Neurocysticercosis

Erich Schmutzhard
Innsbruck, Austria

Chair, EAN Task Force
Neurology & Africa

Clinical symptoms, diagnosis, and treatment of neurocysticercosis

Hector H Garcia, Theodore E Nash, Oscar H Del Brutto

Lancet Neurol 2014; 13: 1202–15

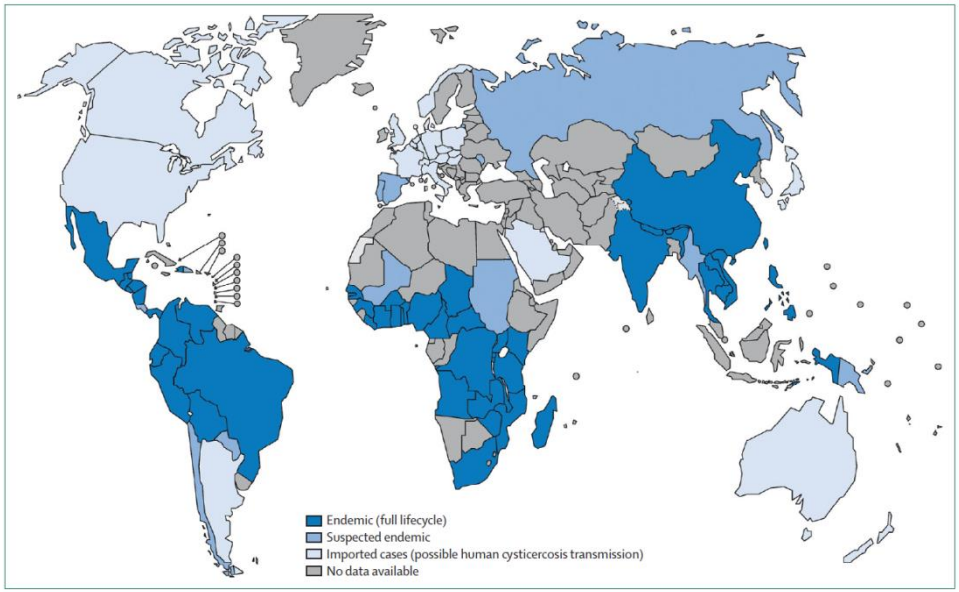


Figure 1*: Geographical prevalence of *Taenia solium
Reproduced from the *First WHO report on neglected tropical diseases*[10] by permission of the World Health Organization.

Neurology and Cysticercosis
Neurocysticercosis

Seizures or epilepsy

Focal neurological deficits

Intracranial hypertension

Cognitive decline

headache

associated stroke

involuntary movements

Neurocysticercosis and Epilepsy in SSA

Pub-med search 1972 – 10/2016:

Keywords: neurocysticercosis, Africa, epilepsy: 55 hits

1st publication: 1976

Neurocysticercosis and Epilepsy in SSA

Pub-med search 1972 – 10/2016:

Keywords: neurocysticercosis, Africa, epilepsy: 55 hits

1st publication: 1976 – in French

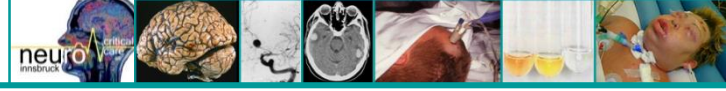
1st case report:

Dumas, M., Ndiaye, I.P., Dumas, J.P. & Gueye, M. (1976). Cysticercose cérébrale: deux nouveaux cas Sénégalais. Bull Soc Med Afr Noire, 21: 203 - 211

1st systematic survey:

Dumas M, Grunitzky K, Belo M, Dabis F, Deniau M, Bouteille B, Kassankogno Y, Catanzano G, Alexandre MP (1990) Cysticercosis and neurocysticercosis: epidemiological survey in North Togo.

.Bull Soc Pathol Exot;83:263-74.



