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Institut Tropical et de Santé Publique Suisse

Assoziiertes Institut der Universität Basel

Andreas Neumayr
Department of Medicine

Swiss TPH Winter Symposium 2017

Helminth Infection – from Transmission to Control

Evaluation of a Novel Treatment Approach for the Treatment of Human Cystic Echinococcosis

Intracystic albendazole sulfoxide instillation in a sheep model

Funding

R03 International Research in Infectious Diseases (IRID) grant of the National Institute of Health (NIH), USA

Timeline

2016 – 2020

Collaborators

- Swiss TPH
- Universidad Peruana Cayetano Heredia, Lima, Peru
- Universidad Nacional Mayor de San Marcos, Lima, Peru

Team

Dr. Saul J Santivanez, Peru

Dr. Andreas Neumayr, Switzerland

Dr. Hector H. Garcia, Peru

Dr. Cesar M. Gavidia, Peru

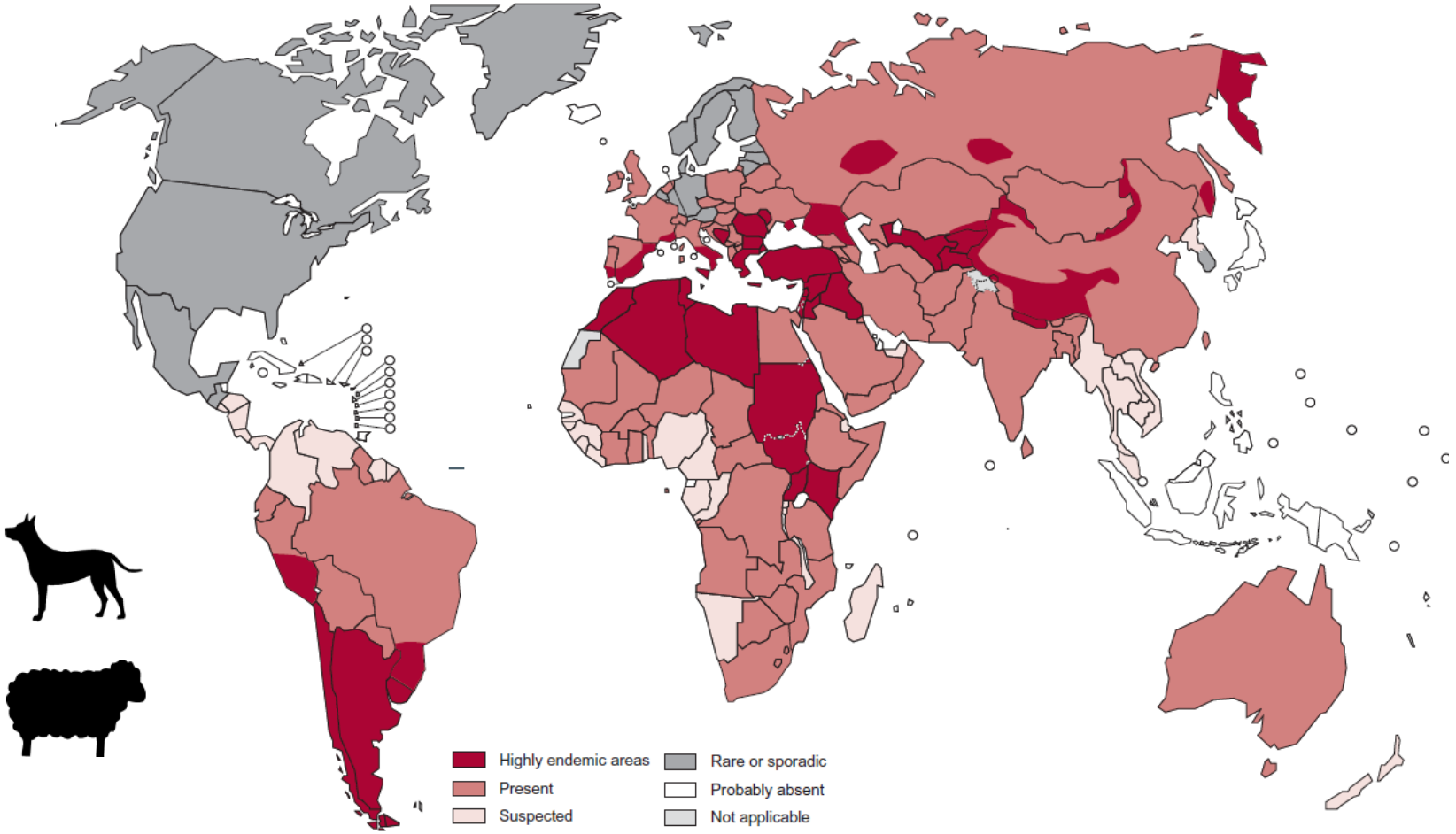
Dr. Enrico Brunetti, Italy

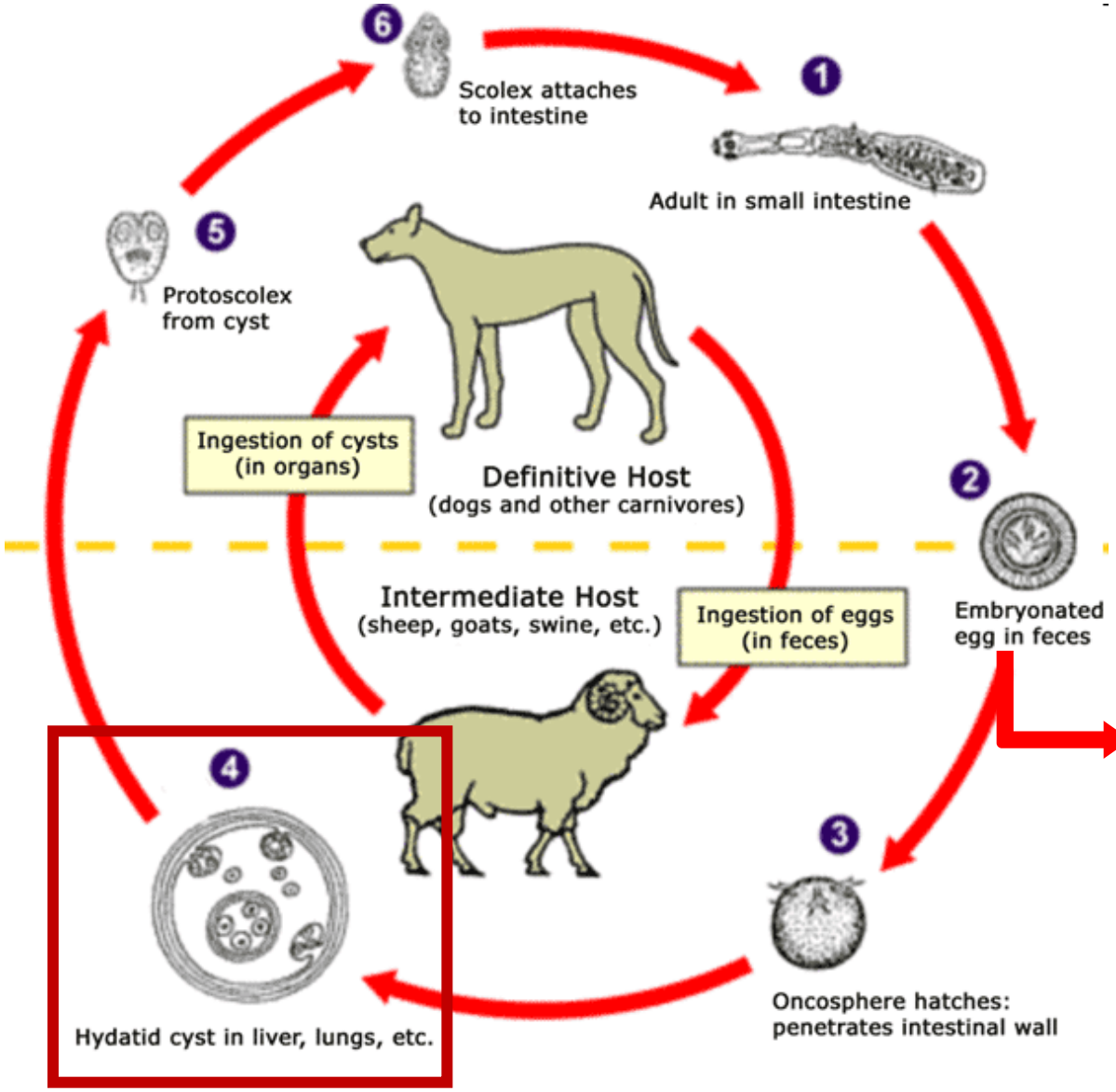
Dr. Robert H. Gilman, USA

Dr. Armando E. Gonzalez, Peru

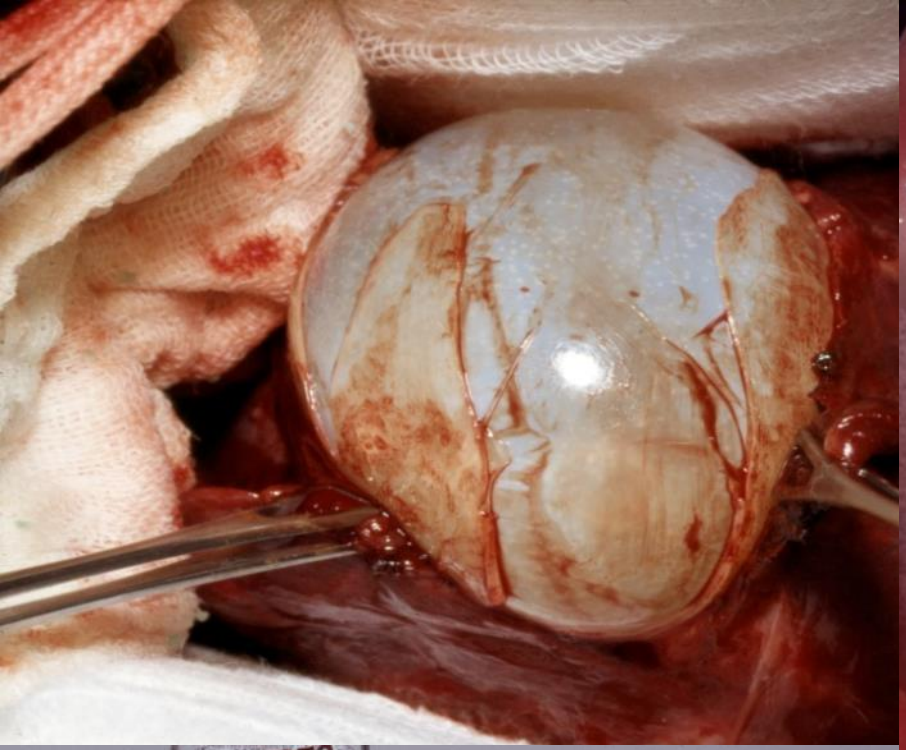
Dr. Richard J. Horton, U.K.

