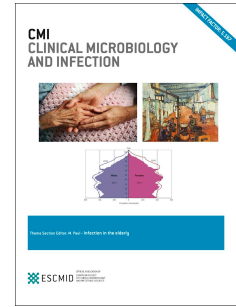


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Alveolar echinococcosis in immunocompromised hosts

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1 **Narrative review**

2 **Alveolar echinococcosis in immunocompromised hosts**

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24 **ABSTRACT**

25 **Background.** Alveolar echinococcosis (AE) results of an infection with the larval stage of *Echinococcus*
26 *multilocularis*. It has been increasingly described in individuals with impaired immune
27 responsiveness.

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

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

35 **Content.** Seventeen publications were found, including 13 reports of 55 AE in immunocompromised
36 patients (AE/IS) and 4 retrospective studies of 755 AE immunocompetent patients (AE/IC) and 115
37 AE/IS (13%). The cohorts included 9 (1%) solid organ transplantation (SOT) recipients, 2 (0.2%) HIV
38 patients, 41 (4.7%) with chronic inflammatory/autoimmune diseases (I/AID) and 72 (8.3%) with
39 malignancies. SOT, I/AID and malignancies, but not HIV infection, were significantly associated with
40 AE (odds ratios of 10.8, 1.6, 5.9 and 1.3, respectively). Compared to AE/IC, AE/IS was associated with
41 earlier diagnosis (PNM stages I-II: 49/85 (58%) vs 137/348 (39%), $p<0.001$), higher rate of atypical
42 imaging (24/50 (48%) vs 106/375 (28%), $p<0.01$) and lower sensitivity of serology (19/77 (25%) vs
43 265/329 (81%), $p<0.001$). Unusually extensive or disseminated infections were described in SOT and
44 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 AE to immunocompromised patients and think about AE when finding a liver lesion.

48 Further research should address gaps in knowledge of AE/IS. Especially, extensive and accurate
49 records of AE cases have to be collected by multinational registries.

50 **KEYWORDS**

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

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53 INTRODUCTION

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

61 PATHOPHYSIOLOGY OF ALVEOLAR ECHINOCOCCOSIS

62 Human infection occurs after accidental ingestion of eggs, which release an oncosphere that accedes
63 to the blood circulation, then establishes in any vascularized organ, with a preferential location in the
64 liver. There, it develops into the larval stage, also called metacestode (Fig 1) [3]. In accidental hosts,
65 such as humans, the metacestode is a heterogeneous multicystic or multivesiculated structure that
66 actively proliferates at its periphery. The parasite is surrounded by a strong infiltration of immune
67 cells associated with dense fibrotic tissue, neovessels and epithelioid cells, and containing central
68 caseous necrosis and calcifications [4].

69 Host-parasite interactions in human tissues lead to various clinical presentations. In most infected
70 individuals (detected upon species-specific serology), no parasitic lesion is observed, suggesting that
71 the parasite has been killed early [2]. In about 20% of cases, the metacestode aborts spontaneously
72 at a later stage, forming a calcified non-viable parasite lesion, etiologically diagnosed on the basis of
73 a positive serology, or upon histology and PCR [5]. These are called aborted or died-out lesions [2,3].
74 Finally, the evolutive form of AE, consisting of a viable parasite which continuously develops until its
75 host dies, affects only a small percentage of infected individuals [2].

76 The initial pro-inflammatory Th1/Th17 immune response is considered to be putatively efficient
77 against the parasite (Table 1) [6]. In susceptible hosts, the response progressively turns into a mixed

78 Th1/Th2 response, with contribution of regulatory T CD4⁺FoxP3⁺ lymphocytes (Treg) and IL-10
 79 secretion, allowing parasite survival [6]. Humoral immunity, although present, appears as not
 80 effective in the control of AE.

81 **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]

82

83 **DIAGNOSIS**

84 Diagnosis relies on conventional imaging techniques (ultrasonography (US), Magnetic Resonance
 85 Imaging (MRI), Computed Tomography (CT)) and detection of anti-*Echinococcus* antibodies [18,19].
 86 Serological assays are of major interest, as most commercially available anti-*Echinococcus* ELISA (e.g.
 87 using EgHF, EgP, Em2, Em2+ or EmVF antigens) and immunoblot assays have a high sensitivity for AE
 88 diagnosis (80-98%) [18,20]. Specificity of these assays is excellent in the general population (>95%),
 89 however cross-reactions are frequent in patients with cystic echinococcosis (CE) due to *Echinococcus*
 90 *granulosus* (13-86%, depending on the technique used) [20]. Although CE and AE imaging are
 91 different, it is recommended to use *E. multilocularis*-specific assays (anti-Em2, anti-Em2+) to avoid

92 cross-reactions. Furthermore, the anti-*Echinococcus* IgG immunoblot can display species-specific
93 patterns, in favour of either *E. multilocularis*, *E. granulosus*, or *Echinococcus* sp. infection. In case of
94 negative serology, diagnosis can rely on histology and/or PCR on biopsies.