Geographical distribution of publications

Africa at large:	12		
South Africa:	7	Gabon:	1
Tanzania:	6	Gambia:	1
Burundi	4	Kenya:	1
Cameroon:	4	Mali:	1
Togo	4	Mozambique	1
Burkina Faso	3	Nigeria:	1
Benin:	2	Rwanda:	1
Rep. of Congo:	2		
Senegal:	2		
Uganda:	2		
Zambia:	2		

Life Cycle of *Taenia solium* cysticercus and Its Development in the Brain

Cysticercosis = a **zoonotic** disease,

is caused by the **larval** stage (cysticercus) of the **porcine tapeworm** *Taenia solium*.

In humans, cysticerci are mainly found in the

central nervous system (**brain and spinal cord**), and in **subcutaneous tissue**,
skeletal muscle, and the
eye,

whereas in **pigs** cysticerci mainly lodge in skeletal muscle.

In the brain, **immature cysticerci** appear within some weeks after ingestion of *T. solium* eggs **(stage 1).**

Life Cycle of *Taenia solium* cysticercus and Its Development in the Brain

Stage 2 (some months after egg ingestion) is characterized by **mature cysticerci** with virtually **no** inflammatory response which may persist for many years.

Eventually, after some years, asymptomatic stage 2 cysticerci develop into symptomatic **stage 3** **degenerating cysticerci** that no longer prevent the host's immune response with resulting **intense inflammation** which may lead to clinical signs and symptoms.

In **stage 4**, the cysticercus **calcifies** or **resolves** without scarring.

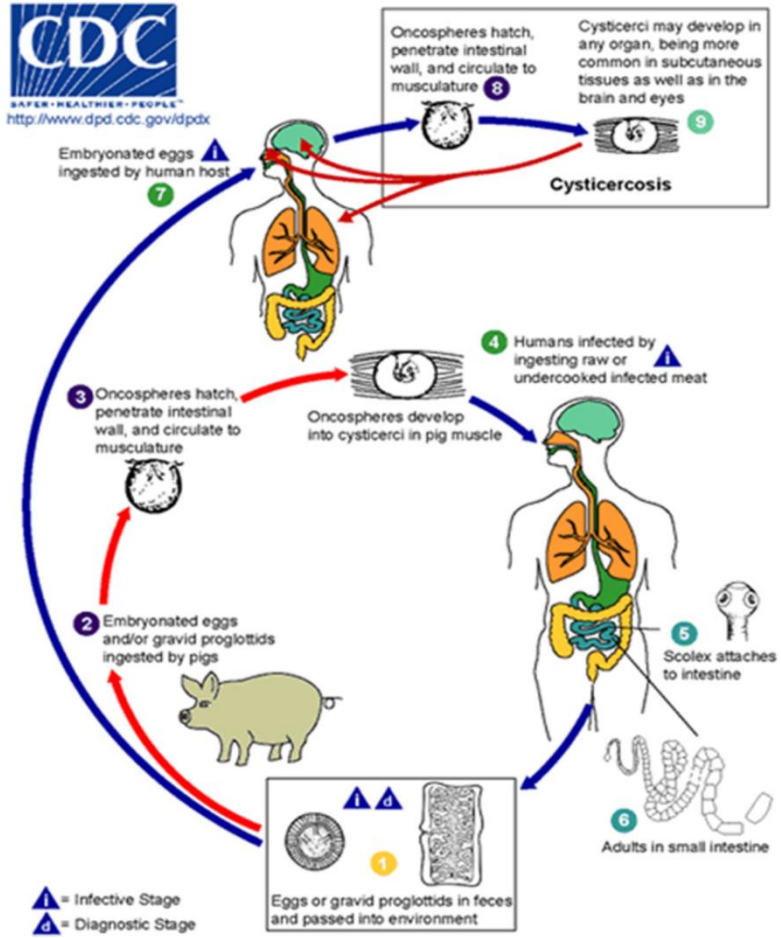


Figure 1 Life cycle of *Taenia solium* cysticerci. Humans become infected with the adult worm by eating undercooked pork containing cysticerci ④ and develop taeniosis (tapeworm infection) ⑤, ⑥. Tapeworm eggs or gravid proglottids are excreted from an infected human host into the environment ① and can be taken up by freely roaming pigs ② that develop porcine

Prevalence of NCC in Sub-Saharan Africa

Suggested calculation of the prevalence rates of NCC

In sub-Saharan Africa, the presence of porcine cysticercosis is well established, but so far only few studies on human cysticercosis/NCC have been conducted.

