FAR EASTERN UNIVERSITY – DR. NICANOR REYES MEDICAL FOUNDATION

*Institute of Medicine*

**DISEASES OF THE COLON**

A written report

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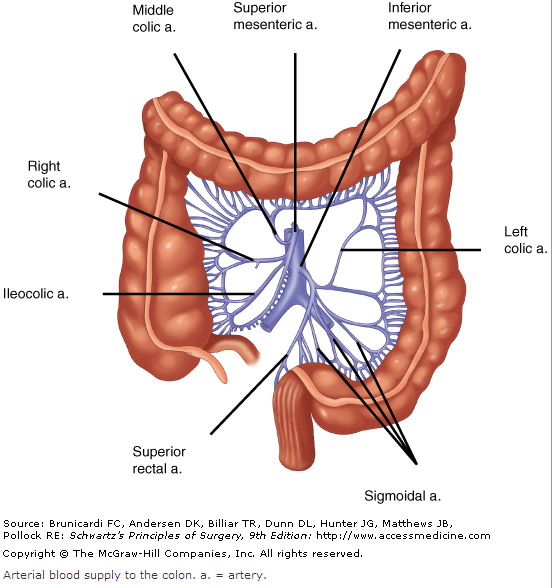
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February 23, 2012

**EMBRYOLOGY AND ANATOMY**

The gastrointestinal tract develops at the 4th week age of gestation. The following organs are midgut derivatives: Ascending colon, and Proximal transverse colon, which receive blood supply from the superior mesenteric artery. The hindgut derivatives are the distal transverse colon, descending colon, rectum, and proximal anus, which receive their blood supply from the inferior mesenteric artery.

The totality of the large intestines measures 3-5 feet. There arefive distinct layers namely: Mucosa, Submucosa, inner circular muscle, outer longitudinal muscle, and Serosa. The intraperitoneal colon and proximal one third of the rectum are covered by serosa; the mid and lower rectum lack serosa.

The colon functions as the major site for water absorption (90% of ileal fluid) and electrolytes regulation (e.g. Cl in exchange for bicarbonates). It is also has flora including anaerobes (e.g. Bacteroides) and aerobes (e.g. E. coli). Ammonia is produced from bacterial degradation.

**IRRITABLE BOWEL DISEASE**

Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by abdominal pain or discomfort and altered bowel habits in the absence of detectable structural abnormalities. No clear diagnostic markers exist for IBS, thus the diagnosis of the disorder is based on clinical presentation. Women are diagnosed with IBS two to three times as often as men and make up 80% of the population with severe IBS.

Pain or abdominal discomfort is a key symptom for the diagnosis of IBS. These symptoms should be improved with defecation and/or have their onset associated with a change in frequency or form of stool.

1. **ABDOMINAL PAIN**: Abdominal pain in IBS is highly variable in intensity and location. Pain in IBS is localized to the hypogastrium in 25%, the right side in 20%, to the left side in 20%, and the epigastrium in 10% of patients. It is frequently episodic and crampy or may be mild enough to be ignored or it may interfere with daily activities. It is exacerbated by eating or emotional stress and improved by passage of flatus or stools.
2. **ALTERED BOWEL HABITS** is the most consistent clinical feature in IBS. The most common pattern is constipation alternating with diarrhea, usually with one of these symptoms predominating. The constipation may at first be episodic, but eventually it becomes continuous and increasingly intractable to treatment with laxatives. Stools are usually hard with narrowed caliber, possibly reflecting excessive dehydration caused by prolonged colonic retention and spasm. Patients whose predominant symptom is constipation may have weeks or months of constipation interrupted with brief periods of diarrhea. In other patients, diarrhea may be the predominant symptom. The diarrheathat accompanies itusually consists of small volumes of loose stools ( < 200 mL). Nocturnal diarrhea does not occur in IBS. It may be aggravated by emotional stress or eating. Stool may be accompanied by passage of large amounts of mucus (*mucous colitis).*
3. **Gas and Flatulence.** Frequent complain of abdominal distention and increased belching or flatulence, all of which they attribute to increased gas. Most IBS patients have impaired transit and tolerance of intestinal gas loads. Also, patients with IBS tend to reflux gas from the distal to the more proximal intestine, which may explain the belching.
4. **Upper Gastrointestinal Symptoms.** Between 25 and 50% of patients with IBS complain of dyspepsia, heartburn, nausea, and vomiting. This suggests that other areas of the gut apart from the colon may be involved.

The pathogenesis of IBS is poorly understood, although roles of abnormal gut motor and sensory activity, central neural dysfunction, psychological disturbances, stress, and luminal factors have been proposed. As with studies of motor activity. IBS patients frequently exhibit exaggerated sensory responses to visceral stimulation. Postprandial pain has been temporally related to entry of the food bolus into the cecum in 74% of patients.

Lipids lower the thresholds for the first sensation of gas, discomfort, and pain in IBS patients. IBS patients have an increased area of referred pain after lipid ingestion. Postprandial symptoms in IBS patients may be explained in part by a nutrient-dependent exaggerated sensory component of the gastrocolonic response. In contrast to enhanced gut sensitivity, IBS patients do not exhibit heightened sensitivity elsewhere in the body. Thus, the afferent pathway disturbances in IBS appear to be selective for visceral innervation with sparing of somatic pathways.

