Intestinal helminthic infections: a narrative review to guide the hepatogastroenterologist

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Abstract

Intestinal helminthic infections are not uncommon in Western Europe, mainly due to modern travel, emigration and globalization. Moreover, some helminthic infections are endemic in Western Europe and are part of the everyday clinical practice. The hepatogastroenterologist should therefore recognize and manage these patients or at least refer them to appropriate reference centers. Signs and symptoms are often unspecific or even absent. Discerning the disease at an early stage avoids expensive diagnostic testing, life-threatening complications and in some cases even further spread of the disease. This review article aims to guide the hepatogastroenterologist when suspecting a helminthic infection by addressing the most prevalent symptoms, summarizing the most probable associated helminthic entities, highlighting practical steps in diagnosis and available treatments. (Acta gastroenterol. belg., **2023,** 86, **460-473**).

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Introduction

Helminths are endemic in less industrialized and developing countries where they represent a serious public health burden. Nevertheless, intestinal helminths gain ground in any part of the world as a result of modern travel, emigration, climate change and consumption of overseas cuisines (1,2).

It is not always necessary to cross continental boundaries to become infected with worms. Some entities, notably *Enterobius* and *Toxocara* know a cosmopolitan spread and are therefore also endemic in Europe (3,4).

Alertness for the problem and critical thinking of gastroenterologists in developed countries should gain interest for several reasons. Severe disease requires years to develop and will only occur under special circumstances. Infections by *Strongyloides stercoralis*, a widespread intestinal nematode, will present as a disseminated, often fatal hyperinfection syndrome following immunosuppressive therapy often used in gastrointestinal patients. Other examples include bleeding varices as the first manifestation of occult *Schistosoma mansoni* infection in case of portal hypertension, and some liver flukes which manifest as cholangiocarcinoma after decades (5). Of note, only a minority of the helminths will cause disease. They likely behave as decent roomies, well-adapted to their hosts, causing no symptoms and deflecting the clinician's suspicion of helminthic infection.

Epidemiology

Helminths are parasitic worms. They are among the most prevalent gastrointestinal pathogens, infecting almost two billion people worldwide, especially in the (sub)tropics. New estimates from the Global Burden of Disease Study 2019 indicate that these helminth infections resulted in more than 1.5 million disability-adjusted life-years (DALYs), a number roughly equivalent to the DALYs caused by measles, malaria and tuberculosis. The number of helminthic infections is declining due to sustained social and economic development, improved sanitation, hygiene and periodic deworming campaigns (6-9). Soil-transmitted helminths (STH) are the most prevalent intestinal worms infecting people in low-income countries. The main species are *Ascaris lumbricoides*, whipworm (*Trichuris trichiura*), hookworms (*Necator americanus* and *Ancylostoma duodenale*) and *S. stercoralis*. These and other helminthic infections persist for decades after migration from endemic countries forming the so-called imported cases of helminthic infections in our regions (10).

In Europe and other industrialized parts of the world, prevalence rates of endemic STH decreased due to wastewater and food control measures implemented decades ago. The last STH outbreak in Western Europe dates back from 1948-1949 when *Ascaris* sp. infected up to 90% of the inhabitants of the German village of Ort Griesheim due to irrigation of the vegetable estates with fouled water (11). Establishing the exact prevalence of helminths in Western regions is challenging due to the peculiar but unspecific clinical presentation and the heterogeneity and incompleteness of data recording. Sparse clinical cases are reported in the form of case reports, scholarly publications and small case series. Belgian data reveal that antibodies against *Schistosoma* are most frequently detected, followed by antibodies against *Strongyloides* among immigrants to our country (Van Esbroeck M., personal communication). Most

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common species with a cosmopolitan distribution, which are therefore endemic in the Western world, are *Echinococcus (*especially *multilocularis)*, *Entero-bius*, *Toxocara*, *Trichinella* and *Taenia* (12-16).

Returning travelers rarely acquire tropical helminthiases when they respect simple hygienic rules. Furthermore, returning travelers often don't carry a worm burden sufficiently high to experience severe illness. Therefore, tropical helminthiasis remains more common, and merits a higher index of suspicion, in immigrants from endemic areas as compared to returning travelers (17).

Currently, there is no notification requirement for any intestinal helminthic infection in Europe, limiting the possibility of epidemiological studies of these infections.

Travel history and clinical features

The presentation of symptomatic disease in secondary and tertiary care settings masks a wider prevalence of asymptomatic infection (18-20). The symptomatology of helminthic infections varies upon several factors: type of the worm, duration of infection, the host's age and immunological status and worm burden.

The most common symptoms that prompt an investigation for helminths include peripheral eosinophilia, chronic diarrhea (with or without malabsorption syn-drome), unexplained cholestasis or mass images of the liver and cutaneous manifestations, of which anal itching is especially relevant to intestinal worms (10,12,14,17-24). Not infrequently, worms are encountered during endoscopy (25).

Appropriate investigation of these symptoms is based in part on relevant epidemiological exposure, including residency and travel in or to an endemic region (Figure 1), but also on risk behavior such as consumption of undercooked food, walking barefooted, contact with animals or swimming in freshwater. Besides the geographical exposure, efforts should be made to understand the clinical timeline such as probable exposure and time of symptom onset to establish the likely incubation period, which is helpful in narrowing the differential diagnosis (Figure 2).

If case of unspecific symptoms in association with an evocative travel/immigration history, the differential diagnosis should include worm infections early on since nonspecific gastrointestinal symptoms often lead to lengthy and expensive investigation cycles, not addressing the prevention of future comorbidity caused by helminthic infections. This is especially applicable when considering immunosuppressants in gastrointestinal disease, keeping in mind the often fatal hyperinfection syndrome caused by *S. stercoralis* in case of reduced host immunity.

To date, no gastroenterological association endorses guidelines on the diagnostic approach of suspected intestinal helminthic infections based on the clinical presentation and/or an individual's migration history.

