



## Pharmacotherapy of Diarrhoea and Constipation

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### Diarrhoea



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### Definitions

- Increase in daily stool weight above 200gm
- Increase in frequency, fluidity or amount
- Differentiate from *incontinence and IBS*
- Acute lasts less than 7 - 14 days
- Chronic lasts more than 2 - 3 weeks

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52-yr-old ♀  
Presenting Complaint:  
Diarrhoea

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### *History of the Presenting Complaint*

- What does the patient mean by "diarrhoea"?
- Acute or chronic?
- ? Nocturnal
- Any new medications?
- Any affected contacts?
- Any suspicious food ingested?
- Any nausea or vomiting?
- ? Abdominal pain
- Any constipation? Any passage of mucus PR?
- ? Arthralgia
- ? Uveitis
- Any blood in stools?
- Any evidence of steatorrhoea?
- Any weight loss?
- Any symptoms of hyperthyroidism?
- Foreign travel?
- Any suggestion of immunocompromised state?

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### *Examination*

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## Physical Examination

- ? Dehydration
- ? Signs of thyrotoxicosis
- Inspect stool
- ? Abdominal tenderness
- ? Abdominal mass
- PR exam ?overflow
- Dermatitis ?Pellagra
- Signs of malabsorption
- ? Flushing/wheeze
- ? Erythema nodosum/pyoderma gangrenosum

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## Differential Diagnosis

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## Acute Diarrhoea

- Medications
- Dietary indiscretion
- Alcohol
- Gastroenteritis
- Psychogenic

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## Chronic Diarrhoea

- Medications (e.g. Antibiotics)
- Cancer chemotherapy
- Laxative abuse
- Infectious
- Irritable bowel syndrome
- Inflammatory bowel disease
- Colorectal tumour
- Villous adenoma
- Malabsorption
- Chronic pancreatitis
- Cystic fibrosis
- Autonomic neuropathy
- Radiation enteritis
- Collagenous colitis
- Overflow (constipation)
- Blind loop syndrome
- Thyrotoxicosis
- Pellagra
- Lactose intolerance
- IgA deficiency
- VIPoma
- Carcinoid syndrome
- Systemic Mastocytosis
- Medullary carcinoma of Thyroid
- MEN syndrome

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## Infectious causes

### Viral

- Rotavirus
- Echovirus
- Norwalk virus
- Adenovirus

### Protozoal

- *Giardia lamblia*
- Amoeba
- Cryptosporidium

### Tapeworm

### Bacterial

- Salmonella
- Campylobacter
- *Clostridium difficile*
- Shigella
- *Staphylococcus aureus*
- *E. coli*
- *Bacillus cereus*
- *Vibrio cholerae*
- *Yersinia enterocolitica*

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## Investigations

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## Investigations

- +/- 48hr fast
- FBC
- SMAC
- TFTs
- Anti-endomysial Abs
- Tumour markers
- Urinary 5-HIAA
- Gut hormone profile
- PFA (calcification, ?chronic pancreatitis)
- Stool for ova + parasites
- Colonoscopy +/- Biopsy
- Hydrogen breath test
- +/- Faecal fat estimation

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## Management

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## Management

- Discontinue offending drugs
- Rehydration therapy
- Isolation precautions
- +/- Antidiarrhoeal agents
- +/- Antibiotics
- Treat underlying cause

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## Acute Diarrhea

### INFLAMMATORY

- Fever & bloody with Leukocytes, volume <1L/ 24 hr secondary to colonic damage
- Shigella, Salmonella, Amebiasis, C.diff, E coli 0157:H7 toxin, Ischemia, UC, Crohn's, Cytomegalovirus

### Non-INFLAMMATORY

- Watery with N/V, volume >1L/ 24hr secondary to small intestine disease
- Norwalk & Rota virus, enterotoxins as Giardia, Staph aureus, Cholera, E coli, Bile acid, Laxatives, Malabsorpt