Studies in rural populations of Uganda, Zambia, and Burkina Faso and in an urban population of Tanzania, that are combining serology and neuroimaging data, are under way (as of August 2016).

A recent meta-analysis on the prevalence of NCC in people with epilepsy, including 12 studies mainly from Latin America, India and sub-Saharan Africa, found that **NCC was the cause of epilepsy in almost 30% of people with epilepsy**

Symptomatic NCC is only the tip of the iceberg and the majority of people with NCC are asymptomatic.

Data regarding asymptomatic NCC cases vary, but autopsy studies and community-based neuroimaging studies indicate that between approximately 50 and 80% of all people affected with NCC may be asymptomatic. Using the conservative estimate of 50% another 0.98-3.18 million people would have latent NCC.

Therefore, the total of all people suffering from NCC (symptomatic and asymptomatic) in sub-Saharan endemic countries would be somewhere between

1.96 and 6.36 million

Neurocysticercosis

DIAGNOSTIC CRITERIA

Del Brutto OH. **Diagnostic criteria for neurocysticercosis.**
Ann Neurol. 2016 Oct 12. doi: 10.1002/ana.24795. [Epub ahead of print]

Table 1 Diagnostic criteria for neurocysticercosis

Diagnostic criteria

Absolute criteria:

- Histologic demonstration of the parasite from biopsy of a brain or spinal cord lesion
- Evidence of cystic lesions showing the scolex on neuroimaging studies
- Direct visualization of subretinal parasites by fundoscopic examination

Major criteria:

- Evidence of lesions highly suggestive of neurocysticercosis on neuroimaging studies
- Positive serum immunoblot for the detection of anticysticercal antibodies
- Resolution of intracranial cystic lesions after therapy with albendazole or praziquantel
- Spontaneous resolution of small single enhancing lesions

Minor criteria:

- Evidence of lesions suggestive of neurocysticercosis on neuroimaging studies
- Presence of clinical manifestations suggestive of neurocysticercosis
- Positive CSF ELISA for detection of anticysticercal antibodies or cysticercal antigens
- Evidence of cysticercosis outside the central nervous system

Epidemiologic criteria:

- Individuals coming from or living in an area where cysticercosis is endemic
- History of frequent travel to disease-endemic areas
- Evidence of a household contact with *T. solium* infection

Degrees of diagnostic certainty

Definitive diagnosis:

- Presence of one absolute criterion
- Presence of two major plus one minor or one epidemiologic criteria

Probable diagnosis:

- Presence of one major plus two minor criteria
- Presence of one major plus one minor and one epidemiologic criteria
- Presence of three minor plus one epidemiologic criteria

Symptomatic NCC in people with epilepsy

Data on sub-Saharan prevalence rates of NCC in people with epilepsy/epileptic seizures come from few countries only with results of over 40% (Cameroon) depending on the serological tests used.

A recent meta-analysis that only included African studies showed a significant **association** between **epilepsy** and **cysticercosis** with an **odds ratio of 3.4.**

Quet F, Guerchet M, Pion SDS, Ngoungou EB, Nicoletti A, Preux. PM. Meta-analysis of the association between cysticercosis and epilepsy in Africa. Epilepsia. 2010;51:830–7.

Epilepsia, 50(5):987–993, 2009
doi: 10.1111/j.1528-1167.2008.01867.x

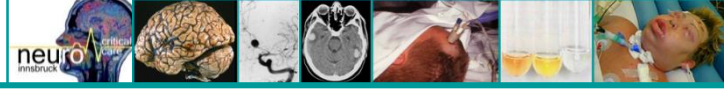
FULL-LENGTH ORIGINAL RESEARCH

Epilepsy and neurocysticercosis in rural Tanzania—An imaging study

*†[1]Andrea Sylvia Winkler, †‡[1]Joachim Blocher, §Herbert Auer, ¶Thaddaeus Gotwald, **William Matuja, and ‡Erich Schmutzhard