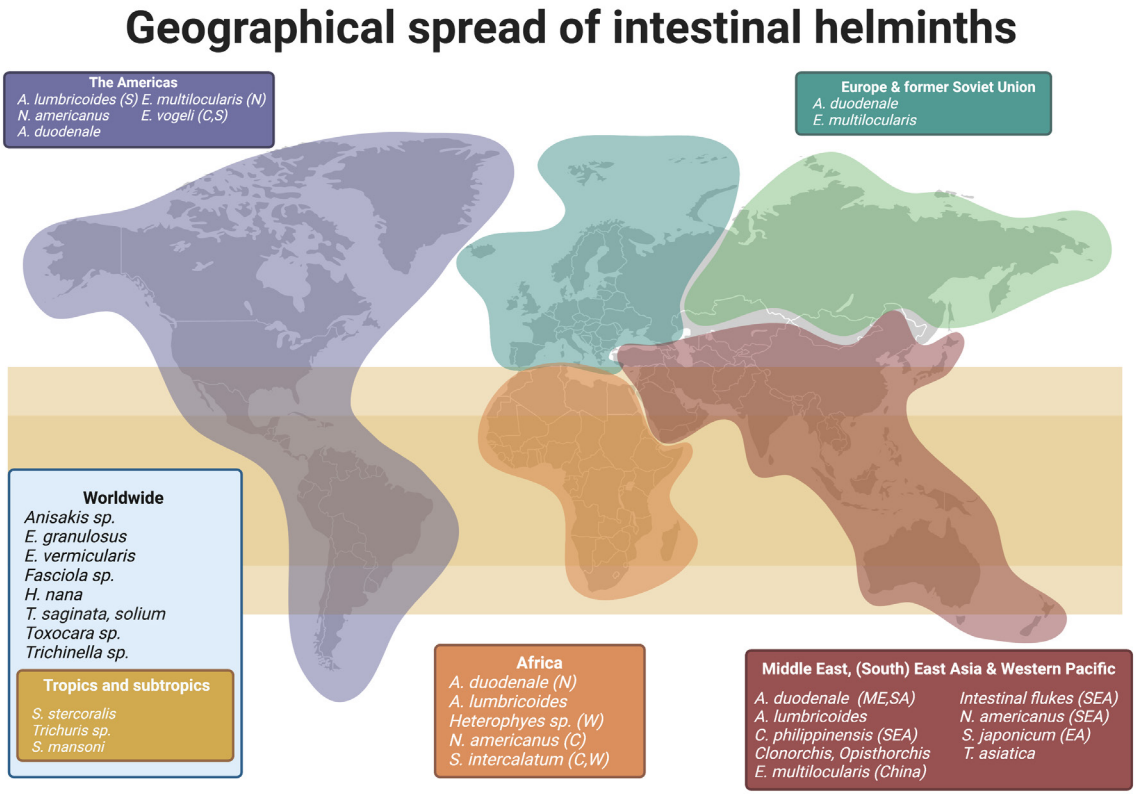

Figure 1. — Geographical spread of intestinal helminths. This figure can be used to differentiate between probable helminthic entitities according to travel and migration history of the patient. S – South, C- Central, N – North, W – West, ME – Middle-East, SA – South Asia, SEA – Southeast Asia, EA – East Asia.

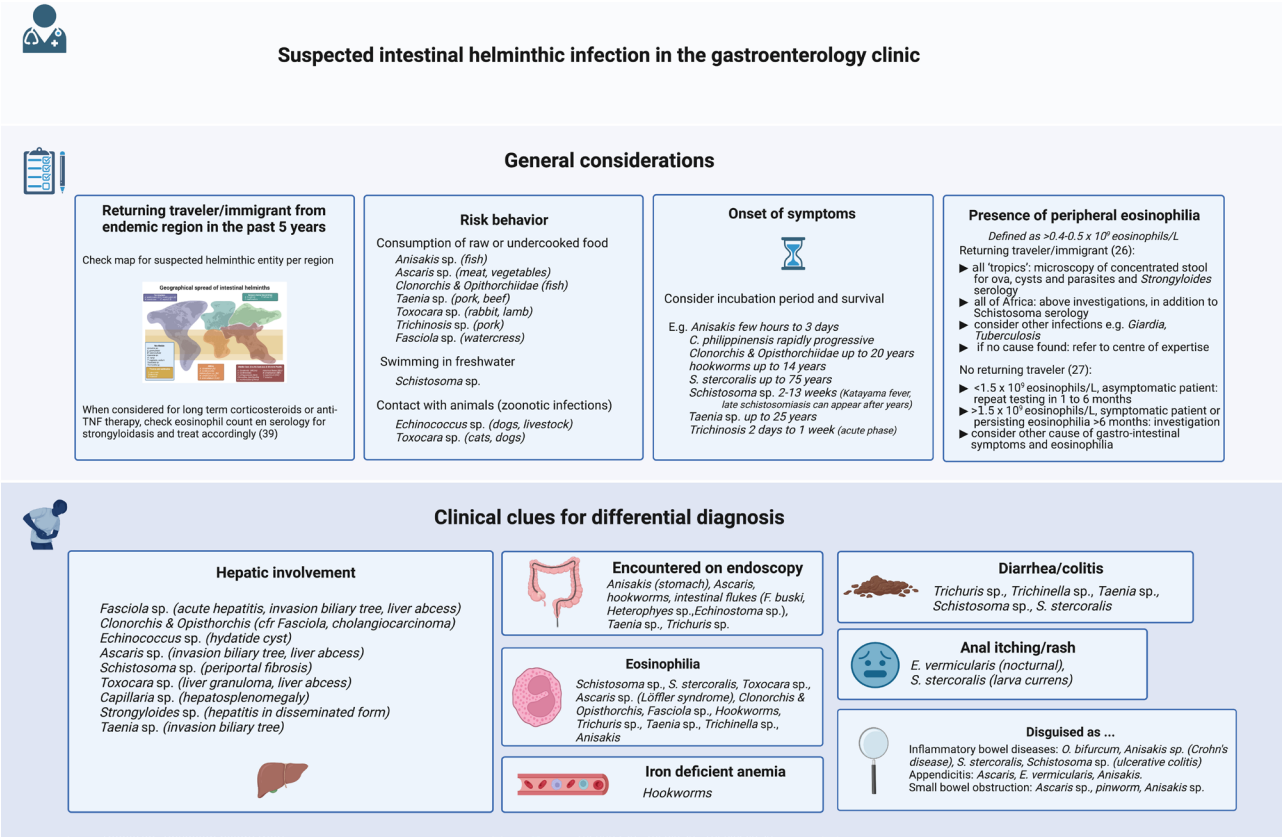

Figure 2. — Suspected intestinal helminthic infection in the gastroenterology clinic. Overview of general considerations and clinical clues to use when suspecting an helminthic infection in order to narrow differential diagnosis.