## Evaluation

- Most pt with acute diarrhea respond in 5-7 d for rehydration and antidiarrheal agents
- Isolation rate of pathogen from stool < 3%
- Stool leukocytes is inexpensive test to differentiate inflammatory vs non-inflammatory types
- Sigmoidoscopy indicated for Proctitis, C diff, UC, Ischemic colitis

## Management

### Inflammatory

- Antidiarrheal agents are avoided
- Moderate to severe cases; start empiric Abx: Ciprofloxacin, TMP-SMA, Erythromycin
- Always treat: C diff, Amebiasis, Enteric fever, Shigella, STDs

### Non-inflammatory

- Rehydration is most important
- Loperamide offers relief, Anticholinergic contraindicated for megacolon
- Always treat: Cholera, Giardiasis, Traveler's diarrhea



## Salmonella food poisoning

- Contaminated poultry especially egg yolk
- Incubation : 8- 48 Hrs
- Diarrhea, low temp. Bacteria grow on surface with little invasion
- No Abx unless immune compromised
- Pt remains as carrier for up to 2 months

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## Enteric fever

- Caused by Salmonella typhi, incubation 2 w
- Fever, bradycardia, altered behavior, constipation followed by diarrhea
- 2nd week: Rose spots on abdomen & thorax, Splenomegally and Lymphadenopathy
- Rx: Chloramphenicol, Ciprofloxacin, Ampicillin

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## Traveler's diarrhea

- E coli produces heat labile enterotoxin and heat stable, causes 40 - 75%
- Diarrhea lasts 3- 5 days
- Other pathogens - Shigella, Salmonella, Rotavirus, Giardia
- Rx: Ciprofloxacin, TMP- SMA, Aztreonam

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## Chronic Diarrhea

- Persists > 2 weeks
- Do stool cultures, ova and parasites
- Stool collection for 48 - 72 Hrs for weight, fat content, lytes and osmolality
- Sigmoidoscopy for visualization of mucosa and biopsy

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## Osmotic Diarrhea

- Stool osmotic gap (Normally <50)  
Measured - Estimated (Na + K) X 2
- Stool volume decreases with fasting
- Common causes
  - Lactose intolerance
  - Sorbitol
  - Laxatives
  - Antacids

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## Secretory Diarrhea

- Increased intestinal secretion or decreased absorption with > 1 L diarrhea
- Little change with fasting
- Endocrine diseases

VIPoma  
carcinoid  
syndrome  
Bile salts

medullary carcinoma  
Zollinger- Ellison

Villous adenoma

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## Inflammatory Diarrhea

- Fever , hematochezia and abdominal pain
- Causes
  - Ulcerative colitis
  - Crohn's disease
  - Microscopic colitis
  - Radiation enteritis
  - Malignancy

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## Malabsorption

- Wt loss, anemia, vitamin deficiency with fecal fat > 7 - 10 g/24 Hs
- Causes
  - Tropical sprue
  - Whipple's disease
  - Pancreatitis
  - Bacterial overgrowth
  - ( vagotomy , diabetes )

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## Infections

- Chronic infectious agents
  - Giardia
  - Entamoeba histolytica
  - Cyclospora
- AIDS related infections
  - Cytomegalovirus
  - Cryptosporidium

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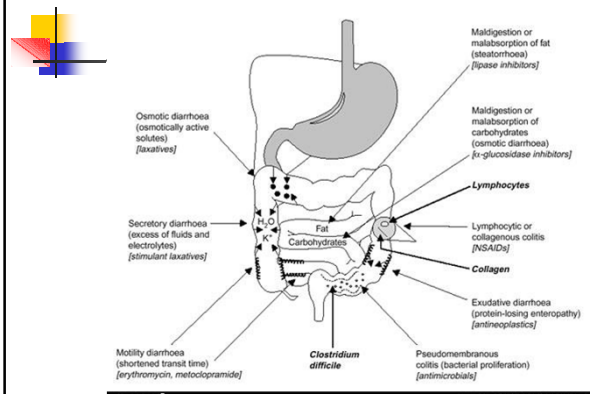
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## Drug Induced Diarrhoea




