Trends in Parasitology

CellPress
REVIEWS

Opinion

Helminth Therapy – From the Parasite Perspective

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Studies in animal models and humans suggest that intentional exposure to helminths or helminth-derived products may hold promise for treating chronic inflammatory-associated diseases (CIADs). Although the mechanisms underlying 'helminth therapy' are being evaluated, little attention has been paid to the actual organisms in use. Here we examine the notion that, because of the complexity of biological symbiosis, intact helminths rather than helminth-derived products are likely to prove more useful for clinical purposes. Further, weighing potential cost/benefit ratios of various helminths along with other factors, such as feasibility of production, we argue that the four helminths currently in use for CIAD treatments in humans were selected more by happenstance than by design, and that other candidates not yet tested may prove superior.

Dysregulation of Immune Function after Loss of Keystone Species from the Ecosystem of the Human Body

For hundreds of millions of years, vertebrates developed intricate and extensive connections with symbionts in their environment and inside their own bodies. The evolutionary process governing this development led to a vertebrate immune system that functions as an 'interface' with symbionts, supporting the growth of mutualistic symbionts as well as repelling pathogenic invaders [1–4]. However, the line between friend and foe is contextual in some cases, with environmental factors profoundly affecting the impact of symbiotic relationships on both host and symbiont. Perhaps nowhere in nature is this contextual nature of symbiosis more evident than in the relationship between helminths and humans.

Within a century, helminths have gone from being ubiquitous to all but absent in developed countries [1,5]. Despite the fact that many helminths are deleterious to their hosts, well-powered, controlled studies in at-risk pediatric populations show that a dramatic reduction in moderate helminth colonization does not improve health [6,7], suggesting that, although helminths can contribute to morbidity and mortality of specific individuals, they are not a significant contributor to disease from a population perspective if they are present in 'moderate' amounts. Further, mounting evidence supports the view that the complete loss of these organisms has dire consequences for human health [8,9]. Turton's demonstration, more than 40 years ago, that infection with helminths could reverse seasonal allergies was only the first in a series of studies in humans and in animal models showing the potential benefits of helminths for health [10]. Further, epidemiological studies demonstrate that the absence of helminth colonization inversely correlates with a global rise in **chronic inflammation-associated diseases** (**CIADs**) (see Glossary) [11–15]. Originally formulated as the **Hygiene Hypothesis** in the late 1980s, thinking in the field has been aggressively refined and is now formulated as the **Old Friends Hypothesis** and/or **Biome Depletion Theory** [16]. The latter paradigms appreciates the importance of an array of microbes as well as helminths as being necessary for immune system development and regula-

Highlights

Helminth therapy (HT) appears to be a promising concept to oppose inflammatory mechanisms underlying chronic inflammation-associated diseases because helminths are recognized as one of the keystones of the human biome.

So far, the majority of HT studies describe the mechanisms by which helminths manipulate the host immune system, but little consideration has been given to the actual tested helminths.

Here, we summarize the knowns and unknowns about the helminths used in HT and tested in disease models.

Specific eligibility criteria need to be addressed when evaluating prospective helminths for HT, such as feasible domestication, controlled exposure to population, and positive cost/benefit ratio.

Future directions of HT studies include host and helminth interactions, optimizing therapeutic helminth conditions, and how to use helminths prophylactically.

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tion [1,2,4]. Thus, helminths, like bacteria, include some species that are highly pathogenic, but are also apparently necessary for immune development, regulation, and function.

Restoring Regulation: Treating CIADs by Intentional Exposure to Helminths

CIADs are a collection of diseases that share common, ostensibly unrelated risk factors and occur predominantly in postindustrialized societies [14]. Well known representatives include Crohn's disease (CD), multiple sclerosis (MS), rheumatoid arthritis (RA), and seasonal allergies [17]. A range of neuropsychiatric disorders, including migraine headaches, anxiety disorders, chronic fatigue syndrome, and major depressive disorder are also CIADs [18,19]. The current therapy for many if not most CIADs is lengthy, costly, and of limited efficacy, with adverse effects [20,21]. At the same time, a growing body of research shows that reintroduction of helminths into the ecosystem of the gut appears to be a promising approach toward treating CIADs [8,22–24]. Helminths are regarded as master manipulators of host immunity, having developed a number of approaches to diverting or redirecting immune responses as well as to oppose inflammatory mechanisms [9,25,26]. The appreciation of 'worm-manipulators' led to a novel therapeutic strategy called **helminth therapy (HT)** [27,28].

Despite the growing body of literature describing the mechanisms by which helminths manipulate the human immune system [25,26,29,30], the actual helminths that might be considered for therapy have not been given careful and systematic consideration. Thus, the main goal of this opinion is to summarize knowledge about the helminths currently used for HT in humans [9,22,31] and other (ca. 35) helminths tested as potential therapeutic agents in experimental model systems (Table 1; see also Table S1 in the supplemental information online). Following this summary, we provide an assessment of the suitability of current therapeutic worms for HT in humans and (re) formulate criteria for new helminths that might be used for HT. In addition, we provide a list and brief description of **helminth-derived compounds** (**HDeCs**) that have been experimentally tested to prevent CIADs (Tables 1 and S1). Finally, we address expected future directions in the field of HT.

From Testing HDeCs to the Use of Live Helminths

Biomedical research exploring the potential of helminths for treating CIADs often favors HDeCs over living helminths [32] (Tables 1 and S1). Avoiding the use of live worms has inherent advantages, preventing the possibility that the therapeutic agent might spread into the environment or migrate in unusual or unexpected ways within a given host [33]. The approach has proven successful in terms of developing a wide range of drug candidates [22,34,35]. Further, the approach fits well with current drug development pipelines, avoiding difficulties associated with intellectual property that can profoundly impede the use of living organisms in biomedical research [33,36,37]. The use of HDeCs, rather than live helminths, often faces imposing technical challenges, including decreased biological activity of recombinant proteins due to limitations of current expression systems [35]. However, it is hoped that such challenges are surmountable, as technology associated with *in vitro* expression systems continues to advance at a steady pace.