The only available tools are the British Infection Association recommendations using travel history to guide investigation of eosinophilia and the more recent British Society for Haematology guideline for the investigation and management of eosinophilia (26,27). The former dates back to 2010, but a recent retrospective comparative study confirmed these guidelines' relevance with a satisfactory diagnostic yield despite the changes in global burden of helminthic diseases and travel patterns (17). These guidelines recommend that depending on exposure and clinical features, concentrated stool microscopy for ova, cysts and parasites and serology for *Strongyloides* sp. should be performed in travelers or residents from all tropical regions (Africa, Asia and Caribbean). They recommend terminal urine microscopy and serology for schistosomiasis in those returning from Africa (Figure 2).

This manuscript focuses on the most common helminths involving the gastrointestinal and hepatobiliary tract. In the first section, we describe the helminths stratified in 5 possible clinical presentations: eosinophilia, diarrhea, iron deficiency anemia, unexpected endoscopic findings and liver involvement. Worms are listed according to their prevalence in European laboratories. Next, we give recommendations on diagnosis and treatment. Table 1 summarizes clinical clues for diagnosis. Table 2-5 summarize helminth-specific diagnostic and therapeutic considerations, stratified by clinical presentation.

Table 1. — **Clinical clues for diagnosis**

S. stercoralis (hyperinfection): disseminated skin lesions (larva currens) +- eosinophilia, especially in the immunocompromised patient with a travel or migration background.
Schistosoma: history of exposure to fresh water, abdominal pain, fever, diarrhea and eosinophilia.
Toxocara: persistent eosinophilia and exposure to cats and dogs.
Trichinella: peri-orbital edema, myalgia and eosinophilia in patients exposed to undercooked pork, sometimes preceded by typical symptoms of food poisoning.
Hookworms: eosinophilia and iron-deficient anemia.
Enterobius vermicularis: nocturnal perianal itching.
Anisakis: heavy epigastric pain shortly after eating raw fish.
Taenia: weight loss and discovery of proglottids in the stool.
Ascaris: a history of regurgitating a worm or passing a large worm in the stool in patients living in or visiting endemic regions.
Fasciola: prolonged fever, abdominal pain, tender hepatomegaly, liver lesions and eosinophilia.
Clonorchis & Opisthorchis: secondary sclerosing cholangitis or cholangiocarcinoma is a patient born in (South)east Asia.
Echinococcus: exposure to dogs and cattle with tender hepatomegaly and a liver mass.

Table 2. — **Available diagnostic test and main therapeutic strategies for helminths causing peripheral eosinophilia (28-33)**

Helminth	Available diagnostic tests Sample	Comments	Available at routine labs	Available in reference lab (TAT)	Treatment
S. stercorales	1. Serology **Serum**	- Gold standard. - Consider in patients who are or will be on immunosuppressive therapy. - Cross-reactions with other nematodes. - Serological titre decreases after treatment.	No	Yes (3-7 days)	Positive serology is sufficient to start treatment given the risk of disseminated strongyloidiasis in case of future immunosuppressive treatment. Chronic infection: one dose of oral ivermectin (200 µg/kg), followed by a second dose 2 weeks later. Disseminated infection: requires an intensive treatment of ivermectin (200 µg/kg) once daily until 2 weeks after stool negativation.
	2. Microscopy **Feces**	- Baermann's concentration technique for detection of larvae (appear in feces 2-3 weeks after initial infection) on fresh, unfixed feces (minimum 20 g). Not possible on watery, loose or refrigerated stool. - Eggs occur only sporadically in cases of severe diarrhea.	No	Yes (2 days)	
Schistosoma	1. Serology **Serum**	- No distinction between different *Schistosoma spp.* - Cross-reaction with other trematodes. - Early schistosomiasis: serum collection at least 6 to 12 weeks after infection. - Repeated infection: no distinction between resolved and active infection. - Antibodies persist for several years after successful treatment.	No	Yes (7 days)	Early schistosomiasis (Katayama fever): short course of high-dose prednisolone with or without praziquantel 40-60 mg/kg orally in 2 or 3 doses the same day; repeat praziquantel in 4-6 weeks when all worms are mature Late schistosomiasis: Praziquantel 40 mg/kg orally in 1 or 2 doses the same day
	2. Microscopy **Feces, urine** **Biopsy**	- Late stage intestinal disease of *S. mansoni, S. japonicum*: eggs appear intermittently and in small amounts in stool 25-60 days after initial infection. - Repeated fecal examinations can be useful. - Concentration methods are recommended. - Intestinal and hepatic biopsies can reveal eggs surrounded by granulomas.	Yes Yes	Yes Yes
	3. Abdominal US	Abdominal US scoring system uses a liver parenchyma image pattern, portal thickening and portal hypertension to score the stage of the disease.	NA	NA	
Toxocara	1.Serology **Serum**	- Due to cross-reactions with other nematodes, serology for *Toxocara* is only useful for confirmation of a clinical suspicion. - No microscopy! In humans larvae do not develop into adult worms	No	Yes (5 days – 2 weeks)	Infection can be self-limited, avoid unnecessary biopsies/treatment. If treated: albendazole 400 mg twice daily for 5 days combined with prednisone 60 mg/day in case of severe disease. Mebendazole is an alternative to albendazole, but is clearly inferior
	(2. Microscopy) **Biopsy**	*Toxocara* Larvae within eosinophilic granulomatous lesions	NA	NA	
	(3. Ophthalmoscopy)	Ocular toxocariasis: diagnosis sometimes by chance on routine ophthalmoscopy.	NA	NA	

Abbreviations: TAT - turnaround time, NA – not applicable.

