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Detection of *Taenia solium* Taeniasis Coproantigen Is an Early Indicator of Treatment Failure for Taeniasis

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Taenia solium **causes taeniasis and cysticercosis, a zoonotic complex associated with a significant burden of epilepsy in most countries. Reliable diagnosis and efficacious treatment of taeniasis are needed for disease control. Currently, cure can be confirmed only after a period of at least 1 month, by negative stool microscopy. This study assessed the performance of detection by a coproantigen enzyme-linked immunosorbent assay (CoAg-ELISA) for the early evaluation of the efficacy of antiparasitic treatment of human *T. solium* taeniasis. We followed 69 tapeworm carriers who received niclosamide as standard treatment. Stool samples were collected on days 1, 3, 7, 15, 30, and 90 after treatment and were processed by microscopy and CoAg-ELISA. The efficacy of niclosamide was 77.9% (53/68). Thirteen patients received a second course of treatment and completed the follow-up. CoAg-ELISA was therefore evaluated for a total of 81 cases (68 treatments, 13 retreatments). In successful treatments ($n = 64$), the proportion of patients who became negative by CoAg-ELISA was 62.5% after 3 days, 89.1% after 7 days, 96.9% after 15 days, and 100% after 30 days. In treatment failures ($n = 17$), the CoAg-ELISA result was positive for 70.6% of patients after 3 days, 94.1% after 7 days, and 100% after 15 and 30 days. Only 2 of 17 samples in cases of treatment failure became positive by microscopy by day 30. The presence of one scolex, but not multiple scolices, in posttreatment stools was strongly associated with cure (odds ratio [OR], 52.5; $P < 0.001$). CoAg-ELISA is useful for the assessment of treatment failure in taeniasis. Early assessment at day 15 would detect treatment failure before patients become infective.**

Neurocysticercosis (NCC) is the most frequent cause of late-onset epilepsy in the world and a growing public health problem in developed countries (8, 9, 12, 30). This zoonotic cestode has a complex two-host life cycle. Humans are the only definitive host of the adult tapeworm. However, both humans and pigs may harbor the larval stage (cysticerci) in their tissues (10). The tapeworm is composed of a scolex or head, a neck, and a series of proglottids (immature, mature, and gravid as they are separated from the scolex by new proglottids). Each gravid proglottid contains around 50,000 eggs, which are intermittently removed and released into the environment with the feces. Humans and pigs are infected by ingestion of *Taenia* eggs by the fecal-oral route. The embryos contained in the eggs are released, cross the intestinal mucosa, and are then dispersed throughout the body by the circulatory system. Humans complete the cycle when they consume poorly cooked pork infected with cysticerci, which then develop into an intestinal tapeworm (33).

The standard diagnostic tool for taeniasis is stool microscopy to detect *Taenia* sp. eggs after concentration. Its specificity is high with a trained operator, but its sensitivity is low because of the variable numbers of eggs excreted in stools and the small volume of stools that are examined (10). Also, microscopy cannot distinguish between *Taenia solium* and *Taenia saginata*. Detection of specific tapeworm antigens in stools using a coproantigen enzyme-linked immunosorbent assay (CoAg-ELISA) has better diagnostic sensitivity. The CoAg-ELISA for *T. solium* was developed by Allan and collaborators and is currently the most reliable test for the diagnosis of taeniasis. This ELISA is performed using hyperimmune rabbit sera raised against somatic antigens of the adult *T. solium* worm (1). In epidemiological settings, this assay detects around 2.5 times more cases of taeniasis than does microscopy (3, 11). Somatic antigens are released even at immature, prepatent tapeworm stages and can be detected from the first week after infection, as demonstrated in animal models (6). This technique was 98% sensitive and 99% specific when evaluated by Zamora et al. in 2004 using 42 known positive stool samples and 163 controls (75 stool samples from patients from an area of Peru where taeniasis is not endemic and 88 stool samples from U.S. volunteers) (34). Serum stage-specific antibodies against the adult tapeworm can also be detected by immunoblotting or ELISA. These assays seem highly sensitive and specific; however, their positive predictive value depends on the survival span of circulating antibodies, about which much remains unknown (15, 16, 21, 32).

