

GASTROINTESTINAL PATHOPHYSIOLOGY II

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IRRITABLE BOWEL SYNDROME

ESSENTIALS OF THE DIAGNOSIS

- **Chronic functional disorder** characterized by
 - **Abdominal pain**
 - **Alterations in a bowel habits**
- Limited evaluation to **exclude organic cause** of symptoms
- Symptoms begin **late teens to early 20's**

GENERAL CONSIDERATIONS

- Variable combo of chronic/recurrent GI symptoms
- Not explained by structural or biochemical abnormalities
- Several clinical entities under this broad rubric
 - Chest pain of unclear origin (noncardiac c/p)
 - Nonulcer dyspepsia
 - Biliary dyskinesia (sphincter of Oddi dysfunction)
 - Large overlap between these entities
 - 1/2 pt with noncardiac chest pain have IBS
 - 1/3 w nonulcer dyspepsia have IBS
- **No definite test to establish diagnosis**
- Diagnosis based on
 - Compatible profile
 - Exclusion of other "organic" disorders
- Defined as idiopathic clinical entity characterized by some combination of chronic symptoms:
 - Abdominal pain
 - Altered or fluctuating bowel freq + stool consistency
 - Abdominal distention and bloating
 - Varying degrees of anxiety and depression
- This combo of symptoms a.k.a.
 - "Spastic colitis"
 - "Mucous colitis"
- Patients may have other functional complaints
 - Dyspepsia
 - Heartburn
 - Chest pain
 - Fatigue
 - Urologic dysfunction
 - Gyn problems

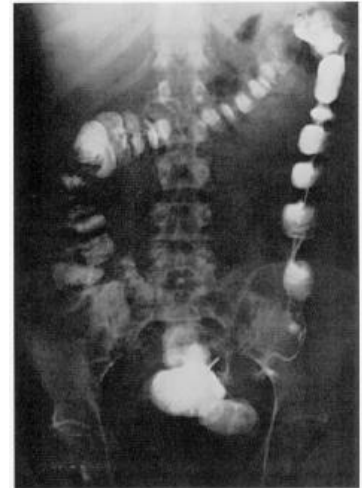


Seen here is a **loop of bowel** attached via the mesentery. Note the extent of the veins. Arteries run in the same location. Thus, there is an extensive anastomosing arterial blood supply to the bowel, making it more difficult to infarct. Also, the extensive venous drainage is incorporated into the portal venous system heading to the liver. ..



The small yellow-tan patches over the surface of the small intestine are lacteals filled with chylomicrons absorbed from the gut after a meal rich in lipids. The chylomicrons are then transported to the liver via the portal circulation

- Idiopathic clinical entity which is chronic
 - lower abdominal symptoms
 - bowel complaints
- May be continuous or intermittent
- Current working definition base on one or both of the following
 1. Abdominal pain that is either
 - Relieved by defecation or
 - Associated with change in frequency/consist of stools
 2. Disturbed defecation as evidenced by 2 of following
 - Altered stool frequency (>3/d or <3/w)
 - Altered stool form (lumpy-hard, watery)
 - Altered stool passage (straining, urgency, incomplete evacuation)
 - Bloating or abdominal distention
 - Passage of mucus
- Other somatic complaints may be present
 - Dyspepsia, heartburn
 - Chest pain, fatigue, urologic dysfunction, gyn symptoms, anxiety/depression



Barium Enema Radiograph:
Illustrates hype-haustral
contractions in IBS

- **Disorder is extremely common**
 - Up to 20% of adult pop have symptoms compatible
 - Most never seek medical attention
 - Extremely common presenting problem primary care and GI

PATHOGENESIS

- Clinical manifestation of heterogeneous group of disorders
- Several pathophysiologic mechanisms have been identified

Abnormal Motility:

- Abnormal myoelectrical and motor abnormalities in colon and small intestine
- Correlates with periods of abdominal pain and stress
- Unknown whether primary motility disorder or secondary to psychosocial stress
 - Differences reported between pt with constipation-predominated vis diarrhea-predominated syndromes

Heightened Visceral Nociception:

- Lower visceral pain threshold
- Report pain at lower volumes (vs control subjects)
 - Colonic gas insufflation
 - Colonic balloon inflation
- Absolute intestinal gas volume is normal (washout studies)
- Rectal urgency despite small rectal volumes stool

Psychosocial Abnormalities:

- > ½ patients who seek medical attention have
 - Depression/anxiety
 - Somatization
- Patients not seeking medical attention are similar psychologically to normal individuals
- Psychologic problems may influence perception/reaction
 - Illness
 - Minor visceral sensations

CLINICAL FINDINGS

Symptoms and Signs

- **Lifelong and chronic**
- Begin late teens to early 20's
- Present 3 months before dx is considered
- Diagnosis via compatible s/s and excluding organic dis

Four symptoms are particularly common

1. **Abdominal distention**
2. **Abdominal pain which is relieved w defecation**
3. **More frequent stools w onset of abdominal pain**
4. **Looser stools with onset of abdominal pain.**

- 90% IBS have 2 or more vs 30% with organic disorders
- Predictive value much lower in >60 yrs where organic disease is more common

Abdominal pain

- Intermittent, crampy - lower abdominal region
- Relieved by defecation - worsened by stress
- May be worsened 1-2 hrs after meals
- Does not occur at night - does not interfere with sleep