*Department of Neurology, Ludwig-Maximilians-University, Munich, Germany; †Haydom Lutheran Hospital, Manyara Region, Tanzania; ‡Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria; §Department of Medical Parasitology, Clinical Institute of Hygiene and Medical Microbiology, Medical University Vienna, Vienna, Austria; ¶Department of Radiology, Medical University of Innsbruck, Innsbruck, Austria; and **Department of Neurology, Muhimbili National Hospital, Dar es Salaam, Tanzania

Conclusion: For the first time in sub-Saharan Africa, we give evidence within a large-scale neuroimaging study that NCC, a so far neglected infectious disease, represents a major cause of epilepsy.



Overview on pathological and clinical characteristics of NCC

NCC can cause a variety of **symptoms and signs** depending on the

number,

size,

stage, and

location of the pathological changes, as well as the

inflammatory host response,

or it can also be **clinically asymptomatic.**

Diagnosis of NCC in Sub-Saharan Africa

Diagnosis of NCC has been well established and is mainly based on

-neuroimaging and

-immunodiagnosis.

Diagnostic testing should be initiated if NCC is suspected on **clinical** grounds, e.g. epileptic seizures in people coming from areas **endemic** for cysticercosis.

The analysis of cerebrospinal fluid of patients with NCC may indicate parasitic disease or show mononuclear pleocytosis and eosinophilia, depending on disease activity and the location of lesions.

Cell counts rarely exceed 100 cells/µl.

Protein levels can be increased to within the range of 50–300 mg/dl, but

glucose levels are usually normal.

The diagnostic value of standard analysis of cerebrospinal fluid is debatable and unremarkable in most cases,

Serological tests for *T. solium* cysticercosis should be performed in suspected cases.

Antigen/antibody enzyme-linked immunosorbent assay (ELISA) and

immunoblots in serum and/or cerebrospinal fluid

are available, whereby a

➔ **positive antigen** ELISA indicates **active disease** with viable cysticerci and a

➔ **positive antibody** ELISA and/or immunoblot demonstrates **exposure to the parasite**, but **not** necessarily **active disease**

Although positive serological and/or DNA-based tests may give the first indication, the gold standard of NCC diagnosis is **neuroimaging, including cCT and/or cerebral magnetic resonance imaging,** both of which are generally not available in sub-Saharan Africa.

Serology may help in areas without CT scanners or may indicate who should go for cCT examination and thus save resources. A recent study from Tanzania indicated a sensitivity of 100% and a specificity of 84% for diagnosis of **active NCC** using ***T. solium* cysticercosis antigen ELISA,** whereas a study from South Africa demonstrated much lower sensitivity and specificity using the same *T. solium* cysticercosis antigen ELISA in a different study population.

OPEN ACCESS Freely available online

PLOS | NEGLECTED TROPICAL DISEASES

Added Value of Antigen ELISA in the Diagnosis of Neurocysticercosis in Resource Poor Settings

Sarah Gabriël[1☯], Joachim Blocher[2,3*☯], Pierre Dorny[1], Emmanuel Nji Abatih[1], Erich Schmutzhard[2], Michaeli Ombay[4], Bartholomayo Mathias[4], Andrea Sylvia Winkler[5]

1 Department of Biomedical Sciences, Institute of Tropical Medicine, Antwerp, Belgium, **2** Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria, **3** Department of Neurology, University Medical Centre Göttingen, Göttingen, Germany, **4** Mental Health Unit, Haydom Lutheran Hospital, Mbulu, Tanzania, **5** Department of Neurology, Technical University Munich, Munich, Germany

Conclusions: In areas where neuroimaging is absent, NCC diagnosis according to the existing criteria is problematic. Taking into account its limitations for diagnosis of inactive NCC, antigen detection can be of added value for diagnosing NCC in PWE by supporting diagnostic and treatment decisions. Therefore, we recommend a revision of the "Del Brutto diagnostic criteria" for use in resource poor areas and suggest the inclusion of serum antigen detection as a major criterion.