95 Discrimination between evolutive and aborted lesions in humans is often difficult. Currently, the best
96 marker to assess viability of the parasite is the detection of anti-recEm18 antibodies, which can be
97 detected by ELISA (commercially available), with 45-80% sensitivity and 99-100% specificity for
98 evolutive AE [18,20,21], and/or PET-scan [19].

99 Advanced imaging techniques allow staging of the disease using the PNM classification proposed in
100 2006 [22]. This system is based on three parameters similarly to the TNM system for tumours: P for
101 the location and extension of the parasite within the liver (P0 to P4), N for the involvement of
102 neighbouring organs (N0 or N1), and M for the metastasis (M0 or M1). Depending on the PNM
103 classification, AE cases are then staged from I to IV, i.e. the less and the most severe, respectively.

104 **OVERALL FINDINGS REGARDING IMMUNOCOMPROMISED PATIENTS**

105 A total of 170 AE patients with immunosuppressive conditions (AE/IS) were mentioned in the
106 literature, including 57 SOT recipients, 4 HIV-positive patients, 45 patients with inflammatory or
107 auto-immune disorder (I/AID), 72 with cancer and 2 with a primary immune disorder (PID) (Table 2).
108 Of note, 8 patients had both cancer and I/AID, and 1 SOT recipient had an haematological
109 malignancy. Four retrospective cohort studies were published, one from France (1982-2012) [23],
110 two others from Switzerland (late 90's-2020) [24,25], and one from Canada (2013-2020). Altogether,
111 these studies described 115 AE/IS cases with previously mentioned backgrounds vs 755 AE cases in
112 immunocompetent individuals (AE/IC). An increasing number of AE/IS cases was highlighted (6/166
113 AE cases (3.6%) in 1992-2002, vs 42/229 AE cases (18.3%) in 2002-2012 in the French cohort, $p < 0.01$)
114 [23]. By comparing the prevalence of each immunosuppressive condition between AE patients and
115 the general population, SOT, I/AID and malignancies, but not HIV infection, were overrepresented
116 among AE patients (odds ratios of 10.8, 1.6, 5.9 and 1.3, respectively) (Table 3).

117 **Table 2. Summary of published cases and cohorts of alveolar echinococcosis in**
 118 **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 ⁴	41 ⁴	Yes	[23–25,32,35–37]
Malignancies	0	72 ⁵	No	[23–25,32]
Primary immune disorder	2	0	Yes	[38,39]

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

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

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

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

124 ⁴ Including 12 patients with rheumatoid arthritis, 9 with non-rheumatoid arthritis, 2 with vasculitis, 4
 125 with another chronic inflammatory disease (inflammatory bowel disease, sarcoidosis, collagenosis,
 126 Still disease), 3 with another autoimmune disease (systemic lupus, Sjögren's syndrome, autoimmune
 127 encephalitis) and 14 not specified

128 ⁵ Includes 44 solid cancers, 12 haematological malignant diseases and 16 “malignancies” (not
 129 specified)

130 **Table 3. Prevalence of immunosuppressive conditions in alveolar echinococcosis patients and**
 131 **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

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

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

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

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

140 ⁴ Statistical test: Fisher’s exact test

141

142 Compared to AE/IC, AE/IS cases were diagnosed more often incidentally (66/86 (77%) in AE/IS vs
 143 144/341 (42%) in AE/IC, p<0.001) and, consequently, earlier in the parasite development (PNM
 144 stages I-II: 49/85 (58%) in AE/IS vs 137/348 (39%) in AE/IC, p<0.01). Clinical presentation of the
 145 symptomatic cases was not compared between AE/IS and AE/IC. Importantly, AE/IS was significantly
 146 associated with false negative serology compared to AE/IC patients (58/77 (75%) in AE/IS vs 64/329
 147 (19%) in AE/IS, p<0.001), but this could be also related to earlier diagnosis [19]. A high frequency of
 148 atypical liver ultrasound and CT imaging findings were described in the French cohort (48%, 24/50),
 149 suggesting cancer metastasis (36%, 18/50), liver abscess (8%, 4/50), haemangioma (2%, 1/50) or