Cystic echinococcosis - *E. granulosus*

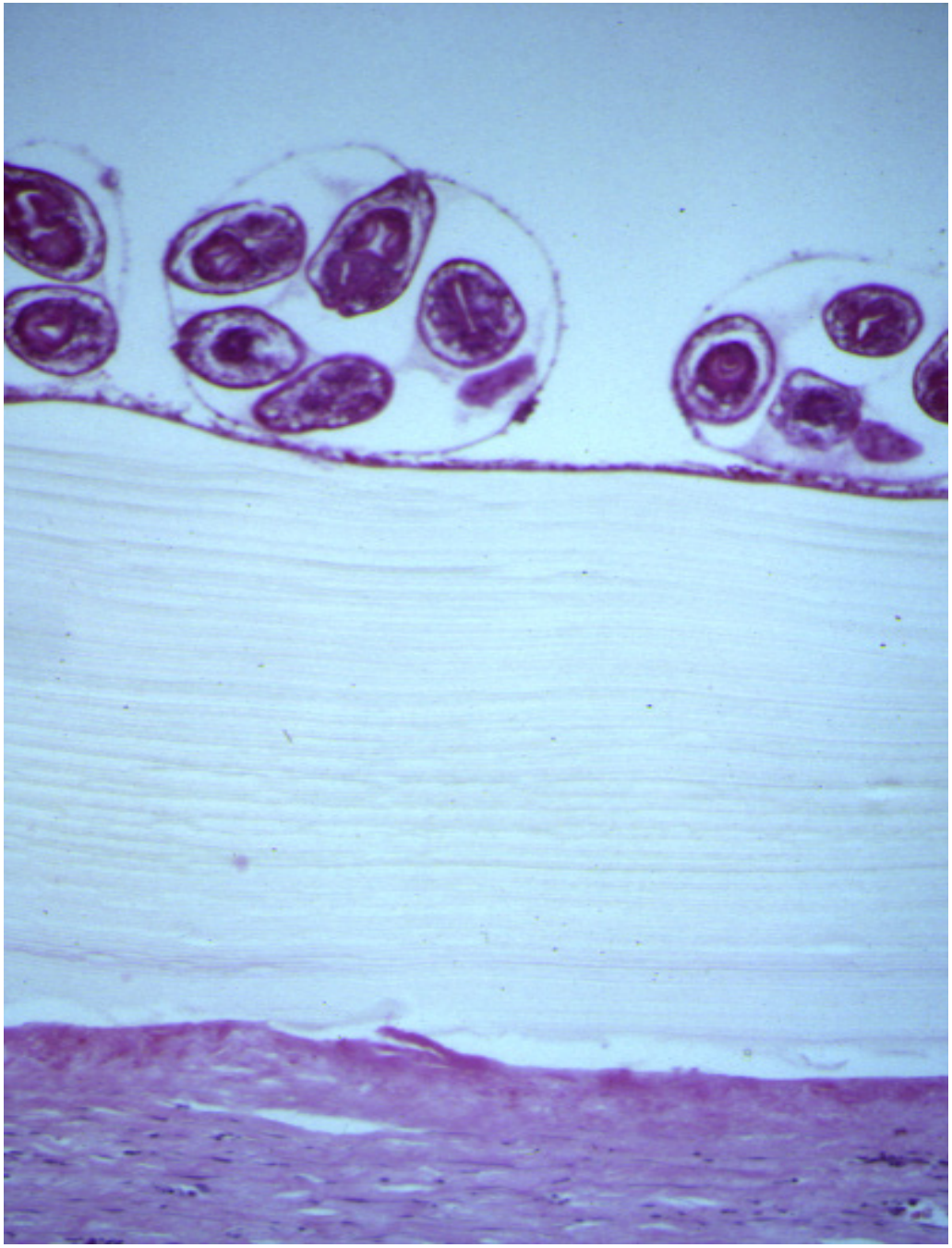




70% liver cysts
20% lung cysts
10% other location




250
200
150
100
50



Cyst lumen

Brood capsule

Protoscolices

Germinal layer

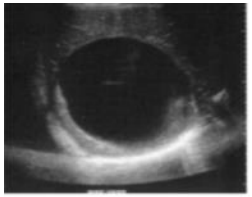
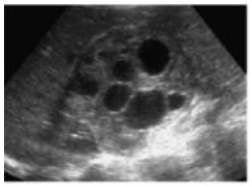
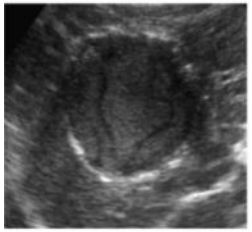
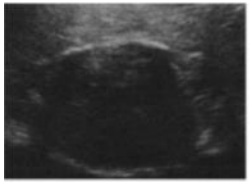
Laminated layer