Neuroimaging not only is essential for

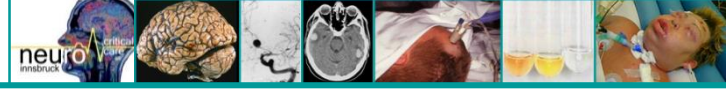
➔ **confirmation** of diagnosis, but also represents the only method that

➔ **differentiates between active and inactive disease**.

Treatment of NCC in Sub-Saharan Africa

Current state of the art treatment

Briefly, treatment approach depends on whether the disease is intraparenchymal or extraparenchymal. Neuroimaging is mandatory to visualize the location of the NCC lesion(s). Therefore, the algorithm of shown below cannot be transferred one to one to resource-poor settings. In this algorithm, only **active intraparenchymal** and **symptomatic** (e.g. epileptic seizures) disease requires treatment with triple therapy, i.e.
-**antihelminthic** drugs (praziquantel 50 mg/kg per day for 15–30 days plus albendazole 15 mg/kg per day for 8–15 days),
-**steroids** and
-**antiepileptic** medication.



Treatment of NCC in Sub-Saharan Africa

Current state of the art treatment

…. Steroids should be initiated together with antihelminthic drugs to prevent perifocal edema in intraparenchymal disease and ideally should be administered for as long as the patient is symptomatic (e.g. severe progressive headache, acute symptomatic epileptic seizures), but at least for the first days antihelminthic treatment is given.

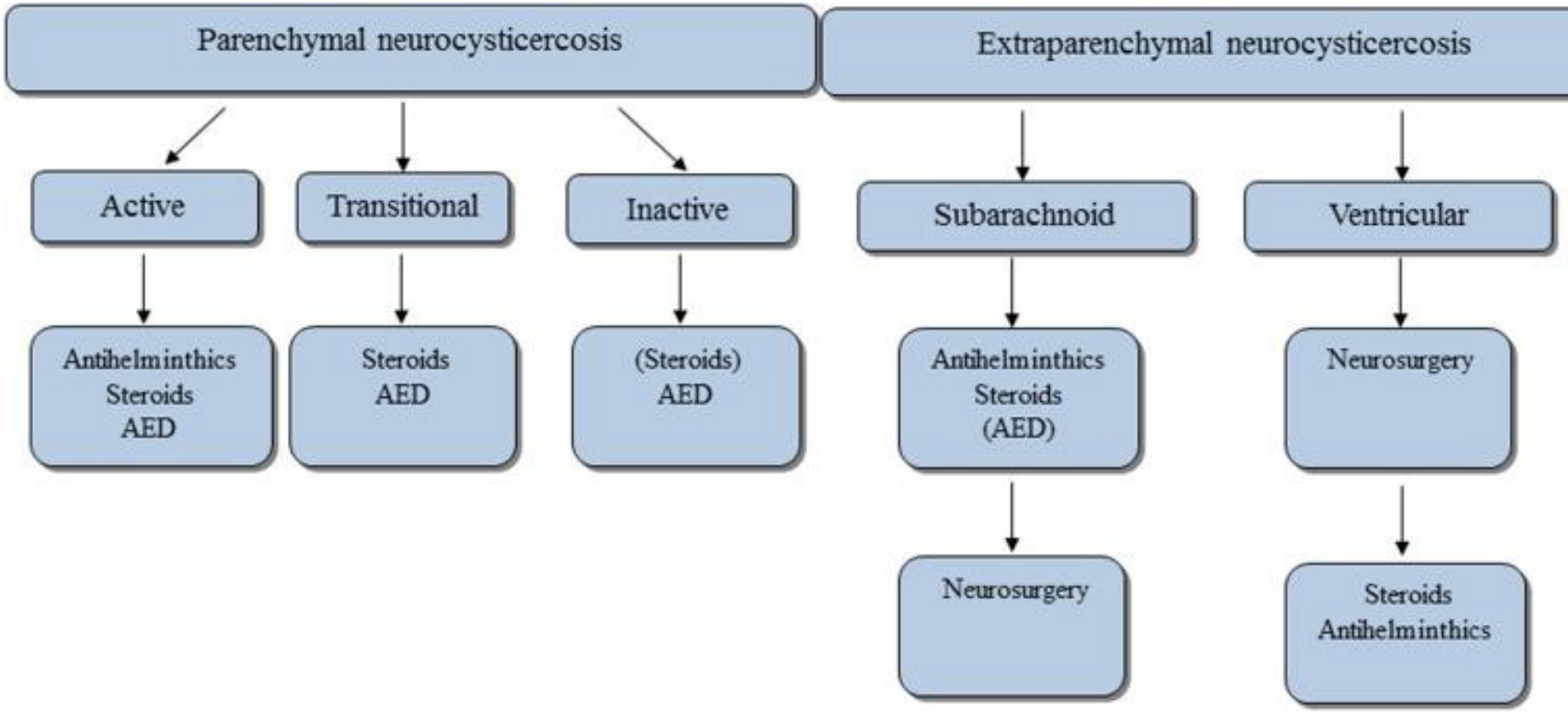
So far, steroid doses in the treatment of NCC have not been standardized

