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Review

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Intestinal Parasitic Infections in 2023

Monjur Ahmed

Abstract

Intestinal parasites include intestinal protozoa and intestinal helminths. Intestinal parasitic infections (IPIs) pose a global health problem affecting over one billion people worldwide. Although these infections are predominantly seen in the developing world, they are frequently seen in the developed countries, particularly in immunocompromised patients. Patients' clinical presentations generally include diarrhea, dysentery, abdominal pain, nausea, vomiting, nutritional deficiency, iron deficiency anemia, anal and perianal itching, and rarely intestinal obstruction. The intestinal parasites have similarities in their mode of transmission and life cycle. The stool test is the primary way of diagnosing IPIs. Treatment is given with various anti-parasitic agents. However, appropriate preventive measures are essential for successfully controlling the IPIs.

Keywords: Intestinal protozoal infections; Intestinal helminths; Parasites of the gut; Life cycles of intestinal parasites; Treatment options of intestinal parasites

Introduction

Intestinal parasitic infections (IPIs) are among the most critical public health problems worldwide. Patients infected with these parasites suffer from significant morbidity and mortality. The intestinal parasites are broadly classified into protozoa and helminths (Table 1). Although IPIs are more commonly seen in developing countries, they are also increasingly being seen in developed countries due to the globalization of food, international travel, and migration. This review will discuss the epidemiology of common IPIs, including their mode of transmission, short life cycles, clinical presentations, diagnosis, management, prevention, and pathways to investigate patients in whom intestinal parasites are suspected.

Epidemiology

The prevalence of IPIs varies from country to country. Due to various geographical, social, and environmental factors, they are the most prevalent diseases in developing countries, particularly in sub-Saharan Africa (SSA), Asia, Latin America, and the Caribbean. These include tropical and subtropical climates, overcrowding, inadequate sanitation, insufficient pure water supply, low income, low level of education with poor knowledge about hygiene, food handlers with IPIs, and poor personal hygiene [1]. According to the World Health Organization (WHO), 1.5 billion people, i.e., 24% of the world population, have IPIs, mainly the soil-transmitted helminths (geohelminths) *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whipworm), *Ancylostoma duodenale*, and *Necator americanus* (hookworms) [2]. More than 50% of the population has IPIs in some of the regions of SSA. *Giardia lamblia*, *E. histolytica*, and cryptosporidium are the most common intestinal protozoal infections in developing countries. In developed countries, intestinal protozoal infections are more common than intestinal helminthic infections [3]. In the United States, *Giardia lamblia, Cryptosporidium parvum, Blastocystis* spp., *Cyclospora cayetanensis, Cystoisospora belli,* and *Entamoeba histolytica* are the common intestinal protozoal infections, and *Enterobius vermicularis* is the most prevalent helminthic infection [4].

Common IPIs

The life cycle of intestinal protozoa and helminths differs from each other. Protozoa are unicellular and can multiply in the human body, whereas helminths are multicellular and cannot generally multiply in the human body. As discussed below, there are certain standard features in the life cycle, mode of transmission, clinical presentation, treatment, and prevention of IPIs.

Giardiasis

Giardia duodenalis (also known as *Giardia lamblia* or *Giardia intestinalis*) is a flagellate parasite that is a major cause of epidemic or sporadic diarrhea worldwide. Giardia infection rate can be as high as 30% in developing countries and 7% in developed countries [5]. In the developed world, it is the most common cause of parasitic diarrhea [6]. It exists in the vegetative/active trophozoite form and the infective cyst form. Human infection occurs when the giardia duodenalis cysts in fecal-contaminated water or food are ingested. The fully formed cyst is oval, 8 - 18 µm by 7 - 10 µm in size, and contains four nuclei. The cysts are dormant and hardy and can survive in

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Division of Gastroenterology, Department of Medicine, Thomas Jefferson University, Philadelphia, PA 19107, USA.
Email: monjur.ahmed@jefferson.edu

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Table 1. Names of Protozoa and Helminths

Protozoa	Helminths
Giardia duodenalis	*Enterobius vermicularis*
Cryptosporidium parvum and *Cryptosporidium hominis*	*Ascaris lumbricoides*
Blastocystis spp.	*Trichuris trichiura*
Cyclospora cayetanensis	*Ancylostoma duodenale, Necator americanus*
Cystoisospora belli	
Entamoeba histolytica	

cold water for up to 3 months. After ingestion, the cysts get exposed to gastric acid, bile, and trypsin in the duodenum. As they travel to the proximal small intestine below the level of the ampulla of Vater, excystation occurs, releasing trophozoites (two trophozoites per cyst) [7]. The trophozoites are 9 - 21 µm long, 5 - 15 µm wide, and 2 - 4 µm thick, containing two large nuclei, a median-pear-shaped body, one ventral sucking/adhesive disc, and eight flagellae. Many trophozoites adhere to the brush borders of the enterocytes by their sucking/adhesive discs, and many remain in the lumen of the duodenum. They multiply by binary fission into numerous trophozoites. The trophozoites move towards the distal small bowel where encystation of the trophozoites occurs. The cysts travel through the colon and get excreted in the stool, where they are instantly infectious.

Pathogenesis

Giardia trophozoites damage the brush border epithelium, shorten the microvilli and disrupt the epithelial barrier function [8]. Rarely can they cause intraepithelial lymphocytosis, crypt hyperplasia, and villous atrophy. There can be neutrophilic and eosinophilic infiltrates in the epithelial layer as well. All these changes lead to nutrient malabsorption, diarrhea, and steatorrhea [9]. Giardiasis can cause disaccharidase deficiency due to loss of absorptive surface and impair sodium-dependent D-glucose and water absorption but can cause chloride hypersecretion [10].

Presentation

Patients generally present with diarrhea, abdominal cramps, nausea, gas, and bloating sensation. Patients with chronic giardiasis may present with the full spectrum of carbohydrate, protein, fat, vitamins, minerals, and water malabsorption, leading to diarrhea, steatorrhea, and weight loss. As giardiasis is more common in common variable immunodeficiency (CVID), patients with CVID may present with diarrhea or malabsorption syndrome due to giardiasis [11].