Endocyst (parasite)

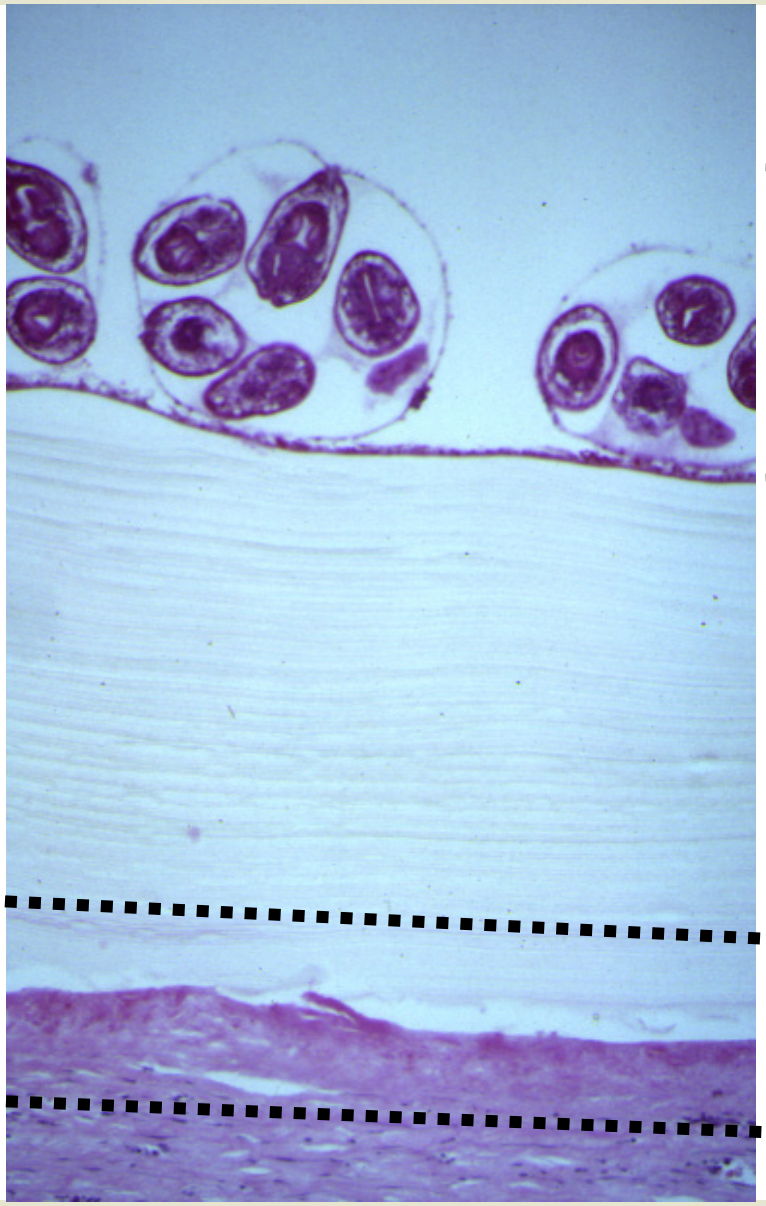
1–2 mm

Pericyst (host tissue)

