3 The Role of Surgery in Treating Parasitic Diseases of the Gastrointestinal Tract from Protozoa

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Introduction

Protozoa (from the Greek words *protos* [meaning first] and *zoon* [meaning animal]) constitute common inhabitants of the human gastrointestinal tract [1]. The majority of protozoa can easily change from their active feeding form (trophozoite) to the inactive and resistant form (cyst), which is also responsible for the process of transmission (Fig. 3.1). The most common route of transmission is fecal-oral, mostly through the consumption of undercooked meat or contaminated water [2]. In comparison to the majority of helminths, parasitic protozoa have the innate capacity to replicate within the host's corpus, which does explain not only their survivability but also the burden of disease they can cause from a single exposure [1]. Lumen-dwelling protozoa are subdivided into the following phyla based on their motility abilities: (a) Mastigophora (flagellates), (b) Sarcodina (amebae), (c) Sporozoa, and (d) Ciliophora (ciliates) [3].

Even though they mostly represent non-pathogenic commensals or cause just mild disease, protozoa may cause significant morbidity and mortality in certain occasions. The low socioeconomic status of developing countries along with the suboptimal conditions of hygiene renders it easier for intestinal protozoa to flourish with a consistently high incidence [2]. On the other hand, they have occasionally been accused of causing diarrheal or other enfeebling diseases, especially in the immunocompromised as well as in developed countries [4–7]. The better sanitary conditions of these countries lead to an ignorance against the severity of disease that enteric protozoa can engender [8]. Consequently, they are sometimes omitted from

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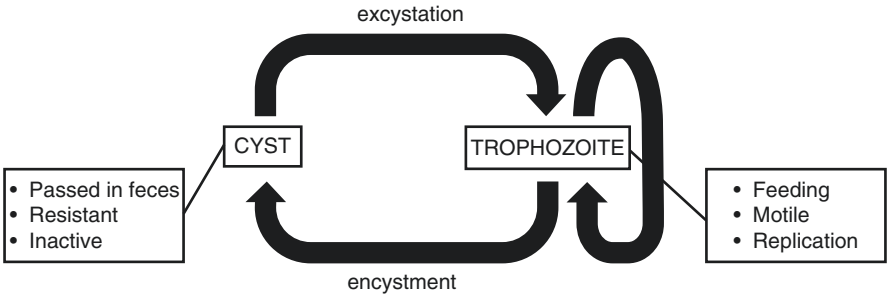

Fig. 3.1 Typical protozoal life cycle

Table 3.1 Common protozoan pathogens causing gastrointestinal infection that may require surgical intervention

1. Mastigophora (flagellates)
Giardia lamblia (or *G. duodenalis* or *G. intestinalis*)
Dientamoeba fragilis
Trypanosoma cruzi
2. Sarcodina (amebae)
Entamoeba histolytica
3. Sporozoa
Cryptosporidium parvum
Cyclospora cayetanensis
4. Ciliophora (ciliates)
Balantidium coli

the differential diagnosis, and thus severe complications may arise; under such circumstances, medical therapy is usually inadequate to eliminate the disease, and surgical intervention is inevitable.

This chapter aims to highlight the role of surgery against the protozoal disease of the gastrointestinal system through the discussion of the most common intestinal protozoa individually (Table 3.1).

Mastigophora (Flagellates)

Giardiasis

Giardia lamblia (also known as *G. duodenalis* or *G. intestinalis*) is a flagellate protozoon contributing to a significant number of epidemic or sporadic cases of diarrhea worldwide [9]. The first patient afflicted by giardiasis was described in 1681 by Van Leeuwenhoek [10], but the organism was rediscovered and named in 1859 by Lamb [11]. *G. lamblia* is subdivided into seven molecular types (A through G) with types A and B constituting the primary human pathogens [12]. Risk factors for giardiasis infection include poor hygiene conditions and lack of water treatment resources [9]; people are in particularly high risk during backpacking or recreational

water use activities or consuming water from surface wells [13]. Admittedly, giardiasis in one of the most common pathogens causing diarrheal disease in international travelers returning to the USA and Europe [14–16]. Although water-borne and food-borne are the main ways of transmission, little children attending day-care facilities are also at an increased risk (fecal-oral transmission), as well as men having sex with men (oral-anal contact) [13, 17]. Patients with cystic fibrosis, hypogammaglobulinemia, IgA deficiency, and decreased secretion of gastric acid constitute high-risk candidates for *G. lamblia* infection [13, 18, 19].