Once the parasite has gone into the transitional stage (=stage 3 degenerating cysticercus), antihelminthics may no longer be needed as the parasite is already attacked and destroyed by the host. Current advice is that the symptomatic patient with epileptic seizures should be maintained on symptomatic treatment only, i.e. steroids and antiepileptic medication.

In **inactive symptomatic** disease the patient should receive antiepileptic mediation **only if seizures are present.**

If perilesional edema is obvious, steroids may be beneficial, although there are only anecdotal reports.

Treatment of extraparenchymal disease is much more tedious and in most cases requires lengthy treatment regimens with antihelminthic medication and steroids.



Winkler AS, 2012

Efficacy of combined antiparasitic therapy with praziquantel and albendazole for neurocysticercosis: a double-blind, randomised controlled trial

Hector H Garcia, Isidro Gonzales, Andres G Lescano, Javier A Bustos, Mirko Zimic, Diego Escalante, Herbert Saavedra, Martin Gavidia, Lourdes Rodriguez, Enrique Najar, Hugo Umeres, E Javier Pretell, for The Cysticercosis Working Group in Peru

Lancet Infect Dis 2014; 14: 687–95

	Albendazole plus praziquantel (n=39)	Standard albendazole (n=41)	Increased albendazole (n=38)	Overall p value
One to two cysts				
Viable cysts at baseline	27	22	23	0·284
Mean per patient (SD)	1·4 (0·6)	1·1 (0·3)	1·3 (0·6)	0·281
Cyst range	1–3*	1–2	1–3*	..
Number of patients	20	20	18	..
Viable cysts at day 180	10	6	3	0·237
Mean per patient (SD)	0·5 (0·7)	0·3 (0·5)	0·2 (0·4)	0·162
Cysts resolved	17/27 (63%)	16/22 (73%)	20/23 (87%)	0·141
Patients cured	12/20 (60%)	14/20 (70%)	15/18 (83%)	0·287
Three or more cysts				
Viable cysts at baseline	171	142	142	0·179
Mean per patient (SD)	9·0 (4·8)	6·8 (4·2)	7·1 (4·4)	0·245
Cyst range	3–19	3–18	3–18	..
Number of patients	19	21	20	..
Viable cysts at day 180	11	112	74	<0·0001
Mean per patient (SD)	0·6 (1·0)	5·3 (4·2)	3·7 (3·1)	0·0001
Cysts resolved	160/171 (94%)	30/142 (21%)	68/142 (48%)	<0·0001
Patients cured	13/19 (68%)	1/21 (5%)	5/20 (25%)	<0·0001

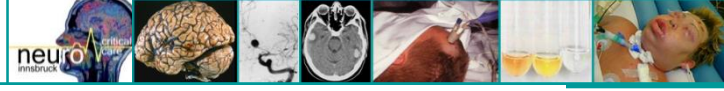
Data are n/N (%), unless otherwise indicated. *In each of these groups, an additional cyst was identified in the MRI of one patient after they had been randomised in the one to two cysts stratum.

