

Fifth Edition

First Principles of Gastroenterology

The Basis of Disease and an Approach to Management

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JANSSEN-ORTHO

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Ischemic Disease of the Intestine

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1. INTRODUCTION

Intestinal ischemia occurs when the delivery of oxygen to the tissue is insufficient to support its metabolic demand. Intestinal oxygen delivery can be impaired by both systemic and local vascular conditions. Atherosclerotic vascular disease is often implicated as a factor responsible for intestinal ischemia associated with altered systemic hemodynamics and accounts for the higher incidence of intestinal ischemia in the elderly population. Intestinal tissue blood flow and oxygen delivery may also be impaired as a result of locally mediated events within the intramural circulation of the gut. Such local events have been implicated in intestinal ischemia seen in both young and old patients. The true incidence of intestinal ischemia is unknown. Although overt cases are usually diagnosed correctly, it is generally believed that the condition is often misdiagnosed in those presenting with non-specific abdominal pain. Indeed clinical manifestations of intestinal ischemia are varied and they depend on the site and method of vascular compromise as well as the extent of bowel wall necrosis.

2. CLASSIFICATION OF INTESTINAL ISCHEMIA

Many clinicians broadly classify intestinal ischemia into acute or chronic disease. However, because certain acute events may change to a chronic condition, a clear-cut classification of ischemic bowel disease using this two-category system is not always applicable. Since the extent of intestinal ischemia and the pathological consequences depend on the size and the location of the occluded or hypoperfused intestinal blood vessel(s), we find it useful to classify ischemic bowel disease according to the size and type of the vessel(s) that are hypoperfused or occluded (Figure 1). Accordingly, intestinal ischemia may

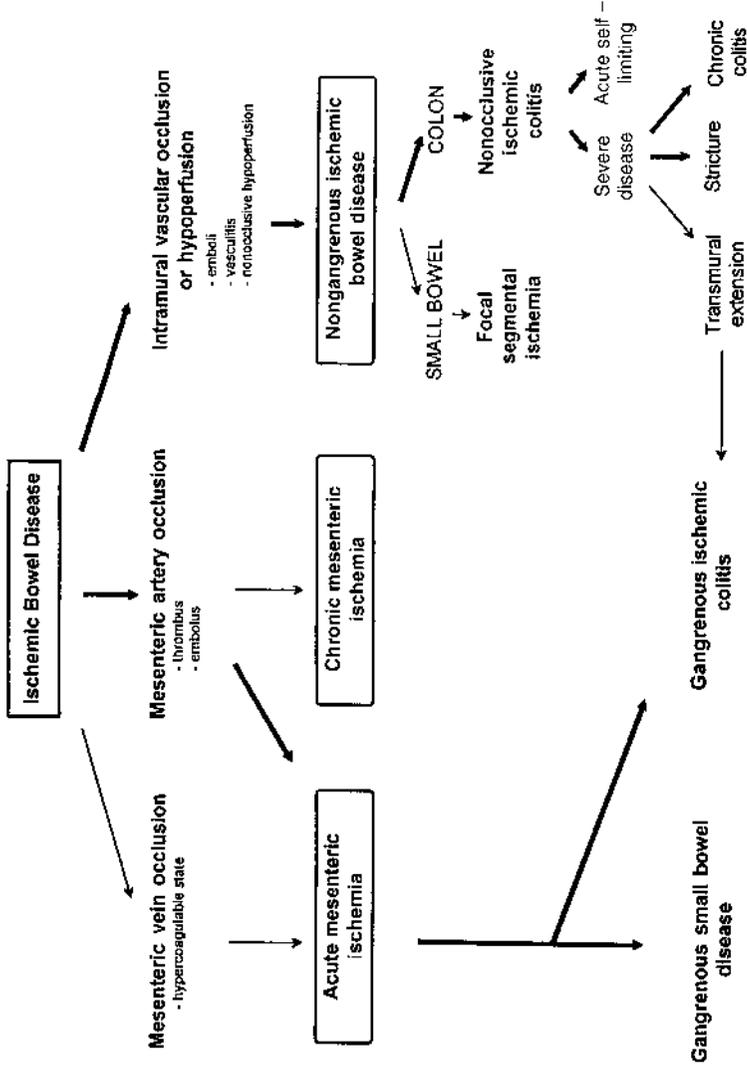


FIGURE 1. Classification of ischemic bowel disease. The more common pathways are indicated by heavier arrows.