Giardiasis can be asymptomatic in 10–15% of the patients, but most of them typically present with acute giardiasis symptoms, such as diarrhea (95%), malaise (86%), foul-smelling fatty stools (75%), abdominal cramping (70%), nausea (70%), and bloating (50%) [13, 20]. The incubation period for diarrhea from *G. lamblia* is approximately 1–2 weeks, and the onset is indolent; disease duration lasts 2–4 weeks with treatment and 6 or more weeks without treatment, while giardiasis is generally considered self-limited. Chronic disease may either develop after acute symptoms when the disease does not resolve on its own or even without a previous acute illness and usually presents in one-third of the patients [21]. Symptoms that should raise concern for chronic disease include loose stools without diarrhea, steatorrhea, significant weight loss, malabsorption (hypoalbuminemia and vitamin deficiency), malaise, and depression. Differential diagnosis should include microbial diarrhea caused by *Salmonella* or *Campylobacter*, as well as celiac disease, tropical sprue, Whipple's disease, lactose intolerance, irritable bowel syndrome (IBS), and Crohn ileitis [13]. Definitive diagnosis is established via antigen detection immunoassays or nucleic acid amplification assays in stool samples and stool microscopy.

Antimicrobial agents and supportive care, i.e., fluid and electrolyte imbalance, are the mainstay of treatment for giardiasis. Treatment should be initiated as soon as the diagnosis is made, even in asymptomatic patients to preclude further transmission. Therapeutic agents commonly implemented are tinidazole and nitazoxanide, as well as metronidazole, albendazole or mebendazole, paromomycin, furazolidone, quinacrine, secnidazole, and ornidazole [13, 22, 23]. The only exception to prompt treatment includes pregnant and lactating women with mild symptoms that can retain their nutrition and hydration status; in these patients, treatment should be delayed at least until the second trimester in order to avoid any potential teratogenic effects of the drugs [24]. If the patient's condition necessitates treatment during the first trimester, paromomycin should be first-line, while during second and third trimester, multiple agents may be appropriate, such as paromomycin, tinidazole, metronidazole, or nitazoxanide [24]. In the case of resistance to treatment or relapse, medical therapy is still warranted [13, 25].

Surgical intervention may be required only under certain circumstances. Data suggest that *G. lamblia* may be the accused of causing cholecystitis [11], and thus, cholecystectomy should be performed. However, the diagnosis in these cases is mostly incidental during the histopathologic examination of the surgical specimen. *G. lamblia* is also one of the causes of nodular lymphoid hyperplasia of the gastrointestinal tract [26, 27]. Although treatment eradicates the symptoms caused by giardiasis in these cases [28], typically neither the number nor the size of the

nodules seems to regress [29], and due to the risk of malignant transformation, surgical resection may be the only therapeutic option [27, 30]. Even though infection from *G. lamblia* is managed medically in the vast majority of cases, the surgical community should be aware of this protozoal infection as surgical patients may also be part of the patient pool. Individual cases of giardiasis postoperatively after transplant surgery, Roux-en-Y gastric bypass, or other surgical operations involving manipulation of the gastrointestinal tract have been published in the literature to date [31, 32]. Notably, *G. lamblia* trophozoites have also been found in the fine-needle aspiration specimens of patients with pancreatic cancer, who apart from pancreatic resection may also require antimicrobial treatment [33, 34].

Dientamoeba fragilis

Dientamoeba fragilis is an ameboflagellate that causes infection of the gastrointestinal tract not via invasion, but rather via epithelial irritation [35]. Transmission occurs through the orofecal route, and *Dientamoeba* infections have higher prevalence in Australia [36], the USA [37], the Netherlands [38], and Oman [39]. Residing in rural areas and exposure to pets seem to be risk factors for *Dientamoeba* infections [40]. Notably, *Enterobius vermicularis* (the human pinworm) seems to assist *Dientamoeba* in terms of its transmission [41].

