Ministry of Healthcare of Ukraine
Poltava State Medical University

GUIDELINES
FOR STUDENTS
INDEPENDENT WORK
IN THE PRACTICAL CLASSES PREPARING

Academic discipline	Internal medicine
Module	Current practice of internal medicine
Content module	Management of the patients with main symptoms and syndromes in gastroenterology clinic
Study subject	**Management of the patients with diarrhea** **Management of the patients with constipation**
Course	VI
Faculty	of foreign students training

1. **Relevance of the topic**: Diarrhea lasting >4 weeks warrants evaluation to exclude serious underlying pathology. In contrast to acute diarrhea, most of the causes of chronic diarrhea are noninfectious. The classification of chronic diarrhea by pathophysiologic mechanism facilitates a rational approach to management, although many diseases cause diarrhea by more than one mechanism. Constipation is a common complaint in clinical practice and usually refers to persistent, difficult, infrequent, or seemingly incomplete defecation. Because of the wide range of normal bowel habits, constipation is difficult to define precisely. Most persons have at least three bowel movements per week; however, low stool frequency alone is not the sole criterion for the diagnosis of constipation. Many constipated patients have a normal frequency of defecation but complain of excessive straining, hard stools, lower abdominal fullness, or a sense of incomplete evacuation. The individual patient‟s symptoms must be analyzed in detail to ascertain what is meant by "constipation" or "difficulty" with defecation.

2. The main goal: To be able to choose and put into practice the approach to the patient with diarrhea and constipation, to put diagnosis and to determine tactics of treatment and prophylaxis. Specific goals:

- To select the information indicating the cause of diarrhea and constipation;
- To create a scheme of diagnostic search;
- To identify the other signs of diseases that runs with diarrhea and constipation (general examination, palpation, percussion, auscultation);
- To analyze and interpret the changes in the results of the laboratory and instrumental methods of investigation, depending on the course of the disease;
- To formulate and justify a preliminary diagnosis according to modern classifications;
- To conduct differential diagnostics of diseases with the diarrhea and constipation;
- To develop a strategy of treatment depending on the disease and the existing complications;
- To provide medical care;
- To assess the patient's prognosis and to propose a plan of preventive actions;
- To apply deontological communication skills with patients.

3. **Basic knowledge, abilities, skills (interdisciplinary integration)**

Discipline	To know	To be able to
Anatomy	The structure of the gastrointestinal tract, blood supply, innervation	
Histology	The structure of the esophagus, stomach, intestines, liver, gallbladder, pancreas in health and disease	To interpret results of endoscopy, USI and biopsy
Regional anatomy	Interposition of the gastrointestinal organs	
Physiology	Indicators of gastrointestinal tract function, its value	To determine the function of gastrointestinal organs
Morbid anatomy	Changes in the structure of gastrointestibal tract organs in pathology	
Radiology	Radiological changes at pathology of gastrointestinal organs	Analyze the radiological picture of the chest cavity and abdominal cavity
Propaedeutic therapy	Diseases with abdominal pain as leading symptom	Perform an objective examination of the patient, analyze the clinical and laboratory results
Pharmacology	The mechanism of action, indications and contraindications for	Prescribe the drugs of these groups

	the IPP, H2-blockers, antacids, prokinetics, antibiotics, enzymes, pain killers, antispasmodics	

4. Do the tasks for independent work during preparation for classes.

4.1. The list of key terms, parameters, characteristics:

Term	Definition
Gluten enteropathy	is a chronic progressive immune-mediated intestinal inflammatory disease that is characterized by genetically determined *gluten intolerance*, diffuse atrophy of mucous membrane, and leads to generalized malabsorption.
EMA, anti-tTG	antiendomysial and anti-tissue transglutaminase antibodies that are associated with celiac disease
Irritable bowel syndrome	is a functional bowel disorder in which recurrent abdominal pain occurs at least 1 day per week during the past 3 months and is associated with defecation or a change in bowel habits.
Ulcerative colitis	is a heterogeneous chronic inflammatory bowel disorder that may affect the colon and rectum.
Crohn‟s disease	is a heterogeneous inflammatory transmural, granulomatosis bowel disorder that may affect different sites of the gastrointestinal tract.
Toxic megacolon	is the clinical term for an acute toxic colitis with dilatation of the colon which occurs when inflammation spreads into the deeper layers of colon.

4.2. Theoretical questions for the lesson:

1. Give the definitions of celiac disease, enteropathy, non-specific colitis, Crohn‟s disease and irritable bowel syndrome.
2. Specify the risk factors of celiac disease, enteropathy, non-specific colitis, Crohn‟s disease and irritable bowel syndrome.
3. Name the pathophysiological mechanisms of celiac disease, enteropathy, non-specific colitis, Crohn‟s disease and irritable bowel syndrome.
4. Name the diagnostic criteria of celiac disease, non-specific colitis, Crohn‟s disease and irritable bowel syndrome.
5. What are the endoscopic characteristics of celiac disease, enteropathy, non-specific colitis, Crohn‟s disease and irritable bowel syndrome?
6. Modern classification of celiac disease, enteropathy, non-specific colitis, Crohn‟s disease and irritable bowel syndrome.
7. Specify the principles and features of celiac disease, enteropathy, non-specific colitis, Crohn‟s disease and irritable bowel syndrome pharmacotherapy according to modern recommendations.
8. What lifestyle modifications should be recommended for patients with celiac disease, enteropathy, non-specific colitis, Crohn‟s disease and irritable bowel syndrome?

4.3. Practical tasks that are performed in class:

1. Etiology of celiac disease is:

1) bacteria

2) NSAIDs
3) geneticreason
4) chemical damage
2. The only available treatment for celiac disease is:
1) a strict lifelong gluten-free diet
2) corticosteroids
3) probiotics
4) antibiotics
3. Irritable bowel syndrome is a functional bowel disorder in which recurrent abdominal pain occurs:
1) at least 3 days per week during the past 1 months and is associated with defecation or a change in bowel habits. Symptom onset should occur at least 6 months before diagnosis and symptoms should be present during the last 3 months.
2) at least 1 day per week during the past 3 months and is associated with defecation or a change in bowel habits. Symptom onset should occur at least 6 months before diagnosis and symptoms should be present during the last 3 months
3) at least 1 day per week during the past 3 months and is associated with defecation or a change in bowel habits. Symptom onset should occur at least 9 months before diagnosis and symptoms should be present during the last 3 months.
4) at least 1 day per week during the past 3 months and is associated with defecation or a change in bowel habits. Symptom onset should occur at least 1 year before diagnosis and symptoms should be present during the last 6 months.
4. Inflammatory bowel disease refers to:
1) enteritis
2) IBS
3) ulcerative colitis and Crohn's disease
4) all mentioned
5. A cobblestone mucosa on lower endoscopy makes the doctor think about:
1) Non-specific ulcer colitis
2) Bacterial colitis
3) Crohn's disease
4) IBS
6. Transmural inflammation is distinctive feature for:
1) Non-specific ulcer colitis
2) Bacterial colitis
3) Crohn's disease
4) IBS
7. 5-aminosalicylic acids include:
1) prednisolone
2) budesonide
3) mesalazine
4) azathioprine
8. Anti-TNF-α antibodies include:
1) budesonide
2) sulfasalazine
3) azathioprine
4) infliximab
9. Drug therapy of the acute flare of Crohn‟s Disease, mild activity***:***
1) "Salofalk" 3-4,5 g/day
2) "Budenofalk" 60 mg/day
3) Prednisolone 60 mg/day
4) Azathioprine 2-3 mg/kg/day

10. Topical forms in proctitis and left-sided ulcerative colitis can be treated with:

1) Budesonide per os 8-12 mg a day
2) Budesonide per rectum 2-4 mg a day
3) Antibiotics
4) Mesalazine per rectum 3-4 mg/kg/day

Topic Content

MANAGEMENT OF PATIENT WITH DIARRHEA

Diarrhea lasting >4 weeks warrants evaluation to exclude serious underlying pathology. In contrast to acute diarrhea, most of the causes of chronic diarrhea are noninfectious. The classification of chronic diarrhea by pathophysiologic mechanism facilitates a rational approach to management, although many diseases cause diarrhea by more than one mechanism.

Secretory diarrheas are due to derangements in fluid and electrolyte transport across the enterocolonic mucosa. They are characterized clinically by watery, large-volume fecal outputs that are typically painless and persist with fasting. Because there is no malabsorbed solute, stool osmolality is accounted for by normal endogenous electrolytes with no fecal osmotic gap.

MEDICATIONS. Side effects from regular ingestion of drugs and toxins are the most common secretory causes of chronic diarrhea. Hundreds of prescription and over-the-counter medications (see earlier section, "Acute Diarrhea, Other Causes") may produce diarrhea. Surreptitious or habitual use of stimulant laxatives (e.g., senna, cascara, bisacodyl, ricinoleic acid [castor oil]) must also be considered. Chronic ethanol consumption may cause a secretory-type diarrhea due to enterocyte injury with impaired sodium and water absorption as well as rapid transit and other alterations. Inadvertent ingestion of certain environmental toxins (e.g., arsenic) may lead to chronic rather than acute forms of diarrhea. Certain bacterial infections may occasionally persist and be associated with a secretory-type diarrhea.

BOWEL RESECTION, MUCOSAL DISEASE, OR ENTEROCOLIC FISTULA. These conditions may result in a secretory-type diarrhea because of inadequate surface for reabsorption of secreted fluids and electrolytes. Unlike other secretory diarrheas, this subset of conditions tends to worsen with eating. With disease (e.g., Crohn‟s ileitis) or resection of <100 cm of terminal ileum, dihydroxy bile acids may escape absorption and stimulate colonic secretion (cholerheic diarrhea). This mechanism may contribute to so-called idiopathic secretory diarrhea or bile acid diarrhea (BAD), in which bile acids are functionally malabsorbed from a normal-appearing terminal ileum. This idiopathic bile acid malabsorption (BAM) may account for an average of 40% of unexplained chronic diarrhea. Reduced negative feedback regulation of bile acid synthesis in hepatocytes by fibroblast growth factor 19 (FGF-19) produced by ileal enterocytes results in a degree of bile-acid synthesis that exceeds the normal capacity for ileal reabsorption, producing BAD. An alternative cause of BAD is a genetic variation in the receptor proteins (β-klotho and fibroblast growth factor 4) on the hepatocyte that normally mediate the effect of FGF-19. Dysfunction of these proteins prevents FGF-19 inhibition of hepatocyte bile acid synthesis. Partial bowel obstruction, ostomy stricture, or fecal impaction may paradoxically lead to increased fecal output due to fluid hypersecretion.