Evolution / stages of echinococcal cysts

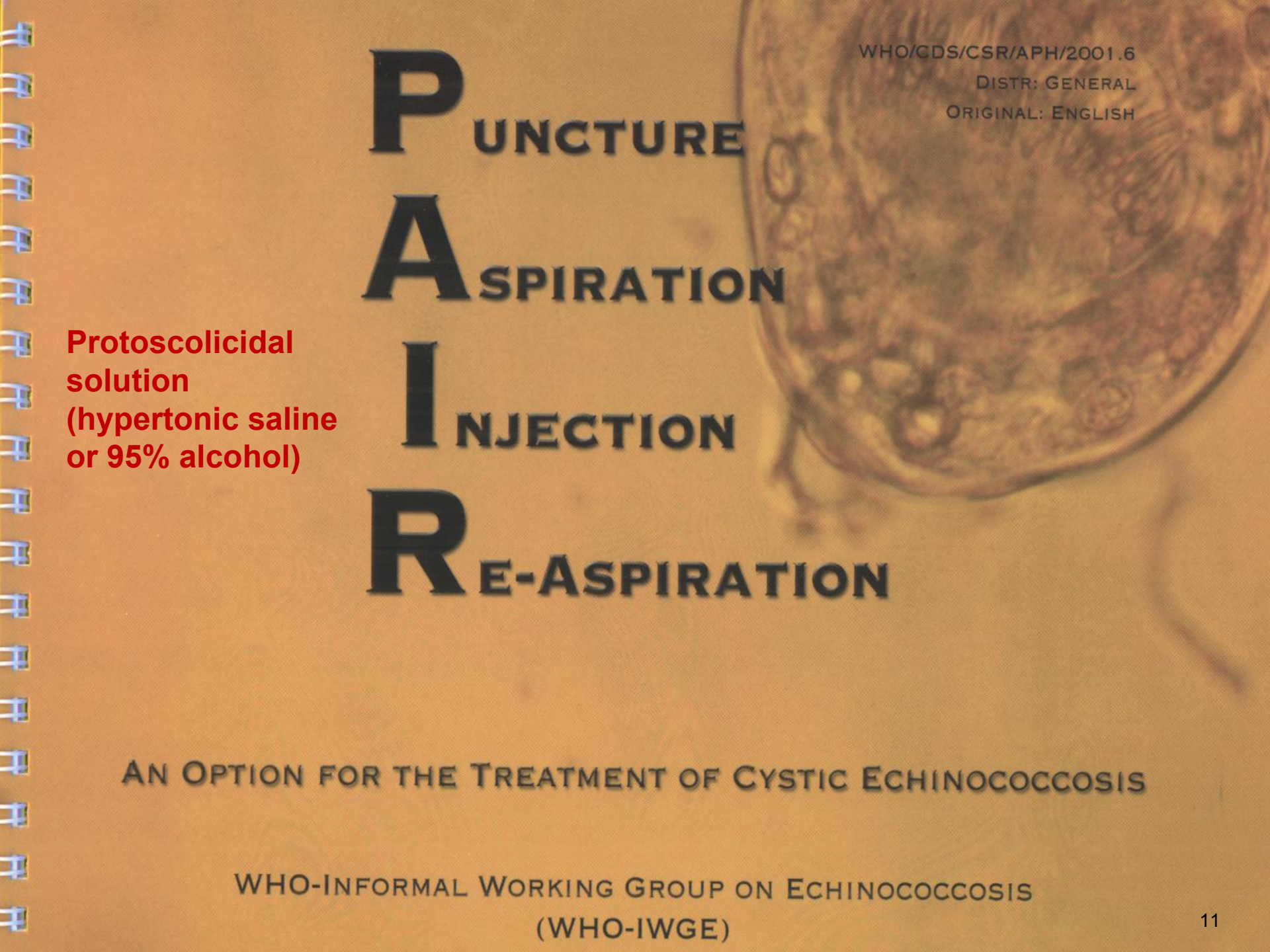
WHO cyst classification		Description	Cyst stage	Treatment options
CE 1		unilocular unechoic cystic lesion with double line sign	**Active**	• drug therapy • percutaneous treatment
CE 2		multiseptated, `rosette-like´, `honeycomb´cyst		• drug therapy • surgery
CE 3A		cyst with detached membranes (`water-lily-sign´)	**Transitional**	• drug therapy • percutaneous treatment
CE 3B		cyst with daughter cysts in solid matrix		• drug therapy • surgery
CE 4		cyst with heterogenous hypo/hyperechoic content, no daughter cysts	**Inactive**	**no therapy**
CE 5		solid plus calcified wall		

Drug treatment with oral benzimidazoles (Albendazole; >1970s)



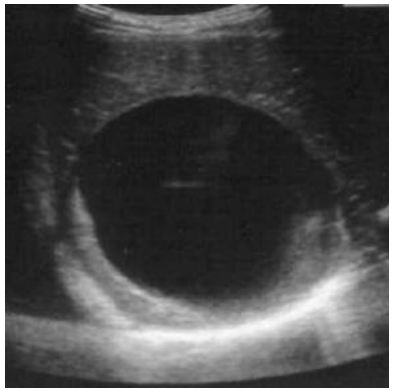
"PAIR" (percutaneous treatment; >1980s)

Surgery



Protoscolicidal solution (hypertonic saline or 95% alcohol)

Cyst stage depending outcome of PAIR



CE 1

CE 3a

85% success

15% failure

- CE2 with many daughter cysts
- CE3b predominantly solid with daughter cysts

PAIR / percutaneous treatment related problems

Problem 1: Risk of anaphylaxia

OPEN ACCESS Freely available online

PLOS | NEGLECTED TROPICAL DISEASES

Justified Concern or Exaggerated Fear: The Risk of Anaphylaxis in Percutaneous Treatment of Cystic Echinococcosis—A Systematic Literature Review

Andreas Neumayr[1]*, Giuliana Troia[2], Chiara de Bernardis[2], Francesca Tamarozzi[2], Sam Goblirsch[3], Luca Piccoli[2], Christoph Hatz[1], Carlo Filice[4], Enrico Brunetti[2]

1 Swiss Tropical and Public Health Institute, Basel, Switzerland, **2** Division of Infectious and Tropical Diseases, University of Pavia, IRCCS S. Matteo Hospital Foundation, WHO Collaborating Centre for Clinical Management of Cystic Echinococcosis, Pavia, Italy, **3** Department of Medicine and Pediatrics, University of Minnesota, Minneapolis, Minnesota, United States of America, **4** Ultrasound Unit, Department of Infectious Diseases, University of Pavia, IRCCS S. Matteo Hospital Foundation, WHO Collaborating Centre for Clinical Management of Cystic Echinococcosis, Pavia, Italy