result from occlusion/hypoperfusion of a large mesenteric vessel (mesenteric artery or vein) or from occlusion/hypoperfusion of smaller intramural intestinal vessels. In each of these situations the resultant intestinal ischemia may be acute or chronic. In addition, it is important to point out that vessel occlusion/hypoperfusion may be the result of a mechanical intraluminal obstruction (i.e., embolus or thrombus) or the result of decreased blood flow due to vasospasm, increased blood viscosity, hypotension or other similar conditions. The latter is referred to as *nonocclusive ischemia*. Therefore, the etiology of vessel occlusion/hypoperfusion may be the basis for subclassification of ischemic bowel disease. A clinically important further classification is whether the ischemia-induced necrosis is transmural (*gangrenous ischemia*) leading to peritonitis, or remains intramural (*nongangrenous ischemia*) resulting in localized disease. Figure 1 attempts to combine these different aspects of subdivision in a comprehensive classification.

3. MESENTERIC VASCULATURE

3.1 Anatomy

The blood flow to the splanchnic organs is derived from three main arterial trunks: the celiac, the superior mesenteric and the inferior mesenteric arteries (Figures 2–5). The celiac artery supplies blood to the foregut (stomach and duodenum), the superior mesenteric artery supplies blood to the midgut (duodenum to transverse colon), and the inferior mesenteric artery is responsible for blood to the hindgut (transverse colon to the rectum). Each of these three arterial trunks supplies blood flow to its specific section of the gastrointestinal tract through a vast arcade network. This arcade system is an effective collateral circulation and is generally protective against ischemia, since blood can reach a specific segment of gut via more than one route. As shown in Figure 2, additional vascular protection is obtained from vascular connections between the three arterial systems. Communication between the celiac system and the superior mesenteric system generally occurs via the superior pancreaticoduodenal and inferior pancreaticoduodenal arteries. The superior mesenteric and inferior mesenteric systems are joined by the arch of Riolan and the marginal artery of Drummond, vessels that connect the middle colic artery (a branch of the superior mesenteric artery) and the left colic artery (a branch of the inferior mesenteric artery). In addition, communication also exists between the inferior mesenteric artery and branches of the internal iliac arteries via the rectum. The caliber of these collateral connections varies considerably depending on the existence of vascular disease, but it is important to realize that in chronic states of vascular insufficiency, blood flow to an individual system can be maintained through these collateral connections even when an arterial

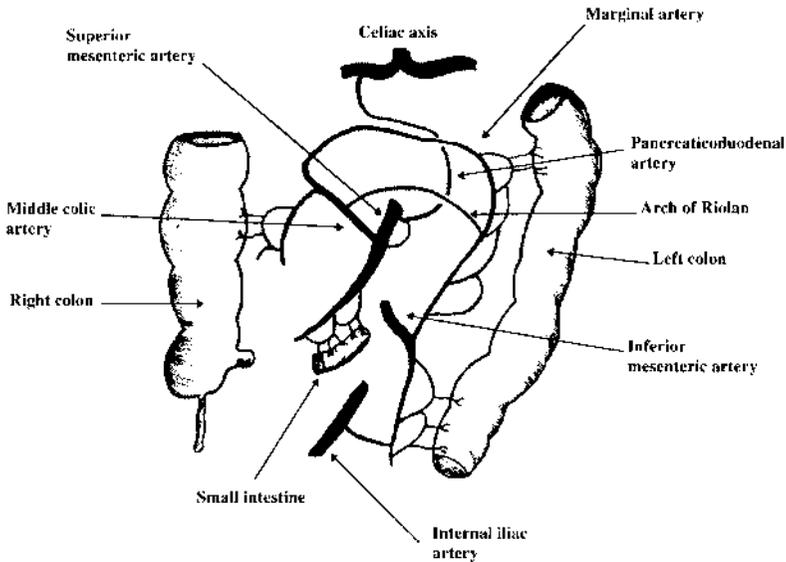


FIGURE 2. Schematic representation of splanchnic circulation.

trunk is completely obstructed. It is not uncommon to find one or even two arterial trunks completely occluded in the asymptomatic patient with chronic vascular disease. In fact, there are reports of occlusion of all three trunks in patients who are still maintaining their splanchnic circulation. However, in up to 30% of people, the collateral connections between the superior and inferior mesenteric arteries, via the arch of Riolan and the marginal artery of Drummond, can be weak or nonexistent, making the area of the splenic flexure particularly vulnerable to acute ischemia. This region of poor collateral circulation is often referred to as a “watershed area.”