It has been proposed that these exaggerated responses may be due to: (1) increased end-organ sensitivity with recruitment of "silent" nociceptors, (2) spinal hyperexcitability with activation of nitric oxide and possibly other neurotransmitters, (3) endogenous (cortical and brainstem) modulation of caudad nociceptive transmission, and (4) over time, the possible development of long-term hyperalgesia due to development of neuroplasticity, resulting in permanent or semipermanent changes in neural responses to chronic or recurrent visceral stimulation.

The role of central nervous system (CNS) factors in the pathogenesis of IBS is strongly suggested by the clinical association of emotional disorders and stress with symptom exacerbation and the therapeutic response to therapies that act on cerebral cortical sites.

Functional brain imaging studies shows the following:

1. Mid-cingulate cortex - a brain region concerned with attention processes and response selection shows greater activation in IBS patients. Modulation of this region is associated with changes in the subjective unpleasantness of pain.
2. Prefrontal lobe - contains a vigilance network within the brain that increases alertness. These may represent a form of cerebral dysfunction leading to the increased perception of visceral pain.

Thus, patients with IBS frequently demonstrate increased motor reactivity of the colon and small bowel to a variety of stimuli and altered visceral sensation associated with lowered sensation thresholds. These may result from CNS–enteric nervous system dysregulation.

IBS may be induced by GI infection. About a third of IBS patients experienced an acute "gastroenteritis-like" illness at the onset of their chronic IBS symptomatology. The microbes involved in the initial infection are : *Campylobacter*, *Salmonella*, *Shigella.* The serotonin (5HT)-containing enterochromaffin cells in the colon are increased in a subset of IBS-D patients. Since serotonin plays an important role in the regulation of GI motility and visceral perception, the increased release of serotonin may contribute to the postprandial symptoms of these patients and provides a rationale for the use of serotonin antagonists in the treatment of this disorder.

Because IBS is a disorder for which no pathognomonic abnormalities have been identified, its diagnosis relies on recognition of positive clinical features and elimination of other organic diseases. Clinical features suggestive of IBS include the following:

* recurrence of lower abdominal pain with altered bowel habits over a period of time without progressive deterioration,
* onset of symptoms during periods of stress or emotional upset,
* absence of other systemic symptoms such as fever and weight loss, and small-volume stool without any evidence of blood.

Because the major symptoms of IBS—abdominal pain, abdominal bloating, and alteration in bowel habits—are common complaints of many GI organic disorders, the list of differential diagnoses is a long one. The quality, location, and timing of pain may be helpful to suggest specific disorders. Pain that is due to IBS must be differentiated from other cause of pain.

The American Gastroenterological Association has delineated factors to be considered when determining the aggressiveness of the diagnostic evaluation. These include: the duration of symptoms, the change in symptoms over time, the age and sex of the patient, the referral status of the patient, prior diagnostic studies, a family history of colorectal malignancy, and the degree of psychosocial dysfunction.

Most patients should have a complete blood count and sigmoidoscopic examination. In those who have diarrhea stool specimens should be examined for ova and parasites. In those >40 years, an air-contrast barium enema or colonoscopy should also be performed. If the main symptoms are diarrhea and increased gas, the possibility of lactase deficiency should be ruled out with a hydrogen breath test or with evaluation after a 3-week lactose-free diet. In patients with concurrent symptoms of dyspepsia, upper GI radiographs or esophagogastroduodenoscopy may be advisable. In patients with postprandial right upper quadrant pain, an ultrasonogram of the gallbladder should be obtained.

**DIVERTICULAR DISEASE**

Two types of diverticula occur in the intestine: a **true diverticula,** which is a saclike herniation of the entire bowel wall, or a **false or pseudodiverticula,** which involves only a protrusion of the mucosa through the muscularis propria of the colon, and is the most common type of diverticulum affecting the colon.

The protrusion occurs at the point where the nutrient artery, or *vasa recti*, penetrates through the muscularis propria, resulting in a break in the integrity of the colonic wall. Diverticula commonly affect the sigmoid colon. This anatomic restriction may be a result of the relative high-pressure zone within the muscular sigmoid colon. Thus, higher amplitude contractions combined with constipated, high-fat content stool within the sigmoid lumen results in the creation of these diverticula.

*Diverticulitis* , or inflammation of a diverticulum, is related to the retention of particulate material within the diverticular sac and the formation of a fecalith. Consequently, the vasa recti is either compressed or eroded, leading to either perforation or bleeding.

Hemorrhage from a colonic diverticulum is the most common cause of hematochezia in patients >60 years, yet only 20% of patients with diverticulosis will have gastrointestinal bleeding. Most bleeds are self-limited and stop spontaneously with bowel rest.

Colonoscopy is done for localization of diverticular bleeding. It may be both diagnostic and therapeutic in the management of mild to moderate diverticular bleeding. Angiography is indicated for stable patient with massive bleeding. Segmental resection of the colon aims to eliminate the risk of further bleeding. Selective infusion of vasopressin can be given to stop the hemorrhage, although this has been associated with significant complications, including myocardial infarction and intestinal ischemia.

Acute uncomplicated diverticulitis characteristically presents with fever, anorexia, left lower quadrant abdominal pain, and obstipation. Generalized peritonitis indicates the presence of a diverticular perforation.

