Landscape analysis: management of neurocysticercosis with an emphasis on low- and middle-income countries

Commissioned by the
World Health Organization

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WHO/HTM/NTD/NZD/2015.05

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A. Literature selection

A literature search was conducted using the following search engines: PubMed, PubMed Central, Cochrane, Embase, GoogleScholar, Medline and ScienceDirect. Papers were mainly collected from PubMed using the following search terms and combinations thereof: “treatment”, “management”, “neurocysticercosis”, “resource-poor”, “Asia”, “Africa”, “South America”, “Latin America”, “HIV/AIDS”, “spinal”. Cross-linked literature was screened and added, where appropriate. No time restrictions concerning the year of publication limited the literature search.

Primary selection of English language citations was conducted according to title and abstracts. In a second step eligible full articles or electronic publications were assessed for sought topics. Duplicates were removed (on title, author, year, journal, DOI). Moreover, clinical notes, letters to the editor and PubMed comments were initially included in the search procedure. Selection of citations for the landscape analysis was tailored to acquisition of data from or about low- and middle-income countries (LMIC). If this criterion was met, no geographical limitation was applied.

Background information on *Taenia solium* (neuro)cysticercosis was retrieved from the WHO/FAO/OIE Guidelines for the surveillance, prevention and control of taeniosis/cysticercosis (Murrell et al. 2005) and a book chapter on neurocysticercosis in sub-Saharan Africa (Winkler 2013) as well as selected recent reviews on NCC (Winkler et al. 2009a, Nash & Garcia 2011, Garcia et al. 2011a, Takayanagui et al. 2011, Winkler 2012, Garcia et al. 2014a).

Moreover, literature collections by AS Winkler were screened and added, if appropriate, to supplement data predominantly for sub-Saharan Africa.

Articles were excluded, if they

- did not relate to humans
- did not relate to LMIC, or highly endemic areas
- did not discuss issues relevant to diagnosis, management and control of T. solium (neuro)cysticercosis

A chart illustrating the search and exclusion process is presented in figure 1.

B. Prevalence of neurocysticercosis in low- and middle-income countries

Neurocysticercosis (NCC) represents the most common helminthic infection of the central nervous system (Del Brutto 2006) and is endemic in most countries of Latin America, Asia and sub-Saharan Africa.

1. Seroprevalence of *Taenia solium* cysticercosis in Latin America, Asia and sub-Saharan Africa

Community-based estimation of the prevalence of NCC is difficult as neuroimaging would have to be applied to a large population putting seemingly healthy people at risk of radiation, and therefore has been performed rarely so far (Fleury et al. 2003). In contrast, the prevalence of human *T. solium* cysticercosis in communities has been assessed, as this requires blood analysis only.

In Latin America, including Mexico, Peru, Ecuador, Guatemala and Bolivia the prevalence of *T. solium* cysticercosis as measured by antibody-ELISA and/or western blot was 3.7-12.2%, 5-24%, 10.4%, 10-17% and 22.4%, respectively (Flisser et al. 2003, Murrell 2005, Flisser & Gyorkos 2007, Flisser 2013).

In Asia, seroprevalence data are scarce, but reports are slowly emerging showing that *T. solium* cysticercosis presents a non-negligible public health problem. Most Asian studies demonstrate high seroprevalence rates using mainly antibody-ELISA and/or western blot (Rajshekhar et al. 2003). Indonesia is the best examined country when it comes to community-based data with seroprevalence rates of 2-13%, but has also shown estimates of as high as 50% in Irian Jaya (Simanjuntak et al. 1997, Subahar et al. 2001). Reports from China demonstrate prevalence rates of 2-6%, which may climb to 11% in some provinces. It was estimated that around three million people with cysticercosis live in China (Rajshekhar et al. 2003, Li et al. 2006).

In sub-Saharan Africa, community-based seroprevalence data on *T. solium* cysticercosis are emerging. In cysticercosis endemic areas of the Democratic Republic of Congo, Tanzania, Burkina Faso and Zambia the seroprevalence rates of *T. solium* cysticercosis as measured with an antigen-ELISA were 22%, 17%, 10% and 5.8%, respectively (Carabin et al. 2009, Kanobana et al. 2011, Mwape et al. 2012, Mwanjali et al. 2013).

2. Prevalence of neurocysticercosis in Latin America, Asia and sub-Saharan Africa

Reports on autopsy results mainly come from Latin America and show NCC in 5.9%, 2.8% and 2.4% of the examined cases in Peru, Mexico and Brazil, respectively (Murrell 2005). As autopsy results are not routinely available indirect hospital- or community-based approaches are used to get an impression about the prevalence of people with NCC in certain populations and often people suffering from epileptic seizures/epilepsy (PWE) or

other neurological disorders are included into these studies. Description of hospital-based NCC cases mainly through examination of PWE are numerous in Latin America and India and will not be reported here, instead the analysis will focus on community-based studies which are more representative.

A recent meta-analysis of epilepsy and NCC in Latin America revealed a median NCC proportion among PWE of 32.3% (Bruno et al. 2013). Community-based studies from Honduras, Peru, Bolivia and Ecuador determining the prevalence of NCC among people with active epilepsy based on serology and computed tomography (CT) showed the following results: Honduras 36.6% (Medina et al. 2005), Peru 35.1% (Moyano et al. 2014), Ecuador 33% (Del Brutto et al. 2005) and Bolivia 27.4% (Nicoletti et al. 2005). In a previous study from Peru, 54% of people with active epilepsy and 14% of individuals without seizures undergoing CT had NCC (Cruz et al. 1999). Another Peruvian study looked at CT-based NCC prevalence in PWE (active and inactive), which yielded 38.5%, and in people without epilepsy subdivided in those with positive and negative serology, showing 34% and 13.8%, respectively (Montano et al. 2005). A study from Guatemala that included PWE (not specified whether active or inactive) and people without epilepsy showed a CT-based NCC prevalence of 47% and 24%, respectively (Garcia-Noval et al. 1996). A study from Mexico that was designed to determine the seroprevalence rates of cysticercosis and taeniosis found 70% of people (7/10) with a history of seizures to have NCC lesions on CT scan (Schantz et al. 1994). The calculation of a morbidity estimate for Latin America yielded approximately 400 000 people suffering from symptomatic NCC (Bern et al. 1999).

In China (Sichuan Province), PWE (not specified whether active or inactive) within a community-based study that was designed to assess the prevalence of *T. solium* taeniosis/cysticercosis had a significantly higher *T. solium* cysticercosis seroprevalence (16.4%) compared to those without epilepsy (2.5%; Li et al. 2006). A study that was conducted in a south Indian community recruited people with active epilepsy and found that 34% had NCC based on CT and serology (Rajshekhar et al. 2006).

In sub-Saharan Africa prevalence rates of NCC in PWE are mainly based on serological results and are contributed from a few countries only with results of over 40% (Cameroon) and over 50% (Burundi), depending on the serological tests and the methodological approaches used (Mafojane et al. 2003, Nsengiyumva et al. 2003, Zoli et al. 2003a,b, Winkler et al. 2009a). High seroprevalence rates of NCC in PWE of whom a selected amount was confirmed with neuroimaging has also been reported from Burkina Faso and Rwanda (Millogo et al. 2012, Rottbeck et al 2013). 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 et al. 2010). More details on the prevalence of NCC (serology and neuroimaging) are available from South African studies (Mafojane et al. 2003), where one study found 50.6% of newly diagnosed PWE showing lesions of NCC on neuroimaging (Campbell et al. 1987). One neuroimaging based study in sub-Saharan Africa outside South Africa demonstrated definite NCC lesions on CT in 2.4% of PWE, lesions highly suggestive of NCC were present in 11.3% and lesions compatible with NCC were seen in 4.2%. The NCC lesions were significantly more common in PWE compared to the controls (Winkler et al. 2009c). Unpublished CT data from

over 1000 PWE from *T. solium* (neuro)cysticercosis endemic areas of three African countries (Tanzania, Uganda, Malawi) indicate prevalence rates from 2-3% in urban areas and from over 10% in rural areas (unpublished data AS Winkler). The highest prevalence rate of CT confirmed NCC in PWE of over 50% outside South Africa comes from a study in Zambia (personal communication J Blocher and S Gabriel).

The total of all people suffering from NCC, including symptomatic and asymptomatic cases, would be estimated somewhere between 2.56-8.30 million (Winkler 2013) based on the range of epilepsy prevalence data available, which is between 4-13/1000 for sub-Saharan Africa (Edwards et al. 2008, Winkler et al. 2009b), and the contribution of NCC to epilepsy in approximately 30% of cases (Ndimubanzi et al. 2010). To that number people with other neurological symptoms/signs due to NCC and those asymptomatic have been added (for more details refer to Winkler 2013). These figures would however come down if only areas confirmed with endemic *T. solium* (neuro)cysticercosis would be considered. Currently a population of NCC based epilepsy of 0.76-2.46 million and a population of symptomatic NCC of 0.95-3.08 million are estimated for sub-Saharan Africa (Winkler 2013). The latter numbers also include people with other neurological disorders resulting from NCC such as headaches, whereby the occurrence of headaches seems to be underestimated in NCC related symptoms/signs (personal experience AS Winkler), which suggests that the actual number of people suffering from symptomatic NCC may even be higher. Interestingly, a high proportion (18.4%) of psychiatric inpatients showed results attributable to NCC on western blotting in a Venezuelan community (Meza et al. 2005). Prevalence rates of 144/1000 were reported in rural settings in Ecuador (Cruz et al. 1999). The prevalence of NCC in patients with psychiatric disorders so far has not been explored on the African continent and may further increase total numbers of those suffering from symptomatic NCC. The same amount of people suffering from symptomatic NCC would also suffer from asymptomatic NCC, if assuming that 50% of all cases do not display symptoms. Latent NCC cases when harbouring *T. solium* cysticerci can become symptomatic at any time due to the natural course of disease or in the context of mass treatment received for different intestinal parasites (Ramos-Zuniga et al. 2013) or soil-transmitted helminths and schistosomiasis (Winkler 2013).

3. Prevalence of neurocysticercosis in special populations

A trend of higher ages in subjects with both epilepsy and NCC and late seizure onset as compared to other aetiologies was reported (Blocher et al. 2011). This has also been observed in endemic settings on the South American continent (Medina et al. 1990, Rigatti et al. 1999, Del Brutto et al. 2005, Nicoletti et al. 2005). However, some studies from Latin America, Asia and sub-Saharan Africa clearly demonstrate NCC in children and adolescents and therefore these age groups have to be considered when it comes to the planning of community-based studies. In addition, one also needs to be aware of the presence of NCC in children in the context of the potentially hazardous mass drug administration with albendazole and/or praziquantel for other helminthic parasites and the evaluation of differential diagnoses in childhood epilepsy (Cruz et al. 1999, Montano et al. 2005, Li et al. 2006, Nkouawa et al. 2010a). An interesting phenomenon is also the increasing prevalence

in Muslim countries previously not endemic to NCC. This may be due to increased international travel or immigrants from pork eating countries that are asymptomatic *T. solium* carriers with the potential of causing autochthonous cases of NCC without the need for infected pigs (Khan et al. 2011, Del Brutto 2013, Farahani et al. 2013).

C. Burden of neurocysticercosis

Burden of disease calculations usually rely on two main components: health adjusted life years and monetary impact. The former can be expressed as Quality Adjusted Life Years (QALYs) or Disability Adjusted Life Years (DALYs). QALYs usually require age/gender incidence rates of the disease, distribution and duration of symptoms/sequelae and death rates. DALYs rely on the same epidemiological information, but in addition require disability weights associated with each symptom, whether treated or not. For monetary burden calculation similar epidemiological information to that of QALYs and DALYs is needed. If incidence rates are not at hand, prevalence rates can be used as well. In addition, data on disease management costs (diagnosis and treatment) considering various symptoms such as epilepsy, headache, hydrocephalus, and psychiatric symptoms, amongst others, as well as productivity losses are required. The monetary burden combines agricultural and human costs (personal communication HC Carabin; the above background information is based on a presentation given by HC Carabin at the Cystinet-Africa Meeting held in Munich, June 2014). To date, burden data has only been collected rather patchily throughout LMIC. The information available will be summarized within the next paragraphs.

Quality of life assessment in people with NCC was performed in three different studies in Latin America using different comparison groups and different quality of life research tools. In Brazil, quality of life (measured by the Functional Assessment of Cancer Therapy Quality of Life Measurement System (FACT-HN version IV)) between PWE or headache and NCC was compared with PWE or headache but without NCC. In general, quality of life was reduced in all four groups, but was lowest in people with headache without NCC, but there was no significant difference between people with and those without NCC (De Almeida et al. 2011).

In Peru, quality of life (measured by the SF-36) was assessed in 14 people with new onset seizures and NCC compared to seven PWE without NCC and 14 healthy matched controls at baseline and after six months of follow-up. The seizures of all PWE were controlled by anti-epileptic drugs (AEDs) and people with NCC received anti-parasitic treatment. PWE and NCC had a lower social functioning score compared to healthy controls at baseline but not at follow-up after six months. This longitudinal effect was not observed for PWE without NCC (Wallin et al. 2012).

In Mexico, quality of life (measured by SF-12 version II) was determined in 220 people with NCC and a variety of neurological symptoms/signs compared to 220 matched controls. People with NCC had lower scores in all domains of the SF-12 compared to their controls (Bhattarai et al. 2011). The same group from Mexico also estimated the DALYs associated with NCC arriving at 0.25 DALYs per 1000 people from Mexico including DALYs lost due to epilepsy and those due to headache (Bhattarai et al. 2012).

A study from Peru assessed the treatment costs and productivity losses related to NCC in 49 affected individuals and found that diagnostic and treatment related costs consume about 58% and 16% of the annual minimum wage salary in the first and second year of case

management, respectively. The total costs related to NCC amounted to 996 $ per person over two years (Rajkotia et al. 2007).

In India, the costs of 59 patients with new onset seizures in the context of solitary cysticercus granuloma were calculated from first time presentation of the patient until resolution of the lesion on CT scan. The total costs yielded 175 $ per patient corresponding to 50.9% of the per capita gross national product (Murthy & Rajshekhar 2007).