The risk of percutaneous treatment related anaphylaxia

5943 percutaneous treatment procedures reported 1980–2010

Lethal complications	No. of cases	% of treated hydatid cysts (n=5517)	% of percutaneous treatment procedures (n=5943)
Lethal anaphylactic shock	2	0,04	0,03
Lethality related to percutaneous treatment procedure	1	0,02	0,02
Lethality not related to percutaneous treatment procedure	2	0,04	0,03
Total	5	0,09	0,08

Lethal anaphylaxia 0.03 % = 3 / 10.000 PAIR-procedures

- Drug related lethal anaphylactic reactions:
  Penicillin 1 – 4 / 10.000 treatment courses

Relatively minor problem

- Allergic reactions to radiographic contrast media used for imaging occur in 1% of patients and are lethal in ≤0.01% of cases

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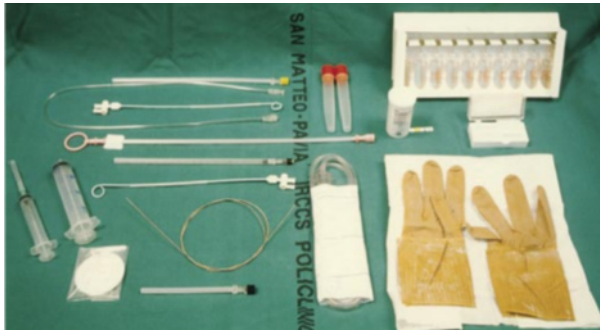
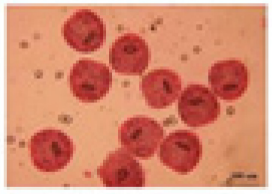
Problem 2: Demanding

PAIR equipment





Oral Albendazole ≥ 3 months

+

Limited bioavailability
Limited efficacy
Limited compliance
Price

WBC + LFT follow-up

Toxicity
Availability
Price

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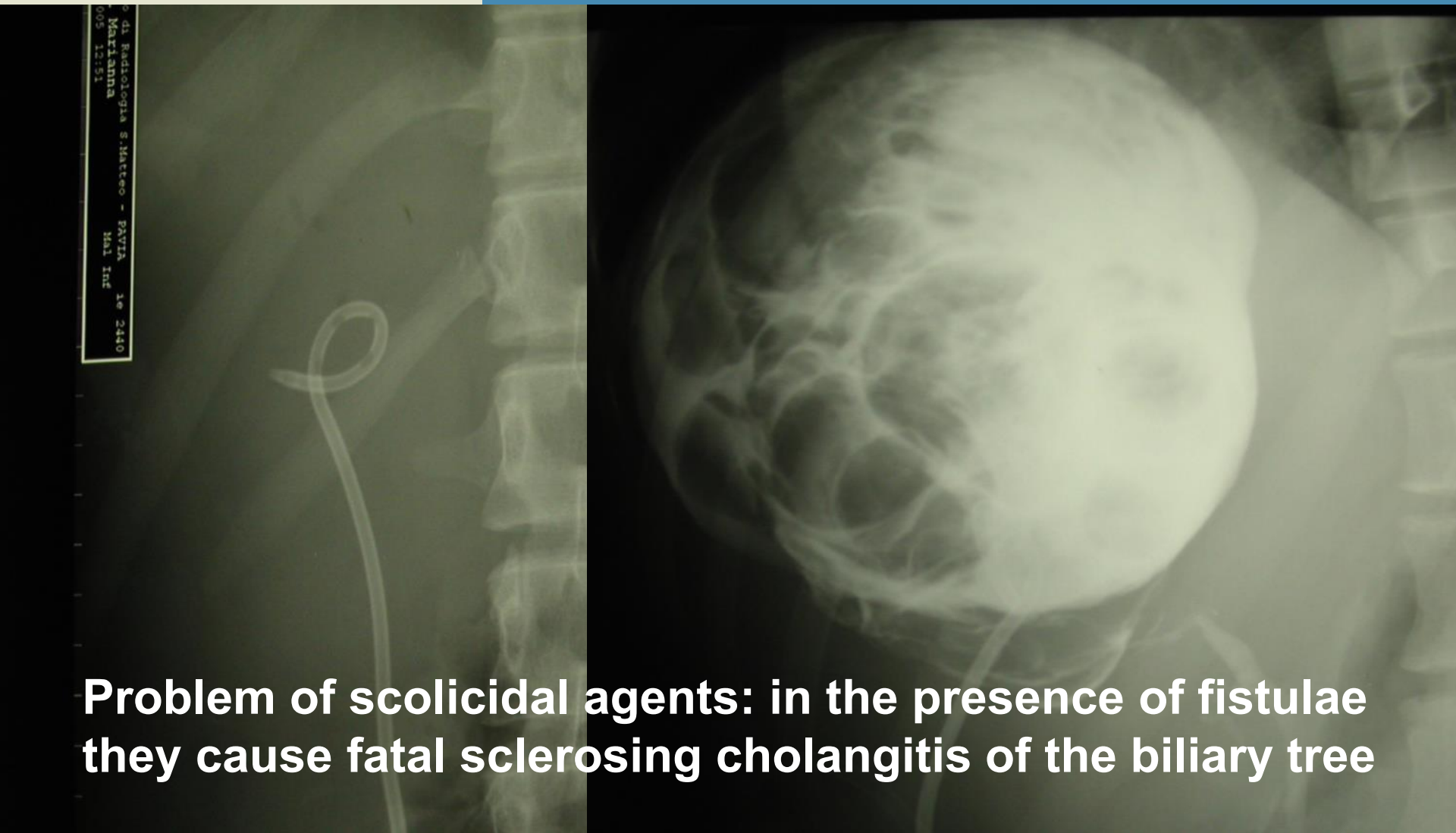
PAIR / percutaneous treatment related problems