Predominant problem may be any of the following

- **Constipation**
- **Diarrhea**
- **Alternating constipation and diarrhea**

- Important to clarify what pt means by terms
- Many report firm stool in am -> progressively loose BM
- Patient c/o visible distention - bloating common (such s/s not clinically evident)
- Acute onset symptoms raises likelihood of organic

Symptoms which do NOT suggest IBD (requiring further investigation)

- Nocturnal diarrhea
- Hematochezia (bloody vs tarry/melenotic stool)
- Weight loss
- Fever

New onset symptoms in patient age > 40 yrs warrants investigation

PHYSICAL EXAM

- Generally unremarkable
- Mild abdominal tenderness (esp lower) is common

DIAGNOSTICS

Laboratory Findings

- 20-50 yrs w presumptive IBS limited exam warranted
- Limited screen for organic disease
 - CBC, ESR
 - Serologic tests, serum albumin
 - Stool for OB
 - 24 hr stool if diarrhea predominates (stool > 300 g/d atypical - evaluate further)
- Flexible sigmoidoscopy for patients age < 40 yrs
- BE or colonoscopy if > 40 and no previous evaluation

TREATMENT

- Measures directed at assisting patient to cope with symptoms
- Reassurance and explanation is the most important intervention
- Life-long chronic but benign condition with exacerbation and quiescent periods
- Emphasis to shift away from cause and toward coping - condition cannot be "cured"

- **Avoid chasing chronic complaints with new/repeat studies**

Dietary Therapy

- Role of dietary triggers never convincingly proved
- Patients commonly report dietary intolerances
- Food diary may be beneficial (symptoms, food intake, life events recorded)
- Lactose, fructose and sorbitol may cause
 - Bloating, distention
 - Flatulence, diarrhea
- Trial of lactose free diet (serves to exclude lactose intolerance)
- Sorbitol present in artificially sweetened foods/meds
- Flatulogenic foods -> pain/distention
 - Brown beans, brussels sprouts, cabbage, cauliflower, raw onions, grapes, plums, raisins, coffee, red wine and beer.
- Caffeine poorly tolerated by most IBS
- Trial of high-fiber diet (20-30 gms/day) recommended
 - 1 tbsp bran powder 2-3 x per day w food or 8 oz liq
 - Some patients have increased gas/distention with bran supplements
- Fiber supplementation may be better tolerated than bran
 - Psyllium
 - Methylcellulose
 - Polycarbophil

PROGNOSIS

- Favorable for overwhelming majority of patients
- Cope with symptoms
 - Lead productive lives

DRUG THERAPY FOR IBS

Anticholinergics: antispasmodic agents - may improve post-prandial pain

- 30-60 minutes ac
- S/E: urinary retention, tachycardia, dry mouth

Levsin (hyoscyamine) 0.125 tid-qid

Levsinex time release now available

Pro-Banthine (propantheline) 15 mg tid

Bentyl (dicyclomine) 10-20 mg qid

Librax (benzodiazepine and anticholinergic) **Librium 5mg/clidinium bromide 2.5:** 1-2 tid

Levsin, Bentyl, Librax most commonly used

Bellergal-S: 1 tab bid - max 16/wk (barbiturate-ergot alkaloid-antichol)

- Phenobarbital 40 mg
- Ergotamine tartrate 0.6 mg
- Levorotary alkaloids of belladonna 0.2 mg

- **Spacol:** 1-2 tabs tid-qid (also avail liq and infant drops prep)

- Hyoscyamine sulfate 0.1037
- Scopolamine HBr 0.0065
- Atropine sulfate 0.0194

Calcium Channel Blockers:

- Relax smooth muscle
- Not well tested in IBS

Antidiarrheal Agents:

- Opioid and other antidiarrheal useful chronic diarrhea
- Can use "prophylactically" where anticipate diarrhea
 - Stressful situations
 - Inconvenient situations: social engagements, etc.

Imodium (loperamide) 2 mg tid-qid

Lomotil (diphenoxylate w atropine) 2.5 mg qid

Anti-constipation agents:

- Trial of fiber supplementation (bran, psyllium, methylcellulose, polycarbophil)
- Fiber-unresponsive pts difficult to manage
- Prokinetic agents: **cisapride (Propulsid)** may help colonic inertia

Psychotropic agents

- Some patients c/o chronic unremitting abdominal pain
 - High incidence of underlying psychiatric disturb
 - Functional impairment
 - Requires frequent office visits
- May benefit from tricyclic antidepressants

Elavil (amitriptyline) 25-50 HS-> 75-150 as tolerated

SSRI may be useful - increasingly frequent use

Sertraline (Zoloft)

Fluoxetine (Prozac)

Paroxetine (Paxil)

Celexa (citalopram)

Alosetron (Lotronex)

- Approved February 2000 for IBS in women where primary symptom is diarrhea
- **Withdrawn from the market - November 2000** (letters of warning issued June 2000)
 - Serious adverse events including 5 deaths
 - 70 cases of serious post-marketing adverse events
 - Ischemic colitis (49 cases)
 - Severely obstructed/ruptured bowels due to severe constipation (21 cases)
 - 37 non-surgical hospital admissions, 10 surgeries; 3 deaths

Mechanism:

- Inhibits activation of type 3 serotonin (5-HT₃) receptors located on neurons in GI tract
- Inhibition decreases intestinal secretion, motility and afferent pain signals

Pharmacokinetics

- Rapidly absorbed after oral administration; peak plasma concentration: 1 hour
- Food decreases absorption
- Half life 1.5 hours
- Extensive hepatic metabolism: cytochrome P450 system (2C9, 3A4, 1A2)
- Excretion: metabolites excreted mostly in urine; partly in feces

