APPENDIX B
Characteristics of Known Enteric Pathogens and Diseases

Oh my aching gut: IBS, Blastocystis, and asymptomatic infection
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This collection of characteristics of established enteric pathogens may be of value in understanding what behavior would be expected from new enteric pathogens.

Prevalence of enteric pathogens in asymptomatic individuals
1. In Egypt, 21% of asymptomatic individuals have been found to carry Entamoeba histolytica, while 24% carry Entamoeba dispar [1].
2. In Greece, among asymptomatic individuals, less than 1% were found to carry E. histolytica while 8% carried E. dispar [1].
3. In a study of a slum in Brazil, 11% carried E. histolytica, and 9% carried E. dispar [1].
4. Immunocompetent individuals infected with the identical genotype of E. histolytica can exhibit very different clinical presentations [1].

Host genotype and expression of symptoms in enteric infections
1. Researchers have suggested that symptoms seen in disease result from the combination of infection with host genetic factors.
2. Infection with Helicobacter pylori is asymptomatic in many individuals, but polymorphisms that influence production of the cytokine IL-1 can predispose infected individuals toward the development of gastric cancer [2].
3. Asymptomatic carriers of Vibrio cholerae exist. The same polymorphisms which confer immunity to symptoms in Vibrio cholerae infection have been found to be responsible for the development of cystic fibrosis [3].
4. Certain blood types may be correlated with symptomatic and asymptomatic gastrointestinal infection [4].
5. Additional polymorphisms may be responsible for producing the wide range of symptoms seen in infection with E. histolytica [1].
6. The genetic polymorphisms that confer susceptibility to disease in items 2-5 above are common and carried by healthy individuals.
7. In fact, in Zulu, the word for the disease caused by amoebic liver abscess is isigwebedhla, which means a disease of strong young men [1].
8. Mice are generally immune to E. histolytica, but that immunity is lost in IL-10 knockout mice [5]. IL-10 is a cytokine with immunosuppressive (anti-inflammatory) activity.
9. Some studies have suggested that HIV status is not a significant factor in expression of symptoms with E. histolytica [6, 7].
10. A study of *E. histolytica* infection found that certain individuals who were likely to be exposed never developed symptoms and also never developed a serological response. The phenomenon was correlated with family lineage, suggesting a genetic link [8, 9].

11. Variation can exist between ethnic groups in the prevalence of polymorphisms [10]. Some Mexican populations carry a gene which increases the risk of the development of amoebic liver abscess [1].

**TNF-Alpha in *Entamoeba histolytica* infection**

1. TNF-α is an important component of the immune system, and provides protection against bacterial infection and some types of cancer. The use of anti-inflammatory medications that inhibit production of TNF-α can reactivate viral and bacterial infections in patients [11].

2. But the use of a TNF-α inhibitor reduces the severity of infection with *E. histolytica* in mice [12].

3. TNF-α is a chemo-attractant for *E. histolytica* [13].

**Serotonin in enteric infections**

1. Researchers have suggested serotonin may play a role in host immune response in enteric infections [14].

2. *E. histolytica* has been found to induce serotonin secretion in enteric epithelial cells [15].

3. Serotonin has been found to increase the activity of *E. histolytica* infection *in vitro* [16] and the severity of infection *in vivo* [17].

4. Patients with symptomatic infection with *E. histolytica* can show elevated serum levels of serotonin [18].

**Irritable bowel syndrome**

1. IBS patients exhibit polymorphisms that cause high TNF-α production, slow serotonin uptake, and low IL-10 production [19, 20].

2. The prevalence of IBS in Mexico City is 35% [21].

3. US citizens returning from international travel exhibit a rate of new-onset persistent gastrointestinal illness or IBS of more than 39% (27/68) [22].

4. Selective serotonin re-uptake inhibitors, which are sometimes used in the treatment of IBS, inhibit production of TNF-α and increase production of IL-10 [23, 24].

