# DIARRHEA AND MALABSORPTION

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**Table 17-7** Defects in Malabsorptive and Diarrheal Disease

| Disease | Intraluminal Digestion | Terminal Digestion | Transepithelial Transport | Lymphatic Transport |
|---|---|---|---|---|
| Celiac disease | | + | + | |
| Environmental enteropathy | | + | + | |
| Chronic pancreatitis | + | | | |
| Cystic fibrosis | + | | | |
| Primary bile acid malabsorption | + | | + | |
| Carcinoid syndrome | | | + | |
| Autoimmune enteropathy | | + | + | |
| Disaccharidase deficiency | | + | | |
| Whipple disease | | | | + |
| Abetalipoproteinemia | | | + | |
| Viral gastroenteritis | | + | + | |
| Bacterial gastroenteritis | | + | + | |
| Parasitic gastroenteritis | | + | + | |
| Inflammatory bowel disease | + | + | + | |

+ indicates that the process is abnormal in the disease indicated. Other processes are not affected.

# Malabsorption

- Diarrhea is often the principal presenting complaint. However, it may be mild.
- Abdominal pain is unusual except in cases of chronic pancreatitis, Crohn's disease, or pseudo-obstruction (eg, scleroderma).
- Flatus and weight loss
- Steatorrhea is the characteristic finding.
- Bulky, frothy, greasy, yellow or clay-colored stools

# Malabsorption

- Symptoms are caused by the effects of osmotically active substances in the GI tract or by nutritional deficiencies that develop
- Defective absorption of fats, fat- and water-soluble vitamins, proteins, carbohydrates, electrolytes and minerals, and water.

# Other associated diseases

- Cystic fibrosis
- CFTR gene abnormality interferes with bicarbonate, sodium, water secretion
- Chloride levels elevated in sweat
- Addison's disease
- Plasma cortisol levels low
- Zollinger-Ellison
- Elevated gastrin levels

# Other associated diseases

- Abetalipoproteinemia
- Retinitis pigmentosa
- Neuropathy
- Procoagulant deficiency
- Hepatic steatosis
- Anemia with acanthocytes (Burr cells)
- Autosomal recessive (MTTP gene)
- Enterocytes unable to absorb or transport lipoproteins
- Triglycerides accumulate (Oil Red O stain positive)
- Diagnose with lipoprotein electrophoresis

# Signs of malabsorption

- Weight loss, glossitis, carpopedal spasms, absent tendon reflexes, cutaneous bruising, flatulence, and abdominal distention, bloating, or discomfort resulting from increased intestinal bulk and gas production.
- Steatorrhea is prominent.
- The malnutrition screening tool (Have you lost weight without trying? How much? Decreased appetite?) detects those at risk for nutritional disturbances with a positive likelihood ratio (LR+) of 13; LR-, 0.3.

# Steatorrhea

- Steatorrhea may occur with even relatively normal appearing stools.
- Usually they are pale, soft, bulky, malodorous stools that stick to the side of the toilet bowl or float and are difficult to flush away.
- Steatorrhea is most likely to occur in celiac disease or tropical sprue.

# Secondary nutritional deficiencies

- Iron deficiency occurs in celiac disease and after gastrectomy.
- Folate deficiency occurs in celiac disease and in sprue.
- Vitamin $B_{12}$ deficiency occurs in blind loop syndrome and after resection of the distal ileum and stomach.
- Thiamine (vitamin $B_1$) deficiency as well as vitamin $B_{12}$ deficiency may cause paresthesia.
- Severe riboflavin **(**vitamin $B_2$) deficiency may cause a sore tongue and angular stomatitis.

# Secondary nutritional deficiencies

- Vitamin A, vitamin C, and niacin deficiencies seldom cause clinical problems.
- Vitamin K is fat-soluble.
- Deficiency can lead to hypo-prothrombinemia with bruising and a bleeding tendency.

# Secondary nutritional deficiencies

- Calcium deficiency is common, caused partly by vitamin D deficiency with impaired absorption and partly by $Ca^{2+}$ binding with unabsorbed fatty acids.
- Osteopenia may be a presenting sign.
- Calcium deficiency may cause bone pain and tetany.
- Infantile rickets is rare, but osteomalacia may occur in severe adult celiac disease
- Elevated alkaline phosphatase.

# Secondary nutritional deficiencies

- Protein malabsorption may lead to hypo-proteinemic edema, usually of the lower limbs.
- Dehydration, $K^+$ loss, and muscle weakness can follow profuse diarrhea.
- Secondary endocrine deficiencies may result from malnutrition
- For example, primary or secondary amenorrhea is an important presentation of celiac disease in young women.

# Clinical observation

- Any combination of weight loss, diarrhea, and anemia should raise the suspicion of malabsorption.
- Look for signs of nutrient malabsorption. Screen all for osteoporosis.
- Simple clinical observation may provide the appropriate diagnostic strategy.
- Small bowel biopsy may be the only test required.

# Laboratory diagnosis of malabsorption

- Direct measurement of fecal fat is the most reliable test for establishing malabsorption.
- Steatorrhea is absolute evidence of malabsorption.
- Fecal fat > 6 g/day is abnormal on a Western diet of 50-150 g/day of fat.

# D-xylose absorption

- A D-xylose absorption test is an indirect but relatively specific measure of proximal small-bowel absorption.
- Active transport of the sugar is not required.
- Abnormal findings are usual in primary jejunal disease [sprue] but rare in other causes.
- <1.2 g D-xylose in a 5 hour urine collection following a 5 g oral dose of D-xylose is diagnostic.

# Watery diarrhea

- Secretory
- Characterized by isotonic stool and persists during fasting.

  Laxatives: senna, bisacodyl, castor oil, docusate

  Medications: SSRI, ACE, diuretics, theophylline
- Osmotic
- The diarrhea fluid is more than 50 mOsm more concentrated than plasma and abates with fasting.

  Laxatives: salts, milk of magnesia

  Magnesium containing liquid antacids

  Sweeteners: sorbitol, xylitol, mannitol

  Lactose

# Watery diarrhea

- Excess carbohydrate intake
- 50g of a 200g carbohydrate diet passes through unabsorbed and precipitates osmotic diarrhea
- Truncal vagotomy
- The osmotic change in the bowel lumen precipitates diarrhea
- Symptoms typically occur within 90 minutes of ingestion.
- Alcohol
- Villous adenoma
- Prostaglandin E secretion

# Watery diarrhea

- Endocrine dysfunction
- Gastrinoma
- VIP
- Extensive ileal resection
- Conjugated bile acids secreted by $Na^+$ dependent active pump stimulate colonic mucosal secretion
- Occasionally seen following cholecystectomy
- Irritable bowel syndrome

# Watery diarrhea

- If blood in watery stool, consider inflammatory bowel disease

- Bile acid production, secretion, and reabsorption are servo controlled
- Diseases associated with diminished production or secretion rarely cause steatorrhea

# Lactase deficiency

- Symptoms include explosive diarrhea with abdominal bloating and gas after milk ingestion.
- Reducing substances found in stool
- Galactose, glucose.
- This is not malabsorption.
- Lactase deficiency is also manifested in malabsorption syndromes.
- Lactase activity lost after childhood except in those of northern European ancestry.

# Diarrhea

- Diarrhea is high volume output of liquid stool.
- Soft stools with urgency reflect proctitis, not diarrhea.
- Gastroenteritis is acute diarrhea without fever
- Viral
- Food poisoning
- Giardia
- Dysentery is diarrhea lasting more than one day and associated with fever and abdominal pain
- Bacterial

# Gastroenteritis

- Acute diarrheal illness probably viral:
- Norovirus and Rotavirus present with hyperacute onset
- Vomiting usually present
- Resolves spontaneously in 24-48 hours.
- Constitutional symptoms common with Rotavirus; usually involves children.
- Vibrio infection also presents with acute diarrhea. No spontaneous resolution.