Taeniasis/cysticercosis is an eradicable zoonotic disease of which the tapeworm carrier is the only source of infection; thus, effective treatment of taeniasis is an important intervention in clinical settings, as well as for control programs (29). Currently, niclosamide is considered the treatment of choice, and its efficacy is claimed to be >90% (4, 5, 7). However, posttreatment evalua-

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tions have been based on microscopy, likely overestimating the efficacy of niclosamide. This study was designed to assess the ability of CoAg-ELISA to detect treatment success or failure early for *T. solium* tapeworm carriers.

MATERIALS AND METHODS

Study design. This was a prospective study of recently treated *T. solium* tapeworm carriers to assess the performance of CoAg-ELISA in defining the efficacy of treatment on days 3, 7, 15, and 30 posttreatment.

Study population and settings. This study was performed at the Center for Global Health of the Universidad Peruana Cayetano Heredia in Tumbes, on the Northern Coast of Peru (24). The study included consecutive patients with taeniasis due to *T. solium* who received antiparasitic treatment with niclosamide (7, 18). This diagnosis was confirmed by the recovery of parasitological material (gravid proglottids or a scolex) for histological species definition and/or PCR followed by restriction enzyme analysis (23). Participants were asked to collect all immediate posttreatment stools and to collect follow-up stool samples on days 1, 3, 7, 15, 30, and 90 posttreatment. These patients had been diagnosed in epidemiological studies by our group in the Tumbes area and had been prescribed treatment according to the standard of care (oral niclosamide in a single dose of 2 g for adults, 1.5 g for children weighing more than 35 kg, and 1 g for children weighing 11 to 34 kg). All patients were asked to consume a low-fiber diet 3 days before antiparasitic treatment and were purged with NuLytely (105 g/liter polyethylene glycol 3350, 1.43 g/liter sodium bicarbonate, 2.8 g/liter sodium chloride, 0.37 g/liter potassium chloride) 2 h before and after treatment (7, 18). The study and consent forms were reviewed and approved by the Institutional Review Board of the Universidad Peruana Cayetano Heredia.

Study intervention. All stool samples excreted on the day of treatment were collected, and a macroscopic search for proglottids and scolices was performed. Follow-up stool samples were also collected on days 1, 3, 7, 15, 30, and 90 after treatment and were processed for both microscopy and CoAg-ELISA. Successful treatment was defined as negative results for egg detection by microscopy and negative results by CoAg-ELISA at day 90 or later. Treatment failure was defined as a positive stool microscopy result or two consecutive CoAg-ELISA-positive stool samples at day 30 posttreatment or later. Uncured patients received a second course of niclosamide and were monitored in a similar manner for an additional 90-day period.

Preparation and analysis of fecal samples. Stool samples were collected, preserved by homogenization in phosphate-buffered saline–formaldehyde at 5% (1:4), shaken, and left to sediment. Twenty milliliters of the homogenized sample was processed by stool microscopy after concentration (tube sedimentation) (25, 31).

Coproantigen ELISA detection. Aliquots (1.5 ml) of the stool supernatant were used for CoAg-ELISA after centrifugation at room temperature at 3,200 × *g* for 10 min. The CoAg-ELISA technique was performed essentially as described by Allan et al., by using hyperimmune rabbit anti-*T. solium* IgG as the capture antibody and peroxidase-labeled goat anti-*T. solium* IgG as a conjugate (1, 3). Processed samples were read with a spectrophotometer (Molecular Devices Inc., Sunnyvale, CA) at 650 nm. Using a known positive pool (P1), we calculated the percentage of positivity (PP) as (optical density [OD] of the sample)/(OD of P1) × 100, in order to increase the comparability of the results between plates. A cutoff was determined using a receiver operating characteristic (ROC) curve.