Considering the economic implications of *T. solium* (neuro)cysticercosis in sub-Saharan Africa, a comprehensive estimate of the monetary burden of cysticercosis in the *T. solium* (neuro)cysticercosis hyperendemic Eastern Cape Province of South Africa was calculated. There were an estimated 34 662 people with NCC associated epilepsy in the Eastern Cape Province in 2004. The monetary burden of *T. solium* (neuro)cysticercosis per capita was between US$ 2.6 and US$ 4.8, which is substantial when compared to annual health expenditures of US$ 41.3 per capita for people living in poor dwellings in that province. The overall monetary burden was calculated to vary from US$ 18.6 million to US$ 34.2 million depending on the method used to estimate productivity losses. The epilepsy prevalence of the Eastern Cape Province, the proportion of PWE seeking medical care and the proportion of epilepsy cases attributable to NCC as well as the proportion of work time lost due to NCC were found to have the most influence on the estimated monetary burden (Carabin et al. 2006). The total societal cost due to *T. solium* (neuro)cysticercosis in the main pig-breeding region of West Cameroon (West, Southwest and Northwest Provinces) was also recently estimated (Praet et al. 2009). Based on an epilepsy prevalence of 3.6%, the number of people with NCC associated epilepsy was estimated at 50 326, representing 1.0% of the local population, whereas the number of pigs diagnosed with cysticercosis was estimated at 15 961 (based on lingual examination results), which corresponds to 5.6% of the local pig population. The total annual costs due to *T. solium* (neuro)cysticercosis in West Cameroon were estimated at € 10.3 million, of which 4.7% were due to losses in pig production and 95.3% to direct and indirect losses caused by human *T. solium* (neuro)cysticercosis. The monetary burden per case of human NCC amounted to € 194 and the average number of DALYs lost was 9.0 per 1000 people per year which was higher than estimates for some other neglected tropical diseases (Praet et al. 2009, Winkler 2013).

DALYs for NCC have also been calculated within the systematic analysis for the Global Burden of Disease study and were estimated at 7 DALYs per 100 000 people globally, which put them into the lower range compared with other neglected tropical disease (Murray et al. 2012). This may be an underestimation and methodological issues have been raised with the approach of calculation.

D. Pathology of neurocysticercosis and its associated clinical characteristics

NCC can be found anywhere in the central nervous system (brain and spinal cord) and multiple lesions in the same individual are common and are frequently observed in different pathological stages (Nash et al. 2005, Garcia et al. 2014a). A true predilection for certain brain regions has not been ascertained, although some authors claim that the cortex and the basal ganglia are most frequently affected (Nash et al. 2005), but there is good evidence that NCC lesions are located more in supra- than infratentorial regions of the brain. 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 host immune response and the genotype of the parasite, or it can also be clinically asymptomatic (Winkler 2013). Post-mortem studies have shown that in up to 50% of people with NCC the cerebral lesions were asymptomatic (De Almeida & Torres 2011). There may be single or multiple cysticerci in the brain (intraparenchymal NCC, approximately 80% as opposed to extraparenchymal NCC) and, in extreme cases, encephalitis may ensue. Single enhancing (intraparenchymal) lesions representing solitary cerebral cysticercus granuloma (SCG) seem to be a separate entity that has been described mainly in patients from the Indian subcontinent (Kishore & Misra 2007, Garg 2008a, Chaurasia et al. 2010, Winkler 2013).

The host immune response against the parasite is yet another important determining factor in the pathology/pathophysiology of NCC and has also implications for serodiagnostics (Fleury et al. 2010, Verma et al. 2011a, Garcia & Cysticercosis Working Group in Peru 2012, Saenz et al. 2012, Sciutto et al. 2013, Bobes et al. 2014). Clinical studies and a collection of case reports from all over the world highlight that there is a tendency to increased inflammatory reaction in females (Rangel et al. 1987, Fleury et al. 2004).

1. Intraparenchymal neurocysticercosis

Intraparenchymal NCC is usually associated with a more benign prognosis compared to extraparenchymal presentations (Nash et al. 2005, Winkler et al. 2009a, Nash & Garcia 2011, Takayanagui et al. 2011, Winkler 2012, 2013). Lesions may remain asymptomatic, and the exact numbers vary between 50-80% of those affected (Sanchez et al. 1999, De Almeida & Torres 2011).

A systematic review on the clinical manifestations in people with NCC showed that the majority of symptomatic adult cases (78.9%) had epileptic seizures (Carabin et al. 2011). In their attributed frequency epileptic seizures were followed by headaches in 27.7% of people (Carabin et al. 2011), although this may be an underestimation. Headache in people with NCC can be acute or chronic, and presents as tension-type or migraine-like episodes (Cruz et al. 1999, Mishra 2007). Headache can also indicate raised intracranial pressure (Serpa et al. 2006). Furthermore, adults with NCC also present with focal neurological signs (11.8%), signs of intracranial hypertension (16.3%), meningitic symptoms/signs (5.6%), gait abnormalities (5.6%) and altered mental state/psychiatric symptoms (28.1%), among others (Carabin et al. 2011, Garcia et al. 2014a, Leon et al. 2005).

Epileptic seizures - may they be simple/complex partial or secondary generalized - are widely reported to be the most common presenting symptom/sign in people with NCC, occurring in 70-90% of patients (Del Brutto et al. 1992, Pal et al. 2000, Garcia et al. 2003, Garcia et al. 2014a, Leon et al. 2015) and the leading symptom that makes patients or their caregivers seek medical attention (Bhattarai et al. 2012), although other rare focal neurological signs/syndromes have also been described (Singh et al. 2003, Jha & Kumar 2007, Singhi et al. 2008, Mesraoua et al. 2012, Prasad et al. 2012).

Epileptic seizures mainly occur in two settings, either as acute symptomatic seizures in the context of active cysts or granuloma formation or as "chronic epilepsy". Epileptic seizures of the acute symptomatic type are thought to be caused by parenchymal irritation because of active inflammation occurring with the death of the cysticercus and seizures of the "chronic epilepsy" type have been postulated to be due to gliosis (Nash et al. 2004) or sporadic perilesional oedema (Fujita et al. 2013) associated with end-stage calcified lesions (Nash et al. 2005, Nash et al. 2014). Clinically it is most important to differentiate these two types of seizures as initiation and withdrawal of treatment differ (see below and **figures 2** and **3**). Of late there is increasing evidence that NCC, in particular its calcified stage, may be associated with hippocampal sclerosis, although possible pathomechanisms are still being speculated on (Del Brutto et al. 2014).

Epileptic seizures may be the only neurological sign, especially in people with solitary cerebral cysticercus granuloma from India that bears a good prognosis compared to infection with multiple cysticerci (Singh et al. 2001). Patients mainly present with partial onset seizure with or without generalization and have a high risk of seizure recurrence during resolution of the granuloma despite being on AEDs (13-48%), although most patients respond well to AEDs after resolution of the granuloma (seizure recurrence 15%; Singh et al. 2001, Rajshekhar & Jeyaseelan 2004, Singh et al. 2010). In general, the majority of solitary cerebral cysticercus granuloma seem to resolve naturally within one year which has implications for treatment with anthelmintics as discussed below (Rajshekhar 2001). Contrary to India, multiple lesions mainly of the intraparenchymal type seem to prevail in people with NCC from Latin America, sub-Saharan Africa and other Asian countries, although scientific publications on NCC related neuroimaging from sub-Saharan Africa and Asian countries other than India are rare (Winkler 2012, 2013).

2. Extraparenchymal neurocysticercosis

In extraparenchymal NCC, cysticerci may lodge in the ventricular system or subarachnoid space and a potentially life-threatening acute intracranial hypertension may develop. Cerebrospinal fluid (CSF) flow obstruction most frequently occurs when cysts lodge in the fourth ventricle and progressively causes hydrocephalus. The latter may also be caused by subarachnoid NCC mainly of the basal cistern type due to cysticercotic meningitis. Associated signs of brainstem dysfunction or rarely Parkinson Syndrome may develop with ventricular and subarachnoid NCC (Bickerstaff et al. 1952, Nash et al. 2005, Nash & Garcia 2011, Takayanagui et al. 2011, Del Brutto 2012a, Winkler 2012, 2013, Garcia et al. 2014a). Nash & Garcia in their review (2011) subdivided extraparenchymal NCC into four sub-groups,

consisting of ventricular NCC, subarachnoid NCC of the brain convexity, subarachnoid NCC of the Sylvian fissure and basal subarachnoid NCC owing to different locations, pathologies and ensuing clinical characteristics.

Subarachnoid neurocysticercosis of the brain convexity and the Sylvian fissure

Cysts in the subarachnoid space may invade the Sylvian fissures or other sulci or be located at the brain convexity. In the latter location, cysts may grow into the parenchyma to so-called giant cysts reaching several centimetres in diameter (in comparison, a normal intraparenchymal cysticercus should not measure more than 20 millimetres in diameter (Nash et al. 2005)) and behave like mass-occupying lesions (Nash & Garcia 2011). Giant cysts are also reported to occur more frequently in immunocompromised subjects (Soto Hernandez et al. 1996). They may cause intracranial hypertension, focal neurological signs or epileptic seizures and may be difficult to differentiate from intraparenchymal cysts (Del Brutto et al. 1993, Colli et al. 2002a, Proano et al. 2001, Umredkar et al. 2009). Giant cysts usually respond well to medical treatment compared to subarachnoid cysts in the basal cisterns, although treatment may have to be extended (Proano et al. 2001). Cysts in the Sylvian fissure are less benign and may present as “racemose cysts” (see below) as well as giant cysts with mass effect and also involve adjacent brain structures such as the middle cerebral artery causing infarct and haemorrhage (Nash et al. 2005, Nash & Garcia 2011; see below and **figure 3**).

Basal subarachnoid neurocysticercosis

Subarachnoid cysts invading the basal cisterns may lead to a clinical form that is associated with an intense inflammatory reaction. Fibrosis and progressive thickening of the leptomeninges (chronic meningitis) may develop. Arachnoiditis, which can lead to communicating hydrocephalus and vasculitis, can also result. In addition, cysts may directly compress arterial vessels at the base of the brain and cause cerebral infarcts. Furthermore, various neurological signs may point to nerve entrapment and chiasmatic syndrome may develop (Nash et al. 2005, Fleury et al. 2011, Nash & Garcia 2011, Takayanagui et al. 2011, Winkler et al. 2009a, Winkler 2012, 2013). The basal subarachnoid NCC type often presents as “racemose NCC”, growing by abnormal proliferation of membranes and resembling a “bunch of grapes” on various neuroimaging modalities (Cardenas et al. 2010, Agapejev 2011, Motsepe & Ackerman 2012). This variant occasionally also occurs with the other subarachnoid forms. Mortality rates of over 20% have been reported for “racemose NCC” (Pittella 1997). As illustrated by case reports from rural settings in Asia and Latin America there may be extremely fulminant progression (Martinez et al. 1995, Aditya et al. 2004, Jarupant et al. 2004, Takayanagui & Odashima 2006, Rocha et al. 2008, Diehl Rodriquez et al. 2012, Motsepe & Ackerman 2012). Low accessibility to adequate health care likely exacerbates this already difficult-to-treat form of NCC (see below and **figure 3**).

Ventricular neurocysticercosis

Ventricular NCC may present with signs of increased intracranial pressure (acute and chronic) caused by the cyst itself or by inflammation leading to ependymitis. Patients may present with acute or chronic signs of raised intracranial pressure or may suffer from chronic cognitive decline and psychiatric dysfunction. In some cases brainstem impingement, especially when the cyst is located in the fourth ventricle, may lead to neurological signs. Some cysts may grow abnormally large or even present as "racemose NCC". Endoscopic cyst removal and/or CSF shunting represent the treatment of choice (see below; **figure 3**). CSF shunting may also be necessary for hydrocephalus developing from basal subarachnoid NCC (Nash et al. 2005, Nash & Garcia 2011, Takayanagui et al. 2011, Del Brutto 2012a, Winkler 2012, 2013). Mortality rates as high as 50% mainly within two years after CSF shunting were reported, if hydrocephalus secondary to cysticercotic meningitis or other causes for CSF flow obstruction were present (Sotelo & Marin 1987, Colli et al. 2002a). Hence, ventricular and basal cisternal locations of cysts seem to be the most malignant forms of NCC.

3. Other forms of neurocysticercosis

Additionally, intracranial hypertension may occur in patients with cysticercal encephalitis, which relates to massive parenchymal infection inducing an intense immune response with diffuse brain oedema (Rangel et al. 1987, Takayanagui et al. 2011, Winkler 2013). Spinal cord involvement is rare and accounts for 1-5% of all NCC cases. Cases have been reported from Latin America (Brazil, Mexico, Peru), South Africa and Asia (Thailand, Korea and mainly India; (Martinez et al. 1995, Colli et al. 2002b, Jarupant et al. 2004, Ahmad, & Sharma 2007, Agrawal et al. 2008; Mohapatra et al. 2008, Chhiber et al. 2009, Shin & Shin 2009, Choi et al. 2010, Callacondo et al. 2012, Motsepe & Ackerman 2012, Shin et al. 2012).

A recent publication from Peru reports the association of subarachnoid NCC and spinal cord disease with involvement of the spinal subarachnoid space in 60% of patients. The authors conclude that more rigorous performance of magnetic resonance imaging of the spine in people with subarachnoid NCC is needed (Callacondo et al. 2012).

E. Paediatric considerations

Taken together our search terms yielded a clear predominance of information on NCC in children and adolescents from India, Peru, Brazil and Mexico (Cruz et al. 1999, Morales et al. 2000, Ferreira et al. 2001, Talukdar et al. 2002, Montano et al. 2005, Antoniuk et al. 2006, Kumar et al. 2006, Mandal et al. 2006, Rajshekhar et al. 2006, Saenz et al. 2006), but there are also reports from China (Li et al. 2006) and South Africa (Swingler et al. 2006). In children with NCC from a series of studies conducted in Latin America, mainly single colloidal parenchymal cysticerci were seen, but heavy infection was also described. Calcifications were seen less often and the development of hydrocephalus and basal subarachnoid disease seemed to be rare (Morales et al. 2000, Antoniuk et al. 2006, Saenz et al. 2006, Garcia et al. 2014a). The most frequent clinical presentation in children is epileptic seizures followed by headaches and signs of elevated intracranial pressures (Singhi et al. 2000). The only major difference compared to adults is that children portray relatively little psychiatric symptoms (Forlenza et al. 1997, Carabin et al. 2011). Clinical, radiological and inflammatory differences between NCC in children and adults have to be considered when deciding on treatment options (Saenz et al. 2006).