Physical examination shows that the patient may have abdominal distention and signs of localized or generalized peritonitis. Laboratory examination shows leucocytosis. In a plain abdominal film, rarely, a patient may present with an air-fluid level in the left lower quadrant. Resection is done for giant diverticulum of the sigmoid colon to avoid impending perforation. CT scan is best for diagnosis of diverticulitis, with following findings: sigmoid diverticula, thickened colonic wall >4 mm, and inflammation within the pericolic fat ± the collection of contrast material or fluid. In 16% of patients, an abdominal abscess may be present. Symptoms of irritable bowel syndrome (IBS) may mimic those of diverticulitis. Therefore, suspected diverticulitis that does not meet CT criteria or is not associated with a leukocytosis or fever is not diverticular disease.

Barium enema or colonoscopy should not be performed in the acute setting because of the higher risk of colonic perforation associated with insufflation or insertion of barium-based contrast material under pressure. It should be performed ~6 weeks after an attack of diverticular disease.

*Complicated diverticular disease* is defined as diverticular disease associated with an abscess or perforation and less commonly with a fistula. Perforated diverticular disease is staged using the Hinchey classification system. In complicated diverticular disease with fistula formation, common locations include cutaneous, vaginal, or vesicle fistulae. These conditions present with either passage of stool through the skin or vagina or the presence of air in the urinary stream (pneumaturia). Colovaginal fistulae are more common in women who have undergone a hysterectomy.

**Hinchey classification of diverticulitis:**

* Stage I: perforated diverticulitis with a confined paracolic abscess.
* Stage II: perforated diverticulitis that has closed spontaneously with distant abscess formation.
* Stage III: noncommunicating perforated diverticulitis with fecal peritonitis (the diverticular neck is closed off and therefore contrast will not freely expel on radiographic images).
* Stage IV: perforation and free communication with the peritoneum, resulting in fecal peritonitis.

**Medical Management**

1. Asymptomatic diverticular disease is best managed by diet alterations. Patients should be instructed to eat a fiber-enriched diet that includes 30 g of fiber each day. Supplementary fiber products such as Metamucil, Fibercon, or Citrucel are useful. The patient should also be instructed to avoid nuts and popcorn, which may obstruct the lumen of a diverticulum.
2. Symptomatic diverticular disease is defined as radiographic and hematologic confirmation of inflammation and infection within the colon. It is treated initially with antibiotics and bowel rest. The current recommended antimicrobial coverage is trimethoprim/sulfamethoxazole or ciprofloxacin and metronidazole targeting aerobic gram-negative rods and anaerobic bacteria. Unfortunately, these agents do not cover enterococci, and the addition of ampicillin to this regimen for nonresponders is recommended.

**Surgical Management**

In patients who are low risk,surgical therapy can be offered to patients who have had at least two documented attacks of diverticulitis requiring hospitalization or those who do not rapidly improve on medical therapy. Surgical therapy is indicated in all low surgical risk patients with complicated diverticular disease. The goals of surgical management of diverticular disease are: controlling sepsis, eliminating complications such as fistula or obstruction, removing the diseased colonic segment, and restoring intestinal continuity.

Surgical objectives include removal of the diseased sigmoid down to the rectosigmoid junction. Failure to do this may result in recurrent disease. The current options for uncomplicated diverticular disease include an open sigmoid resection or a laparoscopic sigmoid resection. The benefits of laparoscopic resection over open surgical techniques include early discharge (by at least 1 day), less narcotic use, and an earlier return to work. However, laparoscopic resection is associated with a longer operative procedure and is more costly. The complication rates between open and laparoscopic surgery are similar.

The options for the surgical management of complicated diverticular disease include the following: (1) proximal diversion of the fecal stream with an ileostomy or colostomy and sutured omental patch with drainage, (2) resection with colostomy and mucus fistula or closure of distal bowel with formation of a Hartmann's pouch, (3) resection with anastomosis (coloproctostomy), or (4) resection with anastomosis and diversion (coloproctostomy with loop ileostomy or colostomy).

For Hinchey stages I and II disease, percutaneous drainage followed by resection with anastomosis about 6 weeks later. Hinchey stage III disease is managed with a Hartman's procedure or with primary anastomosis and proximal diversion. Recurrent diverticular disease develops in patients following inadequate surgical resection.

**INFLAMMATORY BOWEL DISEASE**

Epidemiology of this disease varies with different geographic areas. The highest incidence is in Europe, the United Kingdom, and North America. The incidence of IBD, especially Ulcerataive Colitis (UC), is rising in Japan, South Korea, Singapore, northern India, and Latin America, areas previously thought to have low incidence.

The first peak age of onset of UC and CD is at 15 and 30 years, respectively. The 2nd peak occurs between the ages of 60 and 80 years, respectively. The male to female ratio in Ulcerative Colitis is 1:1, and for Chron’s Disease 1.1–1.8:1.

Risk factors include cigarette Smoking, use of Oral Contraceptives, appendectomy (but is protective against Ulcerative Colitis), and family history (genetics).

Etiology involves **exogenous Factors**, which is the normal luminal flora, and **host Factors** , including the intestinal epithelial cell barrier function, innate immune function, and adaptive immune function. As such, IBD is currently considered an inappropriate response to the endogenous microbial flora within the intestine, with or without some component of autoimmunity.