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## Rational Antibiotic Therapy

Most cases are self limiting and subside with supportive therapy

### Indication of antibiotic therapy

- Cholera
- Febrile bloody diarrhoea
- Travelers diarrhoea
- extremes of age
- Food handlers
- Immunocompromised
- Day care attendee
- Residents of institutional facility
- Epidemic outbreaks

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## Rational Antibiotic Therapy

### Problems of empiric therapy-

- In children- most cases are viral 50 – 90%
- Emerging drug resistance
- Side effects
- Alteration of gut flora
- Induction of disease producing phage e.g; Shigatoxin phage induced by quinolones
- Not effective in EHEC, salmonella enterocolitis

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## Therapeutic recommendations

- **Shigella**- TMP-SMZ, Cipro, Norflox
- **Salmonella**-Quinolones, Ceftriaxone
- **V.cholerae** - Doxycycline, Tetracycline, Erythromycin
- **E. coli**-Cipro, norflox
- **C. difficile**-Metronidazole, Vanco
- **Cryptosporidium**- Paromomycin
- **Isospora**- TMP-SMZ,
- **Cyclospora**-TMP-SMZ

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## Drugs for symptomatic treatment

- **Loperamide:**
  - inhibits hypermotility by direct action on opioid receptors in bowel wall.
  - Its inhibition of peristalsis is the result of
    - decreasing the activity of both the longitudinal muscles (preparatory and reflex phases) and
    - the circular muscles (reflex phase).
  - Contra indicated:
    - blood in stools and high fever.
    - in patients with acute ulcerative colitis or pseudomembranous colitis associated with broad spectrum antibiotics.
    - avoided and be discontinued promptly if constipation, abdominal distension or symptoms and signs suggestive of ileus develop.
    - administration may precipitate toxic megacolon in patients with inflammatory bowel disease

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### Diphenoxylate / atropine

- Diphenoxylate is a piperidine opioid that is structurally related to meperidine.
- It increases gastrointestinal contractions but disrupts aboral peristaltic motility, thereby increasing the transit time of intestinal contents.
- The prolonged transit time facilitates absorption of fluid and solutes throughout the intestinal tract.
- subtherapeutic atropine present to discourage overdose

- **CONTRA-INDICATIONS:**
  - Diarrhoea associated with antibiotic induced pseudomembranous entero-colitis
  - Fever
  - Sensitivity to the substance.
  - Should not be administered to children younger than four years, because of their susceptibility to the effects of overdosage.
  - Prostatic enlargement, paralytic ileus or pyloric stenosis, ulcerative colitis, closed angle glaucoma, angle closure.

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## Kaolin / pectin

- Kaolin is a gastrointestinal adsorbent. The mechanism of action of pectin in diarrhoeas is unknown.
- When this is fed to healthy human subjects, only a small amount is recovered in the faeces.
- However, in patients with diarrhoea, much larger amounts may be eliminated unchanged. The unchanged material may act in the bowel as an adsorbent and protective.
- For the symptomatic treatment of colitis, enteritis, dysentery and diarrhoea associated with food poisoning and in alkaloidal poisoning.

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## Constipation



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## CONSTIPATION

The definition of constipation includes the following:

- infrequent bowel movements (typically <3 times per wk),
- difficulty in defecation (straining during more than 25% of bowel movements or a subjective sensation of hard stools),
- or the sensation of incomplete bowel evacuation (tenesmus).

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64-yr-old ♂

## Presenting Complaint: Constipation



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## History



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## History of the Presenting Complaint



- What does the patient mean by "constipation"?
- How long has constipation been present?
- Is it intermittent or constant?
- Is there diarrhoea?
- Is there abdominal pain?
- Is tenesmus present?
- Any PR bleeding?
- Has the patient lost weight?
- Has the patient vomited?
- Is there pain on defecation?
- Does the patient have haemorrhoids?
- Any difficulty with micturition?
- Any features of biological depression?
- Is there enough fibre in the diet?
- Any symptoms of hypothyroidism?
- Any polyuria/polydipsia?
- Any new medications?