HORMONES. Although uncommon, the classic examples of secretory diarrhea are those mediated by hormones. Metastatic gastrointestinal carcinoid tumors or, rarely, primary bronchial carcinoids may produce watery diarrhea alone or as part of the carcinoid syndrome that comprises episodic flushing, wheezing, dyspnea, and right-sided valvular heart disease. Diarrhea is due to the release into the circulation of potent intestinal secretagogues including serotonin, histamine, prostaglandins, and various kinins. Pellagra-like skin lesions may rarely occur as the result of serotonin overproduction with niacin depletion. Gastrinoma, one of the most common neuroendocrine tumors, most typically presents with refractory peptic ulcers, but diarrhea occurs in up to one-third of cases and may be the only clinical manifestation in 10%. While other secretagogues released with gastrin may play a role, the diarrhea most often results from fat

maldigestion owing to pancreatic enzyme inactivation by low intraduodenal pH. The watery diarrhea hypokalemia achlorhydria syndrome, also called pancreatic cholera, is due to a non-β cell pancreatic adenoma, referred to as a VIPoma, that secretes VIP and a host of other peptide hormones including pancreatic polypeptide, secretin, gastrin, gastrin-inhibitory polypeptide (also called glucose-dependent insulinotropic peptide), neurotensin, calcitonin, and prostaglandins. The secretory diarrhea is often massive with stool volumes >3 L/d; daily volumes as high as 20 L have been reported. Life-threatening dehydration; neuromuscular dysfunction from associated hypokalemia, hypomagnesemia, or hypercalcemia; flushing; and hyperglycemia may accompany a VIPoma. Medullary carcinoma of the thyroid may present with watery diarrhea caused by calcitonin, other secretory peptides, or prostaglandins. Prominent diarrhea is often associated with metastatic disease and poor prognosis. Systemic mastocytosis, which may be associated with the skin lesion urticaria pigmentosa, may cause diarrhea that is either secretory and mediated by histamine or inflammatory due to intestinal infiltration by mast cells. Large colorectal villous adenomas may rarely be associated with a secretory diarrhea that may cause hypokalemia, can be inhibited by NSAIDs, and are apparently mediated by prostaglandins.

CONGENITAL DEFECTS IN ION ABSORPTION. Rarely, defects in specific carriers associated with ion absorption cause watery diarrhea from birth. These disorders include defective Cl–/HCO3– exchange (congenital chloridorrhea) with alkalosis (which results from a mutated DRA [down-regulated in adenoma] gene) and defective Na+/H+ exchange (congenital sodium diarrhea), which results from a mutation in the NHE3 (sodium-hydrogen exchanger) gene and results in acidosis. Some hormone deficiencies may be associated with watery diarrhea, such as occurs with adrenocortical insufficiency (Addison‟s disease) that may be accompanied by skin hyperpigmentation.

Osmotic diarrhea occurs when ingested, poorly absorbable, osmotically active solutes draw enough fluid into the lumen to exceed the reabsorptive capacity of the colon. Fecal water output increases in proportion to such a solute load. Osmotic diarrhea characteristically ceases with fasting or with discontinuation of the causative agent.

OSMOTIC LAXATIVES. Ingestion of magnesium-containing antacids, health supplements, or laxatives may induce osmotic diarrhea typified by a stool osmotic gap (>50 mosmol/L): serum osmolarity (typically 290 mosmol/kg) – (2 × [fecal sodium + potassium concentration]). Measurement of fecal osmolarity is no longer recommended because, even when measured immediately after evacuation, it may be erroneous because carbohydrates are metabolized by colonic bacteria, causing an increase in osmolarity.

CARBOHYDRATE MALABSORPTION. Carbohydrate malabsorption due to acquired or congenital defects in brush-border disaccharidases and other enzymes leads to osmotic diarrhea with a low pH. One of the most common causes of chronic diarrhea in adults is lactase deficiency, which affects three-fourths of nonwhites worldwide and 5–30% of persons in the United States; the total lactose load at any one time influences the symptoms experienced. Most patients learn to avoid milk products without requiring treatment with enzyme supplements. Some sugars, such as sorbitol, lactulose, or fructose, are frequently malabsorbed, and diarrhea ensues with ingestion of medications, gum, or candies sweetened with these poorly or incompletely absorbed sugars.

WHEAT AND FODMAP INTOLERANCE. Chronic diarrhea, bloating, and abdominal pain are recognized as symptoms of nonceliac gluten intolerance (which is associated with impaired intestinal or colonic barrier function) and intolerance of fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs). The latter‟s effects represent the interaction between the GI microbiome and the nutrients.

Fat malabsorption may lead to greasy, foulsmelling, difficult-to-flush diarrhea often associated with weight loss and nutritional deficiencies due to concomitant malabsorption of amino acids and vitamins. Increased fecal output is caused by the osmotic effects of fatty acids, especially after bacterial hydroxylation, and, to a lesser extent, by the neutral fat. Quantitatively, steatorrhea is defined as stool fat exceeding the normal 7 g/d; rapid-transit diarrhea may result in

fecal fat up to 14 g/d; daily fecal fat averages 15–25 g with small-intestinal diseases and is often >32 g with pancreatic exocrine insufficiency. Intraluminal maldigestion, mucosal malabsorption, or lymphatic obstruction may produce steatorrhea.

INTRALUMINAL MALDIGESTION. This condition most commonly results from pancreatic exocrine insufficiency, which occurs when >90% of pancreatic secretory function is lost. Chronic pancreatitis, usually a sequel of ethanol abuse, most frequently causes pancreatic insufficiency. Other causes include cystic fibrosis; pancreatic duct obstruction; and, rarely, somatostatinoma. Bacterial overgrowth in the small intestine may deconjugate bile acids and alter micelle formation, impairing fat digestion; it occurs with stasis from a blind-loop, smallbowel diverticulum or dysmotility and is especially likely in the elderly. Finally, cirrhosis or biliary obstruction may lead to mild steatorrhea due to deficient intraluminal bile acid concentration. MUCOSAL MALABSORPTION. Mucosal malabsorption occurs from a variety of enteropathies, but it most commonly occurs from celiac disease. This gluten-sensitive enteropathy affects all ages and is characterized by villous atrophy and crypt hyperplasia in the proximal small bowel and can present with fatty diarrhea associated with multiple nutritional deficiencies of varying severity. Celiac disease is much more frequent than previously thought; it affects ∼1% of the population, frequently presents without steatorrhea, can mimic IBS, and has many other GI and extraintestinal manifestations. Tropical sprue may produce a similar histologic and clinical syndrome but occurs in residents of or travelers to tropical climates; abrupt onset and response to antibiotics suggest an infectious etiology. Whipple‟s disease, due to the bacillus Tropheryma whipplei and histiocytic infiltration of the smallbowel mucosa, is a less common cause of steatorrhea that most typically occurs in young or middle-aged men; it is frequently associated with arthralgias, fever, lymphadenopathy, and extreme fatigue, and it may affect the CNS and endocardium. A similar clinical and histologic picture results from Mycobacterium avium-intracellulare infection in patients with AIDS. Abetalipoproteinemia is a rare defect of chylomicron formation and fat malabsorption in children, associated with acanthocytic erythrocytes, ataxia, and retinitis pigmentosa. Several other conditions may cause mucosal malabsorption including infections, especially with protozoa such as Giardia; numerous medications (e.g., olmesartan, mycophenolate mofetil, colchicine, cholestyramine, neomycin); amyloidosis; and chronic ischemia.

POSTMUCOSAL LYMPHATIC OBSTRUCTION. The pathophysiology of this condition, which is due to the rare congenital intestinal lymphangiectasia or to acquired lymphatic obstruction secondary to trauma, tumor, cardiac disease or infection, leads to the unique constellation of fat malabsorption with enteric losses of protein (often causing edema) and lymphocytopenia. Carbohydrate and amino acid absorption are preserved.

<u>Inflammatory diarrheas</u> are generally accompanied by pain, fever, bleeding, or other manifestations of inflammation. The mechanism of diarrhea may not only be exudation but, depending on lesion site, may include fat malabsorption, disrupted fluid/ electrolyte absorption, and hypersecretion or hypermotility from release of cytokines and other inflammatory mediators. The unifying feature on stool analysis is the presence of leukocytes or leukocytederived proteins such as calprotectin. With severe inflammation, exudative protein loss can lead to anasarca (generalized edema). Any middle-aged or older person with chronic inflammatory-type diarrhea, especially with blood, should be carefully evaluated to exclude a colorectal tumor.

IDIOPATHIC INFLAMMATORY BOWEL DISEASE. The illnesses in this category, which include Crohn‟s disease and chronic ulcerative colitis, are among the most common organic causes of chronic diarrhea in adults and range in severity from mild to fulminant and life-threatening. They may be associated with uveitis, polyarthralgias, cholestatic liver disease (primary sclerosing cholangitis), and skin lesions (erythema nodosum, pyoderma gangrenosum). Microscopic colitis, including both lymphocytic and collagenous colitis, is an increasingly recognized cause of chronic watery diarrhea, especially in middle-aged women and those on NSAIDs, statins, proton pump inhibitors (PPIs), and selective serotonin reuptake inhibitors (SSRIs); biopsy of a normal-appearing colon is required for histologic diagnosis. It may coexist

with symptoms suggesting IBS or with celiac sprue or drug-induced enteropathy. It typically responds well to anti-inflammatory drugs (e.g., bismuth), to the opioid agonist loperamide, or to budesonide.

PRIMARY OR SECONDARY FORMS OF IMMUNODEFICIENCY. Immunodeficiency may lead to prolonged infectious diarrhea. With selective IgA deficiency or common variable hypogammaglobulinemia, diarrhea is particularly prevalent and often the result of giardiasis, bacterial overgrowth, or sprue.

EOSINOPHILIC GASTROENTERITIS Eosinophil infiltration of the mucosa, muscularis, or serosa at any level of the GI tract may cause diarrhea, pain, vomiting, or ascites. Affected patients often have an atopic history, Charcot-Leyden crystals due to extruded eosinophil contents may be seen on microscopic inspection of stool, and peripheral eosinophilia is present in 50–75% of patients. While hypersensitivity to certain foods occurs in adults, true food allergy causing chronic diarrhea is rare.

OTHER CAUSES Chronic inflammatory diarrhea may be caused by radiation enterocolitis, chronic graft-versus-host disease, Behçet‟s syndrome, and Cronkhite-Canada syndrome, among others.

Dysmotility Causes. Rapid transit may accompany many diarrheas as a secondary or contributing phenomenon, but primary dysmotility is an unusual etiology of true diarrhea. Stool features often suggest a secretory diarrhea, but mild steatorrhea of up to 14 g of fat per day can be produced by maldigestion from rapid transit alone. Hyperthyroidism, carcinoid syndrome, and certain drugs (e.g., prostaglandins, prokinetic agents) may produce hypermotility with resultant diarrhea. Primary visceral neuromyopathies or idiopathic acquired intestinal pseudoobstruction may lead to stasis with secondary bacterial overgrowth causing diarrhea. Diabetic diarrhea, often accompanied by peripheral and generalized autonomic neuropathies, may occur in part because of intestinal dysmotility. The exceedingly common IBS (10% point prevalence, 1–2% per year incidence) is characterized by disturbed intestinal and colonic motor and sensory responses to various stimuli. Symptoms of stool frequency typically cease at night, alternate with periods of constipation, are accompanied by abdominal pain relieved with defecation, and rarely result in weight loss.

