Strongyloidiasis: what every gastroenterologist needs to know

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Abstract: Strongyloidiasis is caused by the intestinal roundworm, *Strongyloides stercoralis*, which has the potential for fatal outcome. It may present with vague gastrointestinal symptoms and mimic gastrointestinal diseases such as inflammatory bowel disease, and as such, it should be in the purview of the gastroenterologist. While strongyloidiasis is generally asymptomatic or produces mild symptoms in patients with an intact immune system, individuals who are immunocompromised may develop life-threatening disease through hyperinfection syndrome and disseminated disease. The worm has a complex lifecycle and is able to autoinfect its host, thereby allowing indefinite persistence even decades after initial infection. This leads to cases where travelers, and those who lived in endemic countries, may present years after travel. With its features of prolonged infection, relatively high global prevalence, and potential for fatal outcomes, it is imperative for all clinicians to be aware of this disease. Owing to its involvement with the gastrointestinal system, however, we will outline salient points about strongyloidiasis for the gastroenterologist.

Keywords: chronic parasitic infections, gastroenterology, soil-transmitted helminths, *Strongyloides stercoralis*, strongyloidiasis

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Introduction

Strongyloidiasis is caused by the intestinal soil-transmitted nematode *Strongyloides stercoralis*, which, due to a unique autoinfective capability, leads to a lifelong infection until treated. The autoinfective capacity additionally portends risk of a hyperinfection and fatal dissemination syndrome as the worm, possibly coated by enteric flora, can migrate to sites distant from the bowel, a process during which enteric bacteria are tracked throughout the body. Strongyloidiasis can mimic the presentation of inflammatory bowel disease (IBD). Accidental treatment of *Strongyloides* colitis with immune suppressing medications used to treat IBD has led to fatal outcomes,[1] and as such, strongyloidiasis is a disease with which gastroenterologists should be familiar. We herein review succinctly the pathogenesis and clinical spectrum of disease in order to better situate gastroenterologists to recognize and respond to cases they encounter in their practice.

Epidemiology

Strongyloides is transmitted mainly through barefoot sand or soil exposure in endemic areas. These areas are in the tropics and subtropics, including Africa, Asia, Southeast Asia, Central, and South America, but it is also found in temperate areas (Mediterranean, Australia, and the United States) in specific foci. The roundworm is estimated to infect 10–40% of the population on average in endemic areas, with population prevalence demonstrably higher (~70–90%) in some countries,[2] with an estimate of 30–100 million cases worldwide. Birth, residence in, possible exposure, or short-term to long-term travel to these areas pose epidemiological risk for strongyloidiasis.

Clinical manifestations of acute infections

Like many helminthiases, the spectrum of clinical manifestations of strongyloidiasis is underpinned by the worm's life cycle in the human host.

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Infection occurs when filariform larvae present in sand or soil penetrate intact human skin.[3] At this stage in the life cycle, the only sign may be a low-grade eosinophilia or a penetration site rash similar to the 'ground itch' of hookworm infection. Following penetration, larvae are transported to the lungs *via* hemolymphatics wherein they undergo an obligatory lung migration phase of maturation[3] that may manifest as a Loeffler's-like or pulmonary infiltrates with eosinophilia syndrome, characterized by systemic symptoms (e.g. fever), cough, and high-grade eosinophilia. Following lung migration, maturing larvae are then coughed and swallowed or directly penetrate tissue in order to access the small bowel,[3] where they ultimately reside as adult 'thread worm' females. This enteric phase of development and maturation may be accompanied by the hallmark gastrointestinal symptoms of strongyloidiasis including epigastric burning, upper abdominal pain, and diarrhea. Mature females in the small bowel produce noninfectious rhabditiform larvae,[3] which can mature in the gut to infectious filariform larvae and reinfect the same host *via* penetration of the colonic, rectal, and perianal mucosae. Such autoinfection may be accompanied by the classic pruritus ani that typifies intestinal strongyloidiasis. Once females are mature and reproducing in the gut – a process that may take up to 8–12 weeks following initial infection – larvae are then theoretically detectable in the stool.

Like most helminthiases, the clinical features of *Strongyloides* infection vary according to the worm burden and duration of infection, which, like many parasitic diseases, leads to a wide clinical spectrum of disease. In asymptomatic individuals, the only sign of infection may be mild eosinophilia. It is important to note, however, that eosinophilia is usually absent in patients with hyperinfection syndrome and disseminated disease,[4] and therefore may not be a useful marker of infection in such scenarios.