Table 3. — **Available diagnostic test and main therapeutic strategies for helminths causing resp. diarrhea and iron-deficient anemia (28-33)**

Helminth	Available diagnostic tests Sample	Comments	Available at routine labs	Available in reference lab (TAT)	Treatment
Trichuris trichiura	1. Microscopy **Feces**	- Identification of eggs in stool sample (appear 30 to 90 days after initial infection). - Concentration method recommended. - Severity of symptoms depends on worm burden: quantification of eggs is useful.	Yes (2 days)	Yes (2 days)	Unlike other stool helminths meben-dazole is superior to albendazole and ivermectin. It is dosed 100 mg twice daily for 3 days.
	(2. Macroscopy) **Proctoscopy**	Examination of the rectal mucosa by proctoscopy (or directly in case of prolapses) can occasionally demonstrate adult worms.	NA	NA	
Trichinella	1. Serology **Serum**	3 to 5 weeks after initial infection.	No	Yes (7-14 days)	Infection can be self-limited. Avoid unnecessary biopsies/treatment. If treated: albendazole 400 mg twice daily for 8-14 days combined with prednisolone. Mebendazole is an alternative.
	(2. Microscopy) **Feces** **Muscle biopsy**	- Adult worms or larvae can exceptionally be found in feces. - Invasive and unable to detect early stage of infection but can be useful to confirm the diagnosis	Yes No	Yes Yes	
Hookworms	1. Microscopy **Feces**	- Identification of eggs in stool sample (appear 15-40 days after infection). - No microscopic distinction possible between eggs of both hookworms - Larvae can occur in samples examined at least 12 hours after the sample is produced.	Yes	Yes	Albendazole 400 mg daily for 3 days is superior to mebendazole 100 mg twice daily for 3 days.
	2. Macroscopy **Endoscopy**	Witnessed adult hookworms should be fixed in 5% aqueous formalin before sending to the lab.	NA	NA	

Abbreviations: TAT - turnaround time, NA – not applicable

Table 4. — **Available diagnostic test and main therapeutic strategies for helminths encountered during endoscopy or in the toilet (28-33)**

Helminth	Available diagnostic tests Sample	Comments	Available at routine labs	Available in reference lab (TAT)	Treatment
E. vermicularis	1. Microscopy **Tape test**	- Detection of the eggs on the peri-anal skin - Apply adhesive transparent tape to the peri-anal area in the morning before bathing. Stick the tape on a slide for examination by microscopy. - Repeat on three mornings in the same week to increase sensitivity. - Caution: Eggs are very sticky and immediately infectious. Use gloves and wash hands after manipulation to avoid infection.	Yes	Yes (1 day)	Empirical treatment in symptomatic patient and family members. Two doses of either mebendazole 100 mg or albendazole 400 mg separated by 15 days are administered. All clothes and bed linens should be washed.
Anisakis	1.Macroscopy **Gastroscopy**	Witnessed adult *Anisakis* should be fixed in 5% aqueous formalin	Yes	Yes	Gastric endoscopic removal of the worm is curative.
Taenia sp.	1. Microscopy **Feces**	- Identification of eggs in stool sample (appear 2-3 months after infection). - Eggs of different sp indistinguishable. - Repeated examination and concentration techniques recommended. - Always wear gloves and preferably use tweezers due to the risk of cysticercosis (in case of *T. solium*).	Yes	Yes	Single dose of niclosamide 2mg (most used and available treatment in Belgium) Neurocysticercosis treatment is complicated and depends on the stage and location. Often anti-helminthic treatment is contra-indicated due to the risk of seizures on antigen release.
	2.Macroscopy **Feces** **Surgery,endoscopy**	- Examination of proglottids of *Taenia spp*.: Differentiation between *T. saginata* and *T. solium* possible. - Witnessed adult *Taenia spp.* should be fixed in 5% aqueous formalin.	Yes Yes	Yes Yes	
A. lumbricoides	1. Microscopy **Feces**	- Identification of eggs in a stool sample (appear 2-3 months after infection). - Lung passage: rarely larvae are found in the patient's sputum. However, sputum examination is not routinely recommended.	Yes	Yes	Single oral treatment with albendazole 400 mg. Mebendazole and ivermectin are alternative treatments. Löffler syndrome and hepatobiliary manifestations may require several doses. Extraction during surgery or ERCP, preferentially without sphincterotomy, is rarely necessary.
	2. Serology **Serum**		No	Yes (14 days)	
	3.Macroscopy **Feces,endoscopy, surgery**	Witnessed adult *Ascaris* should be fixed in 5% aqueous formalin.	Yes	Yes	
	4. Imaging	Filling defects during upper gastrointestinal series and ERCP	NA	NA	

Abbreviations: TAT - turnaround time, NA – not applicable

Table 5. — **Available diagnostic test and main therapeutic strategies for helminths involging the liver (28-33)**

Helminth	Available diagnostic tests Sample	Comments	Available at routine labs	Available in reference lab (TAT)	Treatment
Fasciola	1. Serology **Serum**	- Antibodies detectable from 3 weeks after infection. - Cross-reaction with other trematodes. - About one year after the invasion phase, serology can return negative, while the adult worms are still present in the bile ducts.	No	Yes (4-14 days)	Triclabendazole 10 mg/kg on 2 consecutive days.
	2. Microscopy **Feces (Duodenal/bile duct aspirates)**	- Identification of eggs in stool sample (appear 3-4 months after infection). - The presence of eggs in feces does not always indicates infection. - To exclude the possibility of egg passage by eating infected liver, repeat examination under diet control or serology are advised	Yes	Yes	
Clonorchis & Opisthorchiis	Microscopy **Feces**	Identification of eggs in a stool sample (appear 1-4 weeks after infection).	Yes	Yes	Praziquantel 75mg/kg in 3 divided doses over 1 day
Echinococcus	1. Medical imaging **S, CT, MRI**	Imaging based classification is recom-mended E. granulosus: WHO-IWGE or Gharbi's US classification. E. multilocularis: WHO-IWGE PNM classification system.	NA	NA	Patients should be referred to centres with Echinococcus treatment expertise.
	2. Serology **Serum**	- Separate test available for E. granulosus and E. multilocularis. - Possible cross-reaction with other cestodes. - If the cyst is localized in the liver, serologic sensitivity is higher than when the cyst is localized elsewhere in the body (e.g. in the lungs). - A negative serology does not rule out infection.	No	Yes (7-14 days)	CE: image-based, stage-specific approach, helpful for choosing one of the following options: (i) percutaneous treatment, (ii) surgery, (iii) anti-infective drug treatment or (iiii) watch and wait. AE: early diagnosis and radical (tumour-like) surgery followed by anti-infective prophylaxis with albendazole. In later stages, when radical surgery (distance of larval to liver tissue of >2 cm) cannot be achieved; continuous medical treatment with albendazole is the backbone + individualized interventional measures.
	3. PCR **Biopsy**	PCR on cyst material after surgical removal	No	Yes (2 days)	
	(4. Microscopy) **Puncture fluid**	- E. granulosus: Identification of proto-scolices and/or hooks in the puncture fluid. But: diagnostic puncture of the hydatid cyst should not be performed due to possible complications (anaphylactic shock, dissemination). - Eggs are not produced in humans. Diagnosis cannot be made by stool microscopy.	No	Yes	

