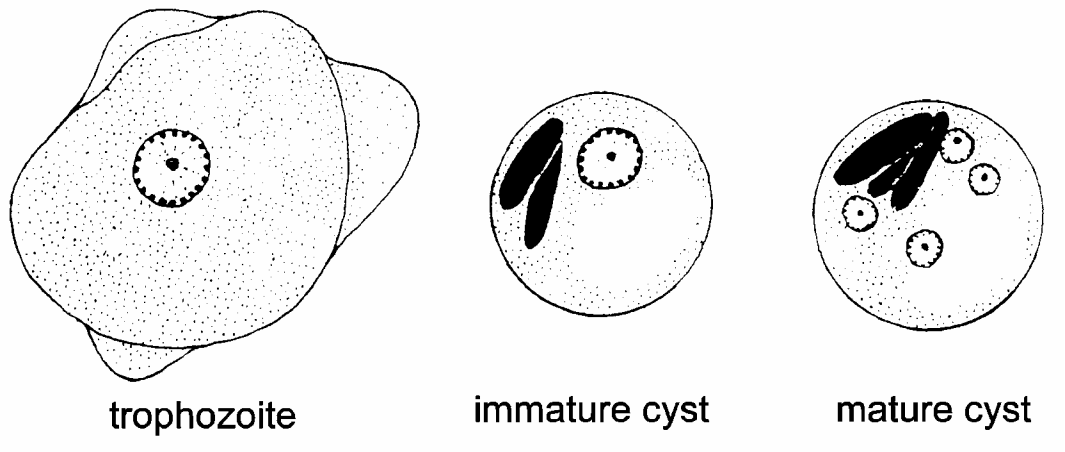
Amebiasis Handout

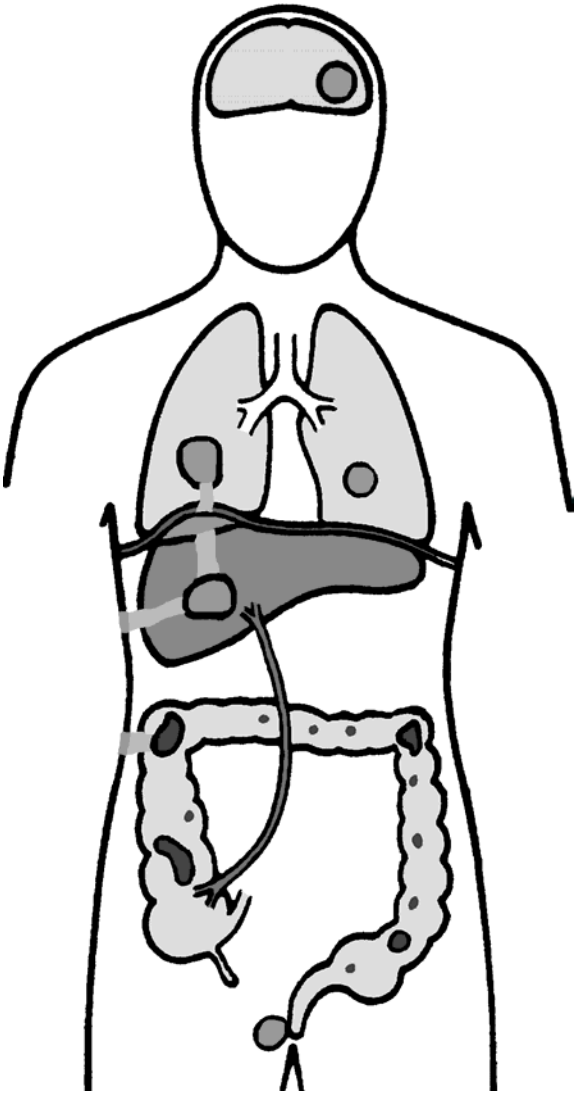
Entamoeba histolytica

- cosmopolitan distribution
- worldwide incidence: 0.2-50%
- no animal reservoirs
- typical fecal-oral life cycle
- facultative pathogen

E. histolytica vs. *E. dispar*

- 1875 Lösch correlated dysentery with amebic trophozites
- 1925 Brumpt proposed two species: *E. dysenteriae, E. dispar*
- 1973 Martinez-Palomo demonstrate differences in agglutination between pathogenic and non-pathogenic strains
- 1978 Sargeaunt and Williams demonstrate zymodeme differences
- 1988-1993 Several investigators demonstrated antigenic and DNA differences.
  - 2.2% rRNA difference
- 1993 Diamond and Clark propose *E. dispar* to describe non-pathogenic species
- 1997 WHO accepts two species