As noted above, acute intestinal strongyloidiasis after recent travel can present with several vague gastrointestinal manifestations including nausea, vomiting, abdominal pain particularly burning epigastric pain or discomfort in the left upper quadrant, diarrhea, and weight loss.[4] Such gastrointestinal symptoms may also signify chronic intestinal strongyloidiasis owing to low-grade autoinfection occurring over years if not decades. Another classic symptom of the infection in either immunocompetent or immunosuppressed individuals where autoinfection is occurring is the presence of a rapidly moving (i.e. migration rate of several cm per hour), pruritic, linear or serpiginous rash with perianal involvement. This dermatologic finding is due to intradermal migration of larvae and is known as larva currens, and it is pathognomonic of strongyloidiasis.[4]

Diagnosis

The appropriate diagnostic tests for strongyloidiasis depend on the clinical syndrome,[1] but generally require a combination of serologic testing and one or more stools for microscopic ova and parasite (O&P) examination. Duodenal and colonic aspirates obtained at endoscopy would also be appropriate specimens for microscopic examination, as are tissue biopsies of the gastrointestinal tract. In the absence of hyperinfection or dissemination, larval burden will be low and as such all direct parasitologic methods of detection that rely on microscopy will be inherently less sensitive than those that detect host antibody response to simple intestinal infection. Thus, for the vast majority of patients screened for strongyloidiasis, serology remains the mainstay diagnostic platform and is highly sensitive.[1,5] In patients with suspected hyperinfection syndrome and dissemination, then larval burden is expected to be much higher and as such, direct parasitologic detection methods – such as O&P examination of stool, urine, sputum, and cerebrospinal fluid (CSF) – become comparatively more sensitive than in asymptomatic or simple intestinal infection.[1,5] Conversely, due to the immunosuppressing factors that predispose patients to hyperinfection and dissemination in the first place, diagnostic tests reliant on antibody production may be falsely negative in patients with disseminated disease.[5]

Patients at risk for fatal disease

Hyperinfection syndrome occurs when the worm's autoinfection cycle accelerates to increase larval load in the gut and lungs, which can lead clinically to a fatal dissemination. Dissemination occurs when the larvae in the accelerated autoinfective cycles migrate out of the bowel to distant sites, a process during which enteric bacteria (and

potentially fungi) are tracked through sterile spaces of the vasculature and central nervous system. Multiple identified risk factors that pose a risk for disseminated disease include corticosteroid therapy, immunosuppressing medications (e.g. rituximab, methotrexate), solid organ or hematopoietic stem cell transplantation, hematologic malignancy, and human T-lymphotropic virus-1 (HTLV-1) infection.[4] Additional minor risk factors include malnutrition, diabetes mellitus, chronic renal failure, and heavy alcohol consumption.[4] Detecting and treating the infection – either using a test and treat strategy or empiric treatment – prior to iatrogenic immunosuppression are imperative as the mortality rate of disseminated disease is estimated to be greater than 85%.[1,6,7]

Patients with hyperinfection syndrome or disseminated disease may present with the same gastrointestinal symptoms as those with simple intestinal strongyloidiasis – that is, nausea, epigastric burning, and diarrhea. Larvae migrating through the intestinal wall can lead to Gram-negative or polymicrobial sepsis and meningitis.[4] Accelerated autoinfection leading to escalating burden of larvae in the lungs can manifest as a severe Loeffler's syndrome characterized by shortness of breath, wheezing, hemoptysis, cough, and respiratory distress. Patients with hyperinfection and dissemination may also present with systemic features such as fever and decreased level of consciousness.[4] Disseminated disease in those patients who have come to medical attention for a gastrointestinal complaint to begin with is almost always preceded by prolonged diarrheal illness, the symptoms of which have escalated due to increasing doses of immunosuppressants used to treat the suspected 'colitis', a period during which larvae can be detected by microscopic examination in stool. Thus, in patients with both epidemiological and clinical risk factors, particularly those of a gastrointestinal nature, clinicians should maintain a low threshold to investigate in order to avoid delays in diagnosis and life-saving therapy.

Challenges for the gastroenterologist: *Strongyloides* colitis

Strongyloides adults typically reside and lay eggs in the small intestine, with hatched larvae then transiting through the large intestine, and potentially penetrating the colonic or rectal mucosa in internal autoinfection.[8] In cases of *Strongyloides*

colitis, the parasite infects the large intestine. This can occur in cases with[9–11] or without hyperinfection syndrome or disseminated infection,[12] although it is less common in cases with simple intestinal infections or isolated larva currens.[10] Furthermore, *Strongyloides* colitis may occur in patients who are immunocompromised or immunocompetent;[8,12] thus, risk factors for disseminated disease alone may not be useful predictors of colitis. The symptoms of *Strongyloides* colitis are akin to those of other causes of inflammatory or infectious colitis, and include lower gastrointestinal tract bleeding,[9] along with the aforementioned nonspecific gastrointestinal symptoms. Distinguishing features of *Strongyloides* colitis are summarized in Table 1.