Although hundreds of HDeCs, from dozens of species, could potentially be tested for therapeutic activity, we have argued that administration of purified factors cannot recapitulate complex biological relationships that have evolved over hundreds of millions of years [4,38]. For this reason, it is anticipated that the use of intact helminths for therapy has substantial and indeed insurmountable advantages over approaches using specific, isolated HDeCs [4]. On the other hand, it could be argued that all helminths are dangerous and should be classified as parasites. However, helminths with little or no adverse effects under controlled conditions of exposure are already available for testing [39,40]. Another argument in favor of HDeCs over live helminths is the fact that it

Glossary

Biome Depletion Theory: the theory states that the loss of species diversity from the ecosystem of the human body in modern industrialized countries leads to immune dysregulation and a subsequent increase in the prevalence of CIADs. Synonymous with the Old Friends Hypothesis, the theory evolved from the Hygiene Hypothesis (see below).

Chronic inflammation-associated diseases (CIADs): a broad class of diseases and conditions caused by chronic inflammation. Accompanied by immune dysregulation, this group of diseases and conditions includes allergies, a range of autoimmune conditions, some neuropsychiatric disorders, and some digestive diseases.

Helminth therapy (HT): a type of medical therapy based on the application of controlled exposure to nonpathogenic or mildly pathogenic worms with the intention of upregulating and suppressing anti-inflammatory and proinflammatory immune responses, respectively.

Helminth-derived compounds (HDeCs): various forms of worm-related components that might potentially be used for therapy; they include freeze-killed eggs, larvae, or adult worms, crude extracts from a part of, or whole, helminth, body fluids obtained from helminths, products secreted or excreted from helminths, or specific bioactive molecules isolated from helminths.

Hygiene Hypothesis: states that an increase in the development of certain hyperimmune and autoimmune diseases in the Western world was associated with the widespread use of components of modern sanitation, such as sewer systems and water-treatment facilities (flushing toilets). In the original formulation, it was the absence of disease early in life that led to increased disease later in life.

Old Friends Hypothesis: synonymous with the Biome Depletion Theory in meaning, this term is commonly used and probably communicates well to the nonscientist. However, since many of the organisms depleted from the ecosystem of the human body (e.g., some helminths) in modern society are potentially dangerous (i.e., not particularly friendly), this term may be less descriptive and accurate than the term 'Biome Depletion Theory'.

may be difficult to manufacture live helminths free of all bacteria and other microbiota, raising concerns that the use of live helminths might result in inadvertent transmission of diseases via helminth vectors. However, many helminths are 'cultured' in humans who can be screened thoroughly for known pathogens using routine methods [41], and other helminths can be cultured in laboratory animals that are routinely housed in highly controlled, pathogen-free conditions. Moreover, the potentially therapeutic stage of some helminths, for example, cysticercoids of the rat tapeworm, are cultured in edible insects that do not harbor disease-causing microbes [42]. Further, manufacturing of the helminth that has been tested most extensively in humans to date, the porcine whipworm, has already been achieved at levels which are approved by the FDA. Helminths are typically administered orally rather than intravenously, suggesting that food-quality production rather than drug-quality production is likely to prove adequate for safety. Thus, based on available information, concerns over difficulty in maintaining production of live helminths free of pathogens appears to be unwarranted.

Somatic migration: migration of helminths through tissues and organ systems of the host, in particular outside of the intestinal lumen.

Although the exquisite biological complexity of live helminths and other factors described above suggests that live helminths will be superior to HDeCs, and will be feasible to produce, research focused on specific HDeCs and their interaction with the immune system is expected to be important for the future of HT. Such efforts, for example, will inform projects aimed at; (i) cultivation or selective breeding of more effective helminths, (ii) developing individualized HT, and (iii) genetically modifying helminths for a wide range of therapeutic purposes [4].

Use of Intact Helminths in Laboratory Model Systems of Disease

Most results showing that colonization with helminths can prevent and/or treat CIADs comes from experimental models of disease (Tables 2 and S1). These studies, recently reviewed [43–47], often involve helminths that may prove difficult to translate to the clinic for use in humans. For example, the often studied, rodent-specific nematode *Nippostrongylus brasiliensis* is extremely pathogenic in laboratory animals, inducing lung deterioration and long-term airway hyper-responsiveness consistent with emphysema and chronic obstructive pulmonary disease [48]. Another frequently studied helminth in laboratory animals, *Heligmosomoides polygyrus*, does not remain in the lumen of the intestine, but rather encysts and subsequently matures in the muscles of the intestine rather than remaining in the intestinal wall [49]. Although these helminths serve as convenient models for testing the effects of HT on CIADs (Table 3), their propensity for induction of pathology precludes their consideration for clinical use.

A wide range of laboratory models of disease have been utilized for testing of HT (Tables 2 and S1). However, the variable approaches used, and the inevitable difference between disease models and disease in humans, make it difficult to know whether the results from such studies can predict human outcomes [50,51]. Perhaps more importantly, regulatory agencies have already demonstrated their willingness to move directly to Phase I/Phase II clinical trials for helminths which are thought to be relatively benign at a given level of exposure. In evidence of this is the number of studies examining the effects of live helminths on humans (Table S1; see also Box S1 in the supplemental information online). Hence, a careful consideration is indeed needed of whether further testing in laboratory models of disease is useful for predictions of what is to be expected in clinical trials [51]. Further, the enormously growing risk of CIADs, apparently as a partial consequence of the virtual elimination of helminths [8,9,13,52], argues for an aggressive approach involving clinical trials rather than further testing in experimental models. However, as described earlier, the use of a range of experimental models is expected to yield a better understanding of the mechanisms underlying HT, and this understanding will possibly be important for the future of the field.