# Food poisoning

- Common bacterial causes:
- Salmonella (non-typhi species)
- Campylobacter
- Shigella

# Food poisoning

- Toxin mediated gastroenteritis has onset 1-8 hours after exposure.
- Food poisoning from Staphylococcus aureus
- OR Bacillus cereus preformed toxins
- Vomiting prominent.
- Resolves spontaneously within 12 hours.
- Toxin mediated gastroenteritis has onset 8-16 hours after exposure.
- Food poisoning from Clostridium perfringens elaborated toxin
- Abdominal cramping prominent.
- Resolves spontaneously within 1-2 days.

# Therapy of gastroenteritis

- Reydration with salt containing fluids and the use of anti-diarrheal medications (loperamide) are safe and effective in treating gastroenteritis.
- BRAT (bananas, rice, applesauce, toast) diet.
- Avoid dairy products as lactose intolerance present after diarrhea.

# Diarrhea

- Diarrhea in hospitalized patient likely toxin producing strain of Clostridium dificile.
- Diagnose by positive toxin assay (minimum three stools sampled). Positive likelihood ratio, LR+, is 14 for positive toxin assay. (LR-, 0.05).
- Oral metronidazole or oral vancomycin employed.
- No anti-diarrheals.
- Relapse up to 25% of patients.

# Dysentery

- If diarrhea for more than one day with fever and abdominal pain, empirical treatment with a fluoro-quinolone is instituted.
- Add a macrolide if Campylobacter likely.
- This is not gastroenteritis.
- Stool culture for treatment follow-up.
- No anti-diarrheals are used
- They may prolong the fever
- They may lead to toxic megacolon
- Increase the risk of hemolytic-uremic syndrome (HUS) in patients with Shiga toxin producing Escherichia coli (STEC).

# Dysentery

- Tenesmus is a common finding in patients with Shigella dysentery
- Right lower quadrant pain is prominent in patients with STEC or entero-invasive Escherichia coli dysentery.

# Dysentery

- Bloody diarrhea
- More likely due to Shigella or Campylobacter
- May also be seen with Salmonella, Yersinia, and entero-hemorrhagic Escherichia coli.
- Salmonella typhi may ulcerate (Peyers patches)
- Entamoeba histolytica
- Bloody diarrhea begins 2-3 days after onset of watery diarrhea.
- Bacteria commonly remain in the stool for 4-5 weeks and re-infection is possible.

# Dysentery

- Stool cultures often negative but are necessary.
- If fecal leukocytes present on smear, the positive likelihood ratio (LR+) of having a positive culture is 4.5. LR-, 0.3.
- If high risk for STEC, withhold antibiotics.
- Antibiotics for Salmonella only if typhoid fever.
- May have to divert bowel temporarily

# Enterocolitis

- Present with diarrhea, abdominal pain, urgency, perianal discomfort, incontinence, and hemorrhage
- Etiology varies with age, nutrition, and host nutritional status.

Table 17-8 Features of Bacterial Enterocolitides

| Infection Type | Geography | Reservoir | Transmission | Epidemiology | Affected GI Sites | Symptoms | Complications |
|---|---|---|---|---|---|---|---|
| Cholera | India, Africa | Shellfish | Fecal-oral, water | Sporadic, endemic, epidemic | Small intestine | Severe watery diarrhea | Dehydration, electrolyte imbalances |
| *Campylobacter* spp. | Developed countries | Chickens, sheep, pigs, cattle | Poultry, milk, other foods | Sporadic; children, travelers | Colon | Watery or bloody diarrhea | Arthritis, Guillain-Barré syndrome |
| Shigellosis | Worldwide, endemic in developing countries | Humans | Fecal-oral, food, water | Children, migrant workers, travelers,nursing homes | Left colon, ileum | Bloody diarrhea | Reactive arthritis, urethritis, conjunctivitis, hemolytic-uremic syndrome |
| Salmonellosis | Worldwide | Poultry, farm animals, reptiles | Meat, poultry, eggs, milk | Children, older adults | Colon and small intestine | Watery or bloody diarrhea | Sepsis, abscess |
| Enteric (typhoid) fever | India, Mexico, Philippines | Humans | Fecal-oral, water | Children. adolescents, travelers | Small intestine | Bloody diarrhea, fever | Chronic infection, carrier state, encephalopathy, myocarditis, intestinal perforation |
| *Yersinia* spp. | Northern and central Europe | Pigs, cows, puppies, cats | Pork, milk, water | Clustered cases | Ileum, appendix, right colon | Abdominal pain, fever, diarrhea | Reactive arthritis, erythema nodosum |
| *Escherichia coli* | | | | | | | |
| Enterotoxigenic (ETEC) | Developing countries | Unknown | Food or fecal-oral | Infants, adolescents, travelers | Small intestine | Severe watery diarrhea | Dehydration, electrolyte imbalances |
| Enteropathogenic (EPEC) | Worldwide | Humans | Fecal-oral | Infants | Small intestine | Watery diarrhea | Dehydration, electrolyte imbalances |
| Enterohemorrhagic (EHEC) | Worldwide | Widespread, includes cattle | Beef, milk, produce | Sporadic and epidemic | Colon | Bloody diarrhea | Hemolytic-uremic syndrome |
| Enteroinvasive (EIEC) | Developing countries | Unknown | Cheese, other foods, water | Young children | Colon | Bloody diarrhea | Unknown |
| Enteroaggregative (EAEC) | Worldwide | Unknown | Unknown | Children, adults, travelers | Colon | Nonbloody diarrhea, afebrile | Poorly defined |
| Pseudomembranous colitis (*C. difficile*) | Worldwide | Humans, hospitals | Antibiotics allow emergence | Immunosuppressed, antibiotic-treated | Colon | Watery diarrhea, fever | Relapse, toxic megacolon |
| Whipple disease | Rural > urban | Unknown | Unknown | Rare | Small intestine | Malabsorption | Arthritis, CNS disease |
| Mycobacterial infection | Worldwide | Unknown | Unknown | Immunosuppressed, endemic | Small intestine | Malabsorption | Pneumonia, infection at other sites |

CNS, Central nervous system; GI, gastrointestinal.

# Cholera

- Abrupt onset of watery diarrhea 1-5 days post exposure
- Voluminous loss of fluid
- Stools resemble rice water
- Fishy odor.
- Oral rehydration often sufficient therapy
- Comma shaped organisms

# Cholera

- Vibrio organisms are noninvasive and remain within the intestinal lumen.
- Cholera toxin, encoded by a virulence phage and released by the Vibrio organism, causes disease.
- Flagellar proteins, involved in motility and attachment, are necessary for efficient bacterial colonization.
- Hemagglutinin, a metalloproteinase, is important for bacterial detachment and shedding in the stool.
- Shellfish and plankton may serve as reservoirs for the bacterium.

# Cholera

- Cholera toxin stimulates adenylate cyclase
- Increases intracellular cAMP
- Opens CFTR
- Releases chloride ions into the lumen.
- Chloride and sodium absorption are also inhibited by cAMP.
- Chloride, bicarbonate, and sodium assumulate within the lumen
- Massive osmotic diarrhea results
- Mucosal biopsies show only minimal histologic change.