Controlled trials and meta-analyses have yielded conflicting results on the role of anthelmintic drugs in treating paediatric NCC cases worldwide, especially since there have been reports on spontaneous resolution of cysts (Garg 2008a,b). Moreover, single colloidal parenchymal cysticerci that seem to prevail in children are related to a better prognosis. The beneficial role of anthelmintics is to be interpreted with caution considering efficacy of symptomatic therapy alone (Ruiz-Garcia et al. 1997, Baranwal et al. 1998, Singhi et al. 2000, Talukdar et al. 2002).

Antiepileptic management in children with NCC does not seem to be straight forward and has been associated with longer AED treatment, more seizures after AED introduction as well as trial of more AEDs and at maximal dose when compared to children with benign partial epilepsies. Therapy with multiple AEDs was necessary in 20% of children with NCC. The recurrence rate of seizures in children with NCC was 54.4% and this was not significantly associated with number of lesions and disease activity seen on CT scans or the presence of EEG abnormalities (Ferreira et al. 2001).

F. Considerations in people with HIV/AIDS

Most NCC endemic areas are also endemic for HIV/AIDS and interaction of the two diseases, as described for HIV/AIDS and malaria and HIV/AIDS and tuberculosis, would seem plausible. Indeed, acceleration of the clinical course of HIV/AIDS in patients co-infected with *T. solium* cysticerci has been suggested based on the manipulation of the immune system by the parasite (Foyaca-Sibat & Ibanez-Valdes 2003a,b). An adverse effect of co-infection with other helminths such as soil-transmitted helminths, *Onchocerca volvulus* and *Schistosoma* spp., amongst others, on HIV/AIDS progression has also been described and deworming of HIV-positive patients has been suggested in order to delay HIV/AIDS progression. In a meta-analysis of three randomized-controlled trials deworming people with HIV/AIDS showed a clear benefit in attenuating or reducing plasma viral load and/or increasing CD4 counts. Given that these studies evaluated different helminth species and different interventions, the authors conclude that further trials are warranted to evaluate species-specific effects and to document long-term clinical outcomes following deworming (Walson et al. 2010). Also, evaluation of the effect of chronic helminth co-infection in people with HIV/AIDS that in addition suffer from NCC has not been undertaken so far, but may offer important clues as to the course of HIV/AIDS itself or the associated NCC, or both.

When changing perspective and looking at the course of NCC in people with HIV/AIDS results are rather conflicting. In South Africa, NCC has been described as one of the most important focal brain lesion in people with HIV/AIDS with neurological signs depending on the location of the lesion. Interestingly intraventricular NCC seems to be especially common in patients with HIV/AIDS from South Africa presenting with epileptic seizures and signs of increased intracranial pressure, among others. Treatment with ventriculo-peritoneal shunts carries a bleak prognosis, whereas anthelmintics together with steroids show a better outcome in these patients. These reports from South Africa are fairly worrying and repeated regular treatment with short courses of praziquantel together with steroids have been advocated for HIV/AIDS patients from highly endemic areas to reduce the rate of re-infection which may accelerate the course of disease, if left untreated (Foyaca-Sibat & Ibanez-Valdes 2003a). However, to date no systematic studies on co-infection with *T. solium* cysticerci in people with HIV/AIDS have been conducted in sub-Saharan Africa, but observations from South Africa indicate that co-infection is high (Foyaca-Sibat & Ibanez-Valdes 2003b).

Conversely, a study from northern Tanzania that examined the prevalence of NCC in people with HIV/AIDS and their age, gender and village matched controls based on *T. solium* cysticercosis serology (EITB and rT24 western blot as well as antigen-ELISA) and CT scan results showed no difference with regards to the prevalence of *T. solium* (neuro)cysticercosis in the two study populations (unpublished results V Schmidt and AS Winkler). The results from Tanzania are supported by those from a Mexican autopsy study showing that NCC was less common in people with HIV/AIDS (1.1%) compared to control autopsies (2.4%; Jessurun et al. 1992).

As host cellular immune response may play a role in restricting the growth of the parasite, a higher incidence of racemose and giant cyst forms of NCC has been associated with HIV

seropositivity (Soto Hernandez et al. 1996). However, one should not essentially relate co-infection with a more malignant course of NCC, since there have been reports of relatively benign course and satisfactory response to therapy (Okome-Nkoumou et al. 2010, Motsepe & Ackerman 2012). A review including 27 HIV/AIDS cases with NCC mainly from Latin America and sub-Saharan Africa has shown that the most frequent clinical presentation was that of multiple parenchymal active lesions (viable cysts and enhancing lesions). More than half of the patients had a positive *T. solium* cysticercosis serology and 85% of them responded well to anthelmintic therapy (with and without concomitant steroids), which is similar to that reported from the general population (Garcia & Del Brutto 2005, Serpa et al. 2007). Case fatality rate (12%) was high, which may be explained by other HIV/AIDS associated infections in addition to that of NCC (Serpa et al. 2007).

Studies from India and Mexico have shown that seroprevalence of *T. solium* cysticercosis in patients with HIV/AIDS is lower than in the non-HIV/AIDS population, which may point to an impaired immunoreactivity with unreliable detection of *T. solium* cysticercosis antibodies (Jessurun et al. 1992, Parija & Gireesh 2009). The fact of unreliable *T. solium* cysticercosis serodiagnosis could present a substantial problem in the HIV/AIDS population with focal neurological signs in whom tuberculous meningitis/tuberculoma and toxoplasmosis, two diseases with different therapeutic approaches, represent the most important differential diagnoses (Lattuada et al. 2007, Winkler 2013). Besides altered serological findings mild to absent enhancement to iodinated or gadolinium contrast was also observed in NCC subjects. Some authors speculated that there may also be altered imaging findings in co-infected subjects and contributed the weak contrast enhancement among their patients with NCC to a weakened immune response or impaired cellular immunity (Soto Hernandez et al. 1996). However, large-scale studies assessing this phenomenon are missing.

Prasad et al. (2006) treated three people with HIV/AIDS from Latin America and recommend including the CD4 count in the decision whether to start therapy for NCC or to consider other diagnoses. In the context of HIV infection patients with a higher CD4 count were more likely to have symptomatic NCC that requires treatment (Prasad et al. 2006). In addition, people with HIV/AIDS with asymptomatic NCC may develop an immune reconstitution inflammatory syndrome when starting on highly active antiretroviral therapy that may convert asymptomatic to symptomatic NCC with acute neurological symptoms/signs (Serpa et al. 2007).

G. Diagnostic criteria for neurocysticercosis

1. Laboratory diagnostics

A variety of serological tests for *T. solium* cysticercosis (in-house and commercial) including detection methods for specific antibodies (Ab), mostly IgG, and for circulating parasite antigen (Ag) in serum and CSF are available (Dorny et al. 2003, Winkler et al. 2009a, 2012, 2013, Rodriguez et al. 2012, Garcia et al. 2014a). To date the most specific test for Ab detection is the enzyme-linked immunoelectrotransfer blot (LLGP-EITB), an immunoblot of seven cysticercus glycoproteins, purified by lentin-lectin chromatography, with a specificity approaching 100% and a sensitivity varying from 70 to 90 % depending on the number of cysts present. It is frequently falsely negative in patients with a single intracranial cysticercus (including the Indian variant of solitary cerebral cysticercus granuloma) or in those with calcified cysticerci (Tsang et al. 1989, Nash et al. 2005). Ab positivity not necessarily indicates active disease and Ab are also present in people from *T. solium* endemic areas without obvious disease (Garcia et al. 1994). Also, there are conflicting results as to the performance in CSF and sensitivity and specificity of Ab detection in CSF have been reported to be lower when compared to serum (Nash et al. 2005).

Since the preparation of purified antigens relies on the availability of helminthic material, recombinant (e.g. rT24 and rGP50) and synthetic (e.g. sTsRs1) Ag have been developed from the LLGP fraction and offer new perspectives (Hancock et al. 2006, Noh et al. 2014). The recombinant Ag rT24 for *T. solium* cysticercosis has recently been combined with the recombinant Ag rES33 for *T. solium* taeniosis in a lateral flow device in order to enable affordable, reliable and easy-to-perform point-of-care case detection or confirmation of *T. solium* taeniosis/cysticercosis (Handali et al. 2010).

For the differentiation between active and inactive NCC and the monitoring of anti-parasitic therapy, monoclonal Ab (MoAb)-based tests directed at defined parasite Ag are commonly used and show variable sensitivities according to number, stage and location of lesion (best performance with subarachnoid cysts in the basal cisterns and with ventricular cysts), but demonstrate high specificity (Dorny et al. 2003, 2004, Nash et al. 2005, Michelet et al. 2011, Fleury et al. 2013). Although the performance of Ag-ELISA in serum has its value, especially when positive, the sensitivity of the Ag-ELISA is significantly higher in CSF with falsely negative results mainly due to single intracranial cysticercus (Correa et al. 2002, Michelet et al. 2011). Most of the Ag-ELISA assays are still in-house tests, although the B158/B60-Ag-ELISA protocol (Dorny et al. 2003, 2004) has now been commercialized.

Multiplex analysis represents a further step ahead and can be realized through Luminex Screening and Performance Assays for simultaneous detection of Ab, Ag and DNA and quantification of multiple target analytes. Magnetic beads technology is used in Luminex MAGPIX® and requires small sample volumes, is cost-effective and allows researchers to collect more data in less time (Zhang et al. 2014).

Furthermore, DNA-based methods for diagnosis of *T. solium* cysticercosis in CSF have been developed. Preliminary results indicate variable levels of sensitivity but close to 100% specificity (Almeida et al. 2006, Hernandez et al. 2008, Michelet et al. 2011). More recently, a quantitative PCR targeting the cyclooxygenase-2 gene was designed to detect DNA in CSF (Jambou et al. unpublished and mentioned in Rasamoelina-Andriamanivo et al. 2013). However, standard PCR requires sophisticated equipment including an energy intensive thermal cycler for heating and cooling cycles during the amplification of DNA and therefore is not suitable for field studies. Techniques promoting amplification of DNA in a simple heating block or water bath facilitates their application in resource-poor settings and include the loop-mediated isothermal amplification (LAMP) PCR (Nkouawa et al. 2010b), amongst others. The combination with a lateral flow dipstick would make the LAMP especially field friendly (Khunthong et al. 2013). Point-of-care diagnostics clearly represent the challenge of the future and should be designed for use in resource-poor settings without much equipment at hand as a bedside test e.g. for dispensaries that very often represent the first medical contact for patients. This refers to molecular as well immunological diagnostic tests, both often meeting with technical difficulties during development for point-of-care use (Rasamoelina-Andriamanivo et al. 2013).

CSF analysis in NCC may also show signs of parasitic disease, especially in intraventricular/subarachnoid forms of NCC, including slightly elevated cell count (usually not exceeding 100 cells/µl, demonstrating mononuclear pleocytosis and eosinophilia) and increased protein levels in the range of 50 to 300 mg/dl. Low levels of glucose are usual in case of inflammatory CSF (Sotelo & Del Brutto 2002). The cellularity in CSF seems to correlate with levels of Ab and Ag and *T. solium* PCR-positive as well as EITB-positive samples had a higher cell count than those negative (Michelet et al. 2011).

In cases with the subtype of a solitary cerebral cysticercus granuloma Ab and Ag immunodiagnostic tests in serum and CSF show a low sensitivity and therefore should only be used in combination with neuroimaging as negative results do not preclude the presence of the disease (Rajshekhar 1993, Rajshekhar & Oommen 1997, Singh et al. 1999).

2. Neuroimaging

Neuroimaging is the method of choice when it comes to diagnosis of NCC, the determination of need for medical or surgical treatment and the assessment of effectiveness of interventions (Nash et al. 2005, Garcia et al. 2014a). It includes cranial CT and/or magnetic resonance imaging (MRI), which should be combined with serological tests. In neuroimaging, only a lesion showing the scolex (= head of the parasite) is classified as a definite NCC lesion and considered pathognomonic (Pal et al. 2000, Del Brutto et al. 2001, Del Brutto 2005, Serpa et al. 2006). **Active** NCC is defined as the presence of any cystic lesions (with or without scolex) or lesions with ring enhancement. Nodular enhancing lesions are often termed **transitional**. In contrast, parenchymal calcifications are classified as **inactive** (Nash et al. 2004, 2006). Lesions highly suggestive of NCC are of the active, transitional and inactive type. The latter should only be included if calcifications are solid, dense and multiple

and located supratentorially measuring 1-10 millimetres in diameter in the absence of any other disease that may explain the calcifications. In addition, cranial lesions in different evolutionary stages further support the diagnosis of NCC (Nash et al. 2005).

In resource-poor settings mainly CT is used, if available. MRI enables clinicians to perform a more precise disease staging and case follow-up. It also shows higher sensitivity in detection of obscure lesions, such as the recognition of perilesional oedema or gliosis and degenerative changes of the parasite, as well as small cysts that may be located in the brain stem, cerebellum and cerebral ventricles. Moreover, racemose vesicles at the level of the posterior fossae and basal cisterns can often be visualized in acceptable quality using MRI (Martinez et al. 1995, Pradhan et al. 2000, De Souza et al. 2010, 2011, Takayanagui et al. 2011, Garcia et al. 2014a). CT occurs to be more sensitive in the detection of calcifications (20%-60% of cysts will eventually calcify (Nash et al. 2005)), which seem to be directly associated with seizure generation/activity, either through perilesional oedema or gliosis, and plays a critical role in the decision making in how long to treat with AEDs (Pradhan et al. 2000, Nash et al. 2004, Nash et al. 2005, Singh et al. 2010, Rathore et al. 2013, Garcia et al. 2014a).

As neuroimaging is often unavailable in sub-Saharan Africa, serological results are important for guidance as to which patient should be referred to an imaging centre. Ideally, the diagnosis of NCC should be based on both neuroimaging and immunodiagnostic/molecular biological test results. Together with clinical and epidemiological criteria they have been summarized in the diagnostic criteria for NCC suggested by Del Brutto et al. Based on diagnostic strengths these diagnostic criteria are further divided into “absolute”, “major”, “minor” and “epidemiological” which, in turn, are combined to degrees of diagnostic certainty yielding a “definitive” or a “probable” diagnosis of NCC (Del Brutto et al. 1996, 2001, Del Brutto 2005, Nash et al. 2005, Del Brutto 2012b, Garcia et al. 2014a; for more details refer to **table 1**). However, these diagnostic criteria have their obvious limitations in resource-poor settings and Gabriel et al. (2012) state that in areas where neuroimaging is absent, NCC diagnosis according to the existing criteria is problematic. They assume that antigen detection can be of added value for diagnosing and treating NCC and consequently recommend a revision of the "Del Brutto diagnostic criteria" for use in resource-poor areas (Gabriel et al. 2012).