Diagnosis

Giardiasis is confirmed by detecting the presence of giardia trophozoites, cysts, or giardia-specific antigen in the stool sample or giardia trophozoites in duodenal fluid or duodenal biopsy [12]. As the Centers for Disease Control and Prevention (CDC) recommends, a stool sample should be collected thrice over several days. The test of choice is stool microscopy with direct fluorescent antibody (DFA) because of its increased sensitivity (93% to 100%) and specificity (99.8% to 100%). Other tests include stool microscopy with trichrome staining, enzyme immunoassay (EIA), rapid immunochromatographic cartridge assays, and molecular assays for subtyping different giardia genetic assemblages (A-H) [13]. Giardia cysts are generally seen in wet mount preparations, whereas giardia trophozoites are typically seen in trichrome staining. Giardia antigen test is also highly sensitive (> 90%) and specific (100%).

Treatment

The nitroimidazoles like metronidazole and tinidazole are potent agents against giardiasis. The usual dose of metronidazole is 500 to 750 mg/day for 5 to 10 days (median efficacy 88%) or a single dose of 2 to 2.4 g (median efficacy 48%). The usual dose of tinidazole is 300 mg/day for 7 days (median efficacy 87%) or a single dose of 1 to 2 g (median efficacy 92%) [14]. Metronidazole becomes activated inside the giardia trophozoites as its nitro group is reduced by its electron transport protein, "ferredoxins". The reduced metronidazole can then damage the DNA of giardia.

Cryptosporidiosis

Cryptosporidiosis is a diarrheal illness caused by cryptosporidium. Cryptosporidium is an intracellular protozoan that can cause both human and veterinary infections. There are many species of cryptosporidium, but human infection is mainly caused by *Cryptosporidium parvum* and *Cryptosporidium hominis*. The disease is present worldwide and mainly transmitted through water (drinking water and recreational water). However, the fecal-oral route and inhalation of infected droplets into the respiratory tract are also well-known. Ingested cryptosporidium oocysts travel to the small bowel where excystation occurs, each oocyst releasing four infectious sporozoites. The sporozoites attach to the epithelial cells, where they become enveloped by a dense layer of apical membrane and reside in a parasitophorous vacuole outside the epithelial cell cytoplasm. Each sporozoite then undergoes asexual multiplica-

tion, forming eight merozoites within that vacuole called type I meront. The merozoites released from type I meront invade the mucosal surface layer and undergo sexual multiplication with the formation of type II meront. The merozoites then differentiate into microgametocytes and macrogametocytes, fertilizing to form the zygote. Each zygote then forms four sporozoites within thick-walled or thin-walled cysts. Thick-walled cysts can infect a new individual when excreted in the stool [15]. They can withstand the harsh environment and survive in chlorinated water (swimming pools), public water supply, rivers, lakes, and fruits and vegetables. Thin-walled cysts get involved in autoinfection.

Pathogenesis

Cryptosporidium affects the small bowel mucosa, but distal jejunum and ileum are more severely affected. The sporozoites alter epithelial barrier function and increase intestinal permeability [16]. They cause diarrhea mainly by increasing the secretion of water and electrolytes through their enterotoxic effect. In the animal model, inhibition of glucose-stimulated sodium absorption from the enterocytes, lymphocytic infiltration in the lamina propria, crypt hyperplasia, and villous atrophy were observed [17].

Presentation

In immunocompetent individuals, cryptosporidiosis generally causes self-limiting acute diarrhea. However, in immunocompromised individuals (acquired immunodeficiency syndrome (AIDS), solid organ transplant, on chemotherapy), it may cause chronic protracted diarrhea, acalculous cholecystitis, sclerosing cholangitis, and acute pancreatitis [18]. Waterborne outbreaks are more common than foodborne outbreaks. More than 50% of waterborne diarrhea related to swimming in public swimming pools is caused by cryptosporidium [19].

Diagnosis

Cryptosporidiosis is confirmed by detecting cryptosporidium oocyst in the stool sample. It is recommended to collect a few stool samples over several days. Stool microscopy with acid-fast staining is done to visualize the oocysts, which appear pink. Other detection methods include direct fluorescent antibody testing, enzyme immunoassays, and polymerase chain reaction (PCR).

Treatment

Antibiotic treatment is unnecessary as the disease is self-limiting in immunocompetent individuals. Patients should take plenty of fluid to prevent dehydration. If diarrheal episodes do not improve, the antibiotic nitazoxanide 500 mg BID for 3 days can be given. The medication can eradicate cryptosporidium in 6-75% of cases but may take 5 days to cure diarrhea in about 80% of cases [20]. As the parasite is resistant to chlorinated water, CDC strongly recommends that all patients with active infection who have completed treatment not swim in the swimming pool for at least 2 weeks after the resolution of symptoms. Nitazoxanide may not be effective in immunocompromised individuals unless their immune status is improved. Patients with HIV/AIDS should receive highly active anti-retroviral therapy (HAART) for symptomatic improvement of cryptosporidiosis.

Blastocystosis

Blastocystosis is the infection caused by *Blastocystis* spp. (previously called *Blastocystis hominis*). Blastocystis is a strict anerobic enteric protozoan of unknown pathogenic potential. It is the most common protozoan in human fecal samples [21]. It is widely distributed throughout the world, but the prevalence is much higher in developing countries (about 50%) than in developed countries (about 20%) [22]. The protozoa can produce infective cysts (3 to 5 μm in diameter) that can develop into vegetative forms (5 to 40 μm). *Blastocystis* spp. is polymorphic, and the different morphological forms include vacuolar, granular, amoeboid, non-vacuolar, and multi-vacuolar forms [23, 24]. Fecal-oral route is the primary mode of transmission of *Blastocystis* spp. The risk of infection increases if someone ingests contaminated water or food, comes in contact with infected animals, or gets exposed to a daycare environment. The life cycle of *Blastocystis* spp. has yet to be fully understood. Thick-walled cysts, predominantly vacuolar forms, are excreted in the human stool. Humans get infected through the fecal-oral route. The cysts infect colonic epithelial cells and multiply asexually by binary fission. Vacuolar forms develop into multi-vacuolar and ameboid forms. By schizogony, the ameboid forms give rise to thick-walled cysts excreted in the stool.