Factitial diarrhea accounts for up to 15% of unexplained diarrheas referred to tertiary care centers. Either as a form of Munchausen syndrome (deception or self-injury for secondary gain) or eating disorders, some patients covertly self-administer laxatives alone or in combination with other medications (e.g., diuretics) or surreptitiously add water or urine to stool sent for analysis. Such patients are typically women, often with histories of psychiatric illness, and disproportionately from careers in health care. Hypotension and hypokalemia are common co-presenting features. The evaluation of such patients may be difficult: contamination of the stool with water or urine is suggested by very low or high stool osmolarity, respectively. Such patients often deny this possibility when confronted, but they do benefit from psychiatric counseling when they acknowledge their behavior.

Approach to the patient. The laboratory tools available to evaluate the very common problem of chronic diarrhea are extensive, and many are costly and invasive. As such, the diagnostic evaluation must be rationally directed by a careful history, including medications, and physical examination. When this strategy is unrevealing, simple triage tests are often warranted to direct the choice of more complex investigations. The history, physical examination, and routine blood studies should attempt to characterize the mechanism of diarrhea, identify diagnostically helpful associations, and assess the patient‟s fluid/electrolyte and nutritional status. Patients should be questioned about the onset, duration, pattern, aggravating (especially diet) and relieving factors, and stool characteristics of their diarrhea. The presence or absence of fecal incontinence, fever, weight loss, pain, certain exposures (travel, medications, contacts with diarrhea), and common extraintestinal manifestations (skin changes, arthralgias, oral aphthous ulcers) should be noted. A family history of IBD or sprue may indicate those possibilities. Physical findings may offer clues such as a thyroid mass, wheezing, heart murmurs, edema,

hepatomegaly, abdominal masses, lymphadenopathy, mucocutaneous abnormalities, perianal fistulas, or anal sphincter laxity. Peripheral blood leukocytosis, elevated sedimentation rate, or C-reactive protein suggests inflammation; anemia reflects blood loss or nutritional deficiencies; or eosinophilia may occur with parasitoses, neoplasia, collagen-vascular disease, allergy, or eosinophilic gastroenteritis. Blood chemistries may demonstrate electrolyte, hepatic, or other metabolic disturbances. Measuring IgA tissue transglutaminase antibodies may help detect celiac disease. Bile acid diarrhea is confirmed by a scintigraphic radiolabeled bile acid retention test; however, this is not available in many countries. Alternative approaches are a screening blood test (serum C4 or FGF-19), measurement of fecal bile acids, or a therapeutic trial with a bile acid sequestrant (e.g., cholestyramine or colesevelam).

A therapeutic trial is often appropriate, definitive, and highly cost-effective when a specific diagnosis is suggested on the initial physician encounter. For example, chronic watery diarrhea, which ceases with fasting in an otherwise healthy young adult, may justify a trial of a lactose-restricted diet; bloating and diarrhea persisting since a mountain backpacking trip may warrant a trial of metronidazole for likely giardiasis; and postprandial diarrhea persisting following resection of terminal ileum might be due to bile acid malabsorption and be treated with cholestyramine or colesevelam before further evaluation. Persistent symptoms require additional investigation. Certain diagnoses may be suggested on the initial encounter (e.g., idiopathic IBD); however, additional focused evaluations may be necessary to confirm the diagnosis and characterize the severity or extent of disease so that treatment can be best guided. Patients suspected of having IBS should be initially evaluated with flexible sigmoidoscopy with colorectal biopsies to exclude IBD, or particularly microscopic colitis, which is clinically indistinguishable from IBS with diarrhea; those with normal findings might be reassured and, as indicated, treated empirically with antispasmodics, antidiarrheals, or antidepressants (e.g., tricyclic agents). Any patient who presents with chronic diarrhea and hematochezia should be evaluated with stool microbiologic studies and colonoscopy.

In an estimated two-thirds of cases, the cause for chronic diarrhea remains unclear after the initial encounter, and further testing is required. Quantitative stool collection and analyses can yield important objective data that may establish a diagnosis or characterize the type of diarrhea as a triage for focused additional studies. If stool weight is >200 g/d, additional stool analyses should be performed that might include electrolyte concentration, pH, occult blood testing, leukocyte inspection (or leukocyte protein assay), fat quantitation, and laxative screens.

For secretory diarrheas (watery, normal osmotic gap), possible medication-related side effects or surreptitious laxative use should be reconsidered. Microbiologic studies should be done including fecal bacterial cultures (including media for Aeromonas and Plesiomonas), inspection for ova and parasites, and Giardia antigen assay (the most sensitive test for giardiasis). Small-bowel bacterial overgrowth can be excluded by intestinal aspirates with quantitative cultures or with glucose or lactulose breath tests involving measurement of breath hydrogen, methane, or other metabolite. However, interpretation of these breath tests may be confounded by disturbances of intestinal transit. Upper endoscopy and colonoscopy with biopsies and small-bowel x-rays (formerly barium, but increasingly CT with enterography or magnetic resonance with enteroclysis) are helpful to rule out structural or occult inflammatory disease. When suggested by history or other findings, screens for peptide hormones should be pursued (e.g., serum gastrin, VIP, calcitonin, and thyroid hormone/thyroid-stimulating hormone, urinary 5-hydroxyindolacetic acid, histamine).

Further evaluation of osmotic diarrhea should include tests for lactose intolerance and magnesium ingestion, the two most common causes. Low fecal pH suggests carbohydrate malabsorption; lactose malabsorption can be confirmed by lactose breath testing or by a therapeutic trial with lactose exclusion and observation of the effect of lactose challenge (e.g., a liter of milk). Lactase determination on small-bowel biopsy is not generally available. If fecal magnesium or laxative levels are elevated, inadvertent or surreptitious ingestion should be considered and psychiatric help should be sought.

For those with proven fatty diarrhea, endoscopy with smallbowel biopsy (including aspiration for Giardia and quantitative cultures) should be performed; if this procedure is unrevealing, a small-bowel radiograph is often an appropriate next step. If smallbowel studies are negative or if pancreatic disease is suspected, pancreatic exocrine insufficiency should be excluded with direct tests, such as the secretin-cholecystokinin stimulation test or a variation that could be performed endoscopically. In general, indirect tests such as assay of fecal elastase or chymotrypsin activity or a bentiromide test have fallen out of favor because of low sensitivity and specificity.

Chronic inflammatory-type diarrheas should be suspected by the presence of blood or leukocytes in the stool. Such findings warrant stool cultures; inspection for ova and parasites; C. difficile toxin assay; colonoscopy with biopsies; and, if indicated, small-bowel contrast studies.

Treatment of chronic diarrhea depends on the specific etiology and may be curative, suppressive, or empirical. If the cause can be eradicated, treatment is curative as with resection of a colorectal cancer, antibiotic administration for Whipple‟s disease or tropical sprue, or discontinuation of a drug. For many chronic conditions, diarrhea can be controlled by suppression of the underlying mechanism. Examples include elimination of dietary lactose for lactase deficiency or gluten for celiac sprue, use of glucocorticoids or other anti-inflammatory agents for idiopathic IBDs, bile acid sequestrants for bile acid malabsorption, PPIs for the gastric hypersecretion of gastrinomas, somatostatin analogues such as octreotide for malignant carcinoid syndrome, prostaglandin inhibitors such as indomethacin for medullary carcinoma of the thyroid, and pancreatic enzyme replacement for pancreatic insufficiency. When the specific cause or mechanism of chronic diarrhea evades diagnosis, empirical therapy may be beneficial. Mild opiates, such as diphenoxylate or loperamide, are often helpful in mild or moderate watery diarrhea. For those with more severe diarrhea, codeine or tincture of opium may be beneficial. Such antimotility agents should be avoided with severe IBD, because toxic megacolon may be precipitated. Clonidine, an α2-adrenergic agonist, may allow control of diabetic diarrhea, although the medication may be poorly tolerated because it causes postural hypotension. The 5-HT3 receptor antagonists (e.g., alosetron) may relieve diarrhea and urgency in patients with IBS diarrhea. For all patients with chronic diarrhea, fluid and electrolyte repletion is an important component of management. Replacement of fat-soluble vitamins may also be necessary in patients with chronic steatorrhea.

MANAGEMENT OF PATIENT WITH CONSTIPATION

Constipation is a common complaint in clinical practice and usually refers to persistent, difficult, infrequent, or seemingly incomplete defecation. Because of the wide range of normal bowel habits, constipation is difficult to define precisely. Most persons have at least three bowel movements per week; however, low stool frequency alone is not the sole criterion for the diagnosis of constipation. Many constipated patients have a normal frequency of defecation but complain of excessive straining, hard stools, lower abdominal fullness, or a sense of incomplete evacuation. The individual patient‟s symptoms must be analyzed in detail to ascertain what is meant by “constipation” or “difficulty” with defecation.

Stool form and consistency are well correlated with the time elapsed from the preceding defecation. Hard, pellety stools occur with slow transit, whereas loose, watery stools are associated with rapid transit. Both small pellety or very large stools are more difficult to expel than normal stools.

The perception of hard stools or excessive straining is more difficult to assess objectively, and the need for enemas or digital disimpaction is a clinically useful way to corroborate the patient‟s perceptions of difficult defecation.

Psychosocial or cultural factors may also be important. A person whose parents attached great importance to daily defecation will become greatly concerned when he or she misses a daily bowel movement; some children withhold stool to gain attention or because of fear of pain

from anal irritation; and some adults habitually ignore or delay the call to have a bowel movement.

Pathophysiologically, chronic constipation generally results from inadequate fiber or fluid intake or from disordered colonic transit or anorectal function. These result from neurogastroenterologic disturbance, certain drugs, advancing age, or in association with a large number of systemic diseases that affect the GI tract. Constipation of recent onset may be a symptom of significant organic disease such as tumor or stricture. In idiopathic constipation, a subset of patients exhibit delayed emptying of the ascending and transverse colon with prolongation of transit (often in the proximal colon) and a reduced frequency of propulsive HAPCs. Outlet obstruction to defecation (also called evacuation disorders) accounts for about a quarter of cases presenting with constipation in tertiary care and may cause delayed colonic transit, which is usually corrected by biofeedback retraining of the disordered defecation. Constipation of any cause may be exacerbated by hospitalization or chronic illnesses that lead to physical or mental impairment and result in inactivity or physical immobility.

Approach to the patient.A careful history should explore the patient‟s symptoms and confirm whether he or she is indeed constipated based on frequency (e.g., fewer than three bowel movements per week), consistency (lumpy/hard), excessive straining, prolonged defecation time, or need to support the perineum or digitate the anorectum to facilitate stool evacuation. In the vast majority of cases (probably >90%), there is no underlying cause (e.g., cancer, depression, or hypothyroidism), and constipation responds to ample hydration, exercise, and supplementation of dietary fiber (15–25 g/d). A good diet and medication history and attention to psychosocial issues are key. Physical examination and, particularly, a rectal examination should exclude fecal impaction and most of the important diseases that present with constipation and possibly indicate features suggesting an evacuation disorder (e.g., high anal sphincter tone, failure of perineal descent, or paradoxical puborectalis contraction during straining to simulate stool evacuation).