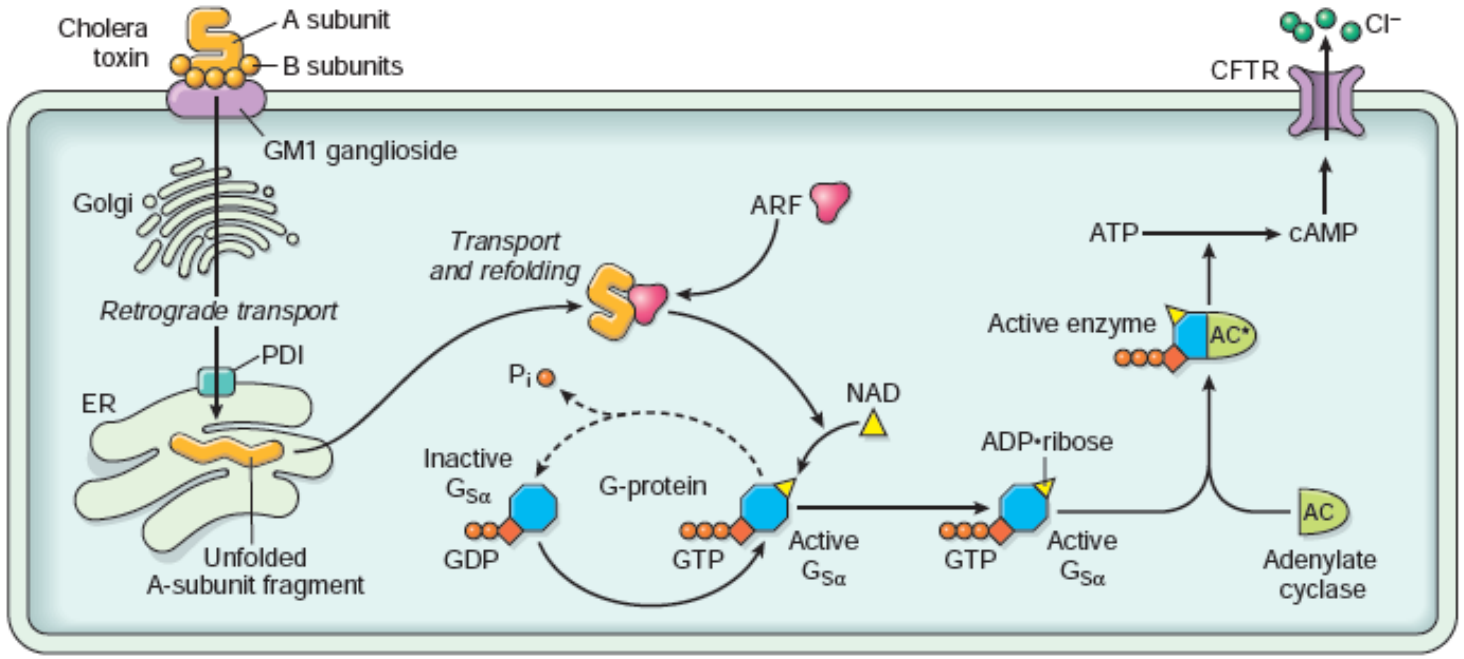



**Figure 17-27** Cholera toxin transport and signaling. After retrograde toxin transport to the endoplasmic reticulum (ER), the A subunit is released by the action of protein disulfide isomerase (PDI) and is then able to access the epithelial cell cytoplasm. In concert with an ADP-ribosylation factor (ARF), the A subunit then ADP-ribosylates $G_s\alpha$, which locks it in the active, GTP-bound state. This leads to adenylate cyclase (AC) activation, and the cAMP produced opens CFTR to drive chloride secretion and diarrhea.

# Campylobacter jejuni

- Common bacterial enteric pathogen
- Important cause of traveler's diarrhea.
- Flagella allow Campylobacter to be motile.
- This facilitates adherence and colonization, which are necessary for mucosal invasion.
- Cytotoxins that cause epithelial damage and a cholera toxin-like enterotoxin are also released by some isolates.
- Invasive antigen (B) also produced.
- Enteric fever occurs when bacteria proliferate within the lamina propria and mesenteric lymph nodes

# Campylobacter

- Campylobacter infection can result in reactive arthritis, primarily in patients with HLA-B27.
- Other extraintestinal complications:
- Erythema nodosum
- Guillain-Barré syndrome
- Campylobacter found in 50% of cases
- Molecular mimicry as cause
- Campylobacter are comma-shaped, flagellated, gram-negative organisms.
- Grow best at 42C at low Oxygen levels
- Mild inflammatory changes noted on intestinal biopsy

# Erythema nodosum

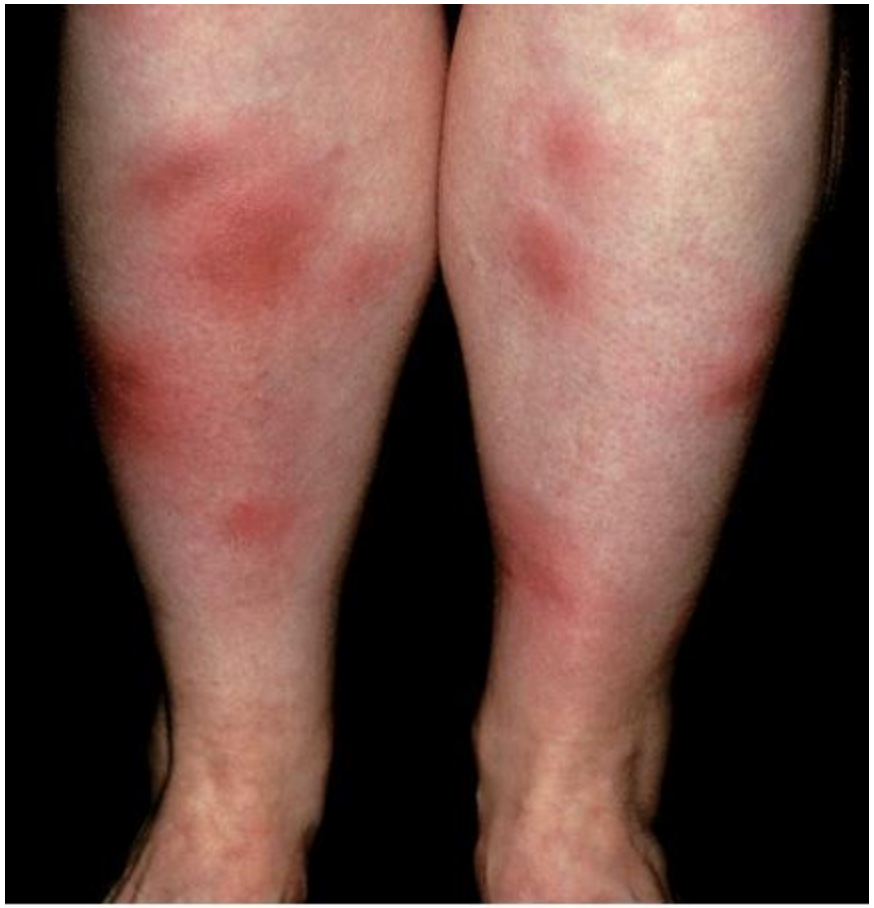


Fig. 7-23 Accessed 07/16/2010

Source: Wolff K, Johnson RA: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology, 6th Edition:* http://www.accessmedicine.com

# Shigella

- Gram-negative unencapsulated, nonmotile, facultative anaerobes that belong to the Enterobacteriaceae family and are closely related to enteroinvasive E. coli.
- Humans as the only reservoir
- Shigella are resistant to the harsh acidic environment of the stomach
- Once in the intestine, organisms are taken up by specialized epithelial cells, M (microfold).
- M cells are specialized for sampling and presentation of luminal antigens.

# Shigella

- Proliferate intracellularly, escape into the lamina propria, and are phagocytosed by macrophages, in which they induce apoptosis.
- The resulting inflammatory process damages surface epithelia and allows Shigella to gain access to the basolateral membranes of colonic epithelial cells
- The preferred domain for invasion.
- All Shigella spp. carry virulence plasmids, some of which encode a type III secretion system capable of directly injecting bacterial proteins into the host cytoplasm.

# Shigella

- S. dysenteriae serotype 1 also release the Shiga toxin (STX)
- Inhibits protein synthesis, resulting in host cell damage and death.
- Shigella infections are most prominent in the left colon, but the ileum may also be involved
- The mucosa is hemorrhagic and ulcerated, and pseudomembranes may be present.
- 1 week incubation period
- 50% develop dysentery (bloody diarrhea)

# Shigella

- Reactive arthritis, urethritis, and conjunctivitis that preferentially affects HLA-B27-positivemen between 20 and 40 years of age is a complication of infection. (Reiter's syndrome)
- Hemolytic-uremic syndrome, which is typically associated with enterohemorrhagic E. coli (EHEC), may also occur after infection with S. dysenteriae serotype 1 that secrete Shiga toxin.