Although many infected patients remain asymptomatic, the most common manifestations are diarrhea, abdominal pain, anorexia, nausea, weight loss, and vomiting [42]. As *Dientamoeba* localizes in the colon, it can cause colitis; thus it should be included in the differential diagnosis of eosinophilic colitis [43], while the definitive diagnosis is made via stool microscopy or polymerase chain reaction (PCR) [44].

Asymptomatic individuals diagnosed with *Dientamoeba* in their stools do not require any form of treatment. However, patients with diarrhea or abdominal pain for more than 7 days diagnosed with *Dientamoeba* infection should be treated with either of the following agents: metronidazole, paromomycin, iodoquinol, doxycycline, or tetracycline [45–47]. All of them appear to be efficacious, while paromomycin has the shorter treatment course (7 days) and thus is suggested by some experts [35].

Data suggest that surgery may be required under particular circumstances in order to treat *Dientamoeba* infection or its complications. Indeed, multiple reports showed that *Dientamoeba* could lead to appendicitis, and hence, appendectomy is the mainstay of treatment on this occasion [48].

Trypanosoma cruzi

Trypanosoma cruzi is the cause of Chagas disease a zoonotic disease transmitted by hematophagous triatomine vectors (a type of reduviid bugs), particularly in North, Central, and South America; it usually manifests with cardiomyopathy and

gastrointestinal disease [49]. Other modes of transmission include blood transfusion, organ transplantation, and via contaminated water or food, while Chagas disease can also be transmitted congenitally [50].

T. cruzi infection can be distinguished in two phases, acute and chronic. Acute phase begins after 2 weeks of incubation and constitutes a 2- to 3-month period of nonspecific symptomatology, such as fever, lymphadenopathy, and hepatosplenomegaly [51]. Some patients develop chagoma (inflammation and swelling) at the site of inoculation, while inoculation through the conjunctiva manifests as the Romaña sign (unilateral swelling of both eyelids) [50]. Severe acute infection is seen in less than 1% of the patients, and it frequently manifests as pericardial effusion, acute myocarditis, or meningoencephalitis [52]. On the other hand, chronic disease develops over years or even decades and presents as Chagas cardiomyopathy, megaesophagus, esophageal carcinoma, or megacolon [52].

Anti-trypanosomal agents with proven efficacy include benznidazole and nifurtimox [49], but they are not adequate to prevent the progression of Chagas digestive disease [53, 54]. The goal in the management of megaesophagus is to ameliorate the resting pressure in the lower esophageal sphincter; hence stages I, II, and III are managed either with surgery (laparoscopic Heller's myotomy and fundoplication) or with pneumatic dilation (avoided in stage IV due to high risk of rupture). Stage IV disease may necessitate esophagectomy if laparoscopic Heller's myotomy is inadequate to obtain positive outcomes in terms of symptom improvement [55]. *T. cruzi* infection increases the risk of esophageal carcinoma, and if this devastating complication arises, esophagectomy may be required. Megacolon-induced constipation can initially be managed conservatively with high-fiber diet, laxatives, and fecal disimpactions. Indications for surgical intervention include severe constipation not amenable to conservative management or complications, such as sigmoid volvulus and stercoral ulcer; in such occasions, rectosigmoidectomy with retrocecal interpositioning or with end-to-side low colorectal anastomosis can be performed [56].

Sarcodina (Amebae)

Entamoeba histolytica (Amebiasis)

Entamoeba histolytica is the cause of intestinal or extraintestinal infection in around 50,000,000 patients per annum and the cause of death in approximately 100,000 people worldwide per year [57, 58]. Amebiasis was firstly described by Fedor Aleksandrovich Losch in 1875 [59]. Four *Entamoeba* species, namely, *E. histolytica*, *E. dispar*, *E. moshkovskii*, and *E. bangladeshi*, are responsible for intestinal amebiasis [60]. *E. dispar*, which is not pathogenic, is ten times more common than *E. histolytica*, which is pathogenic [57]. Although its occurrence has been described worldwide, developing countries exhibit higher prevalence rates due to poor socioeconomic conditions, and some of the areas with increased infection rates include, but are not limited to, India, Mexico, Africa, and Central and South America [61].