**Age in expression of symptoms in enteric protozoal infections**

1. Symptomatic infection with *E. histolytica* is more common in adults than children [25, 26].

2. *Giardia lamblia* assemblage B has been found to be correlated with asymptomatic infection in children, but not adults [27].
3. IBS and blastocystosis are more common in adults, especially those aged 30-50 years [28-31].

4. Children produce lower levels of inflammatory cytokines [32]. These cytokines stimulate production of TNF-α.

Counter-intuitive findings in epidemiological studies
1. In a study of a slum in Brazil, the pathogenic *E. histolytica* was actually found more frequently than the non-pathogenic *E. dispar* in asymptomatic individuals [1].

2. Physicians have reported the appearance of groups of individuals in whom infection with *Giardia* and *E. histolytica* is not correlated with symptoms [33, 34].

3. A study of homosexuals in San Francisco found infection with *Giardia* and *E. histolytica* was uncorrelated with symptoms [35].

4. Studies by the same researcher found that *Blastocystis* infection was uncorrelated with symptoms [36-38].

5. In general, there is a poor correlation between the ability to detect protozoal infections and the patient’s symptomatic status. This is true in *Giardia lamblia* infection [39], *E. histolytica* infection, and *Cryptosporidium* infection [40].

Treatment of enteric pathogens
1. The ability of organisms to develop metronidazole resistance varies substantially between different species [41].

2. Some enteric protozoal infections have few treatment options – *Cyclospora* and *Cryptosporidium* do not respond to many antiprotozoal drugs that are used successfully in the treatment of other protozoal infections [42].

3. *In vitro* study has found iodoquinol to be one of the least effective drugs against *Blastocystis* infection [29].

4. In enteric infections, treatment with an anti-infective can improve symptoms without eradicating the pathogen responsible for the symptoms [43].

Symptoms of infection with enteric pathogens
1. *E. histolytica* can present with abdominal pain and constipation, rather than diarrhea [26].

2. Abdominal pain and constipation are the most common symptoms of blastocystosis, not diarrhea or fever [44].

3. Prior study has concluded that *Blastocystis* is non-pathogenic because infection is not associated with visible damage in endoscopy [45].

4. Additionally, IBS is considered a functional disorder because of lack of findings in endoscopy, X-rays and blood tests [46].

5. Colonic tissue samples from IBS patients have been found to produce a high level of a serine protease which produces symptoms associated with IBS when introduced into mice [47]. The study was unable to identify the source of the protease.
6. Proteases may influence gastrointestinal motility through protease-activated receptor-2 activation [48].

Enteric disease and psychiatric symptoms
1. Infection with *E. histolytica* has been associated with a psychiatric condition called "amoebic neurosis" [49].
2. Soldiers returning from World War II exhibited psychiatric symptoms and "debility" which was associated with long-term *E. histolytica* infection [50]. Symptoms subsided following antiprotozoal treatment. The disease was most prevalent in army units deployed in the Middle East.
3. The symptoms of widespread pain, diarrhea and weight loss in IBS have been presumed to be an expression of somatic illness. Psychiatrists have suggested the symptoms are related to sexual abuse [51] or the accumulation of life’s stresses [52].
4. Subsequent research has found that the colonic tissue in IBS patients produces high levels of a serine protease which activates nerve cells directly through the protease-activated receptor-2 (PAR2) pathway [47].
5. The proteases were produced by biopsies from patients with constipation-predominant IBS, diarrhea-predominant IBS, and inflammatory bowel disease (IBD).
6. PAR2 was the second member of a series of PARs which was discovered in 1994 through analysis of the human genomic library [53].
7. PAR2 receptors are present on a variety of cells in the human body, including cells in the gastrointestinal tract, pancreas, kidney, liver, airway, prostate, ovary, and eye, smooth muscle, T cell lines, neutrophils, and certain tumor cell lines [53].
8. Elevated serine protease levels are found in patients with diarrhea predominant IBS, but not patients with infectious viral or bacterial diarrhea [54].
9. PAR2 activation has been implicated in the pathogenesis of *Helicobacter pylori* infection [55] and PAR2 gene expression is enhanced in infection with *E. histolytica* [56].
References:


