PNM stage I-II of disease at diagnosis	49/85 (58%)	137/348 (39%)	$p < 0.001$	Diagnosed earlier, due to systematic check-up ¹	[23,24,32]
Misleading US and CT imaging (cancer metastasis, abscess, haemangioma or hematoma)	24/50 (48%)	106/375 (28%) ²	$p = 0.008$	Higher rate of atypical imaging	[23,41,42]
Sensitivity of serology	19/77 (25%)	265/329 (81%)	$p < 0.001$	Lower sensitivity of serology	[23,24,32]
Regression at 1 year under benzimidazole treatment	21/41 (51%)	50/187 (27%)	$p < 0.01$	Higher efficacy of benzimidazole	[23]
Benzimidazole side effects	19/48 (40%)	7/35 (20%)	$p = 0.093$	Slightly higher frequency of side effects	[23,43]

Mortality imputable to	0/50	3/187	p=1.0	Not significantly	[23]
AE	(0%)	(2%)		different	

152 US, ultrasound; CT, computed tomography

153 ¹This observation was described in European countries, benefiting from advanced health care
154 procedures, but can vary according to health policies

155 ² Data obtained from two retrospective studies of AE imaging. The populations were not strictly
156 composed of AE/IC cases, as AE/IS were not excluded.

157 **ALVEOLAR ECHINOCOCCOSIS AND SOLID ORGAN TRANSPLANT RECIPIENTS**

158 Due to their mechanisms of action on cellular immunity, immunosuppressive agents used for the
159 prevention of graft rejection (cyclosporin, tacrolimus, mycophenolate) theoretically facilitate AE
160 progression. Indeed, solid organ transplant (SOT) recipients were the first patients described with
161 rapidly extensive AE. In 1990, two patients who had liver transplantation for AE salvage and pre-
162 existing pulmonary lesions, were reported as having rapidly growing lung lesions [26], and between
163 1990 and 1992, recurrence of AE was observed in the transplanted liver [26,27]. In 2003, Koch et al.
164 reported a 10-year survival of 45%, in a retrospective cohort of 45 patients, managed by liver
165 transplantation for otherwise untreatable AE between 1985 and 1998 [28]. Among the twenty deaths
166 observed during follow-up, 5 (25%) were due to relapse, and 9 (45%) were perioperative deaths.
167 They highlighted the detection of new parasitic lesions (mostly in brain and lungs) in 16% (6/45), and
168 graft invasion in another 16% (6/45). Similar clinical presentations were also reported in kidney and
169 lung transplant recipients [29–32]. These data suggest that SOT recipients can present unusually
170 rapidly progressive AE, with an increased risk of dissemination.

171 **ALVEOLAR ECHINOCOCCOSIS AND HIV/AIDS**

172 While HIV and *E. multilocularis* co-infection is often taken as an example of the opportunistic
173 behaviour of the parasite, only few cases have been reported to date. The first was published in

174 1997, and was diagnosed in a six-year-old girl with AIDS [33]. The clinical presentation displayed
175 multiple unusual features: the young age of the patient, the extensive parasite growth and the
176 negative serological testing. Furthermore, the girl had a dramatically low CD4⁺ T cell count (12/mm³)
177 and a negative lymphoproliferative assay with *E. multilocularis* antigen. A second case was published
178 7 years later, in a 40 year-old male [34]. Although the patient was immunocompromised over nearly
179 a decade (CD4⁺ T cells between 27 and 150/mm³), the parasite had an usual growth rate, as the
180 lesion was retrospectively observed on a CT scan performed 8 years before AE diagnosis. Only 2/870
181 (0.2%) HIV patients were mentioned in retrospective studies [23,24]. Altogether, these reports
182 showed that HIV is an uncommon condition for accelerated AE development. Only a dramatically low
183 CD4⁺ T cell count appears to favour the parasite growth (< 20-50/mm³).

184 **ALVEOLAR ECHINOCOCCOSIS AND CHRONIC INFLAMMATORY DISEASES OR AUTO-IMMUNE** 185 **DISORDERS**

186 As for SOT, I/AID are theoretically adequate backgrounds for rapidly progressive AE. Indeed, most of
187 these disorders are treated with long-term immunosuppressive therapies, which often have broad-
188 spectrum effects on immune effectors (e.g. steroids, methotrexate...) or an anti-Th1 biological
189 activity (e.g. TNF- α inhibitors, anakinra (IL-1 receptor antagonist)...). Such cases were actually
190 reported in patients affected with auto-immune encephalitis and rheumatoid arthritis [35–37].
191 Among the retrospective cohorts of AE/IS, 40/115 patients (35%) had I/AID, and at least 14/115
192 (12%) and 6/115 (5%) were treated with methotrexate and TNF- α inhibitors, respectively [23–25,32].
193 Of note, at least 27/115 (23%) were treated with steroids, without specification concerning the
194 indication (SOT, malignancy, I/AID or other) nor the dosage. Although it seems probable that all
195 immunosuppressive regimens do not equally favour AE, fundamental and clinical data suggest that
196 long-term administration of steroids or TNF- α inhibitors could accelerate AE progression. Other
197 immunosuppressive therapies were observed in patients with accelerated AE, such as rituximab

198 (anti-CD20) [23,30,37], however they are mostly associated with steroids or TNF- α inhibitors, which
199 prevent to reliably conclude on their imputability.