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## Examination

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## Physical Examination

- ? Signs of dehydration
- ? Distended abdomen
- ? Abdominal mass
- ? Bowel sounds
- Rectal examination
- ? Faecal occult blood
- ? Stigmata of hypothyroidism
- ? Features of scleroderma
- ? Evidence of Parkinson's disease
- ? Evidence of multiple sclerosis
- Anal reflex

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## Differential Diagnosis

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## Medications

- Anticholinergics
- Iron
- Diuretics
- Opiates
- Purgative abuse
- Antidepressants
- Aluminium salts
- Calcium salts
- Calcium channel blockers

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## Mechanical

- Colorectal tumours
- Hernias
- Volvulus
- Bowel obstruction

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## Anorectal

- Anal fissure
- Rectal prolapse
- Haemorrhoids
- Proctitis

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## Neuromuscular

- Advanced age
- Irritable bowel syndrome
- Diverticular disease
- Scleroderma
- Hirschsprung's disease
- Paralytic ileus

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## Endocrine/Metabolic

- Hypothyroidism
- Hypercalcaemia
- Diabetes mellitus
- Pregnancy
- Dehydration
- Hypokalaemia
- Porphyrria
- Lead poisoning

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## Neuropsychiatric

- Depression
- Spinal cord injury
- Cauda equina syndrome
- Multiple sclerosis
- Parkinson's disease
- Stroke
- Anorexia nervosa

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## Investigations

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## Investigations

- FBC
- SMAC
- Fasting glucose
- ESR
- TFTs
- Tumour markers
- PFA
- Barium enema
- Flexible sigmoidoscopy
- Colonoscopy +/- Biopsy
- +/- MRI Spinal cord
- Anorectal manometry

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## Management

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## Management

- Discontinue offending drugs
- Rehydrate
- High fibre diet
- Laxatives
- +/- Manual evacuation
- Treat underlying condition

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### Medications include:

**Bulk-forming agents** (fibers), fiber is the best medication for long-term treatment.

**Emollient stool softeners**, emollient stool softeners are easier to use but they lose their effectiveness with chronic administration. These drugs are best employed for prophylaxis in a short-term setting, such as in patients receiving a postoperative narcotic prescription

### Rapidly acting

- stimulants

- osmotics

- lubricants

Rapidly acting lubricants and laxatives often are employed for acute and chronic constipation. However, their use should be limited for acute episodes because of the long-term risk of habituation and/or toxicity.

Conversely, patients must understand that bulk-forming agents generally do not work rapidly and have to be used on a long-term basis.

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### Drug Category: *Bulk agents* -- Chronic prophylaxis and/or treatment of constipation in patients without anatomic outlet obstruction.

<b>Drug Name</b>	<b>Psyllium</b> (Metamucil, Fiberall) -- Dosages vary depending on whether the preparations contain sugar or are sugar-free (the former are 50% sugar). They must be taken with water or they may cause obstruction.
<b>Adult Dose</b>	15-60 g PO with at least 8 glasses of water qd
<b>Pediatric Dose</b>	7.5-15 g PO with at least 4 glasses water qd

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<b>Drug Name</b>	<b>Methylcellulose</b> (Citrucel) -- Theoretically nonfermentable, less gas-producing products are better tolerated than psyllium. Occasionally, patients who cannot tolerate one preparation may do well with another product.
<b>Adult Dose</b>	15-60 g fiber PO qd with at least 8 glasses of water qd
<b>Pediatric Dose</b>	7.5-15 g PO with at least 4 glasses of water qd