The presence of weight loss, rectal bleeding, or anemia with constipation mandates either flexible sigmoidoscopy plus barium enema or colonoscopy alone, particularly in patients >40 years, to exclude structural diseases such as cancer or strictures. Colonoscopy alone is most cost-effective in this setting because it provides an opportunity to biopsy mucosal lesions, perform polypectomy, or dilate strictures. Barium enema has advantages over colonoscopy in the patient with isolated constipation because it is less costly and identifies colonic dilation and all significant mucosal lesions or strictures that are likely to present with constipation. Melanosis coli, or pigmentation of the colon mucosa, indicates the use of anthraquinone laxatives such as cascara or senna; however, this is usually apparent from a careful history. An unexpected disorder such as megacolon or cathartic colon may also be detected by colonic radiographs. Measurement of serum calcium, potassium, and thyroid-stimulating hormone levels will identify rare patients with metabolic disorders.

Patients with more troublesome constipation may not respond to fiber alone and may be helped by a bowel-training regimen, which involves taking an osmotic laxative (e.g., magnesium salts, lactulose, sorbitol, polyethylene glycol) and evacuating with enema or suppository (e.g., glycerine or bisacodyl) as needed. After breakfast, a distraction-free 15–20 min on the toilet without straining is encouraged. Excessive straining may lead to development of hemorrhoids, and, if there is weakness of the pelvic floor or injury to the pudendal nerve, may result in obstructed defecation from descending perineum syndrome several years later. Those few who do not benefit from the simple measures delineated above or require long-term treatment or fail to respond to potent laxatives should undergo further investigation. Novel agents that induce secretion (e.g., lubiprostone, a chloride channel activator, or linaclotide, a guanylate cyclase C agonist that activates chloride secretion) are also available.

A small minority (probably <5%) of patients have severe or “intractable” constipation; about 25% have evacuation disorders. These are the patients most likely to require evaluation by gastroenterologists or in referral centers. Further observation of the patient may occasionally reveal a previously unrecognized cause, such as an evacuation disorder, laxative abuse,

malingering, or psychological disorder. In these patients, evaluations of the physiologic function of the colon and pelvic floor and of psychological status aid in the rational choice of treatment. Even among these highly selected patients with severe constipation, a cause can be identified in only about one-third of tertiary referral patients, with the others being diagnosed with normal transit constipation.

Measurement of Colonic Transit. Radiopaque marker transit tests are easy, repeatable, generally safe, inexpensive, reliable, and highly applicable in evaluating constipated patients in clinical practice. Several validated methods are very simple. For example, radiopaque markers are ingested; an abdominal flat film taken 5 days later should indicate passage of 80% of the markers out of the colon without the use of laxatives or enemas. This test does not provide useful information about the transit profile of the stomach and small bowel. Radioscintigraphy with a delayed-release capsule containing radiolabeled particles has been used to noninvasively characterize normal, accelerated, or delayed colonic function over 24–48 h with low radiation exposure. This approach simultaneously assesses gastric, small bowel (which may be important in ∼20% of patients with delayed colonic transit because they reflect a more generalized GI motility disorder), and colonic transit. The disadvantages are the greater cost and the need for specific materials prepared in a nuclear medicine laboratory.

Anorectal and Pelvic Floor Tests. Pelvic floor dysfunction is suggested by the inability to evacuate the rectum, a feeling of persistent rectal fullness, rectal pain, the need to extract stool from the rectum digitally, application of pressure on the posterior wall of the vagina, support of the perineum during straining, and excessive straining. These significant symptoms should be contrasted with the simple sense of incomplete rectal evacuation, which is common in IBS.

Formal psychological evaluation may identify eating disorders, “control issues,” depression, or post-traumatic stress disorders that may respond to cognitive or other intervention and may be important in restoring quality of life to patients who might present with chronic constipation.

A simple clinical test in the office to document a non-relaxing puborectalis muscle is to have the patient strain to expel the index finger during a digital rectal examination. Motion of the puborectalis posteriorly during straining indicates proper coordination of the pelvic floor muscles. Motion anteriorly with paradoxical contraction during simulated evacuation indicates pelvic floor dysfunction.

Measurement of perineal descent is relatively easy to gauge clinically by placing the patient in the left decubitus position and watching the perineum to detect inadequate descent (<1.5 cm, a sign of pelvic floor dysfunction) or perineal ballooning during straining relative to bony landmarks (>4 cm, suggesting excessive perineal descent).

A useful overall test of evacuation is the balloon expulsion test. A balloon-tipped urinary catheter is placed and inflated with 50 mL of water. Normally, a patient can expel it while seated on a toilet or in the left lateral decubitus position. In the lateral position, the weight needed to facilitate expulsion of the balloon is determined; normally, expulsion occurs with <200 g added or unaided within 2 min.

Anorectal manometry, when used in the evaluation of patients with severe constipation, may find an excessively high resting (>80 mmHg) or squeeze anal sphincter tone, suggesting anismus (anal sphincter spasm). This test also identifies rare syndromes, such as adult Hirschsprung‟s disease, by the absence of the rectoanal inhibitory reflex.

Defecography (a dynamic barium enema including lateral views obtained during barium expulsion or a magnetic resonance defecogram) reveals “soft abnormalities” in many patients; the most relevant findings are the measured changes in rectoanal angle, anatomic defects of the rectum such as internal mucosal prolapse, and enteroceles or rectoceles. Surgically remediable conditions are identified in only a few patients. These include severe, whole-thickness intussusception with complete outlet obstruction due to funnel-shaped plugging at the anal canal or an extremely large rectocele that fills preferentially during attempts at defecation instead of expulsion of the barium through the anus. In summary, defecography requires an interested and

experienced radiologist, and abnormalities are not pathognomonic for pelvic floor dysfunction. The most common cause of outlet obstruction is failure of the puborectalis muscle to relax; this is not identified by barium defecography, but can be demonstrated by magnetic resonance defecography, which provides more information about the structure and function of the pelvic floor, distal colorectum, and anal sphincters.

Neurologic testing (electromyography) is more helpful in the evaluation of patients with incontinence than of those with symptoms suggesting obstructed defecation. The absence of neurologic signs in the lower extremities suggests that any documented denervation of the puborectalis results from pelvic (e.g., obstetric) injury or from stretching of the pudendal nerve by chronic, long-standing straining. Constipation is common among patients with spinal cord injuries, neurologic diseases such as Parkinson‟s disease, multiple sclerosis, and diabetic neuropathy. Spinal-evoked responses during electrical rectal stimulation or stimulation of external anal sphincter contraction by applying magnetic stimulation over the lumbosacral cord identify patients with limited sacral neuropathies with sufficient residual nerve conduction to attempt biofeedback training.

In summary, a balloon expulsion test is an important screening test for anorectal dysfunction. Rarely, an anatomic evaluation of the rectum or anal sphincters and an assessment of pelvic floor relaxation are the tools for evaluating patients in whom obstructed defecation is suspected and is associated with symptoms of rectal mucosal prolapse, pressure of the posterior wall of the vagina to facilitate defecation (suggestive of anterior rectocele), or prior pelvic surgery that may be complicated by enterocele.

Treatment. After the cause of constipation is characterized, a treatment decision can be made. Slow-transit constipation requires aggressive medical or surgical treatment; anismus or pelvic floor dysfunction usually responds to biofeedback management. The remaining ~60% of patients with constipation has normal colonic transit and can be treated symptomatically.

Patients with spinal cord injuries or other neurologic disorders require a dedicated bowel regimen that often includes rectal stimulation, enema therapy, and carefully timed laxative therapy. Patients with constipation are treated with bulk, osmotic, prokinetic, secretory, and stimulant laxatives including fiber, psyllium, milk of magnesia, lactulose, polyethylene glycol (colonic lavage solution), lubiprostone, linaclotide, and bisacodyl, or, in some countries, prucalopride, a 5-HT4 agonist. If a 3-to 6-month trial of medical therapy fails, unassociated with obstructed defecation, the patients should be considered for laparoscopic colectomy with ileorectostomy; however, this should not be undertaken if there is continued evidence of an evacuation disorder or a generalized GI dysmotility. Referral to a specialized center for further tests of colonic motor function is warranted. The decision to resort to surgery is facilitated in the presence of megacolon and megarectum. The complications after surgery include small-bowel obstruction (11%) and fecal soiling, particularly at night during the first postoperative year. Frequency of defecation is 3–8 per day during the first year, dropping to 1–3 per day from the second year after surgery.

Patients who have a combined (evacuation and transit/motility) disorder should pursue pelvic floor retraining (biofeedback and muscle relaxation), psychological counseling, and dietetic advice first. If symptoms are intractable despite biofeedback and optimized medical therapy, colectomy and ileorectostomy could be considered as long as the evacuation disorder is resolved and optimized medical therapy is unsuccessful. In patients with pelvic floor dysfunction alone, biofeedback training has a 70–80% success rate, measured by the acquisition of comfortable stool habits. Attempts to manage pelvic floor dysfunction with operations (internal anal sphincter or puborectalis muscle division) or injections with botulinum toxin have achieved only mediocre success and have been largely abandoned.

CELIAC DISEASE

Synonyms: Gluten-sensitive enteropathy, Gluten enteropathy, Non-tropical sprue.

Definition. Gluten enteropathy is a chronic progressive immune-mediated intestinal inflammatory disease that is characterized by genetically determined *gluten intolerance*, diffuse atrophy of mucous membrane, and leads to generalized malabsorption.

Classification. Classic form (active form with gastrointestinal symptoms), non-classic (when gastroenterological symptoms are minimal or absent, but there are extra intestinal symptoms) and asymptomatic.

Epidemiology. Most common in the Irish, British, and other northern European populations. Screening studies for the antiendomysial (EMA) and anti– tissue transglutaminase (anti-tTG) antibodies that are associated with celiac disease suggest a prevalence in white populations of about 1%. About 20% of patients diagnosed with irritable bowel syndrome or with microscopic (lymphocytic) colitis have celiac disease.

Etiology. Geneticdisease, associated with HLA-DQ2 and HLA-DQ8. Autosomal-dominated. Disease manifests only after peroral gliadineconsumption. High-risk groups for celiac disease include first-degree relatives and individuals with type 1 diabetes mellitus, autoimmune thyroid disease, primary biliary cirrhosis, Turner‟s syndrome, or Down syndrome.

Pathogenesis.*Gluten* is a protein of gramineous plants (cereals) such as wheat, barley, rye. *Gliadin* is alcohol-soluble component of gluten, which can be produced from gluten by pathologic proteolysis and trigger intestinal inflammation in susceptible individuals. A 33-mer peptide that is a natural digestion product of α2-gliadin may be important in the pathogenesis of celiac disease. This peptide resists terminal digestion by intestinal brush-border proteases and contains three previously identified antigenic epitopes. It also reacts with tissue transglutaminase and stimulates human leukocyte antigen (HLA)-DQ2-restricted intestinal T-cell clones from individuals with celiac disease.

One group of scientists considers that celiac disease is an immune mediated injury to enterocytes accompanied by serum antibodies to gliadin.

tTG (the autoantigen recognized by EMA) may enhance intestinal inflammation by deamidation of select glutamine residues in gliadin to negatively charged glutamic acid. In the deamidated form, most gliadin peptides have a higher binding affinity for DQ2 and are more potent stimulants of glutensensitized T cells. Villous atrophy may be caused by inflammation that is triggered by γ-interferon released from DQ2- or DQ8-restricted CD4 T cells in the lamina propria. Alternatively, intraepithelial lymphocytes may directly kill intestinal epithelial cells under the influence of IL-15 released from stressed enterocytes.