# Non-typhoid salmonella

- Possess virulence genes that encode a type III secretion system capable of transferring bacterial proteins into M cells and enterocytes.
- The transferred proteins activate host Rho GTPases, triggering actin rearrangement and bacterial endocytosis.
- Flagellin activates TLR5 on host cells
- Lipopolysaccharide activates TLR4
- Increase inflammatory response

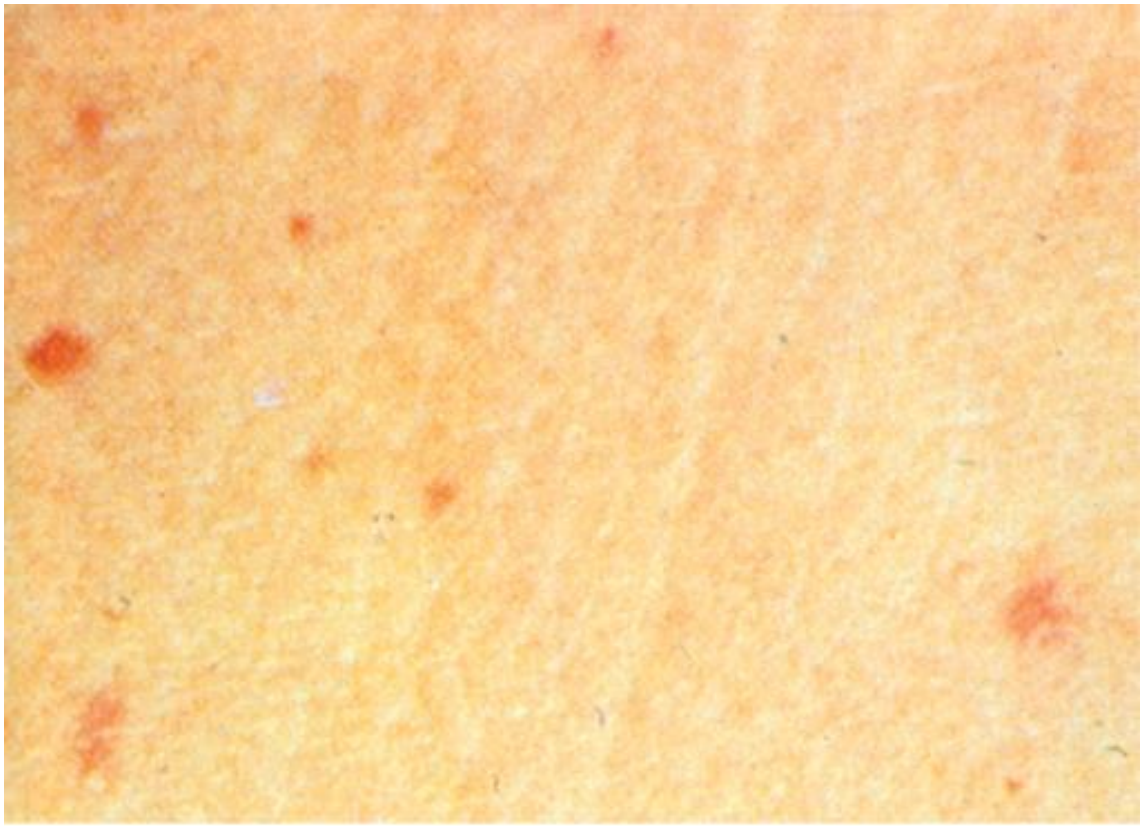
# Typhoid fever

- Enteric fever
- The majority of cases in endemic countries are due to S. typhi, while infection by S. paratyphi is more common among travelers
- Humans as only reservoir
- Gallbladder colonization with S. typhi or S. paratyphi may be associated with gallstones and the chronic carrier

# Typhoid fever

- Classic features are fever, abdominal pain and hematochezia
- First week of illness:
- Rising ("stepwise") fever associated with chills, although frank rigors are rare
- Second week of illness:
- Abdominal pain develops and "rose spots" (faint salmon- colored macules on the trunk and abdomen) may be seen

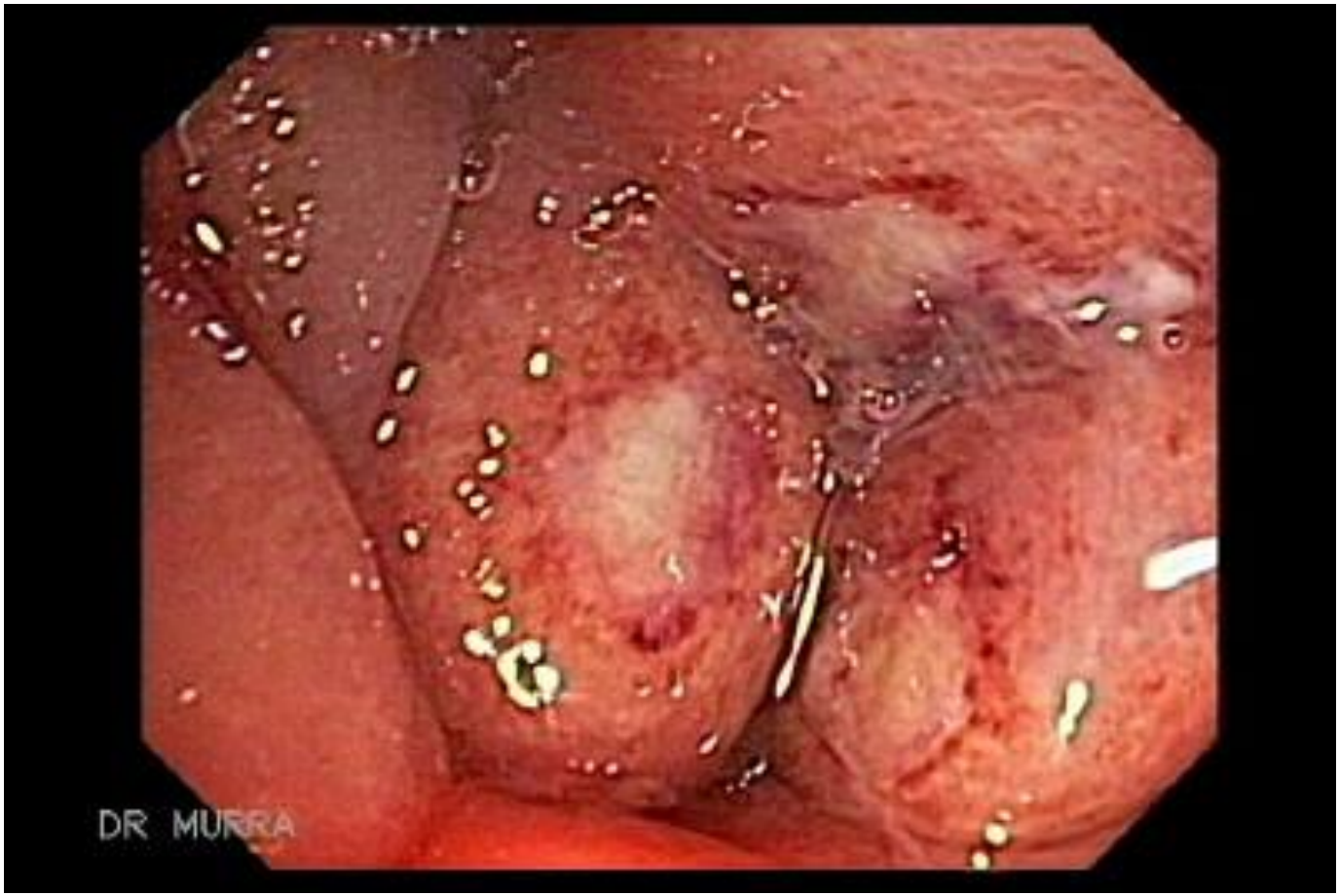
# Rose spots



# Typhoid fever

- Third week of illness:
- Hepatosplenomegaly, intestinal bleeding and perforation due to ileocecal lymphatic hyperplasia of the Peyer's patches may occur
- Perforation is four times more common in men than women

# Ulcerated Peyer's patches




https://www.gastrointestinalatlas.com/english/Typhoid_ulcers.html

# Typhoid fever

- Salmonella survive gastric acid and are taken up by M cells in the small intestine.
- There are an abundance of M cells in the dome epithelium over the Peyer patches.
- Infection causes Peyer patches in the terminal ileum to enlarge into sharply delineated, plateau-like elevations.
- Draining mesenteric lymph nodes are also enlarged.