Data analysis. Positive predictive values of CoAg-ELISA for treatment failure and negative predictive values of CoAg-ELISA for cure at days 3, 7, 15, and 30 after niclosamide treatment were extracted from 2 × 2 contingency tables comparing the CoAg result with the treatment outcome (cure or failure) at each time point. The proportions of positive CoAg-ELISA results in treatment failures and negative CoAg-ELISA results for cured patients were calculated as cumulative proportions at each time point. A similar analysis was done for microscopy. Finding the tapeworm scolex in the immediate posttreatment stool sample was also evaluated as a predictor of efficacy. Data analysis was performed on STATA software (StataCorp, College Station, TX).

TABLE 1 Cumulative percentages of CoAg-ELISA results in the follow-up of antiparasitic treatment of *T. solium* infection

Days after treatment	Successful treatments ($n = 64$)		Treatment failures ($n = 17$)	
	% negative CoAg results (no. of patients with negative results/total no.)[a]	95% CI	% positive CoAg results (no. of patients with positive results/total no.)[a]	95% CI
3	62.5 (40/64)	50.2–73.3	70.6 (12/17)	60.1–96.0
7	89.1 (57/64)	79.1–94.5	94.1 (16/17)	72.7–98.6
15	96.9 (62/64)	89.3–99.0	100 (17/17)	81.5–100
30	100 (64/64)	94.5–100	100 (17/17)	81.5–100
90	100 (64/64)	94.5–100	100 (17/17)	81.5–100

[a] Not all patients complied with sample collection at all times. This analysis loses a total of 12 weakly positive results at day 7 ($n = 1$), 15 ($n = 5$), 30 ($n = 2$), and 90 ($n = 4$) in successful treatments and 1 negative result at day 90 in treatment failures.

RESULTS

Between 2004 and 2007, parasitic material was recovered and allowed species definition in 86 individuals with a presumptive diagnosis of taeniasis who had received antiparasitic treatment followed by a purgative according to the standard of care. Sixty-nine of these individuals were confirmed as *T. solium* tapeworm carriers; 16 were diagnosed as *T. saginata* carriers; and in 1 case, the characterization was inconclusive. The 69 patients with *T. solium* infection were mostly women (48 [69.6%]) and had a mean age of 33 years (standard deviation [SD], 15.7 years). Follow-up of the initial treatment was completed for 68 out of 69 patients. Treatment efficacy in this population was 77.9% (53/68; 95% confidence interval [95% CI], 66.7 to 86.2%). All 15 individuals with treatment failure had a positive CoAg-ELISA result, and all but 1 had a parasitological diagnosis (a finding of *Taenia* eggs [$n = 14$], proglottids [$n = 10$], or a scolex [$n = 9$]) as a confirmation of failure at day 30 or 90 or during retreatment. The individual without parasitological confirmation of treatment failure had consistently increasing CoAg-ELISA values at days 3, 7, 15, and 30, and a decision to re-treat was taken; samples became CoAg-ELISA negative after retreatment. Thirteen of the 15 uncured patients received a second course of niclosamide and were followed up in a similar manner; 11 out of 13 were cured after the second treatment. Failure after a second treatment was demonstrated in one case by a gradual increase in coproantigen levels (up to 8 times on a logarithmic scale) after an initial drop to borderline immediately after treatment and by expulsion of more parasitic material after a third retreatment in the other case. Thus, we considered 81 courses of treatment and follow-up (68 treatments and 13 retreatments) in order to evaluate the performance of CoAg-ELISA and microscopy at days 3, 7, 15, and 30.

Performance of the coproantigen ELISA in posttreatment follow-up. The cumulative proportions of cured and uncured patients and their respective CoAg-ELISA results are shown in Table 1. In every case of treatment failure, the CoAg-ELISA was positive after day 15 of follow-up. For cured patients, CoAg-ELISA results became negative at day 30 in all cases.

The predictive values of a negative CoAg-ELISA result for suc-

TABLE 2 CoAg-ELISA results at days 3, 7, 15, and 30 after treatment

Days after antiparasitic treatment[a]	CoAg-ELISA result[b]				PV[c] (% [no. of corresponding results/total]) of:	
	Positive		Negative			
	NC	C	NC	C	Failure	Cure
3	12	17	2	40	41.4 (12/29)	95.2 (40/42)
7	16	4	0	50	80 (16/20)	100 (50/50)
15	16	7	0	55	69.6 (16/23)	100 (55/55)
30	17	2	0	62	89.5 (17/19)	100 (62/62)

[a] Not all patients complied with sample collection at all times.
[b] NC, patients who were not cured; C, cured patients.
[c] PV, predictive value.