Of note, the Del Brutto diagnostic criteria do not apply to solitary cerebral cysticercus granuloma for which diagnostic criteria have been developed separately including clinical and CT criteria all of which have to be fulfilled to make a diagnosis of solitary cerebral cysticercus granuloma (Rajshekhar & Chandy 1997, Nash et al. 2005).

3. Neurological/psychiatric examination and electroencephalography

The medical history of people presenting with neurological signs/symptoms to health services in *T. solium* (neuro)cysticercosis endemic areas may give indirect evidence of an underlying cause of NCC. In this context the acquirement of information regarding the

occurrence of subcutaneous nodules or taeniosis in the patient or other family members, reports of an unusual high prevalence of epilepsy in the household of the patient or in the neighbourhood, the presence of free-roaming pigs and the consumption of pork, amongst others, may be useful (Nash et al. 2005).

Focal signs have been described in a multitude of case reports (Singh et al. 2003, Jha & Kumar 2007, Singhi et al. 2008, Takayanagui et al. 2011, Mesraoua et al. 2012, Prasad et al. 2012) from LMIC, but NCC more frequently presents with epileptic seizures and/or headache and signs of increased intracranial pressure or may be clinically silent. Routine neurological examination represents no useful tool in the ultimate diagnosis of NCC. However, it is indispensable in the follow-up of patients to early recognize exacerbation of NCC related neurological symptoms/signs, which may be associated with disease progression or oedema due to anthelmintic treatment (Del Brutto 1995, Morales et al. 2000).

In an exiguous amount of case reports and reviews - predominantly from India, Brazil, Mexico and Venezuela (Rajaonarison et al. 2001, Mishra & Swain 2004, Meza et al. 2005, Verma et al. 2011b, Shah & Chakrabarti 2013, Bianchin et al. 2013) - the implication of (neuro)psychiatric symptomatology in particular psychosis (Mahajan et al. 2004, Verma & Kumar 2013), mood disorders (Mishra & Swain 2004, Onoe 2005, Chatterjee & Ghosh 2013), or dementia (Ramirez-Bermudez et al. 2005, Ciampi de Andrade et al. 2010, Jha & Ansari 2010) has been emphasized as possible presenting feature, symptoms/signs of disease progression as well as adverse event related to treatment and has to be actively sought for in patients with NCC. Overall it seems that NCC still represents a neglected organic cause of mental illness and further comparative studies are highly warranted to optimize case management.

Complementary diagnostic tools like electroencephalography (EEG) have relatively wide application even in the rural settings of LMIC, since they are more readily available compared to imaging modalities. Needless to say that EEG has the advantage of its lower cost. Its use appears in literature from many of the endemic regions (Del Brutto et al. 1992). EEG may detect generalized or focal slowing of electrical activity suggesting brain pathology or may reveal epileptiform activities. It will however not diagnose NCC for which neuroimaging is mandatory. Overall, in resource-poor settings EEG finds its most frequent use in the follow-up of patients to assess seizure recurrence, to judge the efficacy of AEDs and to decide if and when the latter can be safely discontinued (Pradhan et al. 2003, Verma & Misra 2006, Lossius et al. 2004, Specchio et al. 2008, Sharma et al. 2013). Moreover, the informative value of EEG may be more sophisticated as demonstrated by a study from India, where both ictal and interictal as well as intracranial EEG recordings during surgery for NCC have been performed (Rathore et al. 2013). This group elaborated on the link between AED-resistant epilepsy and calcified neurocysticercal lesions. Calcifications seem to be correlated with unilateral hippocampal sclerosis in the studied population. Perilesional gliosis uncovered by neuroimaging and/or histopathology may contribute to epileptogenicity of calcified lesions. This is suggested by EEG abnormalities detected by electrodes approaching the respective territories on extracranial or intracranial EEG. The authors state that resection

of both calcifications as well as sclerotic hippocampal tissue favours a more likely seizure-free outcome (Rathore et al. 2013).

H. Pharmacotherapy and surgical approaches to treatment of neurocysticercosis

Currently, there are no standard treatment guidelines for NCC, although suggestions have been made (Garcia et al. 2002, 2011a, Nash et al. 2005, 2006, Serpa et al. 2006, Winkler et al. 2009a, Singh et al. 2010, Nash & Garcia 2011, Takayanagui et al. 2011, Gonzales & Garcia 2012, Winkler 2012, 2013, Garcia et al. 2014a). Therefore treatment has to be tailored to the individual case. The goal of anthelmintic - more precisely anticysticercal - therapy can be defined as the destruction of cysts (between 60-85% of parenchymal brain cysticerci are cleared after standard courses of treatment (Nash et al. 2005, Garcia et al. 2014a)) with concurrent control of the host immune response using anti-inflammatory medication such as corticosteroids. This strategy has been used worldwide and prevents the prolonged inflammation related to cyst degeneration. It therefore improves clinical evolution and outcome (Takayanagui et al. 2011).

Only active disease needs treatment with anthelmintic drugs and/or steroids. Dosages and the duration of treatment can be highly variable and mainly depend on the number, size, location and developmental stage of the cysts, their surrounding inflammatory oedema, clinical symptoms or signs (their acuteness and severity) as well as potential risk factors of treatment. On the one hand, care needs to be taken not to "over-treat" as the administration of anthelmintic drugs can cause cerebral oedema and worsen symptoms and, on the other hand, one has to be prepared to extend treatment for some months as the penetration of drugs into cysts can be poor. The follow-up of patients has to be ensured, ideally with neuroimaging, but this may not be available in resource-poor settings (Nash et al. 2006, Serpa et al. 2006, Nash & Garcia 2011).

Although treatment has to be flexible, there are some rules of thumb that should be followed. The administration of anthelmintic drugs may elicit or increase pre-existing cerebral oedema and therefore is contraindicated in cases with increased intracranial pressure, subarachnoid NCC in close proximity to blood vessels and NCC encephalitis (Garcia et al. 2014a). In these conditions, steroids should be administered alone and may later be combined with anthelmintic drugs. In intraparenchymal active NCC without signs of increased intracranial pressure, steroids should be administered simultaneously with anthelmintic treatment, at least for the first week (Winkler 2012, 2013). The treatment regimens are discussed below, but may have to be extended using higher doses in complicated forms such as subarachnoid and ventricular NCC (Bittencourt et al. 1990, Yee et al. 1999, Gongora-Rivera et al. 2006, Garcia et al. 2002, Rocha et al. 2008, Nash & Garcia 2011). There have been reports of spontaneous resolution and benign course in case of intraparenchymal NCC (Garg 2008a). Considering risks and possible lack of long-term benefits there has been intense controversy about the indications of anthelmintic therapy. One has to be aware of the fact that most information originates from uncontrolled studies from endemic areas that show significant selection bias and randomized placebo-controlled trials as well as meta-analyses are rare and still indicate conflicting results concerning the indication of anthelmintics (Garcia et al. 2002, Garg 2008 a,b). It seems as if medical management of enhancing lesions in the transitional stage is of greatest controversy with

recommendation reaching from no treatment to treatment with anthelmintic s or steroids or a combination thereof (Nash et al. 2005).

1. Praziquantel

Praziquantel (PZQ) is widely available in sub-Saharan Africa and displays strong activity against schistosomes and cestodes (Takayanagui et al. 2011). The drug has relatively good oral bioavailability with inter-patient variation. The most effective regimen applies 50mg/kg in three divided doses over two weeks to 30 days. Alternatively, 25 mg/kg given two-hourly in a single day scheme lead to a 90% reduction of the direct costs in relation to the traditional scheme as shown by studies from Peru, Mexico and Ecuador (Sotelo & Jung 1998, Pretell et al. 2000, Garcia et al. 2002, Medina-Santillan 2002, Takayanagui et al. 2011). The single day course may be useful in patients with low cyst burden or single parenchymal cysts. However, it shows limitations in its use in multicystic disease (Pretell et al. 2001), which unfortunately is the prevailing phenotype in most LMIC (Winkler 2012, 2013). Another solution may be a high-dose short-term treatment with 100mg/kg PZQ in three divided doses every two hours followed by corticosteroids (Corona et al. 1996, Pretell et al. 2001). Even with normal dosage and course of treatment cure rates with anthelmintic drugs in general seem to be low. In untreated patients, 40% of cysts are cleared and in treated patients 60% of cysts disappear after one course of treatment. Furthermore, rebound inflammation may occur after abrupt withdrawal of anthelmintics and/or steroids and may be due to overcompensation of the immune system after removal of treatment with anti-inflammatory medication (Nash & Garcia 2011).

2. Albendazole

The anthelmintic drug of choice is Albendazole (ALB; better penetration into the central nervous system, greater cysticidal effect, less interaction with other drugs (see below) and lower price compared to PZQ (Nash et al. 2005, Garcia et al. 2011a, Nash & Garcia 2011, Garcia et al. 2014a)) which is also a broadspectrum anthelmintic drug but with relatively little to no effect on schistosomes and the adult *T. solium* tapeworm. Unfortunately, it is not broadly available in sub-Saharan Africa. Not many dose range studies have been conducted for ALB in NCC and initially the previously used scheme for hydatid disease had been adopted (Takayangui et al. 2011). The regimen has been adapted according to worldwide clinical experience and currently a one- to two-week course of 15mg/kg in two divided doses twelve hours apart has been recommended (Garcia et al. 2002, Winkler et al. 2009a, Nash & Garcia 2011, Carpio 2012, Winkler 2012, 2013).

A Mexican study detected considerable variation in pharmacokinetic properties and plasma concentrations of ALB sulfoxide. It was concluded that those findings were most likely related to bioavailability issues and may vary with ethnicity. One fourth of the study population absorbed ALB as little as 30%. Although not demonstrated, low drug exposures might therefore be associated with treatment failure, which warrants therapeutic drug monitoring, if available (Castro et al. 2009).

As the clearance of cysts with both ALB and PZQ is not satisfactory, studies have tried higher doses of 30 mg/kg/day, but the safety profile so far has not been assessed (Garcia et al. 2011a). A study from Mexico showed that an ALB course at 30 mg/kg/day during eight days combined with corticosteroids is safe and more effective than the usual dose in subarachnoid NCC (Gongora-Rivera et al. 2006). Routine use of this dosage in extraparenchymal NCC in a Mexican hospital setting has not shown any increase in side effects with the most frequent side effect being alopecia in around 10% of the patients (personal communication A Fleury). A single cycle of high-dose ALB however seems to be insufficient in intraventricular NCC and giant cysticerci requiring re-treatment. Some authors re-treat if cysts persist on neuroimaging at three or six months (Gongora-Rivera et al. 2006). Also, there is no consensus on the re-treatment regimen which may include the same dose of ALB, a combination of ALB (15 mg/kg/day) and PZQ (50 mg/kg/day) or a combination of ALB (15 mg/kg/day) and ivermectin (10 mg/d; personal communication A Fleury). Ivermectin has been suggested as an alternative in the management of severe forms of NCC resistant to habitual anthelmintic treatment by a minute collection of case reports from Colombia and Mexico (Diazgranados-Sanchez et al. 2008, Cardenas et al. 2010).

Treatment with ALB has also shown to be effective in solitary cerebral cysticercus granuloma in that it accelerated resolution of the granuloma with the possibility of early withdrawal of AEDs and also offered some protection against recurrence of seizures (Rajshekhar 1993, Del Brutto et al. 2006, Thussu et al. 2008, Singh et al. 2010). However, methodological shortcomings of some of the trials have been pointed out (Rajshekhar 2008) and it is unclear whether ALB should be administered alone or in combination with steroids (Singh et al. 2010). An earlier study even demonstrated that treatment with anthelmintics may not be required at all (Singh et al. 2001).

3. Combined treatment with albendazole and praziquantel

There is a relative scarcity of clinical trials assessing a potential role of combined anthelmintic therapy in NCC. Most knowledge relies on case reports from Peru, Mexico, Ecuador and Mali (Sotelo & Jung 1998, Carpio et al. 1995, Maiga et al. 2009, Cardenas et al. 2010, Garcia et al. 2011b). However, it has been demonstrated from serum samples using liquid chromatography-mass spectrometry that PZQ augments ALB sulfoxide plasma concentrations, which may implicate treatment benefit in terms of shorter duration of treatment and therefore less time to exposure of common adverse effects (Garcia et al. 2011b). A trial of combination therapy in NCC using ALB and PZQ has recently been conducted showing an increased cysticidal effect in patients with multiple cerebral cysts without increased side effects (Garcia et al. 2014b). To the contrary, a preliminary study from Mexico using ALB and PZQ in extraparenchymal NCC patients resistant to ALB alone did not show better efficacy (personal communication A Fleury).

4. Side effects and interactions of anthelmintic medication

Both drugs are considered to be tolerated well. Most frequently seen adverse effects include alopecia, gastrointestinal distress, fever, rash, dizziness and hepatic dysfunction. During therapy, exacerbation of neurological symptoms including seizures, vomiting and headaches as well as CSF pleocytosis have been described (Takayanagui & Jardim 1992, Garcia et al. 1997), especially when used without anti-inflammatory co-medication. Metabolism of PZQ and ALB is increased with simultaneous usage of AEDs - in particular phenytoin and carbamazepine - and the levels of PZQ are reduced when the drug is administered together with steroids, while the levels of ALB are increased. Co-administration of histamine H_2-antagonists like cimetidine or ranitidine may increase the bioavailability of PZQ and therefore have some value as adjunctive medication (Jung et al. 1990, 1997, Serpa et al. 2006, Mansur 2010, Winkler 2013). In addition, a high carbohydrate diet and grapefruit juice is associated with increased PZQ concentrations, whereas a high fat diet may augment ALB plasma levels. (Jung et al. 1997, Sotelo & Jung 1998). Those dietary considerations have to be taken into account when informing patients about their medication to optimize treatment benefit.

Also, in resource-poor settings, patients may not be particularly compliant with treatment and thereby contribute to exacerbation of side effects. The best solution would be to keep the patient in hospital for the time of treatment, but due to financial expenses the patient may not agree.