Table 1. Summary of Helminths, Their Life Stages, and Compounds Used in Helminth Therapy[a]

Helminths	Life stages used in HT	Helminth form tested in HT			*In vivo/in vitro* models
		Live worms	HDeCs	Specific compounds[c]	
Trematoda					
Fasciola hepatica	Adult	✓	Ag[b]/ ESPs	Proteins	Allergies, MS, RA, T1D *in vitro* cell culture
Schistosoma japonicum	Adult	–	–	Proteins, killed eggs	IBD, MS, RA *in vitro* cell culture
	Eggs		Ag		
Schistosoma mansoni	Adult	✓	Ag/ESPs	Proteins, glycan, glycoprotein, killed eggs	Allergies, IBD, MS, RA, T1D, obesity *in vitro* cell culture
	Larvae		Ag		
	Eggs		Ag		
Clonorchis sinensis	Adult	–	Ag	Protein	Allergies, IBD *in vitro* cell culture
Cestoda					
Hymenolepis diminuta	Adult	✓	Ag/ESPs	Helminth-influenced cells[d]	IBD, RA *in vitro* cell culture
	Larvae		–		
Taenia taeniiformis	Larvae	✓	ESPs	–	*In vitro* cell culture
Taenia crassiceps	Larvae	✓	Ag/ESPs	Helminth-influenced cells	MS, RA, T1D *in vitro* cell culture
Taenia solium	Adult	✓	–	Protein	IBD *in vitro* cell culture
	Larvae		Ag		
Echinococcus granulosus	Larvae	–	Ag	Protein	IBD *in vitro* cell culture
Echinococcus multilocularis	Larvae	–	ESPs	Protoscolexes compound, *alveococcus* vesicles	*In vitro* cell culture
Nematoda					
Spirurida					
Acantocheilonema vitae	Adult	–	–	Protein, glycoprotein	Allergies, IBD, RA *in vitro* cell culture
	L4 larvae				
Brugia malayi	Adult	–	Ag	Proteins, peptide	Allergies, IBD, RA, T1D *in vitro* cell culture
	Larvae		Ag/ESPs		
Dirofilaria immitis	Adult	✓	ESPs	Protein	T1D *in vitro* cell culture
Litostomoides sigmoidalis	Adult	✓	Ag	–	T1D
	L3 larvae		–		
Onchocerca volvulus	Adult	–	–	Protein	*In vitro* cell culture
	L4 larvae				
Wuchereria bancrofti	Adult	–	–	Protein	T1D
Strongylida					
Ancylostoma caninum	Adult	–	ESPs	Peptide	Allergies, IBD *in vitro* cell culture
Ancylostoma ceylanicum	Adult	–	Ag/ESPs	Peptide	Allergies, IBD *in vitro* cell culture
Heligmosomoides polygyrus	Adult	✓	Ag/ESPs	Helminth-influenced cells, protein	Allergies, IBD, RA, T1D, obesity *in vitro* cell culture
	L3 larvae		–		

Table 1. (continued)

Helminths	Life stages used in HT	Helminth form tested in HT			*In vivo/in vitro* models
		Live worms	HDeCs	Specific compounds[c]	
Haemonchus contortus	Adult	–	–	Glycoprotein	*In vitro* cell culture
	L3 larvae		Ag		
Necator americanus	L3 larvae	✓	–	–	Allergies, CED, IBD *in vitro* cell culture
Nippostrongylus brasiliensis	Adult	✓	ESPs	Protein	Allergies, RA, obesity *in vitro* cell culture
	L3 larvae		–		
Oxyurida					
Enterobius vermicularis	Adult	✓	–	–	MS
Syphacia obveolata		✓	–		RA
Rhabditida					
Strongyloides stercoralis	Adult	✓	–	–	Allergies, MS
Strongyloides venezuelensis	Adult	✓	–	–	T1D
	L3 larvae		ESPs		
Ascaridida					
Anisakis simplex	L3 larvae	–	ESPs	Glycoprotein	Allergies, IBD *in vitro* cell culture
Ascaris lumbricoides	Adult	✓	–	Protein	Allergies, IBD, MS
Ascaris suum	Adult	–	Ag	Protein helminth-influenced cells	RA *in vitro* cell culture
	Eggs		Ag		
Toxocara canis	Adult	–	Ag/ESPs	–	*In vitro* cell culture
Enoplida					
Trichinella pseudospiralis	Adults	✓	–	–	MS
Trichinella spiralis	Adults	✓	–	Protein, killed larvae, helminth-influenced cells	Allergies, IBD, MS, RA, T1D *in vitro* cell culture
	Larvae				
Trichuris muris	Eggs	✓	–	–	IBD *in vitro* cell culture
Trichuris trichiura	Adults	✓	–	–	IBD, MS
Trichuris suis	Adults	✓	ESPs	Lipid	Allergies, IBD, MS *in vitro* cell culture
	TSO		–		

[a]This table contains brief, simplified information from Table S1, in which there is also the list of primary references. Abbreviations used in this table: CED, celiac disease; ESPs, excretory/secretory products, material released by a part of, or the whole, helminth's stage; HDeCs, helminth-derived compounds; HT, helminth therapy; IBD, inflammatory bowel disease; MS, multiple sclerosis; RA, rheumatoid arthritis; T1D, type-1 diabetes; TSO, *Trichuris suis* ova.
[b]Ag: crude antigen from the helminth's stage, soluble extract from a part of, or the whole, helminth's stage (synonyms: stage extract, crude extract, crude soluble antigen, whole antigen, soluble stage proteins). This category also includes HMW Ag (high-molecular-weight fraction of an antigen, usually >50 kDa), crude antigen from laminated layer of hydatid cyst, pseudocoelomic fluids or hydatid fluids.
[c]Specific compound: particular antigenic substance which was either isolated from a worm or ESPs, or its recombinant or synthesized form. This category comprises several types of biomolecule. For details see Table S1.
[d]Helminth-influenced cells: T or B lymphocytes adopted from animals which are colonized by the helminth.