IBD is a polygenic disorder that gives rise to multiple clinical subgroups within UC and CD. ***CARD15*** (caspase-associated recruitment domain containing protein 15) – Chr 16 (LOSS of FUNCTION in CD) is expressed by intestinal epithelial cells, Paneth cells, monocytes, macrophages, and dendritic cells. Polymorphisms are also detected in **DLG5 and the IL-23 receptor.**

Under normal conditions, the mucosal immune system is unreactive to luminal contents due to oral tolerance**.** In IBD this suppression of inflammation is altered, leading to uncontrolled inflammation.In both UC and CD, an inflammatory pathway emerges from the genetic predisposition in which activated CD4+ T cells in the lamina propria secrete inflammatory cytokines.

The immune inflammatory response is perpetuated by T-cell activation. Examples are IL-1, IL-6, and TNF (produced in response to infection but are usually turned off or inhibited at the appropriate time to limit tissue damage. THIS IS NOT THE CASE FOR IBD). There is imbalance between the proinflammatory and anti-inflammatory mediators.

*Salmonella* sp., *Shigella* sp., *Campylobacter* sp., *Clostridium difficile* may initiate IBD. In an IBD patient, the normal flora is likely perceived as if it were a pathogen (e.g. *Bacteroides*, *Clostridia, Escherichia)*. Psychosocial factors and acute daily stress worsen symptoms.

**Macroscopic Features** show evidence of mucosal disease involving the rectum to proximal parts to involve all or part of colon (**40–50%** rectum and rectosigmoid ; **30–40%:** extend beyond the sigmoid but not involving the whole colon; **20%** (+) total colitis.) It follows a PROXIMAL SPREAD IN CONTINUITY. Backwash ileitis is observed. The following are specific findings:

* Mild inflammation : erythematous, fine granular surface (sandpaper)
* Severe disease: mucosa is hemorrhagic, edematous, and ulcerated
* Long Standing disease: inflammatory polyps (pseudopolyps) - result of epithelial regeneration
* Fulminant disease: toxic colitis or megacolon (bowel wall thins and the mucosa is severely ulcerated) --perforation

**Microscopic Features** happen to the mucosa and superficial submucosa (deeper layers unaffected except in fulminant disease). There is mucosal vascular congestion, with edema and focal hemorrhage, and an inflammatory cell infiltration. Signs of Chronicity are observed: architecture of the colon is distorted, and basal plasma cells and multiple basal lymphoid aggregates.

Chron’s Disease affects mouth to the anus. The rectum is often spared. Affectation is segmental with skip areas in the midst of diseased intestine. There are perirectal fistulas, fissures, abscesses, and anal stenosis. It is a transmural process. Aphthous or small superficial ulcerations characterize mild disease. Stellate ulcerations fuse longitudinally and transversely to demarcate islands of mucosa (**"cobblestone" appearance)**. Pseudopolyps can form.

Major symptoms of UC include diarrhea, rectal bleeding, tenesmus, passage of mucus, and crampy abdominal pain. The severity of symptoms correlates with the extent of disease. Symptoms usually present for weeks or months. If with proctitis, patient usually passes fresh blood or blood-stained mucus. If the lesion extends beyond the rectum, blood is usually mixed with stool or grossly bloody diarrhea may be noted. Diarrhea may be nocturnal and/or postprandial. Severe pain is not a prominent symptom. Anorexia, nausea, fever and weight loss may be evident.

|  |  |  |  |
| --- | --- | --- | --- |
| **Ulcerative Colitis Disease Presentation** | | | |
|  | **Mild** | **Moderate** | **Severe** |
| Bowel movements | <4 per day | 4–6 per day | >6 per day |
| Blood in stool | Small | Moderate | Severe |
| Fever | None | <37.5°C mean | >37.5°C mean |
| Tachycardia | None | <90 mean pulse | >90 mean pulse |
| Anemia | Mild | >75% | 75% |
| Sedimentation rate | <30 mm |  | >30 mm |
| Endoscopic appearance | Erythema, decreased vascular pattern, fine granularity | Marked erythema, coarse granularity, absent vascular markings, contact bleeding, no ulcerations | Spontaneous bleeding, ulcerations |

Complications of UC includes a catastrophic illness, massive hemorrhage (1%), toxic megacolon (5%) requiring urgent colectomy, perforation, which is the most dangerous; rarely toxic colitis – severe ulceration, and stricture (5-10%).

Chron’s Disease, on the other hand, presents with the following:

1. **Ileocolitis** 
   * terminal ileum
   * right lower quadrant pain and diarrhea
   * Pain is usually colicky; it precedes and is relieved by defecation
   * low-grade fever
   * Weight loss
   * inflammatory mass may be palpated in the right lower quadrant of the abdomen
   * "string sign“
   * Bowel obstruction
   * Localized wall thinning, microperforation and fistula formation to the adjacent bowel, the skin, or the urinary bladder, or to an abscess cavity in the mesentery
2. **. Jejunoileitis**
   * Malabsorption (hypoalbuminemia, hypocalcemia, hypomagnesemia, coagulopathy, and hyperoxaluria )
   * Steatorrhea
   * Nutritional deficiencies
   * Vertebral fractures, Pellagra, megaloblastic anemia and neurologic symptoms.
   * Diarrhea is characteristic of active disease
3. **Colitis and Perianal Disease**
   * low-grade fevers, malaise, diarrhea, crampy abdominal pain, hematochezia
   * Gross bleeding is not as common
   * Pain in passage of fecal material
   * Decreased rectal compliance 🡪 diarrhea
   * Stricturing
   * Fistulas 🡪 malabsorption
   * Perianal incontinence, large hemorrhoidal tags, anal strictures, anorectal fistulae, and perirectal abscesses
4. **Gastroduodenal Disease**
   * nausea, vomiting, and epigastric pain
   * second portion of the duodenum 🡪 *H. pylori*–negative gastritis
   * gastric outlet obstruction (advanced disease)