Strongyloides colitis as a mimic of ulcerative colitis or IBD

While the symptoms of *Strongyloides* colitis may overlap substantially with IBD, so too may the endoscopic or histological findings, which can closely mimic the disease.[9,13,14] Given the ever-increasing mobility of populations at risk of IBD to areas conferring risk of strongyloidiasis, the possibility of IBD coexisting with strongyloidiasis must also be considered. The definitive diagnosis of *Strongyloides* colitis is made through microscopic detection of larvae in colonic tissue.[8] The absence of notable larvae histopathologically, however, does not exclude infection; thus, it is important for pathologists to be aware of distinctive histopathologic features. Features that distinguish strongyloidiasis from IBD, and ulcerative colitis (UC) in particular, include (1) a skip pattern of inflammation, (2) distal attenuation of disease with near-universal rectal sparing, (3) eosinophil rich infiltrates of the lamina propria, (4) relative preservation of crypt architecture and Goblet cell mucin production, and (5) frequent involvement of submucosa.[10]

Distinguishing between strongyloidiasis and UC/IBD is imperative to prevent erroneous administration of immune-suppressing medications, which would naturally treat inflammatory causes of colitis, but will, with certainty, worsen the clinical course and outcome of *Strongyloides* colitis.[1,10,14] In addition, it is important to screen and diagnose patients from endemic areas or those with high epidemiological risk factors prior to initiating immunosuppressive treatment as this could worsen the outcome of possible *Strongyloides*

Table 1. Summary of review points for the gastroenterologist.

Strongyloides colitis	
Diagnosis	Microscopic detection of larvae in colonic tissue through histopathology; microscopic detection of larvae in effluents through O&P exam of stool, sputum urine, and other body fluids Serologic detection of *Strongyloides*-specific antibodies
Difference between strongyloidiasis and IBD or UC	Strongyloidiasis characterized by larva currens, skip pattern of inflammation, distal attenuation of disease with near-universal rectal sparing, eosinophil rich infiltrates of the lamina propria, preservation of crypt architecture and Goblet cell mucin production, and frequent involvement of submucosa
Treatment	Ivermectin and ivermectin + albendazole for severe infection
Treatment to avoid before screening of those at risk of dissemination	Iatrogenic immunosuppression, corticosteroid therapy, and immunosuppressing medications
IBD: inflammatory bowel disease; UC: ulcerative colitis.	

colitis. If diagnostic tests are unavailable due to factors like cost-effectiveness or urgency of needed immunosuppression, then empiric ivermectin treatment should be considered. The recommended treatment for strongyloidiasis is oral and subcutaneous ivermectin with or without albendazole depending on the clinical syndrome.[1] Treatment for simple intestinal strongyloidiasis is ivermectin 200 μg/kg/day po once daily on days 1 and 2 or two doses separated by 14 days.[1] Ambulatory patients with *Strongyloides* colitis or mild hyperinfection (characterized by gut and respiratory symptomatology in the absence of sepsis or severe clinical manifestations) can be treated with a 7-day course of ivermectin, while those who are hospitalized or critically unwell should be treated with both daily ivermectin (200 μg/kg/day) and the second-line agent albendazole (400 mg twice daily) until clinical improvement and cessation of larval shedding in the stool and previously positive effluents (such as sputum and endotracheal aspirates) are achieved.[1] Restoring natural Th2 function – which is the host response most critical to controlling intestinal helminthiases[15,16] – by reducing immunosuppressant medications where feasible is an important component of treatment of disseminated disease and hyperinfection.

Conclusion

Upon exposure, strongyloidiasis can occur in patients, and due to its capacity for autoinfection, strongyloidiasis is a lifelong infection until treated. Owing to the fatal complications of hyperinfection syndrome and disseminated disease, patients with underlying immune suppression and epidemiological risk should be treated with ivermectin promptly and empirically. A high degree of clinical suspicion is warranted in those with risk factors. The differentiation between *Strongyloides* colitis and UC/IBD for gastroenterologists is critically important to ensure the appropriate management of patients. Full systematic review of the literature was not undertaken for this review; as such, the data and information presented herein do not represent a comprehensive evidence-based approach to the clinical problem of *Strongyloides* colitis, and as such, may not fully extend across geographies, demographics, and practice settings.

Declarations

Author contributions
Sabrina Yeung: Data curation; Formal analysis; Investigation; Writing – original draft; Writing – review & editing.

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