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Module: Constipation and Diarrhea

Learning Objectives

Attitudes

- Understand the impact of changes in bowel function on quality of life
- Be aware that there are many iatrogenic causes of constipation and diarrhea that may be particularly applicable in palliative care patient populations

Knowledge

- Describe the normal physiology of bowel regularity and name the factors that contribute to constipation and diarrhea
- List the management options for constipation and diarrhea and describe the mechanisms of action of each
- Describe the potential adverse effects of treatments for constipation and diarrhea
- Describe your approach to a patient with bowel habit abnormalities including assessment and potential treatments and your rationale for your treatment strategy

Skills

- Effectively evaluate and manage constipation in palliative care patient populations
- Effectively evaluate and manage diarrhea in palliative care patient populations

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Constipation

Definition:

- Acute: Less than six months; decrease in frequency or increase in difficulty initiating a bowel movement.
- Chronic: Longer than six months; fewer than three bowel movements per week. Patients may also complain of increased straining or incomplete evacuation.

Bowel Function:

Four interrelated factors contribute to bowel function: (1) water content of stool, (2) gut motility, (3) solid stool content (such as fiber and bacteria), and (4) resistance (or lack thereof) to passage of stool.

1. Water content—While 8-9L of fluid enters the gut, the majority is absorbed in the small bowel and only 1 L of fluid is released from the terminal ileum to the colon. Water is further absorbed by the colon so that daily stool content is 80-120 g/ 24 hours, a small fraction of what entered the gut. Variations above or below this value by 100 ml/ day led to diarrhea or constipation, respectively. Fast transit results in less water being absorbed (diarrhea). Slow gut transit results in more water being absorbed (constipation).

2. Motility—Gut motility is affected by extrinsic nerve stimulation and intrinsic systems speeding up or slowing down the gut. Greater motility is associated with looser stools (less water absorbed) and decreased motility with harder stools (more water absorbed).

- **Extrinsic system**
    - Sympathetic outflow: T5–L2: inhibitory function via noradrenaline to decrease peristalsis, gut fluid secretion and blood flow *(Figure 1)*
    - Parasympathetic outflow: cranial distribution via Vagus nerve (stomach-splenic flexure); Pelvic (sacral) nerves S2-4 (descending colon to anus): promotes peristalsis, gut fluid secretion, blood flow, and inhibits ileocecal and anal sphincters
    - Supratentorial control: medial prefrontal and anterior cingulate gyrus: timing and initiation of defecation
- **Intrinsic system**
    - Binding of certain gut receptors increases gut motility (acetylcholine, motilin), and others decrease motility (mu [opioid] receptors, dopamine). Nerve plexi in the wall of the gut responds to signals from these and other receptors. Mechanical stretch stimulates motility.
        - Myenteric Plexus: Main plexus to control peristalsis within the GI tract.
        - Meissner (Submucosal) Plexus: controls secretory activity and blood flow within the GI tract

3. **Stool volume**—Increased stool volume results in increased motility (up to a point). When the diet is lacking in fiber, bulk fiber can alleviate constipation by increasing stool volume. However, excessive gut dilation impedes motility. Bulk laxatives, especially when taken with inadequate water or when there is a primary motility disorder, can result in large impactions.

4. **Resistance to stool passage**—Mechanical obstruction, pain with defecation (and resulting anal tightening), and pelvic floor dyssynergia interfere with stool passage. Conversely, lubricants (mineral oil enemas) and detergent laxatives (docusate) may reduce resistance and ease stool passage.

Symptoms Commonly Associated with Constipation

- Increased passage of gas
- Abdominal pain; rectal pain
- Change in stool caliber
- Oozing of liquid or stool (fecal incontinence)
- Anorexia; early satiety; nausea

Constipation-Etiologies

Mechanical Obstruction

- Intraluminal: colon cancer
- Extraluminal: malignant ascites, peritoneal carcinomatosis (ovarian, colon), adhesions, volvulus

Drug-Induced

- Opioids: fentanyl and methadone may be less constipating than others
- Anticholinergics, tricyclic antidepressants, neuroleptics, antihistamines
- Chemotherapy, especially vinca drugs (vincristine, vinblastine)
- Serotonin-antagonist antiemetics
- Levodopa
- Calcium channel antagonists
- Iron, aluminum-containing antacids, barium
- Laxative abuse