5. Treatment with anti-inflammatory drugs

In ventricular, subarachnoid and encephalitic (multiple intraparenchymal cysts with oedema development) NCC one has to consider a reactive increase of intracranial pressure that may be caused by inflammation due to cyst degeneration either naturally or with the use of anthelmintic medication. For this reason in these complicated conditions outpatient treatment has to be discouraged, since – although rare – decompensation of intracranial hypertension has been reported (Takayanagui & Jardim 1992, Garcia et al. 1997). However, the occurrence of this potentially life-threatening complication can be minimized by the simultaneous use of steroids in ventricular and subarachnoid forms and administration of steroids only in patients with massive infection (= encephalitic form; Winkler 2012, 2013). In patients with a low to medium amount of intraparenchymal cysts who do not show severe symptoms/signs of intracranial hypertension steroids should be initiated together with anthelmintic drugs and ideally should be administered for as long as the patient is symptomatic (e.g. chronic progressive headache, acute symptomatic epileptic seizures) but at least during the first days anthelmintic treatment is given. Although the use of steroids for controlling inflammation has been well demonstrated, it must be mentioned that due to their immunosuppressive properties, their use could be involved in the non-response to cysticidal drugs in patients with extraparenchymal NCC (Cardenas et al. 2010). Studies evaluating this aspect are necessary.

So far steroid doses in the treatment of NCC have not been standardized (Nash et al. 2011, Garcia et al. 2014c, Nash et al. 2014). Prednisone is recommended at a dosage of 1 mg/kg per day either p.o. or i.v.. Alternatively, dexamethasone can be used at 6-8 mg/d (Garcia et al. 2014c), maximum of 30mg/day, p.o. or i.v.. Metabolism of both drugs may be increased by AEDs (Serpa et al. 2006, Mansur 2010). To date there are four controlled trials of the use of steroids in NCC conducted in single enhancing granulomatous lesions. Treatment regimens consisted of prednisolone 1 mg/kg for 10 days with a four-day taper with and without AEDs, prednisolone 1 mg/kg for 7 days with a three-day taper without AEDs and methylprednisolone 1 g/1.72 m^2 for 5 days without AEDs. All studies showed a decrease in epileptic seizures and three showed a significant clearance of cysts on CT (Mall et al. 2003, Garg et al. 2006, Prakash et al. 2006, Kishore et al. 2007, Winkler 2013, Nash et al. 2014). A recent study that compared dexamethasone 6 mg/d for 10 days and 8 mg/d for 28 days followed by a 2-week taper together with standard antiparasitic treatment (ALB 15 mg/kg/day for 14 days) found that the higher steroid dose reduced seizures significantly during the length of the antiparasitic treatment and for a short period after its withdrawal (Garcia et al. 2014c). Although the use of steroids for the treatment of NCC shows clear beneficial effects, one needs to be aware of their abrupt withdrawal which may lead to rebound neurological symptoms/signs; therefore steroids need to be tapered off slowly (Garcia et al. 2014a).

Alternative non-hormonal anti-inflammatory agents are dextrochlorpheniramine (12-24 mg/day), ketoprofen (150-300 mg/day), and immunosuppressants such as azathioprine (2-4 mg/kg/day). For patients who develop chronic or recurrent cerebral inflammation, methotrexate may be useful as a corticosteroid sparing or replacement agent (Keiser & Nash 2003), yet there are no data from resource-poor settings.

6. Treatment with anti-epileptic medication

In the rural sub-Saharan settings AEDs (phenobarbitone, phenytoin and occasionally carbamazepine) are relatively easily accessed. As opposed to other endemic settings of LMIC, valproate is stocked only occasionally in sub-Saharan Africa, and most times is not delivered through the national pharmacies, but relies on private donations. Single first line therapy using the three available AEDs usually enables adequate seizure control in people with NCC, although the effect has only been demonstrated with phenobarbitone and carbamazepine (Blocher et al. 2011). Experience with treatment of NCC associated seizures from a Mexican hospital setting indicate that phenytoin and valproate are also effective in treating seizures from NCC (personal communication A Fleury). A recent study comparing responses to AEDs in people with epilepsy and calcified NCC, those with other structural cerebral lesions and those without obvious cerebral lesions has shown no difference in treatment response in the three groups which may indicate that free access to and choice of all available AEDs does not improve seizure outcome in people with NCC (Leon et al. 2015). Dosing and potential side effects of the four major AEDs have been summarized in **table 2** (Winkler 2013)**.**

When should treatment be initiated?

AED treatment should be initiated if seizure activity is recurrent, irrespective of whether epileptic seizures occur within the setting of symptomatic cysticerci or calcifications. According to the latest guidelines of the International League Against Epilepsy (Fisher et al. 2005) treatment should already be initiated after the first epileptic seizure if an underlying lesion is present, or in the circumstances of a resource-poor setting, is suspected (Winkler 2012, 2013). Treatment of symptomatic seizures and recommendations for withdrawal of AEDs in the context of NCC have been summarized in **figure 2**.

Which anti-epileptic drug should be chosen?

Epileptic seizures in the context of NCC are of the secondary generalized type. Frequently physical examination does not reveal neurological signs. Therefore, in practice, it is difficult to differentiate epileptic seizures related to NCC from other aetiologies. Due to its dual efficacy in partial and secondary generalized seizures carbamazepine would be the drug of choice in generalized epilepsies with an obvious or assumed focal start. This is the case with epileptic seizures related to NCC. Phenobarbitone, phenytoin and valproate can also be used for treatment of generalized epilepsy with a focal start, but a substantial side effect profiles may limit their use and impair compliance (Winkler 2012, 2013; **table 2**). Interestingly it has been shown that adverse cutaneous reactions to phenytoin, including benign generalized skin rashes and anticonvulsant hypersensitivity syndrome, were more frequent in a set of patients with solitary cerebral cysticercus granuloma as compared to seizures caused by other conditions or multiple cyst NCC (Singh et al. 2004). Adverse cutaneous reactions observed in this study also included potentially severe reactions such as Steven-Johnson syndrome. There is paucity of clinical trials or meta-analyses assessing the incidence of treatment related side effects of the various AEDs in patients with NCC. Very often phenobarbitone is the only therapeutic option and indeed its efficacy and safety for the common epilepsies has been confirmed in various observational studies from resource-poor regions. Comparing phenobarbitone to carbamazepine, phenytoin and valproate there was no evidence to suggest that phenobarbitone caused more adverse events (Zhang et al. 2011). In addition phenobarbitone is the most cost-effective and widely available AED and therefore seems suitable for use in most LMIC (Brodie & Kwan 2012).

How to treat empirically with anti-epileptic medication?

Serological results and/or the appearance of lesions on neuroimaging may guide the AED choice for PWE in areas endemic for *T. solium* (neuro)cysticercosis. Absence of these diagnostic tools however does not preclude initiation of empiric treatment, which requires adequate patient surveillance. If seizures still recur on sufficient doses, switching to another AED may be necessary. Limited resources and avoidance of frequent side effects that can be synergistic, hence reduce patients' compliance, would warrant AED monotherapy (Winkler 2012, 2013). It is self-evident that patients have to be informed about side effects of AEDs, especially the potentially ensuing tiredness, in order to increase compliance. Short follow-up

visits at the epilepsy clinic are necessary to monitor clinical remission and compliance, since the majority of patients may stop medication at once when the seizures have died down. This may lead to severe withdrawal seizures of potentially life-threatening character (Winkler 2012, 2013).

When to withdraw anti-epileptic medication?

Withdrawal of AEDs in the context of NCC relies on individualized clinical decisions, as formal guidelines are non-existent. In neurological practice, discontinuation of AEDs usually is considered in people with epilepsy who have been seizure-free for two years or longer. However, in the context of sub-Saharan Africa one year may be justified (Edwards et al. 2008). The decision to withdraw AEDs must weigh the risk of seizure recurrence against the benefits in terms of medical, emotional and social implication of treatment. The factors associated with a higher-than-average risk of seizure relapse include partial seizures, the presence of an underlying neurological condition or brain lesions and abnormalities on EEG at the time of withdrawal, amongst others (Specchio et al. 2008). Predictors for remaining seizure-free after withdrawal of AEDs over one year were normal neurological examination and use of carbamazepine prior to withdrawal (Lossius et al. 2004). In the context of NCC, this means that patients with normal neurological examination, those with clearance of NCC lesions and those that were treated with carbamazepine stand a good chance of remaining seizure-free after withdrawal of AEDs. However, well-planned longitudinal studies are necessary to confirm the above assumptions (Winkler 2012, 2013). Observations on seizure recurrence so far seem to point into the opposite direction with seizure recurrence rates of between 15-88% after withdrawal of AEDs (Del Brutto 1994, Ferreira et al. 2001, Talukdar et al. 2002, Rajshekhar & Jeyaseelan 2004; personal communication A Fleury), although it may be argued that recurrence is due to too early AED withdrawal and/or residual calcifications at least in some of the cases (Del Brutto 1994, Rajshekhar & Jeyaseelan 2004, Gonzales & Garcia 2012). For withdrawal of AEDs in patients with NCC that have access to CT, neuroimaging may guide the clinician as to when withdrawal of AEDs in PWE with NCC seems justified (**figure 2**). In the absence of neuroimaging modalities the clinician may attempt to get serial *T. solium* cysticercus antigen levels (Nguekam et al. 2003) or EEG recordings for follow-up. If those are not at hand one may start slow tapering of AEDs under close supervision after the patient was seizure-free for at least a year (Winkler 2012, 2013), although others suggest two years (Nash et al. 2005). In patients with solitary cysticercus granuloma AEDs may be withdrawn within weeks after resolution of the granuloma as seizure recurrence seems to be low, although patients with calcifications (approximately 20% (Rajshekhar 1998)) may require extended treatment (Murthy & Reddy 1998, Singh et al. 2001, Rajshekhar & Jeyaseelan 2004, Nash et al. 2005, Singh et al. 2010).

7. Surgical treatment

Antecedent to the advent of anthelmintic drugs, surgery was the mainstay of NCC therapy and most studies assessing its role stem from India and Latin America (Colli et al. 1986, Del Brutto et al. 1993, Colli et al. 1993, Colli et al 2002a, Husain et al. 2007, Suri et al. 2008, Goel et al. 2008, Proano et al. 2009, Torres-Corzo et al. 2010, Gonzales & Garcia 2012, Sinha &

Sharma 2012, Rathore et al. 2013). Placement of ventriculo-peritoneal shunts, endoscopic approaches, lesionectomy and temporal lobectomy in the setting of temporal cysts with associated hippocampal sclerosis are the options for surgical treatment nowadays. Debridement of adhesions related to arachnoiditis and/or ventriculitis has also been conducted. It has to be emphasized that in resource-poor settings often the only surgical option is shunt placement in patients with hydrocephalus due to NCC, which bears a high morbidity and mortality (Colli et al. 2002a, Proano et al. 2009, Rajshekhar 201, Torres-Corzo et al. 2010). Shunt viability may be enhanced by administration of prednisolone of 50 mg three times a week with or without anthelmintic treatment and by using an open-ended shunt (Suastegui et al. 1996, Kelly et al. 2002, Garcia et al. 2014a). In sub-Saharan Africa, longitudinal studies on outcome of shunt placement with sufficient amount of patients so far have not been conducted. However, unpublished data and personal experience of one of the authors (AS Winkler) support a highly unfavourable outcome and therefore referral of patients suffering from NCC to surgery has to be considered very carefully.

The first-line indication of surgery lies with the ventricular form of NCC, although a recent report from China suggests good outcome of patients that underwent microsurgical management of cerebral intraparenchymal cysticercosis (Ou et al. 2012). In addition, if pharmacological management has failed, operative methods can also be considered as second-line treatment in subarachnoid forms of extraparenchymal NCC, especially in the "giant cyst form". In both cases cyst removal and/or reduction of intracranial pressure represent the main goal of neurosurgical treatment (Winkler 2012).

As a final overview treatment options for NCC have been summarized according to NCC characteristic and disease stage in **figure 3**.

I. Treatment in the absence of neuroimaging

The majority of patients in resource-poor settings have neither access to neuroimaging nor to *T. solium* cysticercosis Ag-ELISA. Though positive results on *T. solium* cysticercosis Ag-ELISA may indicate active disease (Gabriel et al. 2012), treatment with anthelmintics must not be initiated on the basis of serology alone as cyst stage and presence of oedema cannot be estimated. Potential aggravation of raised intracranial pressure related to anthelmintic drugs precludes "blind trials" with ALB or PZQ, as those may result in quick deterioration of the patient's condition and death due to brain herniation. Hence in the absence of neuroimaging patients should be treated symptomatically only, i.e. using analgesics, steroids and AEDs for headache, other signs of increased intracranial pressure due to inflammation (brain oedema) and epileptic seizures, respectively (Garcia et al. 2012, Winkler 2012, 2013).

1. Symptomatic treatment with anti-inflammatory medication

The administration of steroids as symptomatic treatment in patients with signs and symptoms of increased intracranial pressure, such as neck stiffness, vomiting and chronic progressive headache in the context of suspected but not imaging-confirmed NCC, is debatable and has to be decided on an individual basis. A classical scenario where steroid administration may be advisable is in patients with acute symptomatic seizures who come from a *T. solium* (neuro)cysticercosis endemic area. High doses of steroids may be started in these patients and tapered once symptoms abate. At the same time AEDs should be initiated on which the patient will be maintained until fit for withdrawal (Winkler 2012, 2013; **figure 2**).

CSF analysis offers additional information to exclude other potentially life-threatening causes of acute symptomatic seizures. Important differential diagnoses in NCC endemic regions mainly include cerebral malaria, bacterial or tuberculous meningitis and encephalitis. The result of CSF analysis is usually unequivocal for bacterial meningitis and in that case steroids must not be started without antibacterial treatment. Findings in tuberculous meningitis and viral encephalitis may resemble those in NCC (although most patients with intraparenchymal NCC show unremarkable results on cerebrospinal fluid testing) with an unspecific medium increase in cell count and no major other obvious abnormalities, especially in a resource-poor setting where protein and glucose often are not measured. Eosinophil granulocytes may be elevated in NCC, but this is no mandatory observation. Therefore differential diagnosis may prove difficult, but a trial of steroids will not harm patients with tuberculous meningitis or viral encephalitis as brain oedema may be present and administration of steroids to these patients may even ameliorate symptoms (Nakano et al. 2003, Ramachandran 2012, Winkler 2012, 2013).