200 **ALVEOLAR ECHINOCOCCOSIS AND MALIGNANCIES**

201 The few reports of AE concomitant to malignancy were compiled in retrospective cohorts. Out of the
202 115 AE/IS detailed cases, 44 (38%) had solid cancer (15 of the digestive tract, 9 of the respiratory
203 tract, 15 urogenital or breast, 1 of the skin and 3 others), 12 (10%) had haematological malignancies
204 (4 myeloproliferative syndrome, 6 lymphoproliferative syndrome, 1 Fanconi anaemia) and 16 (14%)
205 had unspecified malignancy [23–25,32]. The median time between onset of immunosuppressive
206 condition (IS) and AE diagnosis was shorter for solid cancers than for other conditions, probably
207 because AE was often diagnosed incidentally during extensive workup (83%) [23]. Despite the high
208 number of AE diagnosed in patients with malignancies, no clear evidence of aggressive AE has been
209 reported. On the contrary, these cases often benefited from an earlier management due to
210 incidental diagnosis [23].

211 **PRIMARY IMMUNE DEFICIENCIES**

212 Only two cases of AE were described in patients with PID, both were young patients (14 and 17 yo)
213 with Hyper-IgE Syndrome (HIES) [38,39]. This rare PID is characterized by recurrent skin and lung
214 infections, eosinophilia and elevated IgE serum levels. The syndrome is associated with a defect of
215 the Th17 response, leading to bacterial and fungal opportunistic infections [44]. The fact that these
216 two young patients presented with disseminated AE is highly unusual, as the mean AE incubation
217 time is between 5 and 15 years [2]. Even if more evidence needs to be collected, these observations
218 suggest that Th17 defects, including *Card9-Syk* deficiencies, could favour AE development [45].

219 Unlike most of PIDs, such deficiency can be diagnosed in apparently healthy children or adults
220 [46,47]. The part of such defects in unusually extensive AE is currently not known. Further studies
221 (extensive analysis of immune cell populations, complete workup for autoimmunity, whole-genome
222 sequencing) are needed to ensure that rare and yet undiagnosed PIDs are not hidden beyond those

223 atypical cases, particularly when they occur in children. Indeed, taken together, 21 paediatric case
224 reports have been described in the literature (median age 12 years), including 24% under 10 years
225 and 24% with disseminated lesions [33,39,48–57]. In almost all cases, assessment of immune status
226 was unreported or limited to T CD4⁺ and T CD8⁺ cell counts and HIV serology. However, it should be
227 kept in mind that atypical presentations may be not only related to immune disorders, but can be
228 associated with vascular abnormalities, as illustrated in cases of extrahepatic AE in patients with
229 portal hypertension [58,59], portosystemic shunt [56], or hereditary haemorrhagic telangiectasia
230 [60].

231 **IMPLICATIONS**

232 Alveolar echinococcosis is an emerging opportunistic infection, favored by alteration of cellular
233 immunity. Thus, populations at risk for progressive AE are those exposed to long-term
234 immunosuppressive therapy such as cyclosporin, TNF- α inhibitors or steroids, or with prolonged and
235 severe immune deficiency. While data are scarce regarding other treatments, especially biotherapies,
236 physicians should be aware that the use of such drugs could accelerate progression and
237 dissemination of AE. Analysis of the previously published retrospective studies showed that SOT,
238 I/AID and cancer are associated with AE. Considering the occurrence of rapidly extensive AE in SOT
239 and I/AID patients, it seems probable that therapies used in these backgrounds increase the risk of
240 developing evolutive AE. For this reason, serological screening could be proposed to these patients
241 before onset of the immunosuppressive therapy, even if the benefit of such recommendation should
242 be evaluated. Abdominal imaging could be proposed as well to these patients, if not previously done.
243 Whether cancer is actually a risk factor is not clear, as it can be associated with AE diagnosis due to
244 extensive check-up, as suggested by the short delay between cancer and AE diagnoses [23].
245 Conversely, it could be even hypothesized that AE is a risk factor of cancer, as it induces chronic
246 immunosuppression by itself [4]. Finally, HIV infection does not seem to be a risk factor, nor a
247 significant cause of progressive AE.

248 **LIMITATIONS**

249 Our review has some limitations as it relies on retrospective cohorts and case reports, which made it
250 at risk of declaration bias. Also, we decided to restrain our analysis to well-defined
251 immunocompromised backgrounds, i.e. SOT, I/AID, HIV infection, malignancy and PID. However,
252 other backgrounds can be associated with opportunistic infections, such as cirrhosis, pregnancy,
253 asthma or diabetes. Of note, both retrospective cohort studies from Switzerland included such
254 patients, without detailing if their characteristics were different from other backgrounds.