Metabolic

- Hypercalcemia; hypokalemia
- Diabetes (neuropathy); hypothyroidism; uremia

Neurologic

- Spinal cord injury: in high (quadriplegic), constipation common. In cauda equina injury, bowel atony with severe constipation and overflow incontinence due to parasympathetic denervation of sigmoid and/or rectum
- Paraneoplastic autonomic neuropathy (such as in small cell lung cancer, carcinoid tumors)
- Polymyositis

- Parkinson's
- CVA
- Myotonic dystrophy

Miscellaneous

- Dehydration, inactivity, bed rest
- Confusion, depression
- Pain on defecating: hemorrhoids, anal fissure, infection
- Generalized pain
- Irritable bowel syndrome
- Loss of normal bowel routine
- Inadequate privacy or positioning (use of bed pan)
- Management

General Measures

- Prophylaxis whenever possible
- Reverse treatable causes
- Restore daily bowel routine
- Increase fluids and activity as much as tolerated by clinical condition

Assessment Includes:

- History: ask about duration of constipation, associated abdominal pain, straining, incomplete evacuation, frequency of BM, Bristol score in addition to medical, surgical, medication and dietary history.
- Physical examination: abdominal examination for distention, tympany, tenderness; rectal examination to assess cutaneo-anal reflex, fecal impaction, rectal stricture or mass, sphincter tone and contraction.
- Laboratory test review: exclude hypercalcemia, hypothyroidism, hypokalemia, diabetes as etiologies of secondary constipation.
- Imaging review: radiographs may be needed to exclude bowel obstruction and assess stool burden; CT scan can also assess megacolon or diverticulosis.
- Endoscopy- to rule out intraluminal cause of obstruction, in selected cases.

Drug Therapy—Drug Classification

Large-bowel stimulants (senna, bisacodyl, cascara, casanthranol, phenolphthalein)

- Directly increase bowel motility (require intact nerve plexi to work)
- Require transformation in liver (phenolphthalein, bisacodyl) or gut (senna, cascara)
- Common to have abdominal cramps and increased gas
- Senna, available as granules, pills, or liquids

Detergent Laxatives: (docusate, castor oil), also referred to as "wetting agents."

- Decrease surface tension, allow greater absorption of water/fat into dry stool
- Docusate a weak laxative (available as a sodium salt [Colace] or calcium salt [Surfak])
- There is abundant evidence suggesting that Colace should be utilized with conjunction with other agents.
- Docusate tastes bad (like concentrated soap). Liquid docusate should not be given by mouth. Pills may dissolve in patients' mouths. (Patients with dementia have a high risk, and docusate should be avoided in this population.)
- NOTE: Castor oil is not recommended owing to expense, bad taste, and bowel stimulant effects.

Bulk Laxatives: (psyllium, methylcellulose, polycarbophil, bran)

- Soluble and insoluble fiber supplements; inexpensive
- Require increased fluid intake for activity
- Abdominal cramps, increased gas, and allergic reactions can occur
- Best use in ambulatory patients with reasonable gut motility without bowel obstruction who can take large volumes of liquid
- NOTE: When used without increased fluid intake, constipation will worsen. Recommend no more than 30 grams/daily.

Osmotic Laxatives: (magnesium hydroxide, lactulose, sorbitol, glycerin suppositories, polyethylene glycol 3350 [GoLYTELY, MiraLAX], mannitol)

- Nonabsorbable sugars; work via osmotic effect in small and large bowel
- Lactulose, expensive, bad tasting, and increases abdominal gas; sorbitol, less expensive alternative; taste improved by mixing with apple juice
- Polyethylene glycol 3350, used as a bowel prep, can be given in smaller doses for constipation; MiraLAX (powder) has an advantage of being completely tasteless and can be added to any volume of fluids or food
- Glycerin suppositories osmotically draw in water and lubricate hard stool

Saline Laxatives: (magnesium citrate or phosphate, sodium phosphate)

- Contain poorly absorbed salts and work osmotically; increase gastric, pancreatic, and small-bowel secretions
- Note: Do not use magnesium or phosphate products in patients with renal failure; do not use sodium products in patients with heart, liver, or kidney failure.