2. Pros and cons of symptomatic treatment only

One may argue that treating symptomatically only could potentially jeopardize the long-term outcome of the patients both in terms of cysticercus clearance and severity of epileptic seizures. However, the benefit of using anthelmintics remains controversial and has been a worldwide debate. A well-designed study showed that treatment with ALB in addition to AEDs significantly cleared the parasite and reduced seizure frequency, especially those with generalization, when compared to the control group that received AEDs only (Garcia et al. 2004). Another study from the same group also showed that treatment with ALB in addition to AEDs improved cognition and quality of life in patients with NCC after six months on treatment (Wallin et al. 2012). Those results are challenged by a study, which reported that ALB and AEDs did not show greater benefit than therapy with AEDs alone. The combination treatment led to increased hospital admission, increased seizure frequency, more cases of encephalopathy and deaths. A greater proportion of lesions calcified compared to the group that was treated with AEDs alone, in which more lesions resolved completely (Das et al. 2007). As particularly sub-Saharan Africa is lacking imaging facilities as compared to other endemic regions and “blind treatment” with anthelmintics may cause severe side effects in terms of cerebral oedema, most African physicians do not have a choice but to only treat symptomatically (Winkler 2012, 2013).

J. Prevention of neurocysticercosis

1. Prevention of *Taenia solium* taeniosis and porcine cysticercosis

T. solium taeniosis/(neuro)cysticercosis is a disease of the poor and is rampant in communities with a low standard of sanitation and hygiene. Further risk factors include free-range pig farming, close contact of humans and pigs and inadequate meat inspection (Willingham & Engels 2006, Pondja et al. 2010). As free access of pigs to human faeces plays a crucial role in the maintenance of the life cycle of *T. solium* cysticerci, education on proper community-based sanitation, building and usage of latrines that are inaccessible to pigs and education on community-friendly pig rearing (restraining pigs, vaccination programs) are indispensable. Furthermore, meat inspection procedures as well as controlled slaughter have to be in place and farmers have to be educated about how to recognize infected pork. Hygienic measures such as hand washing after toilet use and before preparing food, amongst others, has to be advocated as it can prevent human cysticercosis which develops through ingestion of eggs from a tapeworm carrier through the faecal-oral route after contact with a tapeworm carrier, contaminated water or food (Winkler et al. 2009a).

2. Treatment of *Taenia solium* taeniosis

In addition to prevention of human taeniosis/(neuro)cysticercosis and porcine cysticercosis both diseases should be treated adequately. In theory, eradication of NCC through eradication of human taeniosis (destroying the source of infection and preventing the spread of cysticercosis, both in humans and in pigs) and porcine cysticercosis (prevention of new cases of taeniosis) seems possible (Pawlowski 2008). Although the term eradication has been replaced by “control and reduction of NCC” in *T. solium* taeniosis/(neuro)cysticercosis endemic areas the aim is certainly still a valid one (Pawlowski et al. 2005, Willingham et al. 2008). How could this be achieved?

For the control of human taeniosis mass drug administration of chemotherapeutics directed against *T. solium* (the adult pork tapeworm) to communities endemic for *T. solium* taeniosis/(neuro)cysticercosis has been discussed at length, but so far no firm decision as to its instalment in sub-Saharan Africa has been reached (Pawlowski 2008). The drug of choice for treatment of human taeniosis would be niclosamide (2 g) in a single dose, although higher doses (3 g) and repeat doses have also been discussed, combined with a laxative (e.g. magnesium sulphate 30g) It is not absorbed and therefore has virtually no side effects, but unfortunately it is not available in most countries of sub-Saharan Africa (Pawlowski et al. 2005; personal communication B Abela-Ridder). PZQ, which is available, seems to be effective as well at dosage of 5-10 mg/kg (Pawlowski 1990a,b, Pawlowski et al. 2005). However, when given without concomitant steroids perifocal oedema around cysticerci in the brain or spinal cord may ensue due to release of parasite antigen from viable cysticerci and could in turn evoke neurological symptoms/signs in the treated individual. This observation mainly relies on case reports and clinical experience (Johnson 1986, Torres et al. 1988, Flisser et al. 1993; unpublished reports of neurological side effects after mass drug

administration of PZQ for schistosomiasis from Malawi, DRC and Southeast Asia), but a large community-based study on neurological side effects after mass drug administration of PZQ is underway. Preliminary results suggest that exacerbation of asymptomatic NCC is possible and may depend on the degree of endemicity of *T. solium* cysticercosis (unpublished results W Harrison and AS Winkler). Another approach may be a more focally directed treatment as clustering of human cysticercosis around tapeworm carriers has been shown to be present (Lescano et al. 2009). However, the uncertainty of the occurrence of undesirable neurological side effects still remains, although their detection seems more favourable in a focal setting rather than in whole communities.

The discussion on the efficacy and the side effect profile of niclosamide and PZQ at various doses so far has not come to a firm conclusion and more data is needed to underpin one or the other treatment regimen (personal communication HH Garcia and A Flisser). In that context a new and promising approach comes from a Chinese study that successfully used pumpkin seeds combined with areca nut extract in community-based treatment of human taeniosis in northwest Sichuan Province. The results showed that the traditional Chinese herbal treatment was highly effective in expelling intact tapeworms in over 89% of taeniosis cases, whereas side effects were only mild and transient (Li et al. 2012).

For details on treatment of porcine cysticercosis please refer to the landscape analysis on *T. solium* taeniosis and porcine cysticercosis performed by L Doble.

Considering transmission dynamics, chemotherapy of human taeniosis seems a crucial step towards control of NCC and definitely deserves further evaluation, whereas treatment of porcine cysticercosis, e.g. using oxfendazole (Gonzalez et al. 1996), seems more like an add-on procedure stabilizing the results of human chemotherapy (Pawlowski 2006). However, as described in a review from Madagascar the combination of the above described measures, i.e. prevention/education and treatment of humans and pigs will have to be tailored to affected communities and strongly depends on local policies, financial means and available expertise, amongst others, and, in an ideal setting, should include all of the above components (Rasamoelina-Andriamanivo et al. 2013).

3. Successful prevention programmes as role models

In recent years numbers of reported NCC cases have declined in Mexico, Peru, Ecuador and Honduras (Flisser & Correa 2010, Medina et al. 2011, Alcaron & Del Brutto 2012, Gilman et al. 2012, Flisser 2013).

In the Mexican setting, the author quotes the following reasons for the decline of incident NCC: 1) the abundant literature published by the Mexican scientific and medical communities working on *T. solium* cysticercosis; 2) the establishment of a National Programme for the Control of *T. solium* since 1994; 3) the improvement of living conditions in social, economy and health sectors (Flisser 2013). In addition Official Mexican Guidelines for the Control and Prevention of Taeniosis/Cysticercosis were established in 1994 and reporting of the diseases was mandatory for the whole country. These guidelines also

included that tapeworm carriers have to be treated orally with a single dose of PZQ at 10 mg/kg. In addition to other suggested control measures a huge information campaign was launched through the distribution of hundreds of thousands of pamphlets with basic information targeted to different populations (pig breeders, butchers, cooks, food stand workers and the general population). The Mexican guidelines were revised and published again in the official national newspaper in 2004 (Flisser 2013).

In Peru, a control package is currently being field tested in a population of approximately 80.000 people and includes three rounds of mass niclosamide chemotherapy in humans, five rounds of oxfendazole chemotherapy of pigs, and a porcine vaccine (TSOL18). Preliminary results suggest that focal elimination was obtained and persisted for over a year in most villages. It is not reported whether this also reflected on the reduction of NCC associated epilepsy (Gilman et al. 2012).

In Honduras, a community-based intervention programme was launched in 1997 and included education and media campaigns, animal husbandry training for pig farmers, construction of water projects and proper sewage disposal, deworming of Salama County school students and ongoing taeniosis surveillance and led to the reduction of NCC associated epilepsy (Medina et al. 2011).

In Ecuador, the reduction of incident NCC cases was viewed in the context of increased number of houses with piped water and proper sewage disposal and the increased availability of neuroimaging machines which allow recognition of NCC cases and appropriate treatment. It seems that a community programme like in the three other countries was not in place (Alcaron & Del Brutto 201).

K. Evidence and gaps in neurocysticercosis case management in low- and middle-income countries

1. Prevalence of *Taenia solium* (neuro)cysticercosis in low- and middle-income countries

Evidence: There is a good body of evidence that NCC is of public health concern in many *T. solium* taeniosis/(neuro)cysticercosis endemic areas of LMIC, but there is also recent indication of reduction in NCC cases in some countries of Latin America. Most prevalence data comes from Latin America, whereas data from Asia (except India and Indonesia) and data from sub-Saharan Africa (except South Africa) are only very patchily available. However, data that is available points towards an emerging massive health problem in parts of Southeast Asia and sub-Saharan Africa with projected numbers of around three million people with cysticercosis in China and the same number of people with symptomatic NCC in sub-Saharan Africa. Recently, case reports of NCC have also emerged from Muslim countries.

Gaps: More prevalence, incidence and mortality data on NCC is needed from Asia and sub-Saharan Africa, including Muslim countries, in order to complement burden of disease data and bring on board appropriate stakeholders to enforce allocation of resources to NCC detection/confirmation and case management.

2. Burden of neurocysticercosis

Evidence: There is little data on the burden of NCC, but evidence from the few studies performed suggests that quality of life is reduced in people with NCC, but that there is also a tendency towards improvement with adequate treatment. Only two studies have looked at DALYs so far and have calculated 0.25 (Mexico) and 9 (Cameroon) DALYs per 1000 people. In the systematic analysis for the Global Burden of Disease study, 7 DALYs per 100 000 people were attributed to cysticercosis globally, which may be an underestimation. Also, the monetary burden of NCC seems to be substantial, mainly arising from direct or indirect epilepsy associated costs, especially when related to local circumstances such as people's minimum wages or the annual health expenditure.

Gaps: More NCC burden data is needed from throughout LMIC, best in a standardized way with comparable methodological approaches. This seems crucial to raise awareness in LMIC, especially in those endemic countries that have not yet recognized NCC as a public health problem. In addition, the causes for reduction of quality of life in people with NCC need to be much better characterized, considering neurological and/or psychiatric symptoms/signs, or impaired social functioning and/or stigma due to epilepsy.

3. Pathology of neurocysticercosis and its associated clinical characteristics

Evidence: The pathology and its related clinical symptomatology have been well described, mainly based on data from Latin America and India. Also the classification into intra- and extraparenchymal disease, including subarachnoid and ventricular NCC, seems to be used fairly uniformly. A sub-group of intraparenchymal NCC, termed solitary cerebral cysticercus granuloma, has been identified with reports mainly originating from India. Recently, the importance of spinal NCC has been emphasized by studies from Latin America. The description of the pathological presentation of NCC mainly relies on neuroimaging as

autopsy often is not an option and has important implications for case management and prognosis.

Gaps: There is paucity of data describing the pathological presentation of NCC in vast areas of Southeast Asia and sub-Saharan Africa either due to lack of neuroimaging possibilities or unawareness of the disease. Comparative studies with regards to clinical presentation of NCC, which is determined by the underlying pathology that, in turn, depends on immunological and genetic factors, seem important for drafting region specific management guidelines.

4. Paediatric considerations

Evidence: There is by now a good body of evidence that paediatric NCC poses a problem in various regions of the world. There seems to be clinical, radiological and inflammatory differences between NCC in children and adults and those would need to be considered when it comes to the development of management guidelines. Treatment of paediatric NCC with anthelmintics is discussed controversially and management with AEDs does not seem to be straight forward.

Gaps: In many countries NCC of childhood and adolescence has not yet entered the list of differential diagnoses for epilepsy and therefore awareness would need to be raised. There is great uncertainty as to which cases would need anthelmintic treatment and also about the regimen of AEDs in those children suffering epileptic seizures. With regards to these aspects randomized controlled trials are highly warranted in children with NCC and their results need to be included in clear management guidelines.

5. Considerations in people with HIV/AIDS

Evidence: Many regions of this world that are endemic for *T. solium* taeniosis/(neuro)cysticercosis are also endemic for HIV/AIDS. There is some suggestion of pathophysiological interaction of NCC and HIV/AIDS when it comes to disease progression and in that context co-infection with other helminths also seems to play a role. Studies on the prevalence and clinical characteristics of NCC in people with HIV/AIDS are conflicting ranging from benign to severe presentations. The observed low prevalence of NCC in people with HIV/AIDS in some areas may partially be due to low environmental infection pressure and/or altered sensitivity and specificity of serological tests during immunosuppression. NCC in people with HIV/AIDS seems to respond well to medical treatment, although shunt placement has been observed to carry a bleak prognosis. It has been suggested to initiate medical treatment according to CD4 level, but systematic studies are missing.

Gaps: There is clear paucity of prevalence data of NCC in the HIV/AIDS population in vast areas of Southeast Asia and sub-Saharan Africa outside South Africa. In addition, there are knowledge gaps with regards to treatment and its outcome in this patient group and randomized controlled trial are needed to inform management guidelines for this special population.

6. Diagnostic criteria for neurocysticercosis

Evidence: The mainstay of the diagnosis of NCC is based on neuroimaging in combination with immunodiagnostic or molecular biological tests. Laboratory diagnostics are at hand in

various formats, but often require high-tech equipment and do not replace neuroimaging. Diagnostic criteria for NCC have been suggested by Del Brutto and co-workers and include results from neuroimaging and laboratory diagnostic tests as well as clinical and epidemiological aspects, although modifications to these criteria have been suggested. Diagnostic criteria for solitary cerebral cysticercus granuloma have been developed separately. Clinical examination of patients with NCC and application of EEG, if available, must not be neglected and has a clear place in follow-up management after initiation of treatment. Recent reports from Latin America and India show neuropsychiatric symptoms/signs to be highly prevalent in people with NCC with clear implication for symptomatic treatment.

Gaps: A presumptive diagnosis of NCC (case detection and confirmation) in people from resource-poor settings would rely on easy-to-use point-of-care laboratory diagnostics that still need to be developed and made available. Laboratory results may also point the way towards which patients would need neuroimaging, although initiation of treatment with anthelmintics on the basis of laboratory tests alone has to be discouraged. In low-resource regions, the insufficient availability of CT scanners represents a clear limitation for adequate diagnosis of NCC, which points towards the modification of the diagnostic criteria used so far. When it comes to clinical examination, the presentation of patients with neuropsychiatric symptoms/sign has been neglected, but may greatly contribute to disease burden. Systematic studies in this respect are needed.