Complications include perforation (1-2%), commonly in the ileum, peritonitis of free perforation (colonic), and intraabdominal and pelvic abscesses (10–30%). Laboratory examinations reveal elevated ESR and CRP with hypoalbuminemia, anemia, and leukocytosis (more severe). Endoscopy shows rectal sparing, aphthous ulcerations, fistulas, and skip lesions, thickened folds, “cobblestoning”. Barium enema may show strictures. Colonoscopy provides for examination and biopsy of the terminal ileum. Upper endoscopy reveals gastroduodenal involvement. Wire Wireless capsule endoscopy (WCE) allows direct visualization of the entire small-bowel mucosa.

**Radiographic Features**: String sign and wide gaps of normal or dilated bowel between involved segments. **CT enterography** is becoming the first-line test for the evaluation of suspected CD and its complications. **MRI** may prove superior for demonstrating pelvic lesions such as ischiorectal abscesses.

Serologic markers for IBD include: **pANCA** - perinuclear antineutrophil cytoplasmic antibodies found in 60–70% of UC and 5–10% of CD. **ASCAs:** anti-*Saccharomyces cerevisiae* antibodies are present in 10–15% of UC, 60–70% of CD, and 5% of non-IBD controls are ASCA-positive.

**Differential Diagnosis for IBD**

|  |  |  |
| --- | --- | --- |
| **Infectious Etiologies** | | |
| Bacterial    Salmonella    Shigella    Toxigenic Escherichia coli    Campylobacter    Yersinia    Clostridium difficile    Gonorrhea    Chlamydia trachomatis | Mycobacterial    Tuberculosis    Mycobacterium avium  Parasitic    Amebiasis    Isospora    Trichuris trichura    Hookworm    Strongyloides | Viral    Cytomegalovirus    Herpes simplex    HIV  Fungal    Histoplasmosis    Candida    Aspergillus |

|  |  |  |
| --- | --- | --- |
| Noninfectious Etiologies | | |
| Inflammatory    Appendicitis    Diverticulitis    Diversion colitis    Collagenous/lymphocytic colitis    Ischemic colitis    Radiation colitis/enteritis    Solitary rectal ulcer syndrome    Eosinophilc gastroenteritis    Neutropenic colitis    Beçhet's syndrome    Graft-versus-host disease | Neoplastic    Lymphoma    Metastatic carcinoma    Carcinoma of the ileum    Carcinoid    Familial polyposis | Drugs and Chemicals    NSAIDs    Phosphasoda    Cathartic colon    Gold    Oral contraceptives    Cocaine    Chemotherapy |

**Extraintestinal Manifestations of IBD**

* **Dermatologic**

a*. Pyoderma gangrenosum: 1–12% of UC*

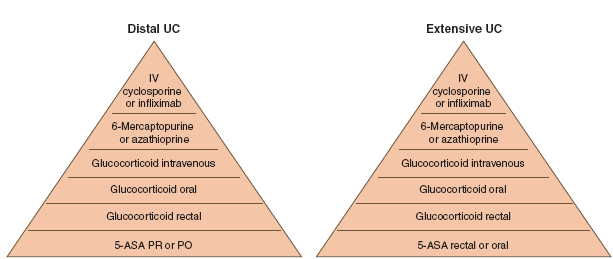
* + Associated with severe disease
  + Dorsal surface of the feet and legs but may occur on the arms, chest, stoma, and even the face.
  + begins as a pustule and then spreads concentrically
  + single or multiple and grow as large as 30 cm
  + Require IV antibiotics

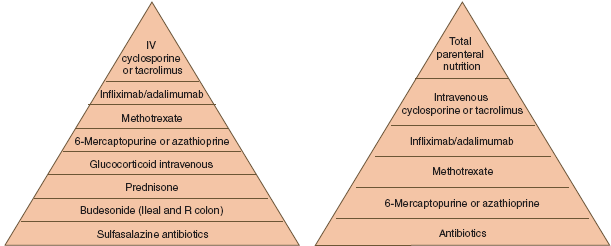
b. *Pyoderma vegetans , pyostomatitis vegetans, Sweet's syndrome, metastatic CD, psoriasis, perianal skin tags*

* **Rheumatologic**
* *Peripheral arthritis (CD)* : asymmetric, polyarticular, and migratory; affects large joints of the upper and lower extremities
* *Ankylosing spondylitis (CD)* : spine and pelvis; continuous and progressive; permanent skeletal damage and deformity
* **Ocular**
  + conjunctivitis,
  + anterior uveitis/iritis
  + Episcleritis
* **Hepatobiliary**
  + Hepatic steatosis (biopsy)
  + Hepatomegaly, fatty liver
  + Cholelithiasis is more common in CD
  + intrahepatic and extrahepatic bile duct inflammation and fibrosis
* **Urologic**
  + Calculi
  + Ureteral obstruction
  + Fistulas
  + nephrolithiasis (10–20%) occurs in patients with CD following small-bowel resection
* **Metabolic Bone Disorder**
  + Low bone mass 🡪 fractures
  + Osteonecrosis 🡪 hips more often than knees and shoulders
* **Thromboembolic Disorder**
* Risk of both venous and arterial thrombosis even if the disease is not active
* Hypercoagulable state

**Medical treatment** for IBD include the following:

* 5-ASA Agents – mainstay (sulfasalazine)
* Glucocorticoids – moderate to severe conditions
* Antibiotics
* Azathioprine and 6-Mercaptopurine
* Methotrexate – reduce GC dosage
* Cyclosporine – severe UC
* Tacrolimus
* Anti-TNF Antibody
* Nutritional Therapies





**Surgical Treatment**

|  |  |
| --- | --- |
| Ulcerative Colitis | Crohn's Disease |
| Intractable disease | Small Intestine |
| Fulminant disease | Stricture and obstruction unresponsive to medical therapy |
| Toxic megacolon | Massive hemorrhage |
| Colonic perforation | Refractory fistula |
| Massive colonic hemorrhage | Abscess |
| Extracolonic disease | Colon and Rectum |
| Colonic obstruction | Intractable disease |
| Colon cancer prophylaxis | Fulminant disease |
| Colon dysplasia or cancer | Perianal disease unresponsive to medical therapy |
|  | Refractory fistula |
|  | Colonic obstruction |
|  | Cancer prophylaxis |
|  | Colon dysplasia or cancer |

**BENIGN TUMORS OF THE COLON: POLYPS OF THE COLON**

Polyps are discrete mass lesions that protrude into the intestinal lumen. Although most commonly sporadic, they may be inherited as part of a familial polyposis syndrome. Polyps may be divided into three major pathologic groups: mucosal neoplastic (adenomatous) polyps, mucosal nonneoplastic polyps (hyperplastic, juvenile polyps, hamartomas, inflammatory polyps), and submucosal lesions (lipomas, lymphoid aggregates, carcinoids, pneumatosis cystoides intestinalis). The nonneoplastic mucosal polyps have no malignant potential and usually are discovered incidentally at colonoscopy or barium enema. Of polyps removed at colonoscopy, over 70% are adenomatous; most of the remainder are hyperplastic. Adenomatous polyps have significant clinical implications and will be considered furtheR. Hyperplastic polyps are increasingly called “serrated polyps” due to their saw-tooth mucosal architecture. Serrated polyps now are classified into three subgroups: hyperplastic polyps, sessile serrated adenomas, and traditional serrated adenomas. Small hyperplastic polyps (< 5 mm) located in the rectosigmoid region are of no consequence, except that they cannot reliably be distinguished from adenomatous lesions other than by biopsy. The significance of large hyperplastic polyps located proximal to the rectum is uncertain. “Sessile serrated adenomas” refers to a subset (15%) of serrated polyps that have abnormal architecture and cellular proliferation. “Traditional serrated adenoma” refers to polyps with serrated polyps with cytologic dysplasia. Still misdiagnosed by some pathologists as hyperplastic polyps, it now is recognized that both sessile and traditional serrated adenomas harbor an increased risk of colorectal cancer similar to other adenomas.

**Nonfamilial Adenomatous Polyps**

Histologically, adenomas are classified as tubular, villous, tubulovillous, or serrated. Adenomas may be flat, sessile or pedunculated (containing a stalk). They are present in 30% of adults over 50 years of age. Their significance is that over 95% of cases of adenocarcinoma of the colon are believed to arise from adenomas. It is proposed that there is an adenoma to carcinoma sequence whereby colorectal cancer develops through a continuous process from normal mucosa to adenoma to carcinoma. The majority of cancers arise in adenomas after inactivation of the *APC* gene leads to chromosomal instability and inactivation or loss of other tumor suppressor genes. By contrast, cancers arising from serrated adenomas appear to have CpG island methylation that leads to *BRAF* oncogene activation or inactivation of mismatch repair genes with microsatellite instability. Most adenomas are small (< 1 cm) and have a low risk of becoming malignant; < 5% of these enlarge with time. Adenomas are classified as “advanced” if they are ≥ 1 cm, or contain villous features or high-grade dysplasia. Advanced adenomas are believed to have a higher risk of harboring or progressing to malignancy. It has been estimated from longitudinal studies that it takes an average of 5 years for a medium-sized polyp to develop from normal-appearing mucosa and 10 years for a gross cancer to arise. In a 2009 meta-analysis of 18 studies in average-risk populations, the pooled prevalence of advanced adenomas is 6% and colorectal cancer 0.3%.

*Clinical and Laboratory Diagnosis*

Most patients with adenomatous polyps are completely asymptomatic. Chronic occult blood loss may lead to iron deficiency anemia. Large polyps may ulcerate, resulting in intermittent hematochezia.

FOBT, FIT, and fecal DNA tests are available as part of colorectal cancer screening programs (see Chapter 39). FIT is a fecal blood immunochemical test for hemoglobin that is more sensitive than guaiac-based tests for the detection of colorectal cancer and advanced adenomas. In prospective studies, the FIT and other new fecal tests detected 40–60% of advanced noncancerous adenomas.

