Constipation

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Constipation

- Abnormally infrequent and difficult passage of feces through the lower GI tract
- Symptom, not a disease
- Disorder of movement through the colon and/or rectum
- Can be caused by a variety of diseases or drugs

Causes of constipation

1. In most cases of chronic constipation, no specific cause is found (chronic idiopathic constipation)

2. Lifestyle Factors
   a) Inadequate fluid intake
   b) Decreased food intake
   c) Inappropriate bowel habits
   d) Immobility

3. Medications

4. Endocrine and Metabolic disorders
   a) Hypothyroidism
   b) Hypercalcemia
   c) Hypokalemia
   d) Pheochromocytoma

Causes of constipation

5. **Neurologic**
   a) Parkinson's disease
   b) Multiple sclerosis
   c) Spinal lesions
   d) Damage to sacral parasympathetic nerves
   e) Autonomic neuropathy (Diabetes mellitus)
6. **Psychological**
   a) Depression
   b) Eating disorders (e.g., anorexia nervosa)
7. **GI disorders:**
   a) Irritable bowel syndrome
   b) Diverticulitis
   c) Hemorrhoids and anal fissures
   d) Tumors
   e) Hernia
   f) Hirschsprung's disease.
8. **Pregnancy**

Drugs causing constipation

1) NSAIDs (inhibit prostaglandin synthesis)
2) Opiates: Orally administered opiates have greater inhibitory effect than parenterally administered agents
3) Anticholinergics
4) Antihistamines
5) Antiparkinsonian agents (e.g., benztropine or trihexyphenidyl)
6) Phenothiazines
7) Tricyclic antidepressants
8) Antacids containing calcium carbonate or aluminum hydroxide
9) Barium sulfate
10) Calcium channel blockers
11) Clonidine
12) Diuretics (nonpotassium-sparing)
13) Ganglionic blockers
14) Iron preparations
15) Muscle blockers (D - tubocurarine, succinylcholine)

Mechanism of drug-induced constipation

1. **Drugs with anticholinergic action**

GIT motility is under parasympathetic (cholinergic) control.

Parasympathetic stimulation → ↑motility

Drugs with anti-cholinergic effect (whether it is their main action or a side effect) →↓motility → constipation

Mechanism of drug-induced constipation

2. Opioids:

Opioids cause constipation by:

A) Increasing the smooth muscle tone, suppressing forward peristalsis, raising sphincter tone at the ileo-cecal valve and anal sphincter. This delays passage of feces through the GIT → increase in absorption of electrolytes and water in the small intestine and colon → constipation

B) Reducing sensitivity to rectal distension.

Mechanism of drug-induced constipation

3. Electrolyte disturbance as hypokalemia or hypercalcemia

4. Laxative abuse (leads to atonic intestine)

Treatment of constipation

General measures:

Definition: Fiber is that part of food that resists enzymatic digestion

Effect of fiber: Fiber reaches the colon unchanged.

- Colonic bacteria → Fermentation →
  - Short-chain fatty acids (→ prokinetic effect)

1) Increase the amount of **fiber** consumed daily fruits, vegetables, bran and cereals).
   - Increased bacterial mass (→ increased stool bulk).
   - Fiber that is not fermented → osmotic effect →increases stool bulk.
2. Increasing **fluid** intake.
3. Regulation of bowel habits
4. Regular exercise.
5. Treatment of the cause
6. For drug causes of constipation, a non constipating alternatives should be used. If no alternatives exist, lower the dose.

Treatment of constipation

- If general measures alone are inadequate or not applicable (*e.g.*, because of old age), they may be supplemented with bulk-forming agents, osmotic laxatives or stimulant laxatives.
- When stimulant laxatives are used, they should be administered at the lowest effective dosage and for the shortest period of time to avoid abuse

Definitions

Laxatives	Cathartics
Drugs that help evacuation of formed fecal material from the rectum	Drugs that help evacuation of unformed, usually watery fecal material from the entire colon.