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<b>Drug Category: <i>Saline laxatives</i> -- Acute treatment of constipation in absence of bowel obstruction.</b>	
<b>Drug Name</b>	<b><i>Magnesium citrate</i></b> <b><i>magnesium hydroxide</i></b> (Philips' Milk of Magnesia) -- Causes osmotic retention of fluid, which distends the colon and increases peristaltic activity; promotes emptying of bowel. Works within 3 h PO or 15 min PR. May cause electrolyte imbalance, especially in young children or patients with renal insufficiency.
<b>Adult Dose</b>	Magnesium citrate: 11-18 g PO Magnesium hydroxide: 2.4-4.8 g PO Magnesium sulfate: 10-30 g PO

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<b>Drug Category: <i>Osmotic agents</i> -- Useful for long-term management of constipated patients with slow colonic transit who are refractory to dietary fiber supplementation.</b>	
<b>Drug Name</b>	<b><i>Lactulose</i></b> -- Produces osmotic effect in the colon, resulting in bowel distention and stimulation of peristalsis.
<b>Adult Dose</b>	20-30 g (30-45 mL) PO q1-2h; adjust dose slowly to produce 2-3 soft stools daily Alternatively, 200 g diluted with 700 mL of water or NS via rectal balloon catheter and retain 30-60 min q4-6h
<b>Pediatric Dose</b>	5 g/d (7.5 mL) after breakfast

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**Drug Category: *Stimulant laxatives*** -- These agents commonly are used to treat acute constipation and are the most common class of laxatives.

<b>Drug Name</b>	<b><i>Senna</i></b> (Senokot) -- Anthraquinone is hydrolyzed by colonic bacteria into its active compound. More potent than cascara sagrada and results in considerably more abdominal pain. Usually produces its action 8-12 h after administration.
<b>Adult Dose</b>	0.12-0.25 g PO qd
<b>Pediatric Dose</b>	<6 years: Not recommended >6 years: Administer as in adults

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<b>Drug Name</b>	<b><i>Bisacodyl</i></b> (Dulcolax) -- Stimulates peristalsis possibly by stimulating the colonic intramural neuronal plexus. Alters water and electrolyte secretion, resulting in net intestinal fluid accumulation and laxation. Provokes defecation within 24 h and may cause abdominal cramping.
<b>Adult Dose</b>	5-15 mg PO as single dose 10 mg PR as single dose
<b>Pediatric Dose</b>	<6 years: Not established >6 years: 5-10 mg (0.3 mg/kg) PO hs or before breakfast

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<b>Drug Name</b>	<b><i>Castor oil</i></b> -- Reduced to ricinoleic acid. It decreases net absorption of fluid and electrolytes and stimulates peristalsis. Acts on the small intestine.
<b>Adult Dose</b>	15-60 mL PO once
<b>Pediatric Dose</b>	5-10 mL PO once

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**Drug Category:** *Lubricant laxatives* -- Acute or subacute management of constipation; lubricate intestine and facilitates passage of stool by decreasing water absorption from intestine.

<b>Drug Name</b>	<b>Mineral oil</b> -- More gentle than some other rapidly acting laxatives. Generally works within 8 h. Long-term use is accompanied by concerns of lipid pneumonia, lymphoid hyperplasia, and foreign body reactions.
<b>Adult Dose</b>	15-45 mL PO as 1-time dose or qd or as retention enemas
<b>Pediatric Dose</b>	1-4 teaspoons PO qd

