Strongyloidiasis

[Editor: This document is a synthesis of the evidence relating to diagnosis and management of strongyloidiasis, and commentary on this evidence from individuals with particular expertise or interest. Strongyloidiasis has proven to be a controversial topic, and there is not necessarily consensus between all the contributors, particularly about the application and interpretation of the serology test for strongyloides. We provide here the rationale and thinking behind the strongyloides component of the 'worms' protocols.

Other aspects of the 'worms' protocol have only been partially covered.

The key differences between this protocol and the earlier edition of the CARPA manual are:

- *Encouraging a higher index of suspicion for strongyloides, based on broader range of clinical symptoms that may be due to strongyloides infection*
- *Stressing the importance of excluding strongyloidiasis in people who will be given immunosuppressive treatments and may have occult strongyloides infection*
- *Treatment with ivermectin for people over the age of five years*

Population screening has been advocated by two of the major contributors (WP and RS), however, other advisers and the editorial committee believe there are significant unresolved problems with the interpretation of the serology result when used as a screening tool.

WP and RS also recommend using serology to monitor effectiveness of treatment. We believe this is not warranted without a good understanding of the likelihood of reinfection and the natural decay rate of sero-positivity. However, if there is clinical suspicion of re-infection or persisting infection, then repeated serology may clearly be warranted.

Sources used for this document were

- *Direct searching and appraising of the available literature*
- *Evidence summaries from 2002 Darwin Evidence Based Medicine workshop (prepared by Drs Johnston and Morris)*
- *Discussion paper for the CARPA manual prepared by Drs Page and Van Ingen Schenau and Ms Karen Dempsey*
- *Community newsletter about Strongyloidiasis in Aboriginal Australia by Assoc Prof Speare*
- *Contributions and commentary on the above documents provided to the CARPA editor by*
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Issues are discussed under the following headings:

- *Prevalence*
- *Aetiology and life cycle*
- *Clinical picture*
- *Diagnosis*
- *Treatment*
- *Community control strategies.]*

Prevalence

An estimated 50 to 100 million people are infected worldwide[1,2] and community prevalence rates of above 5% are considered hyperendemic.[3] In Australia, infection with strongyloides is common in northern Aboriginal communities and individual cases are also seen among immigrants from tropical countries and returned travellers, including military veterans.[4]

Selected groups in the NT have had faecal or serological testing, however information about the proportion of people sampled, how they were selected and which segments of the population they were drawn from is not readily available. In general these have demonstrated relatively high and widely varying rates of positivity. See table 1.

A well-designed long-term prevalence study of parasites in children from five Aboriginal communities in the Kimberly region of Western Australia found a prevalence in stools of only 0.26%.[5] Other studies from communities in the Kimberleys and north Queensland have reported rates of around 30%.[6]

The Alice Springs Hospital laboratory reports finding strongyloides (and the other worms covered in the CARPA protocol, except that hookworm is not common in children that have not been living in the Top End) in stool specimens from Central Australian children, but no analysis of the relative frequency of different gut parasites has been performed (pers. comm. Fran Morey ASH micro lab).

Prevalence: Comment/conclusion

In spite of the limitations of studies to date and the limitations of interpreting serology in endemic populations (see section on diagnosis below), it is reasonable to conclude that there is a very high prevalence of strongyloides infection in northern Australian Aboriginal communities. The high prevalence is of clinical importance because of the risk of precipitating severe disseminated disease in asymptomatic individuals, with immunosuppressant therapies (see section on clinical picture below).

Table 1: Summary of studies of indices of infection with strongyloides in Aboriginal patients in the Top End of the NT

Group	Year	Method	Percent positive	Reference
East Arnhem community 1	1996	Single stool specimens using the Harada-Mori technique	15% positive	Aland7
East Arnhem community 2	1993	Single stool specimens	41% of 29 people tested	Flannery8
East Arnhem community 3	1993	Serology	59.6%	Flannery8
Royal Darwin Hospital study of children under five admitted with diarrhoea.	2002	Stool examination	7.2% (12 cases in total)	Kurkuruzovic9
Cases diagnosed in under five-year-olds admitted to RDH over a one-year period	1993	Stool examination	37 cases	Fisher10
Patients with incidentally identified eosinophilia. (Clinical audit by GP members of the Top End Division of General Practice)	2001	Serology	56% positive 32% of 143 patients with eosinophilia were tested	Page11