Pathogenesis

Blastocystis spp. is found chiefly adhered to the colonic epithelium [25]. The protozoa produce cysteine proteases which break down the tight junction protein of epithelial cells, increasing intestinal permeability, degrading IgA, and inducing an inflammatory response in the colon [26]. *Blastocystis* spp. can also activate complements releasing anaphylatoxins which can activate mast cells and produce urticaria [27].

Presentation

The patient may remain asymptomatic or present with diarrhea, abdominal pain, gas, bloating, nausea, anal itching, palmoplantar pruritus, or urticaria.

Diagnosis

Blastocystis spp. can be detected by stool microscopy (direct

smear, trichrome-stained smear, iodine-stained smear), culture, and PCR testing. The vacuolar form is most commonly found in stool smears; the amoeboid form is only seen in culture [28]. PCR testing is considered the gold standard for detecting *Blastocystis* spp. [29].

Treatment

As the role of *Blastocystis* spp. in producing clinical symptoms is controversial, treatment is not warranted as long as the patient is asymptomatic with few cysts in the stool. Treatment with antimicrobial agents should be offered in symptomatic patients (gastrointestinal (GI) or dermatologic) with many cysts in the stool to eradicate the infection. Metronidazole is the drug of choice, given as 250 to 750 mg three times daily or 1,500 mg orally once daily for 10 days [30]. If there is a lack of response to metronidazole, the next antimicrobial to try is trimethoprim (TMP)/sulfamethoxazole (SMX). It has the advantage of using in pregnancy [31]. In case of metronidazole failure, nitazoxanide can also be used. Paromomycin helps treat *Blastocystis*-associated cutaneous lesions like palmoplantar pruritus or urticaria [32]. Other drugs used in case reports or small series to eradicate *Blastocystis* spp. include tinidazole, ketoconazole and iodoquinol.

Cyclosporiasis

Cyclosporiasis is a diarrheal illness caused by the protozoan *Cyclospora cayetanensis*. It is universally distributed but more common in the tropical and subtropical regions of the world, where the risk of infection is seasonal. People become infected after consuming food and water contaminated with feces containing sporulated oocysts. In developed countries, it is the second most common cause of IPI; infection outbreaks are associated with consuming contaminated fresh produce (raspberries, cilantro, mesclun lettuce, snow peas, basil) imported from endemic regions. The unsporulated oocysts (8 to 10 µm in diameter) are not infective when passed in the stool. They sporulate in the environment after 1 - 2 weeks at temperatures between 71.60 and 89.60 °F. Each infective sporulated oocyst has two sporocysts, each containing two sporozoites. After ingesting contaminated food and water by a host, the sporulated oocysts travel to the lumen of the small bowel, where excystation occurs with the release of sporozoites (4 per sporocyst). The sporozoites invade the duodenal and jejunal enterocytes. Inside the epithelial cells, the sporozoites multiply asexually to form schizonts which contain merozoites. The merozoites develop to form microgamonts and macrogamonts (sexual multiplication), fertilizing to form unsporulated oocysts in the enterocytes. They are subsequently excreted in the feces [33].

Pathogenesis

In the small intestine, Cyclospora can cause dilation of vessels, congestion of villous capillaries, reactive erythema, diffuse mucosal edema, mixed inflammatory cells infiltrate, and shortening and widening of intestinal villi [34].

Presentation

Patients generally present with voluminous watery diarrhea, abdominal discomfort, flatulence, nausea, fatigue, and weight loss. In immunocompetent individuals, symptoms may resolve in a few days. Nevertheless, in immunocompromised individuals, particularly those with AIDS, diarrhea can be prolonged, severe, and recurrent.

Diagnosis

Cyclospora cayetanensis can be detected by stool examination. As patients may not shed enough oocysts in their stool, stool samples should be taken at least three times on alternate days within 10 days to get > 95% detection rate [35]. Modified acid-fast staining, real-time PCR assays by BioFire GI panel, ultraviolet (UV) fluorescent microscopy and flow cytometry are the currently available methods to detect Cyclospora.

Treatment

The treatment of choice is trimethoprim/sulfamethoxazole (TMP 160 mg/SMX 800 mg) twice daily for 7 days in symptomatic patients. Ciprofloxacin can be an alternative treatment but is less effective than TMP/SMX [36]. Another alternative treatment is nitazoxanide which is effective (71-87% of cases) and well tolerated [37].

Cystoisosporiasis

Cystoisosporiasis is a small intestinal disease caused by the obligate intracellular protozoa *Cystoisospora belli* (previously called *Isospora belli*). Although it is primarily seen in tropical and subtropical regions (South and Central America, the Caribbean, Africa, India, and South East Asia), it is widely distributed worldwide. In developed countries, cystoisosporiasis is mainly seen in immunocompromised individuals with HIV infection and AIDS, people living in institutions or poor sanitary conditions, travelers coming back from the endemic regions, and recent immigrants [38]. The transmission mode is fecal-oral, i.e., through consuming food or water contaminated with human feces or oral-anal contact in homosexual men [39]. The life cycle of *Cystoisospora belli* starts when the non-infective immature oocysts containing one or rarely two sporoblasts are excreted in the human feces (diagnostic stage). The sporoblast then multiplies into two, so each oocyst now contains two sporoblasts. The sporoblasts then become sporocysts by secreting a cyst wall.

Further division of the sporocysts leads to the formation of four sporozoites in each mature oocyst (infective stage). Each fully mature oocyst containing two sporocysts and four

sporozoites is about 23 - 36 in length and 12 - 15 µm in width. These infective mature oocysts of cystoisospora can survive in the environment for months. Human infection occurs after the ingestion of mature oocysts. They travel to the small bowel where excystation occurs, releasing their sporozoites. The sporozoites enter into the small intestinal epithelial cells, where asexual multiplication occurs with the development of trophozoites, schizonts, and merozoites. The sexual stage starts after about a week with the formation of male and female gametocytes. They fertilize to form oocysts to be released into the environment through fecal excretion [40].

Pathogenesis

Cystoisospora can cause inflammatory infiltrates of neutrophils, lymphocytes, plasma cells, and numerous eosinophils in the lamina propria, villous atrophy, and crypt hyperplasia in the small intestine [41].