Adverse Effects

- Generally well tolerated
- Constipation common; sometimes severe (resulted in withdrawal of drug)
- Acute ischemic colitis has occurred; increased aminotransferase activity

Other Therapies:

- Behavior modification with relaxation techniques
- Hypnotherapy
- Psychiatric evaluation for underlying psychologic abnormalities
- Pain management center for severe disability

INFLAMMATORY BOWEL DISEASE

Includes **ulcerative colitis (UC)** and **Crohn's disease (CD)**

A.k.a. "chronic idiopathic inflammatory bowel disease"

ULCERATIVE COLITIS:

- Chronic recurrent disease
- Diffuse mucosal inflammation involving only the colon
 - Involves rectum or rectosigmoid only: 40-50%
 - Include descending colon (left-sided colitis) 30-40%
 - Entire colon (panotitis): 20%

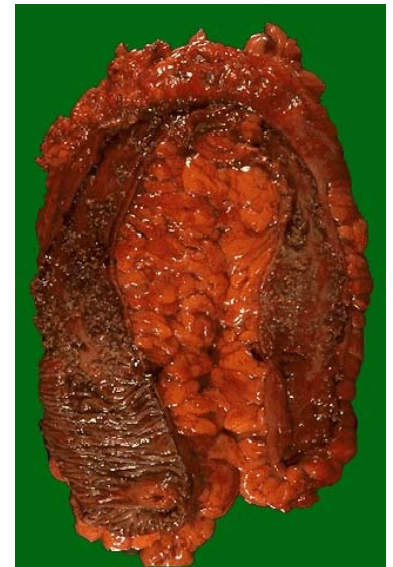
- CROHN'S DISEASE:

- Chronic, recurrent disease characterized by patchy transmural inflammation
 - Involves any segment of GI tract (common terminal ileum, colon, perianal)
 - Mouth to anus (can be indistinguishable from UC is limited to colon)
- Skip lesions: Segmental involvement w areas of normal-appearing mucosa adjacent to inflamed mucosa
- Complications from transmural inflammation (strictures, obstruction, fistulas, abscess)

- UC and CD different entities but same drugs used to treat both
- No specific treatment for disease despite in spite of research
- Disease is treated symptomatically (see :Inflammatory Bowel Disease: Drug Therapies)
- Extraintestinal manifestations are possible (see chart under "Crohn's Disease")



Left: Crohn's disease
Right: UC



Crohn's disease involving the small intestine. Here, the mucosal surface demonstrates an irregular nodular appearance with hyperemia and focal superficial ulceration. The distribution of bowel involvement with Crohn's disease is irregular with more normal intervening "skip" areas.

Extensive **ulcerative colitis (UC)**. The ileocecal valve is seen at the lower left. Just above this valve in the cecum is the beginning of the mucosal inflammation with erythema and granularity. As the disease progresses, the mucosal erosions coalesce to linear ulcers that undermine remaining mucosa. Colonoscopic views of less severe UC are seen below, with friable, erythematous mucosa with reduced haustral folds.

EPIDEMIOLOGY

- More common
 - Northern Europe and North American vs central Europe, Asia, Africa, S Amer
 - Jewish vs non-Jewish (more common in Ashkenazi vs Sephardic or Oriental)
 - Whites vs non-whites (gap is narrowing)
- Equal distribution men vs women
- Bimodal peak: 15-25 yrs; lesser incidence 55-65 yrs
- Positive family hx is greatest risk factor (factor of 30X-100X); 15% have 1st relative

ETIOLOGY

- Exact cause is enigmatic; recently described immunopathic alterations
- Proposed complex immunologic mechanisms
- Proposed infectious agents etiology: C. difficile and Mycobacterium species

CLINICAL PRESENTATION

- Onset is classically subacute over weeks
- Stools gradually become looser, containing blood and with increasing frequency
- Occasional sudden onset resembling acute infectious colitis
- Presentation can be mild to severe w signs of toxicity depending on degree of inflammation
 - Toxic presentation: fever, tachycardia, elevated WBC, colon dilation
 - Extreme mild presentation: discovered incidentally to other diagnostic procedures

DIFFERENTIATION OF ULCERATIVE COLITIS FROM CROHN'S DISEASE

FINDING	ULCERATIVE COLITIS	CROHN'S DISEASE
Small bowel involvement?	No although mld terminal (backwash) ileitis may be present	Yes, usually apparent on upper GI testing with small-bowel follow-through on CT
Perianal disease?	No	Yes
Extraintestinal manifestations	Yes	Yes
Typical histologic findings	Nontransmural lesions, neutrophilic cryptitis, crypt abscesses	Transmural lesions, granulomas, giant cells
Malabsorption?	No	Yes (nutrients, bile salts)
Vitamin deficiencies	Rare	Yes
Fistula or perforation	No	Yes (free perforation or communication with bowel or bladder)

**PATHOLOGIC MANIFESTATIONS
THAT MAY MIMIC INFLAMMATORY
BOWEL DISEASE**

Infectious organisms and disease

- Campylobacter species
- Salmonella species
- Shigella species
- Yersinia species
- E coli (O157:H7)
- Clostridium difficile
- Amebiasis
- Gonorrhea
- Syphilis
- Herpes simplex virus
- Cytomegalovirus

Vascular diseases

- Vasculitis
- Systemic lupus erythematosus
- Polyarteritis nodosa

Miscellaneous disorders

- Ischemic colitis
- Microscopic colitis (lymphocytic and collagenous)
- Radiation colitis or proctitis
- Solitary rectal ulcer syndrome
- Neutropenic cecitis
- Diverticulitis
- Eosinophilic gastroenteritis