Table 2: Symptoms possibly associated with S. stercoralis infection in children before and 24 days following treatment with either albendazole or ivermectin (N = 333)15

Symptom	Before treatment	24 days after treatment	X2	p
Cough, without evidence of a cold	59 (18%)	22 (6%)	19.2	p<0.001
Abdominal distension	35 (11%)	10 (3%)	14.9	p<0.001
Diffuse itching	17 (5%)	8 (2%)	3.4	
Visible urticaria	11 (3%)	2 (0.6%)	6.4	p<0.050
Larva migrans	9 (3%)	0	9.1	p<0.010

Aetiology and life cycle

The usual mode of infection is penetration of skin by infective larvae from the soil or direct contact with faeces. The larvae are then carried in the bloodstream to the right side of the heart. They enter the alveolar spaces in the lungs, ascend the bronchial tree and are swallowed. In the small intestine the larvae mature into adult female worms and penetrate the mucosa of the proximal small bowel where they lay eggs. This occurs 17 to 28 days after the initial infection. The eggs hatch in the intestinal mucosa to release rhabditiform larvae that migrate to the lumen of the bowel.

Three cycles are possible.

1. **Direct host-soil-host cycle**: The rhabditiform larvae in the faeces become infective filariform larvae that can then infect a host. This is direct transmission from faeces to new host. This direct cycle is not seen in other common helminths such as hookworm and Trichuris, which require maturation of eggs in the soil before becoming infective. Thus, faeces is a direct source of contamination.
2. **Indirect cycle:** The rhabditiform larvae in the faeces enter the soil and develop into free-living male and female adults, which reside and reproduce in the soil, thus creating a reservoir of infection independent of the human host. Current thinking is that there is only one free-living cycle and it is thought that faecal contaminated soil is infective for about three weeks (pers. comm. Assoc Prof Rick Speare).
3. **Autoinfection or hyperinfection cycle:** The rhabditiform larvae develop into infective filariform larvae before they are passed in the stool. The filariform larvae can penetrate the colonic wall or perianal skin and enter the circulation to repeat the migration that establishes ongoing internal reinfection. Replication occurs through a process called parthenogenesis. Migratory routes involving organs other than the lungs may predominate.[12] This cycle allows strongyloidiasis to persist for decades after the host has left an endemic area.

Aetiology: Comments/conclusions

Infection, which may or may not be symptomatic, can persist in an individual for decades.

Clinical picture

Acute infections in children

A study of 333 children in Zanzibar, found to be stool-positive for strongyloides infection, reviewed symptoms before and after treatment with either albendazole or ivermectin. The results are summarised in table 2. This gives an indication of what the more common manifestations of acute infection in children may be.

Both Australian and international studies[9,13] including a systematic review[14] demonstrate that:

- Malnutrition predisposes children to infection with strongyloides

- Infestation with helminths, including strongyloides, are unlikely to be an important contributor to poor growth in children

Children with infestation with strongyloides are more likely to be hypokalaemic and wasted than children with diarrhoea caused by other pathogens.[9]

Potential symptoms in children and adults with chronic infection
Textbooks[1,16] report that infection is usually asymptomatic but may affect any organ of the body including:

- Skin: larva currens (migratory, changing hour to hour), raised itchy patches, lesions over lower back and buttocks, recurrent urticaria
- Respiratory: dyspnoea, bronchospasm, gross haemoptysis, pneumonia, lung abscess
- GIT: subacute obstruction or segmental ileus, ulcerative colitis with intestinal perforation and peritonitis, vague abdominal complaints, epigastric pain and tenderness
- Urinary tract infections, granulomata and/or abscesses occur in liver and kidney[17]
- CNS signs or symptoms
- Systemic: gram-negative bacteraemia or meningitis, disseminated strongyloidiasis
- Blood: eosinophilia is present in 10–50% of people with positive tests for strongyloidiasis.
- Abnormal chest X-rays[18]
- MRI is able to detect CNS changes that a CAT scan shows as negative[2]

Disseminated strongyloidiasis
Asymptomatic infection can persist for decades and not be recognised. There have been many reported deaths in patients commenced on high dose immunosuppressive therapy in whom asymptomatic infection was not identified, and disseminated disease was precipitated.[19,20,21]

Clinical picture: Comments/conclusions
In the Top End there are three important clinical manifestations of infection with S. stercoralis in Aboriginal communities.