Presentation

Patients generally present with non-bloody, watery diarrhea, malaise, and abdominal cramps. The clinical course depends on the patient's immune status. In immunocompetent individuals, diarrhea is self-limiting, lasting 7 to 10 days [42]. But in immunocompromised individuals, particularly in AIDS patients, diarrhea can be chronic and severe leading to significant dehydration, electrolyte disturbance (hypokalemia, acidosis due to bicarbonate loss), and weight loss [43]. The patient may also present with steatorrhea due to intestinal villous atrophy and fat malabsorption. Acalculous cholecystitis and chronic cholecystitis due to cystoisospora have been reported in immunocompromised [44] and immunocompetent individuals [45]. Peripheral eosinophilia can occur in cystoisospora infection.

Diagnosis

Cystoisospora can be detected in stool samples. Stool samples should be collected a few times over a few days because of intermittent shedding. Stool samples for routine ova and parasites cannot detect cystoisospora. Thin-walled, ellipsoidal oocysts can be visible on a simple wet stool smear in heavy infection. Preferred detection methods include acid-fast staining, fluorescent microscopy, and PCR [46, 47]. Cystoisospora can also be detected in duodenal aspirate or duodenal biopsy.

Treatment

In immunocompetent individuals, rehydration is the main line of therapy. Nevertheless, TMP/SMX (160/800) for 7 to 10 days is the treatment of choice in immunocompromised patients. Alternative agents include pyrimethamine (50 - 75 mg once a day or in divided doses) + folinic acid or leucovorin (10 - 25 mg daily) for 14 days and ciprofloxacin (500 mg twice daily) for 1 week.

Amebiasis

Amebiasis or amebic dysentery is a colonic infection caused by *Entamoeba histolytica*. It is the second most common parasitic disease worldwide. A few non-pathogenic entamoeba species include *Entamoeba dispar, Entamoeba coli, E. hartmanni, E. polecki, Endolimax nana, Iodamoeba buetschlii* and *Entamoeba bangladeshi* [48]. Although amebiasis is widely distributed worldwide, it is more common in tropical and developing countries with poor sanitation and fecal contamination of water supplies. About 100 million people are affected by *E. histolytica* worldwide, with an annual mortality of more than 100,000 [49]. In developed countries, it occurs in individuals who have traveled back from endemic areas, in persons with oral-anal sex or man-to-man sex as a sexually transmitted disease, and in immunosuppressed and institutionalized persons [50]. The primary mode of transmission is fecal-oral, i.e., oral intake of contaminated food or water containing cysts of *Entamoeba histolytica*. The life cycle of *Entamoeba histolytica* starts with ingesting their mature cysts present in water, food, or hands contaminated with fecal matter. The cysts travel from the mouth to the small intestine, where excystation occurs, releasing trophozoites. Trophozoites migrate to the colon where they may 1) remain in the colonic lumen (non-invasive infection) and continue to form cysts that pass in the stool (asymptomatic carriers) or 2) invade the colonic mucosa (amoebic colitis) or 3) spread to the extra-intestinal sites (liver, lungs, brain) by vascular invasion (extra-intestinal disease) [51]. Each Entamoeba mature cyst is usually 12 to 15 µm in diameter, spherical in shape, quadrinucleated, and generally found in solid stool. The cysts are resistant to chlorine and can survive in the environment with their infectious potential for a few days to weeks because of their walls (category B biodefense organisms). Each Entamoeba trophozoite usually measures 15 to 20 µm, looks more elongated, is mononucleated with granular cytoplasm, and is in loose stool. The trophozoites die readily in the external environment, and even if they are ingested, they cannot survive in gastric juice.

Pathogenesis

The trophozoites of *E. histolytica* compete with colonic microbiota and adhere to the colonic mucus layer through their galactose/N-acetyl-D-galactosamine (Gal/GalNAc) lectin (adhesion protein complex), which binds to the abundant galactose and N-acetyl-D-galactosamine residues of colonic mucin [52]. Subsequently, they breakdown the protective mucus layer through their various glycosidases (sialidase, N-acetylgalactosaminidase, and N-acetylglucosaminidase), glycoside hydrolase β-amylase and cysteine proteinases (amebapores) [53]. The secreting proteinases allow the trophozoites to kill the host cells and engulf red blood cells. In response, colonic goblet cells produce and secrete plenty of MUC2 mucin. A lack of MUC2 mucin in the epithelial layer produces pro-inflammatory cytokines (interferon (IFN)-γ, tumor necrosis factor (TNF)-α, and interleukin (IL)-13), inflammation, epithelial cytolysis, and apoptosis [54]. The pathogenicity of *E. histolyti-*

ca depends on the pathogen-associated molecular pattern of *E. histolytica* as well as the host's innate immune response (secretory IgA, mucin) to recognize and eliminate *E. histolytica* [55]. Histologically, mucosal edema, thickening, discrete ulcers, and sometimes submucosal flask-shaped ulcers are seen. In some cases, the trophozoites of *E. histolytica* can breach the mucosal epithelial layer and travel through the portal venous system to the liver causing liver abscess, and subsequently through the systemic circulation to the lungs, pericardium, brain, and other sites causing metastatic amebic abscesses.

Presentation

Many patients (about 90%) can remain asymptomatic. Dysentery (diarrhea with mucus, blood, and hematophagous trophozoites in the stool) is the most common presenting symptom (in 40% of cases). Patients with amebic colitis may also present with grumpy abdominal pain and mild watery or non-bloody diarrhea [56]. Certain risk factors can increase the severity and mortality. These include alcoholism, corticosteroid use, immunosuppression due to HIV/AIDS, malignancy, malnutrition, young age, and pregnancy [57]. Another uncommon presentation is right lower quadrant pain and mass (ameboma) due to hyperplastic granulation tissue formation in the cecum or ascending colon. Ameboma generally occurs in partially treated or untreated cases of amebic colitis [58]. Other complications of amebic colitis include toxic megacolon, necrotizing colitis, and fistulizing perianal ulceration. The most common extra-intestinal manifestation is an amebic liver abscess in 4% of patients with amebic colitis [59]. It is mainly seen in the immigrant population and travelers from the endemic area. It is 7 to 12 times more common in adult males than in adult females, and peak incidence occurs in the third, fourth, or fifth decades of life. Alcoholic liver disease, immunosuppression, and consumption of indigenously brewed alcohol in the tropics are other risk factors for developing amebic liver abscess [60]. The classic presentation of an amebic liver abscess includes fever, epigastric or right upper quadrant abdominal pain, cough, and tender hepatomegaly. An amebic liver abscess can be complicated by rupture into the peritoneal, pleural, and pericardial cavity, inferior vena cava thrombosis, pulmonary embolism, and dissemination with the formation of brain abscess [61].