Prokinetic Drugs

(bethanechol, neostigmine, metoclopramide)

- Decrease bowel transit time via increased motility. Of limited usefulness for colonic hypomotility due to toxic effects (bethanechol and neostigmine, cholinergic; metoclopramide, dopaminergic)
- Note: Do *not* recommend prokinetic drugs as neostigmine requires cardiopulmonary monitoring.

Lubricant (mineral oil)

- Can cause malabsorption, perianal irritation, and lipoid pneumonia aspiration with oral intake. Enemas may be useful for hard stools encountering resistance in passage.
- NOTE: Do not give orally or administer with docusate products.

Enemas And Suppositories

- Bisacodyl suppository (10 mg), action in 15 to 60 minutes • Glycerin suppository, action in 30 minutes
- Sodium phosphate enema (Fleet)
- Tap water, oil retention, soap suds enemas

Opioid Antagonists (indirect prokinetics in opioid-induced constipation)

- Naloxone: variable results; may induce opioid withdrawal
- Others: methylnaltrexone, naloxegol, nalmetidine, alvimopan; promising results in clinical trials

Other

- Octreotide has shown efficacy in managing constipation from the paraneoplastic autonomic neuropathy in small cell lung cancer.
- Intestinal secretagogues, such as Lubiprostone or Linaclotide (both increase luminal fluid secretion) can be used for chronic constipation.

Dietary Laxatives

Many home recipes and/or natural food stores have products that contain a combination of raisins, prunes, applesauce, figs, and dates, with or without senna (also called Power Pudding).

Trade Names: All available over the counter except for lactulose and polyethylene glycol products

- Metamucil, Perdiem, Fiberall (psyllium)
- Citrucel (methylcellulose)
- Fiberall, Fibercon (calcium polycarbophil)
- MOM (magnesium phosphate)
- Colace (docusate sodium); Surfak (docusate calcium)
- Senokot (senna); Senokot S (senna and docusate)
- Peri-Colace (docusate and casanthranol)
- Dulcolax (bisacodyl); Carter's (bisacodyl)
- Nature's Remedy (cascara)
- Ex-Lax, Feen-a-Mint (phenolphthalein); Correctol, Doxidan (phenolphthalein and docusate)
- Haley's M-O (mineral oil and magnesium hydroxide)
- Magnesium citrate (magnesium citrate)
- Chronulac, Cephulac (lactulose)
- Fleets Enema (sodium phosphate)

Drug Therapy— Management Plan

NOTE: The following agents should be avoided: mineral oil, castor oil, and phenolphthalein.

1. For prophylaxis (such as for a patient starting opioids) or for recent constipation start:

- Psyllium product, only if patient able to increase fluid intake
- Senna product, milk of magnesia, or docusate are all viable options
- Increase dose of each product as needed (no upper dose limit except MOM in patients with renal failure); if no bowel movement at eight to 12 Senokot doses per day or 60 to 80 mL of MOM per day, go to Number. 2.

2. For constipation refractory to Number 1, check for fecal impaction (see Number 4); start:

- Bisacodyl (Dulcolax) PO 5 mg, up to 3 tablets TID
- If no response, use one Dulcolax suppository.

3. For constipation refractory to Number 2, check for fecal impaction (see Number 4); start:

- Magnesium citrate, eight oz, or
- Lactulose, sorbitol, MiraLAX, or Fleet enema.

4. For patients with impaction:

- Use sedatives and analgesics to relieve stress and pain of disimpaction.
- Lubricate rectum; give glycerin suppository or oil-retention enema.
- Manually disimpact rectum.
- Give enemas to clear rectum.
- Increase daily oral laxative program.

Diarrhea

Definition:

Acute: Greater than 3 bowel movements per day or increase of stool weight to greater than 200g per day over less than 4 weeks

Chronic: Greater than 3 bowel movements per day or increase of stool weight to greater than 200g per day over greater than 4 weeks

It is important to consider the patient's characterization of bowel movements as many often complain of loose or watery stool without elevated stool weight. Further, fecal incontinence is also an important complication to consider in the patient with diarrhea, and once treated, fecal incontinence can also improve.