In developed countries, amebiasis is more commonly seen in immigrants, international travelers, and expatriates [57]; however, only 0.3% of the total number of international travelers with diarrheal disease are infected by *E. histolytica* [62]. Sexually active homosexuals and long-term institutionalized patients are also in particularly high risk of transmission [63], and the most common routes of transmission are orofecal and human-to-human transmission [57].

Most of the *Entamoeba* infections are asymptomatic, and *E. histolytica* is the most common pathogen (90%), as *E. dispar* and *E. moshkovskii* are usually nonpathogenic. The development of invasive disease is determined by the strain of *E. histolytica*, as well as by the age, immune condition, and genetic susceptibility of the patient [61]. Symptomatic intestinal amebiasis frequently develops over a period of 1–3 weeks with subacute onset of symptoms, which consist of mild diarrhea to life-threatening dysentery, abdominal pain, bloody diarrhea, or even the complications of amebiasis, such as amebic colitis, toxic megacolon (fulminant colitis), perforation of the gastrointestinal tract, intraabdominal abscess, amebic appendicitis, amebic granuloma, amebic stricture, and perianal amebiasis [57, 64]. In rare occasions, intestinal amebiasis can mimic inflammatory bowel disease (IBD) by causing a syndrome of chronic diarrheal disease, weight loss, and abdominal pain with no dysentery. Differential diagnosis should include bacteria diarrheal disease from *Escherichia coli*, *Shigella*, *Salmonella*, *Campylobacter*, *Clostridium difficile*, or *Vibrio* species and IBD or ischemic bowel disease. Diagnosis is made via stool microscopy, colonoscopy with histological examination of the specimen, antigen detection, serology, or molecular identification.

In terms of treatment, *E. histolytica* infections should always be treated, even in asymptomatic patients, while there is no need for treating *E. dispar* [61]. There is no unanimous recommendation for treating *E. moshkovskii*, but treating symptomatic patients may be sound. A 7- to 10-day metronidazole (or tinidazole or nitazoxanide) course is the mainstay of treatment for invasive colitis followed by a luminal agent (paromomycin) for the elimination of intraluminal cysts [65]. In the case of bacterial superinfection or even amebic colitis, broad-spectrum antibiotics should be administered [66]. Broad-spectrum antibiotic therapy should also be initiated in patients with known or suspected peritonitis, bowel perforation, or intraabdominal abscesses, while most patients require surgical intervention as soon as possible [67]. For localized disease, partial colectomy with colostomy is advised over primary anastomosis, while extensive disease usually requires total colectomy. Amebic appendicitis is a rare complication that requires prompt management and taking the patient to the operating room for an appendectomy.

Extraintestinal amebiasis entails amebic liver abscess, as well as the involvement of other organs such as the heart, lungs, and brain [68]. Amebic liver abscess is usually seen in adult males between 40 and 50 years old [69–71] and is attributed to the ascending flow of amebae through the portal venous system [72]. It may take between 8 and 20 weeks to become symptomatic, and the most common clinical manifestations include 1–2 weeks of right upper quadrant abdominal pain along with high fever, sweating, cough, weight loss, and anorexia, while ultrasonography,