Results in Humans Using Intact Organisms

The knowledge that helminths have been all but eradicated by modern society, and that helminths are potent modulators of immune function, fostered the idea that HT may be used as a therapy for the treatment of CIADs in humans [9,22,26,31]. Although HT has shown promise in

Table 2. Overview of *in vivo* Inflammatory Disease Models Used in Helminth Therapy[a]

Human CIAD	CIAD induction	Animal models
Crohn`s disease	AI	TNBS- or DNBS-induced colitis
Ulcerative colitis	AI	DSS- or oxazolone-induced colitis
	–	Idiopathic chronic diarrhea (macaques)
IBD-like	AT	T cell transfer model of chronic colitis
	KO	Mdr1a-spontaneous colitis
Type 1 diabetes	IM	NOD mice model
	AI	Cyp-accelerated diabetes in NOD mice
	AI	STZ-induced diabetes
Rheumatoid arthritis	AI	Collagen-, CFA- or zymosan-induced arthritis
	AT	K/BxN-induced arthritis
	IM	MRL/MpJ polyarthritis model (also model for SLE)
Multiple sclerosis	AI	Experimental autoimmune encephalomyelitis
Dermal allergies	AI	DFNB-induced contact hypersensitivity
	AI	OVA-atopic eczema
Respiratory allergies	AI	LPS- or CXCL8-induced pulmonary neutrophil model
	AI	OVA- or Derp1-induced allergic airways inflammation
Other allergies	AI	Ocular allergic inflammation
	AI	Food allergy
	AI	OVA-induced delayed-hypersensitivity
Obesity	HFD	High-fat diet-induced obesity

[a]The information in this table enlightens the disease models used in HT (see also Table S1), and it refers only to CIAD models. Abbreviations: AI, adjuvant-induced model, a model of disease in animals induced by some chemical substance; AT, adoptive transfer model, disease induction mediated by transfer of immune cells or antibodies between wild-type and specific animal strains; CFA, Freund's complete adjuvant; CIADs, chronic inflammatory-associated diseases; Cyp, cyclophosphamide; CXCL8, interleukin 8; Derp1, peptidase 1 from house dust mites; DFNB, dinitrofluorobenzene; DNBS, dinitrobenzene sulfonic acid; DSS, dextran sodium; HFD, high-fat diet-induced model; IM, inbred murine model; K/BxN, mice expressing both the T cell receptor transgene KRN and the MHC class II molecule A(g^7); KO, gene knock-out model; LPS, lipopolysaccharide; Mdr1a mice, mice lacking key multidrug-resistance genes; MRL, Murphy Roths large; NOD mice, non-obese diabetic mice; OVA, ovalbumin; SLE, systematic lupus erythematosus; STZ, streptozotocin; TNBS, trinitrobenzene sulfonic acid.

some cases [8,39,42], it is still not approved as standard-of-care medical treatment anywhere in the world. However, HT has been evaluated in several clinical trials and is used by thousands of individuals described as 'self-treating' and who utilize social networks to evaluate treatment regimens, determine supplier and product reliability, and track new ideas and information. Fortunately, if collected systematically, and by individuals with expertise in sociomedical studies, results obtained by self-treaters provide a rich source of information [53]. Effectiveness as well as side effects are sometimes described by self-treaters themselves, sometimes by suppliers and distributors of helminths, but more often by physicians treating patients who have self-treated using HT [39,40,42]. Using Facebook, Yahoo, HelminthWiki, and other webpages (Box S1), self-treating individuals share their experience and advice, and summarize scientific and medical knowledge concerning HT. At least six helminth providers (Box S1) market products containing vertebrate-colonizing life stages of one or more of four therapeutic helminths [ova of *Trichuris suis* (TSO) and *Trichuris trichiura* (TTO), larval stages of *Necator americanus* (NA) and *Hymenolepis diminuta* (HDCs)].

Table 3. General Information about the Biology, Host Specificity, and Pathogenicity of the Tested Helminth Candidates[a]

Helminth	LC	Host(s)	Pathology	Predilection site in host
Trematoda				
Clonorchis sinensis (*CS*)	ID	IH1- water snails; IH2 – fish DH – Ho	DH – due to larval migration through liver (*CS*, *FH*) and gut wall (*FH*); inflammation due to adult dwelling in biliary ducts (*CS*, *FH*); *FH* infection can lead to anemia, jaundice, and long-term inflammation	DH – liver, biliary ducts
Fasciola hepatica (*FH*)		IH – water snails DH – ruminants, other mammals incl. Ho		
Schistosoma japonicum (*SJ*)		IH – water snails DH – Ho	DH – dermatitis due to larval migration, fibrotic reactions in small intestine (*SJ*, *SM*) and liver due to egg migration (*SJ*), often accompanied by severe immunopathology; *SM* is responsible for thousands of deaths annually	DH – mesenteric veins around small intestine (*SJ*, *SM*) and liver (*SJ*)
Schistosoma mansoni (*SM*)				
Cestoda				
Hymenolepis diminuta	ID	IH – invertebrates DH – rats and other rodents, Ho	DH – asymptomatic	DH – small intestine
Taenia crassiceps (*TC*)		IH – rodents, rarely Ho DH – canids	IH – inflammation due to larvae development and dwelling in tissue; *TSo* – neurocysticercosis of Ho when infected with egg; DH – asymptomatic	IH – liver (*TTa*); muscles (*TSo*, *TC*); peritoneal and pleural cavity (*TC*); DH – small intestine (*TSo*, *TC, TTa*); brain (*TSo*)
Taenia solium (*TSo*)		IH – suids DH – Ho		
Taenia taeniiformis (*TTa*)		IH – rodents, rabbits DH – felids		
Echinococcus granulosus (*EG*)		IH – rodents (*EM*), ruminants, pigs (*EG*), accidentally Ho (*EM*, *EG*); DH – canids	IH – type/extent of pathological conditions depend on the larval cyst location; infections of *EG* and also *EM* lead often to the host death (incl. human)	IH – liver, lungs, brain, and other organs due to dissemination of larvae with blood
Echinococcus multilocularis (*EM*)				
Nematoda				
Spirurida				
Acanthocheilonema viteae (*AV*)	ID	IH – arthropods DH – rodents	DH – type & extent of pathological conditions depend on the localization of adults and somatic migration of microfilariae (L3/L4 larvae); *OV* cause blindness, *BM* and *WB* cause lymphatic filariasis	DH – blood (*AV*, *DI*, *LS*, *OV*); eyes (*OV*); lung arteries & heart (*DI*); lymph (*BM*, *WB*); pleural cavity (*LS*); tissues and skin (*AV*, *OV*)
Litomosoides sigmodontis (*LS*)				
Dirofilaria immitis (*DI*)		IH – arthropods DH – dogs & rarely Ho		
Brugia malayi (*BM*)		IH – arthropods; DH – Ho		
Onchocerca volvulus (*OV*)				
Wuchereria bancrofti (*WB*)				
Strongylida				
Ancylostoma caninum (*ACa*)	D	Dogs, accidentally Ho	Larval stages – somatic migration through skin (*ACa*), intestinal wall (*ACe*, *HP*), lungs (*NA*, *NB*) causing tissue damage; adults – sucking of blood in predilection site, often leading to host anemia (*ACa, ACe, HC, NA, NB*)	Primary hosts – small intestine (*ACa, ACe, HP, NA*, *NB*); abomasum (*HC*) *ACa* in Ho – skin, rarely intestine without development of adults
Ancylostoma ceylanicum (*ACe*)		Ho, cats, dogs, rodents		
Heligmosomoides polygyrus (*HP*)		Rodents		
Haemonchus contortus (*HC*)		Ruminants		