7. Pharmacotherapy and neurosurgical approaches to treatment of neurocysticercosis

Evidence: To date there are no standard treatment guidelines for NCC, although numerous suggestions have been made. NCC is only treated when symptomatic and management needs to be tailored to the individual case with a choice of anthelmintic , anti-inflammatory and anti-epileptic medication as well as neurosurgical approaches. Treatment of diagnosed NCC has to follow set rules and can be dangerous if not monitored appropriately. An attempt has been made to allocate treatment regimens to the various sub-groups of intra- and extraparenchymal disease and has been summarized in **figure 3**.

Gaps: Standard management guidelines for NCC need to be developed observing various pathological/radiological and clinical presentations of NCC and the involved contraindications for anthelmintic treatment such as inactive NCC and diffuse brain oedema. In addition, a set of guidelines for symptomatic treatment and its withdrawal needs to be developed not only for epilepsy, but also for neuropsychiatric symptoms/signs. Vulnerable populations such as children and people suffering from HIV/AIDS will have to be considered and may need extra guidelines. Integration of management of NCC into primary health care would seem rather challenging, as specialist knowledge is required when it comes to treatment with anthelmintic medication, but may be possible if symptomatic treatment alone is considered. The most important question remains to decide on which patients to refer to specialist centres and which patients to treat locally, which is challenging in the context of absent neuroimaging. A diagnostic flowchart observing the availability of diagnostic tools would have to be developed identifying those patients that need triple therapy (**figure 3**) and those patients that can be maintained on symptomatic therapy only.

Treatment with anthelmintic medication

Evidence: There is a huge body of evidence that both PZQ and ALB are effective in the treatment of active symptomatic intraparenchymal NCC, although ALB seems to have greater cysticidal effect compared to PZQ. One course of standard anthelmintic treatment does not kill all cysts and cysts may also resolve spontaneously, querying the necessity of treatment with anthelmintic medication, especially in solitary cerebral cysticercus granuloma. There is evidence in multicystic disease that a combination therapy of anthelmintic and anti-inflammatory drugs improves outcome, although no firm conclusion on standard treatment regimens has been drawn and combination trials of PZQ and ALB are currently underway. Treatment of extraparenchymal NCC remains a challenge, but first reports of potential benefits of higher doses, repeated treatment and combination of various cysticidal drugs, always together with anti-inflammatory medication, have emerged. Bioavailability of anthelmintic drugs in different ethnicities may play a role when it comes to treatment outcome and has not been investigated systematically so far.

Gaps: More clear-cut large multicentre randomized controlled trials are needed in order to evaluate the impact of ALB and PZQ on NCC case management. There is an important paucity of controlled trials especially on the African continent. Most data on management of NCC are based on observations from Latin America and India. In multicystic intra- and extraparenchymal NCC, randomized controlled trials should observe the following aspects: PZQ versus ALB, variation in dose and length of treatment, treatment regimens in re-treatment of treatment failure cases, consideration of different pharmacokinetics in different ethnicities and the contribution of different *T. solium* species to treatment success.

Treatment with anti-inflammatory medication

Evidence: The use of steroids in controlling inflammation has been well documented in subarachnoid, ventricular and encephalitic NCC, either alone or in combination with anthelmintic medication. There is also evidence from controlled trials in patients with solitary cerebral cysticercus granuloma that prednisolone 1mg/kg per day over a period of 5-7 days decreases epileptic seizures and contributes to early resolution of cysts on CT.

Gaps: To date randomized controlled trials of the use of anti-inflammatory drugs (type of drug, dosage, route of administration and length of treatment) in intra- and extraparenchymal multicystic disease, alone or in combination with anthelmintic medication, are missing. In addition, there is no data on the role of anti-inflammatory drugs in the non-response to cysticidal drugs in patients with extraparenchymal NCC, which may be caused by their immunosuppressive effect. Treatment failure of subarachnoid NCC is frequent, even when anti-inflammatory drugs are given in sufficiently high doses over a prolonged period of time. In this context, other non-steroidal anti-inflammatory drugs, such as methotrexate, should be explored systematically.

Treatment with anti-epileptic medication

Evidence: There are clear guidelines from the International League Against Epilepsy as to when treatment with AEDs has to be initiated. If there is an underlying lesion, treatment

needs to be started after the first seizure irrespective of whether the seizure is due to acutely symptomatic disease or chronic epilepsy. Suggestions for withdrawal of AEDs are less clear and range from being seizure-free for a couple of months to two years and do not necessarily depend on the presence of neuroimaging. The recurrence rate of epileptic seizures has not been investigated well, but there is some suggestion that it may be high. There is good evidence that most patients can be maintained on AED monotherapy in the usual doses and that AEDs available in LMIC, such as carbamazepine and phenobarbitone, seem to be effective for seizure control. The efficacy and safety of phenobarbitone, which not only is the widest available AED but also the cheapest, for the common epilepsies has been confirmed in various observational studies from resource-poor regions.

Gaps: There are no randomized controlled trials for the use of AEDs in patients with NCC. Although both carbamazepine and phenobarbitone have been demonstrated to be effective in NCC, systematic studies are missing. In addition clear withdrawal guidelines in the absence of neuroimaging would need to be established.

Surgical treatment

Evidence: There is a good body of evidence that surgical management is the first-line choice in people with ventricular NCC mainly through endoscopic removal of the cyst and CSF shunting. The latter has also its place in subarachnoid NCC complicated by hydrocephalus. Although sophisticated microsurgical approaches have been reported to tackle intraparenchymal cysts, this is not an option for most resource-poor settings where the only neurosurgical technique available is shunt placement which often carries a bleak prognosis. Treatment with anti-inflammatory drugs may be beneficial and prolong shunt viability.

Gaps: Clinical data on the outcome of shunt placement are scarce and are virtually absent from sub-Saharan Africa. Additional anti-inflammatory treatment has to be investigated systematically in a prospective study design and results should be included into recommendations for shunt placement in patients with hydrocephalus from NCC.

8. Treatment in the absence of neuroimaging

Evidence: There is almost no data on treatment of NCC in resource-poor settings without access to neuroimaging, although discussion has been sparked by various experts who almost unanimously agree that treatment with anthelmintics must not be started in the absence of neuroimaging, but that patients with NCC and epileptic seizures should be started on AEDs irrespective of whether neuroimaging is available or not. However, expert opinions are less clear on whether people with assumed symptomatic NCC can be safely started on anti-inflammatory medication.

Gaps: Treatment guidelines for people with NCC in the absence of neuroimaging will have to be established. Two major questions that need to be asked in this context are: 1. Would immunodiagnostic tests contribute to information necessary for treatment of people with NCC in the absence of neuroimaging? 2. Can anti-inflammatory drugs be safely started without neuroimaging in people with a presumptive diagnosis of active symptomatic NCC?

9. Prevention and control of neurocysticercosis

Evidence: Control/elimination of NCC can be achieved through prevention and treatment of human *T. solium* taeniosis and/or porcine cysticercosis. Human *T. solium* taeniosis responds to treatment with niclosamide and PZQ but not ALB, although niclosamide seems to be less effective than PZQ. Distribution of PZQ for anti-helminthic treatment in areas co-endemic for *T. solium* taeniosis/(neuro)cysticercosis can be hazardous and there is emerging evidence that PZQ may cause conversion from asymptomatic to symptomatic NCC with the well-known consequences. The latest knowledge on successful prevention and treatment of porcine cysticercosis has been summarized in the landscape analysis on *T. solium* taeniosis and porcine cysticercosis by L Doble which the reader is referred to for more information. Of late, a reduction in incident cases of NCC has been observed in some countries of Latin America which may be due to community-based prevention programmes or improved living conditions or both. There is evidence of successful community-based prevention programmes for *T. solium* taeniosis/(neuro)cysticercosis in terms of reduction of NCC from Mexico, Peru and Honduras which may serve as role models for programmes on the Asian or African continent. Within the Mexican programme there was also a good reporting/surveillance system in place which potentially could be adopted by other countries.

Gaps: A mandatory reporting/surveillance system for *T. solium* taeniosis/(neuro)cysticercosis is highly warranted, if one aims at targeting effective intervention strategies. From literature data as well as direct correspondence with World Federation of Neurology delegates it became evident that most endemic countries do not have reporting systems for *T. solium* taeniosis/(neuro)cysticercosis in place, and that they do not have data on NCC prevalence/incidence or a clear view on case management. Mandatory reporting of cases, cysticercosis and taeniosis, to public health authorities seems also indispensable if one seeks to detect transmission foci early enough to be able to offer adequate case management and save additional costs related to delayed or unnecessary treatment. The transmission cycle of *T. solium* cysticerci has been well established and human taeniosis seems to play a pivotal role. There has been some controversy on whether to used PZQ or niclosamide. The latter represents a safe drug for treatment of people with *T. solium* taeniosis in NCC endemic areas (for more details please refer to the landscape analysis on *T. solium* taeniosis and porcine cysticercosis). Due to its advantageous side effect profile with regards to NCC and possible use in pregnant women it may prove to be a useful drug for mass eradication of *T. solium* taeniosis, although no systematic data on its efficacy compared to PZQ has become available so far.

Acknowledgments

We are most grateful to the following colleagues regarding their input to the manuscript either through lengthy discussions or advice on specific areas: B Abela-Ridder, J Blocher, HC Carabin, L Doble, T Dua, A Fleury, A Flisser, S Gabriel, HH Garcia, S Handali, W Harrison, T Nash, V Rajshekhar and V Schmidt.

Table 1. Del Brutto Diagnostic Criteria for Neurocysticercosis

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Categories of Criteria	Criteria
Absolute	1. Histologic demonstration of parasite from biopsy of a brain or spinal cord, or 2. Cystic lesions showing scolex on CT or MRI, or 3. Direct visualization of subretinal parasites by funduscopic examination
Major	1. Lesions highly suggestive of neurocysticercosis on neuroimaging studies, or 2. Positive serum EITB for detection of anticysticercal antibodies, or 3. Resolution of intracranial cystic lesions after therapy with albendazole or praziquantel, or 4. Spontaneous resolution of small single enhancing lesions
Minor	1. Lesions compatible with neurocysticercosis on neuroimaging studies, or 2. Clinical manifestations suggestive of neurocysticercosis, or 3. Positive CSF ELISA for detection of anticysticercal antibodies or cysticercal antigens, or 4. Cysticercosis outside the CNS
Epidemiologic	1. Evidence of household contact with *T. solium* infection, or 2. Individuals coming from or living in cysticercosis-endemic area, or 3. History of frequent travel to disease-endemic areas

Definitive diagnosis: 1 absolute criterion, or 2 major +1 minor and 1 epidemiologic criterion; *probable diagnosis*: 1 major 2+ minor criteria, or 1 major 1+ minor and 1 epidemiologic criterion or 3 minor +1 epidemiologic criterion.
ELISA, enzyme-linked immunosorbent assay.

Source: Pediatr Infect Dis J © 2003 Lippincott Williams & Wilkins

Table 2. Antiepileptic medication available in sub-Saharan Africa: drug loading, titration and maintenance doses as well as side effects (in the order of their availability)

Antiepileptic medication (indication)	**Starting dose**	**Titration (~usual adult maintenance dose)**	**Side effects (list non-exhaustive)**	**Route of adminis-tration**
Phenobarbitone (all forms of epilepsy; may be tried in atypical absences, atonic and tonic seizures)	1. 30 mg p.o. 2. (rapid) 50 mg i.v., s.c. or i.m. every 6 h diluted 1:10 with inj. water 3. (status) 20 mg/kg i.v. diluted 1:10 with inj. water (start with 200-400 mg) (maximum rate: 100 mg/min)	30 mg p.o. every 3 days (long half-life) (~60-180 mg/day)	neurological/psychiatric: fatigue, drowsiness, lethargy, pronounced cognitive decline, learning disabilities, headaches, ataxia, nystagmus, dysarthria, depression, agitation, aggression, hyperkinesia (children), confusion (elderly); other: megaloblastic anaemia (may be treated with folic acid**), constipation, rickets and osteomalacia (vitamin D deficiency**), impotence; vitamin K deficiency** and withdrawal seizures in new-borns; teratogenicity rapid titration in status: respiratory depression	oral, i.v., s.c., i.m.
Carbamazepine (partial (simple and complex) and secondary generalised tonic-clonic seizures; some primary generalised seizures; not in absences and myoclonic seizures)	200 mg	200 mg every 3-5 days (~800-2000 mg/day)	skin: from transient erythematous rash*** (frequent) to Stevens-Johnson syndrome, photosensitivity lupus erythematosus; blood: leucopenia, thrombocytopenia, agranulocytosis, aplastic anaemia; cardiovascular: conduction disturbances, thromboembolism; gastro-intestinal: nausea, vomiting, cholestatic jaundice, hepatitis, constipation, diarrhoea, anorexia; genito-urinary: renal failure, proteinuria, impotence; neurological/psychiatric: dizziness, drowsiness, headache, ataxia, confusion, agitation, visual disturbances (double vision often associated with peak plasma levels), dyskinesia, paraesthesia, depression, activation of psychosis; other: alopecia, arthralgia, fever, lymph node enlargement, gynaecomastia, galactorrhoea, pulmonary hypersensitivity, hyponatraemia, oedema, osteomalacia; teratogenicity	oral

Phenytoin (all forms of epilepsy except absence seizures and myoclonic seizures)	1. 300 mg p.o. 2. (rapid) 600 mg p.o. for 3 days 3. (status) 1.5 g i.v. diluted 1:10 with inj. water (first 250 mg as bolus over 10 minutes, next 500 mg in 0.5 to 6 hours, next 750 mg in 1-24 hours according to clinic) (maximum rate: 20 mg/min)	25-50 mg per day (~200-500 mg/day*)	skin and gum: gingival hypertrophy and tenderness, coarse facies, hirsutism, acne, rash*** lupus erythematosus, Stevens-Johnson syndrome, toxic epidermal necrolysis blood: megaloblastic anaemia (may be treated with folic acid**) leucopenia, thrombocytopenia, agranulocytosis, aplastic anaemia; gastro-intestinal: nausea, vomiting, hepatitis, liver failure; neurological/psychiatric: vertigo, double vision, nystagmus, tremor, confusion, dizziness, headache, insomnia dyskinesias; ataxia, slurred speech, nystagmus and blurred vision (are signs of overdosage); peripheral neuropathy, irreversible cerebellar atrophy; other: fever, polyarthritis, lymphadenopathy, rickets and osteomalacia (lowered plasma calcium concentration); teratogenicity rapid titration in status: cardiac dysrhythmias, hypotonia	oral, i.v. (beware of phlebitis)
Valproate (all forms of epilepsy; drug of choice in primary generalised epilepsy, generalised absences and myoclonic seizures; may be tried in atypical absences, atonic and tonic seizures, Salaam attacks; has got similar efficacy to that of phenytoin and carbamazepine in partial epilepsy)	1. 600 mg p.o. 2. (status) 3.6 g i.v. diluted approx. 1:10 with inj. water (first 1.2 g as bolus over 10 minutes, second 1.2 g as bolus over 10 minutes, next 1.2 g in 12-24 hours according to clinic) (maximum rate: 100-200 mg/min)	150-300mg/3d (~ 900-3000 mg/d)	skin: rash, toxic epidermal necrolysis, Stevens-Johnson syndrome, vasculitis, hirsutism, acne; blood: thrombocytopenia, inhibition of platelet aggregation, leucopenia, pancytopenia, red cell hypoplasia, fibrinogen reduction; gastro-intestinal: nausea, vomiting, increased appetite and weight gain, impaired hepatic function leading rarely to fatal hepatic failure****, rarely pancreatitis*****, hyperammonaemia; neurological/psychiatric: ataxia, tremor, dizziness, sedation (rarely lethargy and confusion associated with too high an initial dose), increased alertness, occasionally aggression, hyperactivity and behavioural disturbances, extrapyramidal symptoms, dementia, acute valproate-induced encephalopathy****** other: irregular periods, amenorrhoea, gynaecomastia, hearing loss, Fanconi's syndrome, fatigue, hair loss, oedema	oral, i.v.