1. Acute gastrointestinal infection in children. The more common symptoms appear to be diarrhoea, abdominal distension, urticaria, larva migrans and possibly cough. The diarrhoeal stools have a distinctive odour. Pseudo intestinal obstruction can occur. While strongyloides infection is associated with wasting and hypokalaemia in children, it is not an important contributor to malnutrition. However, malnutrition is a risk factor for acquiring strongyloides.
2. Gram-negative meningitis or septicaemia secondary to intestinal parasites facilitating the entry of gut organisms into the blood stream. This may occur in otherwise asymptomatic adults.
3. Disseminated strongyloidiasis in patients on immunosuppressive therapy. There have been several deaths in the Top End over the last 15 years in patients on high dose immunosuppressive therapy in whom asymptomatic infection was not identified. Protocols for excluding latent infections with organisms such as tuberculosis, strongyloides and melioidosis, prior to immunosuppressive therapy are in place in the Top End.

Diagnosis of Strongyloidiasis

Microscopy

Microscopy is the gold standard for diagnosis. This is usually from faeces. However, other body fluids such as duodenal aspirate and sputum in hyperinfective cases may show the parasite.

Faecal Microscopy

Specificity is high but sensitivity is low (0–50%)[32] and multiple specimens are required.

Cultures

Agar plate is presently considered the most sensitive culture technique (78–100%).[32]

Its limitation is that it relies on detection of viable larvae, and this becomes increasingly difficult as the time from collection to examination of the specimen increases.

The Baermann stool concentration technique (as with the Agar plate) requires viable larvae.[22] The formalin-ether stool concentration techniques has a reported 13–55% sensitivity.32 Harada Mori culture is reported to have a sensitivity of ~26%.

Microscopy and culture: Conclusion/comments

In acute strongyloidiasis and in disseminated strongyloidiasis (high excretors) sensitivity is improved. This is particularly true in hospital settings where the faecal specimens can be examined on the same day. However, for adults who are more likely to be chronic carriers and low excretors, microscopy and culture may be less useful.

Multiple specimens should be sent to improve the sensitivity.

Table 3: A summary of studies of strongyloides ELISA

Publication	Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Faecal test
Schaffel24 Brazil: tertiary hospital	2001	68%	89%	48%	95%	Three stool examinations
Gyorkos25 Population-based study: SE Asian refugees in Canada	1990	95%	29%	30%	95%	Stool examination (not described)
Genta26	1988	88%	99%			Charcoal culture
Bailey27	1989	97%	99%			Culture
Lindo28	1994	80 and 85% (two techniques used)	94 and 97%			Agar plate
Mangali29	1991	95%	96.6%			Tube culture
Gam30	1987	96.6%	98%			
Muhiudden31	1995	92.8%	100%			
Uparanukraw32	1999	63.6%	95.4%			Agar plate

Serology

The strongyloides ELISA test detects serum IgG antibodies to Strongyloides stercoralis. The ELISA uses an arbitrary cut-off optical density point to determine positive and negative cases. A high cut-off point will have a lower sensitivity, higher specificity and therefore more false negatives. A low cut-off point will have a higher sensitivity and many false positives. The period from infection to seroconversion is unknown and acute cases may be stool positive but seronegative.[9] The proportion of people who remain seropositive after successful treatment is not known.[6] Filariasis and ascariasis can cause cross-reactivity in the ELISA test.[16] However, in remote communities in the Northern Territory where these parasites are uncommon, they are unlikely to contribute to false positives.[23] A summary of serological studies is presented in table 3.

Few of the studies calculated the predictive value of the test for the particular population that was studied. This information is important for the interpretation of the test and needs to be calculated for different population groups as it is greatly affected by the prevalence of the infection in each population. A large recent study of serology among Brazilian in-patients (Schaffel24 – see table below) calculated a positive predictive value (PPV) of 48% and a negative predictive (NPV) value of 95% for the strongyloides ELISA. This PPV means that only about half of those individuals with positive serology actually had strongyloides infection.

The NPV means that 95% of those with negative serology did not have infection with strongyloides. Another population-based study of SE Asian refugees in Canada found the test had a predictive value of 30%.

Statistical techniques have been developed to try to overcome these limitations of available tests for strongyloides and other parasites where results from stool examinations generally underestimate the prevalence, and serology generally results in overestimation. Using a Bayesian approach, simultaneous inferences about the population prevalence and the sensitivity, specificity, and positive and negative predictive values of each diagnostic test are possible.[33] These may be adaptable to the setting of Aboriginal communities in northern Australia.