Diagnosis

The various diagnostic tests for amebic colitis include: 1) Microscopic examination of fresh stool sample or rectal swab with wet mount, iodine-stain, and trichrome-stain should be done three times because of intermittent excretion of trophozoites. The presence of hematophagous trophozoites suggests *E. histolytica*. In only 30% of cases, the organism can be demonstrated. Again, detecting trophozoites or cysts on microscopy cannot differentiate *E. histolytica* from other non-pathogenic Entameba because they can be morphologically indistinguishable. 2) Stool for *E. histolytica*-specific coproantigen by enzyme-linked immunosorbent assay (ELISA), immunofluorescence, or radioimmunoassay using anti-trophozoite antibodies or monoclonal antibody against a specific epitope on *E. histolytica* [62]. This allows early diagnosis of amebic colitis. 3) Stool for *E. histolytica*-specific nucleic acids by PCR is accurate and rapid with high sensitivity and specificity in diagnosing both colonic and extra-colonic amebiasis [63]. Loop-mediated isothermal amplification (LAMP) can be used to diagnose *E. histolytica* for epidemiological purposes as it is a rapid, accurate, and valuable diagnostic tool [64]. 4) Serology: *E. histolytica*-specific antibody can be detected in the serum by enzyme immunoassay (EIA), ELISA, or indirect hemagglutination test (IHA) and is positive in up to 90% of cases of amebic colitis [65]. However, in endemic areas, this antibody can be persistently positive from previous infections in 35% of residents. 5) Colonoscopy may show edematous mucosa with bloody exudates, erosions, and multiple discrete "flask-like" ulcers in the cecum, ascending colon, and rectum [66]. A biopsy may show mucosal ulcer, granulation tissue, necrosis, exudate, hemorrhage, and many trophozoites with phagocytosed erythrocytes [67].

Laboratory studies in amebic liver abscesses may show leucocytosis (in 75% of cases) and abnormal liver function tests with elevated transaminases and alkaline phosphatase. Imaging studies (ultrasonography - hypo-echoic mass, computed tomography (CT) - hypodense mass with peripheral rim enhancing, or magnetic resonance imaging (MRI) - (hypointensity on T1-weighted image and hyperintensity on T2-weighted image) typically show a solitary abscess in the right hepatic lobe near the liver capsule [68]. Serology for *E. histolytica*-specific antibody and *E. histolytica* galactose lectin antigen by EIA can be positive in 95% and 75% of cases of amebic hepatitis. Concomitant diarrhea may be present in 10-35% of cases. Aspiration of the liver abscess may show acellular proteinaceous debris surrounded by a few trophozoites [69]. The current diagnosis of amebic liver abscess is a combination of serology, imaging, and histology.

Treatment

Pharmacologic treatment is given for the cure and prevention of amebiasis. A 10-day course of luminal agents like paromomycin, diloxanide furoate, or diiodohydroxyquin treats non-invasive infections or cyst passers. Nitroimidazoles are the main line of amoebic colitis or extra-intestinal amebiasis treatment: metronidazole 500 to 750 mg three times daily for 5 to 10 days or tinidazole 2 g daily for 3 days. In a Cochrane database systemic review, tinidazole was found to be more effective in reducing clinical failure and associated with fewer side effects than metronidazole [70]. Amoebic liver abscess is treated by a course of nitroimidazole followed by a course of luminal amebicide - diloxanide furoate 500 mg three times daily for 10 days or paromomycin 500 mg orally three times daily for 5 to 10 days or diiodohydroxyquin 650 mg orally three times daily for 21 days [57]. Nevertheless, there are certain indications of percutaneous aspiration (ultrasound-guided needle aspiration or percutaneous catheter drainage) of amebic liver abscess. These include: 1) Failure of clinical response to antibiotics in 5 to 7 days; 2) Failure of resolution of liver ab-

scess by medical treatment (15% of cases); 3) Abscess with a high risk of rupture (location in the left lobe of the liver or cavitary diameter > 5 cm); and 4) Amebic liver abscess with bacterial co-infection [71].

Enterobiasis

Enterobiasis (oxyuriasis) is caused by *Enterobius vermicularis*, also known as human pinworm or seat worm. It is the most common worm/helminthic infection in the United States. About 40 million people in the USA are infected with *Enterobius vermicularis*. It is most commonly seen in children, institutionalized individuals, homosexual men, and household members of infected persons [72]. It is two times more common in males than in females. It is a tiny thread-like white roundworm; a fully mature adult male worm measures 2 to 5 mm, and a fully mature adult female worm is 8 to 13 mm with a characteristic pointed pin-like tail. The most common mode of transmission is fecal-oral. The other ways of transmission include: 1) direct contact with viable pinworm eggs that may be present in the environmental dust and on the contaminated bedclothes, linen, pajamas, carpets, curtains, cat and dog fur, furniture, and other environmental objects; 2) transfer of eggs from hands to mouth after scratching the anal canal and perianal area - self-inoculation/autoinfection; 3) hatching of eggs in the anal canal followed retrograde migration of larvae into the sigmoid colon and cecum - retro-infection; and 4) sexual contact, particularly during oro-anal sex [73]. The life cycle of *Enterobius vermicularis* starts after the ingestion of embryonated eggs. Larvae hatch in the duodenum, and in 1 - 2 months, they develop into adult worms. The adult worms reside mainly in the cecum, ascending colon, and appendix. The male and female adult worms copulate, but the male worms die soon after copulation. On the other hand, the female worm has a life span of about 100 days. When the host sleeps at night, the gravid female worms migrate to the anal canal, depositing thousands of eggs and causing itching.

Presentation

Patients may remain asymptomatic. The usual presentation is anal or perianal itching [74]. The examination may reveal perianal erythema due to dermatitis. Patients may also present with acute abdominal pain secondary to *Enterobius* appendicitis [75]. Unusual cases of urinary tract infection and female genital tract infection due to pinworm have been reported [76, 77].