150 hematoma (2%, 1/50) instead of typical imaging (heterogeneous mass with calcifications and/or
 151 clustered microcysts) (Fig 2) [23]. This proportion was significantly higher compared to German and
 152 Turkish reports in the whole AE population, showing only 28% (106/375) of atypical imaging findings
 153 ($p < 0.01$) [41,42]. Interestingly, the French retrospective study also reported a better treatment
 154 efficacy in AE/IS patients compared to AE/IC ((21/41 (51%) vs 50/187 (27%) of lesion regression after
 155 1 year of treatment, $p < 0.01$). However, the authors also emphasized the high frequency of side
 156 effects (40%), possibly associated with high concentrations of albendazole sulfoxide in plasma, thus
 157 encouraging pharmacological monitoring in these patients. However, this proportion was not
 158 significantly different from the 20% (7/35) observed in a previous German cohort of AE patients [43].
 159 Mortality was significantly higher in AE/IS compared to AE/IC patients (16/80 (20%) vs 13/313 (4%),
 160 $p < 0.001$), but was not clearly imputed to AE. The main conclusions of these studies are summarized
 161 in Table 4.

162 **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 AE	0/50 (0%)	3/187 (2%)	p=1.0	Not significantly different	[23]

163 US, ultrasound; CT, computed tomography

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

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

168 ALVEOLAR ECHINOCOCCOSIS AND SOLID ORGAN TRANSPLANT RECIPIENTS

169 Due to their mechanisms of action on cellular immunity, immunosuppressive agents used for the
 170 prevention of graft rejection (cyclosporin, tacrolimus, mycophenolate) theoretically facilitate AE
 171 progression. Indeed, solid organ transplant (SOT) recipients were the first patients described with
 172 rapidly extensive AE. In 1990, two patients who had liver transplantation for AE salvage and pre-
 173 existing pulmonary lesions, were reported as having rapidly growing lung lesions [26], and between
 174 1990 and 1992, recurrence of AE was observed in the transplanted liver [26,27]. In 2003, Koch et al.
 175 reported a 10-year survival of 45%, in a retrospective cohort of 45 patients, managed by liver
 176 transplantation for otherwise untreatable AE between 1985 and 1998 [28]. Among the twenty deaths
 177 observed during follow-up, 5 (25%) were due to relapse, and 9 (45%) were perioperative deaths.

178 They highlighted the detection of new parasitic lesions (mostly in brain and lungs) in 16% (6/45), and
179 graft invasion in another 16% (6/45). Similar clinical presentations were also reported in kidney and
180 lung transplant recipients [29–32]. These data suggest that SOT recipients can present unusually
181 rapidly progressive AE, with an increased risk of dissemination.

182 **ALVEOLAR ECHINOCOCCOSIS AND HIV/AIDS**

183 While HIV and *E. multilocularis* co-infection is often taken as an example of the opportunistic
184 behaviour of the parasite, only few cases have been reported to date. The first was published in
185 1997, and was diagnosed in a six-year-old girl with AIDS [33]. The clinical presentation displayed
186 multiple unusual features: the young age of the patient, the extensive parasite growth and the
187 negative serological testing. Furthermore, the girl had a dramatically low CD4⁺ T cell count (12/mm³)
188 and a negative lymphoproliferative assay with *E. multilocularis* antigen. A second case was published
189 7 years later, in a 40 year-old male [34]. Although the patient was immunocompromised over nearly
190 a decade (CD4⁺ T cells between 27 and 150/mm³), the parasite had an usual growth rate, as the
191 lesion was retrospectively observed on a CT scan performed 8 years before AE diagnosis. Only 2/870
192 (0.2%) HIV patients were mentioned in retrospective studies [23,24]. Altogether, these reports
193 showed that HIV is an uncommon condition for accelerated AE development. Only a dramatically low
194 CD4⁺ T cell count appears to favour the parasite growth (< 20-50/mm³).