EXTRA INTESTINAL MANIFESTATIONS

Hepatobiliary

- Primary sclerosing cholangitis
- Cholelithiasis
- Steatosis

Rheumatic

- Enteropathic arthritis
- Ankylosing spondylitis
- Sacroiliitis
- Osteoporosis

Dermatologic

- Erythema nodosum
- Pyoderma gangrenosum
- Aphthous stomatitis
- Perianal skin tags
- Nutritional deficiency disease
- Extraintestinal Crohn's disease

Ocular

- Uveitis or iritis
- Episcleritis

DRUG THERAPIES for IBD

- UC and CD different entities but same drugs used to treat both
- No specific tx for disease despite in spite of research

DRUG THERAPIES

5-Aminosalicylic Acid: (sulfasalazine, olsalazine, mesalamine)

- Topically effective agent vs systemic
- Variety of anti-inflammatory effects
- Used during inactivity to maintain remission
- Absorbed from small intestine
- Minimal colonic absorption
- Several formulas to deliver to colon or small intestine while minimizing absorption

Sulfasalazine (Azulfidine):

- Oldest agent; mechanism of action is unknown
- Most adverse effects related to the inactive carrier sulfapyridine
 - Nausea, dyspepsia, H/A
- 5-aminosalicylic acid linked to sulfapyridine moiety via azo bond.
- Largely unabsorbed in small intestine
- Bacteria in colon cleave 5 aminosalicylic acid (5AA) from sulfapyridine group
- 5AA works topically and is unabsorbed
- Sulfapyridine group is absorbed and causes S/E 15-30% of pts:
- Dose related s/e:
 - nausea, H/A, leukopenia, oligospermia and impaired folate metabolism.
- Allergic and idiosyncratic s/e:
 - Fever, rash, hemolytic anemia, neutropenia, worsened colitis, hepatitis, pancreatitis, pneumonitis.
- Less expensive than other 5AA agents

Oral mesalamine agents (Asacol, Pentasa (slow release))

- 5AA agents coated in various pH sensitive resins or time-released capsules
- **Eliminates sulfapyridine portion which causes most of S/E**
- Dissolve at pH 7.0 -> release 5AA to terminal small bowel and proximal colon
- Releases slowly
- S/E uncommon: nausea, h/a, pancreatitis, nephropathy
- 80% those intolerant of sulfasalazine of 5AA can tolerate

Olsalazine (Dipentum): two 5AA linked by diazo bond

- Not absorbed in small intestine
- Cleaved by colonic bacteria -> 5AA
- Serious s/e rare
- Mild dose related diarrhea in 20% improves w food.

Topical mesalamine: (Rowasa) 5AA suppositories and enemas

- Suppositories: 500 mg
- Enemas: 4 g/60 ml
- Delivers higher conc to distal colon
- S/E extremely rare

Corticosteroids: variety of IV, oral and top formulations

- Short-term use: tx of moderate to severe disease
- Long term use is associated with serious steroid associated S/E
- Clinical trials not available re: choice of agents, route, duration, tapering regimens
- Choice of agents often based on based on personal bias and experience

- **Oral preps:** prednisone, methylprednisolone
- **IV preps:** hydrocortisone, methylprednisolone
- **Topical preps:**
 - Hydrocortisone suppositories (100 mg)
 - Foam (90 mg)
 - Enemas (100 mg)

Immunomodulating agents

Mercaptopurine (Purinethol)
Azathioprine (Imuran)
Cyclosporin A (Neoral, Sandimmune)

- Used for long-term management in 10-15% of patients with refractory CD
- S/E occur in 10% of patients
- S/E: Pancreatitis, bone marrow suppression, infections, allergies, higher risk neoplasm
- CBC weekly x4 then monthly

Antimetabolite

Methotrexate (Folex) - folic acid antagonist
Interferes w DNA synthesis
No evidence to support oral use; Im 1 wk x 16 wks found to have steroid-sparing effects
S/E: nausea, diarrhea, stomatitis; possible bone marrow suppression
Rare: hypersensitivity pneumonitis
CBC and LFTs indicated

Antibiotic

Metronidazole (Flagyl, Protostat)
Clarithromycin (Biaxin)
Ciprofloxacin (Cipro)
Tetracycline

Mechanism of action in treatment is unknown
Current Theories:

Treatment of steroid-induced microperforation, decrease bacterial-induced inflammation products, immunomodulating effects, immune mediators (cytokines, peptides and inflammatory pathways), C difficile control

ANTIMICROBIAL THERAPY IN INFLAMMATORY BOWEL DISEASE

DRUG	INDICATION	ADVERSE EFFECTS
Metronidazole (Folex)	Crohn's disease - Confined to large intestine or affecting both large and small bowel - With severe perianal involvement	Dyspepsia, glossitis, vertigo, metallic taste, reversible neutropenia, thrombocytopenia, peripheral neuropathy (long term use)
Fluoroquinolones	Refractory perianal Crohn's disease and ulcerative colitis	Nausea, diarrhea, headache, rash, abnormalities of liver enzyme levels, external genital pruritus (women)
Tetracycline	Ulcerative colitis and Crohn's disease	Photosensitivity, esophagitis, gastrointestinal symptoms
Antituberculosis agents	Crohn's disease (mixed results)	Abnormalities of liver enzyme levels, heartburn, anorexia, rash, transient leukopenia, headache (with use of rifampin)