Drug treatment of constipation (laxatives)

General indications:

1. Fecal impaction
2. Constipation associated with illness, surgery, pregnancy or poor diet
3. Drug-induced constipation
4. Conditions where bowel strain is undesirable
5. Preparation for surgery or investigations involving the GIT (e.g. sigmoidoscopy)

Classification of laxatives

1. Bulk-forming laxatives
2. Stimulant laxatives
3. Osmotic laxatives
4. Emollient laxatives (fecal softeners)
5. Lubricants

1 Bulk-forming agents (active after 12-36h)

Drugs: (taken as granules, powders or tablets)

1. Methylcellulose
2. Bran
3. Psyllium

Mechanism of action of bulk-forming agents:

They increase stool bulk and water content (make stools bulky (→ stimulate peristalsis) and soft → easy to pass) (similar to natural fiber)

Bulk-forming agents (cont.) (active after 12-36h)

Indications:

1. They are the first-line treatment of constipation
2. Conditions where dietary intake of fibers can not be increased

Precautions:

- Adequate fluid intake to avoid intestinal obstruction

Adverse effects of bulk-forming laxatives:

1. Abdominal distension (due to fermentation).
2. Intestinal obstruction when not consumed with sufficient fluid

Contraindications:

1. Atony of the colon
2. Intestinal obstruction
3. Fecal impaction (should be corrected before administration of fiber)
4. Immobility

2. Stimulant (irritant) laxatives

Dosage forms:

Bisacodyl	**Oral and rectal suppository**
Sodium picosulfate	Oral
Senna and Cascara	Oral
Castor oil	Oral

Mechanism of action and classification of stimulant (irritant) laxatives

- They are given in an ***inactive*** form → hydrolyzed in the GIT into active forms → GIT irritation → modify permeability of the mucosal cells → ↑ fluid and electrolyte secretion in the GIT → distension → evacuation of soft (or liquid) bulky stools. They probably cause direct stimulation of the enteric nerves.

- **According to the site of GIT irritation they are classified into:**

1. Small bowel irritant (hydrolysed in the small intestine by the action of lipases): castor oil
2. Large bowel irritants (hydrolyzed by colonic bacteria):
   a) Bisacodyl and Sodium picosulfate
   b) Senna and Cascara

Stimulant (irritant) laxatives (cont.)

Indications of large bowel irritants:

a) *Bisacodyl and Sodium picosulfate*
b) *Senna and Cascara*

1. Prevention of straining at stool following surgery, myocardial infarction or stroke
2. Painful diseases of the anus, e.g., fissure or hemorrhoids.

Stimulant (irritant) laxatives

1. Bisacodyl and sodium picosulfate:

Dosage forms:

1. Oral (the laxative effects after a dose occurs after 6 – 12 hours; taken at bedtime, it will produce its effect the next morning)
2. Rectal suppository (for bisacodyl only – the laxative effect occurs within 30 to 60 min.)

Indications: (also for cascara and senna)

1. Should not be used for more than 10 consecutive days (due to the possibility of developing atonic colon)
2. Preparation before diagnostic procedures involving the GIT

Stimulant laxatives

Bisacodyl and sodium picosulfate

Adverse effects:

1. Abdominal cramps after each dose
2. Over dosage → catharsis and fluid and electrolyte disturbances.
3. Can damage mucosa and cause inflammation in the colon.
4. Atonic colon (following years of use)

Contraindications:

1. Intestinal obstruction

Stimulant laxatives

2. Cascara and Senna

Dosage forms:

Oral (the laxative effects after a dose occurs after 6 – 12 hours; taken at bedtime, it will produce its effect the next morning)

Adverse effects of long-term use;

- ✓ Abdominal cramps after each dose
- ✓ Over dosage → catharsis and fluid and electrolyte disturbances.
- ✓ Pigmentation of the colonic mucosa (*melanosis coli* 4 – 9 months of use
- ✓ Atonic colon (years of use)

Contraindications:

- ✓ Breast feeding (active compounds are absorbed to a variable degree from the colon and excreted in breast milk)
- ✓ Intestinal obstruction

Stimulant laxatives

3. Castor Oil:

Dosage form:

Oral in a liquid form (laxative effect occurs after 1 – 3h)

Adverse effects:

1. Unpleasant taste
2. Damage to intestinal epithelium and enteric neurons

Uses:

Strong purgative → evacuation of the bowel before surgery and diagnostic procedures