Problem 3: Biliary fistulae



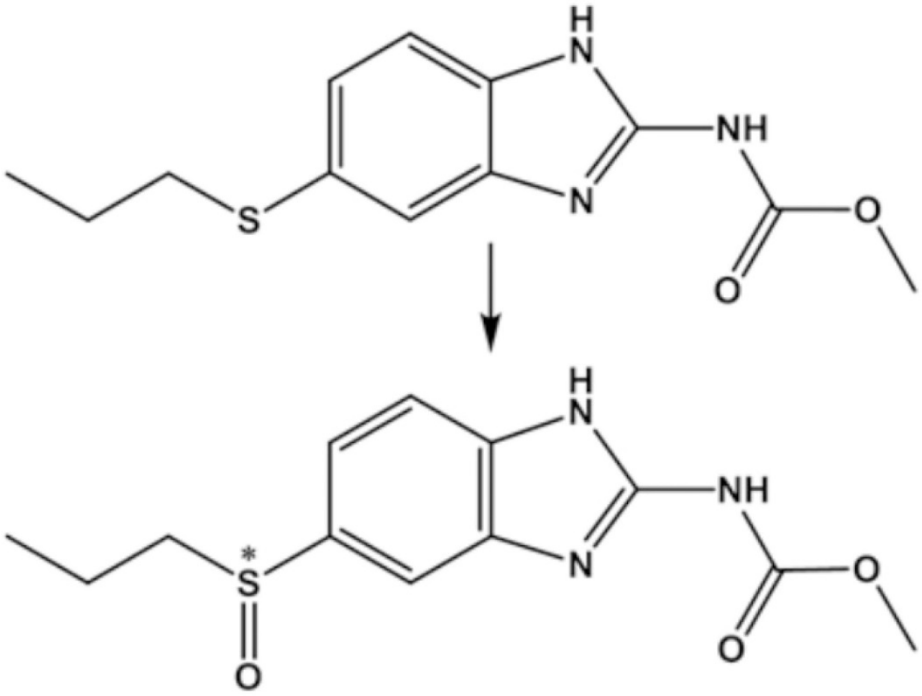
Problem of scolicidal agents: in the presence of fistulae they cause fatal sclerosing cholangitis of the biliary tree

Conclusions:

neither surgery nor PAIR nor longterm oral albendazole treatment are feasible treatment options for resource poor settings and a safe and effective alternative is needed

Why not injecting albendazole into hydatid cysts ?

Albendazole is a "pro-drug" and needs hepatic metabolization into its active form



Albendazole

Albendazole sulfoxid

常州亚邦齐晖医药化工有限公司
CHANGZHOU YABANG-QH PHARMACHEM CO., LTD

检 验 报 告 书
Certificate of Analysis

产品名称 Product	阿苯达唑亚砜盐酸盐 Albendazole Sulfoxide Hcl	批号 Batch #	61113003
生产日期 Manufacture Date	2013.03.08	有效日期 Expiry Date	2017.03.07
数量 Quantity	600 KG		
储存条件 Storage Conditions	密闭、避光保存 Kept In Closed Container, Protected From Light		
检验依据 Specification	QS-0021.01-A		

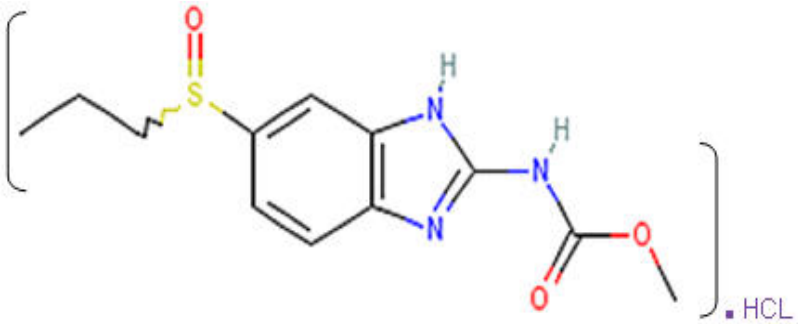
检验项目Test Items	检验标准Specifications	检验结果Results
【性状 Description】	白色或类白色无定形粉末，有特殊气味 White or almost white amorphous powders, Characteristic odour	白色无定形粉末,有特殊气味 White amorphous powders, characteristic odour
【溶解性 Solubility】	应溶于水和丙二醇 Soluble in water and propyleneglicol	完全溶解于水和丙二醇 Soluble in water and propyleneglicol
【水份 Water】	4.00-6.00% (W/W)	4.6%
【熔点 Melting point】	132-137℃	133.5-134.3℃
【砜 Sulphonas】	≤2.0%	0.07%
【微生物】 Microbiological Purity	总细菌数：＜5×10UFC/g Total of Bacterias aerobics total: ＜5×10UFC/g	<10CFU/g
	总霉菌和酵母菌数：＜5×10UFC/g Total of Yeast and Mold: ＜5×10UFC/g	<10CFU/g
【含量 Assay（HPLC）】	94.0%~100.0%	99.78%

结论：检验结果符合QS-0021.01-A标准。
Conclusion: The items tested meet the requirement of QS-0021.01-A.