195 **ALVEOLAR ECHINOCOCCOSIS AND CHRONIC INFLAMMATORY DISEASES OR AUTO-IMMUNE**

196 **DISORDERS**

197 As for SOT, I/AID are theoretically adequate backgrounds for rapidly progressive AE. Indeed, most of
198 these disorders are treated with long-term immunosuppressive therapies, which often have broad-
199 spectrum effects on immune effectors (e.g. steroids, methotrexate...) or an anti-Th1 biological
200 activity (e.g. TNF- α inhibitors, anakinra (IL-1 receptor antagonist)...). Such cases were actually
201 reported in patients affected with auto-immune encephalitis and rheumatoid arthritis [35–37].
202 Among the retrospective cohorts of AE/IS, 40/115 patients (35%) had I/AID, and at least 14/115

203 (12%) and 6/115 (5%) were treated with methotrexate and TNF- α inhibitors, respectively [23–25,32].
204 Of note, at least 27/115 (23%) were treated with steroids, without specification concerning the
205 indication (SOT, malignancy, I/AID or other) nor the dosage. Although it seems probable that all
206 immunosuppressive regimens do not equally favour AE, fundamental and clinical data suggest that
207 long-term administration of steroids or TNF- α inhibitors could accelerate AE progression. Other
208 immunosuppressive therapies were observed in patients with accelerated AE, such as rituximab
209 (anti-CD20) [23,30,37], however they are mostly associated with steroids or TNF- α inhibitors, which
210 prevent to reliably conclude on their imputability.

211 **ALVEOLAR ECHINOCOCCOSIS AND MALIGNANCIES**

212 The few reports of AE concomitant to malignancy were compiled in retrospective cohorts. Out of the
213 115 AE/IS detailed cases, 44 (38%) had solid cancer (15 of the digestive tract, 9 of the respiratory
214 tract, 15 urogenital or breast, 1 of the skin and 3 others), 12 (10%) had haematological malignancies
215 (4 myeloproliferative syndrome, 6 lymphoproliferative syndrome, 1 Fanconi anaemia) and 16 (14%)
216 had unspecified malignancy [23–25,32]. The median time between onset of immunosuppressive
217 condition (IS) and AE diagnosis was shorter for solid cancers than for other conditions, probably
218 because AE was often diagnosed incidentally during extensive workup (83%) [23]. Despite the high
219 number of AE diagnosed in patients with malignancies, no clear evidence of aggressive AE has been
220 reported. On the contrary, these cases often benefited from an earlier management due to
221 incidental diagnosis [23].

222 **PRIMARY IMMUNE DEFICIENCIES**

223 Only two cases of AE were described in patients with PID, both were young patients (14 and 17 yo)
224 with Hyper-IgE Syndrome (HIES) [38,39]. This rare PID is characterized by recurrent infections,
225 eosinophilia and elevated IgE serum levels. The syndrome is associated with a defect of the Th17
226 response, leading to bacterial and fungal opportunistic infections [44]. The fact that these two young
227 patients presented with disseminated AE is highly unusual, as the mean AE incubation time is

228 between 5 and 15 years [2]. Even if more evidence needs to be collected, these observations suggest
229 that Th17 defects, including *Card9-Syk* deficiencies, could favour AE development [45]. Unlike most
230 of PIDs, such deficiency can be diagnosed in apparently healthy children or adults [46,47]. The part of
231 such defects in unusually extensive AE is currently not known. Further studies (extensive analysis of
232 immune cell populations, complete workup for autoimmunity, whole-genome sequencing) are
233 needed to ensure that rare and yet undiagnosed PIDs are not hidden beyond those atypical cases,
234 particularly when they occur in children. Indeed, taken together, 21 paediatric case reports have
235 been described in the literature, including 24% under 10 years and 24% with disseminated lesions
236 [33,39,48–57]. In almost all cases, assessment of immune status was unreported or limited to T CD4⁺
237 and T CD8⁺ cell counts and HIV serology. However, it should be kept in mind that atypical
238 presentations may be not only related to immune disorders, but can be associated with vascular
239 abnormalities [56,58–60].

240 **IMPLICATIONS**

241 Populations exposed to long-term immunosuppressive therapy such as cyclosporin, TNF- α inhibitors
242 or steroids are at risk of progressive AE. While data are scarce regarding other treatments, physicians
243 should be aware that the use of such drugs could accelerate progression and dissemination of AE.
244 Considering the occurrence of rapidly extensive AE in SOT and I/AID patients, serological screening
245 and abdominal imaging (if not previously done) could be proposed to these patients before onset of
246 the immunosuppressive therapy, even if the benefit of such recommendation should be evaluated.
247 Whether cancer is actually a risk factor is not clear, as it can be associated with AE diagnosis due to
248 extensive check-up [23]. Conversely, it could be even hypothesized that AE is a risk factor for cancer,
249 as it induces chronic immunosuppression by itself [4]. Finally, HIV infection does not seem to be a risk
250 factor, nor a significant cause of progressive AE.