# Typhoid fever

- Neutrophils accumulate within the superficial lamina propria, and macrophages containing bacteria, red cells, and nuclear debris mix with lymphocytes and plasma cells in the lamina propria.
- Mucosal damage creates oval ulcers, oriented along the axis of the ileum, that may perforate.

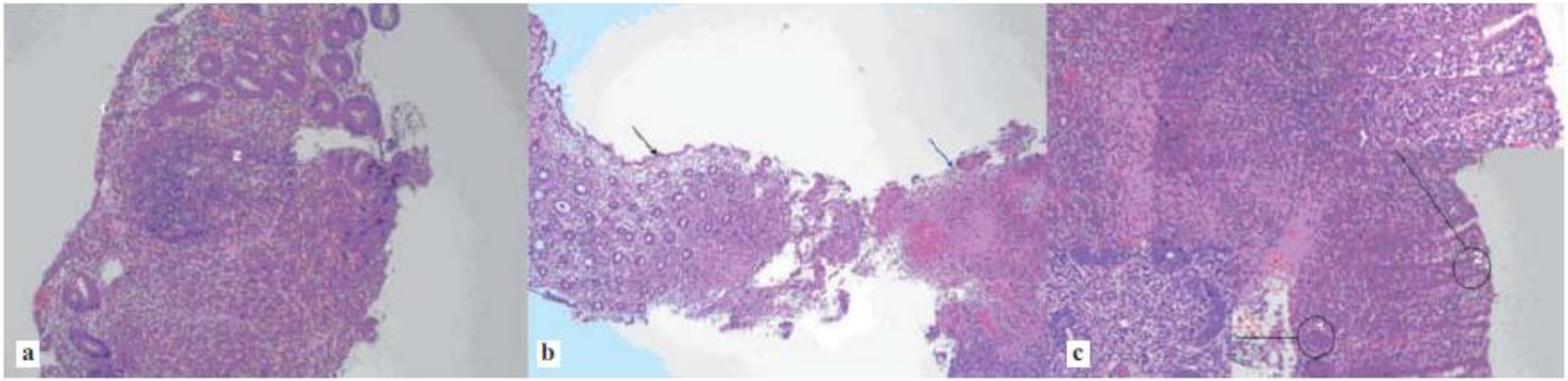



**Figura 3a - Histopathology (HE - 100x): Mucosal fragment of terminal ileum, with atrophy of *villi* (1), a voluminous lymphoid follicle (2), and dense infiltration of mixed inflammatory cells in lamina propria.**

**Figura 3b - Histopathology (HE – 50x): Mucosal fragment of distal intestine, with crypt atrophy (black arrow), an ulceration area (blue arrow), and a dense infiltration of mixed inflammatory cells in lamina propria.**

**Figura 3c - Histopathology – (HE 100x): Intense inflammatory reaction, with abscess of the mucosal crypts (inserts 1- HE 400x; 2-HE 400x).**

Murinello, A, et al., “Typhoid fever: clinical and endoscopic aspects,” J Port Gastrenterol 2008; 15: 76-82

# Typhoid fever

- The draining lymph nodes also harbor organisms and are enlarged due to phagocyte accumulation.
- The spleen is enlarged and soft, with uniformly pale red pulp, obliterated follicular markings, and prominent phagocyte hyperplasia.
- The liver shows small, randomly scattered foci of parenchymal necrosis in which hepatocytes are replaced by macrophage aggregates (typhoid nodules)
- Such nodules may also develop in the bone marrow and lymph nodes.

# Typhoid fever

- Hematogenous dissemination may lead to encephalopathy, myocarditis, pneumonia, and gallbladder infection.
- Sickle cell patients are at risk for development of osteomyelitis.

# Yersinia

- Yersinia invade M cells and use specialized bacterial proteins, called adhesins, to bind to host cell β1integrins.
- A pathogenicity island encodes an iron uptake system that mediates iron capture and transport.
- Enhances virulence and dissemination
- Yersinia infections preferentially involve the ileum, appendix, and right colon.
- The organisms multiply extracellularly in lymphoid tissue, resulting in regional lymph node and Peyer patch hyperplasia as well as bowel wall thickening.

# Yersinia

- The mucosa overlying lymphoid tissue may become hemorrhagic, and aphthous-like erosions and ulcers may develop, along with neutrophil infiltrates (Y.enterocolitica)
- If granulomas (Y. paratuberculosis)
- May mimic appendicitis in young persons
- Extraintestinal symptoms of pharyngitis, arthralgia, and erythema nodosum occur frequently.
- Reactive arthritis is also seen.

# Enterotoxigenic E. coli

- The principal cause of traveler's diarrhea.
- Produce heat-labile toxin (LT) and heat-stable toxin (ST).
- Both induce chloride and water secretion while inhibiting intestinal fluid absorption.
- The LT toxin is similar to cholera toxin
- Binds to adenylate cyclase
- ST toxin effects on transport are similar to those produced by LT
- Bind to guanylate cyclase.

# Enterotoxigenic E. coli

- Produce attaching and effacing (A/E) lesions
- Bacteria attach tightly to the enterocyte apical membranes and cause local loss (effacement) of the microvilli.
- TIR is a product of the ESPE gene which is part of the locus of enterocyte effacement (LEE)
- Inserted into the intestinal epithelial cell plasma membrane.
- Acts as a receptor for the bacterial outer membrane protein intimin
- Is used for molecular detection and diagnosis of EPEC infection.

# Enterotoxigenic E. coli

- Also encodes is a type III secretion system that injects bacterial effector proteins into the epithelial cell cytoplasm.
- Minimal histologic abnormalities.

# Enterohemorrhagic E. coli

- O157:H7 and non-O157:H7 serotypes
- Cows as reservoirs
- Produce Shiga-like toxins
- Hemolytic-uremic syndrome (HUS) and ischemic colitis as complications
- Children at greater risk for HUS

# Enteroinvasive E.coli

- Do not produce toxins
- Invade epithelium and cause limited inflammatory reaction

# Enteroaggregative E. coli

- Attach to enterocytes via adherence fimbriae and are aided by dispersin, a bacterial surface protein that neutralizes the negative surface charge of lipopolysaccharide.
- Produce LT toxin and a Shiga-like toxin
- Minimal histologic damage
- Produce non-bloody diarrhea
- Immunocompromised at risk

# Pseudomembranous colitis

- Clostridium dificile
- Antibotic related alteration of microbiota
- 30% of hospitalized patients colonized
- Fever, leukocytosis, abdominal pain, cramps, watery diarrhea
- May have red cells in stool, but no bloody diarrhea
- 40% recur
- Toxins released cause the ribosylation of small GTPases (e.g., Rho)
- Disrupt the epithelial cytoskeleton, the tight junction barrier, promote cytokine release, and apoptosis.

# Pseudomembranous colitis

- The surface epithelium is denuded, and the superficial lamina propria contains a dense infiltrate of neutrophils and occasional fibrin thrombi within capillaries.
- Superficially damaged crypts are distended by a mucopurulent exudate that forms an eruption reminiscent of a volcano (pathognomonic).
- An adherent layer of inflammatory cells and debris at sites of colonic mucosal injury forms.