Transdermal nicotine

- Smoking has beneficial effect on ulcerative colitis; deleterious effect on Crohn's
- Used as adjuvant therapy for ulcerative colitis but is detrimental for Crohn's disease

Newer immunomodulating agents

Currently under investigation directed at immune function

Heparin, 4-ASA preparations, fish oil, variety of **other immunomodulating agents**

Research directed toward molecular function of the immune system for currently-used drugs

Antimicrobials, corticosteroid preps

Nutritional therapies (under investigation)

- Elemental diets, TPN, glutamine
- Short-chain fatty acids

DIARRHEA

- Common symptom
- Range from acute/self-limiting to severe/life-threatening
- Term is used by pts for wide variety of meanings
 - Increased frequency of BMs
 - Increased stool liquidity
 - Sense of fecal urgency
 - Fecal incontinence

NORMAL PHYSIOLOGY

- 10 L per day of fluid enter duodenum
- All but 1.5 L is absorbed by small intestine
- Colon absorbs most of remaining

- Medical Definition of diarrhea:
 - Production of loose BM at increased frequency (> 2-3 BM per day)
 - Greater than 200-400 gm of stool per day (normal is 100-150 gm/day)
 - Stools which are unformed and watery (increased liquidity)
- Quantification of stool production is necessary only in patients with chronic diarrhea
- Myriad of etiologies for diarrhea
- Important to distinguish acute vs chronic as treatment differs

ACUTE DIARRHEA

- Acute in onset and persists < 3 wks
- Etiologic agents
 - Infectious agents
 - Bacterial toxins:
 - Preformed in food
 - Produced in gut
 - Drugs-induced
 - Variety of mechanisms
 - HIV associated
 -

COMMON ETIOLOGIES

I

Infectious origin:

Similar recent illness in family members

Food poisoning:

- recent ingestion
- Improperly stored/prepared foods
- Other persons similarly affected

Giardia or Cryptosporidium:

- Exposure to unpurified water
- Camping, swimming

Traveler's diarrhea:

recent foreign travel

Clostridia difficile colitis:

Antibiotic administration within preceding

few weeks

HIV associated

- Unprotected anal intercourse
- Infections: proctitis and rectal discharge
- GC, syphilis, lymphogranuloma venereum, herpes simplex

NONINFLAMMATORY DIARRHEA:

- **Small bowel enteritis**
- Infection which disrupts normal absorption or secretory process of small intestine
- Clinical Presentation
 - Watery, non-bloody diarrhea
 - Periumbilical cramps
 - Bloating
 - Nausea/vomiting: any combo
- Typical organisms
 - Toxin producing bacteria (enterotoxigenic E. Coli)
 - Staphylococcus aureus
 - Bacillus cereus
 - C. perfringens
 - Other disruptive agents: viruses, Giardia
- Prominent vomiting suggests viral enteritis or S. aureus food poisoning
- Typically mild diarrhea but may be voluminous
 - Originates in small intestine
 - Ranging from 10 to 200 mL/kg/24h
- Possible sequelae
 - Dehydration with hypokalemia
 - Metabolic acidosis: loss of HCO₃⁻ in stool (example: cholera)
- No fecal leukocytes (no tissue invasion)

INFLAMMATORY DIARRHEA

- **Fever** and **bloody** diarrhea (dysentery) indicates colonic tissue damage
- Caused by invasion or toxin
- Bacterial/amebic invasion:
 - Shigellosis
 - Salmonellosis
 - Campylobacter or Yersinia
 - Amebiasis
- Toxins
 - **C. difficile**
 - **E coli O157:H7**: toxigenic, noninvasive organisms
 - Contaminated meat
 - Unpasteurized juice
 - Results in outbreaks of acute severe hemorrhagic colitis
- Diarrhea is small in volume (<1L/d) because it affects colon vs small intestine
- Colon is affected because organisms involved reside predominantly colon
- Associated with lower left quadrant (LLQ) cramps, tenesmus, urgency
- **Fecal leukocytes** present in infections with invasive organisms
- CMV (cytomegalovirus) in HIV - intestinal ulceration with watery or bloody diarrhea.
- Must distinguish infectious dysentery vs ulcerative colitis *

* UC can present acutely w fever, abdominal pain, bloody diarrhea

CAUSES OF ACUTE INFECTIOUS DIARRHEA

NONINFLAMMATORY	INFLAMMATORY DIARRHEA
<p>Viral</p> <ul style="list-style-type: none"> - Norwalk virus - Norwalk-like virus - Rotavirus <p>Protozoal</p> <ul style="list-style-type: none"> - Giardia lamblia - Cryptosporidium - Cyclospora <p>Bacterial</p> <ul style="list-style-type: none"> - Preformed enterotoxin production <ul style="list-style-type: none"> - S aureus - B cereus - Clostridium perfringens - Enterotoxin production <ul style="list-style-type: none"> - Enterotoxigenic E coli (ETEC) - Vibrio cholerae 	<p>Viral</p> <ul style="list-style-type: none"> - Cytomegalovirus <p>Protozoal</p> <ul style="list-style-type: none"> - Entamoeba histolytica <p>Bacterial</p> <ol style="list-style-type: none"> 1. Cytotoxin production <ul style="list-style-type: none"> - Enterohemorrhagic E coli (O157:H5) - EHEC - Vibrio parahaemolyticus - Clostridium difficile 2. Mucosal invasion <ul style="list-style-type: none"> - Shigella - Campylobacter jejuni - Salmonella - Enteroinvasive E coli (EIEC) - Aeromonas - Plesiomonas - Yersinia enterocolitica - Chlamydia - Neisseria gonorrhoeae - Listeria monocytogenes