The other theory is genetically determined fermentative deficiency that leads to inability to ferment gluten to non-toxic fractions.

Clinical features. Celiac disease usually manifests early in life, at about 2 years of age (after wheat has been introduced into the diet), or later in the second to fourth decades of life, but it can occur at any age. It can be characterized by absent gastrointestinal symptoms and a wide spectrum of non-intestinal manifestations that can involve any organ of the body, and very frequently may be completely asymptomatic.

Classical symptoms are:

- watery diarrhea (is caused by many mechanisms, including a decreased surface area for water and electrolyte absorption, the osmotic effect of unabsorbed luminal nutrients, an increased surface area for chloride secretion (crypt hyperplasia), and the stimulation of intestinal fluid secretion by inflammatory mediators and unabsorbed fatty acids),
- abdominal distention,
- flatulence,
- fatigue,
- weight loss, growth retardation,
- malabsorption: iron, mineral and vitamin deficiency.

Adults with celiac disease often present with anemia or osteoporosis without diarrhea or other gastrointestinal symptoms. These individuals most likely have proximal disease that

impairs iron, folate, and calcium absorption but an adequate surface area in the remaining intestine for absorption of other nutrients.

Other extraintestinal manifestations of celiac disease include rash (dermatitis herpetiformis), neurologic disorders (peripheral neuropathy, ataxia, epilepsy), psychiatric disorders (depression, paranoia), reproductive disorders (infertility, spontaneous abortion), short stature, dental enamel hypoplasia, chronic hepatitis, or cardiomyopathy.

Diagnosis. The diagnosis of celiac disease is made by characteristic changes found on a small intestinal biopsy specimen and improvement when a gluten-free diet is instituted.

An upper endoscopy with biopsy of the duodenum (beyond the duodenal bulb) or jejunum is performed to obtain multiple samples (four to eight) from the duodenum. It is the "gold standard" of celiac disease diagnosis. Mucosal flattening may be observed endoscopically as scalloped or reduced duodenal folds. Characteristic features found on intestinal biopsy include blunted or absent villi, crypt hyperplasia, increased intraepithelial lymphocytes, and infiltration of the lamina propria with plasma cells and lymphocytes. In some individuals, the only abnormal biopsy finding is increased intraepithelial lymphocytes. A hypoplastic mucosa indicates irreversible (end-stage) intestinal disease.

Serologic markers for celiac disease are useful in supporting the diagnosis or in screening, and in monitoring the response to a gluten free diet.

- ✓ EMA (anti-endomysial antibodies) immunoglobulin A (IgA) antibodies, detected by indirect immunofluorescence, are highly sensitive (90%) and specific (90 to 100%) for active celiac disease in skilled laboratory testing.
- ✓ The newer antideamidated gliadin (a biotinylated synthetic γ-gliadin peptide with glutamic acid substituted for glutamine) IgA and IgG antibody immunofluorometric assay has a sensitivity and specificity that approaches that of EMA.
- ✓ The anti-tTG (anti-transglutaminase antibodies) IgA antibody test, when obtained with a serum IgA level, is a cost-effective strategy for screening high-risk groups.
- ✓ **NB!** Patients with mild disease may have negative antibody studies. Anti-tTG, gliadin peptide, and EMA IgA antibodies tests are also negative in individuals with selective IgA deficiency. In these patients, anti-tTG or gliadin peptide IgG antibodies may be helpful in diagnosis.

HLA genotyping is useful to exclude the diagnosis of celiac disease in persons who lack the DQ2 or DQ8 gene.

- Bone densitometry should be performed on all individuals with celiac disease because up to 70% have osteopenia or osteoporosis. Patients with diarrhea and weight loss should be screened for vitamin and mineral deficiencies.Stool fat test may be ordered, to evaluate malabsorption.

Common complications. Iron deficiency, vitamin B12 and folate deficiency, osteoporosis, cancer, malnutrition, lactose intolerance, intestinal ulcers.

Differential diagnosis. Other causesof malabsorption are: immune conditions, hypersensitivity/allergy/eosinophilic gastroenteritis, infection, Whipple"s dis., tropical sprue, bacterial overgrowth, nutritional deficiencies, amyloidosis, lymphoma, lipid storage, short bowel. Diarrhea is common for infectious and non-infectious enteritis, IBS, lactase deficiency, diabetic enteropathy, different colitis.

Treatment. The only available treatment for celiac disease is a strict lifelong gluten-free diet in which the diseased person does not ingest any gluten. Wheat, rye, and barley grains should be excluded from the diet. Rice and corn grains are tolerated. Oats (if not contaminated by wheat grain) are tolerated by most.

Owing to secondary lactase deficiency, a lactose-free diet should be recommended until symptoms improve.

Deficiencies of vitamins and minerals should be replenished. Patients with vitamin D or calcium deficiency should receive supplements, with the dose monitored by 25-OH vitamin D levels and a 24-hour urine test for calcium.

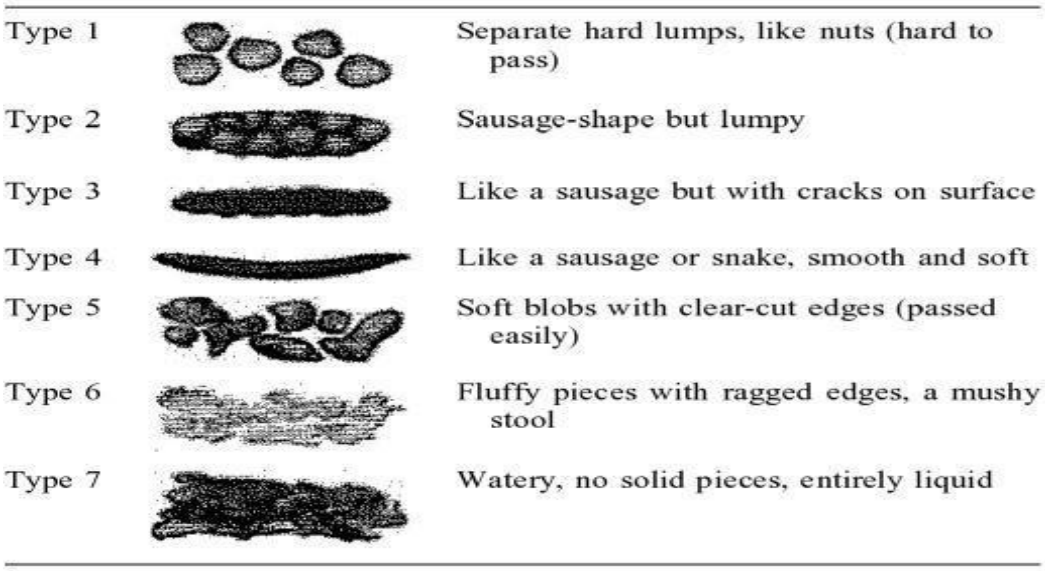
Cobalamin deficiency is more common and usually corrects itself on a gluten-free diet. Symptomatic individuals require supplementation of vitamin B12.

IRRITABLE BOWEL SYNDROME

Definition. Irritable bowel syndrome (IBS) is a functional bowel disorder (FBD) in which recurrent abdominal pain occurs at least 1 day per week during the past 3 months and is associated with defecation or a change in bowel habits. Symptom onset should occur at least 6 months before diagnosis and symptoms should be present during the last 3 months.

Classification.IBS subtypes related to bowel habit abnormalities:

1) IBS with predominant constipation: More than 25% of bowel movements with Bristol stool form types 1 or 2 and less than 25% of bowel movements with Bristol stool form types 6 or 7. Alternative for clinical practice: Patient reports that abnormal bowel movements are usually constipation (like type 1 or 2 in the picture of Bristol Stool Form Scale (BSFS)).
2) IBS with predominant diarrhea (IBS-D): more than 25% of bowel movements with Bristol stool form types 6 or 7 and less than 25% of bowel movements with Bristol stool form types 1 or 2. Alternative for clinical practice: Patient reports that abnormal bowel movements are usually diarrhea (like type 6 or 7 in the picture of BSFS).
3) IBS with mixed bowel habits (IBS-M): more than 25% of bowel movements with Bristol stool form types 1 or 2 and more than 25% of bowel movements with Bristol stool form types 6 or 7. Alternative for clinical practice: Patient reports that abnormal bowel movements are usually both constipation and diarrhea (more than one-fourth of all the abnormal bowel movements were constipation and more than one-fourth were diarrhea, using picture of BSFS).
4) IBS unclassified (IBS-U): Patients who meet diagnostic criteria for IBS but whose bowel habits cannot be accurately categorized into 1 of the 3 groups above should be categorized as having IBS unclassified.



Epidemiology. The world-wide prevalence of IBS is 11,2%. Prevalence rates are higher for women than for men; younger people are more likely to be affected than those older than age 50 years.

Etiological and risk factors. Factors that increase the risk of developing IBS include genetic, environmental, and psychosocial factors. Factors that trigger the onset or exacerbation of IBS symptoms include a prior gastroenteritis, food intolerances, chronic stress, diverticulitis, and surgery. IBS is associated with more psychiatric distress, sleep disturbance, “affective vulnerability,” and “over-adjustment to the environment.”

Pathogenesis.IBS is a multifactorial disorder with a complex pathophysiology. The resulting pathophysiologic mechanisms are variable and patient independent, and include altered gastrointestinal (GI) motility, visceral hyperalgesia, increased intestinal permeability, immune activation, altered microbiota, and disturbances in brain-gut function.

Diagnostic Criteria: recurrent abdominal pain, on average, at least 1 day per week in the last 3 months with symptom onset at least 6 months before diagnosis, associated with 2 or more of the following criteria:

1. Related to defecation
2. Associated with a change in frequency of stool.
3. Associated with a change in form (appearance) of stool.

Diagnosis. For the majority of patients, when diagnostic criteria for IBS are fulfilled and alarm features are absent, the need for diagnostic tests should be minimal.

The diagnosis of IBS should be made based on the following 4 key features: clinical history; physical examination; minimal laboratory tests; and, when clinically indicated, a colonoscopy or other appropriate tests.

Pain can be present anywhere throughout the abdomen, although it is more common in the lower abdomen. A history of disordered bowel habits (eg, constipation or diarrhea or both) should be identified, along with their temporal association with episodes of abdominal pain. Abdominal bloating is present in a majority of IBS patients; abdominal distention may be reported as well, although neither is required to make the diagnosis of IBS. Abnormal stool frequency (>3 bowel movements/day and <3 bowel movements/week) abnormal stool form (types 1-2 or 5-6 of the Bristol scale), excessive straining during defecation, defecatory urgency, feelings of incomplete evacuation, and mucus with bowel movements, although common in IBS, are not specific.

A physical examination should be performed in every patient evaluated for IBS. This reassures the patient and helps to exclude an organic etiology. An anorectal examination is mandatory to identify anorectal causes of bleeding, evaluate anorectal tone and squeeze pressure, and identify dyssynergic defecation.