In non-endemic communities serology has been used to monitor the effectiveness of treatment[34,35] in a manner analogous to the use of treponemal serology to monitor treatment for syphilis. These studies have shown variability in rate of decline of IgG ELISA following treatment. Anecdotally, some practitioners in northern Australia believe that with adequate treatment, serology should become negative within six months. Studies are needed to validate these observations.

Comments/conclusions: Strongyloides serology

Serology is useful, particularly for excluding infection in adults. It is also useful for diagnosing the condition in patients with symptoms, or those at particular risk, such as those about to commence immunosuppressive therapy. Positive tests need to be interpreted in the light of the clinical picture and the original reason the test was done.

The role of serology in the follow-up of individual patients after treatment is strongly advocated by some practitioners. Some clinicians have found it to be useful in patients in non-endemic communities. However, the meaning of positive and negative results requires further study in endemic populations. Until there is better evidence, and better consensus among those with expertise, it is not appropriate that CARPA protocols include follow-up serology. In our view testing prior to immunosuppressive therapy is a more practical way to prevent disseminated disease in individuals than using resources to chase people at six and 12 monthly intervals to ‘ensure cure’ especially when those individuals live in endemic communities and are still at risk of re-acquiring the infection at a future time. Though disseminated strongyloidiasis can occur in people without apparent immuno-suppressing disease or treatment, we believe to be relatively rare and a case management approach rather than a population approach is appropriate.

An incomplete review of known cases at the Royal Darwin Hospital and discussions with relevant physicians suggests that, from anecdotal experience, it is anticipated that there will be up to two cases per year of disseminated strongyloides, almost invariably in people with clear immunosuppressive treatment. There are likely to be a number of cases that are not recognised.

As the predictive value of the test will vary with the prevalence of the infection in the population, more studies in Aboriginal communities are needed to guide the interpretation of the test in these settings. It is particularly important that the PPV and NPV of the test are known before its use can be considered for screening and treatment programmes. In our view it would be better to put resources into facilitating community development, with improved living conditions, which would have a positive impact on many diseases, than to put resources in to programs of mass screening and individual treatment for this one condition where the predictive value of a positive screening test is not known.

The interpretation of serology results in the equivocal range (borderline positive) is especially difficult. It may represent variance due to the testing technique, occult infection, treatment failure or persistent antibodies following successful treatment or spontaneous cure. Interpretation should be in the light of the clinical setting. Further study is needed.

Drug Treatment

Treatment of individuals has relied upon the use of antihelminthic drugs. The main two drugs in use at present are albendazole and ivermectin. Albendazole belongs to the benzimadole group of drugs which include mebendazole and thiabendazole. It also has activity against hookworm, while ivermectin does not. Nitazoxanide is a newer agent currently undergoing trials. It may prove to be effective against trichuris, giardia, cryptosporidium, hymenolepsis and strongyloides.[36]

Evidence summaries about the effectiveness of albendazole and ivermectin against strongyloides infection are presented below.

Albendazole

Search question

Among people with strongyloides infection, does albendazole treatment (compared to no treatment) reduce persistent infection as determined by faecal tests?

Types of evidence reviewed

Evidence summaries, systematic reviews and randomised controlled trials (identified from Clinical Evidence, Cochrane Library, PubMed).

Results

We identified no evidence summaries or systematic reviews. We did not identify any trials that randomised participants with symptoms. We identified two randomised trials that compared treatment with no treatment in individuals with a range of helminthic infections. The first study[37] found a cure rate of 38/47 (81%) with a single dose of 400 mg albendazole vs 17/53 (32%) in the control group. The second study38 described cure rates of 12/25 (48%) after albendazole daily for three days, versus 0/29 (0%) for particpants who received placebo.

Albendazole: Comments/conclusions

Treatment with albendazole is clearly superior to no treatment. In these two studies you would only need to treat two people before one would benefit. However, these treatment regimes were less intensive than that currently recommended in the CARPA STM third edition (three days without a repeat course).

Ivermectin

Search question

Does treatment with ivermectin reduce persistent symptoms or signs of strongyloides infection to a greater extent than the benzimidazole group of antibiotics (albendazole, thiabendazole or mebendazole)?

Types of evidence reviewed
Evidence summaries, systematic reviews and randomised controlled trial identified from Clinical Evidence, Cochrane Library and PubMed.

Results
We identified no evidence summaries or systematic reviews. We identified three trials comparing treatment with ivermectin with treatment with albendazole. A fourth study compared treatment with ivermectin to treatment with thiabendazole. The studies are summarised in table 4 (below).