INFECTIOUS DIARRHEA (GASTROENTERITIS)

ETIOLOGIC AGENTS

Viral:

Common: **Norwalk agent, adenovirus, rotavirus**
 Uncommon: Hepatitis A, poliovirus, calcivirus, astrovirus, coronavirus, HSV, CMV

Bacterial

Common: **E coli**, Aeromonas hydrophilia, **Campylobacter jejuni**
 Uncommon: **Salmonella** sp Y enterocolitica, **Shigella** sp, Vibrios cholerae, Aeromonas
 Increasing: Hemorrhagic E coli (O157:H7, O104:H21)
 Rare: Bacillus cereus, chlamydia, syphilis, gonorrhoea, Plesiomonas shigelloides
 Chronic, particularly AIDS patients: Brachyspira aalborgi (spirochete)
 Other: Listeria monocytogenes (contaminated milk)
 Antibiotic associated: **C difficile**
 Diarrhea in hospitalized patients is most commonly caused by C difficile

Protozoan

Common: **Giardia lamblia, Entamoeba histolytica**
 Uncommon: Toxoplasma gondii, Strongyloides, Cyclospora
 Immunosuppressed: **Microsporidia, Cryptosporidia, Isospora**

Hemorrhagic E coli (O157:H7)

- Diarrhea, nearly always bloody (98%)
- Strongly associated with hemolytic-uremic syndrome
- Main risk factor for acquisition is eating home-cooked hamburger
- Can also occur with unpasteurized juices
- Hand-washing can substantially reduce risk of transmission
- May be most common cause of infectious bloody diarrhea in USA
- Fever may be low or absent during initial infection

TREATMENT

- Traveler's diarrhea: quinolones and bismuth are effective
- Bloody diarrhea: usually due to bacteria - quinolones are mainstay therapy
- Shigella
 - Ciprofloxacin 500 mg bid x 5
 - Azithromycin 500 mg x 1, 250 mg/d x 4d
 - Campylobacter: usually sensitive to fluoroquinolone (resistance reported)

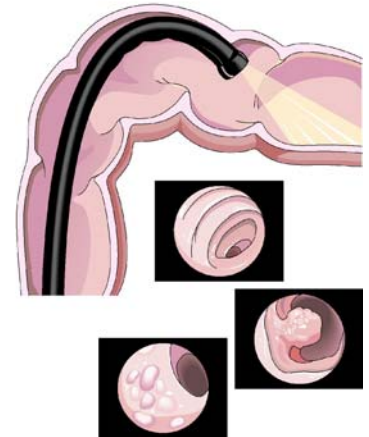
ENTERIC FEVER: : severe systemic illness

- Initial clinical presentation
 - Prolonged high fevers
 - Prostration, confusion
 - Respiratory symptoms
- Subsequent clinical symptoms
 - Abdominal tenderness
 - Diarrhea
 - Rash due to salmonella typhi or salmonella paratyphi
- Sequelae (secondary to infectious organism)
 - Bacteremia
 - Multiorgan dysfunction

EVALUATION

- Over 90% pt w acute have mild, self-limiting illness
- Responds within 5 days to simple rehydration/antidiarrheals
- Lab studies for etiology is unnecessary
 - Costly
 - Often unrevealing
 - Not effect outcome or therapy
 - Isolation rate of bacterial pathogens is < 3%
- Goal of initial evaluation to distinguish pts from more seriously ill ness
- Stool for fecal leukocytes
 - Distinguishes noninflammatory vs inflammatory
 - Easily performed - inexpensive
 - + fecal leukocytes -> inflammatory -> c/s is needed

- Inflammatory with any of the following requires prompt attention
 - High fever (>38.5C)
 - Diarrhea
 - Abdominal pain
 - Abdominal pain not subsiding p 4-5 days
- Patients with symptoms of dehydration must be evaluated
 - Excessive thirst
 - Dry mouth
 - Decreased urination
 - Weakness
 - Lethargy
- P/E
 - General appearance
 - Mental status
 - Volume status
 - Abdominal tenderness or peritonitis
 - Peritoneal findings with C difficile or enterohemorrhagic E coli
- Hospitalization for severe cases
- Stool for **fecal leukocytes** and c/s:



Sigmoidoscopy

STOOL FOR FECAL LEUKOCYTES

INFECTIOUS			NONINFECTIOUS
PRESENT	VARIABLE	ABSENT	PRESENT
Shigella Campylobacter E coli enteroinvasive	Salmonella Yersinia Vibrio parahaemolytica Clostridium difficile Aeromonas	Norwalk virus Rotavirus Giardia lamblia Entamoeba histolytica Cryptosporidium "Food Poisoning" S aureus B cereus C perfringens E coli Enterotoxigenic Enterohemorrhagic	Ulcerative colitis Crohn's disease Radiation colitis Ischemic colitis

- 60-75% pos cultures in pt w dysentery
- Indications for wet mount for amebiasis
 - Travel to endemic areas
 - Homosexuals
- C difficile toxin if history of antibiotic exposure
- If suspect E coli O157:H7: specific serotyping indicated - must alert lab
- Stool for O/P if diarrhea > 10 days (3 specimens)

- Chlamydia, GC, HSV if sexually active with proctitis
- Indications for sigmoidoscopy
 - Acutely ill and severe proctitis
 - tenesmus
 - discharge
 - rectal pain
 - C. difficile colitis suspect
 - To differentiate UC or ischemic colitis from infectious diarrhea