Abbreviations: TAT - turnaround time, NA – not applicable, CE – cystic echinococcosis, AE - alveolar echinococcosis

Eosinophilia

Peripheral eosinophilia defined as an absolute eosinophil count > 0.4-0.5 x 10^9 eosinophils/L, is the most known sign associated with helminthic disease. Strictly speaking, only worms migrating into tissues give rise to eosinophilia. Studies demonstrate a helminthic etiology for eosinophilia in about 40-64% of the patients with a travel history and/or immigrant background. Higher eosinophilic counts (range 0.7 – 1.5 x 10^9 eosinophils/L) are observed in case of co-infection with several helminth species (10,17,34-36). On the other hand, the absence of eosinophilia does not rule out infection, especially in subjects taking immunosuppressive medication (37-40).

For asymptomatic patients with eosinophilia up to 1.5 x 10^9 eosinophils/L, without travel history or residency in helminthic-endemic areas within the last 5 years repeated testing in 1 to 6 months can be considered. Eosinophilia persisting beyond 6 months or > 1.5 x 10^9 eosinophils/L should be further investigated (27). Finally, eosinophilia with associated gastrointestinal symptoms is also observed in inflammatory bowel disease, coeliac disease, chronic pancreatitis, malignancy and primary gastrointestinal eosinophilic disorders besides non-helminthic infections (such as giardiasis or tuberculosis, especially in the returning traveler) (41). Off note, IgE levels do not provide a diagnostic benefit to differentiate helminthic from non-helminthic causes of eosinophilia (35).

Strongyloides stercoralis

Infections with *Strongyloides stercoralis* represent the majority of helminth infections diagnosed in Western laboratories. They mainly affect immigrants from tropical and subtropical regions (10,17,34). Besides infections in immigrants, autochthonous cases from Europe (Northern Italy and San Marino republic) were described during the past decade, especially in elderly people who worked as agricultural workers and/or lived in rural areas in their youth (19,42,43). *S. stercoralis* is a free-living soil helminth that enters the human body when larvae penetrate intact skin. After a period of tissue migration, the filariform larvae settle in the small intestine where they become adults. The female adults lay eggs that hatch into rhabditiform larvae which are released in the feces. Additionally, the larvae have the capability to re-infect the host by penetration of the perianal skin or the distal rectum. This so-called 'auto-infection' may lead to an increased number of parasites in the host and prolonged infection that may extend up to 75 years, even after leaving the endemic area. As long as the parasitic burden remains limited, infected subjects experience minimal or no symptoms. Patients with auto-infection might develop a so-called 'creeping eruption' or larva currens, ie. a serpiginous urticarial rash usually on the buttocks caused by dermal migration from larvae that exited the anus and entered the perianal skin. The linear rash can move up to 10 cm per day. While the evidence for a causal role of chronic helminth infection in gastrointestinal symptoms is debated, some studies recognize clear symptom associations with infection by *Strongyloides* (10,19,37). Patients might present with nonspecific gastrointestinal complaints such as nausea, abdominal pain, weight loss, occult gastrointestinal blood loss or right sided colitis resembling ulcerative colitis. The latter is more often associated with eosinophilia. In general, eosinophilia is absent in up to 56% of patients with proven strongyloidiasis, especially in disseminated forms of infection resulting from immune depressing agents (37).

Disseminated or severe strongyloidiasis, caused by immunosuppression or glucocorticoid administration is of particular interest for the gastroenterologist. Larvae can injure the intestinal mucosa carrying luminal bacteria into the bloodstream resulting in polymicrobial sepsis often causing lethal endocarditis, meningitis, hepatitis (predominant cholestatic liver tests) or pneumonitis. To date recommendations for screening asymptomatic patients for S. stercoralis are based on clinical judgment rather than sound evidence. Current inflammatory bowel disease (IBD) guidelines recommend to consider checking the eosinophil count and serological blood tests for strongyloidiasis for long-term returning travelers and immigrants with IBD from highly endemic countries, especially when considering corticosteroid or anti-TNF therapy, and to treat proven strongyloidiasis before starting immunosuppressants to prevent disseminated disease (44, 45). In contrast to hematological guidelines, no systematic treatment of the suspected infected returning traveler/immigrant is recommended (27).

Schistosoma

Schistosomiasis, also known as bilharziasis, is one of the most prevalent parasitic diseases worldwide, along with strongyloidiasis. The infection is frequently detected in travelers and migrants coming to Europe. Most infections in Europeans occur in travelers visiting a small number of countries in Western and Eastern Africa (46). Four species, ranked in descending order of frequency: S. *mansoni, japonicum, mekongi* and *intercalatum* cause visceral (hepatosplenic and intestinal) schistosomiasis. Schistosomiasis is acquired by swimming or wading in freshwater since the parasite uses freshwater snails as an intermediate host. Cercariae leave the snail and penetrate the intact skin of a suitable mammal, migrate through the bloodstream to the portal venous system (*S. mansoni*) where males and females form 'couples' that migrate to and reside against venous blood flow into the mesenteric veins. Each day, they shed up to a thousand eggs. Some remain trapped in the intestinal wall, some are excreted in the stool and some become lodged in the liver.