255 **PERSPECTIVES**

256 The details of the relationship between immunosuppressive conditions and AE evolution remain
257 unclear (Table 5). This is mostly due to the low number of AE cases, which makes difficult to build
258 consistent cohorts. The next step toward filling this gap in knowledge of AE is to improve and
259 harmonize data collection in endemic countries. Complementarily, fundamental research is of
260 paramount importance to understand the effect of immunosuppressive therapies on AE
261 development. Especially, as humans are usually diagnosed at the late stage of the disease, clinical
262 studies cannot discriminate if immunosuppressive therapies impact invasion through the intestinal
263 barrier, early establishment of the larvae or late stage of AE. Also, more immunological and genetic
264 studies are needed to assess if rare PIDs are responsible for some of the cases of unusually extensive
265 AE.

266 In areas endemic for AE, physicians who manage patients under long-term immunosuppressive
267 therapies should deliver health education, by explaining what AE is and the ways to avoid infection.
268 Overall, the probably most important suggestion to these physicians would be to think about AE
269 when finding a liver lesion.

270

271

272 **Table 5. Unanswered questions about alveolar echinococcosis and immunodeficiencies**

Topic	Questions
Management of patients	<p>Would it be reasonable to perform systematic anti-<i>E. multilocularis</i> serology and abdomen imaging before onset of an immunosuppressive regimen¹ for people living in endemic areas?</p> <p>Should patients with unusually extensive lesions and children with AE benefit from extensive immunological check-up?</p>
Epidemiology	<p>Which immunosuppressive drugs, and what treatment duration, are associated with an increased risk of AE?</p> <p>Is cancer favouring AE, or conversely AE favouring cancer?</p> <p>Are there other backgrounds favouring AE?</p>
Pathophysiology	<p>Do immunosuppressive regimens favour parasite establishment, development, or both?</p>

273 ¹ Especially SOT recipients regimen, TNF- α inhibitors and steroids

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276 **CONFLICT OF INTERESTS**

277 None of the authors declares any conflicts of interest.

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280 **CONTRIBUTION**

281 Conceptualization: F.R.-G. Investigation: B.A. Writing-first draft: B.A. Writing-review and editing: all
282 authors contributed equally.

283 REFERENCES

- 284 [1] Bresson-Hadni S, Spahr L, Chappuis F. Hepatic alveolar echinococcosis. *Semin Liver Dis*
285 2021;41:393–408. <https://doi.org/10.1055/s-0041-1730925>.
- 286 [2] Gottstein B, Wang J, Boubaker G, Marinova I, Spiliotis M, Müller N, et al. Susceptibility versus
287 resistance in alveolar echinococcosis (larval infection with *Echinococcus multilocularis*). *Vet*
288 *Parasitol* 2015;213:103–9. <https://doi.org/10.1016/j.vetpar.2015.07.029>.
- 289 [3] Vuitton DA, McManus DP, Rogan MT, Romig T, Gottstein B, Naidich A, et al. International
290 consensus on terminology to be used in the field of echinococcoses. *Parasite* 2020;27:41.
291 <https://doi.org/10.1051/parasite/2020024>.
- 292 [4] Vuitton DA, Gottstein B. *Echinococcus multilocularis* and its intermediate host: a model of
293 parasite-host interplay. *J Biomed Biotechnol* 2010;2010:923193.
294 <https://doi.org/10.1155/2010/923193>.
- 295 [5] Knapp J, Lallemand S, Monnier F, Felix S, Valmary-Degano S, Courquet S, et al. Molecular
296 diagnosis of alveolar echinococcosis in patients based on frozen and formalin-fixed paraffin-
297 embedded tissue samples. *Parasite* 2022;29:4. <https://doi.org/10.1051/parasite/2022004>.
- 298 [6] Wang J, Gottstein B. Immunoregulation in larval *Echinococcus multilocularis* infection. *Parasite*
299 *Immunol* 2016;38:182–92. <https://doi.org/10.1111/pim.12292>.
- 300 [7] Wang H, Zhang C-S, Fang B-B, Hou J, Li W-D, Li Z-D, et al. Dual role of hepatic macrophages in
301 the establishment of the *Echinococcus multilocularis* metacestode in mice. *Front Immunol*
302 2020;11:600635. <https://doi.org/10.3389/fimmu.2020.600635>.
- 303 [8] Chong S, Chen G, Dang Z, Niu F, Zhang L, Ma H, et al. *Echinococcus multilocularis* drives the
304 polarization of macrophages by regulating the RhoA-MAPK signaling pathway and thus affects

305 liver fibrosis. *Bioengineered* 2022;13:8747–58.
306 <https://doi.org/10.1080/21655979.2022.2056690>.