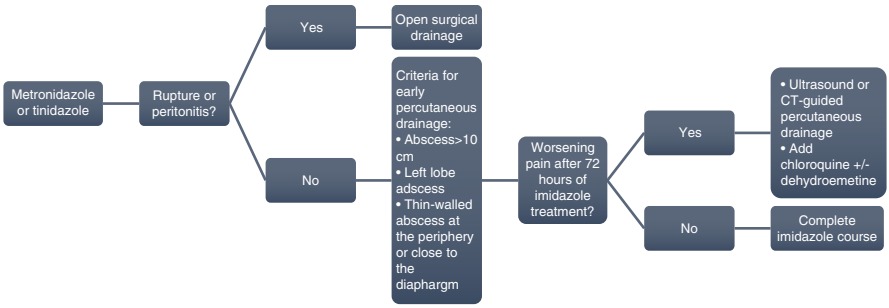

Fig. 3.2 Proposed algorithm on the management of amebic liver abscess

computed tomography scan, and magnetic resonance imaging are useful in guiding toward the diagnosis [57]. Most of these patients develop antibodies that can be detected via serologic testing, but the test may be negative in the first 7 days [73, 74]. Pyogenic liver abscess, echinococcal disease, and malignancy should be included in the differential diagnosis.

Treatment of amebic liver abscess consists similarly of a tissue agent (i.e., metronidazole, tinidazole) followed by a luminal agent, while the role of abscess drainage is when antibiotic therapy is inadequate [57]. Evidence suggests that there is no benefit with drainage following medical therapy in uncomplicated liver abscesses [75]. Clinicians should entertain the idea of abscess aspiration in the following occasions: size >10 cm in diameter, abscess in the left lobe (to prevent rupture into the pericardium), or abscess close to the serosal surface [57]. Another criterion that should be used for determining the appropriateness of drainage is if the patient is on medical therapy for 72 hours and, instead of improving, he or she is experiencing worsening pain [76]. Last but not least, there is no doubt that abscess rupture or peritonitis requires an immediate trip to the operating room. Figure 3.2 depicts a proposed algorithm regarding the management of amebic liver abscess [57].

Sporozoa

Cryptosporidium parvum (Cryptosporidiosis)

Cryptosporidium infection is linked to emerging diarrheal disease and biliary tract disease [77], while initial reports were published in 1975 [78]. *Cryptosporidium parvum* is the primary human pathogen and is separated into two distinct species, namely, *C. hominis* and *C. parvum* [79]. *C. hominis* is predominantly associated with infections in children attending day-care facilities and international travelers, while *C. parvum* infection arises more commonly in humans in close quarters with farm animals [80]. Transmission usually occurs through feces containing *Cryptosporidium* oocysts that have contaminated

drinking or swimming water, food, or residential surfaces, while human-to-human transmission is also possible [81, 82]. Its prevalence is higher in developing nations, but it poses a significant pathogen for both children and the elderly in developed countries [78].

Clinical manifestations depend on a great extent on the immunologic status of the patient. Indeed, immunocompromised individuals may suffer from a life-threatening disease course, while symptoms usually resolve within 7–14 days without treatment in immunocompetent patients [78]; however, asymptomatic patients may sometimes fall in either category [83, 84]. The most typical clinical presentation is secretory diarrhea after a 1-week incubation period accompanied by anorexia, abdominal pain, and fever. Significant volume depletion is associated with worse outcomes and increased mortality rates in the elderly [85]. Long-term effects of *C. parvum* infection have been studied even 1 year after the resolution of acute infection including diarrhea, abdominal, eye or joint pain, weight loss, and symptoms consistent with IBS [86]. Even though symptoms can help guide toward the diagnosis, it is usually established via stool microscopy (acid-fast staining), PCR, or enzyme immunoassays.

As cryptosporidiosis can lead to significant fluid loss, the most reasonable approach is to initiate treatment with an anti-diarrheal agent and in case of severe dehydration to start parenteral nutrition [87]. Aggressive nutritional support helps restore cellular immunity, while HIV/AIDS patients are benefited from early initiation of antiretroviral treatment [78]. Currently, nitazoxanide is the only Food and Drugs Administration approved therapy against cryptosporidiosis, and data from trials suggest that it can shorten disease duration and decrease parasite load [88–90]. If nitazoxanide is not well-tolerated or not available, paromomycin can be used as an alternative agent [91].