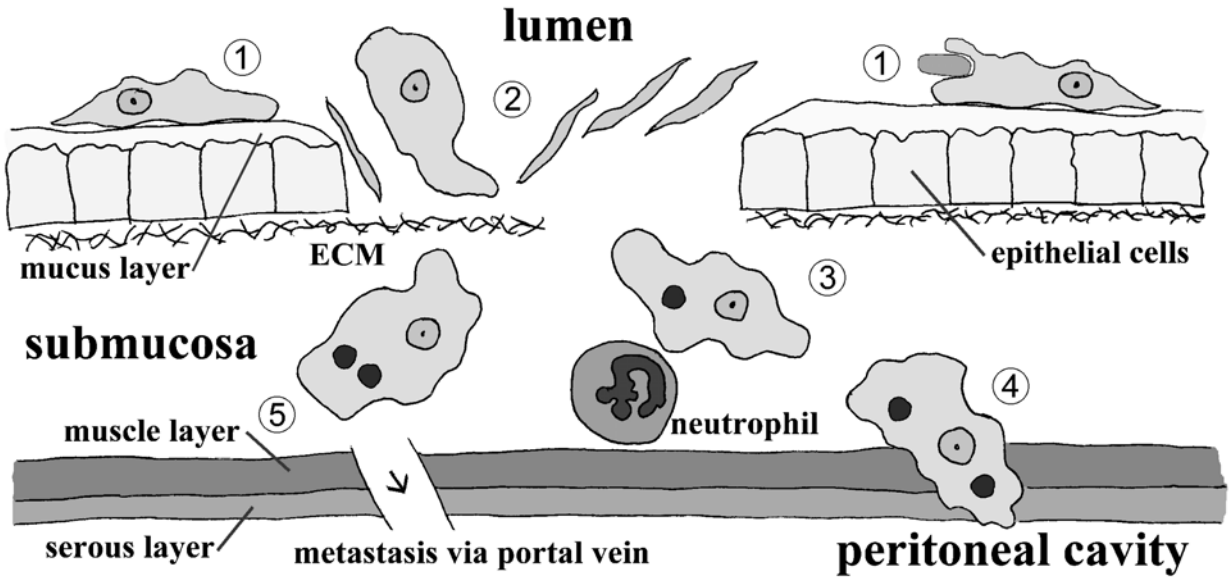
PATHOGENESIS OF AMEBIASIS

non-invasive

- ameba colony on mucosa surface
  - asymptomatic cyst passer
  - non-dysenteric diarrhea, cramps, abdominal discomfort

invasive

- necrosis of mucosa → ulcer
  - dysentery
  - hematophagous trophozoites
- ulcer enlargement → severe dysentery, colitis, peritonitis, occasional ameboma
- metastasis → extraintestinal amebiasis
  - dissemination primarily via blood-stream (eg., portal vein)
  - predominantly liver → amebic abscess
  - other sites infrequent (cutaneous, pulmonary)
  - ameba-free stools common

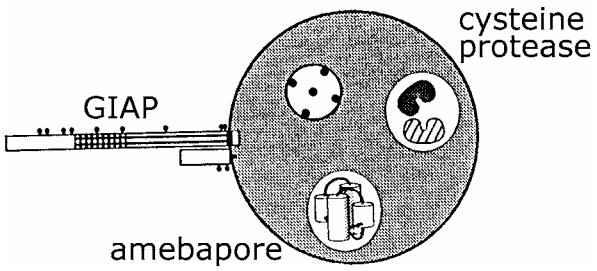


1. *E. histolytica* trophozoites colonize the mucosal surface of the large intestine. The trophozoites adhere to the mucus layer and ingest bacteria and cellular debris from the lumen. Adherence is mediated by a protein called the eh-lectin, or GIAP, which is expressed on the surface of trophozoites. This non-invasive infection is usually asymptomatic, or exhibits symptoms ranging from mild abdominal discomfort to diarrhea and cramps.
2. A breakdown in the mucus barrier can lead to a contact-dependent killing of the epithelial cells. The Eh-lectin also plays a role in this cytolytic activity. In addition, the breakdown of the tissue and extracellular matrix (ECM) implies that proteases are also involved in the pathogenesis. This necrosis of the mucosa will lead to an invasive disease characterized by dysentery (ie, blood and mucus in the feces).
3. The trophozoites will continue to advance laterally and downward into the submucosa producing a 'flask-shaped' ulcer. Necrotic material is found in the center of the ulcer and most of the ameba are at the border between the healthy and damaged tissue. Neutrophils and other immune effector cells are also killed. The ameba are now ingesting host cells instead of bacteria and hematophogous trophozoties can be observed. Ulcers can coalesce and lead to the shedding of patches of mucosa. The severity of the dysentery increases in terms of the number of stools and the amount of mucus and blood.
4. The trophozoites can also penetrate the muscle and serous layers leading to intestinal perforations. Perforation of the intestinal wall is a dramatic event that can lead to peritonitis or leakage into the abdominal cavity. Erosion of blood vessels can lead to massive hemorrhage. An inflammatory thickening of the intestinal wall, called an ameboma, or amebic granuloma, can also be formed in response to the ameba. The ameboma presents as a painful palpable mass that can be mistaken for a tumor.
5. Trophozoites can also gain access to the circulatory system and be disseminated. The liver is the primary site of extraintestinal amebiasis and hematogenous spread to other organs is rare. Metastasis to the liver involves the portal vein which carries blood from the colon directly to the liver. Dissemination to other tissues most often entails the direct extension of hepatic or colonic lesions. Extraintestinal amebiasis is often characterized by ameba free stools.