(continued on next page)

Table 3. (continued)

Helminth	LC	Host(s)	Pathology	Predilection site in host
Necator americanus (*NA*)		Ho		
Nippostrongylus brasiliensis (*NB*)		Rodents		
Oxyurida				
Enterobius vermicularis (*EV*)	D	Ho, primates	Mild pathogenicity associated with perianal laying of eggs by females associated with itching, secondary bacterial infections; pinworms are easily transferable between individuals (*EV* in Ho)	Large intestine and rectum
Syphacia obvelata		Rodents		
Rhabditida				
Strongyloides stercoralis (*SS*)	D[b]	Ho, primates, dogs	Due to somatic migration through lungs and adults dwelling in small intestine; risk of random tissue migration in immunosuppressed subjects; high risk of autoinfection inside the host organism (*SS*)	Small intestine, other tissues (random migration)
Strongyloides venezuelensis		Rodents		
Ascaridida				
Anisakis simplex	ID	IH1 – crustaceans, IH2 – fish, cephalopods DH – marine mammals, accidentally Ho	Due to somatic migration of larvae or adults or adults dwelling in gut	Gastrointestinal tract
Ascaris lumbricoides (*AL*)	D	Ho, primates	Due to hepato-pulmonary migration and dwelling of adults in gut of DH, adults often cause the intestine obstructions, produce toxins (*AL, AS, TCa*); in case of *TCa* infection of Ho – somatic migration through various tissue	Small intestine
Ascaris suum (*AS*)		Suids, accidentally Ho		
Toxocara canis (*TCa*)		Canids; other vertebrates incl. Ho as paratenic host		GIT, tissues (migration of L1); paratenic hosts – various tissues
Enoplida				
Trichinella pseudospiralis (*TPe*)	ID[c]	Primary hosts – birds; other vertebrates incl. Ho	Due to larval somatic migration and their dwelling in muscles (*TSp* – create the cysts)	Adult localized in the small intestine; L1 larvae localized in muscles (*TPe* – without cysts, *TSp* – in cysts)
Trichinella spiralis (*TSp*)		Suids, other mammals incl. Ho		
Trichuris muris (*TM*)	D	Rodents	Due to larval development in the gut mucosa and adults dwelling in the gut lumen, often causing diarrhea due to strong infestations	Adults localized in large intestine (2/3 of adult is embedded in gut wall, 1/3 is in lumen gut lumen)
Trichuris trichiura (*TTr*)		Ho, primates; accidentally suids		
Trichuris suis (*TSu*)		Suids, accidentally Ho		

[a]Abbreviations: D, direct; DH, definitive host; Ho, human; HT, helminth therapy; ID, indirect; IH, intermediate host; LC, life cycle.
[b]LC of *S. stercoralis* includes free-living cycle allowing reproduction for a few generations.
[c]LC is indirect, but one host serves always as IH and DH.

Here, we summarize the knowledge about the therapeutic helminths in humans gained from (~25) clinical studies [22] and from the community of self-treaters, the largest source of data on HT use in humans [39,40,42]:

- TSO.TSO, found widely in domestic pigs, is the most studied helminth used in HT for humans [8]. Early studies with TSO showed excellent success in treating patients suffering from ulcerative colitis (UC) and CD, of which more than half responded to the treatment, and up to

80% of CD patients achieved remission after 24 weeks [54,55]. Nevertheless, major trials with TSO (~250 CD patients) run by Coronado Biosciences (TRUST-I, -II) did not meet predetermined endpoints of improving the patients' response [43]. These failed studies used a modified formulation of TSO which had an acidity more than 100-fold less than the original formulation [39]. Unfortunately, no attempts to repeat the early trials using the original product have been conducted [54,55]. To date, approximately 14 clinical trials testing TSO on various CIADs (CD, UC, RA, MS, psoriasis, and food allergy) are registered, with various results such as (i) recorded some efficacy, (ii) lack of efficacy, (iii) no results posted, or (iv) premature termination [9,22,56,57]. However, these trials often suffer from the use of an apparently inactive formulation or the use of an insufficient dose or duration of treatment when compared with the initial trials. That being said, information regarding the use of commercially available TSO (available only with the low-pH formulation used in the early trials) collected from self-treaters still shows effectiveness consistent with the early studies [39,40]. Thus, it is evident that any formal meta-analysis of data from clinical trials involving TSO [58] is confounded by different formulations of the organism, only one of which is apparently effective, and by inconsistent treatment regimens.

- TTO. Results using TTO in humans consist primarily of reports from self-treatment in individuals suffering from CIADs such as allergies, asthma, CD, UC, autism, etc. [39]. The reported effectiveness reached 100%, depending on the indication. In addition, Broadhurst *et al*. [59] described a case report in which a patient with UC achieved colonization-dependent remission after self-colonization with TTO. Finally, a report from Argentina showed that accidental colonization with TTO halted the progression of MS, whereas MS in patients without helminth colonization continued to progress, as expected [60].
- NA. At least nine clinical trials have been performed to test the effectiveness of NA on patients suffering from a variety of CIADs, including celiac disease, CD, MS, allergic rhinoconjuctivitis, and asthma [9,22]. As with trials involving TSO, the results are variable [61–64]. Again, most information regarding the effectiveness of NA is based on sociomedical studies probing the results of self-treaters, in which NA has been used to treat approximately 50 CIADs. The success rate ranged between 50% and 100% [39]. Interestingly, NA is commonly used by self-treaters in combination with other helminths. Importantly, knowledge obtained from self-treatment suggests that many clinical trials are being conducted with doses that may be too low or with a duration of treatment that may be too short.
- HDCs. HDCs, commonly used both in the laboratory and as a model in educational settings, are readily available from multiple suppliers for HT in humans. However, the effects of HDCs in individuals with CIADs stands alone as being documented only from sociomedical studies evaluating the effects of self-treatment [39,40]. HT using HDCs has been reported to be successful with sometimes high success rates and effectiveness on more than 50 CIADs. The reported adverse effects were rare, but were very evident in a small minority of children. Importantly, reports from self-treatment provided the first evidence that HT may prove useful for the treatment of some neuropsychiatric disorders. In an unusual 'back-translation', reports from use in humans prompted experiments in a laboratory animal model which confirmed the beneficial effects of HDCs on inflammation-induced neuropsychiatric dysfunction [65].
- Accidental helminth colonization of patients. Correale and Farez. [60,66] demonstrated the beneficial effect of intestinal helminths on 12 patients suffering from MS who were accidentally colonized by the following helminth taxa in an uncontrolled fashion: *Hymenolepis nana*, *T. trichiura*, *Ascaris lumbricoides*, *Strongyloides stercoralis,* and *Enterobius vermicularis*. Except for TTO, none of these helminths has been further tested for their potential to be used for HT in the clinical arena.

The Ideal Helminth for HT

Feasibility of Helminth Domestication

A promising therapeutic helminth should meet the criterion of feasibility for controlled production. If the organisms cannot be 'domesticated', with replication of its natural life cycle involving host (s) under standardized conditions (Table S1), it will not qualify as a feasible candidate. While domestication of some helminths requires human hosts due to their limited host specificity (e.g., *T. trichiura* or *N. americanus*), some involve humans as an accidental host, and their cultivation is based on the animal host(s) (e.g., *T. suis* or *H. diminuta*) (Table 3). At present, domestication of helminths might be very difficult or impossible if those helminths utilize life cycles involving multiple intermediate hosts which may, in turn, pose challenges for domestication. (e.g., *Schistosoma* spp., *Echinococcus* spp.; Table 1). However, in the event that HT becomes popular, it is anticipated that expanding markets will drive research in this area, increasing the number of organisms for which production is feasible.

At present, the production of some widely used therapeutic worms might be technically cumbersome and unreasonably expensive. For example, clinically usable TSO requires production in pigs, which serve as reservoirs, with ova being isolated from their feces under very specific conditions to eliminate potential pathogens present in untreated porcine feces [39]. This fact, together with recommended administration every 10–14 days, makes TSO extremely costly. However, economy of scale is expected to alleviate this problem if HT becomes widespread. Nevertheless, the domestication and relatively inexpensive production of other therapeutic worms (NA, TTO, HDCs) is feasible, and it is expected that initial studies in the future involving smaller numbers of patients will benefit from helminths such as these for which production costs are relatively low.

Ability to Control Exposure to the Population

Another important criterion for helminth candidates is the ability to prevent spontaneous spread of the organisms into the environment with unintended exposure to other subjects. The human pinworm, *Enterobius vermicularis*, for example, does not meet this criterion in modern society. On the other hand, although geohelminths utilizing humans as their primary host (e.g., *N. americanus*, *T. trichiura*; Table 3) posed a threat for uncontrolled transmission in the past, it seems likely that sanitation and other factors, such as food processing and storage technologies, have rendered these helminths essentially harmless in modern society [1,2,4]. Other helminths, for which humans usually cannot serve as an effective primary host (e.g., *H. diminuta*, *T. suis*) [67,68], also meet this criterion.

Although the possibilities for severe adverse reactions or uncontrolled transmission of a particular helminth may prevent its use at present, technologies exist which could make such helminths worth consideration for HT. For example, insect control efforts, such as irradiation techniques effective at sterilizing adults [69,70], or genetic modification [71] with a dominant lethal gene [72], might be considered for use in HT. In addition, initial exposure of patients to organisms of a single sex [73] has been shown to be effective at controlling adverse responses to *Schistosoma* species, and may be effective for attenuation of adverse responses to HT. Thus, HT in the future may include helminths which do not currently fit appropriate criteria, but which may fit those criteria following some modification.

The Primary Criterion for Ideal Helminths: Maximizing the Benefit/Cost Ratio

A frequent objection to the concept of HT is that helminths have extracted a horrible toll of suffering and death throughout the world in the past [27,49] and still do so in developing countries [74]. Thus, it is argued that the cost of using helminths is simply too high. However, it is now clear that;

(i) all helminths are not always detrimental [1], even in developing countries [6,75], (ii) starvation, which heightens the dangers of exposure to helminths, has been essentially eliminated in developed countries, (iii) controlled exposure to selected helminths, rather than uncontrolled exposure to unselected helminths, is being considered for HT, and (iv) the costs to society of CIADs associated with the loss of helminths is increasing dramatically. Thus, the benefit to cost ratio for HT in the modern world is clearly very different from that in the past.

While there are dozens of helminth species that might be considered as candidates for HT [27] (Table 1), only four helminths have been utilized for HT in humans. Despite the fact that these four worms are used today, apparently with some degree of success, no systematic search for optimal helminths has been conducted. Other than the four helminths currently in use, the bovine tapeworm is the only other helminth ever used for HT, and this was used by only one self-treating individual for a very limited time [39]. All helminths currently in use were apparently selected because; (i) they are known to be relatively benign when present in controlled numbers, and (ii) they are readily available, either frequently colonizing humans (TTO and NA), commonly found in domesticated animals (TSO), or commonly used in laboratory animals (HDCs). Because the vast majority of relatively benign helminths (Tables 1 and 4) have never been tested in any way, there is a clear need to systematically evaluate helminths as candidates for HT, probing their cost/benefit ratio in a disease-specific manner.

Previously proposed eligibility criteria for therapeutic helminths were focused on the biological properties of the helminths [27,76]. However, the 'ideal helminth' for HT, as defined by the greatest benefit/cost ratio for a specific disease, will be impossible to identify without clinical trials. Even a known history of disease induction may not preclude an organism from use in HT. For example, despite the widespread problems posed for public health by uncontrolled colonization with NA in the past, this helminth, when used in controlled doses, is possibly – based on reports from individuals self-treating with helminths – the best helminth in use today for the treatment of airway hypersensitivity, particularly sensitivity of the airways to chemicals [39]. Further, NA invariably undergoes **somatic migration** during maturation, and it might be assumed that such migration imposes intolerable costs when considering a helminth for HT. However, such migration (through the lungs) may be important for the beneficial therapeutic effect of NA.

Although a large number of helminths may be considered for HT, the pathogenicity of many (Table 3) makes them unlikely candidates. Examples of such pathogenic helminths abound, including the porcine tapeworm, which can form cysts in the human brain, the giant roundworm, which often causes severe gastrointestinal cramping, and the human pinworm, which causes anal itching in many individuals and is easily transmitted from human to human. In addition, as mentioned above, some helminths commonly used in experimental models are unlikely candidates for HT due to their adverse effects.

Concluding Remarks

The loss of helminths from the human biome is one of a few key factors that underlie CIADs in modern society, and the necessity of dealing with the root causes of CIADs is increasing as the burden of these diseases rises. Toward this end, HT has been studied in a variety of experimental models, but the applicability of these studies to human disease is questionable. Nevertheless, utilization in clinical studies and by self-treating individuals is increasing, and the knowledge gained represents the pioneering efforts in what may prove to become a large and productive field of clinical medicine.

Present knowledge regarding HT in humans is hampered by very limited amounts of information and inconsistent application of HT in trials. Indeed, numerous questions remain completely

Outstanding Questions

Where should we begin with a systematic exploration of new candidates for helminth therapy (HT)?

Will helminths, 'enhanced' through breeding or genetic engineering, prove more effective for therapy than naturally occurring helminths? May the use of single-sex helminths, irradiation-sterilized helminths, or some other modified organisms be useful in the long run?

Will repeated exposure to helminths that do not naturally colonize humans prove to be more effective for therapy than occasional exposure to helminths that live for extended periods of time in humans? Will a combination of these helminths be the most effective?

Can inflammatory disease be prevented using prophylactic exposure to helminths in healthy individuals? Can this question be tested given the current pipeline for drug development?

Is individualized medicine appropriate for HT? How should treatment regimens be established? Is the choice of helminths dependent on the disease?

Although the loss of helminths is one factor that predisposes to CIADs, how does the impact of this factor compare with other factors (e.g., diet, chronic stress, vitamin D deficiency, and sedentary lifestyle) that also predispose to CIADs?

Is it possible to establish some parameters, or even a starting point, for clinical trials in humans based on the knowledge obtained from the self-treating community?

The unknown unknowns: might widespread reintroduction of helminths change basic factors in Western society, such as the aging process, resistance to infections, the effects of vaccines or immunosuppressive drugs?

Table 4. Advantages and Disadvantages of Therapeutic and Other Tested Helminths Based on Clinical Trials and Self-treaters[a]

	Advantages	Disadvantages
Current therapeutic helminths		
TSO	▪ Noncommunicable between humans ▪ High effectiveness to many CIADs (80% patients in remission) ▪ Well established dosage (2500 or 5000 ova every 2 weeks) ▪ Minimal adverse effects ▪ Long shelf life ▪ Adult localization in gut	▪ High doses, more than 2500 of ova, which correspond to the same number of larvae ▪ Necessity of frequent recolonization for sustained effect ▪ Costly cultivation
TTO	▪ 50% effectiveness, but limited spectrum of CIADs ▪ Easy and cheap cultivation ▪ Long-term colonization of human (up to 4 years) ▪ Lower price ▪ Long shelf life ▪ Adult localization in gut	▪ Communicable between humans with the risk of spreading to the environment ▪ Humans are the natural host and, thus, uncontrolled colonization ▪ Stronger adverse effects
NA	▪ Effectiveness ranges between 40 and 90% depending on the severity of CIADs; more effective to seasonal allergies ▪ Easy and cheap cultivation ▪ Long-term colonization of humans (up to 1–2 years) ▪ Longer shelf life ▪ Adult localization in gut	▪ Communicable between humans with the risk of spreading to the environment ▪ Strong adverse effects (within larval migration first 2 weeks after challenging, mainly anemia during long-term colonization)
HDCs	▪ High effectiveness to many CIADs (up to 100%) ▪ Easy and cheap cultivation ▪ No or mild adverse effects ▪ Adult localization in gut ▪ Noncommunicable between humans with the minimal risk of spreading to the environment	▪ Necessity for frequent recolonization for sustained effect
Accidentally tested helminth		
Hymenolepis nana	▪ Easy and cheap cultivation ▪ Adult localization in gut	▪ High pathogenicity due to autoinfection – *H. nana* is able to replicate in human gut without intermediate host
Ascaris lumbricoides	▪ Adult localization in gut	▪ High pathogenicity due to hepatopulmonary migration of larval stages and toxin production by adults ▪ Communicable between humans with the risk of spreading to the environment
Strongyloides stercoralis	▪ Easy and cheap cultivation ▪ Long-term colonization of humans (period unknown) ▪ Adult localization in gut ▪ Mild pathogenicity in healthy humans	▪ Highly communicable between humans with the risk of spreading to the environment ▪ Somatic migration ▪ Autoinfective life cycle ▪ Pathogenicity in immunosuppressed persons
Enterobius vermicularis	▪ Easy and cheap cultivation ▪ Adult localization in gut ▪ Long-term colonization of human ▪ No somatic migration ▪ Minimal adverse effects	▪ Occasionally adverse effects in children (pruritus, secondary bacterial infections, appendix inflammation, rarely insomnia or weight loss) ▪ Highly communicable between humans with the risk of spreading to the environment

[a]Abbreviations: HDCs, *Hymenolepis diminuta* cysticercoids; NA, *Necator americanus*; TSO, *Trichuris suis* ova; TTO, *Trichuris trichiura* ova.

untouched (see Outstanding Questions), and a systematic search for helminths with an optimal benefit/cost ratio has yet to begin. Indeed, the selection of helminths currently in use by humans is apparently based in large part on happenstance and ease of access rather than on a systemic search using objective criteria (Figure 1, Key Figure).