307 [9] Joekel DE, Nur S, Monné Rodriguez J, Kronenberg PA, Kipar A, LeibundGut-Landmann S, et al.
308 Agranulocytosis leads to intestinal *Echinococcus multilocularis* oncosphere invasion and hepatic
309 metacestode development in naturally resistant Wistar rats. *Parasitology* 2021;148:53–62.
310 <https://doi.org/10.1017/S0031182020002012>.

311 [10] Wang J, Müller S, Lin R, Siffert M, Vuitton DA, Wen H, et al. Depletion of FoxP3+ Tregs improves
312 control of larval *Echinococcus multilocularis* infection by promoting co-stimulation and Th1/17
313 immunity. *Immun Inflamm Dis* 2017;5:435–47. <https://doi.org/10.1002/iid3.181>.

314 [11] Wang J, Cardoso R, Marreros N, Müller N, Lundström-Stadelmann B, Siffert M, et al. Foxp3+ T
315 regulatory cells as a potential target for immunotherapy against primary infection with
316 *Echinococcus multilocularis* eggs. *Infect Immun* 2018;86:e00542-18.
317 <https://doi.org/10.1128/IAI.00542-18>.

318 [12] Bellanger A-P, Mougey V, Pallandre J-R, Gbaguidi-Haore H, Godet Y, Millon L. *Echinococcus*
319 *multilocularis* vesicular fluid inhibits activation and proliferation of natural killer cells. *Folia*
320 *Parasitol* 2017;64:2017.029. <https://doi.org/10.14411/fp.2017.029>.

321 [13] Chuanshan Z, Wang H, Jing L, Hou X, Li L, Wang W, et al. Involvement of TIGIT in NK cell
322 exhaustion and immune escape in patients and mouse model with liver *E. multilocularis*
323 infection. *Hepatology* 2021. <https://doi.org/10.1002/hep.32035>.

324 [14] Lechner CJ, Grüner B, Huang X, Hoffmann WH, Kern P, Soboslay PT. Parasite-specific IL-17-type
325 cytokine responses and soluble IL-17 receptor levels in alveolar echinococcosis patients. *Clin*
326 *Dev Immunol* 2012;2012:735342. <https://doi.org/10.1155/2012/735342>.

327 [15] Wang J, Vuitton DA, Müller N, Hemphill A, Spiliotis M, Blagosklonov O, et al. Deletion of
328 Fibrinogen-like Protein 2 (FGL-2), a novel CD4+ CD25+ Treg effector molecule, leads to
329 improved control of *Echinococcus multilocularis* infection in mice. *PLoS Negl Trop Dis*
330 2015;9:e0003755. <https://doi.org/10.1371/journal.pntd.0003755>.

- 331 [16] Hübner C, Wiehr S, Kocherscheidt L, Wehrl H, Pichler BJ, Schmid A, et al. Effects of in vitro
332 exposure of *Echinococcus multilocularis* metacestodes to cytostatic drugs on *in vivo* growth and
333 proliferation of the parasite. Parasitol Res 2010;107:459–63. [https://doi.org/10.1007/s00436-](https://doi.org/10.1007/s00436-010-1892-0)
334 010-1892-0.
- 335 [17] Yuan M, Song X, Lv W, Xin Q, Wang L, Gao Q, et al. Effect of anacardic acid against
336 echinococcosis through inhibition of VEGF-induced angiogenesis. Vet Res 2019;50:3.
337 <https://doi.org/10.1186/s13567-019-0621-7>.
- 338 [18] Tappe D, Frosch M, Sako Y, Itoh S, Grüner B, Reuter S, et al. Close relationship between clinical
339 regression and specific serology in the follow-up of patients with alveolar echinococcosis in
340 different clinical stages. Am J Trop Med Hyg 2009;80:792–7.
- 341 [19] Gottstein B, Lachenmayer A, Beldi G, Wang J, Merkle B, Vu XL, et al. Diagnostic and follow-up
342 performance of serological tests for different forms/courses of alveolar echinococcosis. Food
343 Waterborne Parasitol 2019;16:e00055. <https://doi.org/10.1016/j.fawpar.2019.e00055>.
- 344 [20] Kronenberg PA, Deibel A, Gottstein B, Grimm F, Müllhaupt B, Meyer Zu Schwabedissen C, et al.
345 Serological assays for alveolar and cystic echinococcosis-a comparative multi-test study in
346 Switzerland and Kyrgyzstan. Pathog Basel Switz 2022;11:518.
347 <https://doi.org/10.3390/pathogens11050518>.
- 348 [21] Hotz JF, Peters L, Kapp-Schwörer S, Theis F, Eberhardt N, Essig A, et al. Evaluation of serological
349 markers in alveolar echinococcosis emphasizing the correlation of PET-CTI tracer uptake with
350 RecEm18 and *Echinococcus*-specific IgG. Pathogens 2022;11:239.
351 <https://doi.org/10.3390/pathogens11020239>.
- 352 [22] Kern P, Wen H, Sato N, Vuitton DA, Gruener B, Shao Y, et al. WHO classification of alveolar
353 echinococcosis: Principles and application. Parasitol Int 2006;55:S283–7.
354 <https://doi.org/10.1016/j.parint.2005.11.041>.