Pathophysiology

- As explained in the constipation section, approximately 10 L of fluid arrives in the jejunum daily, and following absorption by the small bowel, 800ml – 1000ml is received by the colon.
- Of that, the colon absorbs approximately 900ml/ 24 hours; therefore, feces carry 100ml of water.
- Diarrhea occurs when fecal water output increases above baseline by 100 ml. The broad etiologies of diarrhea either decrease absorption of water or increase water secretion.

Associated symptoms

- Fever
- Weight loss
- Abdominal pain
- Abdominal distention
- Orthostatic hypotension
- Decreased turgor
- Constipation

Etiologies

- **Infectious**: ruling out infection, especially nosocomial etiologies such as C difficile is imperative. Other bacterial sources include E coli, Salmonella, Shigella, Campylobacter jejuni (associated with Guillain-Barre syndrome), cholera should also be considered for acute diarrhea. Include also viral and protozoal etiologies in the differential.
- **Osmotic**: inactive particles draw water into the lumen and promote soft or loose stool. Lactose intolerance is an example and can develop at any stage in life. *** Sorbitol, as seen in in liquid suspensions of medications, can also contribute. Ingestion of mannitol, fructose and lactulose can also lead to osmotic diarrhea.
- **Secretory**: dysfunction of ion transporters due to infection or congenital pathology can lead to diarrhea.
- **Inflammation**: new onset IBD including Crohn's disease, Ulcerative colitis, or microscopic colitis can lead to diarrhea. Crohn's and UC can present with bloody diarrhea.
- **Overflow incontinence:** seen in patients with severe constipation.
- Surgery: reduced surface area after small bowel or colonic resection leads to decreased water absorption or predispose to small intestinal bacterial overgrowth (SIBO). Resection of the terminal ileum can lead to decreased bile acid resorption and bile acid diarrhea.
- **Malignancy**: neuroendocrine tumors of the small bowel (VIPoma, glucagonoma) can lead to diarrhea, but prevalence is rare.
- **Medications**: antibiotics, NSAIDs, SSRI, acid-reducing medications, colchicine, antihypertensives (beta-adrenergic receptor blockers)
- **Autoimmune**: hyperthyroidism, Celiac disease

Evaluation

- History: frequency, duration, volume, urgency, weight loss, stool characteristics (blood, oil, mucous), stool quality (watery, soft), pain with defecation, nocturnal presence, relationship to food, and associated incontinence. Travel history, medical history, medications, and surgeries, and radiation therapy should also be considered.

- Physical exam: abdominal exam (distention, pain), rectal exam (decreased sphincter tone)
- Labs: obtain comprehensive labs including CMP, CBC; stool culture including C difficile testing
- Imaging: radiographs to ensure patient does not have ileus or toxic megacolon. CT may be necessary in selected patients.
- Blood or severe illness may require investigation with flexible sigmoidoscopy or colonoscopy and biopsy.

Drug Therapy-Drug Classification

Once infectious causes, mechanical problems and medication induced etiologies have been eliminated, diarrhea can be treated medically.

- **Loperamide (Imodium):** is a mu-opioid receptor agonist and decreases peristalsis, decreases fluid secretion, delays colonic transit time and increases intestinal absorption.
- **Diphenoxylate (Lomotil):** is an opiate receptor agonist and decreases peristalsis and constricts sphincters
- **Bismuth Subsalicylate**: Exact mechanism is not fully understood, but does prevent intestinal secretion, promotes fluid and electrolyte re-absorption.
- **Bulking agents/Fiber supplementation**: Aids in absorbing water into the GI tract to solidify loose stool
- **Octreotide**: Binds to somatostatin receptors, which sets of multiple downstream effects. This includes acting as an anti-diarrheal by decreasing intestinal motility and promoting absorption of fluids

Management

In general management will depend on the underlying etiology.