TABLE 3 Cumulative percentages of microscopy (after concentration) results in the follow-up of antiparasitic treatment of *T. solium* infection

Days after treatment	Successful treatments ($n = 64$)		Treatment failures ($n = 17$)	
	% negative microscopy results (no. of patients with negative results/total no.)[a]	95% CI	% positive microscopy results (no. of patients with positive results/total no.)[a]	95% CI
3	79.7 (51/64)	68.2–87.7	11.8 (2/17)[b]	3.6–34.7
7	92.2 (59/64)	83.0–96.5	11.8 (2/17)	3.6–34.7
15	100 (64/64)	94.5–100	11.8 (2/17)	3.6–34.7
30	100 (64/64)	94.5–100	23.5 (4/17)	9.7–47.6
90	100 (64/64)	94.5–100	41.2 (7/17)	21.5–64.3

[a] Not all patients complied with sample collection at all times. This analysis loses a total of 8 negative results at days 7 ($n = 2$), 15 ($n = 2$), 30 ($n = 2$), and 90 ($n = 2$) in treatment failures.
[b] Two positive results were found at day 3; these two uncured patients had negative results at days 7, 15, and 30 and became positive at day 90.

cessful cure were 95.2% (40/42) at day 3 and 100% thereafter (50/50 at day 7, 55/55 at day 15, and 62/62 at day 30). The predictive values of a positive CoAg-ELISA result for the detection of treatment failure were 41.4% (12/29) at day 3, 80.0% (16/20) at day 7, 69.6% (16/23) at day 15, and 89.5% (17/19) at 1 month (Table 2). The higher predictive value at day 7 than at day 15 is most likely an artifact due to the fact that fewer samples were examined on that particular day.

Stool microscopy at posttreatment follow-up. The same 81 follow-up courses were considered by stool microscopy. Stool microscopy was a poor indicator of treatment success even at day 30 of follow-up. The cumulative proportions of cured and uncured patients and their respective parasitological results are shown in Table 3.

Posttreatment recovery of the tapeworm scolex. We were able to find at least one tapeworm scolex in the immediate posttreatment stools of 58 of 81 patients (71.6%). In five cases (5/58), more than one scolex was detected. Almost all patients from whom at least one scolex was recovered were cured (56/58; 96.6% [95% CI, 88.3 to 99.1%]), compared with only 34.8% of patients in whom no scolex was found (8/23; 95% CI, 18.8 to 55.1%). It follows that scolex recovery was strongly associated with treatment efficacy (56/58 versus 8/23; odds ratio [OR], 52.5; 95% CI, 10.1 to 273.6; $P < 0.001$). The only two treatment failures in this group corresponded to 2 of the 5 patients from whom more than one scolex was recovered.

DISCUSSION

CoAg-ELISA can reliably predict treatment success or failure as early as 7 days after treatment of human taeniasis caused by *Taenia solium*. In this series, a negative coproantigen result at day 7 or later was an absolute indicator of cure, while only 8% of cured patients remained CoAg-ELISA positive at day 7, and <4% were positive after 1 month. The CoAg-ELISA can identify treatment failures several weeks before the cases become infective, as shown in this work, confirming much earlier studies, in 1988, using a *Hymenolepis diminuta* rat model (22). Not surprisingly, microscopy was unable to detect treatment failures by days 7 and 15 and detected only 2 out of 17 failures by day 30 (11.8%). It is highly likely that a great proportion of the tapeworm strobila is eliminated after treatment, and thus, it takes weeks or months for the parasite to pass gravid progglotids or eggs again. In *de novo* infections, the prepatent period is assumed to be around 3 months (27, 33).