Diagnosis

There are three ways of diagnosing pinworm infection. The classic Scotch tape test is the best. It involves collecting pinworm eggs from the perianal area by touching the perianal skin with transparent sticky tape and removing it immediately early in the morning before a bowel movement and washing. In the lab, the tape is examined under the microscope, placing the sticky side down to a suitable tape. The Scotch test should be done on three consecutive mornings. The second one is examining the perianal area to look for worms 2 - 3 h after going to sleep. The third one is the microscopic examination of the samples from under fingernails to look for pinworm eggs [78].

Treatment

Pyrantel pamoate (11 mg/kg, maximum 1 g/dose orally as a single dose) is most commonly used to treat pinworm infection in the United States. However, the pinworm is also susceptible to mebendazole (100 mg orally as a single dose) and albendazole (400 mg orally as a single dose in an empty stomach). The single-dose treatment should be repeated in 2 weeks. Empiric treatment can be offered in case of high clinical suspicion. Nevertheless, in case of a definitive diagnosis, the patient and his/her all household members, including sexual partners, should be simultaneously treated. Pyrantel pamoate is the preferred drug during pregnancy, as mebendazole and albendazole should be avoided during the first trimester. All the bedclothes should be laundered, and attention should be given to proper hygienic measures to prevent auto-infection and re-infection [79].

Ascariasis

Ascariasis is an intestinal roundworm infection caused by *Ascaris lumbricoides*. It is the largest roundworm that infects humans and is the most common helminthic infection worldwide. More than one billion people suffer from ascariasis, mainly in the tropical and subtropical regions of the world (SSA, East Asia, China, and Latin America) where there is poor sanitation and local soil is contaminated with human feces, but it is uncommon in the USA. The adult female worm is 20 to 35 cm long with a straight tail, the adult male worm is 15 to 30 cm long with a curved tail, and each of them has a diameter of 6 mm. The life cycle of *Ascaris lumbricoides* starts when thousands of eggs are excreted through human feces into the soil. Unfertilized eggs are not infective. The eggs need to be fertilized, and then they become embryonated and infective with the development of larvae inside the eggs after 2 - 4 weeks under optimal conditions like humid, shaded, warm, and moist soil. A human can accidentally ingest this infective egg-contaminated soil through uncooked vegetables and fruits or hand-to-mouth contact. In the small intestine, the larvae hatch from the eggs, invade the intestinal mucosa and migrate to the liver via the portal circulation and to the lungs via the systemic circulation within the first week. After further maturation in the lungs for 10 to 14 days, the larvae penetrate the alveolar walls, travel up the tracheobronchial tree into the throat, and then get swallowed back into the small intestine. Continued maturation of the larvae in the small intestine leads to the development of male and female worms. They copulate in the small intestine. The gravid female can lay about 200,000 eggs a day. The longevity of adult worms is about 1 - 2 years [80].

Presentation

Most of the patients with ascariasis are asymptomatic. Symptomatic patients generally present with abdominal pain, bloating, anorexia, nausea, vomiting, and occasional diarrhea. However, a heavy infestation can cause nutritional deficiency (and growth retardation in children), intestinal obstruction, intestinal perforation, appendicitis, volvulus, and intussusception. Adult worms can block the biliary tree or pancreatic duct, causing cholangitis, cholecystitis, and pancreatitis [81, 82]. The patient may also develop pneumonitis and eosinophilia (Loeffler syndrome) during the migration of larvae into the lungs and present with cough, wheezing, shortness of breath, fever, and hemoptysis [83].

Diagnosis

Stool microscopy to look at Ascaris eggs is the standard method of diagnosing ascariasis. Laboratory studies may show peripheral eosinophilia. In a plain abdomen X-ray, the adult worms can be visible as they contrast against bowel gas (whirlpool effect). Ultrasound, CT, MRI, and endoscopy may locate the adult worms in the bile duct or pancreatic duct.

Treatment

The medications of choice include albendazole (a single dose of 400 mg) or mebendazole (100 mg twice daily for 3 days or a single dose of 500 mg). As a single dose, ivermectin, 100 to 200 µm/kg, is moderately effective against *Ascaris lumbricoides* [84]. Pyrantel pamoate (11 mg/kg/day up to 1 g as a single dose) is the drug of choice during pregnancy. Another option is piperazine 75 mg/kg as a single dose or 50 mg/kg daily for 5 days. As these medications are adult worm killers, treatment should be repeated after 1 - 3 months to allow the larvae to be matured into adults. In case of partial small bowel obstruction, the patient should be kept nothing by mouth, a nasogastric tube should be placed, and an intravenous infusion of fluid and anthelmintic medication should be given. Surgical intervention should be done with laparotomy and enterotomy in case of total small bowel obstruction. Resection of small bowel with re-anastomosis may be needed in case of bowel wall necrosis. After surgery, the patient should be treated with anthelmintics.

Trichuriasis

Trichuriasis is the third most common soil-transmitted intestinal helminthic infection caused by the roundworm *Trichuris trichiura*, also known as human whipworm. It is so called because of its "whip-like" shape with a thin anterior esophagus and a thick posterior anal end. The thin anterior end becomes embedded in colonic crypts. The worms are 3 to 5 cm long, with females larger than males [85]. According to CDC, about one billion people are infected with whipworms. Trichuriasis occurs worldwide but is most common in moist, warm, tropical, and subtropical countries (Asia, Africa, and South America) where poor there is poor sanitation and soil is contaminated with human or animal feces. It is also found in the southeastern parts of the United States. Persons with trichuriasis are frequently coinfected with ascariasis because of similar environmental risk factors. The life cycle of *Trichuris trichiura* starts when unembryonated eggs are excreted through the feces into the soil. The eggs are barrel-shaped, measuring about 50 - 55 µm by 20 - 25 µm, and thick-shelled with a characteristic plug at each end [86]. In the soil, the eggs mature into a cleavage stage, then become embryonated (infective stage) in 2 to 4 weeks. Humans become infected after ingesting embryonated eggs through food and water contaminated with feces. Those eggs hatch in the small intestine releasing larvae. They mature into adult worms and travel to the cecum and ascending colon, establishing themselves by anchoring to the crypts. Adult female worms lay 3,000 to 20,000 eggs per day. The longevity of adult worms is about 1 year.