Non-Invasive and Invasive Isolates of *Entamoeba histolytica*

CRITERIA	NON-INVASIVE	INVASIVE
In Vitro Culture	xenic	axenic
ConA Agglutination	-	+
Complement Resistance	-	+
Zymodemes (isoenzymes)	I & III	II
Numerous Antigenic Differences (eg., GIAP Epitopes)	1-2	1-6
Numerous DNA Sequence Differences (eg., rRNA)	2.2% sequence diversity	
RFLP/DNA Probes	B133 cEH-NP1	P145 cEH-P1

Pathogenic and non-pathogenic isolates of *Entamoeba histolytica* exhibit many phenotypic differences. Some of the first noted differences were the in vitro growth characteristics, agglutination with concanavalin A, and resistance to complement. Pathogenic strains have the ability to grow in axenic cultures (without bacteria) whereas the non-pathogenic strains required bacteria for in vitro growth. The ConA agglutination and complement resistance imply that the outer surfaces of the pathogenic and non-pathogenic strains are different. Isoenzyme analysis revealed different zymodemes for the pathogenic and non-pathogenic strains. Similarly, numerous antigenic differences were noted between pathogenic and non-pathogenic isolates. A well-characterized epitope difference is in a surface protein referred to as galactose-inhibitable adherence protein (GIAP). GIAP (also called eh-lectin) is also implicated to be involved in the ConA agglutination and the resistance to complement. Analysis of DNA and sequencing of genes revealed genotypic differences between the pathogenic and non-pathogenic isolates. A striking variation is the 2.2% difference between the ribosomal RNA gene sequences of pathogenic and non-pathogenic isolates. Unlike some of the other differences, the rRNA cannot contribute to the pathogenesis. Furthermore, rRNA sequences of humans and mice differ by less than 2.2% indicating that the pathogenic and non-pathogenic strains are quite diverged. These differences led to the formation of a new species call *E. dispar*.



POSSIBLE INVASION FACTORS

- host factors (eg, immune response)?
- parasite factors?
  - resistance to host response (eg, complement resistance)
  - adherence properties (eg, GIAP)
  - cytolytic properties (adherence + 'amoebapore')
  - ability to breakdown tissues (eg, secreted proteases)

Epidemiologic Risk Factors

Prevalence	Severity

• lower socioeconomic status
  • crowding
  • lack of indoor plumbing
• endemic area
• institutionalization
• communal living
• promiscuity among male homosexuals
	• children, esp. neonates
	• pregnancy and postpartum states
	• corticosteroid use
	• malignancy
	• malnutrition

Modified from Ravdin (1995) Clin. Inf. Dis. 20:1453

Clinical Syndromes Associated with Amebiasis

Intestinal Disease

- asymptomatic cyst passer
- symptomatic nondysenteric infection
- amebic dysentery (acute)
- fulminant colitis
  - + perforation (peritonitis)
- ameboma (amebic granuloma)
- perianal ulceration

Extraintestinal Disease

- liver abscess
- pleuropulmonary amebiasis
- brain and other organs
- cutaneous and genital diseases

Intestinal Symptoms

- range
  - mild to intense
  - transient to long lasting
- nondysenteric
  - diarrhea
  - cramps
  - flatulence
  - nausea
- dysenteric
  - blood/mucus in stools
  - cramps/pain
  - tenesmus
- ameboma
  - palpable mass
  - obstruction

Diagnosis

Intestinal

- stool examination
  - cysts and/or trophozoites
- sigmoidoscopy
  - lesions, aspirate, biopsy
- antigen detection
  - histolytica/dispar

Extraintestinal (hepatic)

- serology
  - only *E. histolytica*
  - current or past?
- imaging
  - CT, MRI, ultrasound
- abscess aspiration
  - only select cases
  - reddish brown liquid
  - trophozoites at abscess wall

Amebiasis Treatment

Disease	Drug
Asymptomatic	Iodoquinol, Paromomycin, or Diloxanide furoate
Nondysenteric, Dysenteric, or Extraintestinal	Metronidazole or Tinidazole + lumenal agent