The Colon

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Contents

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4.1 Macroscopic Anatomy

4.1.1 Shape and Structure

The colon follows the small intestine. It is approximately 5- to 8-cm-wide and 80- to 150-cm-long and begins after the ileocecal valve and ends at the anus. Its different segments are shown in ◘ Fig. 4.1.

The *ileocecal valve* (or Bauhin's valve) separates the small bowel from the colon and opens into the pouch-like cecum in the right iliac fossa. In the cecal base, a few centimeters below the valve, the appendix, a finger-like thin tube (3- to 5-cm-wide, 5- to 10-cm-long) opens and extends toward the retrocecal region (2/3 of cases) or the pelvis.

The *ascending colon*, or right colon, rises along the right flank for 15–20 cm up to the hepatic flexure. The anterior and lateral surfaces of the ascending colon (like the descending colon) are positioned inside the peritoneal cavity; the posterior surface is retroperitoneal. The outer lateral surface of the colon is attached to the retroperitoneum by the Toldt's fascia which attaches to the lateral taenia.

The *transverse colon* extends 25–40 cm in the upper abdomen between the hepatic flexure at the right hypochondrium and the splenic flexure at the left hypochondrium. These two structures are fixed by the phrenocolic and splenocolic ligaments, respectively, whereas the transverse colon is mobile in the peritoneal cavity. The transverse colon is the point of attachment (along the anterior taenia) of the large omentum, a structure made by the fusion of the visceral and parietal peritonea, containing, among other things, visceral fat and plunging toward the pelvis to cover, like an apron, the abdominal viscera.

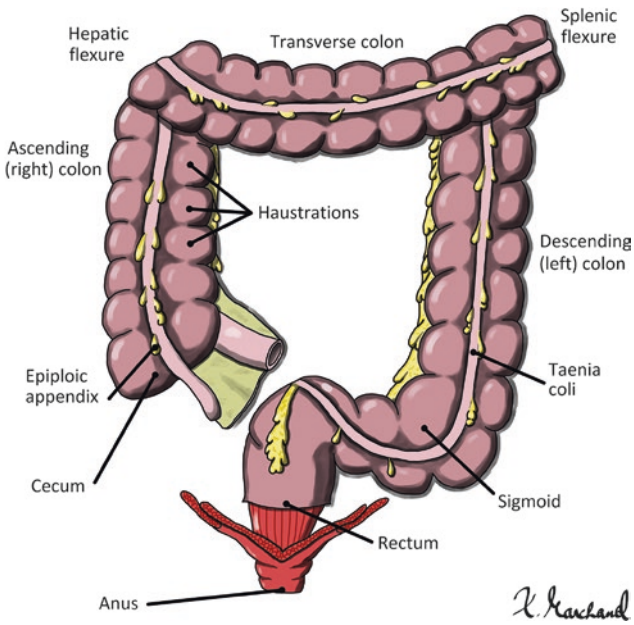
The *left colon*, or descending colon, runs along the left side of the abdomen for 15–20 cm proximal to the sigmoid. Like the right colon, its anterior surface is within the peritoneal cavity, while its posterior surface, attached by the Toldt's fascia to the retroperitoneum, is isolated behind the peritoneal cavity.

The *sigmoid* is an S-shaped colonic segment, often smaller in size and of variable length (15–50 cm). The mobility of the sigmoid in the abdominal cavity makes torsion (volvulus) possible.

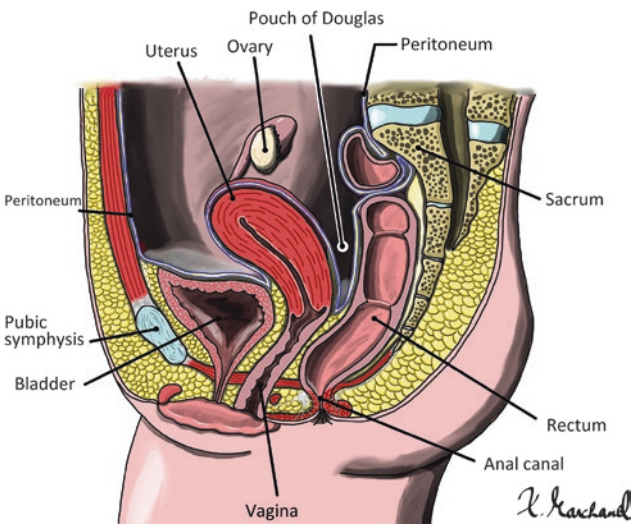
The *rectum* extends 12–15 cm from the anus to the rectosigmoid angle. The posterior rectum, with its mesorectum, rests against the sacrum, while the anterior wall faces the pelvic organs (bladder, uterus) (◘ Fig. 4.2). The rectum is located outside the peritoneum, except for its anterior part which is covered by visceral peritoneum up to 5–10 cm from the anus. This peritoneal recess between the anterior part of the rectum and the pelvic organs is called Douglas' cul-de-sac (or Pouch of Douglas) (where cancerous cells from intra-abdominal tumors can "fall" and form the "Blumer's shelf" that can be palpated on a digital rectal examination as a rigid or indurated area). Inside the rectum, three transverse folds are known as the valves of Houston (anatomical structures however without a decisive physiological role).

The *anal canal*, 2- to 3-cm-long, begins at the mucocutaneous junction where the colonic glandular mucosa meets the cutaneous squamous epithelium. The rectum and anus are described more extensively in the ▶ Chap. 7.

A colon that is distended more than 10–12 cm in width (usually in the transverse or ascending colon) is



◘ **Fig. 4.1** Anatomy of the human colon (anterior view)



◘ **Fig. 4.2** Rectum and pelvis – lateral view in woman: the rectum is extraperitoneal except for its anterior part which is partially covered by the peritoneum

known as a megacolon. An excessively long colon (usually at the expense of the sigmoid) is called a dolichocolon (dolicho: "long" in Greek). The colon appears as a tubular organ, with sacculations, or haustrations, made by contractions of the longitudinal muscles that shorten the colon like an accordion.

4.1.2 Vascular Supply

Arteries The right colon, from the cecum to the proximal transverse colon, is vascularized by branches of the superior mesenteric artery arising from the aorta at the level of the L1 vertebra just above the renal arteries. The left colon and sigmoid are vascularized by the inferior mesenteric artery arising from the aorta at L3 (above the aortoiliac bifurcation at L4) (Fig. 4.3). The transverse colon is vascularized by the Drummond's marginal artery an arcade connecting the superior and inferior mesenteric arteries and running along the mesenteric edge of the transverse colon. The splenic angle region is located in the middle section of this vascular arcade, at the very end of vascular territories from both feeding arteries, and constitutes a watershed zone, an area highly susceptible to ischemic damages in case of hypoperfusion (see Ischemic colitis).

The rectum is vascularized by five rectal arteries (also called hemorrhoidal arteries): the upper, middle (right and left), and lower (right and left). The superior rectal artery is the main one. Arising from the inferior mesenteric artery, it is divided into two branches for the posterior and anterior sides of the rectum. The middle and lower rectal arteries originate from the internal iliac arteries to supply the lower rectum and the genital area.

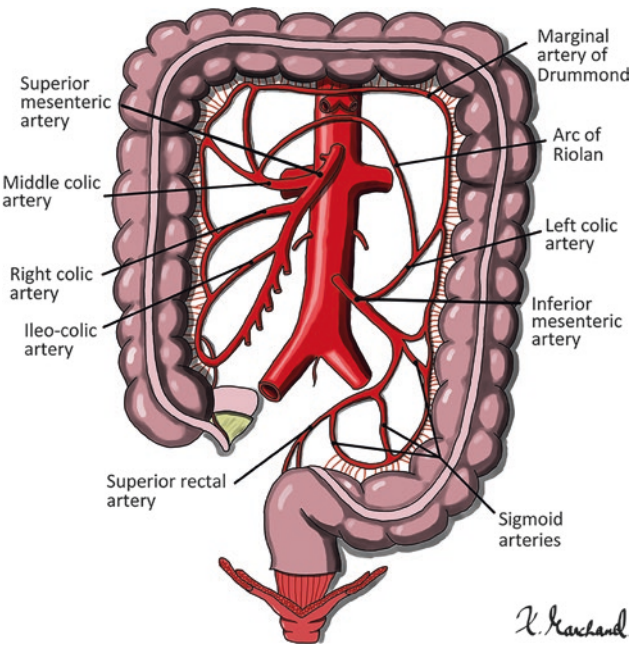


Fig. 4.3 Colon irrigating arteries

Veins Veins follow artery routing. The superior mesenteric vein and inferior mesenteric vein (via the splenic vein) drain into the portal vein toward the liver. For the middle and lower parts of the rectum, venous drainage is toward the internal iliac veins; the fact that the latter does not drain to the liver may explain the higher frequency of pulmonary metastases in rectal cancers compared to colon cancers (where metastases are mainly hepatic).

Lymphatics Lymphatics follow blood vessels. Abdominal lymphatics thus run through the mesentery to the large cistern and then, through the thorax, to the thoracic duct and the left subclavian vein. Lymphatics from the lower rectum and anus drain to lymph nodes in the iliac and inguinal regions.

4.1.3 Innervation

Extrinsic innervation of the digestive tract depends on parasympathetic and sympathetic fibers, efferent as well as afferent, often connected to the central nervous system, including the hypothalamus.

Parasympathetic Fibers Central parasympathetic fibers synapse with cells from the dorsal motor nucleus (and nodose ganglion for afferent fibers) on the floor of the fourth ventricle to give rise to the tenth cranial nerve, the pneumogastric or vagus nerve, which runs down along the esophagus to the abdomen. Parasympathetic fibers also descend into the spinal cord to synapse with sacral roots from S2 to S4.

Abdominal parasympathetic innervation is provided by the vagus nerve for the proximal colon and by pelvic parasympathetic fibers for the more distal colon, i.e., sigmoid and rectum. Pelvic parasympathetic fibers, both motor and sensory, play a decisive role in the evacuation function (see ▶ Chap. 7).

Sympathetic Fibers Sympathetic fibers pass through the spinal cord and the intervertebral nerve roots. The fibers issued from the spinal cord are called "preganglionic fibers" and all go to paravertebral nerve ganglia from where the so-called postganglionic fibers emerge to reach the digestive organs. There are five important neurological nodes (or plexuses) in the abdomen:

- The celiac node located between the aorta and the celiac trunk, from which fibers innervate the foregut organs (stomach, duodenum, etc.).

- The superior mesenteric ganglion located at the junction between the aorta and the superior mesenteric artery receives lower thoracic fibers (from T6 to T12) giving rise to postganglionic fibers innervating the midgut, i.e., small bowel and the proximal colon.
- The inferior mesenteric ganglion, at the aortic root of this artery, receives mainly lumbar fibers from L1 to L3 and innervate the left colon.
- The upper hypogastric plexus, located just in front of the aortic bifurcation, receives lower lumbar preganglionic fibers from L4 to L5 and gives postganglionic fibers innervating the sigmoid and the rectum.
- The pelvic plexus receives sacral fibers from S2 to S4 to innervate the anorectal region and pelvic organs such as the prostate, bladder, seminal vesicles, etc. Damage to these pelvic nerves during rectal dissection can lead to erectile or bladder dysfunction.

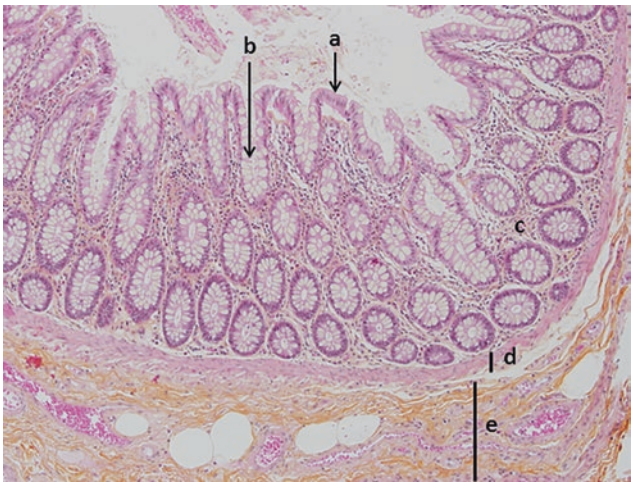
Postganglionic fibers are made of preganglionic nerves crossing the paravertebral ganglion without interruption, or that have merged with sympathetic fibers of different intervertebral nerves (e.g., fibers from the T6/T7 intervertebral space merging with fibers from T7/T8, T8/T9, etc.), or even have synapsed with parasympathetic fibers, resulting in overlapped zones and systems of influence on the innervated organs. The postganglionic fibers of the extrinsic nervous system reach the digestive organs by following the blood vessels that irrigate these organs. In the visceral wall, they usually synapse with nerves of the enteric nervous system (see ► Chap. 3) to influence motor or secretory functions of these organs. The afferent sympathetic fibers (running centrally to vagal nodose ganglion) play a major role in the perception of visceral pain.

4.2 Microscopic Anatomy

Like the other organs of the digestive tract, the wall of the colon is made up of different structural layers: the mucosa facing the intestinal lumen, the submucosa with mucosa feeding vessels and ENS-regulating nerves, the dual-component muscle layer with internal circular muscles and external longitudinal muscles, and the serosa (or adventitia, depending on its relationship to the peritoneum).

4.2.1 Mucosa

The *mucosa* of the colon (■ Fig. 4.4) is made up of crypts lined with a layer of various epithelial cells: the colonocyte, which plays an important role in colonic absorption; mucus cells (or goblet cells), which are numerous especially at the base of crypts; some endocrine cells, including enterochromaffin cells producing serotonin; and other endocrine cells producing GLP, PYY, and somatostatin. This monolayer of epithelial cells rests on a chorion and a muscularis mucosa.



■ **Fig. 4.4** Colon mucosa: (a) colonocyte, (b) goblet cell, (c) lamina propria (or chorion), (d) muscularis mucosae, (e) submucosa. (Photo by G. Soucy)

The *muscularis mucosa*, a thin muscle layer, separates the mucosa from the submucosa and supports the colonic epithelium and its chorion. It is the demarcating site between invasive and noninvasive neoplasia.

The *submucosa*, between the mucosa and the muscularis, is made of connective tissue, blood vessels, lymphatics, and neural fibers (Meissner submucosal plexus).

4.2.2 Muscularis

The colon wall, like the other organs of the GI tract, has two muscle layers working together to assure the motility process.

The *internal muscle layer* is made of circular fibers that generate phasic contractions to mix and propel the colonic content. Sustained and scattered contractions of these circular fibers can also generate prolonged annular contractions forming sacculations called haustrations.

The *external muscle layer* of the colon is peculiar in that it does not provide continuous coverage of the organ. The longitudinal muscle fibers are concentrated in three bands about 8-mm-wide and located at 120 degrees around the colonic circumference. These longitudinal bands, called taenia coli or colonic bands, start at the base of the appendix and are easily visible all along the colon. At the level of the upper rectum, they come together to cover diffusely the entire surface of the

rectal ampulla. These taeniae, by contracting in a sustained manner, shorten the colon like an accordion, thus participating in the formation of haustrations. The taeniae also serve as attachment points for the large omentum on the transverse colon (anterior taenia), as well as for Toldt's fascia on the left and right colon (medial lateral taenia).

The muscle layer is of variable thickness and tends to thicken from the proximal to the distal colon. The sigmoid colon contains a very thick muscle layer that can even become enlarged under certain conditions such as diverticular disease (see ► Sect. 4.9). The cecum, on the other hand, is a few millimeters thin, which explains the increased risk of perforation of this region when there is air distension of the colonic lumen (megacolon), or during endoscopic polypectomy for example.

4.2.3 Serosa

The outer layer of the colon is covered with visceral peritoneum except for the posterior portion of the ascending colon, the posterior portion of the descending colon, and a large part of the rectum. These segments are therefore extraperitoneal.

On the outer surface of the colon, there are small pouches of peritoneum filled with fat and called epiploic appendix. While these structures were thought to be of no pathological significance, it is now known that they can become inflamed to give a clinical picture that resembles diverticulitis or appendicitis and is recognized on a CT scan as epiploic appendagitis (see ► Sect. 4.9).

4.3 Embryology/Development

Embryological development of a large part of the colon is intimately linked to that of the small intestine (see ► Chap. 3). Errors in colonic development may give rise to malrotations most often without great clinical consequences. The development of the distal region is different and may be subject to serious abnormalities as discussed in ► Chap. 7.

By the fourth week of fetal life, the intestine is a tube (closed at both ends) divided into three parts: the foregut, the midgut, and the hindgut. The three parts of the gastrointestinal tract will then grow more or less isolated along their respective vascular axes, i.e., the celiac trunk for the foregut, the superior mesenteric artery for the midgut, and the inferior mesenteric artery for the hindgut. Development of the midgut will give rise to the colon. From the sixth week onward, the lower part of the primitive intestinal loop developing along the superior mesenteric artery will dilate to form the cecal bulge.

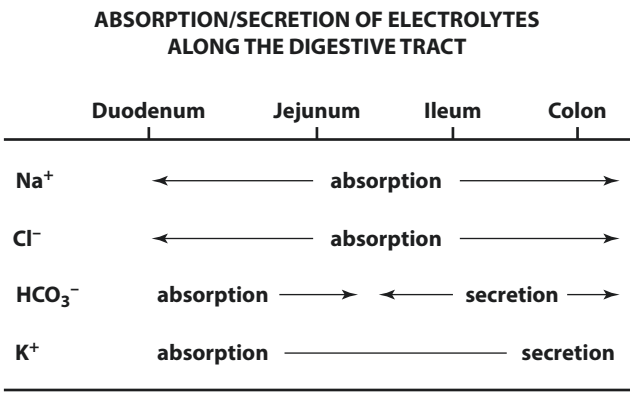
The intestine will then rotate on the axis of the superior mesenteric artery 270 degrees counterclockwise. This rotation is described in three phases of 90 degrees each: (1) the small intestine goes to the right and the colon to the left; (2) the colon is above and the small intestine below the axis of the superior mesenteric artery (the cecum is then at the level of the pyloric region); and (3) the small intestine returns to the left side of the abdomen and the cecum descends toward the right iliac fossa. As the appendix develops in the third phase, during the descent of the cecum, it may be in different positions along the migration path of the cecum: from subhepatic to pelvic position.

Once reintegration has been achieved, as in the case of the duodenum, peritoneal folds will form. The posterior face of the ascending and descending colons will merge with the posterior plane, forming, respectively, the right and left Toldt's fascia. As a result, these parts of the colon are fixed, while the whole of the small intestine, the transverse colon, and the sigmoid colon remain mobile. Defects in these attachments may increase segmental intestinal mobility leading to volvulus or internal hernias.

Abnormalities in the rotation process may occur at any developmental phase, and the intestinal rotation may be incomplete, reversed, etc., leading to various malrotations, many of which may remain without clinical consequence.

4.4 Absorption/Secretion

The colon receives from the small intestine 1–2 liters of chyme per day. This liquid contains water and electrolytes (fluxes of electrolytes along the digestive tract are summarized in ◘ Fig. 4.5), some amount of unabsorbed nutrients, as well as certain substances unabsorbable by the intestine (e.g., fibers). The colon absorbs



◘ **Fig. 4.5** Movements of ions from the proximal digestive tract to the distal colon

almost 90% of this liquid quantity since the fecal volume of water is 100–150 mL/day (in about 200 g of stool daily). Colonic absorption occurs mainly in the right colon and is promoted by the motor mixing and the back and forth movements present in this part of the colon.

4.4.1 Water Absorption

Water is absorbed via the ENaC channel (epithelial sodium channel) and will mainly follow sodium transport movements. The amount of water absorbed by the colon is normally 1–2 liters/day, but it can increase up to 5 liters per day under certain circumstances (e.g., to minimize fluid loss from small intestine diarrhea). Clinically, colectomy is usually well tolerated. In a subject with an ileostomy, gradual adaptation of the body usually reduces fecal fluid loss (normal ileal flow: 1–2 liters/day) to about 800 mL per day. However, the loss of the colonic reabsorption function makes a colectomized subject (with ileostomy or with ileo-rectal or ileoanal anastomosis) particularly susceptible to dehydration during diarrheal episodes.

Aldosterone, in response to circulating hypovolemia (secondary to exaggerated fecal losses for example), is an effective stimulus for ENaC and the absorption of H_2O (and Na^+) by the colon.

4.4.2 Sodium Absorption

Sodium absorption requires active transport mechanisms. The Na^+/K^+-ATPase pump of the basolateral membrane acts in the colonocyte as it did in the enterocyte: driving sodium out of the cell, the intracellular sodium hypoconcentration creates a favorable gradient for the entry of sodium from the intestinal lumen to the cell. Various apical transport mechanisms then allow the entry of sodium (discussed extensively in the chapter on the small bowel), such as a Na^+/H^+ exchanger (NHE2 and NHE3), an aldosterone-regulated sodium channel (ENaC), and an electrochemical gradient established by the HCO_3^-/Cl^- exchanger.

4.4.3 Potassium Movements

Potassium is secreted in the colon. The Na^+/K^+-ATPase pump of the basolateral membrane keeps the cell concentration of potassium high, facilitating its exit from the cell at the apical membrane via high conductance potassium channels.

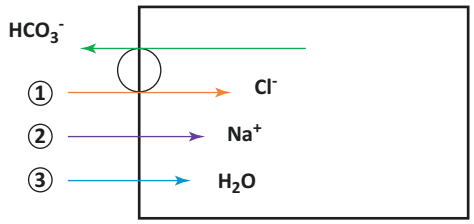


Fig. 4.6 Absorption of Cl^-: (**1**) via an HCO_3^-/Cl- exchanger, Cl^- enters the colonocyte; (**2**) by electrochemical gradient, Na^+ follows Cl^- into the cell; (**3**) H_2O, by osmotic gradient, follows Na^+ and Cl^- into the cell

4.4.4 Chloride Movements

An HCO_3^-/Cl^- exchanger ensures the exit of $HCO3^-$ and the entry of Cl^- into the colonocyte. The entry of Cl^- leads, by means of an electrochemical gradient, to the entry of Na^+, which consequently causes H_2O absorption (Fig. 4.6). A similar mechanism exists in the small intestine (see ▶ Chap. 3). This mechanism is physiologically very active since the congenital deficiency (very rare condition) of this $Cl^-/HCO3^-$ exchanger is a lethal condition where chlorinated diarrhea (high presence of Cl^- in the stool) and metabolic alkalosis (deficiency of HCO_3^- excretion by the intestine) are encountered.

4.4.5 Nutrient Uptake

A certain amount of ingested food is not absorbed by the small intestine and is found in the colon. Some substances, such as fibers, are not absorbable by the human small intestine and therefore reach the colon in large quantities. Other substances are more or less well absorbed in the small intestine; 0–5% of ingested lipids are poorly absorbed by the small intestine, while starch and dietary polysaccharides are poorly absorbed in a variable proportion of 1–20%. These substances that are not absorbed by the small intestine are found in the colon where they can be metabolized and/or utilized, mainly by intestinal microbiota.

Sugars Metabolism Malabsorbed sugars reaching the colon can be fermented by colonic bacteria into short-chain fatty acids (3–4 C atoms) such as butyric acid (or butanoic acid), acetic acid, or propionic acid (or propanoic acid) which can be absorbed by simple diffusion through the colonic cell membrane. Butyric acid is important for the colonocyte: (1) it has an essential trophic effect; (2) it can stimulate its absorption activity. It has been proposed that inhibition of fermentation (and of butyric acid formation) by antibiotics reduces absorption

of sodium and water by colonocytes, which explains diarrhea often encountered when taking antibiotics; (3) it can serve as a nutrient substrate. It is estimated that 10% of the daily caloric intake is due to these short-chain fatty acids absorbed by the colon. In case of malabsorption by the small intestine (e.g., short bowel syndrome), caloric absorption by the colon can increase significantly (up to 25% of the total caloric intake) and allow an important nutritional gain for the patient.

Malabsorption of sugars by the small intestine can be due to a "normal" malabsorption (e.g., sucrose and fructose often absorbed in a variable quantity) or to a "pathological" malabsorption which can be specific (e.g., lactase deficiency) or generalized (by small intestinal or pancreatic diseases). Some sugars are not absorbable by the small intestine, such as lactulose (used as a laxative), sorbitol (used as hypocaloric sugar substitute), raffinose or stachyose from beans, or fibers (cellulose, bran). Malabsorbed sugars are metabolized by colonic bacteria, which cause the formation of short-chain fatty acids (or volatile fats) and other gases such as CO_2, methane, and nitrogen, which explains increased flatulence in presence of malabsorption, as well as particularly malodorous H_2S.

Amino Acids Unabsorbed amino acids can be converted by colonic bacteria into various gases such as indole, mercaptan, etc., which contribute to the unpleasant odor of stools.

Dietary Fibers Dietary fiber is not digestible in humans, but some, including cellulose, can be broken down by colonic bacteria. We distinguish between insoluble fibers (such as lignin, cellulose) contained in bran or wheat cereals and soluble fibers (such as pectin) found in vegetables, psyllium, enriched cereals, etc.

4.4.6 Secretions

Colonic secretion comes mainly from goblet cells, which secrete mucus-containing glycoproteins, defensins, trefoil factor, etc. All these substances are intended to protect the colonic mucosa against, among other things, aggressive bacteria from the intestinal microbiota.

4.4.7 Intestinal Flora (Microbiota)

The human body is composed of 10^{14} cells but also contains 10^{15} microbial cells, mostly living in the digestive tract and especially in the colon. The digestive tract of the newborn is sterile, and its bacillary colonization occurs rapidly after birth when in contact with food and terrestrial environment.

The colon contains a large quantity of bacteria (10^{11} bacteria/mL) from multiple different species. This colonic flora is clearly predominant in anaerobic bacteria (*Bacteroides*, bifidobacteria, lactobacilli, etc.); aerobic bacteria are 100,000 times less frequent (*Escherichia coli*, enterococci, streptococci, *Klebsiella*, etc.). The genome of the intestinal microbiota human is now known. More than 30,000 bacterial species are present! They are classified in various phylogenetic classes: *Firmicutes* [(64% of gut microbiota), *Clostridium*, lactobacilli, enterococci, staphylococci, streptococci, etc.], *Bacteroidetes* [(23%), *Bacteroides*, flavobacteria, etc.], *Proteobacteria* [(8%), *Enterobacteriaceae*, *Escherichia coli*, *Pseudomonas*, etc.], *Actinobacteria* [(5%), corynebacteria, etc.], *Fusobacteria*, and *Verrucomicrobia*.

Intestinal bacteria tend to be considered as harmful, and in the clinical setting stool, cultures are used to identify bacterial pathogens responsible for diseases (*Campylobacter*, *Salmonella*, *Shigella*, etc.). The harmful action of bacteria cannot be denied, as evidenced, for example, by infectious enterocolitis and the syndrome of intestinal bacterial overgrowth in humans (see ▶ Chap. 3), or by inflammatory bowel diseases (e.g., Crohn's disease) that remain absent in germ-free animals (until bacterial colonization). However, the beneficial role of certain bacteria is now realized, as suggested by the development of *Clostridium difficile* colitis (see ▶ Sect. 4.6.1), which occurs almost exclusively with an alteration of intestinal flora by antibiotics, or the therapeutic action of probiotic bacteria in certain diseases (such as IBD), or the participation of the colonic flora in energy intake (discussed previously).

4.4.8 Intestinal Gas

The formation of gas is a normal phenomenon obtained by bacterial fermentation of nutrients arriving in the colon, unabsorbed by the small intestine. Part of this gas is reabsorbed, while the other part is evacuated through the anus. It has been estimated that approximately 1 liter of gas in total (volatile AG, CO_2, CH_4, N_2, etc.) is evacuated normally each day, on average 13 times a day. Exaggerated flatulence, intestinal meteorism (bloating), may constitute the clinical presentation of certain malabsorptions (e.g., lactose intolerance). Intestinal gases can cause visceral distension, which can be uncomfortable especially in people with visceral hypersensitivity (see IBS discussed in Function Diseases section).

4.4.9 Summary

The colon completes the absorption process done by the small intestine. In normal situations, it reabsorbs more than 1 liter of water (and electrolytes such as Na^+)/day and provides the final transformation (and absorption) of nutritive substances (such as carbohydrates) that have escaped small intestinal absorption. In pathological situations, the colon can increase its water absorption capacity by up to five times (e.g., during diarrhea caused by small bowel secretion), as well as its caloric absorption capacity up to 25% of daily requirements (e.g., during malabsorption by short bowel).

Stools (approx. 200 g/day) contain 75% H_2O and 25% nonabsorbable matter (fibers, bacteria, mineral salts, proteins, malabsorbed fats or sugars, etc.). The brown color is due to bilirubin (hence the pale stools in case of biliary obstruction). The foul-smelling odor comes from gases resulting from bacterial fermentation.

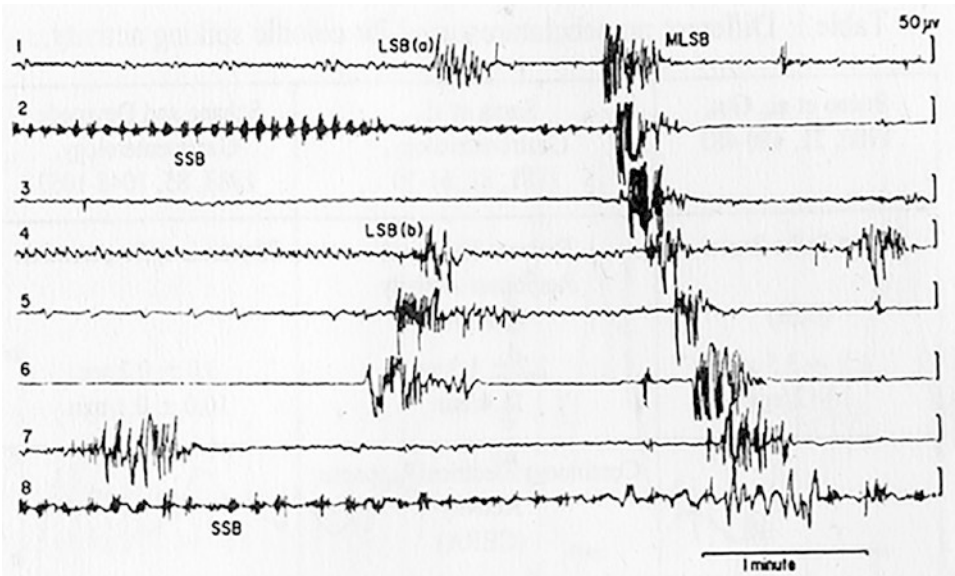
4.5 Motility/Sensitivity

4.5.1 Motility

Transit through the colon is much slower than through any other digestive organ, ingested substances normally taking 1–3 days to pass through the colon. Motility of the colon is complex and less characterized than that of the other digestive organs. Our limited knowledge of colonic motility explains why the nomenclature and characteristics of the patterns or types of colonic contractions remain controversial.

Colonic motility differs from other organs in several ways: (a) the external longitudinal muscle exists as in the other digestive organs, but rather than covering diffusely the entire surface of the organ, the longitudinal colonic fibers are grouped into three thin separated bands or taenias. These taenias seem to induce sustained colonic contractions, shortening the colon like an accordion and generating, with circular contractions, an irregular "sausage-shaped" appearance called haustrations. (b) The electrophysiological activity of the circular muscles is not constant throughout the colon and even seems to vary according to, among other things, the distension of the organ. (c) The electrical activity (pacemaker) of circular muscles does not come from interstitial cells of Cajal (ICC cells) located in the myenteric plexus as in small bowel but rather from ICC cells dispersed in the smooth muscles layer.

An example of a colonic motility profile is shown in ◘ Fig. 4.7. We use this sketch for a better understanding of colonic contractile activity, although we realize that it is questionable since the types of contractions are of different natures and designations according to researchers in the field. Generally speaking, the following can be summarized: (a) a nonmigratory contractile activity of low amplitude and prolonged duration (the result of electrical waves called SSBs in ◘ Fig. 4.7) exists, mainly in the right colon, probably to induce a mixing of luminal substances submitted to bacterial metabolism in this portion of the colon; (b) contractile waves with an



◘ **Fig. 4.7** Electromyographic recording of the colon using eight electrodes distributed along the organ (1, right colon; 2, ……; 8, distal sigmoid) and revealing what researchers (Frexinos, Fioramonti et al. from Toulouse) have identified as "short spike bursts" (SSB), "long spike bursts" (LSB) or "migrating long spike bursts" (MLSB)

anterograde or retrograde direction on short segments and of medium or high amplitude (result of LSBs) exist to ensure a stirring and back and forth movement promoting the absorption of the intestinal chyme and ensuring a slow transfer of the colonic content from proximal to distal, especially in the proximal colon; and (c) large amplitude contractions, starting in the transverse colon and migrating rapidly to the left colon, occur four to six times a day (mass contractions, result of MLSB), to push the fecal bolus to the rectum. This mass contraction activity often occurs after a meal and is part of the "gastrocolic reflex."

Contractile activity of the colon increases during the following events: (1) waking up, motor activity decreases during sleep and increases upon waking; (2) food in the stomach stimulates colonic motor activity, the gastrocolic reflex, probably of neurohormonal origin (CCK?), is responsible for the urge to defecate often felt after a meal and possibly increased in certain diseases such as IBS; (3) stress, via secretion, among others mediators, of corticotropin-releasing factor (CRF); (4) stimulation of cholinergic or NK receptors; and (5) local irritation by certain laxatives such as bisacodyl.

In the clinic, manometric (or electromyographic) analysis of colonic contractility (so useful for the identification of esophageal or anorectal diseases) is very rarely utilized. The speed of transit of the colon can be evaluated by following the progression of radiopaque or isotopic markers: in case of diarrhea, colonic transport, normally about 1–3 days, can be accelerated (to a few hours). In the case of constipation, it can be slowed down over several days. However, the measurement of colonic transit is only necessary in very selected cases.

4.5.2 Sensitivity

The colon, especially the rectum, is the digestive organ where visceral sensitivity has been most extensively studied.

Briefly, pain originating from the colon (or from any GI organ) relies on the following pathways: (1) afferent sensitive fibers detect pain signals in the intestinal wall; (2) the signal is transmitted to a second order neuron in the dorsal horn of the spinal cord and travels to the brain; (3) then central nuclei, responsible for pain sensation, are stimulated; (4) a compensatory mechanism (descending inhibition) is elicitated from the brain to reduce the pain signal coming from peripheral neurons.

Increased visceral sensitivity is found in many patients with irritable bowel syndrome (IBS). As discussed extensively in the Function Disorders section, increased pain sensation in IBS patients may involve dysregulation at any one of the four transmission steps described above.

4.6 Inflammation Disorders

The diagnosis of colitis is most often made clinically during endoscopy. Colonic mucosa is then granular, and/or friable, and/or erosive, and/or ulcerated. Inflammatory damage may be widespread or limited to certain areas. The endoscopic aspect will evoke some of the differential diagnoses mentioned below. Mucosal biopsies taken during endoscopy will be used to confirm and guide the diagnosis.

Colitis is suspected in patients presenting diarrhea, most often accompanied by cramp-like abdominal pain. Rectal bleeding, if not due to hemorrhoids, is a sign of a mucosal break (eruption, ulceration) by the inflammatory process. Bloody diarrhea is colitis until proven otherwise. Mucus may also be present (however, it can also be seen in irritable bowel syndrome, which is characterized by a macroscopically and microscopically normal colonic mucosa).

An inflamed colon may appear on radiological examinations with edematous thickened walls (◘ Fig. 4.8).

4.6.1 Infectious Colitis

Acute Bloody diarrhea or dysentery Acute bloody diarrhea or dysentery is most often caused by bacteria such as *Shigella*, *Campylobacter*, or *Salmonella* (see ▶ Chap. 3). Any infection leading to colonic mucosal breaks is likely to cause bloody diarrhea.

***E. coli* colitis.** Enterohemorrhagic *E. coli* colitis (EHEC) usually affects the transverse colon and often causes bloody diarrhea. It is due to *E. coli* bacteria that produce a Shiga toxin (named after its Japanese discoverer, professor Shiga, in 1897). *E. coli* 0157H7 is the best known bacterium, but other bacterial germs have now been identified (e.g., O104 H4 which was epidemic in Germany and Europe in 2011). The 0157H7 infection is classically contracted by eating undercooked contaminated beef (hence its name "hamburger colitis"). Meat contamination by fecal bacteria occurs during the animal slaughtering; bacteria are present on the outside of the meat and are easily destroyed when meat surfaces are adequately cooked. Undercooked ground meat is most often implicated as a causal factor. Epidemics by ingestion of contaminated water (e.g., Walkerton,

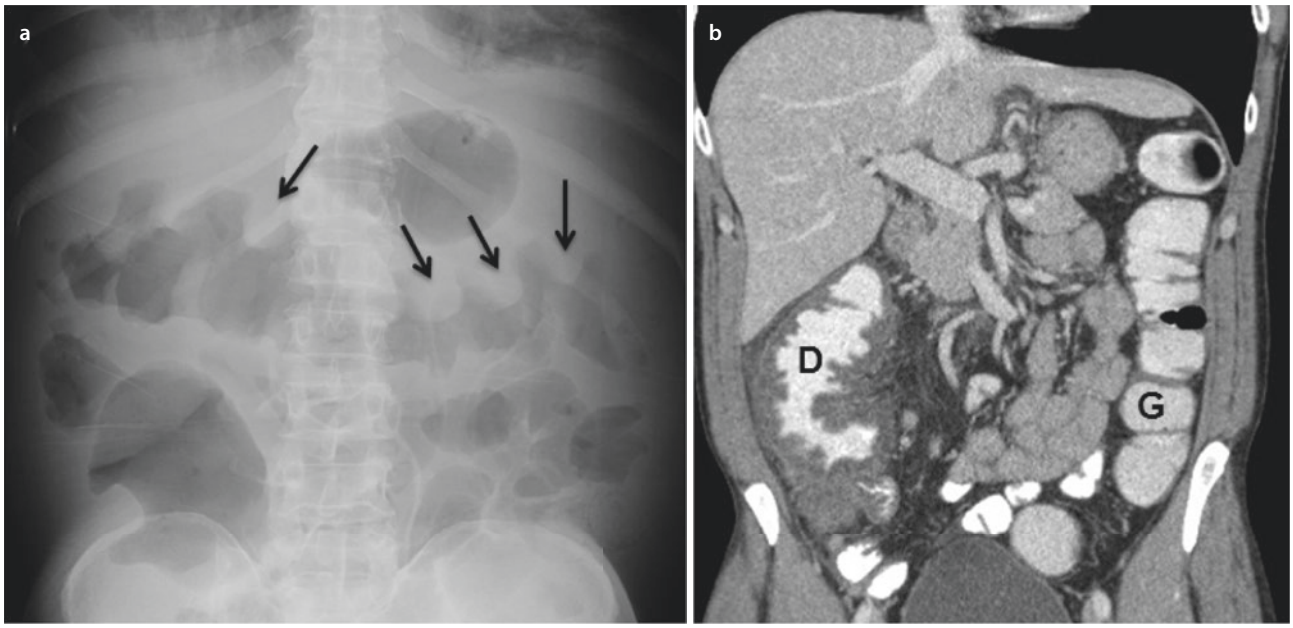


Fig. 4.8 Colitis images: **a** flat plate of the abdomen showing parietal edema of the transverse colon with thumbprint images (indicated by the arrows); **b** CT scan with significant wall thickening of the right colon (D), while the left colon (L) is normal. (Photos from R. Déry)

Ontario in 2001) or by ingestion of fruits or vegetables sprinkled with contaminated water (e.g., Texas spinach in 2005) have occurred.

EHEC colitis usually resolves spontaneously within a few days. Use of antibiotics has been associated with an increased release of bacterial toxins (thus worsening the clinical picture) and is discouraged. However, in the European epidemic of 2011, treatment with azithromycin appeared to have a safe and beneficial effect.

This infection may be complicated by a severe hemolytic process with vascular complications affecting mainly the kidneys (hemolytic uremic syndrome) or the brain (strokes); two-thirds of children with hemolytic uremic syndrome will require hemodialysis.

Yersinia enterocolitica can present with acute onset diarrhea often with ileitis or mimicking appendicitis (pseudoappendicitis). It can also give a subacute picture mimicking Crohn's disease of the ileum or colon.

Pseudomembranous or *Clostridioides difficile* colitis has been recognized since the 1980s. *Clostridioides difficile* (*C. diff* or *C. difficile*; preciously called *Clostridium difficile*) is a bacterium that can be carried asymptomatically and will proliferate during an antibiotic-induced imbalance of the colonic flora. Broad-spectrum antibiotics such as quinolones have been strongly incriminated, but all antibiotics are capable of triggering this problem. Additional contributing factors include hospitalization, immunodeficiencies, use of gastric hyposecretory agents such as PPIs, and advanced age.

C. diff. infection has become a major nosocomial infection in recent years. Its frequency increased seriously in our hospitals, and its severity has become a major problem, particularly with the emergence of new virulent strains of bacteria that lead to severe and possibly fatal colitis.

C. diff. is diagnosed by stool examination, which will reveal the presence of the bacteria itself and/or its toxin (A or B) responsible for colitis. Infection with *C. diff.* can, in 1/3 to 1/2 of the cases, give visible endoscopic signs, which may be nonspecific (erythema, etc.) or may have characteristic appearance with pseudomembranes (Fig. 4.9).

Treatment of *C. diff.* infection is summarized in Table 4.1. It includes its prevention through the judicious use of antibiotics and through hygienic measures designed to limit its transmission (especially in the hospital setting). Certain probiotics designed to maintain an "adequate" intestinal flora have been able to reduce post-antibiotic therapy infection rates. Curative treatment most often uses antibiotics such as metronidazole (250 mg qid or 500 mg tid for 10–15 days p.o. or i.v.), or vancomycin (125–500 mg qid p.o.; i.v. vancomycin does not penetrate the intestine and is therefore not effective), or fidaxomicin (200 mg bid p.o. × 10 days). However, relapses may occur when antibiotics are stopped (≈ 10–20% of cases) and require either prolonged re-retreatment or alternate antibiotic therapy (vancomycin instead of metronidazole, fidaxomicin

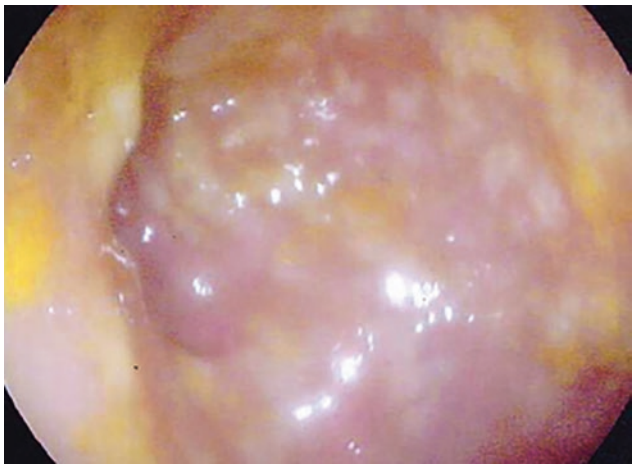


Fig. 4.9 Colonoscopy revealing flaky deposits of pseudomembranes typical of *Clostridioides difficile* colitis. (Photo by P. Poitras)

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Table 4.1 Management of *Clostridioides difficile* infection

Prevention

- Judicious use of antibiotics (especially quinolones)
- Judicious use of PPIs
- Hygiene measures (hand washing, etc.) to limit transmission
- Concomitant administration of probiotics (Bio K, *Saccharomyces boulardii*, etc.)

Treatment

1. Metronidazole po 250 mg qid or 500 mg tid × 2 weeks (or 500 i.v. q 8 hours if vomiting, etc.)
2. Vancomycin 125 mg po q 6 hours × 2 weeks
3. Fidaxomicin 200 mg po bid × 2 weeks
4. If severe: colectomy

Recurrence treatment

1. Change antibiotic (metronidazole → vanco, or, vanco → fidaxo) × 10–14 days
2. Prolonged antibiotic use (and progressive tapering): 7–14 days qid → bid → die
3. New antibiotic: fidaxomicin 200 mg bid × 2 weeks
4. Fecal transplantation

instead of vancomycin). For recurrent relapse fecal transplant has been shown to be curative. Cholestyramine (4.0 g tid) can be used to bind the toxin. In severe cases, especially if megacolon ensues, surgical colectomy may be necessary.

Colonization by *C. difficile* in normal infants ranges from 25% to 80% versus 2% to 15% in adults, with a peak at about 6 months of age. This high carrier rate has been attributed to intestinal immaturity and the lack of protective microbiota to prevent the growth of *C. diff.* The immaturity or lack of receptors for toxin A along the intestinal epithelium explains why there are far fewer *C. diff.* diseases in this age group. The bacterium is more often found in formula-fed babies or in babies born by caesarean section.

Viral colitis. Viral diarrhea is frequent and spontaneously resolves after short courses. Viral infections most typically cause enteritis rather than colitis. Cytomegalovirus (CMV) colitis may emerge in immunosuppressed patients and requires treatment with i.v. ganciclovir.

Parasites. Some parasites can cause colitis. Amoebic colitis must be suspected in any traveller or inhabitant of countries at risk for this infection (tropical countries). Diagnosis can be obtained by examination of stools or by colonic biopsies revealing the pathogen (*Entamœba histolytica* is pathogenic and must be treated; *Entamœba gingivalis*, *E. hartmanni*, *E. coli*, *E. dispar* are however considered nonpathogenic). Treatment will be provided with metronidazole 500–750 mg tid for 1–3 weeks. The infection may be complicated by an amoebic abscess of the liver (easily identifiable on ultrasound) which may be suspected in the presence of high fever, pain in the right hypochondrium, or abnormal liver function tests.

Dientamœba fragilis and *Blastocystis hominis* are other parasites that can affect the colon.

- Nail-cut ulcerations on the rectocolonic mucosa are indications of amoebiasis.
- Bilharziosis (schistosomiasis) is characterized by punctiform, whitish lesions on an erythematous mucous membrane. Mucosal biopsies reveal the parasites or their eggs.

4.6.2 Ischemic Colitis and Colonic Ischemia

Colonic Ischemia Ischemia of the colon, especially in the proximal colon, may be associated with ischemia of the small intestine due to arterial or venous occlusion of the superior mesenteric vessels. Acute intestinal ischemia is a life-threatening emergency that is often difficult to diagnose and treat and whose consequences are particularly severe in the small intestine (see ▶ Chap. 3). If vascular repermeabilization (pharmacologically with anticoagulants/thrombolytic agents or mechanically by radiological or surgical techniques) is impossible or ineffective, resection of the necrotic intestine is necessary.

Ischemia of the colon can be isolated (ischemic colitis described below) and most often affects the distal colon supplied by the inferior mesenteric artery.

Ischemic Colitis Ischemic colitis occurs as a result of a localized reduction in colonic arterial flow either during vascular occlusion (by atheromatosis, more rarely by arteritis, or by embolisms from atheromatous plaques of the abdominal vessels or from heart clots) or as a result of a decreased colonic perfusion flow due to hypovolemia, shock, dehydration, etc. Ischemic colitis is a condition whose frequency increases with age. In more than 3/4 of cases, no obvious cause is found. Colitis is most often attributed to a "low flow" condition and will then mostly involve the "watershed" regions at the distal limit of the arterial irrigation areas: the splenic flexure (at the rim of the territories supplied by the superior and inferior mesenteric arteries) or the rectosigmoid junction (at the junction of the vascularizations by the inferior mesenteric artery and the rectal arteries coming from the iliac vessels).

The *clinical presentation* of ischemic colitis involves acute abdominal pain often more or less localized to the diseased colon segment and accompanied by bloody stools.

The *diagnosis* is frequently suggested on abdominal CT scan (Fig. 4.10) showing segmental colitis (thickened walls due to edema) and which can also reveal obstructed abdominal arteries..

Colonoscopy shows colitis, extended over a more or less long segment, almost always sparing the rectum (irrigated by rectal arteries from iliac arteries), and with suggestive macroscopic features such as an erythemato-erosive mucosa on the antimesenteric edge of the colonic wall (Fig. 4.11) or a bluish or even blackish mucosa in severe cases. Biopsies reveal suggestive histological changes.

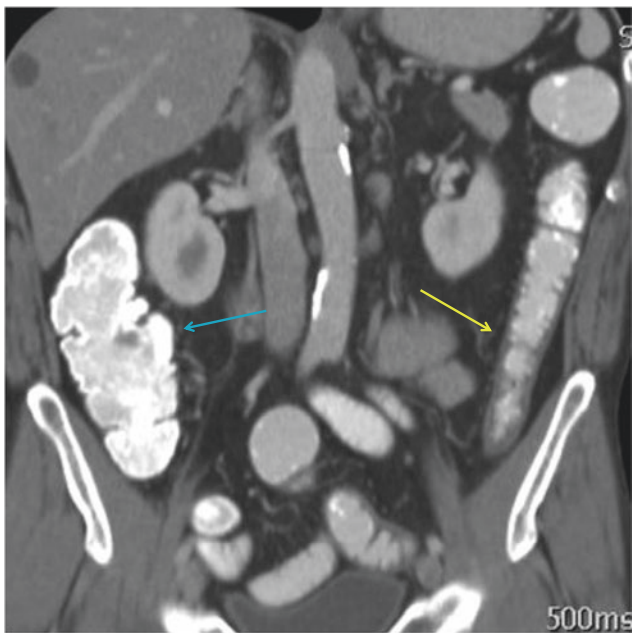


Fig. 4.10 Ischemic colitis seen on CT scan of the abdomen: thickened colon wall (arrows) suggesting colitis of the left colon (compared to the normal right colon), which here was ischemic in origin. (Photo from R. Déry)

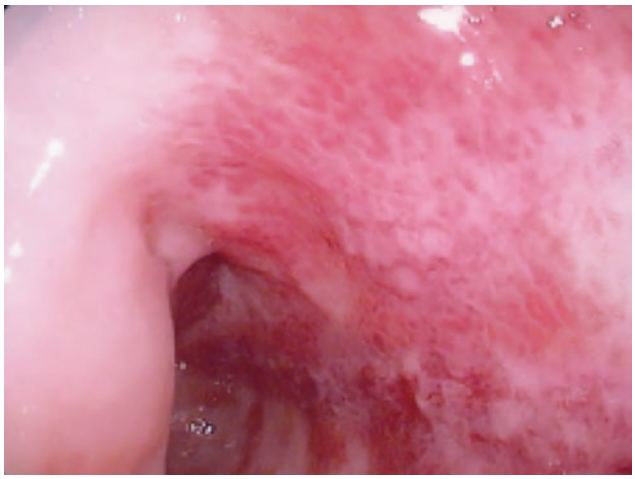


Fig. 4.11 Ischemic colitis as seen endoscopically: the antimesenteric side may be more affected. (Photo by P. Poitras)

Acute *treatment* of ischemic colitis is most often monitoring and supportive treatment (hydration, analgesia, etc.) since the phenomenon will usually regress spontaneously within a few days. In case of transmural involvement, a peritoneal reaction (abdominal rigidity, Blumberg's sign, paralytic ileus, etc.) is possible, but intestinal perforation remains a rare complication. Bleeding sometimes requires transfusion. Surgical treatment is rarely necessary except in cases of proven perforation or uncontrolled bleeding.

Ischemic colitis is usually an isolated, non-repetitive phenomenon that leads to uncomplicated and complete healing of the colonic mucosa; late complications from stenosis developing in the weeks or months following the acute episode are still possible.

Complementary examinations looking for potentially embolic lesions (electrocardiogram, cardiac echography, abdominal Doppler ultrasound, etc.) or for coagulation disorders (deficiency in protein C, S, antithrombin III, mutated factor V Leiden, polycythemia, etc.) are used to detect predisposing conditions in 10–30% of individuals and thus prevent a recurrence of the ischemic problem.

4.6.3 Microscopic Colitis

Microscopic colitis is characterized by a macroscopically normal appearance of the colon and histological abnormalities in the form of epithelial infiltration by lymphocytes (lymphocytic colitis) or a thickening of the submucosal collagen table (also called basal lamina) (collagen colitis). The two abnormalities often coexist.

It is manifested by chronic diarrhea which can be of variable importance, i.e., from mild to very severe (leading to dehydration, hypokalemia, etc.). The etiopathogenesis of this condition remains unknown. It may be associated with celiac disease, with autoimmune diseases (hypothyroidism, rheumatoid arthritis, etc.), and with certain medications (NSAIDs, PPIs).

The evolution may be benign with a moderately severe clinical picture, improving spontaneously or with recurrences. In some cases, however, the disease may be very severe and require aggressive therapy.

The diagnosis requires colonic biopsies.

Basic treatment is loperamide to slow intestinal transit. Bismuth (Pepto-Bismol® 2 tablets qid), 5-ASA (mesalamine 3–4 g/day), cholestyramine (4–12 g die) or various antibiotics may be useful. In more severe cases, "local" corticosteroid therapy (budesonide) or even systemic corticosteroid therapy (prednisone) may be used. Some severe or refractory cases will respond to immunosuppressants (azathioprine or 6-mercaptopurine), anti-TNF infliximab, or anti-integrin vedolizumab. Rarely, severe cases require surgery (total colectomy).

4.6.4 Radiation Colitis

During *acute radiotherapy treatment*, colorectal mucosa may suffer from "mucositis" (as elsewhere in the digestive tract) causing soft, mucoid, hemorrhagic stools that rapidly regress when treatment is stopped.

Long-term complications of radiotherapy are due to small vessels vasculitis, which is a progressive and self-deteriorating condition overtime, and can manifest even years after the irradiation treatment. Proctitis or ischemic-type colitis with mucosal bleeding and parietal fibrosis (with obstructive stenoses and/or rigid wall infiltration) are common. Radiation colitis is mainly localized in the lower rectum in cases of irradiation for prostatic or anorectal neoplasia; it may extend more proximally, especially at the sigmoid level, in cases of irradiation for pelvic diseases (uterus, ovaries).

4.6.5 Colitis in Oncology

Neutropenic colitis (or typhlitis, from the Greek cecum): it occurs in patients with febrile neutropenia under cytotoxic chemotherapy. Affecting mainly the right colon (and the cecum), it can be very severe (mortality rate of 20–60%) and often leads to translocation septicemia.

Its precise cause is unknown, but polymicrobial infection (*Pseudomonas*, E coli, *Bacteroides*, *Candida*) is common. The diagnosis is evoked by CT scan, and colonoscopy is not desirable, given the high risk of perforation.

Supportive treatment, in addition to GM-CSF (granulocyte macrophage colony-stimulating factor), includes broad-spectrum antibiotics (piperacillin-tazobactam, imipenem) and antifungals (amphotericin B).

Colitis on cancer immunotherapy. Patients on checkpoint inhibitors immunotherapy (such as ipilimumab but also nivolumab or pembrolizumab) may develop immune colitis mimicking ulcerative colitis or Crohn's colitis. Corticosteroids and anti-TNFs may be required to control the disease.

4.6.6 Inflammatory Bowel Diseases (IBD): Ulcerative Colitis and Crohn's Disease

Inflammatory bowel disease (IBD) includes two related diseases: ulcerative colitis (UC) and Crohn's disease (CD). Briefly, ulcerative colitis refers to an inflammation limited to the colonic mucosa that begins in the rectum and may extend continuously in the proximal regions of the colon (right, transverse, left colon). Crohn's disease (so named from Dr. Burrill Bernard Crohn (see Fig. 4.12) who identified the condition) is a granulomatous inflammation that can involve all layers of the intestinal wall and affect, often discontinuously, the colon and/or the small intestine (or any other region of the digestive tract). The two colonic diseases can sometimes be difficult to differentiate, and the colitis is then referred to as an "unclassified (or undetermined) coli-

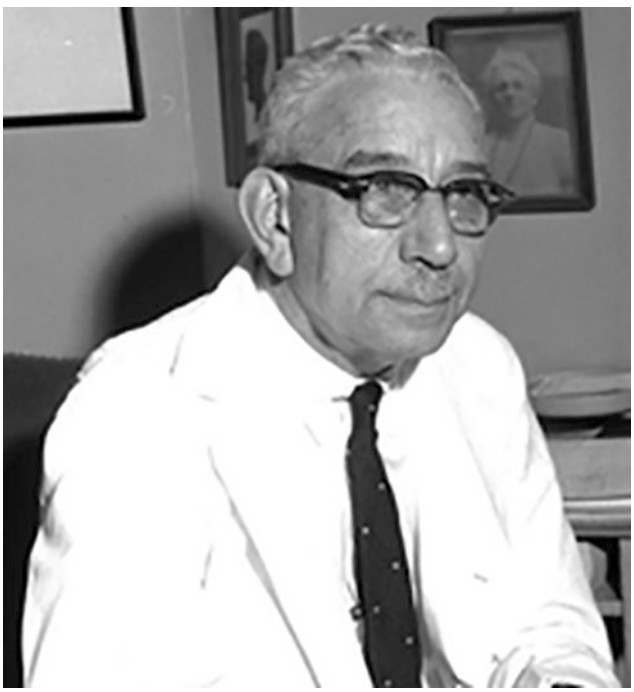


Fig. 4.12 Burrill Bernard Crohn (photo), with colleagues L. Ginzburg and G.D. Oppenheimer of Mount Sinai Hospital in New York, described "regional enteritis" in 1932

tis." Both are as yet of unknown causes and use a relatively similar treatment regimen. Both diseases are chronic (due to our inability to provide curative treatment). They are a most common and serious intestinal ailment seen by the gastroenterologist.

(a) Epidemiology of IBD

IBDs affect up to 500 persons per 100,000 population in Canada. While UC was once considered more common, an increasing frequency of CD is now observed (prevalence per 1000: CU 1.94; Crohn's 2.34). IBD affects both men and women, often with peaks incidence at ages 15–30 and 50–80 years. The incidence appears higher in Jews than in non-Jews, and lower in Blacks or Asians. The incidence also appears elevated in Western countries of the Northern Hemisphere. Canada is one of the countries where IBDs are most common. In the past 30 years, the incidence has been raising in the developing world.

(b) Etiology of IBD

Etiology of IBDs is unknown, but several factors are suspected:

Genetic factors: A family history of IBD in first-degree relatives is found in 10–25% of patients. Studies of twins revealed a concordance of the disease in 6% of heterozygous twins but in 58% of homozygous twins, clearly suggesting a genetic incidence in the development of IBD. Having a parent with inflammatory disease increases the risk of IBD (1/250 people in Canada) by 3–20 times in their children (4% of children). If both parents have inflammatory disease, children have a 20–30% risk of also having IBD. The location of the disease (i.e., small vs. large bowel) and the type of disease (e.g., perforating vs. stenosing disease) are consistent in 50–80% of cases of familial disease.

Many genes have been statistically associated with IBD. The most important mutation was discovered in 2001: mutations in the NOD2 gene located on chromosome 16 appear to predispose to ileal Crohn's disease. Genes abnormalities are related to either a facilitating (e.g., NOD2) or a protective (e.g., IL-10 gene) influence for IBD. The multiplicity of genes involved demonstrates the very likely polygenic nature of these diseases and makes it difficult to apply these discoveries in clinical practice. In 2020, more than 200 genetic abnormalities genetic have been associated with CD and UC.

Immune factors: The autoimmune character of IBD is supported by its association with various autoimmune diseases such as ankylosing spondylitis, arthritis, uveitis, etc.

Environmental factors: the elevated prevalence of IBD in the Nordic countries and Canada may suggest the existence of environmental factors involved in their genesis. However, no dietary, toxic, or other factors are currently identified. Smoking doubles the risk of developing CD and is associated with adverse disease outcomes. Curiously, however, smoking seems to decrease the risk of developing UC and even seems capable of reducing its clinical severity.

Infectious factors: The granulomatous nature of CD is reminiscent of mycobacterial diseases that can affect humans (e.g., tuberculosis) or animals (e.g., bovine ileitis, or Johne's disease, caused by mycobacterium avium paratuberculosis). Spousal transmission of the disease has been reported anecdotally. However, multiple attempts to identify infectious agents or to eradicate the disease with various combinations of antibiotics have not yielded any positive results. An imbalance of the intestinal microbiota (dysbiosis) is also considered as a potential factor inducing inflammation.

«Unicist» theory: A theory that would bring all these hypotheses together would be that (1) in individuals predisposed by genetic mutations (single or multiple, protective or favoring), (2) exposure to (or aggression by) certain "environmental" (or infectious) products triggers IBD (it is interesting to note that in an experimental model mimicking CD, the IL-10 deficient-mutant mouse does not exhibit intestinal inflammation as long as it remains in its germ-free environment) (3) and induces inflammation with lymphocytes and neutrophils producing cytokines, interleukins, TNF, etc.

(c) Clinical Presentation of IBD

UC and CD have characteristic manifestations of each disease (extensively discussed later, see Table 4.3), but it is not uncommon to have difficulty in determining whether a colitis is due to CD or UC (and is then referred to as colitis type, unclassified) or to see a colitis initially diagnosed as UC later manifests itself as CD (for instance, when a person with UC presents a fistula or small bowel disease the diagnosis is changed to CD).

1. ***Ulcerative Colitis:*** UC is a Chronic disease characterized by inflammation of the colonic mucosa that typically begins in the rectum (proctitis) and may extend continuously to more proximal colonic segments such as the left colon (left or distal colitis), or beyond the splenic flexure (extended colitis), or into the cecum (pancolitis). Inflammation in UC, as opposed to CD, is limited to the mucosa and to the colon.

Symptoms of UC. Frequent stools with bleeding and mucus are the cardinal signs of UC. Rectal involvement (proctitis) often results in an increased defecatory rate but without real diarrhea, with urges for bowel movements and/or frequent (but unproductive) need to pass stools (tenesmus). Defecation is frequent, even compelling, with blood and mucus, but each time with only a small amount of stools, which may in fact have normal or even hard consistency. More extensive inflammation compromises normal colonic functions and leads to diarrhea with frequent, soft, or watery stools. Friability

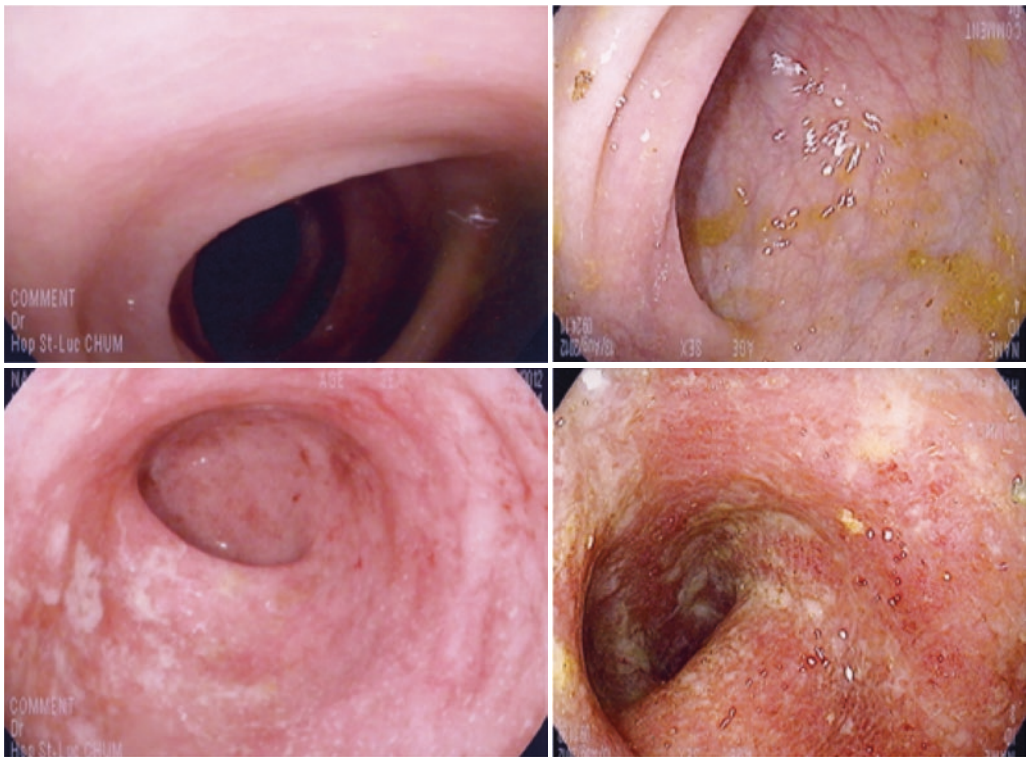


Fig. 4.13 Colonoscopy images of two patients (patient 1, left; patient 2, right) with distal ulcerative colitis showing an abnormal mucosa in the rectosigmoid (bottom images) that is diffusely erythematous, friable, micro-ulcerated, while the upper images show the smooth, shiny mucosa of the normal left colon. (Photos by P. Poitras)

of colonic mucosa is responsible for blood loss, as well as mucus.

At initial presentation, 1/3 of patients have proctitis, 1/3 have left colitis, and 1/3 have extensive colitis or pancolitis. Less than 10% of patients may initially suffer from severe or fulminant colitis, a potentially lethal condition with extensive and severe colon involvement resulting in debilitating symptoms such as severe diarrhea, painful abdominal cramps, blood loss (that may require transfusions), fever, weight loss, undernutrition, etc. Inflammation in these individuals with severe colitis not only can affect the colonic mucosa but can extend to deeper layers of the colonic wall, putting the patient at risk for megacolon (distension of the colon) and perforations.

Digestive complications of UC include:

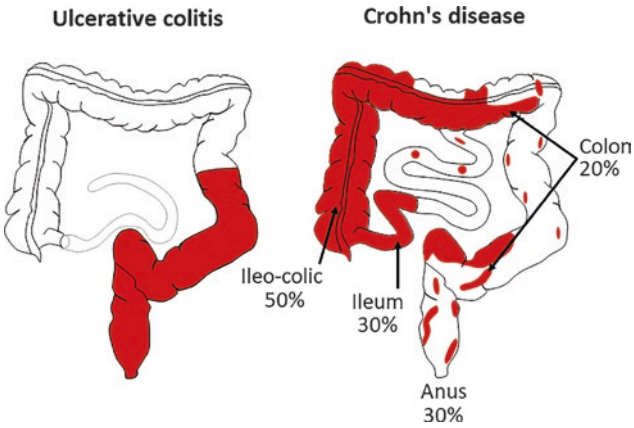
- Colonic hemorrhage is possible but rare. Loss of sufficient blood to cause anemia is common.
- Severe or fulminant colitis occurs in about 15% of patients. The severity of the symptoms (pain, diarrhea, dehydration, etc.), the general health status (undernutrition, etc.) of the patient, the risk of toxic megacolon, etc. then justify hospital treatment.
- Toxic megacolon (distension of the colon with severe colitis and signs of systemic toxicity) is an emergency due to the risk of perforation of the colon (which can lead to mortality in 50% of cases in presence of peritonitis). Failure to respond to intensive medical treatment within 48 hours usually requires an emergency surgical colectomy.
- Development of neoplasia: The probability of developing adenocarcinoma of the colon is increased in individuals with colitis. The risk factors are (1) the extent of the disease, extensive colitis is significantly more at risk than left-sided colitis; (2) the duration of the disease, the risk begins after 8 years and increases by approximately 1% per year (after 20 years, 10% of patients with UC would have developed colonic neoplasia, after 30 years, 20%, etc.); (3) the association with other diseases such as primary sclerosing cholangitis; and (4) probably the importance of the chronic inflammatory reaction (anti-inflammatory treatments with 5-ASA or immunosuppressants seem to have a protective effect). To detect early neoplastic transformation, surveillance colonoscopies (with biopsies) every 1–5 years (depending on risk factors) are recommended. Prophylactic colectomy is a treatment option.

Diagnosis of UC is made by colonoscopy, which shows inflammatory disease that almost invariably affects the rectum and may extend continuously to other colonic segments. The inflammation is characterized by an erythematous, often friable mucosa, possibly with erosions and often covered with muco-pus (Fig. 4.13). In peri-

ods of remission, the mucosa may return to a completely normal appearance. In severe forms, extensive and deep ulcers can be seen. In chronic forms, healed colonic walls (lead pipe colon on radiological exams) or inflammatory polyps (often called pseudopolyps) may be present.

Evolution of UC. In the course of evolution, the extent of the colitis diagnosed in the initial episode may progress more proximally in the colon. In patients with proctitis, the disease may extend proximally in 20–50% of cases. Over the years, the clinical course is most often made up of repeated acute attacks requiring treatments that are fortunately mostly effective. Surgery may be required for resistance to medical treatment or for cancer prophylaxis. It is rarely necessary in the distal forms of colitis and appears to be required in about 20–30% of individuals with more proximal and severe disease. Life expectancy is not significantly affected in patients with UC given the therapeutic modalities now available (discussed later).

2. ***Crohn's disease.*** Identified in 1932 in New York by Doctors B.B. Crohn, L. Ginzburg, and G.D. Oppenheimer, Crohn's disease is a granulomatous inflammation that can involve all layers of the intestinal wall and affect all digestive organs. Crohn's disease is localized to the ileocolic region in ≈50% of patients, or may be limited to the small intestine (more often to the terminal ileum) or to the colon in about 30% of affected patients (◘ Fig. 4.14). The anorectal region is frequently involved (≈30% of patients). The stomach and esophagus may be affected (≈5% of patients).



◘ **Fig. 4.14** Inflammatory sites in IBDs

The colon is thus affected in 2/3 of patients with Crohn's disease. Inflammation, sometimes, may be continuous and superficial as in ulcerative colitis but, more often, characteristically, is discontinuous, patchy, and mixed with skip area of normal mucosa. Mucosal breaks made of superficial erosions in UC may appear in CD as aphthous ulcerations surrounded by normal mucosa to deep penetrating ulcers in severely inflamed colonic walls (◘ Fig. 4.15).

The disease is often described as having an inflammatory, stenosing (1/3 of patients), or perforating (1/3 of patients) profile. Stenosing disease causes narrowing of the intestinal lumen with obstruction and blockage. Perforation of the intestinal wall may occur in the abdominal cavity resulting in peritonitis, abdominal abscesses, etc. or may produce communication(s) (fistula) to surrounding organs (enteroenteric, enterocolic, entero- or colo-vaginal fistula, etc.).

Clinical manifestations of Crohn's disease include:

- Abdominal pain is common in CD. It may be related to obstructive (often ileal) bowel involvement (with cramp-like periumbilical pain) or to trans-parietal inflammation (possibly with abdominal masses) of the intestine or colon. Severe acute pain is present during complications such as intestinal obstruction or during perforation and abscess formation.
- Diarrhea is common. Several pathophysiological factors may be involved: (a) reduced absorption capacity due to intestinal inflammation, surgical resection of the small intestine or colon, enteroenteric or enterocolic fistulas that exclude certain digestive segments from normal bowel function, etc.; (b) intestinal bacterial overgrowth due to stenoses inducing stagnation of bacteria or due to fistulas allowing the recirculation of colonic bacteria toward the proximal intestine; and (c) choleretic diarrhea due to the bile salt malabsorption in the terminal ileum which is affected by inflammation or absent following surgical resection.

Digestive complications of Crohn's disease:

- Digestive bleeding with acute hemorrhage (rare) or chronic blood loss from intestinal ulcers that lead to anemia may occur.
- Obstruction of the small intestine or colon by inflammatory stenoses (likely to respond to anti-inflammatory medical treatment) or by fibrous stenoses (resistant to anti-inflammatory treatment and which will require surgical treatment or endoscopic dilatation).

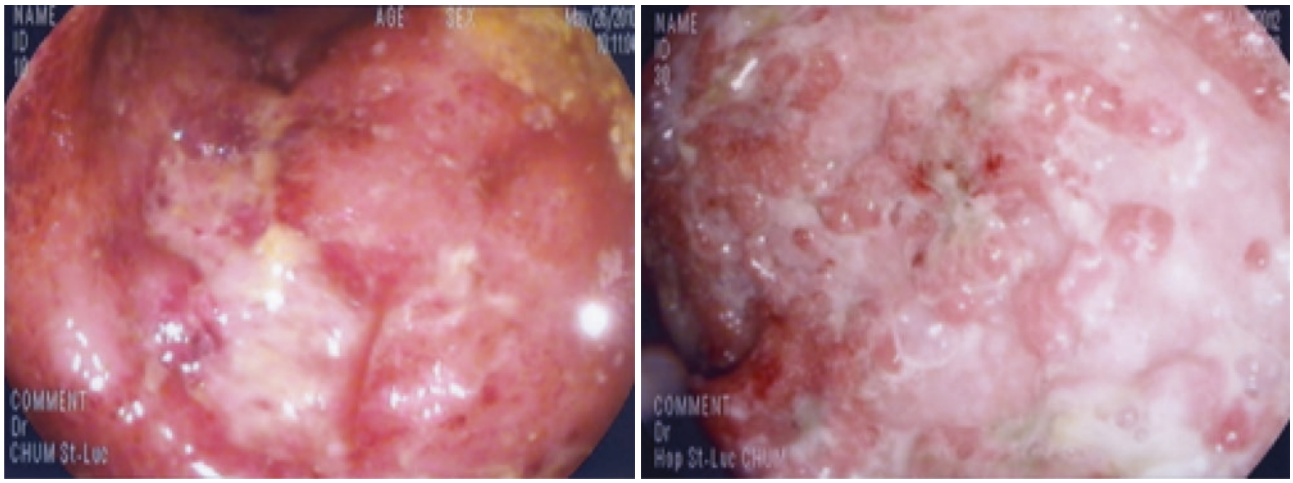


Fig. 4.15 Colonoscopy: in Crohn's disease, inflammatory areas may contain ulcers, either aphthous or ulcerous, often deep and penetrating (which may even rest on a healthy mucosa). Inflammatory areas can be irregularly distributed and mixed with areas of healthy normal mucosa. (Photos by P. Poitras)

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- Perforation of ulcers with peritonitis or formation of abdominal abscesses.
- Fistulas (communication with a nearby organ due to perforation of a penetrating intestinal ulcer):
  - Enteroenteric or entero-colonic fistulas with short-circuiting of intestinal segments or with secondary bacterial overgrowth
  - Entero- or colo-vesical fistulas with pneumaturia or fecaluria, urinary infection (often with multiple germs of digestive origin), risk of pyelonephritis
  - Entero- or colo-vaginal fistulas with passage of air or stool through the vagina and secondary vaginitis
  - Entero-cutaneous fistulas
- Perianal involvement with complicated ulcers leading to pain, abscesses, risk of incontinence due to sphincter destruction, etc. The alteration in quality of life can be significant and may require treatments that are unfortunately radical and mutilating (proctectomy with ileostomy or colostomy).
- Oral injury due to aphthous ulcers.
- Proximal digestive damage with dysphagia or odynophagia in case of esophageal damage, or gastric outlet obstruction if gastric or duodenal damage.
- Increased risk of colon cancer is present (at sites of chronic colon inflammation) in both CD and UC.

Evolution of Crohn's disease. The course of CD is variable and unpredictable. A major Scandinavian study looked at the natural evolution of the disease after its discovery and treatment of the initial episode (Fig. 4.16); many patients (45% of the patients) had a favorable course, while others had acute recurrences repeatedly (32%) or chronic symptoms (19%).

Crohn's disease is often associated with a negative image. However, an administrative database study in the Canadian province of Manitoba revealed that, over a 1-year observation period, 50% of patients with a previous diagnosis of CD had not seen a physician and 60% did not use medication; another analysis showed that, by 5 years, half of this patient population was not using any IBD-related medication A Scandinavian study found that CD patients had lower rates of absenteeism from work than normal population and a higher socioeconomic status. Various observations suggest that 2/3 of the patients have a benign or favorable course with prolonged remissions or easily treatable recurrences, but that 1/3 of the patients will have an aggressive course requiring the use of complex therapeutic strategies. Our inability to predict the disease profile in a specific patient makes it difficult to manage and prevent the disease.

In cases of drug resistance (or certain cases of drug dependence), surgery may be necessary. It is recognized that surgery does not cure the disease and that inflammation may recur in remaining intestinal segments. It is estimated that approximately 50% of CD patients will require surgery.

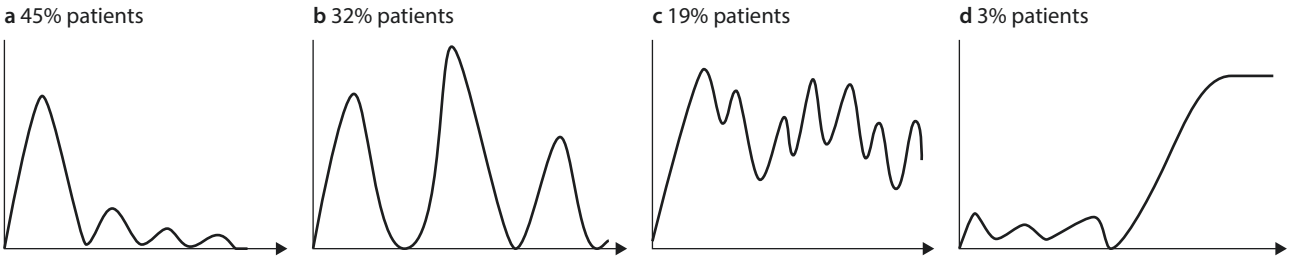


Fig. 4.16 Ten-year course of patients with Crohn's disease (schematic representation according to Solberg et al, 2007): **a** in 45% of patients, after the initial episode the symptoms severity decreased during the follow-up period; **b** 32% of patients had chronic recurrent relapses; **c** 19% had chronic persistent symptoms; **d** in few patients (3%), the disease severity increased during the 10-year follow-up period

(d) Extra GI Manifestations of IBD

IBDs may be associated with abnormalities of several non-digestive organs as summarized in Table 4.2. Some of these manifestations tend to parallel inflammatory bowel episodes (e.g., peripheral arthritis, erythema nodosum, uveitis), while others (e.g., primary sclerosing cholangitis, spondylarthritis) appear to evolve independently.

Table 4.2 Extraintestinal manifestations (20–40% of patients) of IBD

Musculo-skeletal	Peripheral arthritis (follows disease activity) (10–30% of patients)
	Central arthritis (sacroiliac/spondylarthritis) (2–8% of patients)
Cutaneous	Erythema nodosum (10–15% of patients)
	Pyoderma gangrenosum (1–5% of patients)
Ocular	Uveitis, episcleritis (1–5% patients)
Hepatic	Sclerosing cholangitis (3–7% patients) → liver transplantation
	Chronic autoimmune hepatitis
	Gallstones (Crohn's)

(e) Differences and Similarities of IBDs

Ulcerative colitis and Crohn's disease can be differentiated according to the characteristics listed in Table 4.3.

Identification of UC vs. CD is not always an easy task. In up to 20% of cases, it is not clear whether the patient has UC or CD; this is referred to as unclassified colitis. Some patients initially presenting with diffuse colonic involvement and diagnosed as UC can develop overtime CD traits (e.g., perianal or ileal lesions) and see their diagnosis change from UC to CD.

(f) Diagnosis of IBD

IBD will be diagnosed mainly by endoscopic (colonoscopy) or radiological (X-ray, ultrasound, CT scan, MRI) examinations. Serological tests are complementary to the evaluation of the patient but are of little diagnostic significance. Table 4.4 summarizes different options for a diagnostic approach.

Endoscopic examinations: When colitis is suspected, the examination of choice is colonoscopy. The macroscopic appearance will help to differentiate UC (diffuse and continuous inflammation extending from the rectum) from CD (aphthous or deep ulcers, geographic, skip areas of normal mucosa, etc.) or other diseases (ischemic colitis, infectious colitis, etc.). Biopsies can be obtained to clarify the diagnosis (e.g., immune granuloma, although rare, will confirm CD).

Radiological examinations: Barium enema is only exceptionally used nowadays in the management of IBD. Small bowel follow through (X-rays of the small intestine after oral ingestion of a barium solution), once the gold standard for intestinal exploration, is gradually abandoned (to be performant, this test, like other digestive tests such as the barium swallow, barium meal, or barium enema, requires time-consuming attentive assistance for fluoroscopy, and few radiologists maintained interest and expertise for it). Radiological investigation of the small bowel is now based mainly on cross-sectional imaging (CT or MR enterography). Transabdominal ultrasound (with Doppler) is increasingly used for intestinal exploration. MRI and US have the advantage of being performed without radiation and may differentiate inflammatory vs. fibrous nature of stenotic lesions.

Table 4.3 Ulcerative colitis and Crohn's disease can be identified by certain differences

	UC	Crohn
Clinic		
Bloody stools	≈ always	Possible
Mucus	Often	Possible
Diarrhea	≈ always	Common
Abdominal pain	Possible	Common
Abdominal mass	No	Common
Abdominal abscess	No	Possible
Toxic megacolon	Possible	Possible
Colon cancer	Increased risk	Increased risk
Gallstones	No	Possible
Radiology		
Small bowel injury	No	80% patients
Colon injury	Always	70%
Fistula	No	Possible
Stenosis	Rare	Possible
Endoscopy		
Rectal inflammation	≈ always	Possible
"Skip areas"	≈ never	Common
Ileitis	No	80%
Isolated proctitis	Possible	Possible
Pancolitis	Possible	Possible
Diffuse friability	Always	Possible
Aphthous ulcers	No	Common
Healthy/unhealthy mucosa	No	Common
Ulcer(s)	No (except severe colitis)	Common
Pathology		
Granulomas	No	25–40%
Transmural Inflammation	No (except severe)	Yes
Others		
Peripheral arthritis	Possible	Common (25%)
Central arthritis	Possible	Possible
Sclerosing cholangitis	Possible	Possible
P ANCA/ASCA	70%/0	50%(colitis)/30%
Tobacco effect	Protective	Deleterious

Table 4.4 Diagnostic tests for diagnosis and follow-up of IBD

Anomaly sought	« Gold standard »	Others
Inflammation	C-reactive protein	Anemia inflammatory type (iron↓, transferrin↓, ferritin N, platelets ↑)
	Fecal calprotectin	
Intestinal lumen damage	CT enterography	Small bowel follow through X-ray
	MR enterography	Duodeno-jejunoscopy (oral)
	Ileocolonoscopy	Enteroscopy per videocapsule
		Echography
Colon lumen damage	Colonoscopy	CT/MR enterography
		Barium enema (very rarely used)
Extra-luminal damage (abscess, fistula)	CT Scan	MRI (anorectal)

Extra-luminal damage (e.g., abscess, fistula) will be best characterized by axial tomography.

Blood and fecal tests can help monitor systemic inflammatory response and disease activity. Plasma elevation of C-reactive protein is the most commonly used marker, but is not found in all patients. Fecal calprotectin is a good marker of intestinal inflammation.

(g) Treatment of IBD

IBD treatment may be required (1) for the management of an acute episode (acute treatment for induction of remission), or (2) to maintain disease (otherwise active in absence of medication) in a quiescent (remission) state (chronic or maintenance treatment), or (3) to prevent recurrences (preventive or prophylactic treatment). UC and CD differ here in terms of preventive treatment. For UC, prophylaxy with 5-ASA is indicated for most patients since it is an effective and safe treatment. For CD, pharmacological prophylaxis needs to take into account the long-term safety and economic limitations on balance with potential clinical benefits. On the other hand, smoking cessation is an effective prophylactic regimen in CD and is recommended for all patients.

As seen below, IBD management involves several drugs of various therapeutic efficacy, side-effect profile and financial cost.

Corticosteroids: Corticosteroids are very potent drugs and have been used to control inflammatory disorders for decades. They constitute a classical treatment for acute phases of IBDs. Their beneficial effect is usually rapid, within a few days, and observed in most patients.

Corticosteroids are most often taken orally, in initially high doses and gradually reduced at a weekly interval. In the "american" approach, prednisone (5 mg/tablet) is given at 40 mg/day initially, followed by a weekly reduction of 5 mg (i.e., 40 mg/day, once-daily, in the first week; 35 mg/day in the second week; 30 mg in the third week, etc.); experience shows that 70% of patients are rapidly improved by this therapy. The "european" recipe often uses higher doses, i.e., 1 mg/kg of prednisolone (1 mg prednisolone = 1.2 mg prednisone) with a progressive weekly reduction over 12–15 weeks. A favorable response is obtained in approximately 90% of patients undergoing this therapy.

Corticosteroids may be given intravenously [methylprednisolone (Solu-Medrol®) 20 mg i.v. q 6–8 hours] when the patient cannot tolerate the oral route, or when maximum efficacy is sought. They may also be given by rectal administration as a suppository for rectal inflammation, as a foam (Cortifoam®) for rectosigmoid involvement, or as an enema (Betnesol®, Cortenema®, Entocort®, etc.) for disease extended up to the distal left colon.

Corticosteroids have well-known adverse effect on bones, and it is now advised for bone protection to administer calcium supplements (calcium 500+ vitamin D 400 bid) and possibly bisphosphonates [risedronate (Actonel®) 35 mg/week or alendronate (Fosamax®) 70 mg/week], during the course of corticosteroid therapy.

Corticosteroids are without any doubt highly effective in reducing intestinal inflammation and patient symptoms. However, as shown in Table 4.5, they are responsible for multiple side effects that limit their use. Even during the few weeks of corticosteroid therapy for the acute control of IBD, some patients can experience serious side effects (e.g., diabetes, hypertension, psychotic episodes, etc.), and most patients will suffer from cosmetic disorders (Cushingoid appearance, obesity, acne, etc.) as well as insomnia. Prolonged treatment with corticosteroids can have severe and permanent harmful consequences (osteoporosis, adrenal suppression, etc.) and should, by all means, be avoided. There is no evidence that corticosteroids are useful for maintenance of remission, so their role should be strictly reserved for induction of remission.

Table 4.5 Corticosteroids. Side effects

Possible with brief treatment

- Acne (30%)
- Bruises/petechiae (17%)
- Diabetes
- Edema (hydrosodic retention)
- Glaucoma
- Hirsutism (7%)
- Hypertension (20%)
- Moon face (57% of patients)
- Myopathy (7%)
- Obesity/hyperphagia
- Osteonecrosis (5% hip)
- Psychic agitation/depression
- Stretch marks (6%)

With prolonged treatment

- Adrenal suppression
- Delayed healing wounds/post-op anastomosis
- Infections/immunosuppression
- Osteoporosis (50%)

Fortunately, to avoid the side effects of corticosteroid therapy, other treatment options are available (see below; Fig. 4.17). Moreover, it is estimated that approximately 50% of IBD patients will not require corticosteroid treatment.

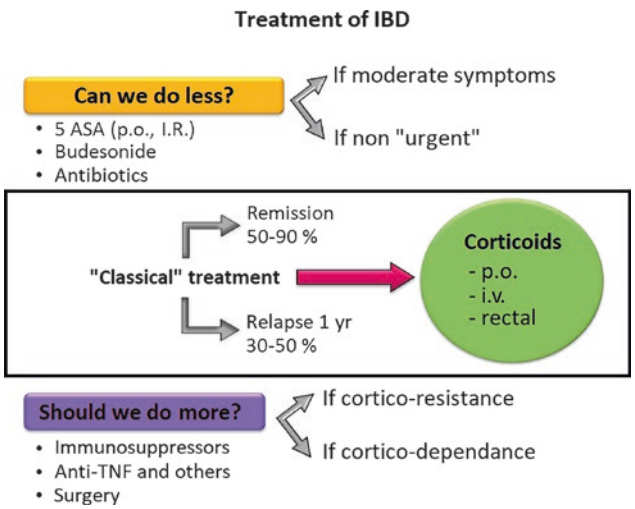


Fig. 4.17 Treatment of IBD

Can We Do Less Than Corticosteroids?

Alternative treatments do exist to avoid corticotherapy. However, they are often less effective than corticosteroids, often acting more slowly (1–3 weeks rather than 1–3 days) and having a beneficial effect in only 1/2 of the patients (rather than 3/4). For the patient whose disease is not too severe and who can afford a delayed clinical remission or risk a therapeutic failure, the following solutions can be considered:

- *5-ASA:* 5-ASA (mesalamine) are aminosalicylates that will have a local anti-inflammatory action on the intestinal mucosa. These drugs are active topically, and only about 20% of ingested doses are absorbed. To allow this topical contact, various pharmaceutical preparations exist to prevent orally ingested 5-ASA from being absorbed in the proximal intestine (and therefore of being ineffective, by not reaching the distal gut) and to allow its delivery to the distal intestine or colon (for a local anti-inflammatory action at the site of injury) (Fig. 4.18). By using 5-ASA that can be activated by colonic bacteria (Salazopyrin®, Dipentum®) or contained in pills dissolvable gradually over time (Pentasa®) or at higher pH (Asacol®, Salofalk®), the therapeutic agent can be released along the distal GI tract.

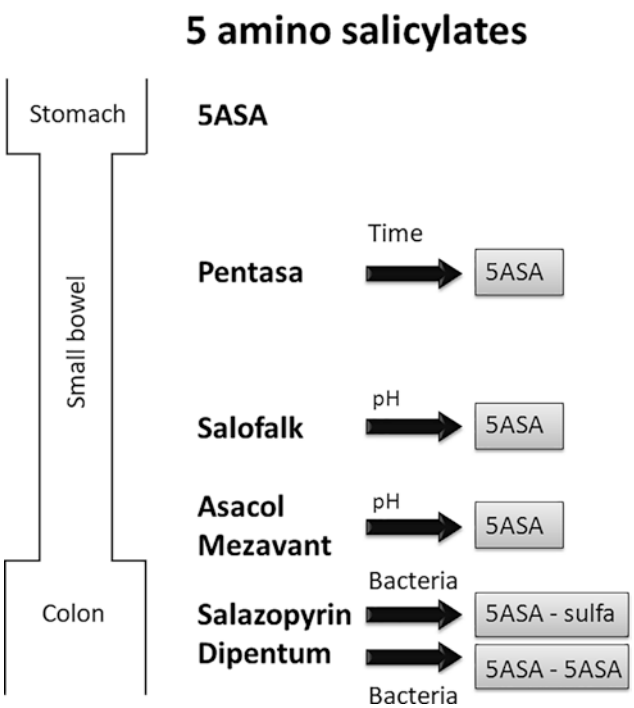


Fig. 4.18 Various preparations of 5-ASA exist for delayed delivery to the colon or small bowel. Pentasa® begins to release 5-ASA in the proximal intestine, and Salofalk® in the distal small intestine, while Asacol®, Mezavant®, Dipentum®, and Salazopyrin® have colonic delivery

For the acute treatment of IBD (more often UC than CD), oral 5-ASA can have a beneficial effect in 50–60% of patients but often with a delay of action of 1–3 weeks. Their low absorption and very limited side-effect profile make them safe pharmaceutical agents even for long-term use.

Sulfasalazine (5-ASA-sulfa) has been shown more than 30 years ago to prevent UC recurrence. New 5-ASA formulations without the sulfa moiety are better tolerated and more effective; they are used for long-term prophylaxis in all UC patients (especially since it has been associated with a decreased risk of colonic adenocarcinoma).

5-ASA can also be administered rectally using suppositories (Salofalk® 1 g or Pentasa® 1 g) which are highly effective in the treatment of proctitis (90% efficacy; more potent than corticosteroids), or by enema (Salofalk® 2–4 g or Pentasa® 4 g) for rectosigmoid inflammation.

- *Antibiotics* may also be useful in the management of IBD. Metronidazole (250 mg qid or 500 mg tid) has long been recognized for the treatment of anorectal CD, ileal CD (although less effective than prednisone), or pouchitis. The efficacy of ciprofloxacin (500 mg bid) has also been reported in several studies (albeit with a limited number of patients). In practice, the combination metronidazole/ciprofloxacin is often used for 2–4 weeks. The mechanism of action of this pharmacological approach remains unknown.
- *Nonsystemic corticosteroids*: budesonide is a potent corticosteroid (budesonide 1 mg = prednisone 5 mg) catabolized as it passes through the liver. Entocort® is a budesonide pill preparation allowing delivery of the corticosteroid in the ileocolonic lumen for a local therapeutic action before it is absorbed into the mesenteric circulation and reaches the liver where it is destroyed. Side effects of budesonide corticosteroid therapy are detectable in only one in four patients. However, its therapeutic efficacy is inferior to prednisone; its onset of action (1–3 weeks) and limited activity (50% of patients) are comparable to 5-ASAs. Cortiment® allows the delivery of budesonide into the colon lumen.

Should We Do More Than Corticosteroids?

In case of corticosteroid resistance or corticosteroid dependence, various therapeutic options are available:

- *Immunosuppressants:* Chronic corticotherapy should never be a viable option for IBD management. Immunosuppressive drugs, although not a panacea, are, since 40 years, part of the therapeutic arsenal for patients with cortico-dependence, as well for those, less common, with cortico-resistance:

- Thiopurines: 6-mercartopurine (Purinethol® 1.5 mg/kg day), or its equivalent azathioprine (Imuran® 2.5 mg/kg day), is classically used in cases of cortico-dependence. They may also be useful in cortico-resistant patients. However, it should be noted that their therapeutic efficacy is often delayed, being apparent after 3–6 months. The main side effect of thiopurines is bone marrow suppression including neutropenia. Measuring TPMT (thiopurine methyltransferase enzyme responsible for thiopurine catabolism) prior to treatment allows detection of enzyme deficits that would expose the patient to toxic levels of the drug; when therapy is initiated, a blood count should be checked every 2 weeks to detect iatrogenic leukopenia or thrombocytopenia. Other side effects of thiopurines include allergic pancreatitis (1–3% of patients) and drug fever. In the long term, an increased risk of lymphoma is recognized. Thiopurines are, however, effective and mostly well tolerated without the disastrous side effects of corticosteroids in most patients.
- Methotrexate may also be used (25 mg/week as a loading dose for 12 weeks and 15 mg/week as a maintenance dose thereafter). Methotrexate appears to be useful in patients with both corticosteroid dependence and corticosteroid resistance. Methotrexate induces its therapeutic effect within 1–3 months. Short-term side effects include myelosuppression (regular monitoring of white blood cells is therefore required) while in the medium- or long-term interstitial pneumonitis or hepatotoxicity are feared. Methotrexate can be administered orally, but for optimal results, intramuscular or subcutaneous administration is preferred.

- *Biological agents (and other new drugs)*: Since the 2000s, biological agents (i.e., pharmaceutical agents consisting of monoclonal antibodies developed in animals, usually mice) to neutralize various pro-inflammatory agents have appeared.
  - Anti-TNFs (antibodies against tumor necrosis factor alpha) are remarkably effective in IBD. Two main preparations are currently available: infliximab (Remicade®, Inflectra® administered intravenously at 5 mg/kg as a loading dose at 0, 2, and 6 weeks prior to maintenance treatment every 8 weeks) and adalimumab (Humira® given subcutaneously in doses of 160 mg at 0, 80 mg at 2 weeks, and 40 mg every 2 weeks thereafter). Other anti-TNF agents (certolizumab, adalimumab) are also available.

    Anti-TNFs alter immune defenses and may promote the development of certain diseases such as tuberculosis and hepatitis B (anti-TNF treatment is contraindicated in the case of untreated abscesses and should not be started until active tuberculosis and viral hepatitis have been ruled out). They are not recommended in patients with recent neoplasia, especially hematological malignancies, or with multiple sclerosis.
  - Anti-integrin vedolizumab prevents lymphocytes from adhering to the intestinal inflammatory site. Entyvio®, given i.v. every 8 weeks, has a targeted action on the intestine with little systemic effect. VARSITY study showed superior improvement with vedolizumab vs. anti-TNF adalimumab in UC patients.
  - Anti-interleukins 12 and 23 ustekinumab known for its beneficial effect against psoriasis is also very useful for the treatment of IBD. Stelara® is administered initially i.v. and then sc every 8 weeks. Other anti-IL-23 drugs are currently under development.
  - An inhibitor of JAK 1 and 3, tofacitinib (a chemically synthesized, nonbiological agent and given orally), initially developed for the treatment of rheumatoid arthritis, is also used for the treatment of ulcerative colitis. Other anti-JAK 1 agents are expected in the near future.

Biologic agents that provide targeted therapy for a factor of the IBD inflammatory cascade (still poorly understood) have revolutionized the management of these diseases. They are highly potent in IBD, and their side-effect profile appears very reassuring. Many physicians believe that they should be used much more often (instead of corticosteroids and immunosuppressants) and much earlier (to influence the course of the disease and prevent complications). However, their cost is currently the limiting factor to a widespread use since the price of an annual therapy (which will be perpetual) is 15,OOO–25,000 $CDN for a single-dose treatment (double or even quadruple doses are common!).

Given the multitude of new therapeutic options currently available (and more are on the way), choosing a specific therapeutic agent (e.g., should one start treatment with an anti-TNF or with an anti-integrin?) can be difficult. It can very rarely be guided by scientific data (comparative studies, efficacy based on patient's phenotype, etc.), and is often left to the physician's judgment and the patient's preference.

Summary

No treatment exists to cure IBD, but numerous medications are available to manage the disease and provide a satisfactory quality of life to IBD patients. Treatment was classically initiated with safest and cheapest drugs before, according to patient response, stepping up to more complex and expensive medications. This

traditional step-up approach (sequence of 5-ASA-corticosteroids-immunosuppressants-biologics) has been recently challenged (since biologics arrival) by the top-down strategy where patients are initially treated with the best medication (biologics) to induce a rapid and perfect recovery before switching to maintenance therapy (possibly) with other drugs and hoping to reduce long-term complications. Most medication insurance plans (private or governmental), for budget reasons, try to limit biologics use to patients refractory to other drugs and, therefore, are indirectly supporting the traditional step-up strategy.

Surgical Treatment of IBD

Surgery, once the only treatment for cortico-resistance or cortico-dependence, was, despite its mutilating effects (ileostomy if proctocolectomy, short bowel syndrome following extensive small bowel resections, etc.), a major actor in IBD management. Its role has been modified by new medical treatments (immunosuppressants in the 1980s and, more recently, biologics). Long-term risk of surgery now appears 25–50% lower in patients diagnosed with IBD in the twenty-first century than in those seen earlier. Surgical treatment is still necessary in medically resistant IBDs (often emergency surgery in acute complicated situations) and can be considered in various selected patients with UC or CD (Table 4.6).

In UC, the only desirable surgery is total excision of the colon, since partial resections are known for a high disease recurrence rate. Total colectomy with proctectomy now includes reconstruction surgery with an ileoanal pouch reservoir and eliminates the need for permanent ileostomy in most patients. Proctocolectomy has a clear benefit as it is the only known treatment to cure UC. It is used in patients resistant to medical treatment (often acute fulminant colitis), and it can be offered in selected cases of medical dependence or as prophylaxis for prevention of adenocarcinoma.

Table 4.6 Surgery in IBD

Crohn's	Ulcerative colitis
25–45% pts. operated in 3 years (prebiologics data) 25–40% of these pts. have a second surgery 30% of these pts. have a third surgery	Proctocolectomy cures the disease
Segmental limited resections if medico-resistance Short resections in medico-dependence?	Proctocolectomy Ileoanal reservoir (pouch) Illeostomy (rare)

Historical series revealed that 15% of CD patients required surgery within 1 year and 50% within 10 years after diagnosis; approximately 25% of these operated patients required a second surgery, and 30% of these twice operated patients may require a third surgery. Crohn's disease can benefit from surgery, which however cannot be curative since the disease will almost invariably reappear (most often in the gastrointestinal tract prior to the resection site). The surgical approach is therefore conservative and aims at limited colonic or intestinal resections, most often in patients resistant to medical treatment. In some cases of drug dependence (e.g., short ileal disease), surgery may be considered. Ileostomy or colostomy are now less commonly done but can still be required, especially in cases of severe anorectal disease.

(h) IBD and Women

IBD is highly prevalent in young women, where it could have specific consequences.

Fertility may be reduced in young women with IBD. Inflammation of intestinal loops in the pelvic area can affect the adjacent fallopian tubes. Surgeries involving pelvic structures (e.g., proctectomy with ileoanal pouch) can induce tubal damage in women (as well as neurological damage and erectile dysfunction in men). The systemic inflammatory state associated with IBD can cause hormonal dysfunction with amenorrhea as well as spontaneous abortion.

Pregnancy is not contraindicated in IBD. Pregnancy has no standardized effect on IBD: during pregnancy, 1/3 of women experience improvement in IBD symptoms, 1/3 feel deterioration, and 1/3 remain in a stable condition. Women who enter pregnancy in remission are most likely to remain in remission. Women using biologics (or thiopurines) are generally maintained right through pregnancy on these agents. Follow-up in a high-risk pregnancy clinic is often desired. Ileostomy and colostomy are not contraindications to pregnancy.

Delivery. Women with an active perineal CD should undergo Cesarean section.

Medication. The majority of therapeutic agents required for IBD can be used safely during pregnancy. 5-ASA and corticosteroids have long been proven safe. Immunosuppressants, as well as more recent biological agents do not pose significant risks to the mother or the fetus. The only prohibited drug is methotrexate because of its well-established teratogenic effects. Ciprofloxacin should also be avoided in the first semester.

On the other hand, birth control pills are not contraindicated in IBD patients.

Breastfeeding. The majority of treatments used in IBD are acceptable while breastfeeding. For most oral medications, a delay of 2–3 hours after taking the medication is suggested before breastfeeding.

Children born from an IBD parent have 4% risk of suffering from IBD; if both parents are affected, the risk increase to 20–30%.

(i) IBD in Children

About 25% of all IBD cases is diagnosed before the age of 18 years, and of this group about 20% will be diagnosed before the age of 10. In pediatrics, 60–70% of IBD is CD. Before the age of 15, CD is more common in boys than girls (1.5/1), while UC is equally prevalent in both sexes. A positive family history of IBD is found in 10–15% of first-generation members. In the early form of IBD, diagnosed before the age of 8 years, immunodeficiency must be ruled out (e.g., chromic septic granulomatosis, IL-10 deficiency); early onset IBD tends to have a less favorable course.

Some diseases such as Turner syndrome are associated with an increased frequency of CD. Growth and pubertal delay are often associated with IBD (CD > UC); and a decrease in growth velocity precedes the onset of digestive symptoms in about half of patients [in fact, Pediatric Crohn's Disease Activity Index (PCDAI) includes growth velocity]. Obesity does not exclude IBD.

Nutritional therapy (with polymeric formulations or others) has been shown as effective as prednisone in inducing remission in children and is often favored for the initial treatment of CD. Immunosuppressive agents, methotrexate or thiopurines, are rapidly introduced in the treatment of IBD in pediatrics. Methotrexate is now more popular than thiopurines since the reports of thiopurine-associated hepatosplenic T-cell lymphoma. Prior to prescribing thiopurines, an assay of the thiopurine-metabolizing enzyme TMPT should be obtained. Levels of thiopurine metabolites can be monitored. Anti-TNF therapy in pediatrics improves growth failure. Three years after a diagnosis of pediatric IBD, more than 10% of patients with UC or CD will have undergone surgery.

4.7 Tumor Disorders

4.7.1 Benign Neoplasms: Polyps

A polyp is an abnormal growth of tissue protruding from the mucosa in the intestinal lumen. Most polyps measure less than 2 centimeters.

Macroscopically, a polyp may be *pedunculated*, i.e., located at the end of a stalk forming like a mushroom, or it may be *sessile*, i.e., stalkless and flattened on the mucosa (Fig. 4.19).

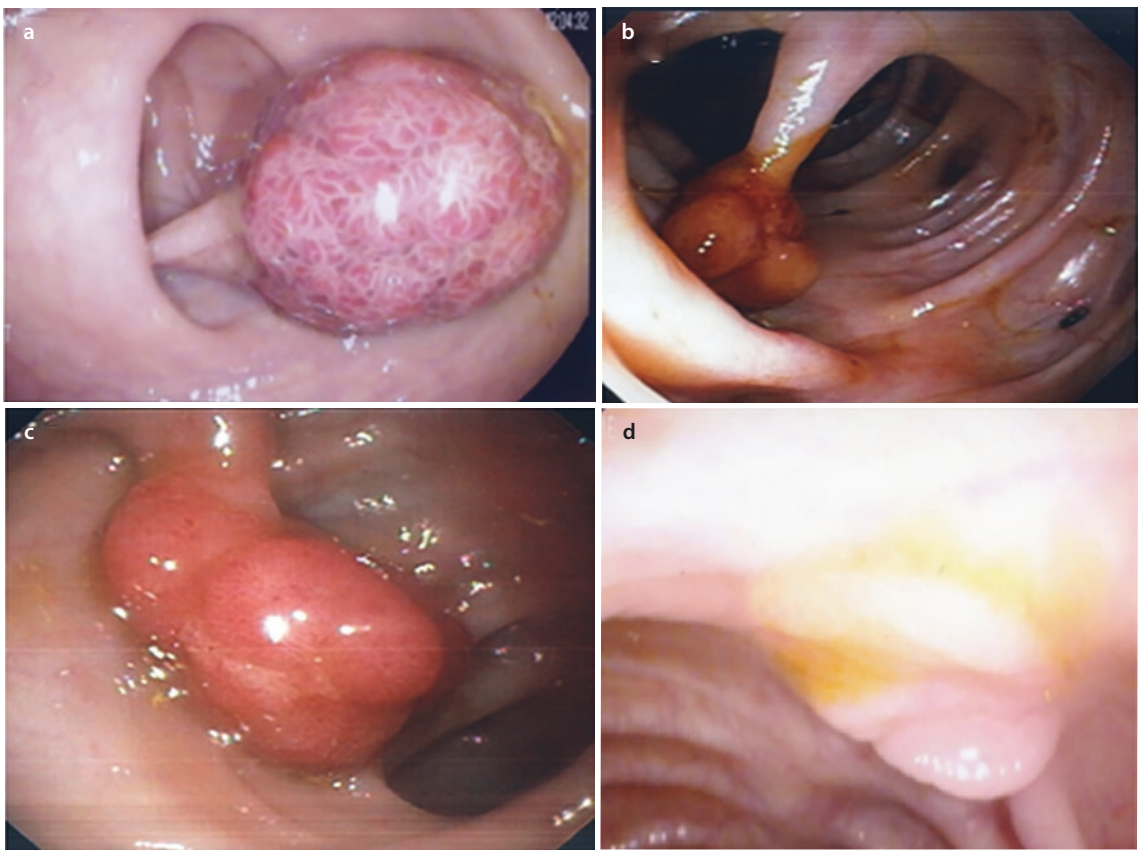


Fig. 4.19 Polyps seen on colonoscopy: **a**–**c** pedunculated; **d** sessile. (Photos by P. Poitras)

(a) Types of Polyps Microscopically, various types of polyps exist:

1. *Adenomatous polyp* constitutes an outgrowth of dysplastic glandular epithelium and is therefore at risk of a malignant transformation. Their exaggerated glandular architecture is presented in three subtypes: *tubulous* in 80% of cases, *tubulovillous*, or *villous* (Fig. 4.20). The adenomatous polyp is the most frequent and most important colon polyps since it is the precursor of colon cancer. Risk of malignant transformation increases with the size of the polyp (<1 cm, <1%; >2 cm, >10%) and its villous character (tubulovillous, 3–5%; villous, 10–40%).
2. *Serrated polyps* represent a family of epithelial polyps characterized by microscopic crypt serration with sawtooth, lace, or garland appearance of the lumen of their epithelial crypts (Fig. 4.20d). Serrated polyps include the following three subtypes:
   - The *hyperplastic polyp* (HP) is an outgrowth of normal colonic epithelium. These polyps are usually small in volume (5–6 mm), most often present in the distal colon, and without malignant potential. This is the most common (60%) of serrated polyps.
   - The *sessile serrated lesion* (SSL) is supported by the muscularis mucosae. It resembles a hyperplastic polyp but with deep dilated crypts with irregular shapes (boat anchor, inverted boot). It is most often located in the right colon and is capable of a malignant transformation. The SSL is often difficult to recognize by fecal or imaging examinations since it is flat, not very elevated on the mucosa, and does not cause major macroscopic mucosal changes; it probably partly explains the unexpected occurrence of colonic cancer in subjects who had negative screening tests a few years earlier (that SSL had been missed on previous endoscopic examinations). SSL and SSL with dysplasia (SSLD) constitute respectively 30% and 5% of serrated polyps.
   - The *traditional serrated adenoma* (TSA, formerly identified as mixed polyp or serrated adenoma) also has a serrated appearance, but unlike the SSL, it has elongated and dysplastic nuclei as the adenomatous polyp, and therefore, in the clinic, it should be treated and monitored as an adenomatous polyp.
3. The *hamartomatous* (or juvenile) polyp is made up of a stroma with hyperabundant lamina propria and

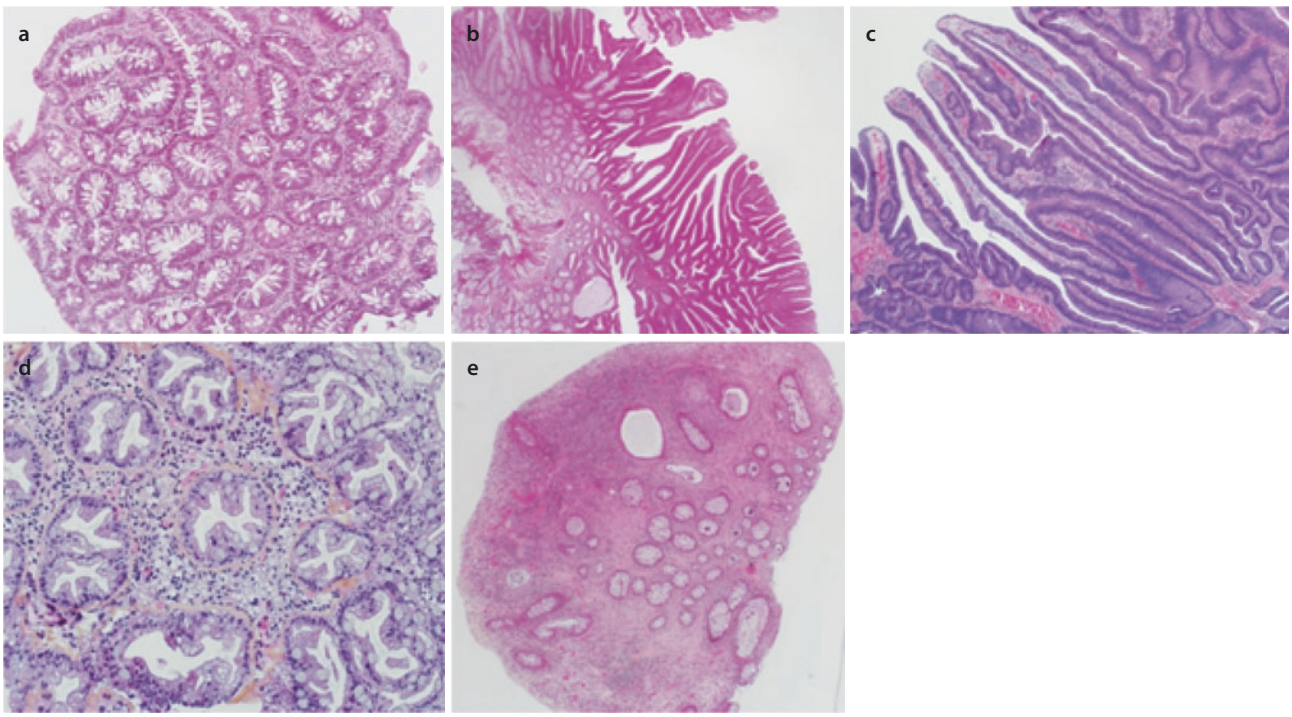


Fig. 4.20 Histology of polyps: **a** tubulous adenoma (note the tubular appearance of the glands); **b** tubulovillous adenoma; **c** villous adenoma (villous extensions are evident here); **d** hyperplastic/serrated polyp (with the sawtooth or lace-like appearance of the crypts); **e** inflammatory polyp. (Photos by G. Soucy)

cystic glands. It is most often unique and is found mostly in children or in certain forms of polyposis.

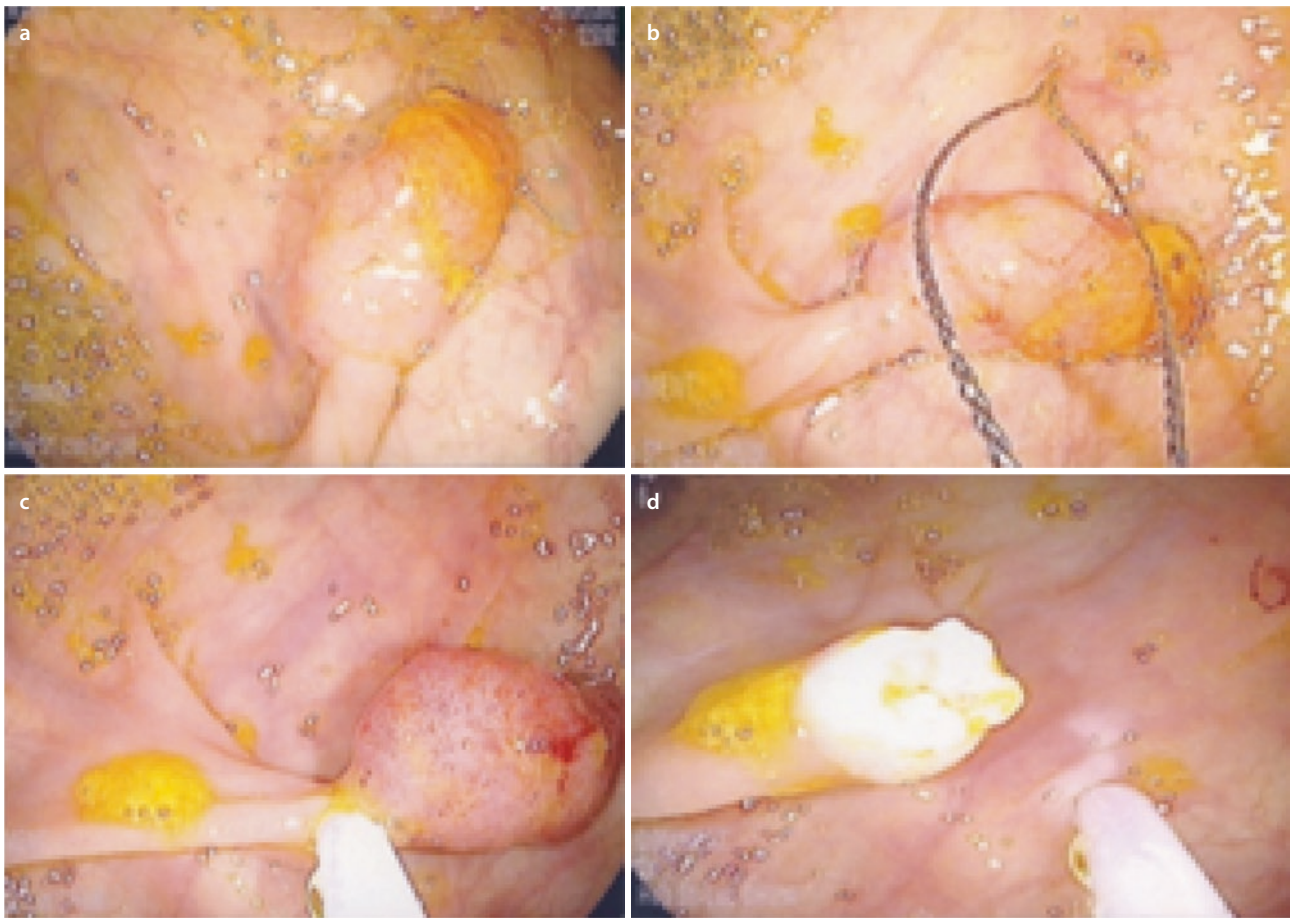
4. The *inflammatory* polyp, or mucosal polyp (or, wrongly, pseudopolyp), consists of either normal or inflamed mucosa and proliferates in inflammatory conditions such as inflammatory bowel diseases like ulcerative colitis or Crohn's disease (◘ Fig. 4.20e).

Polyps are common. Screening colonoscopies in subjects aged 50 years and over identify polyps in 1/4 to 1/3 of individuals. Prevalence of polyps seems to increase with age, since autopsy examinations reveal polyps in about 50% of cases.

(b) Clinical Colonic polyps are mostly asymptomatic. Sometimes, especially with large polyps (>1 cm), their mucosal membrane may be ulcerated or friable and may be the cause of bloody stools (polyps of the left colon) or of silent chronic blood loss (especially if in the right colon). Due to the large diameter of the colonic lumen, colonic polyps can very rarely be large enough to cause blockages. The importance of the polyps lies in their potential for malignant transformations.

Most of the time, polyps are unique or in small numbers and without obvious cause or predisposition. They may also be part of genetic syndromes promoting their development at a young age and in large numbers and are then referred to as polyposis such as familial adenomatous polyposis, Peutz-Jeghers syndrome, etc. (discussed later).

(c) Treatment of Polyps Because of their potential for malignancy, polyps are excised during the colonoscopy examination. A lasso coupled with a coagulation current is used to cut the base or stalk attaching them to the colonic wall (◘ Fig. 4.21). The polyp is then recovered for histological analysis to detect neoplastic cells.



◘ **Fig. 4.21** Colonoscopic polypectomy: the polyp **a** is surrounded by a metal loop **b** clamping the stalk like a lasso **c** and sectioning the stalk **d**. (Photos by P. Poitras)

4.7.2 Malignant Neoplasm: Adenocarcinoma

Colorectal cancer is very common. It affects 5% of the population. Colon cancer unfortunately has a poor prognosis, with nearly 40% of those affected not living beyond 5 years (Table 4.7). It is the second most lethal cancer (after lung cancer); it kills annually more people than breast and prostate cancers taken together.

The prevalence of colorectal cancer increases with age (90% of those affected are over 50 years of age). Men are affected more often than women (RR 1.2), as are blacks more often than whites (RR 1.2) or patients with acromegaly or diabetes. Colorectal cancer is associated with epidemiological factors such as obesity, smoking, and consumption of alcohol and of red or barbecued meat, while physical activity, high-fiber diet, and calcium supplements appear as protective factors against this cancer.

The majority (80–85%) of colon cancers are sporadic. A familial predisposition is suspected (given a seemingly high familial prevalence) in 10–15% of cases but most often without specific gene identification. A familial genetic incidence is well established in 5% of patients (below). The most popular theory proposes that adenocarcinoma of the colon develops from an adenoma.

Table 4.7 Diagnosed cancers (Statistics Canada 2017)

Cancer	%cancers (rank)	Survival 5 years
Lung	13.9% (1)	17% patients
Colon/rectum	13.0% (2)	64%
Breast	12.8% (3)	87%
Prostate	10.3% (4)	95%
Pancreas	2.7% (12)	8%
Stomach	1.7% (14)	25%
Liver	1.4% (18)	19%
Esophagus	1.1% (19)	14%

(a) Risk Factors for Colonic Neoplasia

1. ***Familial genetic syndromes.*** Polyposis syndromes are defined as genetic conditions that lead to the development of a large number of polyps (often more than 100 polyps). Polyposis may be made of adenomatous, hamartomatous, or hyperplastic polyps.

Adenomatous Polyposis

- Familial adenomatous polyposis (FAP) occurs in both men and women, in about 1/5000 individuals. These subjects have more than 100 colonic adenomas that develop even in childhood. The neoplastic transformation process in FAP polyp is not different than in sporadic polyp, but the high number of polyps and their early onset make the development of cancer almost inevitable by the age of 40. This condition is linked to an autosomal dominant transmission of a mutation in APC gene (adenomatosis polyposis colon) located on chromosome 5. FAP may include extracolonic manifestations such as osteomas, desmoid tumors (Gardner syndrome), or intracranial tumors (Turcot syndrome). Extracolonic polyps, mainly in the small bowel (especially in the duodenal region), are known to develop into adenocarcinoma (often at an older age). Attenuated FAP is a more benign form, with affected individuals having a smaller number of polyps (often <100) and a later evolution (around the age of 55) to colonic neoplasia. Screening in childhood of FAP candidates and prophylactic colectomy (at diagnosis) are suggested.
- Hereditary nonpolyposis colorectal cancer (HNPCC), or Lynch syndrome, is the most common of the familial genetic abnormalities of colon cancer. As the name suggests, it is not a polyposis syndrome per se (since there are no multiple polyps). MLH-1, MSH-2, MSH-6, and PMS-2 genes normally involved in the repair process of gene abnormalities are most often the cause of HNPCC. In short, a disorder of these repair genes will not allow the correction or the normally planned repair of gene abnormalities that may occur spontaneously in life or may be induced by various factors (environmental or other), and the transformation of a colonic polyp into cancer is thus accelerated (without increasing the occurrence of polyps). The pathophysiology of HNPCC is therefore different from that of FAP, where the risk of neoplastic transformation is increased due to the low age of appearance of the polyps (evolution from 30 to 40 years of age!) and their large number (out of more than 100 polyps, it is plausible to think that some will evolve unfavorably).

Lynch syndrome is strongly suspected when a family meets the Amsterdam criteria: *one* cancer before age 50 (colorectal, endometrial, small bowel, or ureter), *two* successively affected generations, and *three* people with cancer who are first-degree relatives.

In histopathology, the presence of "microsatellite instability" in resected tumors is suggestive of HNPCC and is often the starting point of a familial genetic investigation to identify individuals with genetic abnormalities (mutations in MLH-1, MSH-2 genes, etc.) and at risk of cancer. Neoplastic damage may be exclusive to the colon (Lynch type 1) or affect other organs including the small intestine, uterus, and urinary tract (Lynch type 2).

Suspicion of HNPCC syndrome or its confirmation by gene screening requires a strategy of close colonoscopic screening every 2–3 years given the rapid progression of neoplasia in these indications, as well as monitoring of the endometrium and urinary tract. Prophylactic therapies by colectomy or preventive hysterectomy are justified but are difficult to plan because of the non-absolute and unpredictable nature of neoplastic development in these individuals with HNPCC.

Hamartomatous Polyposis

- Peutz-Jeghers syndrome is characterized by hamartomatous polyps located mainly in the small intestine and by brownish stains on the oral mucosa. Mutations in STK11/LKB1 gene on chromosome 19 are identified in several families. Small intestinal polyps are mainly responsible for intestinal blockage, either because of their size or because of the intussusception they may cause. An increased risk of neoplasia is found in these individuals (90% patients have cancer at 40–50 years of age); colon cancer seems independent of hamartomas, and neoplasia can also occur in the stomach, pancreas (40% pts), breast (50%), or ovary (10–20%).
- Juvenile familial polyposis is a rare syndrome of hamartomatous polyps found mostly in the colon. Despite their hamartomatous nature, an increased incidence of neoplasia is recognized.
- Cowden syndrome is characterized primarily by multiple hamartomas on various parts of the body including the colon as well as pathognomonic skin lesions (benign tumors of the hair follicle, mouth papules). Most cases are caused by mutations in the ► PTEN gene (tumor suppressor gene) of chromosome 10 and are inherited in an autosomal dominant manner. People who have Cowden syndrome are at an increased risk of developing cancer of the breast (85% patients), ► thyroid, uterus, as well as colon cancer.
- Cronkhite-Canada syndrome is characterized by hamartomatous polyps of the GI tract (colon, small bowel, stomach), diarrhea with malabsorption, and cutaneous signs (dystrophic nails, alopecia, darkening skin). Its cause is unknown and it is not a familial disease.

Hyperplastic Polyposis

- Hyperplastic polyposis is a newly described familial polypoid syndrome characterized by multiple (>5 polyps) large (>1 cm) serrated polyps located in the proximal colon.

2. ***Inflammatory bowel diseases***, such as ulcerative colitis and Crohn's disease, are risk factors for the development of colonic neoplasia. The risk is increased according to (1) the extent of the colitis (pancolitis is significantly more at risk than left colitis), (2) the duration of the colitis (the risk increases by about 1%/year after 8 years of evolution, (3) the presence of uncontrolled inflammation (hence the protective role of 5-ASA, etc.), and (4) the association with liver disease (such as primary sclerosing cholangitis). Colon cancers under these conditions are often aggressive in their evolution and can be at multiple sites. They can be predicted by the presence of dysplastic changes in the colonic mucosa (hence the screening strategy of chromoendoscopy and multiple colonic biopsies for dysplasia).
3. ***A positive family history*** is an important risk factor for colonic neoplasia. The majority of colonic cancers are sporadic, while a positive family history is found in 20% of individuals. The minority (5%) is associated with well-identified gene conditions (familial polyposis, HNPCC as discussed above); in the remaining subjects (about 15%), the gene factors involved are not yet known. The risk of developing colorectal cancer is doubled in the presence of colorectal cancer in a first-degree relative.
4. ***Polyps.*** It has long been known that the risk of neoplastic transformation of an adenomatous polyp increases with the size of the polyp (if less than 1 cm = risk less than 1%; if more than 2 cm = risk >10%) and the histological type (villous polyp = 10–40% cancer, tubulous polyp = 3–5%). The most accepted theory at present is that adenocarcinoma is derived from an adenoma. If it is estimated that colon cancer affects 1/20 people and that polyps are present in 5–10/20 people, it can be deduced that 10–20% of the adenomatous polyps would develop into malignant neoplasia over time.

(b) Pathophysiology of the Development of an Adenocarcinoma

Tumor evolution from adenoma to carcinoma is thought to be due to progressive accumulation over time of mutations affecting several genes that regulate normal cell growth (either by limiting their growth or by promoting it) in body organs (Fig. 4.22). Mutations can be inherited (germline) or acquired (somatic).

- APC (adenomatosis polyposis colon) gene normally involved in cell migration and adhesion is mutated in 60–80% of sporadic cancers in the early stages of carcinogenesis. Germline mutations are key factors in FAP.
- P53 gene on chromosome 17, normally an apoptosis inducer and cell growth limiter, is mutated in advanced cancers.
- Mutations in DNA repair genes are known. About ten repair genes (such as MLH-1, MSH-2, etc.) are normally involved in nucleic acid transcriptional repair during DNA replication. If uncorrected, such errors in the sequence of these cell growth regulatory genes (such as TGF-B) can promote tumor growth. Germline mutations of MLH-1, MSH-2, MSH-6, or PMS-2 are detected in a large number of patients with HNPCC. Short portions of DNA, called microsatellites, are particularly susceptible to these replication errors leading to the loss or gain of various nucleic acids; these "microsatellite" areas can be identified as abnormal (or unstable) by various immunochemical methods used clinically to detect the existence of an abnormality in the DNA repair process.
- MYH is one of the excision repair genes for oxidative damage to DNA. Germline abnormalities of MYH (inducing genomic instability affecting APC or KRas genes) are identified in some cases of polyposis.

Schematically, from colonic mucosa an adenoma is initially formed (probably linked to mutations in the APC gene) and then progress to an adenocarcinoma when several genes regulating cell growth are victims of mutations stimulating their pro-carcinogenic role or preventing their anticarcinogenic action. Multiple genetic abnormalities (e.g., MSH, KRas, P53, etc.) are required for the explosion of malignant cells. Somatic abnormalities may accumulate progressively (and probably in a variable order) over the years (under the impulse of triggers yet to be identified such as "toxic" food, environmental, etc.). Germline abnormalities in these same genes enhance the risk of a neoplastic transformation.

The sequence adenoma → adenocarcinoma is probably true in the vast majority of colonic neoplasia encountered in the Western world. As this process of deterioration and acquisition of pro-cancerous abnormalities evolves over several years, strategies for screening and treatment of polyps are feasible to reduce colorectal cancer deaths.

Non-adenomatous serrated polyps can also lead to colon cancer. Different cellular mechanisms (including a mutation in the BRAF gene) are involved in the malignant transformation of serrated polyps into adenocarcinoma. Rarer and more difficult to detect (since small, flat, and weakly protruding on the mucosa) than adenomatous polyp, serrated polyp probably explains some of the rare colonic adenocarcinomas that appear to be not linked to an adenomatous polyp.

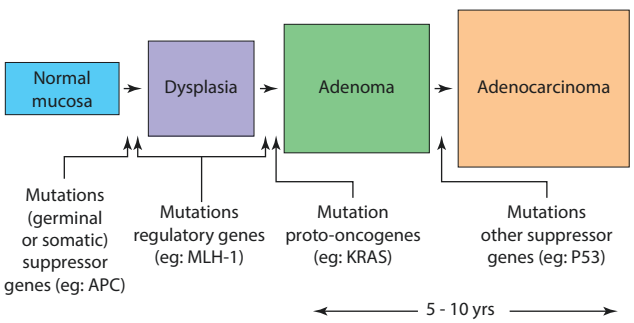


Fig. 4.22 Inherited and acquired germinal and somatic abnormalities involved in the genesis of adenomatous polyps and colon cancer according to the Vogelstein model

(c) Clinical Presentation of Colorectal Cancer

While traditionally common in the distal colon, colon cancer is now recognized to also affect the proximal colon. Cancers of the distal colon can manifest themselves by rectal bleeding, stools of reduced caliber, abdominal pain (of an obstruction type), constipation, or diarrhea (reflex to an obstacle). Cancer of the proximal colon is mainly manifested by iron deficiency anemia caused by occult blood loss (Table 4.8).

Physical examination may reveal an abdominal mass or metastatic hepatomegaly in advanced cases.

Table 4.8 Colorectal cancer: clinical presentation

Proximal colon	Distal colon canceref
Anemia/occult bleeding	Rectal bleeding
Abdominal mass	Change stools caliber
	Change stools frequency constipation/ diarrhea
	Abdominal pain
	Intestinal obstruction
	Abdominal mass

A digital rectal exam is essential to diagnose cancers of the lower rectum.

(d) Classification of Colon Cancer

As for many neoplasms, colorectal cancers are classified according to their degree of invasion to lymph nodes or distant organs. Such classification is essential for the management of the patient and the selection of the therapeutic options. It can often be complete only after surgery and pathological analysis of the removed specimen.

TNM classification (Table 4.9) is now widely used and has replaced the classic Dukes classification. Neoplastic cells are thus derived from the mucosa (T0 in situ according to the TNM classification) and may invade the submucosa (T1), the muscularis (T2), the subserosa (T3), and the serosa (T4a) or, by crossing the wall, reach nearby organs (T4b). Lymphatic invasion results in metastatic nodes in the mesentery (N1 or N2, i.e., < or >3 affected nodes). Venous invasion leads to metastases (M1), mainly hepatic, or pulmonary (mainly in the case of rectal neoplasia).

(e) Diagnosis of Colorectal Cancer

The diagnosis of colonic adenocarcinoma is made by different imaging techniques. The most sensitive method is colonoscopy (Fig. 4.23), which also allows tumor biopsies for histological confirmation of neoplastic disease. Radiological imaging includes barium enema, axial tomography, or virtual colonoscopy (CT scan with 3D reconstruction of the images).

(f) Treatment of Colorectal Cancer

The treatment will be carried out according to the stages of neoplastic invasion (Fig. 4.24).

Surgery: Invasive cancer requires segmental surgical resection including lymphatic drainage territories. Superficial cancer can be adequately treated by endoscopic polypectomy.

Chemotherapy has clear advantages against stage III cancer, i.e., with lymph node involvement. The benefit of chemotherapy is questionable in stage II and is not required in stage I. In stage IV, it can offer palliation.

Chemotherapy typically uses 5FU (thymidylate synthase inhibitor blocking DNA synthesis) in combina-

Table 4.9 Staging and prognosis at 5 years in colorectal neoplasia

TNM classification					*Dukes classification*
Stage	**Tumor**	**Nodes**	**Metastasis**	**Survival 5 years**	
0	Tis (in situ): mucosa	N0 (0)	M0(absent)		
I	T1: submucosa	N0	M0	97%	*A*
I	T2: muscularis	N0	M0	90	
IIa	T3: subserosa	N0	M0	*85*	*B*
IIb	T4: serosa-proximal organs	N0	M0	70	
IIIa	T1–2	N1(1–3)	M0	80	*C*
IIIb	T3–4	N1(1–3)	M0	60	
IIIc	T1–4	N2(>4)	M0	40	
IV	T1–4	N2	M1(present)	10–30	*D*

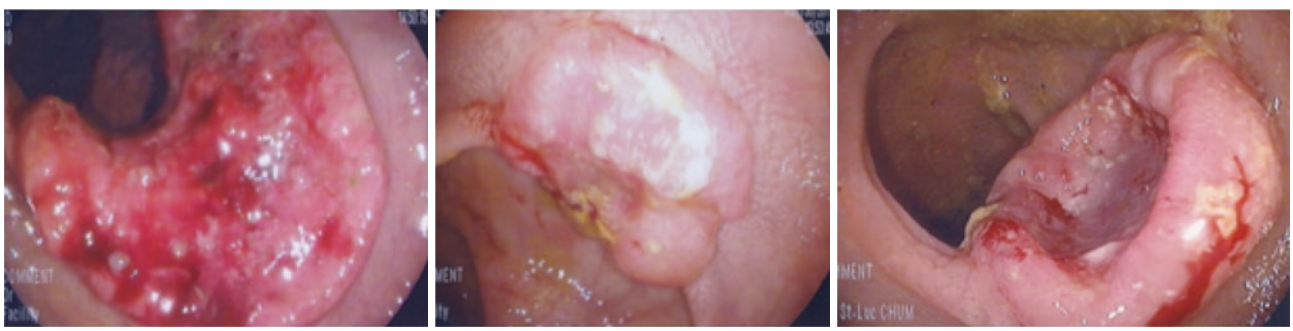


Fig. 4.23 Colon cancer seen on colonoscopy: ulcerated sessile masses. (Photos by P. Poitras)

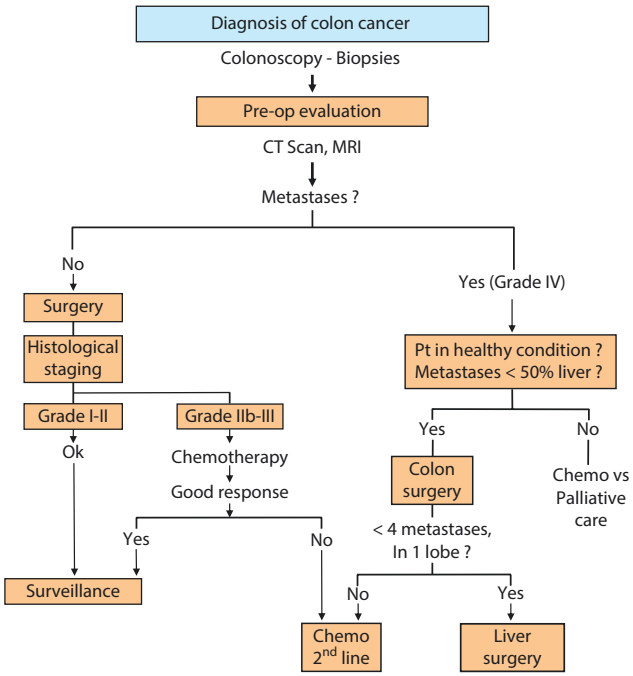


Fig. 4.24 Colon cancer management, based on the cancer staging (TNM stages I–IV) and health status (good condition) of the patient

tion with leucovorin (modulator of 5FU activity). 5FU requires intravenous administration and can be replaced by capecitabine (precursor of 5FU and taken orally). Second-line (and even third or fourth lines) chemotherapy is now common. Agents such as oxaliplatin (apoptosis inducer) or irinotecan (topoisomerase 1 inhibitor) are frequently used (called the FOLFOX or FOLFIRI regimen, respectively). Monoclonal antibodies against VEGF (vascular endothelial growth factor) such as bevacizumab or against EGF (epidermal growth factor) receptors such as cetuximab or panitumumab are also part of the oncological therapeutic arsenal.

Radiotherapy: Preoperative radiotherapy is almost always used in rectal cancer.

Liver metastases: At the time of diagnosis, 18% of patients already have liver metastases and therefore unfortunately have a limited survival of 5–10 months. However, modern chemotherapy allows median survival of about 2 years. Solitary or unilobar liver metastases can be brought to surgical resection with a 5-year survival up to 25–50%.

Neoplastic recurrence after initial treatment is detected in the liver (33% of cases), lungs (20%), or locally at the resection site (20%).

Post-diagnosis follow-up. A colonoscopy is undertaken 1 year post-colon cancer resection and then every 3–5 years. If stage II or higher, CT scans of the abdomen, pelvis, and thorax are obtained every 6–12 months, as well as CEA (carcinoembryogenic antigen) determination for 5 years.

(g) Prevention of Colorectal Cancer

Sreening strategy for prevention of colorectal cancer by early detection is possible due to the development sequence from a polyp to an adenocarcinoma progressing over an extended period of 5–10 years. Colorectal cancer screening strategies have been shown effective in reducing colorectal cancer mortality.

Who to screen? The high incidence of colorectal cancer (5% of population) justifies a screening strategy for everyone.

When to screen? Given the increase in polyps and cancer with age, it is suggested that screening should generally begin at 45–50 years of age. If there is a family history of colonic neoplasia, screening should begin 5–10 years before the age of cancer onset in the family.

How to screen: Colonoscopy will surely be the tool of choice since it is the most effective in detecting colonic lesions and allows immediate treatment of polypoid precancerous lesions. During screening colonoscopies in asymptomatic individuals, polyps are detected in approximately 25–40% of the population. Considering a prevalence of colon adenocarcinoma of 5%, it can be estimated that 1/5 of polyps seen endoscopically would develop into cancer if not resected.

However, colonoscopy has the disadvantage of being an invasive examination, most often performed under sedation, carrying certain risks (colon perforation: 1/1–2000, post-polypectomy bleeding, 1/100; sedation complications, 1/300, etc.) and requiring technical expertise (of limited availability). Other strategies are therefore used, as described in Table 4.10.

At the other end of the spectrum, fecal occult blood test (FOBT) provides a mass screening tool that has been shown effective in many studies; the presence of blood in the stool then warrants further investigation by colonoscopy. This strategy aims to reduce the socioeconomic and medical impact of colonoscopy, as well as to facilitate prevention programs for people uncomfortable with colonoscopy. The classical FOBTs such as Guaiac or Hemoccult methods are of low sensitivity (detecting about 50% of colorectal cancers)/low specificity and should be abandoned. New immunochemical tests (FIT test/fecal immunochemical test using antihuman hemoglobin antibodies) provide better results [detecting >90% of cancer lesions and 50–60% of advanced adenomas (precursors of cancer); 5% of the screening tests are positive (6–8% of them reveal cancer, 35% show significant polyp]. Other diagnostic tools, based among others on the recognition DNA abnormalities, seem promising and could be available in a near future. However, the

Table 4.10 Colorectal cancer prevention: screening methods

Test	Sensitivity	Risks	Disadvantages	If neg.	If positive
Colonoscopy	95–100%	Perforation (1/1000)	Laxative preparation, Sedation (accompanying person)	10 years	Rx made (polypectomy)
Virtual colonoscopy	Polyp 1 cm: 90% >0.6 cm: 80%	X-rays (scan)	Laxative preparation	5 years	Colonoscopy for Dx and Rx
Barium enema	Cancer: 80% Polyp >1 cm: 50%	X-rays	Laxative preparation	5 years	Colonoscopy
Fecal blood (FIT)	Cancer: 90% Advanced adenoma: 50%	0	Stool manipulation	2 years	Colonoscopy
Endoscopic capsule	Polyp >0.6 cm: 80%.	0	Laxative preparation	?	Colonoscopy

Legend: *Dx* diagnosis, *Rx* treatment, *if neg.* if negative: time before next exam

success of these methods of prevention by identifying cancer markers in the stool will still depend on the willingness of subjects to repeat the tests at frequent intervals (a test every 1–2 years is required).

In specific cases, prevention strategies can be adjusted:

- Subjects with familial polyposis (FAP) are subjected to prophylactic colectomy, even at a young age, given the inevitable development of colonic neoplasia before the age of 40 in these individuals. In the presence of a family history of polyposis, screening begins as early as possible at 10–12 years of age.
- Subjects with HNPCC syndrome may undergo colonoscopies every 2 years or even a prophylactic colectomy. Screening usually begins at ≈ 20 years of age.
- Subjects with inflammatory bowel diseases affecting the entire colon and with more than 8 years of evolution are submitted to colonoscopy every 1–5 years with multiple biopsy samples to look for premonitory dysplasia with neoplastic transformation.

Prophylaxis of colorectal cancer:

- Lifestyle: considering the epidemiological associations of colorectal cancer, general measures aimed at normal weight, healthy diet (rich in fiber and vegetables, restricted in deli meats and barbecued meats), physical exercise, and nonsmoking are recommended.
- Chemoprophylaxis with NSAIDs (sulindac) or COX-2 inhibitors (celecoxib) is effective in reducing the development of polyps in individuals at risk such as polyposis. ASA and calcium supplements have been associated with a reduced polyp transformation. However, the benefit of generalized and systematic chemoprophylaxis in colon cancer remains to be demonstrated.

4.7.3 Other Colon Tumors

Apart from polyps and adenocarcinomas, which constitute the vast majority of colon tumors, other tumors, benign or malignant, can be found sometimes in the colon, including lipomas, stromal tumors (GIST), endocrine tumors (NET), lymphomas, etc.

4.7.4 Tropical Specificity

Ameboma is an inflammatory tumor of parasite origin (*Entamoeba histolytica* inflammatory pseudotumor). Clinically, endoscopically or radiologically, it mimics colorectal cancer and is located in the cecum or sigmoid. The diagnosis is made by histology. The tumor melts under amebicide treatment.

4.8 Function Disorders

4.8.1 Irritable Bowel Syndrome (IBS)

Irritable bowel syndrome (IBS) is a term often used by both the public and the medical profession to refer to a variety of functional GI disorders (FGID) in general, for example, a patient suffering from gastric disorders

and functional dyspepsia may be labeled as IBS! Personally, we prefer that FGIDs be clearly identified as proposed by Rome Classification (Table 4.11).

In the medical world in general, the word «functional» is often associated with a "pejorative" meaning, suggesting symptoms not due to organ damage, but rather attributed to psychogenic conditions such as anxiety, somatization, or even purely imaginary. The Rome group of international experts prefers to see functional digestive disorders as digestive symptoms unexplained by lesions (inflammatory or others, that would then be detectable by endoscopic, radiological, histological examinations well available to the medical team) and attributable to disorders in the function of digestive organs (often difficult to show on «standard» medical tests). The misunderstanding comes from the fact that the traditional medical diagnostic approach is quite appropriate to identify lesions by tests such as endoscopy, radiology, histology, etc. but less so to study functions such as motility, sensitivity, etc. In this textbook of gastroenterology, we have used the term "functional" to refer to the function of organs as suggested by the Rome group.

(a) Definition of IBS IBS is characterized by abdominal pain associated with abnormal bowel movements, in the absence of a lesion on diagnostics tests. IBS is the most common and most typical disease of FGIDs.

IBS can be defined as a chronic condition, consisting of symptoms of abdominal pain or discomfort associated with abnormal bowel movements in the form of diarrhea (IBS-D), or constipation (IBS-C), or mixed bowel movements (IBS-M, alternating with days of constipation followed by days of diarrhea; this pattern is near pathognomonic for IBS). It is often associated with gastrointestinal, somatic, or psychological comorbidity. Positive and systematic identification of IBS can be facilitated by diagnostic criteria proposed by Rome IV in 2016 or by Manning in 1978 (Table 4.12).

Table 4.11 Functional GI disorders: Rome Classification IV (2016)

A. Esophageal disorders 1. Functional chest pain 2. Functional heartburn 3. Hypersensitivity to reflux 4. Globus 5. Functional dysphagia	**B. Gastroduodenal disorders** 1. Functional dyspepsia Postprandial distress syndrome (PDS) Epigastric pain syndrome (EPS) 2. Belching disorders Excessive supra-gastric belching Excessive gastric belching 3. Nausea/vomiting disorders Chronic N-V syndrome Cyclic vomiting syndrome Cannabinoid hyperemesis 4. Rumination syndrome	**C. Bowel disorders** 1. Irritable bowel syndrome With constipation With diarrhea With mixed bowel habits Unclassified 2. Functional constipation 3. Functional diarrhea 4. Functional bloating/distension 5. Nonspecific disorder 6. Opioid-induced constipation
D. Centrally mediated GI pain disorders 1. Centrally mediated abdominal pain 2. Narcotic bowel syndrome/opiate hyperalgesia	**E. Gallbladder and Oddi disorders** 1. Biliary pain Functional gallbladder disorder Functional biliary Oddi dysfunction 2. Functional pancreatic Oddi disorder	**F. Anorectal disorders** 1. Functional incontinence 2. Functional anorectal pain Levator ani syndrome Unspecified anorectal pain Proctalgia fugax 3. Defecation disorders Inadequate defecatory propulsion Dyssynergic defecation

Table 4.12 IBS diagnostic criteria

Rome IV criteria	Manning's criteria
Abdominal pain that has progressed for >6 months, recurs at least 1 day/week in the last 3 months, and is associated with two or more of the following: – Related to defecation – Associated with a change in frequency of stool – Associated with change in form (appearance) of stool	Abdominal pain plus 2 of the following: – Pain decreasing after defecation – Pain accompanied by soft stools – Pain accompanied by frequent stools – Abdominal bloating/distension – Feeling of incomplete evacuation – Mucus in the stools

IBS is found in all countries of the world with a prevalence of about 15% of population. In Western world, it mainly affects women (1 man/3 women).

(b) Causes and Pathophysiology of IBS

Genetic factors: A family history of FGID is often present in patients with IBS. Two studies in twins from Australia and the USA found that the diagnosis of IBS was significantly more common in monozygotic than in dizygotic twins (33% vs. 13% and 17% vs. 8%), confirming the genetic hypothesis. However, the US study also found that the existence of IBS in the mother of the twins, whether dizygotic or monozygotic, was an even more important factor for the presence of IBS in the child, thus giving way to not only a genetic but also an "environmental" influence in the onset of the disease.

Childhood trauma is reported in a large number of subjects with IBS. Studies in the USA, France or Australia reported a prevalence of 30–50% childhood sexual abuse in IBS patients. The precise link between these events and IBS has yet to be established, but experimental animal studies confirm that stress in early childhood can have a significant impact on the functioning of the digestive tract in adulthood.

Inflammation is frequently cited as a causal factor for IBS. An increased contingent of inflammatory cells in the GI tract of IBS patients has been detected by some authors (but could not be confirmed by others). Postinfection IBS is a recognized entity; there is a history of enteric infection that appears to initiate the onset of IBS disease in 5–15% of IBS patients, and prospective studies have shown that 5–20% of patients with bacterial gastroenteritis may develop IBS. The inflammatory hypothesis is also supported by the existence of intestinal bacterial overgrowth in some patients, or by the beneficial effect of antibiotic therapy (rifaximin) reported in some publications, or by the suspected efficacy of probiotics in many studies.

Motor theory: IBS intestinal transit perturbations obviously suggest an alteration in digestive motility. Pain, often cramp-like, could be due to high amplitude intestinal contractions. So-called antispasmodic drugs (anticholinergics, anticalcics, etc.) are used clinically to reduce intestinal contractions and abdominal pain. However, motor abnormalities of the colon or small intestine have been detected in only 10–20% of IBS patients, and the motor dysfunction theory seems to explain IBS in only a minority of patients.

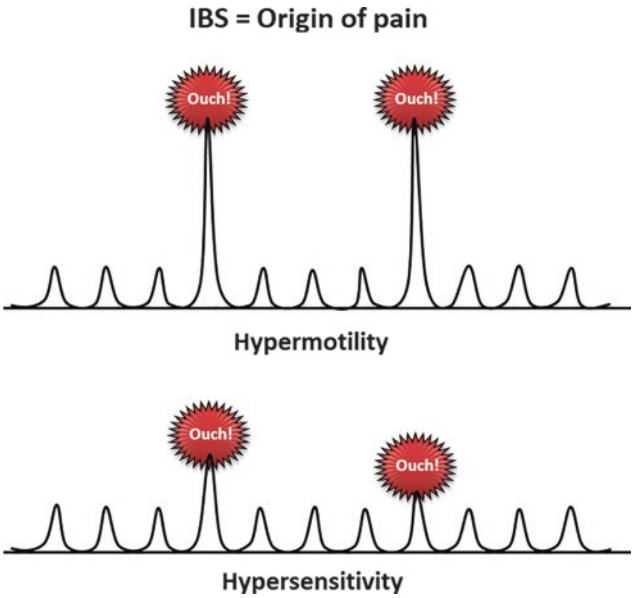


Fig. 4.25 Origin of abdominal pain in IBS. Top, motor theory – high amplitude contractions generate abdominal pain. Bottom, sensitivity theory – lower amplitude contractions can generate pain in a hypersensitive patient

Hypersensitivity theory: If abdominal pain cannot be explained by contractions of exaggerated amplitude, hypersensitivity could explain why contractions of slightly increased (or even normal) amplitude may cause pain in hypersensitive patients (Fig. 4.25).

Studies of colonic sensitivity (usually done by rectum distension of with an inflatable balloon) revealed that IBS patients (1) were hypersensitive to distension (as compared to normal subjects), (2) were sensitized by repeated distensions (in opposition to normal subjects

who become more tolerant), and (3) had aberrant pain irradiation (i.e., exceeding the pain irradiation usually experienced in normal subjects). Hypersensitivity is detectable in 50–90% of patients according to various authors. In some patients, hypersensitivity is organ-specific (colon in IBS, stomach in dyspepsia), while in others it is diffused throughout the GI tract; in many cases, it can affect not only visceral but also somatic sensitivity. Brain imaging studies using functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) have shown that intestinal distension evoked an exaggerated pain signal in the brain of IBS patients. As shown in Fig. 4.26, this exaggerated pain signal could originate from (a) a hypersensitive bowel sending an increased neurological signal to the brain, (b) a normal bowel having its sensory signal amplified as it passes through the spinal cord, (c) a normal peripheral signal amplified centrally, or (d) a normal ascending sensory signal not compensated for by normal descending inhibition mechanisms (Fig. 4.26).

Given the hypersensitivity, mild discomfort may become disabling pain (hyperalgesia), just as a normally imperceptible phenomenon may become source of discomfort or pain (allodynia). Hypersensitivity acts as a sensory amplifier.

Hypersensitivity may account for the fact that food and stress, both normal stimulants of the digestive tract, are triggers of pain or motor symptoms in IBS patients. Hypersensitivity will lead any dietary or psychological

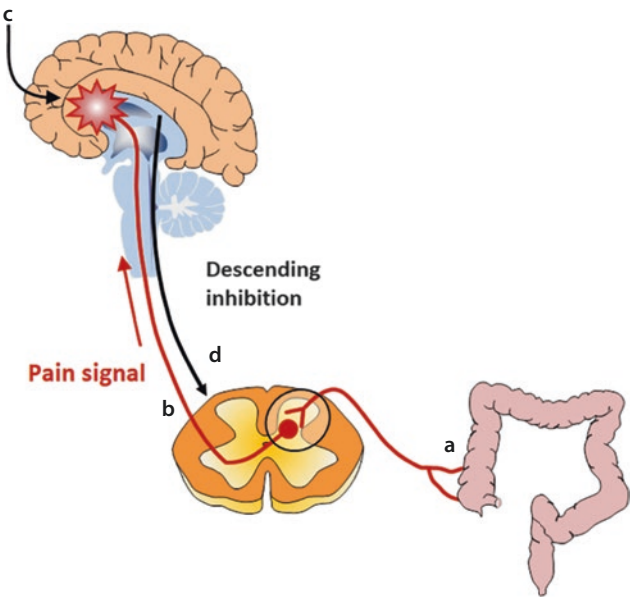


Fig. 4.26 Pain perception: intestinal stimulation is perceived at the central level. Exaggerated perception in IBS may result from an intestinal signal (a) increased from an abnormal intestine, or (b) amplified as it travels through the spinal cord, or (c) amplified as it reaches the brain, or (d) not compensated for by descending inhibition

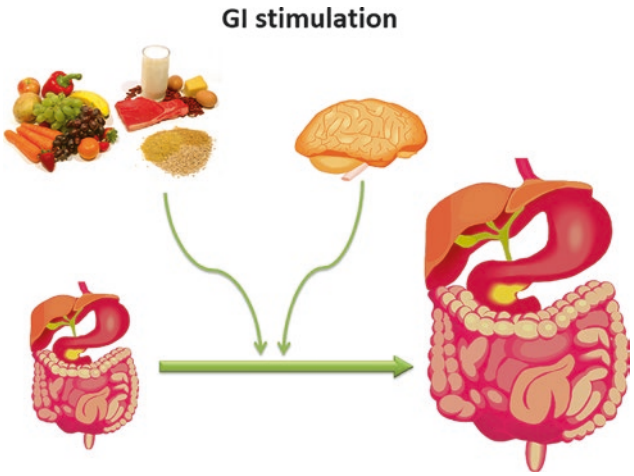


Fig. 4.27 Diet and stress are two normal stimuli of digestive motor function. The so-generated signal is over-perceived in IBS

stimuli to exaggerate the perceived digestive response in these patients (Fig. 4.27).

(c) Diagnosis of IBS

The diagnosis of IBS is not a diagnosis of exclusion, i.e., it is not made exclusively after elimination of lesions. The diagnosis of IBS is based on a positive approach and is based on three points (Table 4.13): (1) a history of symptoms according to type and duration, (2) a normal physical examination, and (3), if necessary, biological examinations without lesions.

1. ***Clinical Symptoms.*** The main dominant symptom as well as accompanying symptoms must be collected and analyzed in a differential diagnosis approach.

Table 4.13 IBS = positive diagnosis

1. **Clinical Symptoms**
   - Main symptom = pain + abnormal stools (Rome/Manning)
   - Accompanying symptoms
     - Digestive comorbidity (functional dyspepsia, proctalgia fugax, etc.)
     - Somatic comorbidity (migraine, fibromyalgia, interstitial cystitis, etc.)
     - Psychogenic comorbidity (anxiety, depression, sleep disorder, etc.)
   - Differential diagnosis
     - Diarrhea
     - Constipation
     - Pain
2. **Clinical examination:** normal
3. **Biological (exclusion) tests:** normal
   - If necessary
   - Taking into account the differential diagnosis

- *Main Symptom.* The goal of the clinical approach is to establish a positive diagnosis based on the main symptom as identified by Rome or Manning criteria [which can be summarized as chronic abdominal pain or discomfort, with abnormal stools in the form of either diarrhea, constipation (or both), and often accompanied by abdominal bloating, mucus in the stool or a feeling of incomplete evacuation].
- *Accompanying symptoms* involving digestive organs other than the colon, non-digestive organs, or psychological health are common in IBS patients.
  - Digestive comorbidity is often present. In addition to the main symptom suggestive of colonic disease, IBS patients frequently complain of other functional digestive symptoms affecting, for example, the stomach (ulcer-like functional dyspepsia or motor dyspepsia), the esophagus (functional dysphagia, globus, etc.), the anorectal region (proctalgia fugax, etc.), etc. These extracolonic digestive symptoms may be present concomitantly with the IBS symptoms, or may have existed in the past, or may appear in the future.
  - Somatic comorbidities (or extra-GI manifestations) are very frequently encountered in patients with IBS (as with other FGIDs): low back pain, headache, fatigue, cardiovascular abnormalities (palpitations, dizziness, etc.), musculoskeletal pain (fibromyalgia), urinary disorders (irritable bladder, interstitial cystitis), reactive hypoglycemia, etc. It is estimated, for example, that 1/3 to 1/2 of patients with IBS have fibromyalgia, just as 1/3 to 1/2 of fibromyalgia patients have IBS.
  - Psychological comorbidities are identified in many patients (anxiety, depression or depressive features, unstable mood, sleep disturbances, etc.).
- *Differential diagnosis* of functional GI symptoms includes lesional abnormalities. Thus, depending on the main symptom (pain with diarrhea or constipation), the differential diagnosis will include different causes of diarrhea (e.g., inflammatory bowel disease, celiac disease, enteric infections, etc.) or of constipation (obstruction by stenotic lesion, motor dysregulation, etc.). Moreover, GI symptoms may be present in psychogenic disorders (such as depression, panic disorders, somatization disorders, etc.), and these conditions must be considered in the differential diagnosis (Fig. 4.28).

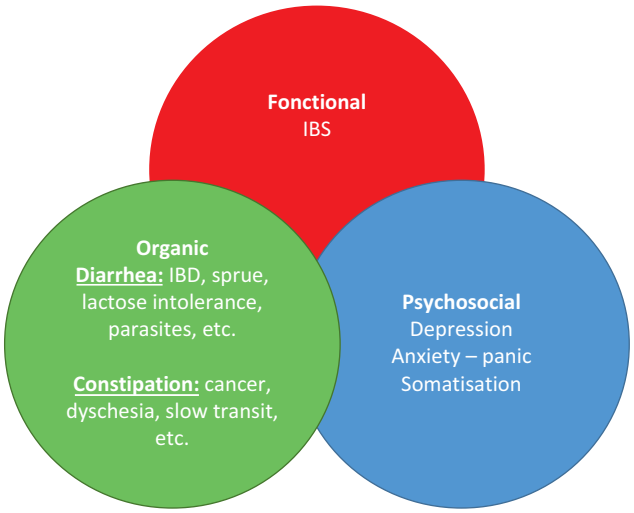


Fig. 4.28 The differential diagnosis of gastrointestinal symptoms includes functional disorders, lesional abnormalities, and psychosocial disorders

2. ***Physical examination.*** A complete physical examination is essential. It is always normal.

3. ***Biological examinations.*** There is no biological test that affirms the diagnosis of IBS (or other FGIDs). Laboratory tests or examinations are used to rule out other digestive pathologies that may be suspected. The differential diagnostic approach (above) is essential to guide the nature of the biological investigation. For example, in the case of diarrhea, an inflammatory bowel disease, gluten enteropathy, intestinal parasitosis, etc. may be considered, just as in the case of constipation, an obstructive lesion of the colon may be considered.

Biological examinations are not always required. Often, the symptoms and the subsequent physical examination will allow to establish the diagnosis. Extensive investigation with blood tests, stool cultures, X-rays, endoscopy, etc. may be warranted in patients with atypical symptoms history and/or physical examination, or with warning signs (red flags) (Fig. 4.29).

(d) Treatment of IBS

The management of IBS is based on a positive diagnosis (following careful questionnaire and physical examination), and a therapeutic trial (Fig. 4.30) is recommended. It has been well established that this approach has a low risk of error and allows a safe and effective management of IBS. Some patients, especially those seen in tertiary settings, will undergo extensive exclusion testing before a diagnosis of IBS is made. The art and science of the physician are often used here to determine how far the investigation should go.

IBS: ALARM SIGNS

HISTORY	EXAM
- Weight loss	- Anemia
- Rectal bleeding	- Abdominal mass
- Nocturnal symptoms	- Signsof intestinal obstruction
- Fever	- Signs of malabsorption
- > 50 yrs	
- Recent onset	
- Family history of cancer, IBD, etc.	

Fig. 4.29 The following symptoms and signs are not typical of IBS and should be considered along with other diagnoses such as neoplasia, inflammation, etc.

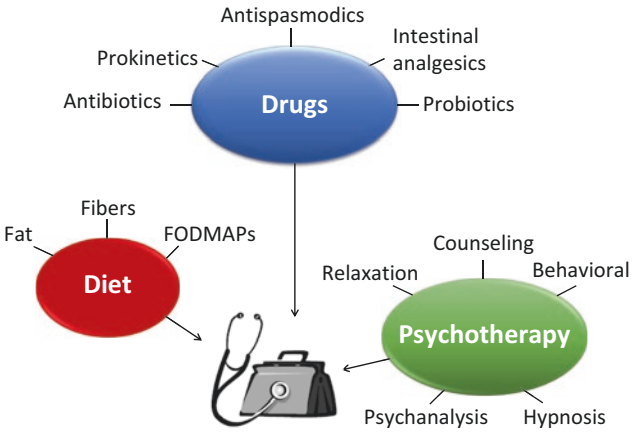


Fig. 4.31 For the treatment of IBS, the physician may use a variety of treatment options

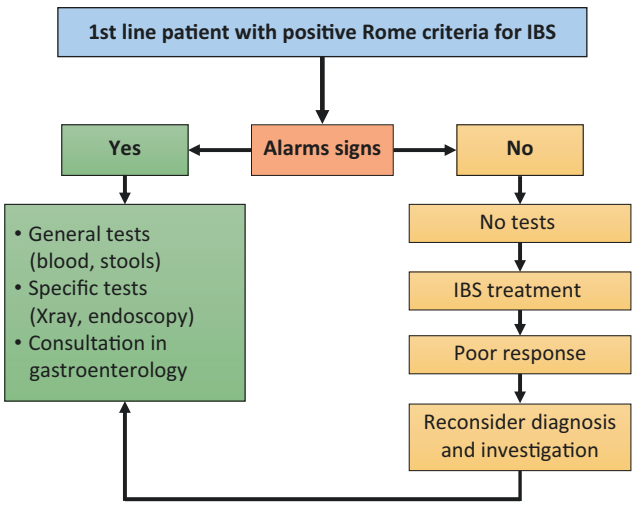


Fig. 4.30 Management of an IBS patient as proposed by N.J. Talley. (Gastroenterological Disorders, 2003)

The treatment of IBS uses a comprehensive approach that includes (1) reassurance and patient education, (2) dietary counseling, (3) pharmacotherapy, and (4) psychotherapy (Fig. 4.31).

1. ***Reassurance and patient information.*** Several studies have shown that the accumulation of negative tests did not have the expected beneficial effect on IBS patients. The "you have nothing because your tests are normal" approach (classical medical strategy used for decades) may sometimes be useful but appears unsatisfactory in most patients. Information to patients is now easier to provide given our knowledge of the motor, sensory, or inflammatory dysfunctions involved in these patients. Popular education material, patients group, etc. are useful tools.
2. ***Nutritional counseling.*** IBS patients often try to relate their digestive symptoms to their food profile. Many may benefit from a consultation with a nutrition professional. Dietary advice is based on findings obtained more through observation and experience than through scientific experimentation. The regimen excluding "FODMAP" [fermentable oligosaccharides, disaccharides (lactose), monosaccharides (fructose), and polyols (sorbitol, xylitol)] has recently been validated. Fiber may be useful in constipated patients, but beware of fiber-induced bloating. Fermentable foods should be ingested with caution in many patients, as should fatty foods (Table 4.14).

Table 4.14 IBS management: general dietary guidance

To consume (with moderation):
- Insoluble fibers
  - Bran
  - Whole-grain cereals
  - Seeds, nuts
- Soluble fibers
  - Pectin: fruits (apple, citrus fruits), vegetables (cabbage, corn)
  - Psyllium
  - Flax seeds

To avoid:
- Fermentable foods
  - Fibers
  - Legumes (chickpeas, lentils, beans)
  - Vegetables (cabbage, broccoli, onion)
  - Dried/candied fruits
- Fats
  - Fried food
  - Sauces (cream)

3. ***Pharmacotherapy.*** The general approach for the treatment of IBS is to identify the main dominant symptom (diarrhea, constipation, or pain) and to focus treatment measures toward this abnormality (■ Table 4.15, ► Chaps. 13 and 15). For example, in the diarrhea patient, medication will be prescribed to slow GI transit (loperamide, etc.), in the constipated patient laxatives or prokinetics will be used and in the predominantly painful patient treatment will include antispasmodic or intestinal "analgesics."

   Probiotics (live microorganisms that, when administered in adequate amounts, produce a host health benefit) are probably useful in the treatment of IBS according to various studies. However, the dose and type of probiotic to be used remain to be clarified. The therapeutic effect of altering the intestinal microbiota is also supported by the beneficial action of the antibiotic rifaximin on IBS symptoms.
4. ***Psychotherapy.*** The importance of stress or other psychogenic conditions in the genesis or manifestation of IBS should be considered. Stress is a normal stimulant of the human digestive system, and intestinal hypersensitivity explains why IBS patients cannot tolerate so-called normal stresses or feel exaggerated pain in face of stress. Several psychotherapy techniques have been satisfactory used in the management of these patients. Hypnosis and behavioral therapy techniques have been studied in particular, but benefits can also be observed with humanistic approaches such as interpersonal therapy, counseling, etc. Patient preference and therapist availability need to be considered. The psychotherapeutic approach has the advantage of offering a prolonged and lasting result compared to pharmacotherapeutic approaches that require chronic medication to avoid a recurrence of symptoms when therapy is stopped.

■ Table 4.15 IBS Pharmacotherapy: by main symptom

Diarrhea	Constipation	Pain
Opiates and derivatives Loperamide 1–8 co die Diphenoxylate 1–6 co die Codeine (po, sc) 15–30 mg qid Eluxadoline 75–100 mg bid *Cholestyramine* 4–8 g die *Tricyclics:* amitriptyline 10–30 mg hs *Antibiotics:* rifaximin *5HT-3 antagonists:* alosetron	*Bulk agents* Dietary fibers Bran Psyllium *"Lubricants"* Mineral oil Lansoyl Docusate *Osmotics* Lactulose PEG Mg^+ Sulfates *"Stimulants"* Bisacodyl Sennosides *Secretors Cl^-* Lubiprostone Linaclotide, plecanatide Misoprostol (?) *"Prokinetics"* 5-HT4 agonists: prucalopride Colchicine (?) *NHK antagonist* Tenapanor	*Antispasmodics* Anticholinergics: dicyclomine, hyoscine Anticalcics: pinaverium Mu opiates: trimebutine Peppermint oil *Tricyclics:* amitriptyline *SSRIs* Fluoxetine Paroxetine Citalopram Venlafaxine *Others* Pregabalin? Linaclotide?

(e) IBS: Summary

IBS is a chronic, nonlethal condition that does not progress to other gastrointestinal conditions (such as inflammatory or neoplastic diseases) but can seriously affect the quality of life of those who suffer from it.

IBS is a common condition (1/6 people!). It is therefore not surprising that IBS is found in patients also suffering from other digestive diseases such as celiac disease, lactose intolerance, IBD, etc. These diseases have symptoms that are often very similar to IBS and can be complex to identify and treat.

The name IBS refers to a heterogeneous group of patients. Past discoveries have taught us that some so-called IBS patients in fact were suffering from lactose intolerance, microscopic colitis, gluten enteropathy, etc. Current research tells us that the symptom pathophysiology is not the same in everyone (some have a condition that responds to antibiotics, others are hypersensitive, etc.). It is therefore illusory to think of a universal treatment. Management of IBS requires a strategy tailored to the individual patient.

Management of IBS requires a combination of science and skill from the physician. How far should the patient be investigated? Which treatment approach should be chosen? These are questions that should be adapted to each patient.

4.8.2 Colon Transit Disorders

Colonic transit usually lasts 1–3 days. *Rapid colon transit* reduces contact time of the chyme with the colonocytes, thus compromising absorption and promoting diarrhea by increasing fecal volume and the number of defecations. A *slow colon transit*, on the contrary, promotes hyperabsorption of colonic fluid generating constipation with a reduction in fecal volume and in defecation frequency.

Fecal transit can be assessed by different methods. The most accurate method uses nuclear medicine scintigraphy to detect progression of ingested isotope ligands marking the fecal chyme; it is used almost exclusively in research. The easiest clinical method is to follow the progression of radiopaque markers on daily X-ray images of the abdomen (1–3 days are normally sufficient to clear the markers). Since colon transit is usually the major component of total digestive transit (esophagus, 5–6 seconds; stomach, 1–4 hours; small bowel, 2–6 hours; colon, 1–3 days), colonic transit can also be assessed by measuring the evacuation time of an orally ingested "colored" marker (e.g., carmine red or activated charcoal), or a telemetric capsule (Smart Pill®). In practice, however, colon transit is only measured in very selected cases.

The causes of colonic transit disturbance are listed in Tables 4.16 and 4.17.

The diagnostic and therapeutic approach to diarrhea and constipation is discussed in the section Digestive Symptoms of this manual.

Table 4.16 Rapid colon transit: causes

Hormone stimulation
- ↑ T4 (hyperthyroidism)
- ↑ Serotonin (carcinoid tumor/syndrome)
- ↑ Thyrocalcitonin (medullary thyroid cancer)

Neuromuscular dysfunction
- Post-vagotomy
- Diabetic neuropathy
- Dysautonomia

Colon mucosa abnormalities
- (↓ absorption, ↑ secretion → ↑ motility)
- Infectious or inflammatory colitis

Exaggerated ileal flux
- Malabsorption/maldiges tion
  - Generalized (celiac disease, pancreatic insufficiency)
  - Specific (lactose intolerance)
- Small intestinal hypersecretion
  - Infections (virus, bacteria, etc.)
  - Metabolic (VIP, etc.)
  - Bile salts

Drugs
- Laxatives
  - Osmolar (Mg, PEG, lactulose, etc.)
  - Stimulants (senna, etc.)
- Prostaglandins (misoprostol, lubiprostone)
- 5-HT4 agonists (cisapride, prucalopride)
- Chemotherapy agents (mucosal cytotoxicity)
- Others with ± identified mechanism: colchicine, quinidine, metformin, olsalazine, lithium, PPIs, ticlopidine, etc.)

Reflex hypermotility
(overflow past an obstructing « lesion »)
- Fecaloma
- Stricture (neoplastic or inflammatory)

« Idiopathic » hypermotility
- Irritable bowel syndrome

4.8.3 Bile Acid Diarrhea

Bile acid diarrhea (BAD) is due to colonic secretion caused by bile acids reaching the colon in excessive quantities since malabsorbed at the distal ileum (as discussed in the ▶ Chap. 3). The colon is completely normal in appearance, and the response to treatment with bile salts binding resins (cholestyramine, etc.) confirms the diagnosis.

BAD occurs under the following conditions: (a) after ileal resection or with ileal diseases (most often Crohn's ileitis) where bile acids are malabsorbed from the ileum and reach the colon in excess quantity; (b) post-cholecystectomy (10% of cases) in which the loss of gallbladder reservoir function results in bile acids delivery to

Table 4.17 Slow colon transit: causes

Obstruction: lesion
- Distal colon: stricture (tumoral or inflammatory)
- Anorectum: stricture, rectocele

Obstruction: functional
- Hirschsprung's disease (rectal aganglionosis)
- Anorectal dyssynergy
- Dyschezia (rectocele, prolapse)

Neuromuscular diseases
- Neural: Parkinson's, multiple s sclerosis, diabetes, intestinal pseudo-obstruction syndrome
- Muscular: scleroderma – Steinert's disease, etc.

Systemic diseases
- Hypothyroidism
- Metabolic disturbances (K^+, Ca^+)

Drugs
- Opiates
- Anticholinergics (including tricyclics, SSRIs)
- Anticalcic agents (verapamil, etc.)
- Anti 5-HT3 (alosetron, etc.)
- Iron/calcium/aluminum supplements

Others
- Colonic inertia (↓ neurological plexus, ICC)
- Dolichocolon?
- Irritable bowel syndrome
- Postoperative Ileus
  - Generalized
  - Colon (Ogilvie's syndrome)

the intestine (and colon) which is no longer synchronized with meals; and (c) in idiopathic (or so-called primary) BAD (often erroneously attributed to IBS-D). Recent work has shown a deficit in FGF19 secretion (inhibitor of bile salts hepatocyte synthesis) by the enterocyte which leads to the overproduction of bile salts by the liver.

4.9 Miscellaneous

4.9.1 Diverticular Disease

A colon diverticulum is made by herniation of colonic mucosa and submucosa through the muscles of the colonic wall (Fig. 4.32). The herniation occurs at the sites of penetration of the vessels passing through the muscularis to irrigate the inner layers of the intestinal wall.

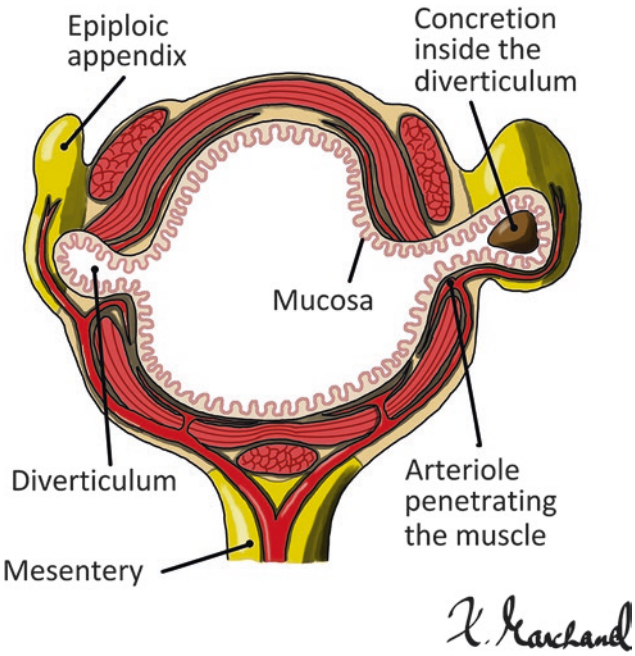


Fig. 4.32 Diagram of a diverticulum: the entry points of the vessels (from deep muscularis to superficial mucosa) are areas of weakness through the circumferential muscle layer where the mucosa (with submucosa) can protrude

Diverticulosis indicates the condition of being a carrier of diverticula. Diverticulitis is inflammation of a diverticulum.

(a) Incidence

Colon diverticula are common. They increase with age. In Western industrialized countries, their prevalence is roughly comparable to age, i.e., at age 50, about 50% of individuals would be affected, at age 70, 70%, etc.

(b) Identification

Diverticula appear as small pockets of 1 to 2 cm projecting outside the colonic wall. They are easily recognizable during a barium enema, CT scan, or colonoscopy (Fig. 4.33). They are located mainly at the sigmoid but may be found throughout the colon.

(c) Etiology

Epidemiological studies have linked colon diverticulosis to low dietary fiber intake by comparing the prevalence of diverticula in industrialized or developing countries where the diet is usually higher in fiber content. It has been suggested that low fiber intake reduces fecal mass and forces the colon to contract more strongly, thus generating muscle hypertrophy (myochosis as described on X-rays) and promoting herniation of the mucosa and

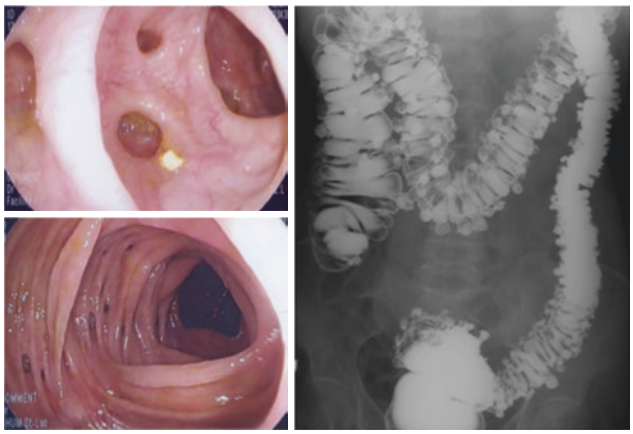


Fig. 4.33 Colon diverticula. Left image, diverticular openings of the colon wall seen in colonoscopy; right image, diverticular sacculations projecting out of the colonic lumen seen here in white contrast during barium enema X-ray. (Photos by P. Poitras)

submucosa internal layers through "weak areas" of the muscle layer. However, the questionable benefit of high-fiber diet in the treatment of diverticular disease raises doubt about the clinical validity of this epidemiologically based hypothesis.

(d) Clinic

Colonic diverticulosis, whatever popular culture may think, is asymptomatic in most cases (except perhaps in some extreme circumstances of muscle hypertrophy, according to our personal opinion). Abdominal pain reported by patients with uncomplicated colonic diverticulosis is most often due to irritable bowel syndrome. Colonic diverticulosis does not require treatment; the once classic high-fiber diet prescribed to hopefully reduce the development of additional diverticula and the occurrence of future diverticulitis is now being questioned.

The clinical importance of colonic diverticulitis lies in the complications that may arise. Colon diverticula can be complicated by bleeding or inflammation (diverticulitis). One popular theory attributes these complications to "abrasive" fecal content stagnating in the diverticular pouch. It is indeed tempting to think that erosion of a blood vessel or perforation of the diverticular wall is due to trauma by hard and/or sharp objects, such as fruit pits, peanuts, etc. stagnating in the diverticular pouch. However, no dietetic or other gesture is known in practice to prevent or avoid diverticular complications.

Diverticulitis is the inflammation of a diverticulum with a peridiverticular inflammatory reaction that classically manifests itself as the triad of (1) pain (most often localized to the left iliac fossa), (2) fever, and (3) leukocytosis.

Diverticulitis is caused by a perforation (most often a micro-perforation) in the thin, fragile wall of the diverticulum. The perforation results in an inflammatory reaction that either (1) is local (parietal edema and inflammation of the pericolic fat) which often seals the micro-perforation, limiting the extent and severity of the damage, or (2) can spread and become complicated with a localized abscess around the colon, or (3) may be accompanied by diffuse fecal spilling into the abdominal cavity resulting in purulent or stercoral peritonitis, or (4) may create a fistula with surrounding organs (most often the bladder).

Diagnosis of acute diverticulitis: (a) Clinical presentation is mainly made by acute abdominal pain (lasting few hours or few days) at the site of diverticulitis, most often the left iliac fossa. (b) Physical examination reveals local sensitivity or localized to diffuse peritoneal signs depending on the severity and extent of the inflammation. Typically, the triad of pain in left iliac fossa, fever, and elevated circulating white blood cells is found. (c) Diagnosis is usually confirmed on abdominal CT scan (Fig. 4.34) which reveals an edematous colon loop (most often the sigmoid) with inflamed pericolic fat; complications (abscess, etc.) may be identified. CT scan, now almost routine exam for abdominal pain assessed in the emergency room, has led to the realization that diverticulitis may present without its classic manifestations of fever and leukocytosis and is much more common than previously thought.

Management of diverticulitis: it relies classically on medical treatment with broad-spectrum antibiotics with gram-negative and anaerobic coverage effective against colonic flora (Table 4.18). Recent studies suggested that in cases of uncomplicated diverticulitis (without severe inflammation, abscess, or sepsis) in immunocompetent patients, symptomatic treatment (analgesics, without antibiotics) may be used. If the patient is able to eat, clear liquid diet is recommended during the acute phase of diverticulitis, and oral antibiotics may be used. Abscess usually requires drainage (if >3 cm), which can be done transcutaneously (radiological approach) in preference to the surgical approach. Severe cases of abscess or peritonitis may require surgery, which will most often involve temporary colostomy, colon resection, and subsequent reanastomosis (so-called two- or three-step surgery). Early diagnosis by CT scan and treatment with antibiotics and percutaneous drainage have revolutionized the management of severe diverticulitis, which previously relied exclusively on surgery and was much more morbid.

Recurrence of diverticulitis occurs in approximately 30% of patients (8% at 1 year, 20% at 10 years. after a first episode; risk increases after recurrences). Recurrence of diverticulitis was a few years ago considered a surgical indication for resection of the colon seg-

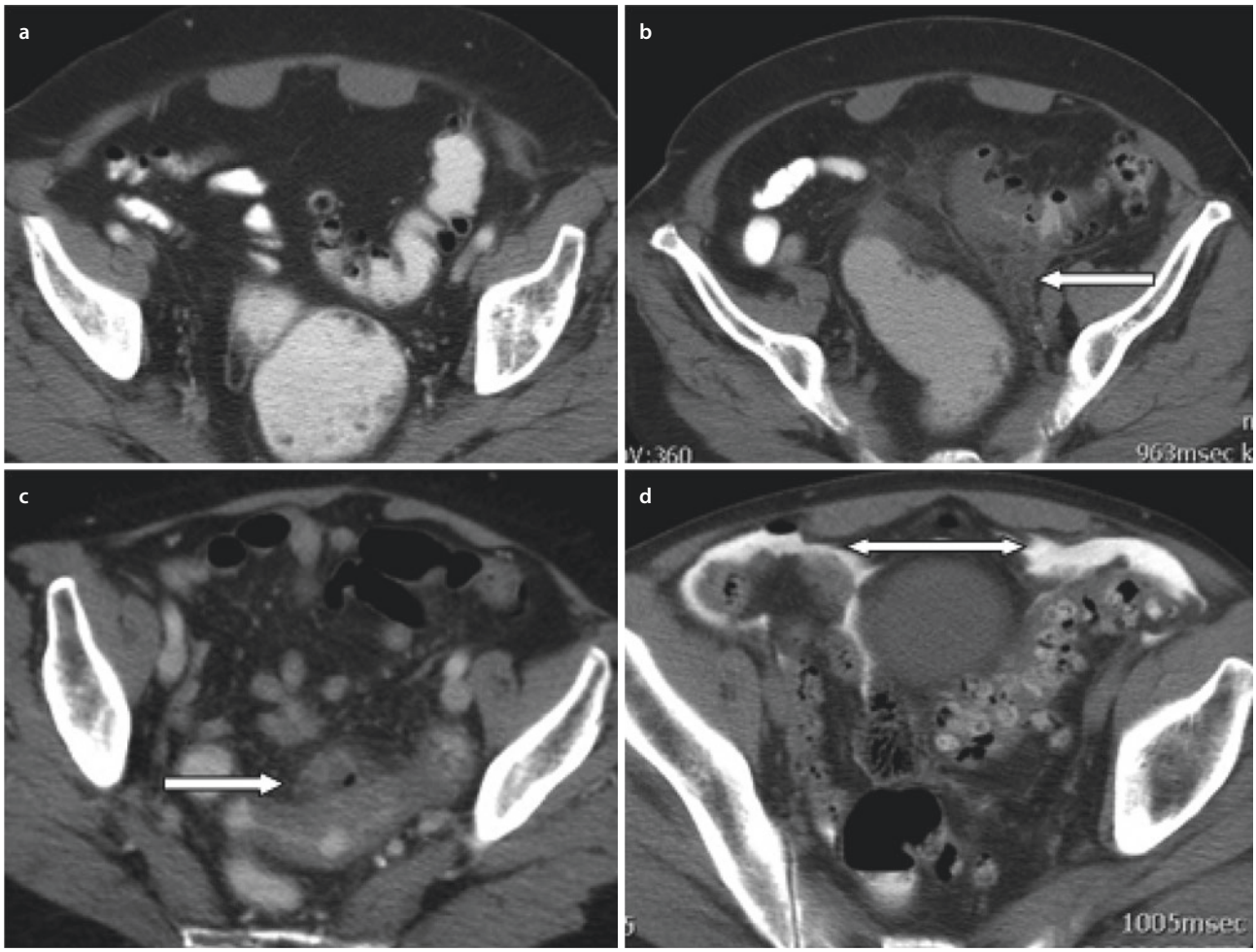


Fig. 4.34 CT scan of the abdomen: **a** uncomplicated diverticulosis (white contrast dye in the colon lumen and small black formations outside the lumen); **b** sigmoid diverticulitis with pericolic (grayish) fat infiltrated by inflammation; **c** acute diverticulitis with wall abscess; **d** perforated diverticulitis with contrast fluid that has fused into the abdominal cavity. (Photos from R. Déry)

ment affected by diverticula. However, given the often benign evolution of the disease (in fact, risk of severe complicated diverticulitis is highest with the first presentation and decreases with recurrences) and the good response to medical treatment, elective "prophylactic" surgery is now limited to immunosuppressed subjects or to some patients with severe complications. It was often recommended to consume fiber supplements in order to reduce the development of new diverticula that may become complicated and to limit fruits seeds and nuts to avoid hurting a fragile diverticular mucosa by these so-called abrasive foods; but none of these recommendations has been shown to effective in altering the course of diverticular disease. Decreased risk of incident diverticulitis has been associated, in «epidemiological» analysis, with «high-quality diet» (high in fiber from fruits, vegetables, and legumes and low in red meat and sweets), physical activity, and weight loss as well as to avoidance of smoking or regular use of NSAIDs.

Diverticular bleeding: A vessel within a diverticulum may erode, resulting in acute digestive bleeding with hematochezia. Diverticular bleeding is the most common cause of lower GI bleeding (see ► Chap. 21). The severity of the bleeding is variable; it may stop spontaneously within a few hours or may be intense and long enough to require transfusions or even therapeutic measures up to surgical resection of the hemorrhagic diverticular segment. Diverticular bleeding, in the majority of cases, is an isolated and nonrecurrent accident (recurrence ≈25% in 5 years).

Table 4.18 Medical treatment of diverticulitis

Diet: clear liquid diet may be used during acute phase

Support treatment (analgesics, no antibiotics) can be used in immunocompetent patients with uncomplicated diverticulitis.

Antibiotics oral treatment (preferred if the patient can eat):

- Ciprofloxacin 500 mg bid + metronidazole 500 mg tid or
- Amoxicillin/clavulinic acid 875/125 bid

Antibiotics intravenous treatment (if the patient cannot take oral medication):

- Ciprofloxacin 400 q 12 h + metronidazole 500 q 8 h or
- Piperacillin/tazobactam 3.375 g q 6 h or
- Ampicillin 2 g q 6 h + gentamicin 1.5 mg/kg q 8 h + metronidazole 500 mg q 8 h or
- Ticarcillin/clavulinic acid 3.1 g q 6 h or
- Meropenem 1 g q 8 h or
- Ertapenem 1 g id

4.9.2 Acute Appendicitis

Acute appendicitis is the most common cause of urgent abdominal surgery. Most often affecting young adults, it can also affect children as well as the elderly. It is due to an inflammation of the appendix, which distends in response to an obstruction of its lumen (normally 3–4 mm), most often by fecal impaction. If not treated promptly, excessive distension can lead to rupture of the appendix and infected peritonitis, which can result in death.

The initial peri-appendicular inflammation perceived by the sensory C fibers (see ▶ Chap. 16) is most often felt in the umbilical region as a dull, vague pain. Progression (after 8–24 hours) of the inflammation toward the peritoneum activates sensory fibers A/Delta, allowing the pain to be felt more precisely in the right iliac fossa.

It is important to diagnose acute appendicitis as early as possible in order to intervene before its perforation. Physical examination, which is not very specific at the beginning of the attack, will later reveal pain with abdominal guarding located in the right lower quadrant and maximal at the McBurney point (point of contact of the appendix tip with the anterior abdominal wall and located 1/2–2/3 the distance connecting on an imaginary line the umbilicus to the anterior superior iliac spine). In cases where the appendix projects toward the retrocecal or pelvic region, psoas or obturator sign (pain in right lower quadrant, respectively, on extension or rotation of the right hip) may be detected.

Appendicitis used to be a clinical condition relying on the clinician's ability to diagnose it and to perform an appendectomy before appendicular rupture occurred. Nowadays, ultrasound or CT scan of the abdomen confirm the diagnosis early (leading to prompt surgical treatment), reveal possible confounding conditions (e.g., tubo-ovarian lesions in women, diverticulitis of the right colon, ileitis, etc.), and avoid unnecessary laparotomies (where a normal abdomen was found despite positive clinical signs).

Acute appendicitis is an urgent condition treated by a usually simple surgical procedure. Treatment with antibiotics may also be done.

4.9.3 Colonic Bleeding

Colon lesions are the most common sources of lower GI bleeding (LGIB). They are manifested by hematochezia, i.e., passage of bright red blood through the anus, but darker (burgundy) blood can be seen with proximal lesions (over time, hemoglobin is altered by intestinal enzymes and bacteria, and the color of blood darkens (red → burgundy → black); the darker the color of blood, the more proximal the bleeding lesion is likely to be).

LGIB is caused by a variety of conditions, the frequency of which varies between series (◘ Table 4.19). However, diverticular hemorrhage is the main cause in all reported series.

The origin of the bleeding will be established at colonoscopy (◘ Fig. 4.35). The diagnosis of diverticular bleeding is most often based on the exclusion of other pathologies (colitis, cancer, etc.) that may cause bleeding, as it is rare that the bleeding from the causal vessel can be visualized during colonoscopy.

Management of LGIB is summarized in ◘ Table 4.20. Lower GI bleeding is discussed extensively in ▶ Chap. 21.

◘ Table 4.19 Causes of lower GI bleeding in various series of literature

Colon diverticulum	10–40% of cases
Colitis	
Ischemic	5–20%
Infectious	3–30%
Inflammatory	2–4%
Radiation	1–3%
Neoplasia or polyps	3–10%
Vascular lesions/angiodysplasias	3–30%
Anorectal lesions (hemorrhoid, fissure, etc.)	5–15%

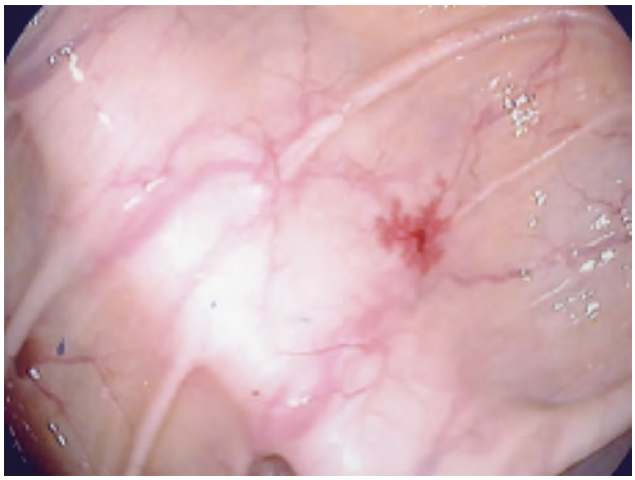


Fig. 4.35 Angiectasis seen on colonoscopy. Possible source of digestive bleeding. (Photo by P. Poitras)

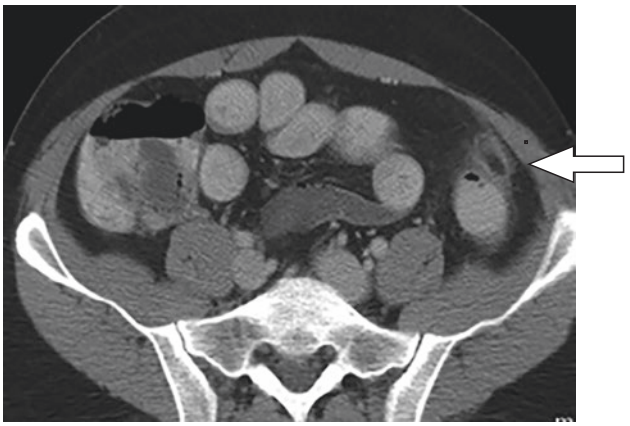


Fig. 4.36 Scan of abdomen showing appendagitis (or epiploic appendicitis): inflammation (infiltrated fat) around an extra-colic round structure differentiable from a diverticulum (with black stained air) by its fat content (more greyish coloration like abdominal fat). (Photo from R. Déry)

Table 4.20 Management of lower GI bleeding

Hemodynamic stabilization
- Iso-osmolar solute (NaCl 0.9 or Ringer's lactate)
- Blood transfusions prn

Identification of the site and cause of bleeding
- Colonoscopy (usually performed 24 hours after patient admission due to the need for colonic lavage preparation)
- Angiography or angioscan (if active bleeding)
- Scintigraphy with labelled red blood cells

Treatment of hemorrhagic lesion
- According to the hemorrhagic cause:
  - Endoscopy with polypectomy, vessel sclerosis, etc.
  - Angiography with arterial embolization
  - Surgery with suture or resection of the causal lesion

4.9.4 Epiploic Appendix/Appendagitis

On the outer surface of the colon, there are small fatty sacs called epiploic appendages. Inflammation of one of these structures (by twisting?) can lead to a clinical picture highly suggestive of diverticulitis. The diagnosis is often a "surprise" revealed on CT scan by a characteristic image (Fig. 4.36). Anti-inflammatory drugs (NSAIDs) help the painful condition to regress within a few days.

4.9.5 Volvulus

Volvulus refers to a twisting of the intestine around its mesenteric pedicle resulting in occlusion of the intestinal lumen and compromising blood supply to the affected organ. Volvulus of the sigmoid is the most common. A long sigmoid (dolichocolon), age (more frequent around 70–80 years), and chronic constipation (secondary to dolichocolon?) are contributing factors.

The patient presents with acute (or subacute) abdominal pain and intestinal obstruction (cessation of materials and gas, vomiting, etc.). The abdomen is distended and tympanic. Signs of visceral suffering (rebound tenderness, etc.) may exist in case of ischemia.

Radiography of the abdomen (flat plate) is often diagnostic by revealing a very distended sigmoid loop (Fig. 4.37a). Barium enema shows the classic "bird's beak" image caused by torsion of the organ. On CT scan, torsion of the mesentery may be visible (Fig. 4.37b).

The sigmoid must be rapidly decompressed, either by means of a rectal tube introduced through the sigmoid torsion or, more often, by colonoscopy. Given an expected recurrence in 50% of patients, surgical correction may be required at a later stage.

Volvulus of the cecum is more rare. Involving torsion of the right ileocolic region, it most often requires urgent surgical treatment.

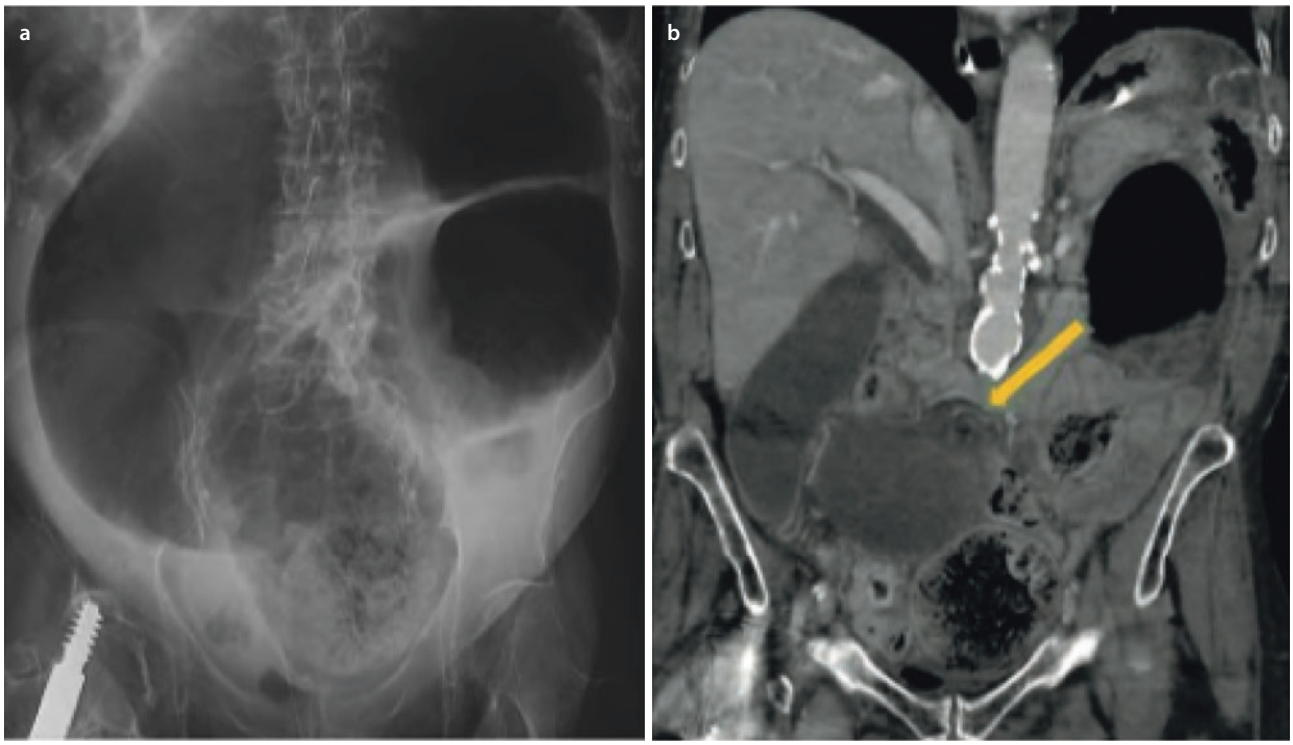


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Fig. 4.37 Volvulus of the sigmoid: **a** on flat plate, the sigmoid is highly distended in a typical "coffee bean" loop; **b** on CT scan, colonic distension is clearly visible and a "swirl" of the mesenteric vessels twisted by the sigmoid rolling is detected (indicated by the arrow). (Photos from R. Déry)

4.9.6 Melanosis Coli

This is a blackish coloration of the colon, giving the appearance of snakeskin (Fig. 4.38), due to the deposition in the mucosa of a dark pigment in constipated patients who make extensive use of anthracene laxatives (senna, etc.).

Melanosis coli was previously considered a risk factor for colonic dysmotility and even for colonic cancer, but it appears now to be only a spectacular harmless marker of intensive laxative use.

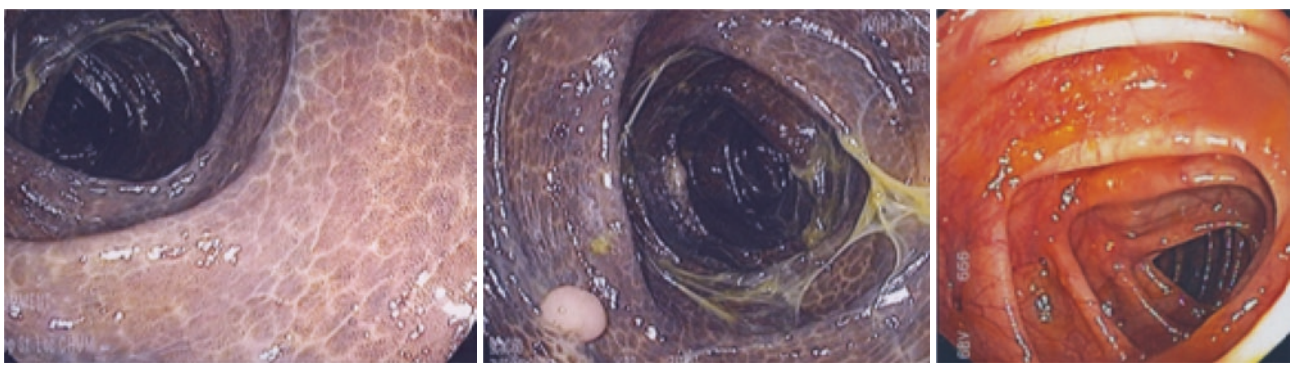
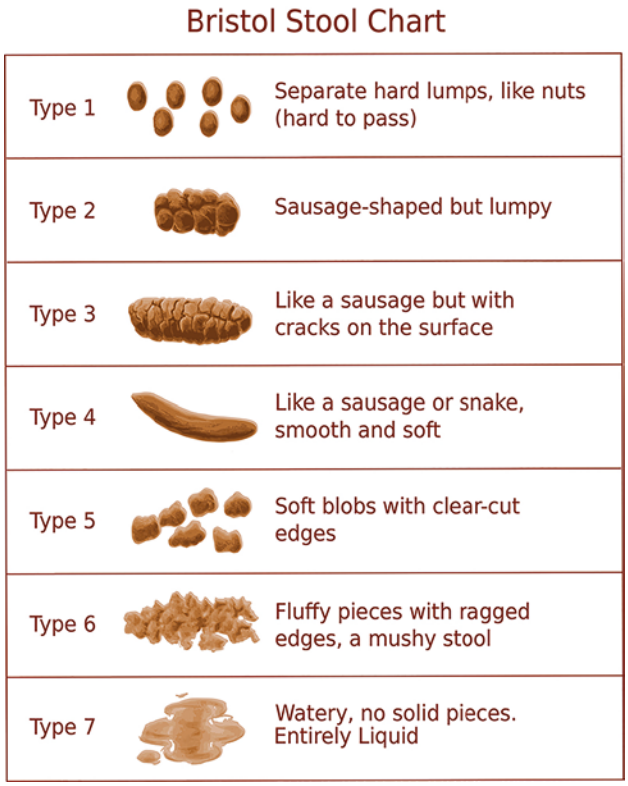


Fig. 4.38 Colonic mucosa seen under colonoscopy showing melanosis coli (quite different from a normal bright pink mucosa shown on the right). (Photos by P. Poitras)

4.9.7 Bristol Stool Chart

Bristol stool chart (or scale), shown on ◘ Fig. 4.39, was used by researchers to quantify stool appearance and obtain a quantitative analysis to statistically compare stool appearance under various conditions (drug treatment, symptoms of diarrhea vs. constipation, etc.). It is sometimes used as a clinical tool by physicians, as well as by patients to report on their stools (« today, instead my usual Bristol 1 or 2, I had a Bristol 4»).

PS: For complementary readings on the colon, see ► Chaps. 13, 14, 15, 16, 21, 22, 25, and 29.



◘ **Fig. 4.39** Bristol stool chart. Types 3 and 4 are considered normal. Types 1 and 2 are seen in constipation, while types 5, 6, and 7 refer to diarrhea