The worm itself evades the immune system. It's the eggs that cause symptoms (46). Clinically early schistosomiasis manifests as Katayama fever. This is an

acute form of the disease that presents within the first 2 to 13 weeks after exposure. Symptoms include fever, malaise, arthralgia, cough and diarrhea along with eosinophilia. A later stage gastrointestinal manifestation is a bloody, especially left sided colitis with tenesmus and mild anemia resembling ulcerative colitis caused by granuloma formation around the egg's trapped in the intestinal wall. In parallel, colonic pseudo-polyps, protein-losing colonopathy and formation of an inflammatory mass in the descending colon may develop. Occasionally *S. japonicum* can give rise to a similar transmural migration in the pyloric region, causing obstruction and gastric bleeding. Finally, hepatosplenic schistosomiasis resulting from accumulated injury by prolonged infection starting during childhood has been described in adolescence to late twenties. Eggs lodging in the hepatic and portal system cause a periportal fibrosis ('Symmers pipestem fibrosis') leading to pre-sinusoidal portal hypertension without compromising hepatocellular function. The typical presentation of decompensated hepatosplenic schistosomiasis is variceal hemorrhage and ascites without obvious hepatic encephalopathy or metabolic liver dysfunction. There are documented cases of adult worms surviving for more than 35 years after a person had left an endemic area. Outside of the scope of this article but worth mentioning is the possibility of eggs lodging in other visceral sites such as bladder, lungs and central nervous system, causing organ-specific symptoms (47).

Toxocara

Toxocariasis is another parasitic infection to consider in travelers returning from the tropics, although it displays a cosmopolitan distribution. It represents the most prevalent zoonotic helminth infection in industrialized countries (12, 48). People become accidental hosts by ingestion of eggs present in soil or plants contaminated by dog or cat feces or more rarely by eating undercooked or raw meat from a contaminated animal such as lamb or rabbit. Most infected people remain asymptomatic. Infections can be associated with systemic symptoms such as fever, skin abnormalities and respiratory symptoms with diffuse abdominal complaints in up to 48% of patients. In visceral larva migrans, the liver, the brain and the eyes are the organs of choice for invasion, where the larvae cause a local inflammatory response. This results in granuloma formation with possible subsequent cholestatic hepatitis and pyogenic abscess(es) (12). Eosinophilia is common during the migration phase. In daily practice, diagnosis of human toxocariasis relies on a constellation of suggestive symptoms, behavior (e.g. recent travel, Pica in children, presence of dogs or cats), eosinophilia and a positive serology (49).

Diarrhea

In contrast to intestinal protozoa, helminths are not a major cause of diarrhea (50,51). Nevertheless, diarrhea can be part of a broader spectrum of gastrointestinal symptoms of helminthic infections or a reflection of a particular phase in the life cycle of the helminth.

Trichuris trichiura

Trichuris dysentery syndrome (TDS) presents as mucoid diarrhea, occasional bleeding and rarely rectal prolapse in patients, usually children, harboring numerous worms. *Trichuris trichiura* or 'whipworm' has a thin tapered anterior region resembling a whip. In endemic regions, mainly tropical countries, it's rather a commensal than a pathogen. It can be visualized during endoscopy as a 3 cm long whip-shaped parasite, especially in the caecum where it matures, mates and lays eggs (52,53).

Trichinella

Trichinosis is a zoonotic disease that is sometimes diagnosed in the returning traveler with diarrhea. Several outbreaks have been reported in Europe during the past decennium (16). *Trichinella* sp. is acquired by ingesting larvae in raw or undercooked meat such as pork. Maturation into adult worms occurs in the intestine, followed by deposition of larvae in the intestinal mucosa. From 2 days to 1 week after ingestion, enteritis can occasionally develop resulting in abdominal pain, nausea, vomiting, diarrhea and low-grade fever sometimes misdiagnosed as viral gastroenteritis or food poisoning. However, presentation with systemic symptoms only, representing a parenteral phase of the infection, is more common. In the latter, eosinophilia, peri-orbital edema and raised creatine phosphokinase corresponding to larvae migration into muscles and other organs, is often observed.

Travelers diarrhea

Guidelines on the etiology, diagnosis and treatment of diarrhea in the returning traveler is beyond the scope of this article. Helminthic and in general protozoal infection should be considered in the returning traveler in case of chronic diarrhea persisting for more than 14 days, diarrhea in the immunocompromised patient and in cases of eosinophilia. Currently, there's no consensus on the optimal diagnostic procedure. However, screening should begin with a microscopic examination of stools to detect ova and parasites, despite this exam's suboptimal and highly observer-dependent sensitivity (54,55).

Apart from the previously described worm diseases, other rare helminthic entities related to diarrhea include capillariasis, hymenolepiasis and intestinal fluke infections. *Capillaria philippinensis* causes a rapidly progressive protein-losing, sprue-like diarrhea often accompanied by a tender hepato- and splenomegaly along systemic symptoms, resulting in death when left untreated. *Hymenolepiasis nana*, a directly human-to-human transmittable tapeworm causes abdominal

pain, diarrhea and anorexia. It's highly prevalent in warm and arid regions such as Egypt. Finally, the most common intestinal flukes (*Fasciolopsis. buski, Heterophyes* sp. and *Echinostoma* sp.), only result in mild gastrointestinal symptoms such as abdominal pain and diarrhea in case of heavy infestation or may be encountered during endoscopy. It is acquired mainly by ingestion of contaminated freshwater fish or plants. Detection of eggs in the stool confirms the diagnosis.

Iron-deficient anemia

Presence of iron-deficient anemia and eosinophilia should rise suspicion of hookworm infection by *Necator americanus* or *Ancylostoma duodenale*. Co-infections have been described. Hookworms represent globally widespread parasites belonging to the group of STH and are endemic in tropical to warm temperate areas lacking adequate sewage facilities. Hookworms are acquired by skin contact with contaminated soil. In contrast to zoonotic hookworms, human hookworms rarely give rise to a pruritic, serpiginous rash called 'cutaneous larva migrans', corresponding to migration through the dermis. Following migration through blood vessels and the lungs, the worms establish themselves in the small intestine where they graze on the intestinal mucosa, ingesting epithelial cells and blood. Mature worms live up to 14 years. Classic or video capsule endoscopy sometimes reveals the presence of a, up to 1 cm, long worm. Only moderate or heavy hookworm infestation causes iron deficiency. The average Western diet high in iron usually prevents anemia development but host factors influencing iron intake and blood loss should be considered.