- 355 [23] Chauchet A, Grenouillet F, Knapp J, Richou C, Delabrousse E, Dentan C, et al. Increased
356 incidence and characteristics of alveolar echinococcosis in patients with immunosuppression-
357 associated conditions. *Clin Infect Dis* 2014;59:1095–104. <https://doi.org/10.1093/cid/ciu520>.
- 358 [24] Deibel A, Meyer zu Schwabedissen C, Husmann L, Grimm F, Deplazes P, Reiner CS, et al.
359 Characteristics and clinical course of alveolar echinococcosis in patients with
360 immunosuppression-associated conditions: a retrospective cohort study. *Pathogens*
361 2022;11:441. <https://doi.org/10.3390/pathogens11040441>.
- 362 [25] Lachenmayer A, Gebbers D, Gottstein B, Candinas D, Beldi G. Elevated incidence of alveolar
363 echinococcosis in immunocompromised patients. *Food Waterborne Parasitol* 2019;16:e00060.
364 <https://doi.org/10.1016/j.fawpar.2019.e00060>.
- 365 [26] Bresson-Hadni S, Franza A, Miguet JP, Vuitton DA, Lenys D, Monnet E, et al. Orthotopic liver
366 transplantation for incurable alveolar echinococcosis of the liver: report of 17 cases.
367 *Hepatology* 1991;13:1061–70.
- 368 [27] Bresson-Hadni S, Miguet JP, Lenys D, Vuitton DA, Viennet G, Becker MC, et al. Recurrence of
369 alveolar echinococcosis in the liver graft after liver transplantation. *Hepatology* 1992;16:279–
370 80. <https://doi.org/10.1002/hep.1840160146>.
- 371 [28] Koch S, Bresson-Hadni S, Miguet J-P, Crumbach J-P, Gillet M, Manton G-A, et al. Experience of
372 liver transplantation for incurable alveolar echinococcosis: a 45-case European collaborative
373 report. *Transplantation* 2003;75:856–63. <https://doi.org/10.1097/01.TP.0000054230.63568.79>.
- 374 [29] Dupont C, Grenouillet F, Mabrut J-Y, Gay F, Persat F, Wallon M, et al. Fast-growing alveolar
375 echinococcosis following lung transplantation. *Pathogens* 2020;9:E756.
376 <https://doi.org/10.3390/pathogens9090756>.
- 377 [30] Geyer M, Wilpert J, Wiech T, Theilacker C, Stubanus M, Kramer-Zucker A, et al. Rapidly
378 progressive hepatic alveolar echinococcosis in an ABO-incompatible renal transplant recipient.
379 *Transpl Infect Dis* 2011;13:278–84. <https://doi.org/10.1111/j.1399-3062.2010.00583.x>.

- 380 [31] Dražilová S, Kinčeková J, Beňa L, Zachar M, Švajdler M, Zavacký P, et al. Alveolar echinococcosis
381 in patient after cadaveric kidney transplantation. *Helminthologia* 2011;48:229–36.
382 <https://doi.org/10.2478/s11687-011-0032-4>.
- 383 [32] Houston S, Belga S, Buttenschoen K, Cooper R, Girgis S, Gottstein B, et al. Epidemiological and
384 clinical characteristics of alveolar echinococcosis: an emerging infectious disease in Alberta,
385 Canada. *Am J Trop Med Hyg* 2021;104:1863–9. <https://doi.org/10.4269/ajtmh.20-1577>.
- 386 [33] Sailer M, Soelder B, Allerberger F, Zaknun D, Feichtinger H, Gottstein B. Alveolar echinococcosis
387 of the liver in a six-year-old girl with acquired immunodeficiency syndrome. *J Pediatr*
388 1997;130:320–3. [https://doi.org/10.1016/s0022-3476\(97\)70364-0](https://doi.org/10.1016/s0022-3476(97)70364-0).
- 389 [34] Zingg W, Renner-Schneiter EC, Pauli-Magnus C, Renner EL, van Overbeck J, Schläpfer E, et al.
390 Alveolar echinococcosis of the liver in an adult with human immunodeficiency virus type-1
391 infection. *Infection* 2004;32:299–302. <https://doi.org/10.1007/s15010-004-3134-9>.
- 392 [35] Diem S, Gottstein B, Beldi G, Semmo N, Diem LF. Accelerated course of alveolar echinococcosis
393 after treatment with steroids in a patient with autoimmune encephalitis. *Cureus*
394 2021;13:e18831. <https://doi.org/10.7759/cureus.18831>.
- 395 [36] Weiner SM, Krenn V, Koelbel C, Hoffmann HG, Hinkeldey K, Ockert D. *Echinococcus*
396 *multilocularis* infection and TNF inhibitor treatment in a patient with rheumatoid arthritis.
397 *Rheumatol Int* 2011;31:1399–400. <https://doi.org/10.1007/s00296-010-1570-7>.
- 398 [37] Dentan C, Mazet R, Gilson M, Marchou-Lopez S, Gaudin P. Rheumatoid arthritis, alveolar
399 echinococcosis, and rituximab: A case report. *Joint Bone Spine* 2012;79:325–7.
400 <https://doi.org/10.1016/j.jbspin.2011.10.014>.
- 401 [38] Reuter S, Buck A, Grebe O, Nüssle-Kügele K, Kern P, Manfras BJ. Salvage treatment with
402 Amphotericin B in progressive human alveolar echinococcosis. *Antimicrob Agents Chemother*
403 2003;47:3586–91. <https://doi.org/10.1128/AAC.47.11.3586-3591.2003>.