Presentation

The clinical manifestations depend on the worm's burden. Patients with light infection remain asymptomatic [87]. Heavy worm load may cause abdominal discomfort or pain, trichuris dysentery (mucoid diarrhea with rectal bleeding), and rectal prolapse [88]. Children may develop iron deficiency anemia, growth retardation, and impaired cognition [89].

Diagnosis

Stool microscopy can find the eggs of *Trichuris trichiura*. WHO recommends using two slides per sample and quantifying eggs per unit weight of stool using the Kato-Katz method [87, 90].

Stool examination may also show red and white blood cells, particularly eosinophils. A colonoscopy can be an excellent diagnostic tool to visualize the adult worms in the right colon if the worm load is mild with male worms without any egg in the stool [91]. A complete blood count may show anemia.

Treatment

Trichuriasis is usually treated with mebendazole 100 mg twice daily or albendazole 200 to 400 mg twice daily for 3 days. Mebendazole is considered the first-line treatment as it is more effective than albendazole. They work by inhibiting the tubulin polymerization of worms [92]. Ivermectin 200 µm/kg/day orally for 3 days has also found to be effective against trichuriasis.

Ancylostomiasis

Ancylostomiasis is a hookworm infection caused by *Ancylos-*

toma duodenale, Necator americanus, and *Ancylostoma ceylanicum.* It is common in developing countries with tropical and subtropical climates, particularly in sandy, moist soils and rural areas with poor sanitation. About 576 to 740 million people are infected by hookworms worldwide [93]. *Ancylostoma duodenale* and *Necator americanus* are the major hookworms, and humans are the primary host. *Ancylostoma ceylanicum* is an animal hookworm that can penetrate human skin, causing cutaneous larva migrans. Adult *Ancylostoma duodenale* males are 7 to 9 mm long, females are 9 to 11 mm long, and their width is 0.2 to 0.5 mm. Adult *Necator americanus* worms are slightly smaller than adult *Ancylostoma duodenale*. They are characterized by the presence of cutting plates or teeth that line their buccal capsules. They are called hookworms as their heads are sharply bent backward, giving the appearance of hooks. The life cycle of hookworms starts when thousands of eggs are excreted through human feces into the soil. Rhabditiform larvae are released from the eggs in 1 to 2 days in warm, moist, and shady soil. These larvae molt twice to become infective filariform larvae (third-stage larvae or L3) in 5 to 10 days. Humans become infected when L3 (600 µm in length) either penetrates through the skin of bare feet (both *Ancylostoma duodenale* and *Necator americanus*) or get ingested (*Ancylostoma duodenale*) [94]. The L3 travels from the skin to the heart and the lungs via the vascular system. During migration into the lungs, type I hypersensitivity reaction occurs within the alveoli (Loeffler syndrome). Then the L3 penetrates the alveolar walls, travels up the tracheobronchial tree to the pharynx, and is swallowed. They travel to the distal jejunum, where they mature into adult worms. The adult hookworms attach to the jejunal walls by their sharp and curved cutting plates and suck blood for nourishment leading to iron deficiency anemia [95]. Blood loss also occurs due to the oozing of blood at the site of attachment of the hookworms. *Necator americanus* causes less blood loss than *Ancylostoma duodenale*. The female worm lays up to 3,000 eggs per day. Eggs are colorless, thin-shelled, measuring 60 - 75 µm by 35 - 40 µm. The life span of adult hookworms is 1 to 2 years, but it can be several years.

Presentation

Patients may remain asymptomatic in light infection. However, in heavy infection, patients may be fatigued due to iron deficiency anemia, abdominal pain, distension, and diarrhea. Rarely, patients may complain of localized itching and skin rash at the filariform larvae penetration site, indicating the first symptoms and signs of infection. During pulmonary migration of larvae, patients may develop Loeffler syndrome - a triad of pulmonary symptoms (cough, wheezing, hemoptysis), migratory pulmonary eosinophilic infiltrates, and peripheral eosinophilia.

Diagnosis

Ancylostomiasis is generally diagnosed by stool microscopy to identify hookworm eggs. The Kato-Katz technique can quantify the eggs per unit weight of stool that can indirectly measure stool burden. A complete blood count may show peripheral eosinophilia [96]. Capsule endoscopy may also detect adult worms in the jejunum.

Treatment

Albendazole and mebendazole are the drugs of choice for treating ancylostomiasis. A single dose of albendazole 400 mg or mebendazole 100 mg twice daily for 3 days or pyrantel pamoate 11 mg/kg (up to 1 g) per day for 3 days are good options to eradicate ancylostomiasis [97]. Patients should be given iron supplementation if there is iron deficiency anemia.

The various treatment modalities of IPIs are summarized in Table 2.

Prevention of IPI

Improvement of personal hygiene, environmental sanitation, health education, and availability of potable water are essential measures for long-term control of IPI. Hand hygiene should be maintained as the fecal-oral route is the primary mode of transmission of intestinal protozoal infections and most of the geohelminths. Adults and children should wash their hands with soap and water before eating. Uncooked food, unwashed fruits, green vegetables, and salads should be avoided in endemic areas. Raw vegetables should be washed with clean water, peeled, and cooked before eating. Food handlers should be checked for IPI and educated about maintaining proper personal hygiene. Food should be properly cooked to the appropriate temperature as recommended. People should avoid drinking water from ponds, lakes, and streams. During traveling, people should drink bottled water or clean water. There should be proper disposal of human waste. People should avoid soil contaminated with human feces. In endemic areas, people should use footwear to avoid exposure to infective larvae, and there should be latrine facilities [94]. Mass treatment of the population in endemic regions with different anthelmintics has been associated with diminished efficacy, resistance, and recurrence [98-100]. One old study suggested that mass treatment with anthelmintics every 4 months, three times a year for 3 years, could be most effective in controlling intestinal worms [101].