Unexpected guests during endoscopy or in the toilet

Apart from the previously discussed hookworms, intestinal flukes and *Trichuris* sp., other helminths might as well surprise the endoscopist.

Enterobius vermicularis

E. vermicularis or pinworm is the most commonly encountered helminth in primary care. Although people of every socio-economic class get infected, the number of diagnoses declined over the past decade. Mainly school-aged children or institutionalized patients are vulnerable to infection. Infective eggs survive for several days and are resistant to most chlorinated agents. Ingestion of eggs, present on the hands of the host after perianal scratching, is the most common infection and transmission route. Pinworms are 0.5 to 13 mm in length. They can be present everywhere along the colon during endoscopy (13). At night, gravid females migrate through the anal canal onto the perianal skin, where they lay eggs, resulting in the typical perianal itching or vulvovaginitis. In addition to this well-known benign condition, *E. vermicularis* may cause appendicitis, intestinal obstruction or enterocolitis. Intestinal perforation is rarely observed (56).

Anisakis

With the increased popularity of sushi and sashimi (raw fish), the prevalence of anisakiasis is on the rise. Many saltwater fish harbor *Anisakid* larvae, causing an early (within 3 days of ingestion) infestation in humans. The disease is self-limiting as the parasites do not survive in humans. Most patients develop acute severe stomach pain within a few hours after ingestion with associated nausea and possibly hematemesis. In rare cases, intestinal anisakiasis causes acute appendicitis or presents as a Crohn's disease mimicker with small bowel obstruction and peritonitis. Diagnosis is confirmed when observing larvae penetrating the gastric wall during endoscopy. Endoscopic removal of the *Anisakid* larvae alleviates symptoms. *Anisakis* is considered an important hidden food allergen, probably causing seafood allergy with potentially severe reactions such as anaphylaxis (57).

Taenia

In case of taeniasis, an intestinal infection of humans with the adult tapeworm, *Taenia* sp., shed off proglottids or single eggs in the stool. These proglottids can be observed in the stool, anus or toilet, alarming the patient. Human infection occurs by eating raw or undercooked beef (*T. saginatum*) or pork (*T. solium)* containing cysticerci (larval cysts). They have a worldwide distribution, including Europe (15, 58). Once ingested, the cysticercus forms a scolex which is attached to the mucosa in the proximal jejunum. Next, several proglottids containing infective eggs develop, which mature into a chain called 'strobila'. Mature parasites can grow to be 2 to 10 meters long; beef tapeworms are the longest. They can live in the small intestine for up to 25 years. When symptomatic, the host complains of mild discomfort, loss of appetite, diarrhea, weight loss and some report white threads in the stool. Very rarely intestinal obstruction occurs. Human cysticercosis, a complication of *Taenia solium* infection is reported in all Western European countries, with the highest number originating from Portugal and Spain. However, most of these infections are acquired outside of Western Europe (15). In this complication, tissue invasion by cysticerci triggers a localized inflammation and mass effect. Involvement of the central nervous system, known as neurocysticercosis, is a significant cause of epilepsy, headache or focal neurological deficits in endemic countries (58,59).

Ascaris

Ascaris lumbricoides is the largest (females can grow up to 49 cm) of the nematodes or roundworms and is one of the most common helminthic infections worldwide (9). Twenty-five percent of the world's population (ie. one billion people) is infected, especially in Asia (73%) and Africa (12%) (22). Human acquisition occurs via ingestion of *Ascaris* eggs in water and food

(e.g. unwashed vegetables) contaminated with feces of humans or pigs. Symptoms usually only develop with a heavy worm burden. In early larval stages, *Ascaris* sp., like other nematodes, can give rise to a Löffler syndrome characterized by fever, pulmonary symptoms and rash caused by eosinophilic infiltrates accumulating in the lung. Intestinal symptoms due to migration of adult worms into the gastrointestinal tract, such as abdominal discomfort, nausea, vomiting, appendicitis or the more severe bowel obstruction in the small bowel and ileocaecal region, appear after weeks to years. Since *A. lumbricoides* is very motile, passage back and forth in the bilio-pancreatic system causes biliary colic, intermittent obstructive cholangitis or pancreatitis and liver abscesses (60). Diarrhea or eosinophilia is rarely present, except in Löffler syndrome (23).

More rare parasites are *Oesophagostomum bifurcum* (nodule worm) and *Dibothriocephalus* (former *Diphyllobothrium)* sp. The former causes inflammatory nodules in the wall of the distal ileum, ileocaecal region or transverse colon, often mistaken for Crohn's disease or intestinal tuberculosis. The latter is a tapeworm acquired by eating undercooked or raw fish which grows up to 12 m in length. It usually causes asymptomatic infections but is sometimes responsible for vitamin B12 deficiency.

Liver involvement

Most of the previously discussed helminths may also manifest with symptoms related to liver invasion. Toxocariasis, schistosomiasis and capillariasis manifest with major hepatobiliary impairment, whereas ascariasis and strongyloidiasis affect the liver less frequently or less severely.

Fasciola

Fascioliasis is caused by the ruminant flukes *Fasciola hepatica* and *Fasciola gigantica*. Infective metacercariae attach to freshwater plants (such as watercress). Once in the host, immature flukes excyst and penetrate the intestinal wall and hepatic capsule to settle in the bile ducts. Acute and chronic infection have a different clinical presentation. The acute phase representing migration of the young flukes through the liver is marked by fever, right upper quadrant pain, hepatosplenomegaly with mild liver biochemical test abnormalities, non-specific gastrointestinal symptoms and often a pronounced eosinophilia. In the chronic obstructive phase, flukes settle into the bile ducts and cause cholangitis, cholelithiasis and eventually biliary cirrhosis or secondary sclerosing cholangitis (61). There's no convincing association with biliary tract malignancy (62).

Clonorchis & Opisthorchis

Clonorchis sinensis and *Opisthorchis viverrini* have similar life cycles and clinical presentations. They infect the host who has eaten contaminated raw or undercooked fish. They migrate into the ampulla of Vater and the bile ducts, where they reside for more than 20 years. Symptomatology is similar to that of fascioliasis and generally consists of fever, right upper quadrant pain, hepatosplenomegaly and eosinophilia. Unique to these liver flukes is the increased risk of developing cholangiocarcinoma in case of chronic infection (62-64).