Contraindications:

1. Intestinal obstruction

3 Osmotic laxatives

1. Saline laxatives (have cathartic action in large doses)

A. Magnesium salts (sulfate, hydroxide or citrate)
B. Sodium phosphate

Mechanism of action:

Poorly absorbed → water retention (osmotic effect) →soft bulky stools → ↑peristalsis → relief of constipation

Magnesium-containing laxatives may stimulate the release of **cholecystokinin**, which leads to intraluminal fluid and electrolyte accumulation and to increased intestinal motility

Uses:

- Enema (causes bowel evacuation after 30 min)
- Oral forms (cause bowel evacuation after 2-5h)

Both forms are used for intestinal evacuation before abdominal radiological procedures, sigmoidoscopy or surgery (cathartics)

Osmotic laxatives

Saline laxatives

Adverse effects:

1. Flatulence, abdominal cramps, diarrhea
2. Intravascular volume depletion
3. Electrolyte disturbances

Contraindications:

1. Renal insufficiency
2. Severe cardiac disease
3. Preexisting electrolyte abnormalities
4. Patients on diuretic therapy

Osmotic laxatives

2. Non-digestible sugars and alcohols

1. Lactulose (disaccharide of galactose and fructose that resists intestinal disaccharidase activity)
2. Sorbitol (monosaccharide)

Mechanism of action:

Lactulose → metabolized by colonic bacteria into short chain fatty acids → osmotic effect → stimulate propulsive activity

Adverse effects:

1. Abdominal distention
2. Diarrhea

Osmotic laxatives (cont.)

Uses:

- **Lactulose: (24-48h)**
  1. Used for treatment of hepatic encephalopathy (↓ blood ammonia by lowering fecal pH →↓growth of ammonia-producing bacteria and conversion of ammonia in the colon to ammonium ion).
  2. Constipation in the elderly patient
  3. Alternative for acute constipation
- **Sorbitol:**

1. Chronic constipation

Osmotic laxatives

3. Polyethylene Glycol-Electrolyte Solutions.

Mechanism of action:

Poorly absorbed, and retained in the lumen of the gut → osmotic effect → increase water content of stools.

Uses:

1. **Cathartic:** high doses.

2. **Laxative:** small oral doses

Osmotic laxatives

4. Glycerin

Dosage form:

Suppository (laxative effect > 30 min.)

Mechanism of action:

Osmotic effect in the rectum.

Adverse effects:

Occasional rectal irritation.

Uses:

Intermittent constipation in children.

4. Fecal softeners/emollient laxatives

Mechanism of action:

1. Reduces surface tension of stools → increases penetration of fluids into feces → soft bulky stools
2. **Docusate salts (sodium or calcium)** (weak laxatives)
3. Stimulate intestinal fluid and electrolyte secretion (by altering mucosal permeability)

Dosage forms:

1. Oral form (active within 1-3 d)
2. Rectal form has a rapid onset of action but is contraindicated in hemorrhoids and anal fissure.

Uses:

Used in hospitalized patients following myocardial infarction or surgery, when straining at defecation should be avoided but activity and fluid intake may be restricted.

Fecal softeners/emollient laxatives (cont.)

2. **Mineral oil:**

Mechanism of action:

1. Indigestible and with minimal absorption. Coat stool and allow easier passage.
2. Inhibit colonic absorption of water → increasing stool weight and decrease stool transit time.

Dosage forms:

Oral or rectal. Laxative effect is noted after 2 or 3 days of oral use.

Indications:

Similar to docusates

Fecal softeners/emollient laxatives

Mineral oil:

Adverse effects:

1. May be absorbed systemically → foreign-body reaction in lymphoid tissue.
2. Decreases absorption of fat-soluble vitamins (A, D, E, and K)
3. When given orally, mineral oil may leak from the anal sphincter.

New agents

Lubiprostone

Mechanism of action:

Opening of chloride channels locally in the GI luminal epithelium, which stimulates chloride-rich intestinal fluid secretion and shortens GI transit time

Uses:

Chronic idiopathic constipation in adults

Adverse effects:

1. Headache
2. Diarrhea, and nausea, as a result of delayed gastric emptying.