Polyps are identified by means of barium enema examinations or CT colonography. Both studies require bowel cleansing with laxatives before the study and insertion of a rectal catheter for air insufflation during the study. CT colonography (“virtual colonoscopy”) uses data from helical CT imaging with computer-enabled luminal image reconstruction to generate two-dimensional and three-dimensional images of the colon. Using optimal imaging software with multidetector helical CT scanners, several studies report a sensitivity of ≥90% for the detection of polyps > 10 mm in size. However, the accuracy for detection of polyps 5–9 mm in size is significantly lower (sensitivity 50%). A small proportion of these small polyps harbor advanced histology (3-7%) orcarcinoma (< 1%). Abdominal CT imaging results in a radiation exposure that may lead to a small risk of cancer. CT colonography is endorsed by US Multisociety Task Force as an acceptable option for screening for colorectal adenomatous polyps and cancer in average risk asymptomatic adults. Barium enema examinations as currently performed detect< 50% of colorectal polyps ≥1 cm in size. Where CT colonography is available, barium enema is no longer recommended due to its poor diagnostic accuracy.

Colonoscopy allows evaluation of the entire colon and is the best means of detecting and removing adenomatous polyps. It should be performed in all patients who have positive FOBT, FIT, fecal, or DNA tests or iron deficiency Anemia as the prevalence of colonic neoplasms is increased in these patients. Colonoscopy should also be performed in patients with polyps detected on radiologic imaging studies (barium enema or CT colonography) or adenomas detected on flexible sigmoidoscopy to remove these polyps and to fully evaluate the entire colon. Capsule endoscopy of the colon has a 73% sensitivity and 79% specificity for detection of adenomas with advanced histology or cancer compared with colonoscopy and cannot be recommended at this time to screen for colorectal neoplasia.

*Treatment*

**Colonoscopic Polypectomy**

Most adenomatous polyps are amenable to colonoscopic removal with biopsy forceps or snare cautery. Large sessile polyps (> 2–3 cm) may be removed in by snare cautery using a variety of techniques (eg, piecemeal or saline-lift assisted mucosal resection) or may require surgical resection. Patients with large sessile polyps removed in piecemeal fashion should undergo repeated colonoscopy in 2–6 months to verify complete polyp removal. Complications after colonoscopic polypectomy include perforation in 0.2% and clinically significant bleeding in 0.3–1% of patients. A malignant polyp is an adenoma that appears grossly benign at endoscopy but on histologic assessment is found to contain cancer that has penetrated through the muscularis mucosae into the submucosa. Malignant polyps may be considered to be adequately treated by polypectomy alone if: (1) the polyp is completely excised and submitted for pathologic examination, (2) it is well differentiated, (3) the margin is not involved, and (4) there is no vascular invasion. The risk of residual cancer or nodal metastasis with favourable histologic features is < 1%. The excision site of these “favorable” malignant polyps should be checked in 3 months for residual tissue. In patients with malignant polyps that have unfavorable histologic features, cancer resection is advisable if the patient is a good operative candidate.

**Postpolypectomy Surveillance**

Adenomas can be found in 30–40% of patients when another colonoscopy is performed within 3–5 years after the initial examination. Periodic colonoscopic surveillance is therefore recommended to detect these “metachronous” adenomas, which either may be new or may have been overlooked during the initial examination. Most of these adenomas are small, without high-risk features and of little immediate clinical significance. The probability of detecting advanced neoplasms at surveillance colonoscopy depends on the number, size, and histologic features of the polyps removed on initial (index) colonoscopy. Patients with 1–2 small (< 1 cm) tubular adenomas (without villous features or high-grade dysplasia) should have their next colonoscopy in 5–10 years. Patients with 3–10 adenomas, an adenoma > 1 cm, or an adenoma with villous features or high-grade dysplasia should have their next colonoscopy at 3 years. Patients with more than 10 adenomas should have a repeat colonoscopy at 1–2 years and may be considered for evaluation for a familial polyposis syndrome

**COLORECTAL CANCER**

It is second to lung cancer as a cause of death from cancer**.** It is more common in female**s** >50 years old.

**Polyps and Molecular Pathogenesis**

* Adenomatous polyps (a grossly visible protrusion)
  + nonneoplastic hamartoma (*juvenile polyp*)
  + hyperplastic mucosal proliferation (*hyperplastic polyp*)
  + adenomatous polyp.
* Only adenomas are clearly premalignant, and only a minority of such lesions becomes cancer.
* Adenomatous polyps – 30% middle-aged, 50% elderly
* <1% of polyps ever become malignant
* Most polyps produce no symptoms and remain clinically undetected.
* Molecular changes, dysplastic lesions, microscopic foci (carcinoma in situ).
  + Point mutations in the K-*ras* protooncogene
  + hypomethylation of DNA
  + Loss of DNA (*allelic loss*) at the site of a tumor-suppressor gene
* Cancers develop more frequently in sessile polyps.
* Histologically, adenomatous polyps may be
  + Tubular
  + villous (i.e., papillary) – most are sessile – become malignant 3x more
  + tubulovillous.
* Adenomatous polyps are thought to require >5 years of growth before becoming clinically significant

**Etiology and Risk Factors**

* Diet
  + Environmental factor; upper socioeconomic populations who live in urban areas; mortality associated with increased consumption of animal fats, calories and meat protein.
* Animal Fats
  + Ingestion of animal fats found in red meats and processed meat leads to an increased proportion of anaerobes in the gut microflora
* Insulin Resistance
  + Large calories + physical inactivity increases prevalence of obesity leading to insulin resistance. Increased IGF-1 is said to stimulate proliferation of intestinal mucosa.
* Fiber
  + Randomized trials failed to show any value of high dietary fiber or high in vegetables and fruits inn preventing recurrence of colorectal adenomas or colorectal cancer
* Hereditary Factors and Syndromes
  + 25% have a family history of the disease, suggesting a hereditary predisposition. Inherited large-bowel cancers can be divided into two main groups: the well-studied but uncommon polyposis syndromes and the more common nonpolyposis syndromes