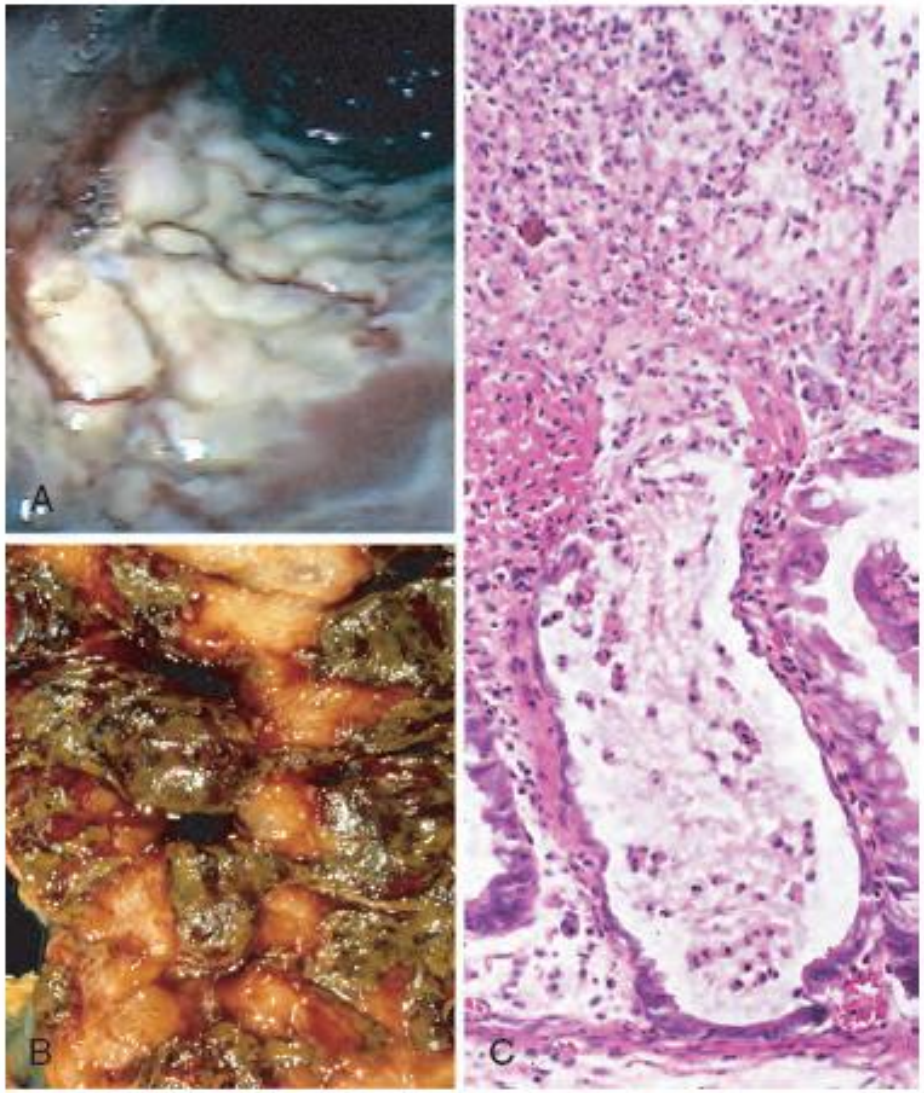



**Figure 17-29** *Clostridium difficile* colitis. **A,** The colon is coated by tan pseudomembranes composed of neutrophils, dead epithelial cells, and inflammatory debris (endoscopic view). **B,** Pseudomembranes are easily appreciated on gross examination. **C,** Typical pattern of neutrophils emanating from a crypt is reminiscent of a volcanic eruption.

# Giardia

- Giardia lambia is associated with well-water consumption as well as day-care settings.
- Diarrhea, weight loss, abdominal cramps.
- Belching, flatulence, foul-smelling stools
- No fever.
- Definitive diagnosis with parasite identification in at least one of three stools examined. Antigen assays also sensitive.
- Oral metronidazole as therapy.

# Giardia

- If Giardia not identified in stool, consider:
- Cryptosporidium
- OR Isospora belli
- Acid-fast organisms that are often found in the immuno-compromised patient.

# Rotavirus

- Highly contagious
- The most common cause of diarrhea in infants and children
- Nausea, vomiting, watery diarrhea, and abdominal pain.
- Common in day care settings
- Biopsy morphology is nonspecific.
- Rotavirus vaccine associated with increased risk of intussusception

# Norovirus

- Most common cause of acute gastroenteritis in adults
- Second only to rotavirus in children
- Nausea, vomiting, watery diarrhea, and abdominal pain.
- Biopsy morphology is nonspecific.
- Immunocompromised at risk (may persist)
- Single stranded RNA virus

# Adenovirus

- A common cause of pediatric diarrhea
- Also affects immunocompromised patients.
- 7 day incubation
- Small intestinal biopsy specimens can show epithelial degeneration but more often exhibit nonspecific villous atrophy and compensatory crypt hyperplasia.
- Viral nuclear inclusions are uncommon.
- DNA virus