Table 2: **Cysticidal efficacy by treatment group and number of cysts**

	Seizure events per day (n)		Seizure rates per year		Seizure rate ratios (95% CI)		
	Persistent infection	Resolved infection	Persistent infection	Resolved infection	Persistent infection	Resolved infection	p value
Overall period*							
All seizures	225	72	4·39	0·84	1·00	0·19 (0·15–0·25)	<0·0001
Partial	217	66	4·24	0·77	1·00	0·18 (0·14–0·24)	<0·0001
Generalised	9	6	0·18	0·07	1·00	0·40 (0·14–1·12)	0·081
Days 61–180†							
All seizures	112	32	5·88	1·62	1·00	0·28 (0·19–0·41)	<0·0001
Partial	108	30	5·67	1·52	1·00	0·27 (0·18–0·40)	<0·0001
Generalised	5	2	0·26	0·10	1·00	0·39 (0·08–1·99)	0·256
Days 181–540‡							
All seizures	113	40	3·51	0·61	1·00	0·17 (0·12–0·25)	<0·0001
Partial	109	36	3·38	0·55	1·00	0·16 (0·11–0·24)	<0·0001
Generalised	4	4	0·12	0·06	1·00	0·49 (0·12–1·95)	0·311

*18 714 patients per days in non-cured periods and 31 273 patients per days in cured periods. †6960 patients per days in non-cured periods and 7200 patients per days in cured periods. ‡11 762 patients per days in non-cured periods and 24 073 patients per days in cured periods.

Table 3: **Seizure frequency and risk by cure status**



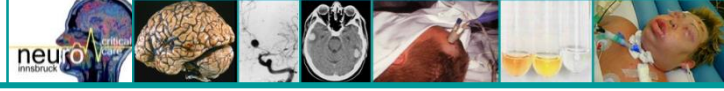
Cochrane Library

Cochrane Database of Systematic Reviews

Antiepileptic drugs for seizure control in people with neurocysticercosis (Review)

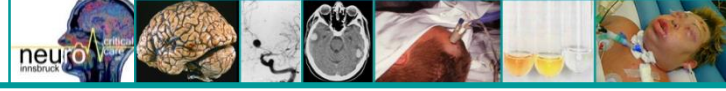
Sharma M, Singh T, Mathew A

Cochrane Database of Systematic Reviews 2015, Issue 10. Art. No.: CD009027.



Authors' conclusions

Despite neurocysticercosis being the most common cause of epilepsy worldwide, there is currently no evidence available regarding the use of AEDs as prophylaxis for preventing seizures among people presenting with symptoms other than seizures. For those presenting with seizures, there is no reliable evidence regarding the duration of treatment required. There is therefore a need for large scale randomised controlled trials to address these questions.

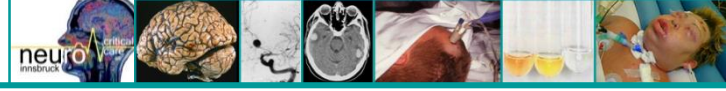


Summary I

Symptomatic NCC may affect between one and three million people throughout *T. solium* taeniosis/cysticercosis endemic areas of sub-Saharan Africa.

Asymptomatic cases are potentially at risk of **developing neurological symptoms/signs through mass drug administration** directed against schistosomiasis, lymphatic filariasis and soil-transmitted helminths.

The clinical presentation of cysticercosis/NCC not only is determined by the prevailing genotype of *T. solium* cysticerci, which seems closely related to that of Latin America, but may also vary individually based on genetic, immunological and environmental factors, among others.



Summary II

Diagnosis and treatment of NCC and its **most common** clinical presentation, i.e. **epilepsy/epileptic seizures,** is rendered difficult by the scarcity of neuroimaging facilities and the lack of an adapted epilepsy classification system together with appropriate antiepileptic treatment, respectively.

Thus, the focus has to be on **symptomatic treatment** of **epileptic seizures** with locally available antiepileptic medication and steroids in selected cases.

Besides treating people with NCC, **prevention strategies** as well as education have to be considered.