Echinococcus

Although rarely reported in Belgium, there has been an increasing incidence in Europe over the last two decades, particularly for alveolar echinococcosis (AE), caused by *E. multilocularis* (65). A recent surveillance of AE and cystic echinococcosis (CE), caused by *E. granulosis* in Belgium in 2021, identified 18 cases (7 AE and 11 CE). All cases of AE resided in Wallonia, while all the CE cases were imported from endemic regions such as Turkey, Morocco, Middle-East or Eastern Europe where the disease is endemic (abstract presented at the annual Belgian Society for Parasitology and Protistology congress 11/2022). *E. granulosis* mainly grows cysts in the liver ('hydatidosis'). *E. multilocularis* is more aggressive, causing progressive, more invasive non-cystic masses with a higher mortality rate. *E. vogeli* ('polycystic echinococcosis') has intermediate clinical features and more frequently spreads to contiguous sites. In endemic regions, *Echinococcus* sp. are common in areas where dogs are used to raise livestock. Dogs, the definitive hosts, acquire the infection by consuming infected organs of sheep or cattle (3). Humans, as intermediate hosts, get infected by eating vegetables contaminated by dog feces containing embryonated eggs. The liver, usually the right hepatic lobe, followed by the lungs, kidney, spleen, brain, muscle and bone are the predominant organs of hydatid cysts development. A hydatid cyst is a complex cyst in which protoscolices are produced asexually. Rupture of such a hydatid cyst releases the viable protoscolices, which set up daughter cysts in secondary sites mainly in the same organ. Distant spread resembling metastatic disease is possible. Growing cyst size in the same organ causes local symptoms such as obstruction, biliary-cystic fistula, cholangitis, pancreatitis, secondary infected pyogenic liver abscesses, hemoptoe and rarely portal hypertension, biliary cirrhosis or Budd-Chiari syndrome. Occasionally, a life-threatening anaphylactic reaction develops in reponse to cyst rupture with release of its content in the abdominal cavity. However, most patients remain asymptomatic for a prolonged time resulting in delayed diagnosis.

Diagnostic work-up

A helminth infection can be diagnosed through serology, microscopic examination of feces both directly and after a concentration procedure, copro-antigen detection tests and molecular detection of

helminth DNA (PCR). Occasionally, the diagnosis is made macroscopically i.e., with the naked eye in case of spontaneous evacuation of the worm (coughing or in the stools) or by endoscopic or surgical removal. The size of the worm should be measured and communicated to the microbiologist. Finally, additional imaging and histologic evaluation of suspected lesions aids in obtaining the diagnosis.

A correct indication for testing, through extensive anamnesis of travel history and risk behavior, is essential to improve the diagnostic yield and avoid misinterpretation of false positive or negative results. Problems such as cross-reaction of antibodies against different helminthic species and the persistence of antibodies after correct treatment, may mislead the clinician. Therefore, good knowledge of the pitfalls of each test and timely communication with an infectiologist and microbiologist is of great importance.

In the past, when microscopy was the only available diagnostic tool, examining three stool samples increased the sensitivity by partially overcoming problems such as the intermittent shedding of certain intestinal parasites and sampling errors. In the era of copro-antigen and molecular tests, the additional yield of a second and third stool sample has decreased. However, examining more than one stool sample may still be helpful for some patients when there's a strong suspicion of helminth or protozoal infection and other diagnostic modalities remain inconclusive. Table 2-5 summarize available diagnostic tests, availability in routine and reference labs, as well as the turnaround time per helminthic entity stratified by clinical presentation.

Treatment

Different treatment options exist depending on which guidelines are followed. Most of the intestinal helminths treated with anthelminthic drugs only, except for some species (e.g. *Echinococcus* sp.) in which a multimodal treatment, often including surgery, is preferred (66).

In Belgium only mebendazole and niclosamide are commercialized anthelminthic agents. The raw material for albendazole is available in Belgium, so the pharmacist can deliver capsules with a magisterial prescription. Based on a prescription and a doctor's statement (available at https://www.fagg-afmps.be/sites/default/files/content/INSP/NARC/artsenverklaring.pdf - NL and https://www.afmps.be/sites/default/files/content/INSP/NARC/declaration-medecin.pdf - FR), the pharmacist will deliver other agents available in neighboring countries (e.g. ivermectin).

Anyhow, if there's any doubt about the diagnosis or if tropical helminthiasis is suspected, timely referral to centre of expertise is recommended; all the more because some drugs such as albendazole, triclabendazole, praziquantel are readily available in those centers.

The main therapeutic strategies for the intestinal helminths discussed are available in Table 2-5.

Are all worms bad?

There seems to be an inverse relationship between the prevalence of helminthic infection and immunopathologies in endemic regions. Epidemiological data and murine experimentation suggest that eliminating helminths contributes to increasing frequency of ulcerative colitis, Crohn's disease, type I diabetes mellitus, rheumatoid arthritis, asthma, multiple sclerosis and auto-immune encephalitis. Helminths are thought to induce microbiome changes and directly modulate the host immune system to attenuate development of antiparasitic immunity, thereby dampening bystander immune pathologies by various mechanisms (67-70). Evidence is mainly made up of animal models of human diseases, case reports and even small-scale trials with deliberate infection of humans with live parasites or defined molecular products from the same parasites (71-73). Randomized controlled trials are required to assess the efficacy of helminth infections/helminthic immunomodulators as a treatment option (74).

Conclusion and prospects for future research

Although rare, intestinal helminthic infections are encountered in the gastroenterologist's practice. In the absence of registration requirements, exact numbers on their prevalence are lacking. Grey literature on the subject made out of case reports, small national series and scholarly publications however point towards their existence, so awareness is crucial for a swift diagnosis. Regarding the diagnosis, one must carefully choose the correct and accurate test and avoid misinterpretation of the test result. To achieve this, a complete history including recent (the past 5 years) travel history, risk behavior, triggers such as immunosuppressive medication and (mostly unspecific) symptoms is essential. Whether or not the gastroenterologist is familiar with helminthic infections, close and timely contact with the microbiologist, infectiologist and a center with experience is recommended. The role of helminthic infections in our immune system and their potential as immunomodulators needs to be elucidated.

Conflict of interest

All authors declare that they have no conflicts of interest.

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