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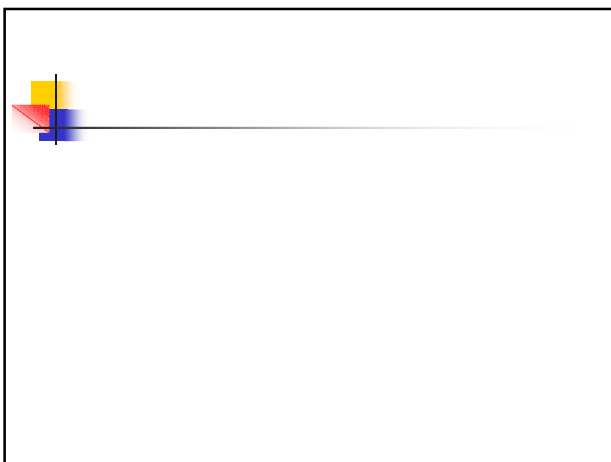
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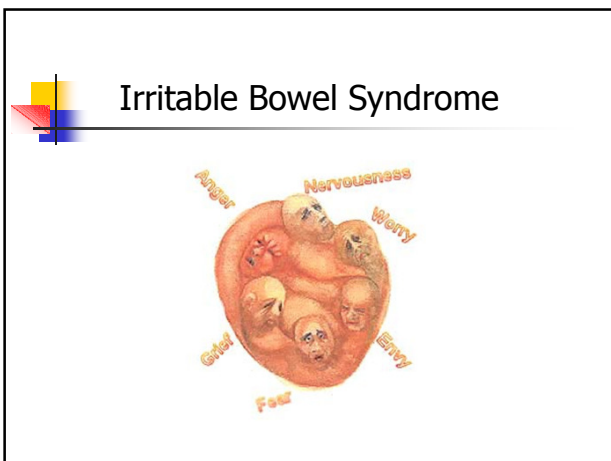
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## IBS – Diagnostic Criteria

- Traditionally, diagnosis of exclusion
- Functional disorder
- Recurrent abdominal pain or discomfort at least 3 days per month during the previous 3 months that is associated with 2 or more of the following:
  - Relieved by defecation
  - Onset associated with a change in stool frequency
  - Onset associated with a change in stool form or appearance

Supporting symptoms include the following:

- Altered stool frequency
- Altered stool form
- Altered stool passage (straining and/or urgency)
- Mucorrhea
- Abdominal bloating or subjective distention

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## IBS – Case Relevant Literature

- Diarrhea, Constipation, Bloating<sup>2</sup>
- Defecation commonly improves pain<sup>1,2</sup>
- Epidemiologic associations with dyspepsia, heartburn, nausea, and vomiting noted<sup>1</sup>
- Pain most frequently in LLQ<sup>1</sup>
- PE: Patients often tense or anxious
- Stress-Related

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## IBS Management

- Common Stressors-
  - VARIABLE: lactose, fructose, fiber, caffeine, carbonated beverages, alcohol, fatty diets, large meals, anxiety.
- Dietary Modification
- CBT<sup>3</sup>
- Pharmacotherapy: TCA's, Tegaserod for constipation, antispasmodics

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## Pharmacotherapy

- Drug therapy is directed toward the dominant symptoms.
- Anticholinergic drugs eg, hyoscyamine may be used for their antispasmodic effects

In patients with diarrhoea, oral diphenoxylate or loperamide may be given before meals. The dose of loperamide should be titrated upward to reduce diarrhea while avoiding constipation

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## Pharmacotherapy...

- For many patients, tricyclic antidepressants (TCAs) help relieve symptoms of diarrhea, abdominal pain, and bloating.
- These drugs are thought to reduce pain by down-regulating the activity of spinal cord and cortical afferent pathways arriving from the intestine.
- Secondary amine TCAs (eg, nortriptyline, desipramine) are often better tolerated than parent tertiary amines (eg, amitriptyline, imipramine, doxepin) because of fewer anticholinergic, sedating antihistaminic, and  $\alpha$ -adrenergic adverse effects.

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## Pharmacotherapy...

- Serotonin receptor modulation may be of benefit. *Tegaserod*, a 5HT<sub>4</sub> agonist, stimulates motility and improves constipation
- SSRIs are also useful, particularly for patients with anxiety or an affective disorder, but may exacerbate diarrhea.

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## Pharmacotherapy...

- Preliminary data suggest that certain probiotics (eg, *Bifidobacterium infantis*) improve IBS symptoms, particularly bloating. The beneficial effects of probiotics are not generic to the entire species but specific to certain strains.
- Certain aromatic oils (carminatives) can relax smooth muscle and relieve pain caused by cramps in some patients. Peppermint oil is the most commonly used agent in this class

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