The next step in the diagnosis of IBS is to perform limited laboratory studies, if not previously performed. A complete blood count (CBC) should be ordered, as the finding of anemia or an elevated white blood cell count warrants further investigation. A C-reactive protein or fecal calprotectin should be measured, as these tests are helpful in excluding IBD in patients with symptoms suggestive of nonconstipated IBS. If inflammatory markers are mildly elevated, but the probability of IBD is low, then tests should be remeasured before performing colonoscopy (if no other indication for colonoscopy exists). Inflammatory markers, including fecal calprotectin, may not be useful in patients with constipation symptoms. Routine thyroid tests are not indicated in all patients, but can be checked if clinically warranted. Serologic tests for celiac disease should be performed in patients with IBS-D and IBS-M who fail empiric therapy. Upper gastrointestinal endoscopy with duodenal biopsies should be performed if serologic tests for celiac disease are positive or if clinical suspicion is high; duodenal biopsies can also be used to identify tropical sprue, which can mimic IBS symptoms. Stool analysis (bacteria, parasites, and ova) may be useful if diarrhea is the main symptom, especially in developing countries where infectious diarrhea is prevalent. A screening colonoscopy is indicated in patients 50 years and older in the absence of warning signs (45 years in African Americans), based on national recommendations. Colonoscopy is also indicated for the presence of alarm symptoms or signs, a family history of colorectal cancer and persistent diarrhea that has failed empiric therapy. Biopsies of different segments of the colon may be required in patients with chronic diarrhea to rule out microscopic colitis. Bile acid malabsorption may be the cause of persistent, watery diarrhea in some patients. If empiric therapy fails, scintigraphic evaluation (75SeHCAT test) or postprandial serum C4 (7a-hydroxy-4-cholesten-3-one) or fibroblast growth factor 19 are diagnostic options, although none are currently widely available. Breath tests to

rule out carbohydrate malabsorption may be useful in some patients with IBS symptoms and persistent diarrhea.

Differential diagnosis. Inflammatory bowel disease, celiac disease, lactose and fructose intolerance, and microscopic colitis.

Treatment. Treatment should be based on symptom type and severity.

Lifestyle modifications that may improve IBS symptoms include exercise, stress reduction, attention to impaired sleep, dietary fiber supplementation remain a cornerstone of IBS management.

IBS-C therapy.Several peripherally acting agents are available to treat IBS-C symptoms. Lubiprostone (8 mg bid) is a luminally acting prostone that selectively activates type 2 chloride channels. Linaclotide is a 14-amino acid peptide that acts as a guanylate cyclase C agonist (290 mg qd). Psyllium (up to 30 g/d in divided doses) can be recommended. Different probiotics may also benefit IBS patients.

IBS-D therapy.Loperamide (2-4 mg; when necessary, titrate up to 16 mg/d), a synthetic peripheral m-opioid receptor agonist that decreases colonic transit, and increases water and ion absorption, is commonly used to treat IBS-D patients. There is increasing evidence to support a role for bile acids (cholestyramine 9 g bid-tid; colestipol 2 g qd-bid; colesevelam 625 mg qd-bid) in the pathophysiology of IBS-D. The US Food and Drug Administration approved rifaximin (550 mg 3 times daily 14 days), a nonabsorbable antibiotic, for the treatment of IBS-D. Alosetron (0.51 mg bid), a highly selective 5-HT3 antagonist, is effective at relieving pain and reducing stool frequency. Other 5-HT3 antagonist can be useful too (Ondansetron 4-8 mg tid; Ramosetron 5 mg qd). Eluxadoline (100 mg bid) is a novel mixed m-receptor agonist/d-opioid receptor antagonist that has been developed as a treatment for patients with IBS-D. Small number of patients experienced sphincter of Oddi dysfunction or self-limited pancreatitis, so Eluxadoline should be used at the lower dose and with careful monitoring in patients who had a history of cholecystectomy or significant ethanol consumption.

Abdominal pain therapy.Smooth muscle antispasmodics (Dicycylomine 10-20 mg qd-qid; Otilonium 40-80 mg bid-tid; Mebeverine 135 mg tid) are used to treat abdominal pain and spasms in all IBS subtypes. Lubiprostone, Linaclotide, Alosetron, Peppermint oil (enteric-coated capsules, 250-750 mg, bid-tid) also have pain relieving activity.

Tricyclic antidepressant agents (Desipramine 25-100 mg qhs; amitriptyline 10-50 mg qhs) appear effective in treating IBS symptoms. Few data are available on the use of selective serotonin reuptake inhibitors in IBS (Paroxetine 10-40 mg qd; Sertraline 25-100 mg qd; Citalopram 10-40 mg qd). Psychological and behavioral treatments relate to helping patients control and reduce pain and discomfort and are seen as ancillary to or augmenting medical treatments. Treatments include cognitive behavioral therapy, hypnosis, and various relaxation methods to reduce muscle tension and autonomic arousal believed to aggravate GI symptoms.

INFLAMMATORY BOWEL DISEASE

Definition. Inflammatory bowel disease refers to two chronic idiopathic inflammatory disorders, **ulcerative colitis and Crohn's disease**. These disorders are diagnosed by characteristic clinical, endoscopic, and histologic features.

Ulcerative colitis is a heterogeneous chronic inflammatory bowel disorder that may affect the colon and rectum.

Crohn's disease is a heterogeneous inflammatory transmural, granulomatosis bowel disorder that may affect different sites of the gastrointestinal tract.

Ulceration from Crohn‟s disease may be transmural and may occur anywhere in the gastrointestinal tract, most commonly in the distal ileum and proximal colon. The hallmark of ulcerative colitis is continuous ulceration starting in the rectum and limited to the colon. Approximately 10% of patients with inflammatory bowel disease have *indeterminant colitis*, a term used when Crohn‟s colitis cannot be differentiated from ulcerative colitis.

Epidemiology. Inflammatory bowel disease occurs worldwide, but the highest incidence is found in North America, the United Kingdom, and northern Europe. The incidence of Crohn‟s disease has risen slowly over time, although ulcerative colitis remains slightly more prevalent than Crohn‟s disease. Crohn‟s disease and ulcerative colitis may occur at any age. The peak incidence of Crohn‟s disease occurs between age 15 and 30 years of age, with a second peak in the seventh decade, more often in female patients. Ulcerative colitis also has a bimodal peak age distribution, with an initial peak between 20 and 40 years of age and second smaller peak beyond the seventh decade.

Etiological and risk factors. Crohn‟s disease and ulcerative colitis are polygenic disorders, for which family history is a risk factor. Although the trigger for inflammatory bowel disease is not known, three major pathways likely activate the disease: a genetic predisposition, immune dysregulation, and an environmental antigen.

The initial gene associated with Crohn‟s disease is NOD2/CARD15, located on chromosome 16 (16q12), and is expressed in intestinal epithelial Paneth cells, macrophages, and dendritic cells. Activation of NOD2 leads to activation of NF-κB, which mediates transcription of numerous proinflammatory cytokines. A mutation in the leucine-rich domain of the NOD2 protein, which interacts with bacterial lipopolysaccharide, leads to failure in activation of NF-κB and is associated with the development of Crohn‟s disease. Toll-like receptor-4 gene polymorphisms are associated with both Crohn‟s disease and ulcerative colitis. Polymorphisms of the interleukin-23 (IL-23) receptor gene are associated with ulcerative colitis and a varied risk of Crohn‟s disease. Human leukocyte antigen (HLA) class II polymorphisms, especially in HLA-DR molecules, may confer increased risk for ulcerative colitis and possibly Crohn‟s as well.

Cigarette smoking is associated with a worse prognosis in patients with Crohn‟s disease but an improved course in ulcerative colitis. Nonsteroidal anti-inflammatory drugs (NSAIDs) appear to be associated with exacerbations of disease, although evidence for this is less definitive. Appendectomy has been suggested as protective against the development of ulcerative colitis. Diet does not clearly affect the course of inflammatory bowel disease.

Pathogenesis.A possible explanation is that the inability of the innate immune system to clear microbial antigens, combined with increased intestinal epithelial permeability to antigens, eventually leads to an overactive adaptive immune response. Microbes likely play a part in the development of inflammatory bowel disease. Both Crohn‟s disease and ulcerative colitis are products of a dysregulated innate immune system that triggers T cells and a humoral response. TH17 cells, which are activated in Crohn‟s disease and ulcerative colitis, are stimulated by IL-23, which is produced by antigen-presenting cells. Variations in single-nucleotide polymorphisms of the gene encoding the receptor for IL-23 are associated with Crohn‟s disease.

Crohn's Disease. As a result of a dysregulated immune system, patients with Crohn‟s disease develop aphthous ulcers, which are superficial mucosal ulcers. As the disease progresses, the ulceration becomes deeper, transmural, and discrete; it may form a serpiginous pattern and may occur anywhere from the esophagus to the anus in a noncontinuous pattern. The most common location for ulceration is the ileocecal region. In some patients, chronic disease leads to the formation of fibrotic strictures, and approximately 30% of patients may develop fistulas. In early Crohn‟s disease, the histopathology is characterized by an acute inflammatory infiltrate in the lamina propria, with cryptitis, and crypt abscesses. Later in the disease process, the crypt architecture becomes distorted, with a lymphocytic infiltrate and a resulting branching and shortening of the crypts. Noncaseating granulomas, which are present in up to 15% of endoscopic biopsy specimens and as many as 70% of surgical specimens, are not unique to Crohn‟s disease but help confirm the diagnosis when other classic features are present. Surgical specimens also may show transmural intestinal wall inflammation and fat creeping on the serosal surface.

Ulcerative Colitis. In mild ulcerative colitis, the mucosa is granular, hyperemic, and edematous in appearance. As the disease becomes more severe, the mucosa ulcerates, and the ulcers may extend into the lamina propria. Ulcerative colitis starts in the rectum and may extend

proximally in a continuous pattern, but it affects only the colon. Pseudopolyps may form owing to epithelial regeneration after recurrent acute attacks. With chronic disease, the colonic mucosa may lose the normal fold pattern, the colon may shorten, and the colon may appear narrowed. In early ulcerative colitis, the histopathology is characterized by epithelial necrosis, an acute inflammatory infiltrate in the lamina propria, cryptitis, and crypt abscesses. In chronic disease, a predominant lymphocytic infiltrate and distortion of crypt architecture are seen.

Classification. Periods: exacerbation, remission. All complaints should be mentioned in diagnosis.

Montreal classification (2005):

Crohn's Disease (CD).

- Subdivision of the group based on age
  - A1 - below or equal to 16 years;
  - A2 - 17 to 40 years;
  - A3 above 40.
- Subdivision of the group based on location
  - L1 - ileal,
  - L2 - colonic,
  - L3 - ileocolonic,
  - L4 - isolated upper disease.
- Subdivision of the group based on behavior
  - B1 - non-stricturing, non-penetrating,
  - B2 - stricturing,
  - B3 - penetrating, p perianal disease modifier
  - P – perianal disease.

Ulcerative Colitis (UC).