审核人/日期：
Reviewed by QA Manager/Date

批准人/日期：
Approved By Quality Director/Date

… a perfect water-soluble Albendazole sulfoxid salt preparation !



Eur Surg Res. 1998;30(6):433-8.

Effect of albendazole sulfoxide solution on the scolices and the hepatobiliary system.

Erzurumlu K[1], Hokelek M, Baris S, Sahin M, Birinci A, Amanvermez R, Tac K.

Author information

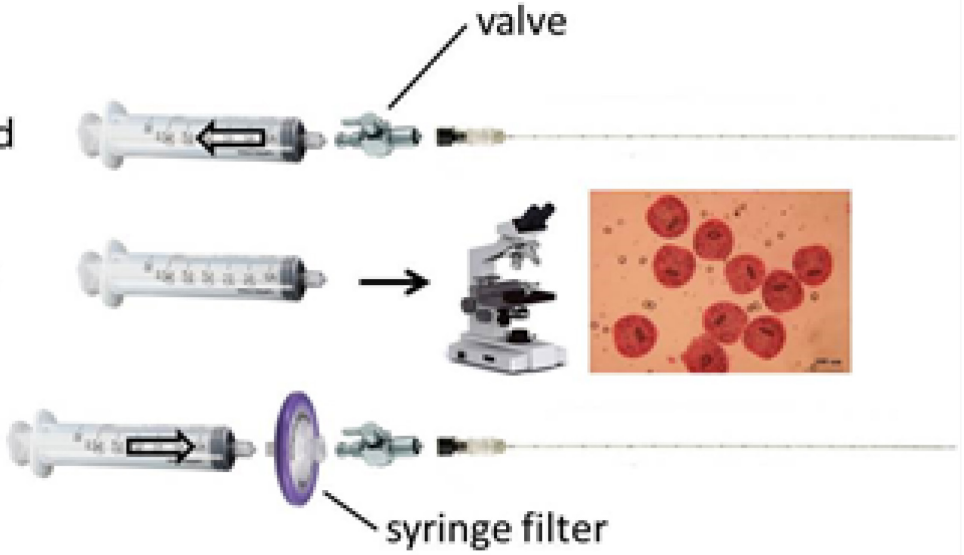
Abstract

The use of scolocidal solutions in the hepatobiliary system may result in caustic sclerosing cholangitis. In this study, the effectivenes of a biological metabolite of albendazole, albendazole sulfoxide, on scolices and the hepatobiliary system was evaluated. In the in vitro study, it was found that 100 microg/ml albendazole sulfoxide solution had strong scolocidal effect in 15 min. In the in vivo study, two experimental groups, each consisting of 8 rabbits aged 3-4 months and weighing 2,500 +/- 250 g, 100 microg/ml albendazole sulfoxide and normal saline were given into the biliary tract. ALP, GGT, SGOT and SGPT values on days 7, 30 and 60 were not found to be significantly increased compared to preoperative values. Total bilirubin values were high in the working group 7 and 30 days postoperatively and on day 30 in the control group, returning back to normal levels on day 60 in both groups. Histopathological evaluation of the liver parenchyma and the biliary system on day 60 revealed no differences between the groups. Consequently, albendazole sulfoxide solution may be used intraoperatively for scolocidal purposes.

Result: Albendazole sulfoxid is non-toxic to the biliary tree, no risk of sclerosing cholangitis

Single step percutaneous treatment procedure with intracystic albendazole sulfoxide instillation

1. Ultrasound guided puncture and aspiration of cyst fluid
2. Confirmation of cyst viability by microscopy
3. Injection of study drug



Aim of study: to replace the classical PAIR procedure for percutaneous treatment of hepatic hydatid cysts

Problems linked to classical PAIR (puncture-aspirate-instillate-reaspirate) technique:

(1) technically demanding (complex multi-step procedure),
(2) instillation of hypertonic saline solution or ethanol into cysts causes fatal chemical cholangitis if cysto-biliary fistulas are present, thus
(3) exclusion of cysto-biliary fistulas (by radio contrast studies) obligatory,
(4) high costs of subsequent oral albendazole therapy (≥3 months)
(5) necessity to monitor systemic toxicity of albendazole therapy

Advantage of novel treatment approach:

(1) assuring a locally maximized and sustained antiparasitic effect,
(2) avoiding systemic toxicity, thus (3) sparing the necessity for resource- and cost demanding monitoring of systemic therapy
(4) avoiding compliance problems and (5) costs linked to the currently necessary prolonged oral therapy.

Challenges

Natural infected sheep:

- cyst size limited
- coinfection with *Fasciola* close to 100%

Option of an infection model currently under evaluation:

time to reasonable cyst size ~ 4-5 years

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Thank you