A few cured patients were CoAg-ELISA positive at 7, 15, or 30 days after treatment. We cannot rule out the possibility that these tapeworms did not die immediately but were only weakened and that the patients were cured later by natural evolution or by their own immunity. This is unlikely, however, since their antigen levels dropped abruptly and stayed very low (though positive as defined by the ELISA cutoff). Alternatively, some tapeworm antigens or cell remnants in the gastrointestinal tract may have remained there and been slowly excreted. Positive results at days 15 ($n = 7$) and 30 ($n = 2$) correspond to low, borderline false-positive results according the calculated cutoff. *Taenia* sp. eggs were found in the stools of two cured patients at day 7 after treatment. This finding is relevant, because even when a purge is used, some treated patients can still be a source of infection even days after treatment. This series was composed of patients treated in a health center after parasitological diagnosis and after a previous period of diet and purging (18). Our results cannot be extrapolated to mass population-based treatment campaigns with niclosamide, where the likelihood of further infectivity should be higher.

As previously reported by our group (18), some patients expelled more than one worm scolex. We found four (8.2%) such cases after the first treatment course, a somewhat lower proportion than the 20% (4/20) reported by Jeri et al. in 2004 (18). Still, multiple *T. solium* infections are not such a rare event. In this series, such patients were less prone to cure and were all women. As expected, scolex elimination is strongly associated with cure, except for individuals with multiple tapeworms (10).

An untreated group for purposes of comparison was not considered, because of ethical reasons, and thus, we cannot rule out the possibility that some parasites died by natural evolution instead of the antiparasitic effect of niclosamide, or that other patients were reinfected. None of these scenarios seem likely. Whether reinfection is possible in human *T. solium* infection is not known and has not been reported. The life span of *T. solium* tapeworms was claimed to be decades, but later epidemiological analysis suggested a few years (2, 17, 19). Thus, considering a life span of 3 years, the natural death of well-established tapeworms in a 2-week period could not account for more than 1 of the 75 (1.3%) tapeworms.

This series included a selected subgroup of patients who were treated after diet and purging, and from whom parasite material was recovered, and thus, we cannot extrapolate the efficacy of

niclosamide (77.9%) to all tapeworm carrier cases. Some considerations here deserve further elaboration. Most other studies on niclosamide have reported higher efficacies, for example, 37/43 (86%) (13), 678/766 (88.5%) (mostly *T. saginata*) (26), 46/47 (98%) (*T. saginata*) (28), and others (5, 7). Efficacy was probably found to be lower in this study because of the higher sensitivity of CoAg-ELISA as a tool for demonstrating the persistence of the parasite. These treatment conditions can hardly have been achieved in massive treatment campaigns (which also do not normally achieve 100% coverage); consequently, it is likely that the efficacy of niclosamide in community-based treatment would be even lower. A lack of efficacy of 20% or more can seriously affect the ability to achieve the objectives of control programs in taeniasis/cysticercosis. In clinical settings, the diagnosis, treatment, and follow-up of *T. solium* tapeworm carriers is also relevant for patients with neurocysticercosis, among whom a higher prevalence of taeniasis, related to the severity of infection, can be expected (14).

The positive predictive value of coproantigen detection was not perfect. If the decision is made to define treatment success at day 7, 7 to 8% of patients with false-positive coproantigen results could end up receiving an unnecessary additional course of treatment. The risks associated with this retreatment are minimal, however, since the effect of niclosamide is only intraluminal, and adverse events are mild and transient.

Tapeworm carriers are a source of infection for themselves, their households, and their villages (19, 20). The effectiveness of treatment must be maximized, and thus, a rapid confirmation of cure (or treatment failure) is important. To allow a period of months for the detection of treatment failure increases the likelihood of losses to follow-up, and thus, some tapeworm carriers will again become sources of infection. Cure of the tapeworm carriers, the only source of infection, is critical for the control of this zoonotic disease. The CoAg-ELISA is a useful technique for early detection of treatment success or failure. Unfortunately, there is no commercial source for this test at this time. This technique must be made available in regions of endemicity at a low cost, in a robust format, to allow its use under field conditions. When available, follow-up with the CoAg-ELISA should be used routinely to evaluate treatment efficacy.

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