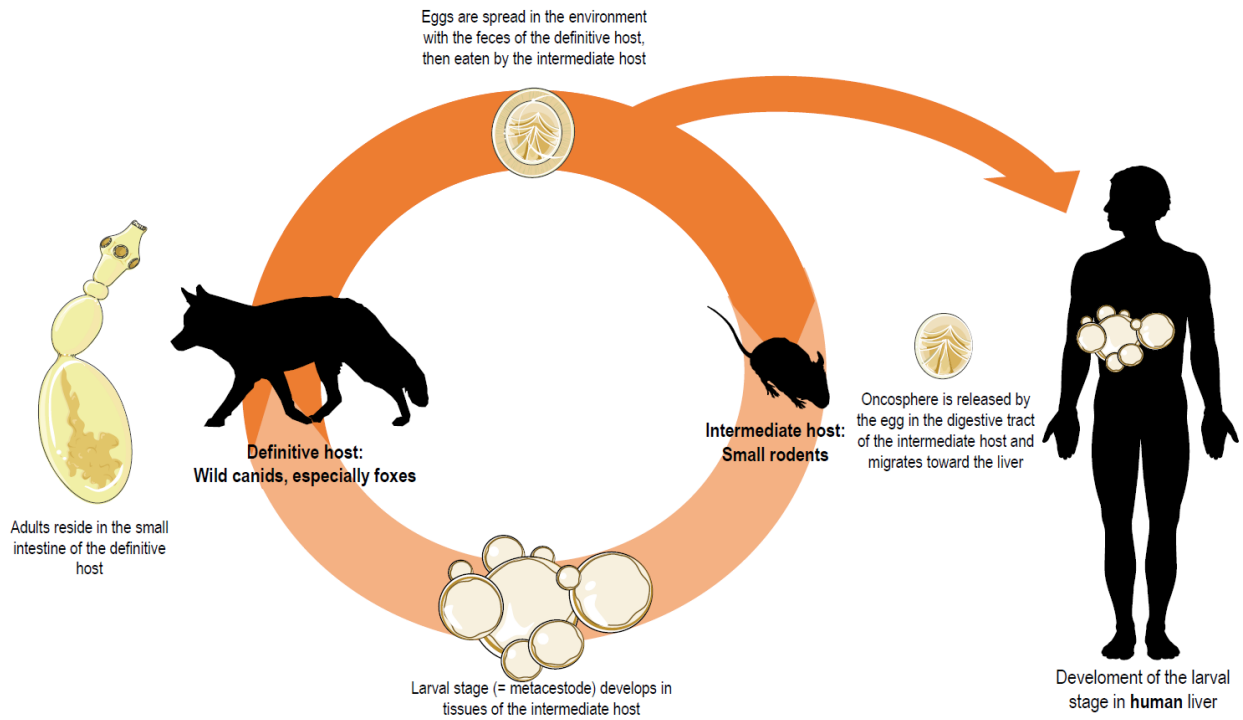
- 404 [39] Haskologlu S, Dogu F, Gollu Bahadır G, Akyuzluer S, Ciftci E, Altun D, et al. An unexpected
405 infection in loss-of-function mutations in STAT3: malignant alveolar echinococcosis in liver. Iran
406 J Allergy Asthma Immunol 2020;19:667–75. <https://doi.org/10.18502/ijaai.v19i6.4936>.
- 407 [40] Cooper GS, Stroehla BC. The epidemiology of autoimmune diseases. Autoimmun Rev
408 2003;2:119–25. [https://doi.org/10.1016/S1568-9972\(03\)00006-5](https://doi.org/10.1016/S1568-9972(03)00006-5).
- 409 [41] Kratzer W, Gruener B, Kaltenbach TE, Ansari-Bitzenberger S, Kern P, Fuchs M, et al. Proposal of
410 an ultrasonographic classification for hepatic alveolar echinococcosis: *Echinococcosis*
411 *multilocularis* Ulm classification-ultrasound. World J Gastroenterol 2015;21:12392–402.
412 <https://doi.org/10.3748/wjg.v21.i43.12392>.
- 413 [42] Kantarci M, Aydin S, Eren S, Ogul H, Akhan O. Imaging aspects of hepatic alveolar
414 echinococcosis: retrospective findings of a surgical center in Turkey. Pathogens 2022;11:276.
415 <https://doi.org/10.3390/pathogens11020276>.
- 416 [43] Reuter S, Jensen B, Buttenschoen K, Kratzer W, Kern P. Benzimidazoles in the treatment of
417 alveolar echinococcosis: a comparative study and review of the literature. J Antimicrob
418 Chemother 2000;46:451–6. <https://doi.org/10.1093/jac/46.3.451>.
- 419 [44] Becker KL, Rösler B, Wang X, Lachmandas E, Kamsteeg M, Jacobs CW, et al. Th2 and Th9
420 responses in patients with chronic mucocutaneous candidiasis and hyper-IgE syndrome. Clin
421 Exp Allergy 2016;46:1564–74. <https://doi.org/10.1111/cea.12787>.
- 422 [45] Lanternier F, Cypowyj S, Picard C, Bustamante J, Lortholary O, Casanova J-L, et al. Primary
423 immunodeficiencies underlying fungal infections. Curr Opin Pediatr 2013;25:736–47.
424 <https://doi.org/10.1097/MOP.0000000000000031>.
- 425 [46] Lanternier F, Mahdavian SA, Barbati E, Chaussade H, Koumar Y, Levy R, et al. Inherited CARD9
426 deficiency in otherwise healthy children and adults with *Candida* species-induced
427 meningoencephalitis, colitis, or both. J Allergy Clin Immunol 2015;135:1558-1568.e2.
428 <https://doi.org/10.1016/j.jaci.2014.12.1930>.