Estimated cure rates
Ivermectin 83–97%
Albendazole 38–77%
(Thiabendazole 95% cf 100% with 95% having short-term adverse effects)

Cure ratios (alb/iver)	**Difference in cure rates**	**NNT**
0.54	38%	2.6
0.79	20%	5.0(randomisation not stated)
0.46	45%	2.2 (small study)

Ivermectin: Comments/conclusions
All comparative studies demonstrated higher cure rates for ivermectin compared with albendazole. You would need to treat between two and five people with ivermectin instead of albendazole before one person would benefit. All studies were conducted in high risk groups for strongyloides infection. Only the first study (Zanzibar) was conducted in an area in which S. stercoralis infection is endemic. The treatment regimen of the largest study was similar to that recommended in CARPA STM third edition for albendazole, except that the CARPA STM recommends repeating treatment with albendazole after one week. The CARPA STM third edition does not currently recommend ivermectin.

All experts agree that the CARPA STM fourth edition should recommend ivermectin as the drug of first choice for adults at a dose of 200 μg/kg for individual patients diagnosed with strongyloides. There is a diversity of opinion about whether patients should receive a single dose as recommended in the antibiotic guidelines, two doses (a week to 10 days apart) or even three doses at monthly intervals. The effectiveness of differing regimens has not been subjected to any trials. Those that argue for three doses do so because of (1) the desire to eradicate larvae that are extra-intestinal for transit periods of approximately one month and (2) concern about promoting resistance to ivermectin, if a single dose is not curative.

For the CARPA STM fourth edition, recommending multiple dosing in patients who are immunosuppressed, or have other reasons for clinical concern is certainly reasonable. Alternatively, two doses a week apart as a general recommendation for all cases may not be unreasonable to keep the guidelines simple, and address some of the worries about single dose therapy.

As the drug is not licensed for use in children the recommendation for albendazole should remain unchanged as the treatment regimen in children under five years. However, ivermectin may be recommended for two- to five-year-olds in individual children after specialist review.

Table 4: Comparative studies of the effectiveness of ivermectin

Population	**Treatment**	**Blinding**	**Random**	**Therapy repeated**	**Time of final follow-up** (No. of specimens examined for'cure')	**Parasitological cure rates**
301 children in Zanzibar 39 endemic	Ivermectin 200 mg/kg vs Albendazole 400mg daily for 3 days	Not stated	Y	N	24 days (2 specs) Albendazole 45%	Ivermectin 83%
211 Japanese adults40 area previously endemic	Ivermectin 6 mg stat vs Albendazole 400 mg/day for 3 days vs Pyrvinium pamoate 5 mg/kg for 3 days	Not stated	Not stated	Y 2 weeks later	12 months (2 specs)	Ivermectin 97% Albendazole 77% Pyrvinium 23%
53 residents of France41 non-endemic	Ivermectin 150–200 mg/kg vs Albendazole 400mg daily for 3 days	N ('open study')	Y	N	90 days (3 specs)	Ivermectin 83% Albendazole 38%
54 residents of USA42 non-endemic	Ivermectin 200 mg/kg stat vs Ivermectin 200 mg/kg on days one and two vs Thiabendazole (50 mg/kg/day) twice daily for 3 consecutive days	Y	Y	N	22 months (single spec only)	Ivermectin single dose 100% Ivermectin two consecutive doses 100% Thiabendazole 95%

Community control strategies

Infection is likely to disappear from a community with improving socioeconomic status as the environmental reservoir diminishes and the infected population ages and dies.[43] Screening and treatment of adults has been tried in Japan – where living conditions had improved markedly and people were no longer being infected from the environment – and at least 10% of the adult population continued to harbour the parasite. A five-year program in which 20% of the adult population were screened with faecal examination each year, and offered treatment if positive, resulted in a slow decline in prevalence rates.44 Chemotherapy directed at groups particularly at risk of infection has been suggested.43 This would require knowledge of prevalence rates, the value of screening tests used and the costs and benefits and the resources required. This information would need to be balanced against the costs and benefits of alternative approaches before a reasonable recommendation could be made.

Community control: Comments/conclusions

There is insufficient information available to determine the value of community-wide screening and treatment programs. In the light of the many other major public health issues facing Aboriginal communities, and difficulties with interpreting serology, CARPA should not recommend community screening and treatment of strongyloides.

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