- Subdivision of the group based on extension
  - E1 - Ulcerative proctitis, involvement limited to the rectum (that is, proximal extent of inflammation is distal to the rectosigmoid junction);
  - E2 - Left sided UC (distal UC), involvement limited to a proportion of the colorectum distal to the splenic flexure;
  - E3 - Extensive UC (pancolitis), involvement extends proximal to the splenic flexure);
- Subdivision of the group based on severity
  - S0 - Clinical remission, asymptomatic;
  - S1 - Mild UC, passage of four or fewer stools/day (with or without blood), absence of any systemic illness, and normal inflammatory markers (ESR);
  - S2 - Moderate UC, passage of more than four stools per day but with minimal signs of systemic toxicity;
  - S3 - Severe UC, passage of at least six bloody stools daily, pulse rate of at least 90 beats per minute, temperature of at least 37.5˚C, haemoglobin of less than 10.5 g/100 ml, and ESR of at least 30 mm/h).

NB! Additional classification of CD: inflammatory/fibrostenotic/with fistulas. By severity: severe (diarrhea more than 6 times a day, fever more than 37,5, pulse rate more than 90, anemia (HB less than 75% of normal rate), BSR more than 50mm/h, intestinal complications); moderate (features between severe and mild); mild (diarrhea less than 4 times a day, normal temperature, normal pulse rate, anemia (Hb more than 100g/l), BSR less than 30 mm/h). Activity of process should be established by *index of Best and CDAI index*!

Additional classification of UC: acute/chronic. Activity should be evaluated by *index of Meyo*!

Clinical features.

Crohn's Disease. The terminal ileum is affected in about 70% of patients with Crohn‟s disease. Primary ileal disease occurs in 30% of patients, whereas ileocolonic disease occurs in 40%.

Symptoms may include abdominal pain, typically in the right lower quadrant, diarrhea, hematochezia, fatigue, palpated abdominal infiltrates, perianal fistulas and absceses. With more severe disease, fever and weight loss may be present. Some patients may present with obstructive symptoms, such as abdominal pain, abdominal distention, and nausea. Only approximately 5% of patients develop Crohn‟s disease in the upper gastrointestinal tract, and esophageal Crohn‟s disease occurs in less than 2% of patients.

Fever may be present if there is an abscess.

Fistulas, which are internal tracks that can occur anywhere in the gastrointestinal tract and connect to various sites, occur in 20 to 40% of Crohn‟s patients. External fistulas, which present with symptoms of fluid discharge from the cutaneous opening, can be enterocutaneous, or perianal. Internal fistulas can be enteroenteric, rectovaginal, or enterocolonic.

Ulcerative Colitis. As with Crohn‟s disease, symptoms and signs of ulcerative colitis depend on the extent and severity of disease. At the time of diagnosis, 14 to 37% of patients have pancolitis, 36 to 41% have disease extending beyond the rectum, and 44 to 49% have proctosigmoiditis.

Symptoms include hematochezia, diarrhea, tenesmus, passage of mucus, urgency to defecate, and abdominal pain. In the setting of proctitis or proctosigmoiditis, patients may have constipation with difficulty defecating. With more extensive and severe colonic involvement, patients may also have weight loss and fever. Patients may also have nausea and vomiting because of abdominal pain, fatigue because of anemia, and peripheral edema because of hypoalbuminemia.

Physical Examination. Oral ulcers may be present in Crohn‟s disease. The location of abdominal tenderness usually reflects the location of intestinal involvement. In Crohn‟s disease, abdominal tenderness is classically in the right lower quadrant and may include fullness or a mass depending on the severity of inflammation. Peritoneal signs may occur when penetrating Crohn‟s disease causes intestinal perforation. Rectal examination may reveal skin tags, hemorrhoids, fissure, and fistulas.

Diagnosis. When diarrhea is the predominant symptom, the initial evaluation should include a thorough medical history, testing for infectious colitis, and screening for endocrine-metabolic disorders such as hyperthyroidism and hypocalcemia. Infections with organisms such as Shigella, Amoeba, Giardia, Escherichia coli, and Campylobacter can be accompanied by bloody diarrhea, abdominal cramps, and an endoscopic picture identical to ulcerative colitis. Stool studies are needed to diagnose or exclude these infections. If hematochezia or abdominal pain are the predominant symptom, the differential diagnosis is broad.

Endoscopic Evaluation. In a patient with symptoms suggestive of inflammatory bowel disease and no evidence for an infection to explain their symptoms, endoscopic evaluation is essential. Colonoscopy is the initial endoscopic test for patients who present with lower gastrointestinal symptoms such as diarrhea and hematochezia, except in the presence of acute severe peritoneal symptoms. Small bowel imaging (such as small bowel follow-through or computed tomography [CT] enterography) may also be needed to determine whether there is small bowel disease or to determine the distribution of disease. Capsule endoscopy is useful if all other endoscopic and radiologic testing is nondiagnostic, but Crohn‟s disease of the small bowel is still suspected. Findings on capsule endoscopy should be followed by endoscopy to obtain biopsies. Capsule endoscopy should not be performed if Crohn‟s disease is complicated by a known small bowel stricture.

Crohn's Disease. Early endoscopic findings in Crohn‟s disease include superficial small mucosal ulcers, also called aphthous ulcers. As the severity of Crohn‟s disease progresses, the ulceration becomes deeper and may become round, linear, or serpiginous. A cobblestone appearance of the mucosa is caused by intersecting longitudinal and transverse ulcers, with "stone" areas representing normal mucosa. Areas of ulceration, which are typically interspersed with normal "skip" areas, may occur anywhere from the esophagus to anus but are most common in the ileocecal region. Isolated colonic disease occurs in 25% of patients, and 60% will have

rectal involvement, thereby making it at times difficult to differentiate from ulcerative colitis. The diagnosis of inflammatory bowel disease is contingent on accurate histopathology, so biopsy of the affected area is key. Findings of an inflammatory infiltrate in the lamina propria and distortion of the crypt architecture support the diagnosis. The diagnosis of Crohn‟s disease may be made by histopathology alone if noncaseating granulomas are seen, but granulomas are rarely found on endoscopic biopsies. The diagnosis of Crohn‟s disease is usually based on a combination of information gleaned from histopathology, colonoscopy, and small bowel imaging.

A skipped pattern of ulceration, ulceration in the small bowel or upper gastrointestinal tract or the presence of fistulas supports the diagnosis of Crohn‟s disease. Colonic and small bowel ulceration occur in several other disorders, including infections that may not be detected by routine stool studies (such as enterohemorrhagic Escherichia coli), vascular disorders, immune-related enterocolitis, neoplasia, diverticulitis, radiation, and medications such as NSAIDs.

Ulcerative Colitis. The diagnosis of ulcerative colitis is based on endoscopic findings and histopathology. Early in the disease process, patients develop diffuse mucosal erythema with loss of the normal mucosal vascular pattern. In mild disease, the mucosa may have a granular and edematous appearance. As the disease becomes more severe, the mucosa becomes more friable, bleeds easily when the mucosa is touched, and may eventually ulcerate. Endoscopic findings, which start in the rectum and may extend proximally in a continuous pattern, affect only the colon. Pseudopolyps may form owing to epithelial regeneration after recurrent attacks in patients with long-standing disease. With chronic disease, the colonic mucosa may lose its normal fold pattern, and the colon may shorten and appear narrowed. Features such as crypt distortion, continuous mucosal inflammation starting from the rectum, absence of granulomas, and absence of small bowel disease are all consistent with ulcerative colitis. Early in the disease process, chronic inflammatory findings, such as crypt distortion, may not be present, and the diagnosis may be more difficult to confirm.

Radiologic imaging is vital and should almost always be obtained when inflammatory bowel disease, particularly Crohn‟s disease, is suspected. Barium studies such as an upper gastrointestinal series, small bowel followthrough, and barium enema are usually necessary to diagnose fistulas and strictures in Crohn‟s disease. If Crohn‟s disease is suspected by colonoscopic examination, a small bowel follow-through is generally obtained to assess the extent, severity, and type of disease (strictures and fistulas) in the small intestine.

CT enterography and magnetic resonance imaging (MRI) enterography are alternatives to a small bowel follow-through. CT enterography may be preferred for the detection of abdominal abscesses, whereas MRI may be preferred for the detection of perineal abscesses and strictures.

Laboratory Findings. Anemia may result from chronic disease, blood loss or nutritional deficiencies of iron, folate, or vitamin B12. A modestly elevated leukocyte count is indicative of active disease, but a marked elevation suggests an abscess or another suppurative complication. The erythrocyte sedimentation rate and C-reactive protein are nonspecific serum inflammatory markers that are sometimes used to monitor the activity of disease. Hypoalbuminemia is an indication of malnutrition.

Serologic markers are supportive but may not be used independently to diagnose inflammatory bowel disease.

Complications.

	CROHN'S DISEASE	**ULCERATIVE COLITIS**
Ocular disorders (uveitis, episcleritis)	+	+
Arthropathy	+	+
Oral ulcers	+	-
Skin disorders (pyoderma	+	+

gangrenosum, erythema nodosum)		
Nephrolithiasis	+	+
Primary sclerosing cholangitis	+	+
Bone disorders (osteoporosis, osteomalacia)	+	-
Thromboembolic disease	+	+
B12 deficiency	+	-
Toxic megacolon	More often	Rarely
Cancer	Less often	More often
Bleeding	+	+
Fistula	+	-
Stricture	+	-
Perianal disease (fissure, skin tags)	+	-

Differential diagnosis.

	CROHN'S DISEASE	**ULCERATIVE COLITIS**
Peak age of onset (years of age)	15-30, 2nd peak in the 7th decade	20-40, 2nd smaller peak beyond the 7th decade
Potential sites of gastrointestinal involvement	Esophagus to anus	colon
Skip areas	+	-
Transmural inflammation	+	-
Ulcers	Fissuring	Superficial
Wall	Thick	Thin
Dilatation	-	+
Type of ulceration	Usually discrete	Continuous
Fistula	+	-
Stricture	+	-
Perianal disease (fissure, skin tags)	+	-
Granulomas	+	-
Fibrosis	Marked	Minimal

Treatment. As the etiology of inflammatory bowel disease has not yet been clarified, casual therapy doesn‟t exist. Consequently, therapy is aimed to reduce or eliminate symptoms during the acute flare or exacerbation as well as to maintain remission. Surgery is employed in life-threatening situations and fistulas and abscesses.

The principal classes of drug used in both ulcerative colitis and Crohn‟s disease are: preparations which release (mesalazine) or split off (sulfasalazine) 5-aminosalicylic acid; topically active (budesonide) and systemically active corticosteroids (prednisolone, 6-methylprednisolone); immunosuppressives (azathioprine , methotrexate). In recent years, anti-TNF-α antibodies (infliximab, adalimumab,certolizumaband natalizumab) have been introduced in the therapy. They can be successful in corticosteroid-refractory disease. Supportive medical therapy, such as antibiotics, antidiarrheal and antispasmodic medications, may also be used.

Crohn's Disease.