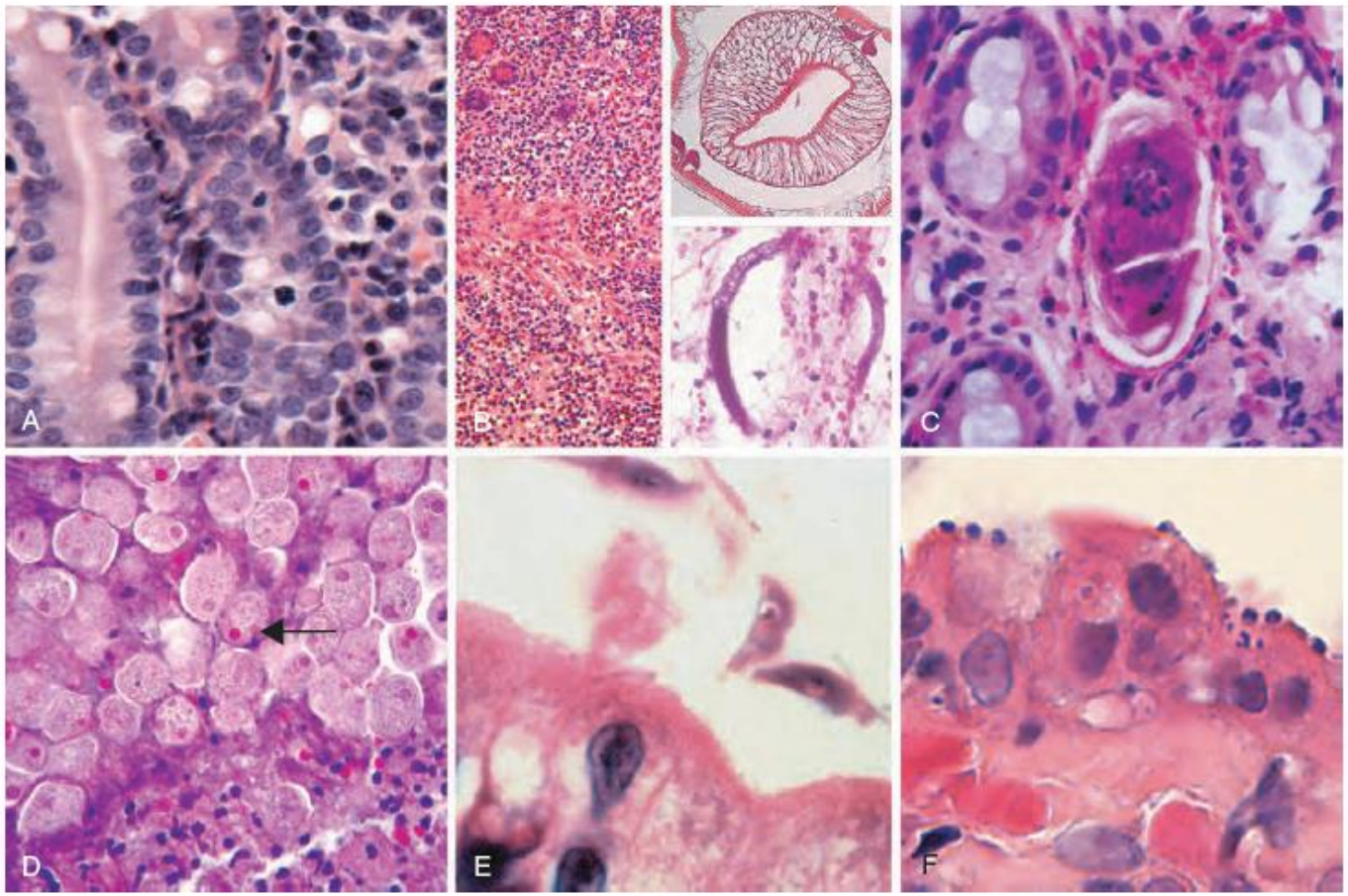



**Figure 17-31** Infectious enteritis. **A,** Histologic features of viral enteritis include increased numbers of intraepithelial and lamina propria lymphocytes and crypt hypertrophy. **B,** Diffuse eosinophilic infiltrates in parasitic infection. This case was caused by *Ascaris* (upper inset), but a similar tissue reaction could be caused by *Strongyloides* (lower inset). **C,** Schistosomiasis can induce an inflammatory reaction to eggs trapped within the lamina propria. **D,** *Entamoeba histolytica* in a colon biopsy specimen. Note some organisms ingesting red blood cells *(arrow)*. **E,** *Giardia lamblia*, which are present in the luminal space over nearly normal-appearing villi, are easily overlooked. **F,** *Cryptosporidia* organisms are seen as small blue spheres that appear to lie on top of the brush border but are actually enveloped by a thin layer of host cell cytoplasm.

# Nematodes

- Ingested eggs hatch in the intestine and larvae penetrate the intestinal mucosa.
- Larvae then migrate from splanchnic to systemic circulation and, finally, enter the lungs to grow within the alveoli.
- Coughed up, they re-enter the intestine and mature into adult worms.
- Marked eosinophilic reaction
- May form hepatic masses
- Require ova stage outside the human (Ascaris lumbricoides)
- Do not require a stage outside the human (Strongyloides stercoralis)

# Necator duodenale and Ancylostoma duodenale

- Hookworms
- Infection is initiated by larval penetration through the skin
- After further development in the lungs the larvae migrate up the trachea and are swallowed.
- Once in the duodenum the worms attach to the mucosa, suck blood, and reproduce.
- Multiple superficial erosions, focal hemorrhage, and inflammatory infiltrates

# Enterobius vermicularis

- Not invasive
- Live in the intestine.
- Adult pinworms living in the intestine migrate to the anal orifice at night, where the female deposits eggs on the perirectal mucosa.
- The eggs cause intense irritation. Rectal and perineal pruritus ensues.
- The intense itching leads to contamination of the fingers, which promotes human-to-human transmission.
- Both eggs and adult pinworms remain viable outside the body, and repeat infection is common.

# Trichuris trichuria

- Not invasive
- A heavy infestation of whipworm may lead to rectal prolapse and bloody diarrhea.

# Schistosoma

- Symptoms of intestinal schistosomiasis are caused by trapping of eggs withinthe mucosa and submucosa.
- Adult worms reside within the mesenteric veins.
- The resulting immune reaction is often granulomatous

# Cestodes

- Diphyllobothrium latum, fish tapeworms
- Taenia solium, pork tapeworms
- Hymenolepis nana, dwarf tapeworms.
- Lives within the intestinal lumen
- The worm derives its nutrients from the food stream and enlarges by formation of egg-filled segments (proglottids).
- Humans are usually infected by a single worm
- Not invasive (no eosinophilia)
- Often asymptomatic

# Entamoeba histolytica

- Present with abdominal pain, bloody diarrhea, weight loss.
- Cysts have a chitin wall and four nuclei
- Resistant to gastric acid
- Cysts colonize the epithelial surface of the colon and release trophozoites (ameboid forms) that reproduce under anaerobic conditions.
- Cecum and ascending colon most often affected

# Entamoeba histolytica

- Amoeba attach to the colonic epithelium, induce apoptosis, invade crypts, and burrow laterally into the lamina propria.
- This recruits neutrophils, causes tissue damage, and creates a flask-shaped ulcer with a narrow neck and broad base.
- Parasites may penetrate splanchnic vessels and embolize to the liver to produce abscesses in about 40% of patients.
- Hematogenous spread
- Obligate anaerobe

# Giardia lamblia

- Flagellated protozoans that cause decreased expression of brush-border enzymes, including lactase.
- Also cause microvillous damage and apoptosis of small intestinal epithelial cells
- Secretory IgA and mucosal IL-6 important for clearing infection.
- Pear shaped torphozoites with two nuclei
- Resistant to chlorine
- Assocciated with day care centers, well water

# Cryptosporidium

- Cysts resistant to chlorine
- Cysts killed by freezing
- Concentrated in ileum and terminal colon
- An entire life cycle, with asexual and sexual reproductive phases, transpires in a single host.
- Watery diarrhea
- Minimal histologic change generally

# Cryptosporidium

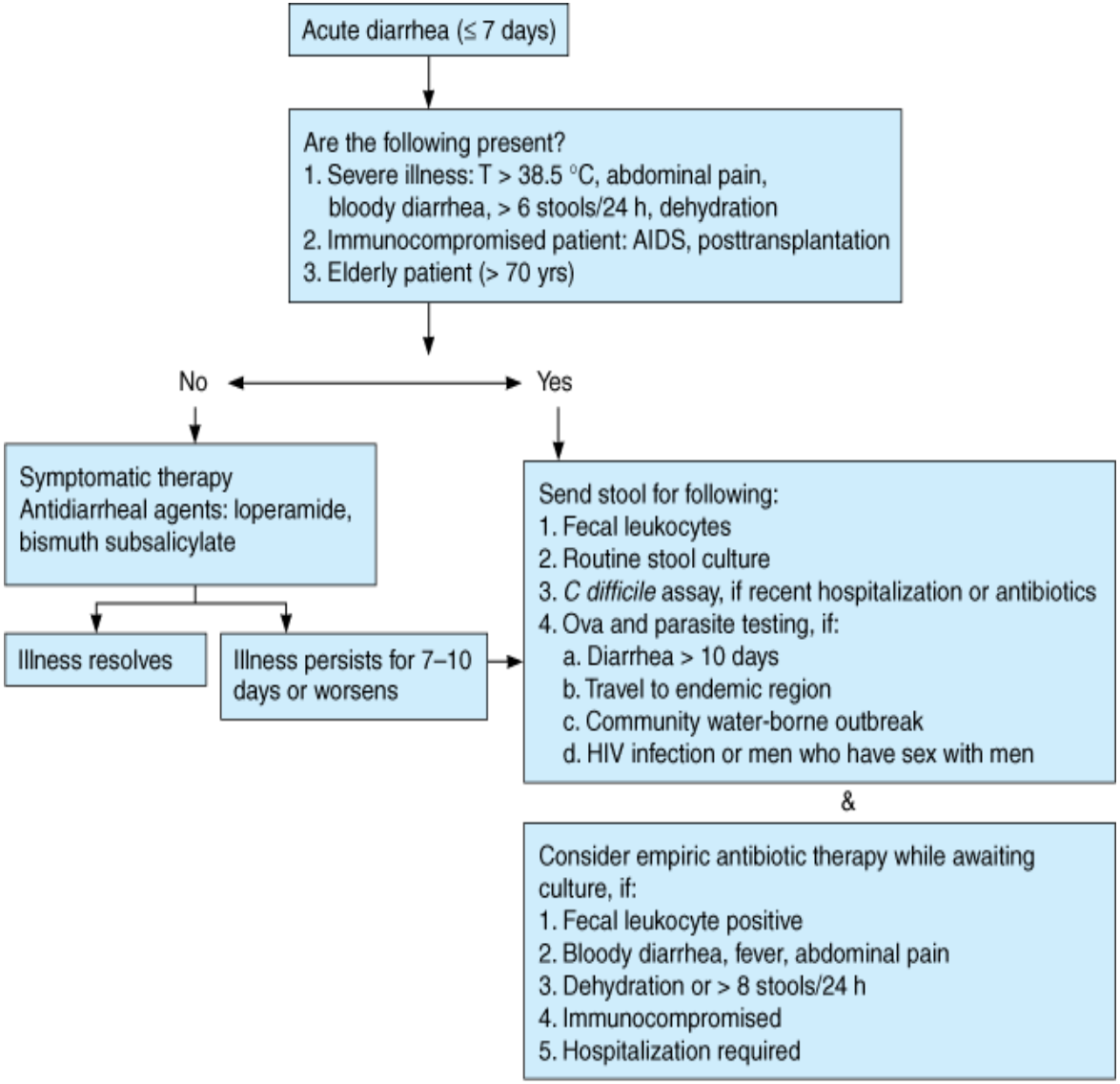
- The ingested encysted oocyte releases sporozoites following activation of proteases by gastric acid.
- The sporozoites are motile and have a specialized organelle that attaches to the brush border and causes changes in the enterocyte cytoskeleton.
- These changes induce the enterocyte to engulf the parasite, which takes up residence in an endocytic vacuole within the microvilli.
- The presence of the parasite leads to sodium malabsorption, chloride secretion, and increased tight junction permeability