- 429 [47] Lanternier F, Pathan S, Vincent QB, Liu L, Cypowyj S, Prando C, et al. Deep dermatophytosis and
430 inherited CARD9 deficiency. *N Engl J Med* 2013;369:1704–14.
431 <https://doi.org/10.1056/NEJMoa1208487>.
- 432 [48] Jonaitytė E, Judickas M, Tamulevičienė E, Šeškutė M. Alveolar echinococcosis in children. *Case*
433 *Rep Pediatr* 2020;2020:5101234. <https://doi.org/10.1155/2020/5101234>.
- 434 [49] Kinčeková J, Hrčková G, Bober J, Vrzgula A, Szabadošová V, Bohuš P, et al. A rare case of
435 alveolar echinococcosis in a 14-year-old child. *Helminthologia* 2008;45:28–31.
436 <https://doi.org/10.2478/s11687-008-0005-4>.
- 437 [50] Honda S, Okada T, Sasaki F, Naito S, Sato N, Kamiyama T, et al. Pediatric alveolar echinococcosis
438 invading the diaphragm and spreading to the chest and abdominal wall. *J Pediatr Surg*
439 2010;45:e13-16. <https://doi.org/10.1016/j.jpedsurg.2009.11.018>.
- 440 [51] Yoshida T, Kamiyama T, Okada T, Nakanishi K, Yokoo H, Kamachi H, et al. Alveolar
441 echinococcosis of the liver in children. *J Hepato-Biliary-Pancreat Sci* 2010;17:152–7.
442 <https://doi.org/10.1007/s00534-009-0114-6>.
- 443 [52] Oral A, Ozturk G, Aydinli B, Kantarci M, Salman AB. An unusual presentation of alveolar
444 echinococcosis in a 12-yr-old immunocompetent child. *Pediatr Transplant* 2012;16:E375-378.
445 <https://doi.org/10.1111/j.1399-3046.2012.01735.x>.
- 446 [53] Guinet C, Guiot E, De Miscal G, Galloy M-A, Rivier A, Petit C, et al. L'échinococcose alvéolaire
447 hépatique : une cause exceptionnelle de douleurs abdominales récurrentes, chirurgicalement
448 curable, chez l'enfant. *Arch Pédiatrie* 2012;19:1200–4.
449 <https://doi.org/10.1016/j.arcped.2012.08.013>.
- 450 [54] Kantarci M, Bayraktutan U, Pirimoglu B, Ogul H, Oral A, Eren S, et al. Multisystem involvement
451 of alveolar echinococcosis in a child. *J Infect Dev Ctries* 2014;8:1494–7.
452 <https://doi.org/10.3855/jidc.4214>.
- 453 [55] Mack I, Wildhaber B, Vassen V, Ritz N. Alveolar echinococcosis in the liver of an adolescent boy.
454 *Arch Dis Child* 2019;104:407. <https://doi.org/10.1136/archdischild-2018-314990>.