Drug therapy of the acute flare (CDAI>150)

- mild to moderate activity: mesalazine “Salofalk” 3-4,5 g/day and/or budesonide “Budenofalk” 9mg/day. Involment of rectum and distal colon allows to prescribe mesalazine and corticosteroids topically (suppositories or –enemas);
- moderate to severe activity: prednisolone 60 mg/day 1 week, 40 mg/day 2nd week, 30 mg/day 3rd week, 25 mg/day 4th week, 20mg/day 5th week, 15 mg/day 6th week, 10mg/day 7th-26th week, gradual reduction after week 27.

Complicated courses of disease.
- Azathioprine 2-3 mg/kg/day;
- Antibiotics, e.g. ciprofloxacin;
- Metronidazole 500-1000 mg/day (7-10 days);
- Methotrexat;
- Anti-TNF-α antibodies. Infliximab (intravenous. Induction: 5 mg/kg IV weeks 0, 2, 6. Maintenance: 5 mg/kg IV q 8 wk5 mg/kg);
- Mercaptopurini (1,5 mg/kg/day),

Therapy for remission.
- relaps prophylaxis with mesalazine 1,5-3 g/day;
- Azathioprine in pations with frequent flares;
- light full diet;
- Colestyramine with chologenic diarrhea;
- Antidiarrheals (codeine, lomotil, loperamide);
- stop smoking.

Ulcerative Colitis.

Drug therapy of the acute flare
- mild activity: mesalazine 3x0,5 g/day (granules or tablets) or 1x3 g/day (granules) or olsalazine 3-4x0,5 g/day or sulfasalazine 3-4x1 g/day. Topical forms in proctitis and left-sided colitis can be administrated. For example, Budesonide “Budenofalk” per rectum 2-4 mg a day.
- moderate to severe activity: therapy like mild activity plus prednisolone initially 40-60 mg/day orally with weekly reduction of the daily dose by 10mg, later 5mg depending on clinical activity.
- severe activity: prednisolone dose initially 100mg or higher, divided into morning and evening dose, possibly intravenous.

Complicated courses of disease.
- Azathioprine 2-3 mg/kg/day;
- consideration of „„curative“" surgery.

Corticosteroids because their risks outweigh their benefits are not used long-term in treatment. Immunosuppressive medications such as azathioprine and biological agents such as infliximab and adalimumab are given only if people cannot achieve remission with 5-ASA and corticosteroids.

Therapy for remission.
- relaps prophylaxis with mesalazine 1-3 g/day orally or olsalazine 2x0,5 g/day or sulfasalazine 2x1 g/day (suppositories and enemas also effective with proctitis/left-sided colitis);
- light full diet.

Materials for self-control:

Situation tasks:

1. A 51-year-old female patient complains of frequent defecation and liquid blood-streaked stools with mucus admixtures, diffuse pain in the inferolateral abdomen, 6 kg weight loss over the previous month. Objectively: body temperature - 37,4^{o}C, malnutrition, skin is pale and dry. Abdomen is soft, sigmoid is painful and spasmodic, makes a rumbling sound. Liver is dense, painful, extends 3 cm below the costal margin. What is the most probable diagnosis? What additional obligatory test is necessary?

2. A 35 y. o. woman consulted a doctor about occasional pains in paraumbilical and iliac region that reduce after defecation or passage of gases. Defecation takes place up to 6 times a day, stool is not solid. Appetite is normal, she has not put off weight. First such symptoms appeared 1,5 year ago, but colonoscopy data reveals no organic changes. Objectively: abdomen is soft, a little bit painful in the left iliac region. Blood and urine are normal. What is the probable diagnosis? What treatment can be prescribed to improve quality of life of the patient?

Tests:

1. A 20-year-old woman has a 3-4 months history of bloody diarrhea; stool examination proved negative for ova and parasites; stool cultures negative for clostridium, campylobacter and yersinia; normal small bowel series; edema, hyperemia and ulceration of the rectum and sigmoid colon seen on sigmoidoscopic examination. Choose the most probable diagnosis:

A. Gastroenteritis
B. Ulcerative colitis
C. Carcinoid syndrome
D. Zollinger-Ellison syndrome
E. Granulomatous colitis

2. Patient D., 48 years old, complains of pain in the lateral part of abdomen, that diminishes after defecation with gases, alternation of diarrhea and constipations. In the anamnesis: dysentery 2 years ago. Palpation of abdomen is painful, with abdominal murmur of colon. What method of examination is the most informative to make up the diagnosis?

A. Rectoromanoscopy
B. Rectal finger exam
C. Colonoscopy
D. Coprocytogram in dynamics
E. US examination of abdominal cavity

3. A 2 y.o. boy was admitted to the hospital with weight loss, unstable discharges, anorexia, following the semolina‟s introduction (since 5 months). The child is adymanic, flabby, with pale dry skin, subcutaneous layer is emaciated. Distended and tensed abdomen, tympanitis on percussion of the upper part of the abdomen, splashing sounds, feces are foamy, light, foul. On coprocytogram: a lot of neutral fat. What is the cause of the disease?

A. Celiakia (celiac disease)
B. Mucoviscidosis (cystic fibrosis)
C. Intestinal dysbacteriosis
D. Chronic enteritis
E. Disaccharidase insufficiency

4. A 43 y.o. male complains of stomach pain, which relieves after defecation, and is accompanied by abdominal winds, rumbling, the feeling of incomplete evacuation or urgent need for bowel movement, constipation or diarrhea in alternation. These symptoms have lasted for over 3 months. No changes in laboratory tests. What is the most likely diagnosis?

A. Irritable bowel syndrome
B. Spastic colitis
C. Colitis with hypertonic type dyskinesia
D. Chronic enterocolitis, exacerbation phase
E. Atonic colitis

5. A 24 y.o. male complains of abdominal spastic pain, which occurs after emotional stress, relieves with defecation, and is accompanied by abdominal winds, constipation and the

feeling of incomplete evacuation. These symptoms have lasted for over 3 months. No changes in laboratory tests, GDS and colonoscopy. What is the most proper treatment of constipation?

A. Antidepressants
B. Antibiotics
C. Lactulose
D. Loperamide
E. Fluocsetine

6. A 33 y.o. woman consulted a doctor about occasional pains in paraumbilical and iliac region that reduce after defecation or passage of gases. Defecation takes place up to 6 times a day, stool is not solid, without mucous and blood. Appetite is normal, she has not put off weight. First such symptoms appeared 1,5 year ago, but colonoscopy data reveals no organic changes. Objectively: abdomen is soft, a little bit painful in the left iliac region. Blood and urine analyses are normal. What is the possible and the most proper treatment of diarrhea in this case?

A. Loperamide
B. Probiotics
C. Antibiotics
D. Lactulose
E. Polyvitamins

7. Teenager, 14 years old, has complaints on diarrhea, weakness, weight loss. The condition worsened after taking of plenty of flour products. Such phenomena are observed from babyhood. Objectively: general state is satisfactory, body weight is reduced, physical development is delayed. The reason of the disease is:

A. Deficit of lactase
B. Invasion with intestinal worms
C. Chronic pancreatitis, syndrome of maldigestion
D. Dysbacteriosis of intestine
E. Gluten enteropathy

8. A 55-year-old female patient complains of frequent defecation and liquid blood-streaked stools with mucus admixtures, diffuse pain in the inferolateral abdomen, 7 kg weight loss over the previous month. Objectively: body temperature - 37, 9oC, malnutrition. Abdomen is soft, sigmoid is painful and spasmodic, makes a rumbling sound. What is the most likely treatment?

A. Sulfasalazine
B. Clarithromycin
C. Probiotics
D. Kreon
E. Amoxicillin

9. A 33-year-old woman has a 3-4 months history of bloody diarrhoea; edema, hyperemia and ulceration of the rectum and sigmoid colon seen on sigmoidoscopic examination. Non-specific ulcer colitis was detected. Select drug group of basic therapy:

A. Antibiotics
B. Aminosalicylates
C. Probiotics
D. Biologic agents
E. Immunomodulators

10. A 70 years old male patient complains of permanent dull pain in the mesogastral region, constipations. What obligatory examine method should be performed?

A. Scintigraphy
B. ERCPG
C. Colonoscopy
D. Liver biopsy
E. X-ray of abdominal cavity

Correct answers for the situation tasks:

1. Non-specific ulcerative colitis.Colonoscopy.
2. Irritable bowels syndrome with predominant diarrhea.Loperamide 2 mg per os.

The answers for the tests:
1-B, 2-C, 3-A, 4-A, 5-C, 6-A, 7-E, 8-A, 9-B, 10-C.

Recommended literature:

1. Goldman‟s Cecil medicine / [edited by] Lee Goldman, Andrew I. Schafer. – 24th ed. USA 2012, Elsevier, p. 2569
2. Feedman H. Application of the Montreal classification for Crohn‟s disease to a single clinician database of 1015 patients/ Can J Gastroenterol. 2007 Jun; 21(6): 363–366.
3. Inflammatory bowel disease. Practice manual / [edited by] Jens Rasenack. – Germany 2010, DR. Falk Pharma GmbH, 98 p.
4. Rome IV criteria: Bowel disorders. Online resource: http://theromefoundation.org/wp-content/uploads/bowel-disorders.pdf

Composed by Radionova T. O.

During the clinical analysis and differential diagnosis the teacher creates problematic situation that makes patients to get some additional information about the disease, to use of case studies, to choice methods of etiological and pathogenetic treatment. It is important to solve situational problems, picture graphs, charts for the assimilation of new knowledge and skills in this lesson.

It is advisable, that the student's tasks at this stage should be accurate and structured. The teacher should inspect writing tasks during the lesson, the results should be discussed.

5.3. The final stage.

The teacher should assess the current practical activity of each student during the lesson by conducting standardized final control by solving situational problems. The analysis of the success of each student, announced evaluation of each student magazine and exhibited in the volume of visits and student achievement. Group leader simultaneously captures evaluations of success roll volume and visits classes of students, teachers certify them with his signature.

The teacher briefly informs students about the topic of the next lesson and instructional techniques to prepare for it.

6. Testing materials are added.

7. Recommended literature:

A. Main:

1. Davidson's Principles and practice of medicine (21st revised ed.) / by Colledge N.R., Walker B.R., and Ralston S.H., eds. - Churchill Livingstone, 2010, - 1376 p.
2. Harrison's Principles of Internal Medicine, 19th Edition / by Longo D.L., Kasper D.L., Jameson J.L. et al. (eds.) McGraw-Hill Professional. 2015. - 4012 p.
3. The Merck Manual of Diagnosis and Therapy (nineteenth Edition) / Robert Berkow, Andrew J. Fletcher and others. - published by Merck Research Laboratories, 2011.
4. Goldman's Cecil medicine / [edited by] Lee Goldman, Andrew 1. Schafer. - 24th ed. USA 2012, Elsevier p. 2569

B. Additional:

1. Feedman H. Application of the Montreal classification for Crohn's disease to a single clinician database of 1015 patients / Can J Gastroenterol. 2007 Jun; 21(6): 363-366.
2. Inflammatory bowel disease. Practice manual / [edited by] Jens Rasenack, - Germany 2010, DR Falk Pharma GmbH, 98 p.
3. Rome IV criteria: functional gastrointestinal disorders, http://theromefoundation.org/rome-iv/roime-iv-journal-articles/

Composed by **as. Radionova T.O.**