# Diarrhea work-up

- Has there been extensive ileal resection?
- If there is a history of extensive bowel resection, consider small bowel overgrowth as cause.
- If there is hypoproteinemia and peripheral edema, consider intestinal lymphangiectasis or eosinophilic gastroenteritis as causes.
- Fever and abdominal pain are not seen with malabsorption.
- Examine the stool.
- Stools may appear normal in malabsorption although laden with excess fat.

# Diarrhea work-up

- Ova and parasite exam on three loose stools.
- Bacterial culture of stool.
- Clostridium dificile toxin search in stool.
- Examine stool for presence of fat globules and undigested food
- Meat or fibers
- Examine stool for presence of blood and white cells.
- Flexible sigmoidoscopy.




Source: McPhee SJ, Papadakis MA: *Current Medical Diagnosis and Treatment 2010,* 49th Edition: http://www.accessmedicine.com



Fig. 15-1
Accessed 03/03/2010

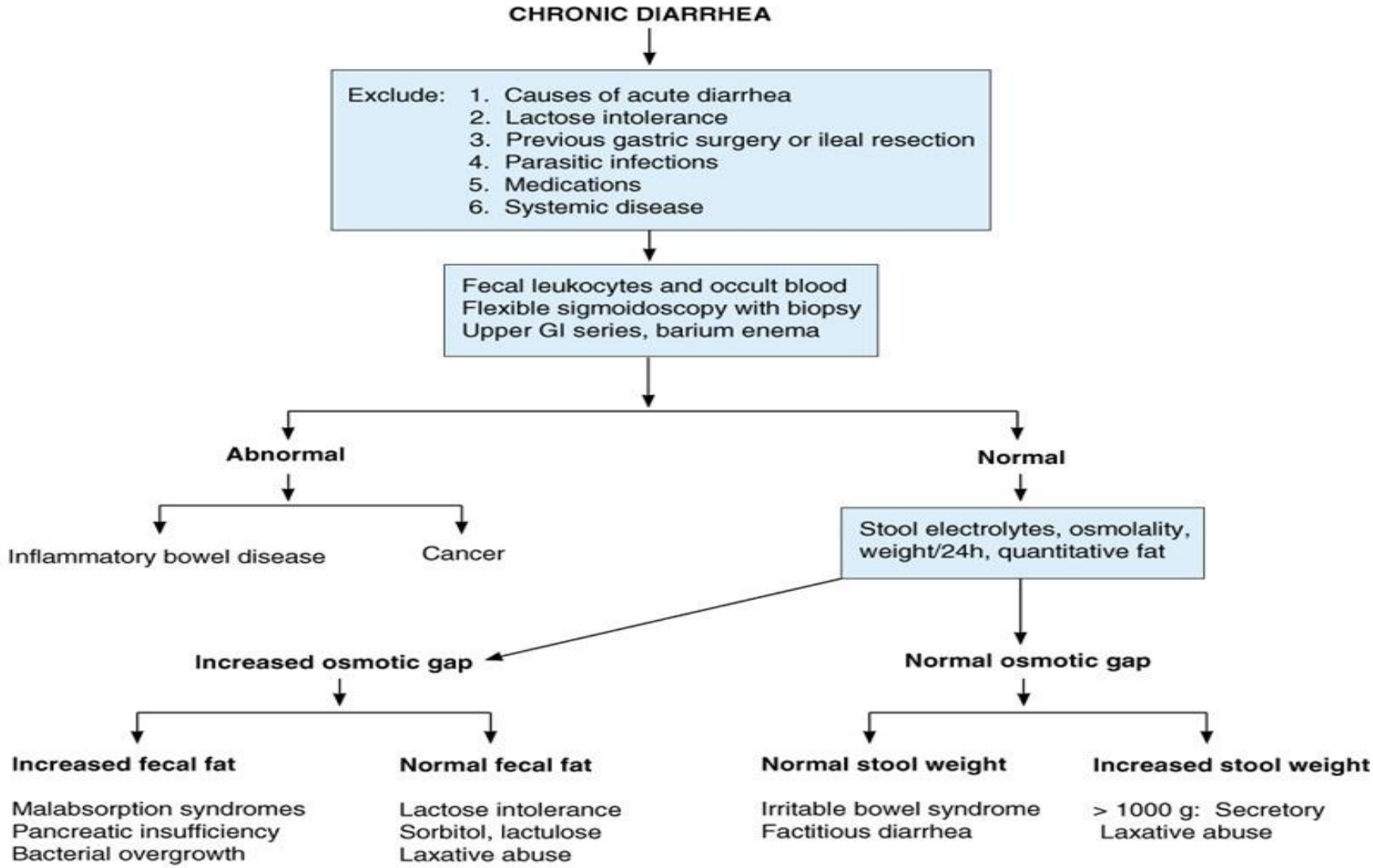





Fig. 15-2 Accessed 03/03/2010

# Diarrhea (immunocompromised)

- If AIDS patient with CD4 count >200 /uL, and on medications, diarrhea is likely medication related.
- If the CD4 count is <200 /uL, and the stool is of large volume
- Cryptosporidium
- Microsporidia
- Mycobacterium avium – intercellulare
- Giardia

# Diarrhea (immunocompromised)

- If the CD4 count is <200 /uL, and the stool is of small volume
- AND if the stool contains leukocytes
- Salmonella
- Shigella
- Clostridium dificile
- CMV
- Entamoeba histolytica
- Kaposi's sarcoma and lymphoma are less likely causes

# Stool inspection

- If the watery stool is bloody, consider:
- Ulcerative colitis.
- Crohn’s disease.
- Milk or soy allergy in infants
- Radiation enteritis
- Leukocytes in the watery stool point to an infectious etiology.

# Stool inspection

- The presence of undigested food fragments suggests either extreme hypermotility or intestinal short circuits (eg, gastrocolic fistula).
- Greasy stools from a jaundiced patient point to biliary cirrhosis or pancreatic cancer.
- Microscopic examination showing fat globules and undigested meat fiber suggests pancreatic insufficiency.
- Oil drops separated from the main stool mass, becoming whitish and firm after cooling, points to pancreatic insufficiency.

# Diarrhea work-up

- If diarrhea ceases with a 24h fast, the cause is dietary.
- To exclude lactase deficiency, resume the normal diet without dairy products to see if the diarrhea recurs.
- If diarrhea persists with a 24h fast, the cause is secretory.
- C. dificile enterotoxin is found in 15% of such patients.
- If pancreatic insufficiency thought to be cause, begin trial of enzyme replacement.

# Diarrhea work-up

- If mucosal injury thought to be cause, small bowel biopsy and quantitative fecal fat determination as necessary steps.
- If there is doubt as to mucosal injury, temporize with a D-xylose study and look for anti-endomysial antibodies in serum (celiac disease)
- Disaccharide deficiency is common in those with mucosal injury.