- **C difficile**: following accurate testing, begin Vancomycin 125mg PO QID for 10 days or Fidaxomicin 200 mg twice daily for 10 days. Recurrent C difficile infection requires treatment management by gastroenterology or infectious disease teams.
- **Other infections**: after evaluation (travel history, bloodwork, CT) and accurate diagnosis some gastrointestinal infections will need antibiotics while others will need supportive care.
- **Medication induced**: thorough evaluation of medication list and discontinuing or decreasing the dose of any medications that may be causing diarrhea.
- **Overflow incontinence**: treatment of underlying constipation/impaction as per previous section.
- **Cancer related**: either to treatment or therapy. After full evaluation and an underlying complication of the cancer or infection has been ruled out, anti-diarrheal medications can be considered. Octreotide is an option that may be pursued for severe diarrhea that does not respond to other agents.
- **Enteral feedings**: consider switching to a different formula osmolality or changing the rate of administration. RCT's indicate that there are instances where adding soluble fiber to the feedings may improve diarrhea.

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Case Scenarios

Case 1: Management of Opioid-Induced Constipation in a Palliative Care Patient

Patient Presentation: A 65-year-old male with metastatic prostate cancer is admitted for evaluation of decreased, hardened bowel movements. He is on scheduled opioid therapy for severe bone pain due to metastatic disease. Following an acute workup, he is diagnosed with opioid-induced constipation (OIC). You are consulted to initiate an appropriate bowel regimen.

Management Approach:

1. **Assess Contributing Factors**:
   - Rule out bowel obstruction, impaction, or other secondary causes.
   - Evaluate hydration status, diet, and mobility.

2. **Pharmacologic Management:**
   - First-line: Stimulant laxatives (e.g., senna or bisacodyl) with or without stool softeners (e.g., docusate).
     - Osmotic laxatives: Polyethylene glycol (PEG) or lactulose if additional softening is needed.
     - Peripherally Acting Mu-Opioid Receptor Antagonists (PAMORAs): Consider methylnaltrexone if refractory to standard laxatives and no contraindications exist.

3. **Non-Pharmacologic Measures:**
   - Encourage hydration, dietary fiber (if tolerated), and mobility as appropriate.
   - Consider rectal interventions (suppositories or enemas) for severe cases.

4. **Palliative Considerations:**
   - Balance symptom relief with patient comfort.
   - Regularly reassess pain control and constipation severity.

Case 2: Palliative Management of Diarrhea in a Patient with Metastatic Colon Cancer

Patient Presentation: A 70-year-old female with metastatic colon cancer presents with multiple loose, non-bloody bowel movements persisting over the past several weeks.

1. **Clinical Considerations:**
   - Given the chronic nature of her symptoms (>4 weeks), a thorough evaluation should rule out common causes, including infectious etiologies (e.g., *Clostridioides difficile*), medication-related effects (e.g., chemotherapy-induced diarrhea), and malabsorption syndromes. Additionally, the impact of diarrhea on quality of life, hydration status, and overall symptom burden should be assessed.

2. **Evaluation:**
   - **History:** Stool frequency, consistency, volume, nocturnal presence, associated pain, weight loss, urgency, incontinence, and medication/surgical history.

- **Physical Exam:** Abdominal distention, tenderness, rectal tone assessment (fecal incontinence vs. overflow).
- **Laboratory Tests:** CBC, CMP (assess for dehydration and electrolyte imbalances), *C. difficile* PCR, stool osmolality/gap (if needed).
- **Imaging (if indicated):** Abdominal X-ray for ileus, CT if suspected obstruction, and endoscopic evaluation for unexplained chronic symptoms.

3. **Management:**
   - **Supportive Care:** Optimize hydration and electrolyte balance.
   - **First-Line Therapy:** Loperamide or diphenoxylate/atropine for symptomatic control.
   - **Alternative/Adjunctive Therapies:**
     - **Bismuth subsalicylate:** Mild anti-secretory effects.
     - **Octreotide:** For refractory secretory diarrhea (e.g., chemotherapy-induced or neuroendocrine-related).
     - **Fiber/Bulking Agents:** May help if diarrhea is worsened by colonic dysmotility.

4. **Palliative Considerations:**
   - Engage in shared decision-making to align treatment with patient goals.
   - Consider the burden of further diagnostic testing versus focusing on symptom relief.
   - Address fecal incontinence, which can improve with appropriate diarrhea management