*has a narrow therapeutic index and the relationship between dose and plasma concentration is non-linear; small dosage increases in some patients may produce large rise in plasma concentration with acute toxic side-effects; a few missed doses or a small change in drug absorption may result in a marked change in plasma concentration.
**consider vitamin administration together with antiepileptic medication
***discontinue; if mild re-introduce cautiously, but discontinue immediately if recurrence
****withdraw treatment immediately if vomiting, anorexia, jaundice or loss of seizure control occurs
*****measure plasma amylase in acute abdominal pain
******withdraw treatment immediately if within the first week of starting medication impairment of consciousness, increased seizure frequency, dysarthria, asterixis

Figure 1. PRISMA 2009 Flow Diagram: NCC landscape

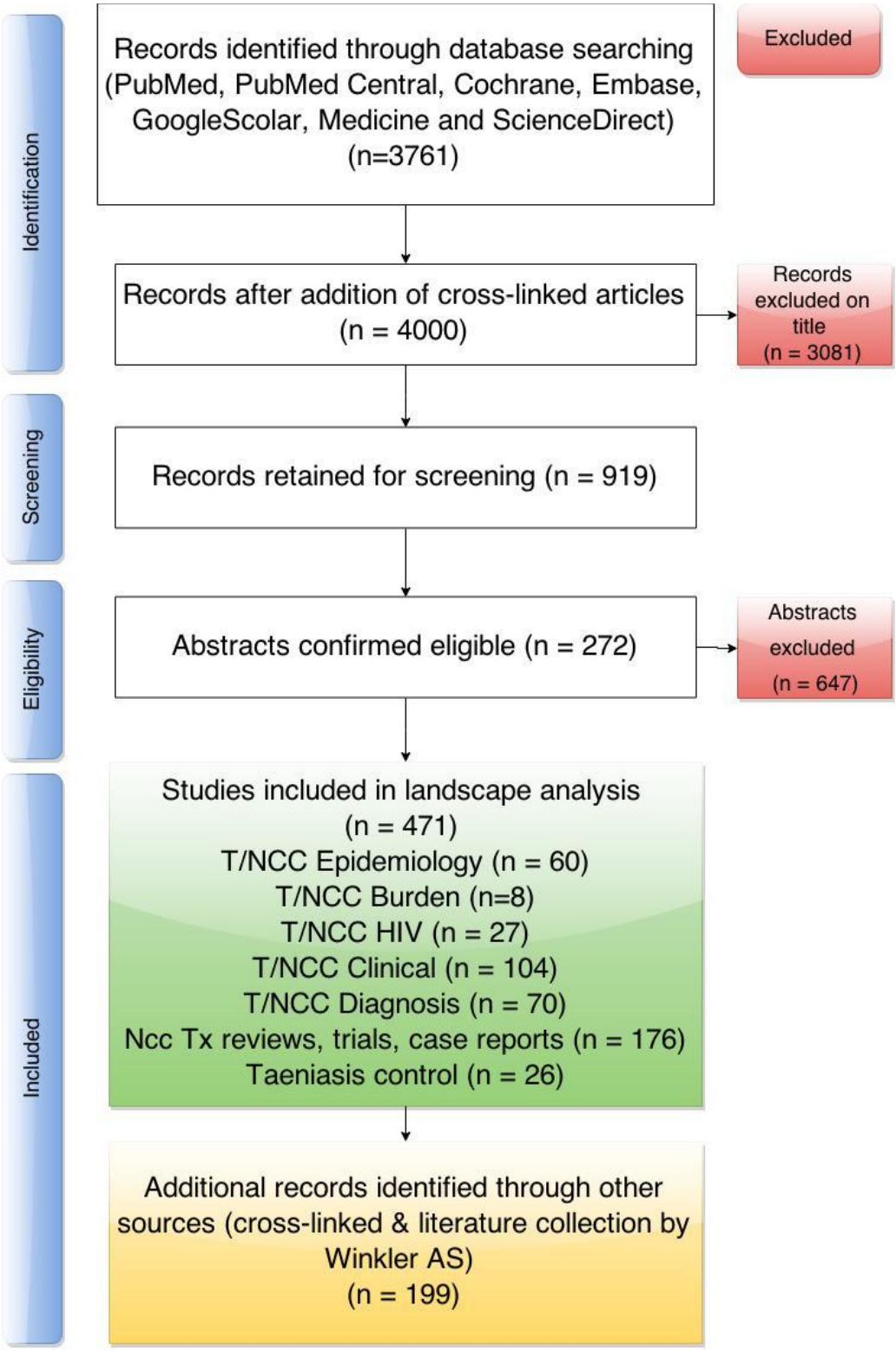


Figure 2. Withdrawal algorithm of anti-epileptic medication in people with epilepsy due to neurocysticercosis. If CT is at hand, the indicated algorithm should be followed. In a nutshell, withdrawal is guided by the presence or absence of intracerebral lesions and by seizure recurrence. Seizure recurrence is defined as at least one seizure during the last year as this seems to be the accepted time frame indicating when to start antiepileptic treatment in resource-poor settings (Edwards et al. 2008). For more details refer to the text.

AED=anti-epileptic drugs, CT=computed tomography

Adapted from Carpio 2012 http://emedicine.medscape.com/article/1168784-overview#a0199

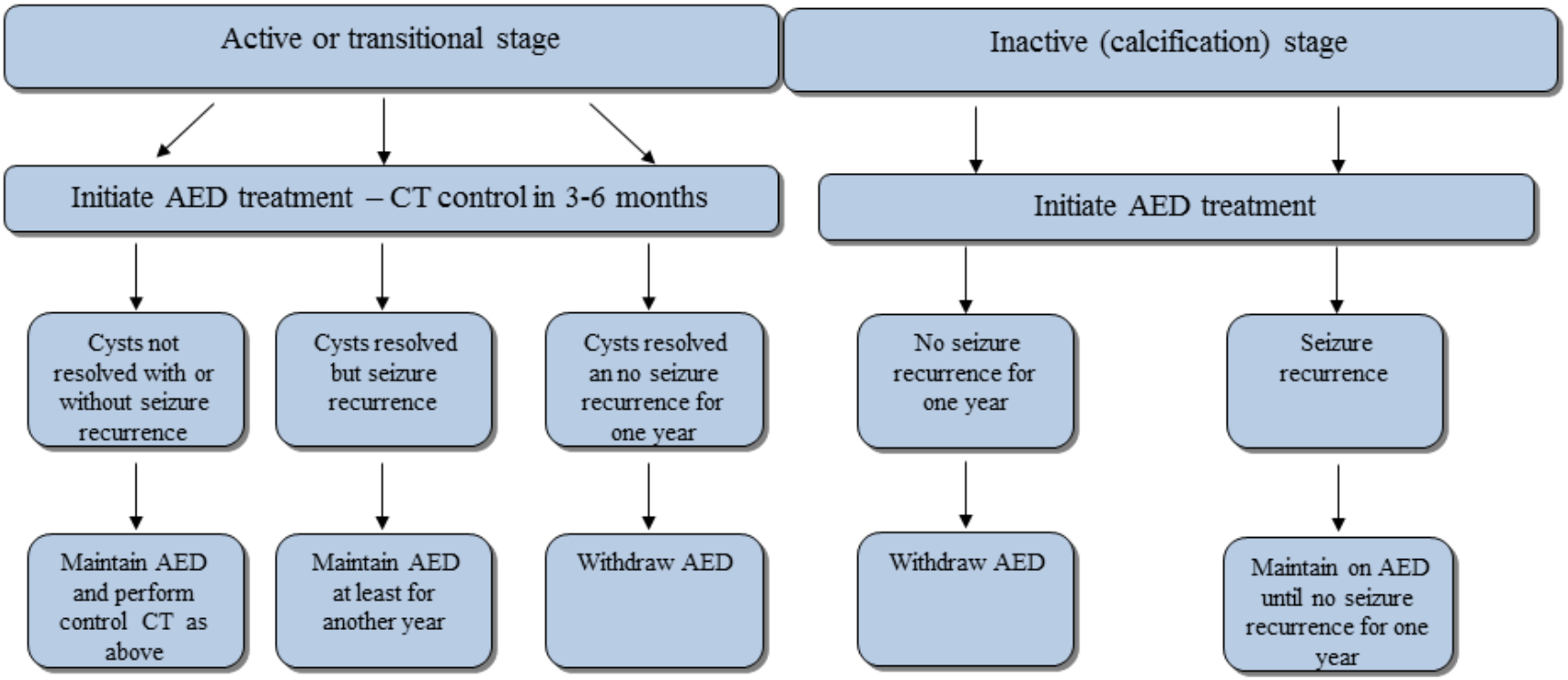
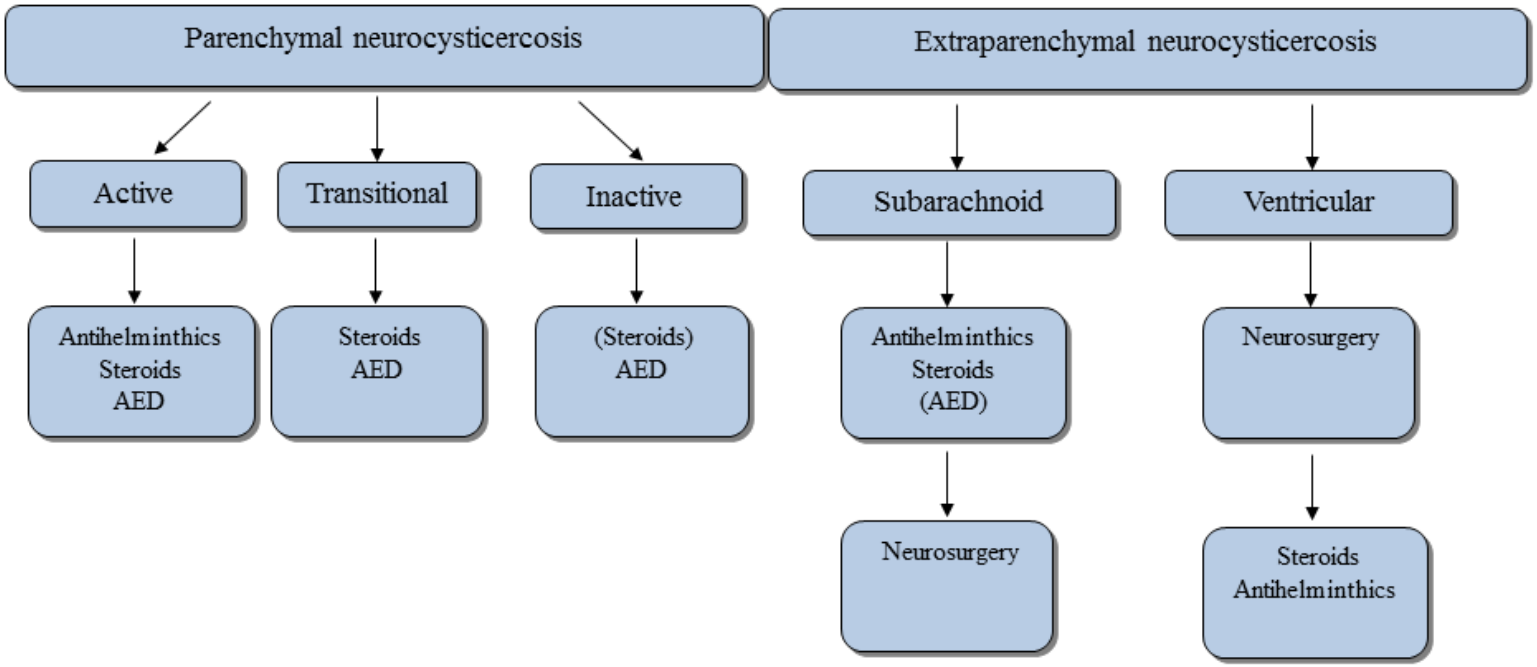


Figure 3. Overview on treatment of neurocysticercosis according to currently suggested guidelines (Nash & Garcia 2011; Carpio 2012). Treatment approach in people with neurocysticercosis is divided into those with intraparenchymal and those with extraparenchymal disease. According to disease stage and localization of lesions different approaches are advocated. Antihelminthic drugs are only administered in active disease. If there are signs of cerebral oedema steroids are used with and without antihelminthic medication. Steroids are also used prophylactically together with antihelminthic medication in active disease without cerebral oedema, as oedema may develop over the course of treatment. In multicystic disease with obvious oedema (=encephalitis) antihelminthic medication must not be used and the treatment of choice are steroids alone or in combination with anti-epileptic medication. The latter is used in all stages whenever epileptic seizures are present. In subarachnoid disease antihelminthic medication together with steroids may have to be given in higher doses and over longer time than in patients with intraparenchymal disease. Neurosurgery may be necessary if hydrocephalus develops. The same is true for ventricular disease, where the first line treatment is surgery with removal of the ventricular cysts. If inflammation is present medical treatment with antihelminthic drugs and steroids may be an option (Nash & Garcia 2011).

AED=anti-epileptic drugs



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