TREATMENT

Diet:

- Overwhelming majority adults have mild diarrhea without dehydration
- Need only adequate fluid intake w CHO + electrolytes
- Rest bowel - avoid stimulants
 - High-fiber foods
 - Fats and milk
 - Caffeine and ETOH
- Frequent feedings of the following
 - Fruit drinks
 - Tea and "flat" carbonated beverages
 - Soft easily digested foods (soup/crackers)

Rehydration:

- Dehydration can occur quickly esp in children
- Oral rehydrate with fluids containing
 - Glucose
 - Na⁺, K⁺, Cl⁻, HC03⁻
 - Citrate
- Oral rehydration mixture: dilute to 1 Liter H2O (50-200 ml/kg/24)
 - ½ tsp salt (3.5 g)
 - 1 tsp baking soda (2.5 g NaHCO₃)
 - 8 tsp sugar (40 g)
 - 8 oz OJ (1.5 g KCl)
- Can also use oral electrolyte solution eg **Pedialyte or Gatorade**
- IV fluids for acutely ill with severe dehydration - lactated Ringer's soln

Antidiarrheal Agents:

- safely used in mild-moderate diarrheal (comfort)
- Opioids: excellent symptomatic relief use with caution
 - Decrease stool number and liquidity
 - Control fecal urgency
- Codeine, paregoric**

- Do NOT use opioids for the following (may worsen diarrhea)
 - Bloody diarrhea
 - High fever
 - Systemic toxicity
- D/C opioids if diarrhea worsened despite therapy

Imodium (loperamide) - preferred RX - opioid without CNS effects
 - 4 mg initially -> 2 mg p each BM (max 16 mg/24h)

Pepto-Bismol (Bismuth subsalicylate)

- 2 tabs or 30 ml qid
- Reduces s/s in traveler's diarrhea
 - Antiinflammatory antibacterial properties
 - Role in other settings poorly studied
- Other agents have little or no testing - minimal or no benefit
 - Lactobacilli
 - Kaolin, pectin
- Anticholinergics contraindicated in acute diarrhea
 - Rare development of megacolon
 - **Diphenoxylate with atropine (Lomotil)**

Antibiotic Therapy

Empiric Therapy - usually not indicated

- Treatment of all patients with acute diarrhea is not warranted
- Most have mild self limiting
 - Viruses
 - Non-invasive bacteria
- Inflammatory (invasive pathogens) usually resolve spontaneously within few days
- Treatment indicated for invasive pathogen with moderate to severe presentation
 - Fever
 - Tenesmus
 - Bloody stool - fecal leukocytes

ANTIMICROBIALS
<ul style="list-style-type: none"> - <u>Fluoroquinolones</u> RX of choice <ul style="list-style-type: none"> - Good coverage invasive bacteria - <u>Salmonella, shigella, Campylobacter, Yersinia, Aeromonas</u> Example: Cipro 500 bid 5-7d - Alternative choices: <ul style="list-style-type: none"> - Bactrim DS (TMP-SMX) bid - Erythromycin 250-500 qid

ANTIBIOTICS NOT RECOMMENDED *	ANTIBIOTICS CLEARLY RECOMMENDED
<ul style="list-style-type: none"> - Non-typhoid Salmonella - Campylobacter - Yersinia <p>Antibiotics do not hastened recovery or reduce period of fecal bacterial excretion.</p> <p>* except for severe/prolonged disease</p>	<ul style="list-style-type: none"> - Shigellosis - Cholera - Extraintestinal salmonellosis - "Traveler's" diarrhea - C. difficile infection - Giardia and amebiasis - STDs: GC, syphilis, chlamydiosis, HSV - AIDS

CHRONIC DIARRHEA

ETIOLOGY: 6 MAJOR CATEGORIES:

Osmotic Diarrheas:

- Stool leaves colon w fecal osmolality = serum (290 milliosmoles /kg)
- Major osmoles: Na⁺, K⁺, Cl⁻, HCO₃
- Osmotic gap:
 - difference between measured osmolality and estimated osmolality (stool or serum)
 - normally less than 50 milliosmoles/kg
- Increase in osmotic gap -> d. caused by ingestion of osmotically active substance
- Most common causes of osmotic d
 - Disaccharidase deficiency (lactase deficiency)
 - Laxative abuse
 - Malabsorption syndromes
- Resolves during fasting
- When caused by malabsorbed carbohydrates ->
 - Bloating - distention - flatulence
 - Increased colonic gas production
- Disaccharidase deficiency extremely common
 - Always consider as possible cause
 - Lactase deficiency LACTOSE INTOLERANCE
 - 3/4 nonwhite adults
 - 25% of Caucasians
 - May also be acquired secondary to
 - Viral gastroenteritis
 - Medical illness
 - GI surgery
- Sorbitol: used as artificial sweetener - gums, candy, medications
- Trial elimination for 2-3 weeks
- Can confirm dx with breath hydrogen test
 - Rise in breath hydrogen (> 20 ppm) after lactose/sorbitol ingestion confirms dx
 - Test is seldom necessary
- Ingestion of magnesium or phosphate compounds considered (laxatives or antacids)
- Surreptitious use of laxatives considered in
 - Young women with eating disorders
 - Pt with psychiatric problems
 - Pt with long history of vague or mysterious med ailments
 - Employment in medical field

Malabsorptive Conditions:

- Major causes
 - Small mucosal intestinal diseases
 - Intestinal resections
 - Lymphatic obstruction
 - Small intestinal bacterial overgrowth
 - Pancreatic insufficiency
- Hallmarks of malabsorption
 - Wt loss
 - Osmotic diarrhea
 - Nutritional deficiencies
- Significant diarrhea without weight loss is not likely malabsorption
- Physical and lab abnormalities of vitamin/minerals
 - Anemia: microcytic or macrocytic
 - Hypalbuminemia
 - Low serum cholesterol
 - Hypocalcemia
 - Elevated PT
- Quantification of fat w suspected malabsorption

Secretory Conditions:

- Increased intestinal secretion or decreased absorption
- Water diarrhea w large volume (1-10 L/d) but normal osmotic gap.
- Little change in stool output during fasting state
- Significant dehydration and electrolyte imbalance - can occur where serious
- Major causes
 - Endocrine tumor: stimulate intestinal or pancreatic secretions
 - Bile salt malabsorption (stimulating colonic secretion)
 - Laxative abuse

Inflammatory Conditions:

- IBD (Crohn's, UC, microscopic colitis)
- Other s/s: abdominal pain, wt loss, hematochezia

Motility Disorders

- Abnormal motility
- Causes: systemic disorders, surgery
- Diarrhea due to rapid transit
- Diarrhea due to stasis: bacterial overgrowth -> malabsorption
- Most common cause is **IBS** many c/o diarrhea but have normal stool weight

Chronic Infections:

- Chronic parasitic infections
- Long list of etiologic agents
- Most common organisms
 - Protozoans: Giardia, E. histolytica, Cyclospora
 - Intestinal nematodes
- Immunocompromised esp AIDS infectious agents cause chronic d
 - Microsporidia, Cryptosporidia, CMV, Isospora belli, Cyclospora and MAC

Factitial Diarrhea 15% of patients with chronic diarrhea

- Surreptitious laxative abuse
- Factitious dilution of stool

EVALUATION

Stool Analysis

1. 24 hr stool collection wt and quantitative fecal fat

- Wt > 300g/24h confirms diarrhea and justifies workup
- Wt > 1000-1500 suggests secretory process
- Fat > 10 g/24 h indicates malabsorption

2. Stool Osmolality

- Osmotic gap confirms diarrhea
- Stool osmolality < serum suggests water or urine added to stool (factitious diarrhea)

3. Stool laxative screen

- Can measure mg, PO₄, sulfate levels
- Phenolphthalein, senna and cascara detected
 - Bright red color after alkalization stool/urine
- Bisacodyl can be detected in urine

4. Fecal leukocytes - implies underlying inflammatory diarrhea

5. Stool for O/P

- Giardia, E. histolytica w wet mounts
- Cryptosporidium, Cyclospora acid-fast staining

Blood Tests:

1. Routine laboratory tests:

- CBC, serum electrolytes, LFT, Ca⁺⁺, PO₄, albumin, TSH, T4, beta-carotene, PT
- Anemia
 - Malabsorption syndromes: B12, folate, Fe
 - Inflammatory conditions
- Hypoalbuminemia
 - Malabsorption
 - Protein losing enteropathies
 - Inflammatory diseases
- Hyponatremia and non-ionic gap metabolic acidosis
 - Profound secretory diarrheas
- Malabsorption of fat-soluble vitamins
 - Abnormal PT
 - Low serum calcium
 - Low carotene
 - Abnormal serum alkaline phosphatase

2. Other laboratory tests

- Suspected secretory diarrhea
 - Serum VIP (VIPoma)
 - Gastrin (Zollinger-Ellison)
 - Cortisol (Addison's)
 - Urinary 5-HIAA (carcinoid syndrome)

Proctosigmoidoscopy with Mucosal Biopsy

- IBD (including microscopic colitis)
- Melanosis coli
- Chronic use of anthraquinone laxatives

Imaging

- Calcification on plain abd film confirms chronic pancreatitis
- Upper GI or enteroclysis: Crohn's, lymphoma, carcinoid syndrome
- Colonoscopy: IBD
- Upper endoscopy small bowel bx - malabsorption due to mucosal diseases
- Upper endoscopy w duodenal aspirate and small bowel bx useful in AIDS
 - Cryptosporidium, Microsporidia, MAC
- CT: chronic pancreatitis or pancreatic endocrine tumor

TREATMENT

Directed at underlying cause

Opioids may be used in mot pt w chronic stable symptoms

AGENTS

Loperamide (Imodium) - 4 mg initially then 2 mg p each LBM (max 16 mg/d)

Lomotil (diphenoxylate w atropine) 1 tab tid to qid

Codeine, Paregoric:

- Avoid due to addictive potential
- Used in chronic intractable
- Codeine dosing: 15-60 mg q 4 h prn
- Paregoric 4-8 ml p each LBM

Clonidine

- Alpha2 adrenergic agonist inhibits intestinal electrolyte secretion
- Patch 0.1-0.2 mg/d for 7 days
- Useful secretory diarrheas, cryptosporidiosis, DM

Octreotide:

- Somatostatin analog
- Stimulates intestinal fluid and electrolyte absorption - inhibits secretion
- Inhibits release of GI peptides
- Useful to treat secretory diarrheas
 - VIPomas and carcinoid tumors
 - Diarrhea associated w AIDS
- Dosing 50 ug to 250 ug SQ tid

Cholestyramine

- Bile salt binding resin
- Useful in pts w bile salt-induced diarrhea due to
 - Intestinal resection
 - Ileal disease
- Dose 4 gms qd to tid