- 455 [56] Joyce J, He X-O, Rozovsky K, Stefanovici C, Fanella S. Disseminated *Echinococcus multilocularis*
456 infection without liver involvement in child, Canada, 2018. *Emerg Infect Dis* 2020;26:1856–9.
457 <https://doi.org/10.3201/eid2608.191644>.
- 458 [57] Yilmaz-Cankaya B, Pirimoglu B. Hepatic alveolar echinococcosis in a child. *Rev Soc Bras Med*
459 *Trop n.d.*;54:e0487-2020. <https://doi.org/10.1590/0037-8682-0487-2020>.
- 460 [58] Reuter S, Seitz HM, Kern P, Junghanss T. Extrahepatic alveolar echinococcosis without liver
461 involvement: a rare manifestation. *Infection* 2000;28:187–92.
462 <https://doi.org/10.1007/s150100050079>.
- 463 [59] Faucher J-F, Descotes-Genon C, Hoen B, Godard J, Félix S, Aubry S, et al. Hints for control of
464 infection in unique extrahepatic vertebral alveolar echinococcosis. *Infection* 2017;45:365–8.
465 <https://doi.org/10.1007/s15010-016-0974-z>.
- 466 [60] Baldolli A, Bonhomme J, Yera H, Grenouillet F, Chapon F, Barbier C, et al. Isolated cerebral
467 alveolar echinococcosis. *Open Forum Infect Dis* 2019;6:ofy349.
468 <https://doi.org/10.1093/ofid/ofy349>.
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471 **Figure 1. Life cycle of *Echinococcus multilocularis*.**

472 Adults of *E. multilocularis* reside in the small intestine of definitive hosts, and spread eggs with their
473 droppings. In intermediate hosts, ingestion of eggs can lead to the development of the larval stage in
474 the liver tissue (or possibly other tissues). The Figure was partly generated using Servier Medical Art,
475 provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.

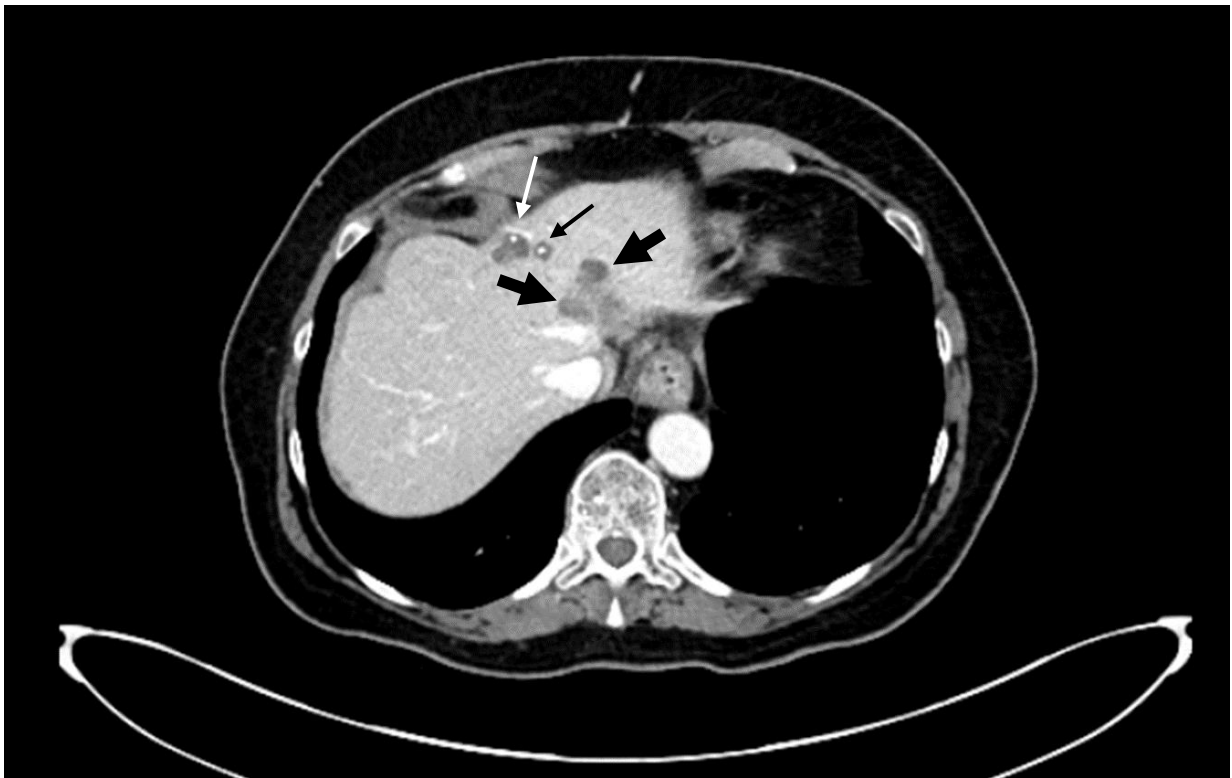


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477 **Figure 2. Fortuitous imaging of liver alveolar echinococcosis.**

478 Injected abdominal CT (axial view, venous phase) performed for an acute sigmoiditis episode in a 65
479 year old woman. She received a kidney transplant 9 years ago and was treated with tacrolimus and
480 mycophenolate mofetil. Punctiform calcifications in the center of 2 small anterior lesions (thin arrows).
481 The largest posterior lesion invades the left and median hepatic veins (thick arrows).

482 Source: Division of Tropical and Humanitarian Medicine, University Hospitals of Geneva, Switzerland.



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