Pathways to Investigate Patients in Whom IPI is Suspected

Stool test: Stool microscopy (wet mount preparation, trichrome stain, formalin-ethyl acetate concentrate, or rapid fecal concentration method/Feconomics) is the most common way of detecting IPIs. Stool should be collected before giving any antibiotics or anti-parasitic agents or doing any contrast-enhanced imaging. The sample should be collected three times over several days and refrigerated until delivered to the laboratory. Modified acid-fast should be done or requested if cryptosporidiosis, cyclosporiasis and cystoisosporiasis are sus-

Table 2. Treatment Modalities of IPIs

Intestinal parasites	Treatment
Giardiasis	Metronidazole orally 500 - 750 mg/day for 5 - 10 days, or tinidazole orally 1 - 2 g single dose.
Cryptosporidiosis	Nitazoxanide orally 500 mg twice daily for 3 days if no improvement of diarrhea.
Blastocystosis	Metronidazole orally 250 - 750 mg thrice daily or 1,500 mg once daily for 10 days, or TMP 160 mg/SMX 800 mg twice daily for 7 days or TMP 320 mg/SMX 1,600 mg once daily for 7 days.
Cyclosporiasis	TMP 160 mg/SMX 800 mg orally twice daily for 7 - 10 days.
Cystoisosporiasis	TMP 160 mg/SMX 800 mg orally twice daily for 7 - 10 days. TMP 160 mg/SMX 800 mg orally twice daily for 7 - 10 days.
Amebiasis	Amebic colitis or extra-intestinal amebiasis: metronidazole 500 - 750 mg thrice daily for 5 - 10 days or tinidazole 2 g daily for 3 days followed by a course of luminal amebicide - diloxanide furoate 500 mg thrice daily for 10 days or paromomycin 500 mg orally thrice daily for 5 - 10 days or diiodohydroxyquin 650 mg orally thrice daily for 21 days.
Enterobiasis	Albendazole 400 mg orally as a single dose; repeat in 2 weeks or mebendazole 100 mg orally as a single dose; repeat in 2 weeks, pyrantel pamoate 11 mg/kg of body weight, not to exceed 1 g, as a single dose; repeat in 2 weeks.
Ascariasis	Albendazole 400 mg orally as a single dose or mebendazole 100 mg orally twice a day for consecutive 3 days.
Trichuriasis	Mebendazole 100 mg orally twice a day for consecutive 3 days or albendazole 400 mg orally daily for consecutive 3 days or ivermectin 200 µg/kg/day orally for consecutive 3 days.
Ancylostomiasis	Albendazole 400 mg orally as a single dose or mebendazole 100 mg orally twice a day for consecutive 3 days or pyrantel pamoate 11 mg/kg (up to a maximum of 1 g) orally daily for consecutive 3 days.

IPIs: intestinal parasitic infections; SMX: sulfamethoxazole; TMP: trimethoprim.

pected. Stool for giardia antigen should be ordered in the initial workup. Stool for BioFire GI panel should also be considered if available as it uses PCR technology to diagnose 22 common GI pathogens. It has been shown to reduce patient and hospital cost in the investigation of infectious diarrhea.

Blood test: Complete blood count may show peripheral eosinophilia and anemia. Serology for *E. histolytica*-specific antibody can be considered in non-endemic areas if amebic colitis is suspected.

Scotch tape test, perianal examination and microscopic examination of the samples from under fingernails should be considered if enterobiasis is suspected.

Imaging studies: Plain X-ray abdomen, CT or MRI can be useful in detecting *Ascaris lumbricoides*.

Role of endoscopy: Upper endoscopy with duodenal biopsy is rarely done to diagnose giardiasis particularly in immunocompromised patients in case of unexplained diarrhea. Video capsule endoscopy can detect Ancylostoma in the small bowel. Colonoscopy can show "flask-shaped ulcers" in amebic colitis, and find *Ascaris lumbricoides, Trichuris trichiura* and *Enterobius vermicularis.*

Summary

Although IPI is mainly seen in developing countries with tropical and subtropical climates, it is virtually distributed worldwide and is increasingly observed in developed countries. In developed countries, intestinal protozoal infections are more common than helminthic infections. Giardiasis is the most common intestinal protozoal infection, and enterobiasis is the most common helminthic infection in developed countries. There are certain similarities in the life cycles of intestinal protozoal infections. The human being ingests cysts excreted in the stool. Excystation occurs in the small intestine releasing many trophozoites or sporozoites. Asexual multiplication followed by encystation occurs in the intestine with subsequent fecal excretion of cysts.

There is also a similarity in the life cycles of *Enterobius vermicularis* and *Trichuris trichiura*. Humans get infected after the ingestion of eggs through the fecal-oral route. Hatching of the eggs occurs in the small intestine with larvae release. They mature into adult worms which reside mainly in the cecum and ascending colon. The gravid females release eggs from there. There is an additional pulmonary stage in ascariasis and ancylostomiasis life cycles. In the case of ascariasis, infective eggs ingested by human beings hatch larvae in the small intestine. They penetrate the mucosal layer and, through the circulation, migrate to the lungs, where they mature, and then they ascend the tracheobronchial tree into the pharynx. They are then swallowed back into the small intestine, where they mature into adult forms. After copulation, the gravid females lay thousands of eggs. On the other hand, ancylostomiasis occurs when the non-infective larvae released from fecally excreted eggs mature in the soil to become infective larvae which penetrate human skin. They migrate to the lungs, travel up the tracheobronchial tree into the pharynx, and are finally swallowed back into the small intestine. They mature into adult worms, and the gravid female worms start laying eggs there. Intestinal protozoal infections generally cause diarrhea except for amebiasis, which usually presents with amebic dysentery. Intestinal helminthic infections have a variety of presentations like anal or perianal itching in case of enterobiasis; abdominal pain, nausea, vomiting, nutritional deficiency, and intestinal obstruction in case of ascariasis; dysentery and rectal prolapse in trichuriasis; iron deficiency anemia, localized itching, and skin rash in case of

ancylostomiasis. Loeffler syndrome is unique to ascariasis and ancylostomiasis.

Stool microscopy (wet mount preparation and trichrome stained smear) can detect protozoan trophozoites, cysts, oocysts, helminth eggs, and larvae, and is the primary way of diagnosing intestinal protozoal and helminthic infections, except cryptosporidiosis, cyclosporiasis and cystoisosporiasis, which are detected by modified acid-fast stain of stool; Cyclospora oocysts appear blue or green under fluorescent microscopy, and *Enterobius vermicularis* eggs are detected by Scotch tape test.

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Conflict of Interest

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Author Contributions

Monjur Ahmed solely contributed to the work.

Data Availability

The author declares that data supporting the findings of this study are available within the article.

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