Under certain circumstances, surgery may be the next appropriate step in patients diagnosed with cryptosporidiosis. In particular, immunodeficient patients can present with biliary tract disease, such as acalculous cholecystitis, sclerosing cholangitis, and pancreatitis [92–94]. Patients with cryptosporidial acalculous cholecystitis will benefit from cholecystectomy, while endoscopic retrograde cholangiopancreatography (ERCP) with or without stent placement may be needed in case of sclerosing cholangitis. There is evidence suggesting that *Cryptosporidium* infection can mimic pancreatic cancer due to the invasion of the pancreatic ducts by the parasites, and according to a report, there has been a patient submitted to gastroduodenopancreatectomy for this reason [95]. Another report of a child treated at Memorial Sloan Kettering Cancer Center for acute myeloblastic leukemia and chronic functional constipation highlights the role of surgery in cryptosporidiosis [96]. This girl's condition was complicated by toxic megacolon and recurrent infection with *Cryptosporidium*, and thus the decision to proceed with a fully diverting, double-barreled ileostomy along with mucous fistula was inevitable. On the whole, the cryptosporidial infection can take place either in the gastrointestinal or in the pancreato-biliary tract; as a result, there is

great necessity to include it in the differential diagnosis of patients with diarrheal disease, to intervene promptly and take the patient to the operating room in case complications arise.

Cyclospora cayetanensis

Cyclospora cayetanensis is a coccidian food- and water-borne protozoon accused of causing diarrheal disease [97]. Its prevalence has been reported all over the world including Southeastern Asia, Central America, the USA, and Africa [98], while it is particularly prevalent among travelers and individuals diagnosed with HIV/AIDS [97, 99].

Many infected people do not exhibit any symptoms, while those who often do present with abdominal pain, watery diarrhea, anorexia, flatulence, fever, anorexia, nausea, and weight loss after a 1-week incubation period [97, 100–102]. Acalculous cholecystitis is another clinical manifestation attributed to *Cyclospora* infection [103]. Diagnosis is made via stool microscopy or PCR, while there no serologic test available to date [104].

A 7- to 10-day course of trimethoprim-sulfamethoxazole (TMP-SMX) is the gold standard of treatment for cyclosporiasis [105, 106]. Nitazoxanide is a decent alternative for patients with sulfa allergy [107], while ciprofloxacin can be used if TMP-SMX is not well-tolerated [108]. However, in the case of acalculous cholecystitis, surgeons need to act in a timely fashion and perform cholecystectomy [100].

Ciliophora (Ciliates)

Balantidium coli

Balantidiasis is caused by *Balantidium coli*, which is the largest protozoon and the sole ciliate afflicting humans [109, 110]. Transmission happens through the orofecal route, while balantidiasis is prevalent among countries in Southeast Asia, South America, and Western Pacific islands [35].

The three types of disease consist of asymptomatic excretion of cysts, acute colitis, and chronic balantidiasis [111, 112]. The spectrum of acute symptomatology includes watery or dysenteric diarrheal disease, nausea, anorexia, weight loss, vomiting, and abdominal pain [112]. Extraintestinal disease with involvement of the liver, lung, or appendix can also take place [35, 113]. Stool microscopy or histopathologic examination of endoscopic biopsy specimens can lead to the diagnosis [114].

Therapeutic agents include tetracycline, doxycycline, metronidazole, or iodoquinol [35]. However, surgical intervention may be required in case of appendiceal involvement (appendectomy) or fulminant dysentery complicated by bowel perforation and peritonitis.

Conclusion

Gastrointestinal infections constitute a significant health issue worldwide not only in developing but also in developed countries, and protozoa pose a significant human pathogen responsible for the enormous burden of disease. Despite the increased susceptibility of immunocompromised individuals, immunocompetent people can also be afflicted by pathogenic intestinal protozoa. In the vast majority of cases, patients present with diarrheal disease along with other symptoms of the gastrointestinal tract that can be managed with medical therapy. Sometimes disease progression may lead to devastating complications that can only be alleviated via surgical intervention. Consequently, both physicians and surgeons should be aware of the broad spectrum of symptomatology that protozoa can lead to in order to intervene promptly and obtain optimal outcomes with minimal morbidity for the patient. Undoubtedly, future research should focus on ways to belittle the burden of disease via prevention of disease transmission, improvement in the sanitary conditions, and development of more efficient and specific antiprotozoal agents.

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