**Polyposis Coli**

* Rare condition
* Appearance of thousands of adenomatous polyps throughout the large bowel.
* Defect in the colonic mucosa, leading to an abnormal proliferative pattern and impaired DNA repair mechanisms.
* AD; no family history, spontaneous mutation
* Deletion in the Chr 5
  + Gardners syndrome – soft tissue and body tumores
  + Turcot’s syndrome – CNS
* If the polyposis is not treated surgically, colorectal cancer will develop in almost all patients before age 40.
* Colectomy – most effective than NSAIDs
* Testing for occult blood in the stool is an inadequate screening maneuver.

**Hereditary Nonpolyposis Colon Cancer**

* Also known as *Lynch syndrome*
* AD; familial history is positive, colorectal cancer in at least 2 generations
* <50 years
* Proximal colon tumors in HNPCC have a better prognosis than sporadic tumors from patients of similar age.
* Associated with germline mutations of several genes, particularly *hMSH2* on chromosome 2 and *hMLH1* on chromosome 3.
* Testing for microsatellite instability"

**Inflammatory Bowel Disease**

* Develop more commonly in patients with ulcerative colitis than in those with granulomatous colitis
* Relatively small risk during the initial 10 years of the disease, but then it appears to increase at a rate of ~0.5–1% per year.
* Cancer may develop in 8–30% of patients after 25 years. The risk is higher in younger patients with pancolitis.

Other High-Risk Conditions

* *Streptococcus bovis* Bacteremia
* Cigarette smoking

**Primary Prevention**

* Aspirin and other NSAIDs
* Oral folic acid supplements and oral calcium supplements
* Antioxidant vitamins such as ascorbic acid, tocopherols, and -carotene are ineffective
* Estrogen-replacement therapy has been associated with a reduction in the risk of colorectal cancer in women

Screening

* Early detection of colorectal cancer
  + digital rectal examinations
  + fecal occult blood testing

\*Screening techniques for large-bowel cancer in asymptomatic persons remain unsatisfactory.

**Clinical Features**

* Presenting Symptoms
  + Symptoms vary with the anatomic location of the tumor.
  + Lesions of the right colon commonly ulcerate, leading to chronic, insidious blood loss without a change in the appearance of the stool.
    - Ascending colon : fatigue, palpitations, angina pectoris , hypochromic, microcytic anemia indicative of iron deficiency.
* Since the cancer may bleed intermittently, a random fecal occult blood test may be negative.
* Since stool becomes more formed as it passes into the transverse and descending colon, tumors arising there tend to impede the passage of stool, resulting in the development
  + abdominal cramping
  + occasional obstruction
  + perforation.
* Cancers arising in the rectosigmoid are often associated with
  + Hematochezia
  + Tenesmus
  + Narrowing of the caliber of stool
  + anemia is an infrequent finding.

**Staging, Prognostic Factors, and Patterns of Spread**

* Prognosis is related to the depth of tumor penetration into the bowel wall and the presence of both regional lymph node involvement and distant metastases.
* Staging system introduced by Dukes and applied to a TNM classification method, in which T represents the depth of tumor penetration, N the presence of lymph node involvement, and M the presence or absence of distant metastases

|  |
| --- |
| **Predictors of Poor Outcome Following Total Surgical Resection of Colorectal Cancer** |
| Tumor spread to regional lymph nodes |
| Number of regional lymph nodes involved |
| Tumor penetration through the bowel wall |
| Poorly differentiated histology |
| Perforation |
| Tumor adherence to adjacent organs |
| Venous invasion |
| Preoperative elevation of CEA titer (>5.0 ng/mL) |
| Aneuploidy |
| Specific chromosomal deletion (e.g., allelic loss on chromosome 18q) |

**Colorectal Cancer: Treatment**

* Total resection of tumor is the optimal treatment when a malignant lesion is detected in the large bowel.
* A colonoscopy of the entire large bowel should be performed to identify synchronous neoplasms and/or polyps.
* The detection of metastases should not preclude surgery in patients with tumor-related symptoms such as gastrointestinal bleeding or obstruction, but it often prompts the use of a less radical operative procedure.
* At the time of laparotomy, the entire peritoneal cavity should be examined, with thorough inspection of the liver, pelvis, and hemidiaphragm and careful palpation of the full length of the large bowel.
* Following recovery from a complete resection, patients should be observed carefully for 5 years by semiannual physical examinations and yearly blood chemistry measurements. If a complete colonoscopy was not performed preoperatively, it should be carried out within the first several postoperative months.
* Radiation therapy
* Systemic therapy for patients with colorectal cancer has become more effective
  + 5-FU remains the backbone of treatment for this disease.
  + Irinotecan (CPT-11)
  + Cetuximab (Erbitux) and panitumumab (Vectibix)
  + Bevacizumab (Avastin) is a monoclonal antibody directed against the vascular endothelial growth factor (VEGF) and is thought to act as an anti-angiogenesis agent.