A systematic exploration of potential helminths for HT is not expected to be trivial. A large number of helminths colonizing both humans [77] and animals [78] might be considered as candidates for use in HT. However, although some selection criteria (Figure 1), described above, are evident, there is no clear way at the present time to predict which helminths will provide the greatest benefit/cost ratio. Indeed, major questions remain, including whether human-specific versus other helminths may prove to be optimal, and whether the best helminth will depend on factors such as patient genotype and diagnosis (see Outstanding Questions).

Although a systematic search of helminths poses a daunting task, some candidates might be worth consideration based on currently available information. For example, the human-specific threadworm, *S. stercoralis*, and the human-specific pinworm, *E. vermicularis*, have shown a beneficial effect on one CIAD [60] but have not been systematically tested. Although apparently beneficial under some conditions, these helminths are not without risks. Threadworm larvae can migrate through different host tissues in immunosuppressed persons [79], and the pinworm easily spreads to the environment, causing unintended colonization of other subjects (Tables 3

Key Figure

Graphical Overview of the (Re)formulated Eligibility Criteria for Present and Future Therapeutic Worm Candidates

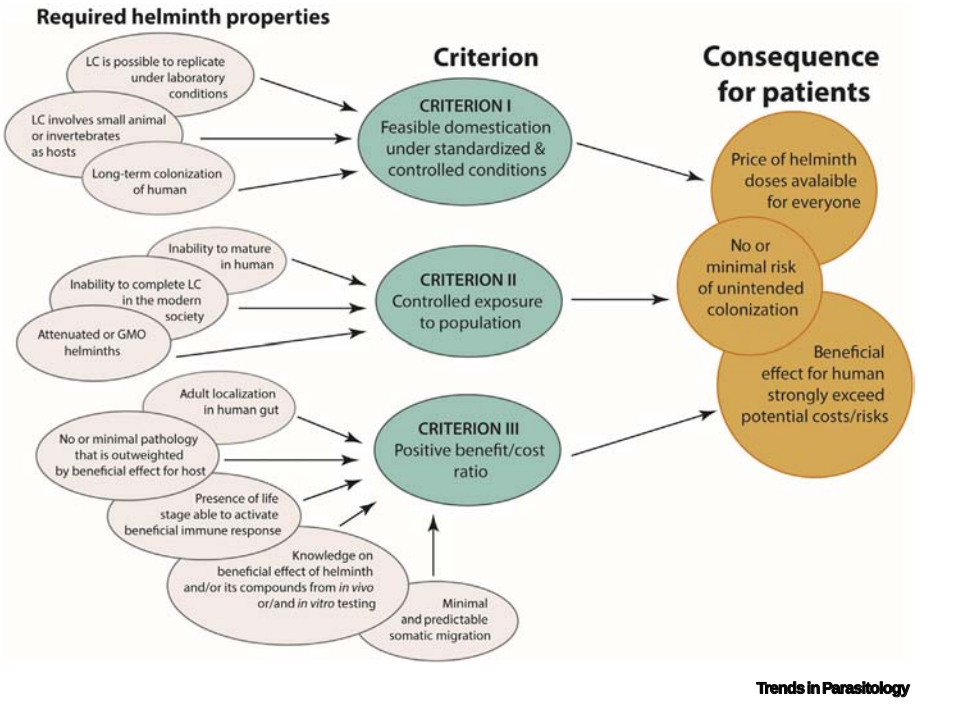

Figure 1. The specified criteria (criteria I–III) are based on the properties of helminths that are suitable for helminth therapy and result in beneficial consequences for patients. Abbreviations: GMO, genetically modified organisms; LC, life cycle.

and 4). Perhaps the potential of these and other helminths, that might be considered too dangerous at the present time, will be tested in the future using genetic modifications or other approaches (e.g., selection of a single sex, sterilization by irradiation, incorporation of lethal, dominant genes) designed to mitigate risks.

Other potentially attractive yet untested candidates include the rodent-specific hymenolepidid tapeworms, *Hymenolepis hibernia*-like and *Hymenolepis microstoma*(-like), which have been found to asymptomatically colonize humans [80–82]. Their biology and life cycles are very similar to that of *H. diminuta*, which is thought to effectively attenuate inflammation associated with many CIADs [39], and recent reports have described their asymptomatic colonization of humans based on molecular analyses [81,82]. However, candidates that can be identified based on currently available information are limited. Because most work on helminths has been motivated by helminth-induced disease, we hypothesize that a wide range of benign, or relatively benign, helminths exist in nature that have yet to be characterized, and that a systematic search of helminths for HT will involve both evaluation of known helminths and a search for helminths that are largely or perhaps entirely uncharacterized and unknown. In summary, selection of helminths for testing in humans is in its infancy and promises to be a challenging yet exciting field of biomedical research.

Acknowledgments

We thank Lucie Řežábková and Milan Jirků for valuable help and comments. This work was supported by Young Investigators project from Human Frontier Science Program (HFSP0078/2015) to K.J.P., and the ERD Funds (OPVVV 16_019/0000759) to J.L.

Supplemental Information

Supplemental information associated with this article can be found online at https://doi.org/10.1016/j.pt.2019.04.009

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