251 **LIMITATIONS**

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

258 **PERSPECTIVES**

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

268 To date, there is no data supporting modified medical treatment or follow up in AE/IS. Even if
269 albendazole seems to be more effective in AE/IS, possibly due to the reduced fibrosis or the earlier
270 diagnosis, it is not clear whether these patients are at risk of late relapse, or if it would be beneficial
271 to extend the duration of treatment and/or follow-up.

272 In areas endemic for AE, physicians who manage patients under long-term immunosuppressive
273 therapies should deliver health education, by explaining what AE is and the ways to avoid infection.

274 Overall, the probably most important suggestion to these physicians would be to think about AE
275 when finding a liver lesion.

276 **Table 5. Unanswered questions about alveolar echinococcosis and immunocompromised hosts**

Topic	Questions
Management of patients	<p data-bbox="603 300 1342 539">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 data-bbox="603 584 1342 685">Should patients with unusually extensive lesions and children with AE benefit from extensive immunological check-up?</p> <p data-bbox="603 730 1342 824">Should treatment and/or follow up duration be extended for these patients?</p>
Epidemiology	<p data-bbox="603 875 1302 976">Which immunosuppressive drugs, and what treatment duration, are associated with an increased risk of AE?</p> <p data-bbox="603 1021 1302 1048">Is cancer favouring AE, or conversely AE favouring cancer?</p> <p data-bbox="603 1093 1302 1120">Are there other backgrounds favouring AE?</p>
Pathophysiology	<p data-bbox="603 1160 1190 1261">Do immunosuppressive regimens favour parasite establishment, development, or both?</p>

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

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280 **CONFLICT OF INTERESTS**

281 None of the authors declares any conflicts of interest.

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283 No external funding was received for this work.

284 **CONTRIBUTION**

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

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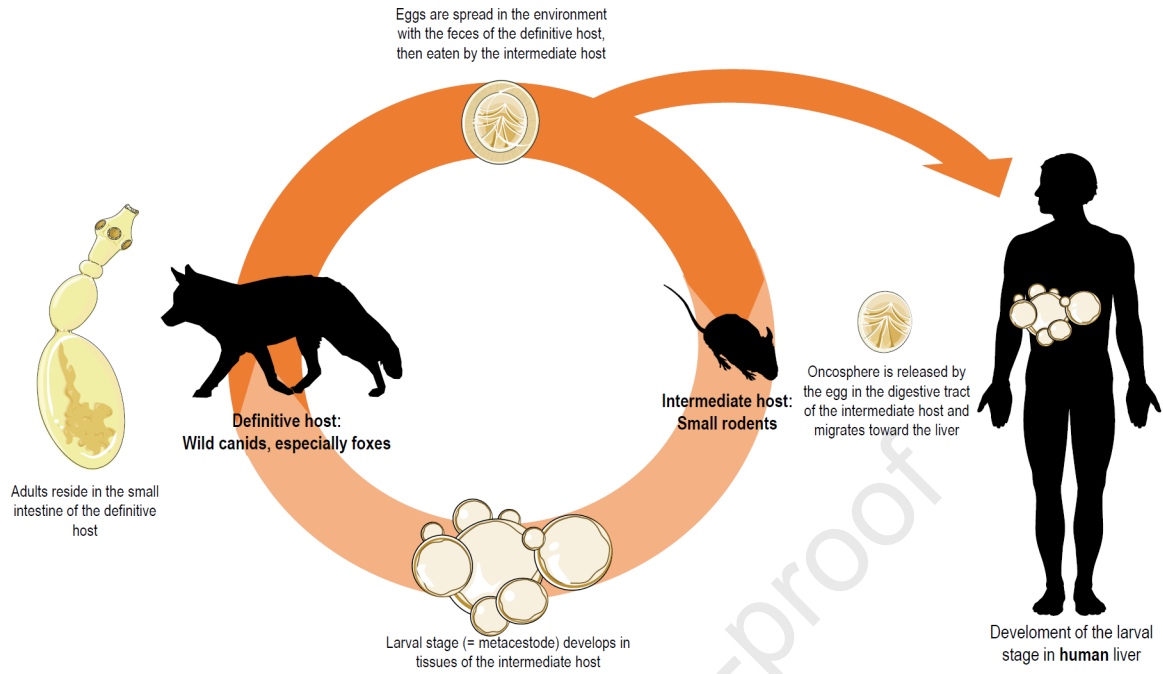
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