3.2 Physiology of Splanchnic Blood Flow

The mesenteric circulation receives approximately 30% of the cardiac output. Mesenteric blood flow is less in the fasting state and is increased with feeding. Blood flow through the celiac and superior mesenteric trunks is about equal (approximately 700 mL/min in the adult) and is twice the blood flow through the inferior mesenteric trunk. Blood flow distribution within the gut wall is not uniform, and it varies between the mucosa and the muscularis. The mucosa has the highest metabolic rate and thus it receives about 70% of the mesenteric blood flow. If one compares gut segments of equal weight, the small bowel receives the most blood, followed by the colon and then the stomach.



FIGURE 3. Angiogram of the celiac arterial system.

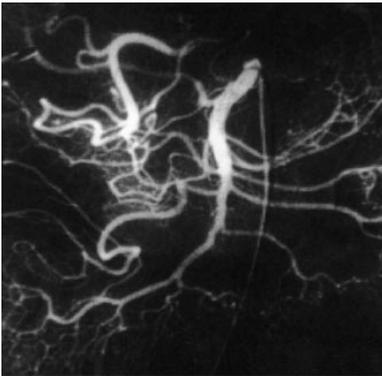


FIGURE 4. Angiogram of the superior mesenteric arterial system.

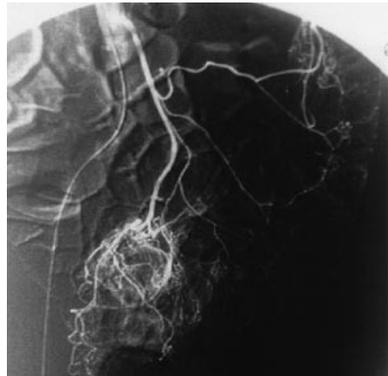


FIGURE 5. Angiogram of the inferior mesenteric arterial system.

Much has been written on the control of gastrointestinal blood flow, and many factors are involved in its regulation. A few important highlights of mesenteric vascular resistance will be discussed here. Vascular resistance is

proportional to $1/r^4$ (where r = the radius of the vessel). Thus the smaller the artery, the greater its ability to effect vascular resistance. It is known that the majority of blood flow control occurs at the level of the arterioles, the so-called resistance vessels. Very little control of blood flow occurs at the level of the large arterial trunks. In fact, the diameter of these large arterial trunks can be compromised by 75% before blood flow is reduced. Additional control of blood flow occurs at the level of the precapillary sphincter. In the fasting state only one-fifth of capillary beds are open, leaving a tremendous reserve to meet increased metabolic demands.

Among the most important control mechanisms of splanchnic blood flow are the sympathetic nervous system, humoral factors and local factors. The sympathetic nervous system through α -adrenergic receptors plays an important role in maintaining the basal vascular tone and in mediating vasoconstriction. Beta-adrenergic activity appears to mediate vasodilation, and it appears that the antrum of the stomach may be particularly rich in these β receptors. Humoral factors involved in the regulation of GI blood flow include catecholamines, the renin-angiotensin system and vasopressin. These humoral systems may play a particularly important role in shock states and in some patients may play a role in the pathogenesis of nonocclusive ischemia. Local factors appear to be mainly involved in the matching of tissue blood flow to the metabolic demand. An increased metabolic rate may produce a decreased pO_2 , increased pCO_2 and an increased level of adenosine, each of which can mediate a hyperemic response.

The vascular endothelium is a source of potent vasoactive substances, such as nitric oxide (vasodilator) and endothelin (vasoconstrictor). Although these endothelial-derived substances may act systemically, it would appear that their major effect is local in a paracrine hormonal fashion. These vasoactive substances have the potential to dramatically alter mesenteric blood flow. In fact, endothelin is one of the most potent vasoconstrictors identified to date. Regulation of mesenteric blood flow in both health and disease by these potent endothelial-derived vasoactive substances remains to be elucidated.

The integration of these control systems and their alteration by factors such as vascular disease, motor activity, intraluminal pressure and pharmaceuticals remains poorly understood. The key to our understanding and successful treatment of intestinal ischemia lies in a better knowledge of this physiology.

3.3 Pathophysiology of Intestinal Ischemia

Intestinal ischemia occurs when the metabolic demand of the tissue supercedes the oxygen delivery. Obviously, many factors can be involved in this

mismatch of oxygen delivery and demand. These include the general hemodynamic state, degree of atherosclerosis, extent of collateral circulation, neurogenic/humoral/local control mechanisms of vascular resistance and abnormal products of cellular metabolism before and after reperfusion of an ischemic segment. Acute occlusion/hypoperfusion of a large mesenteric vessel usually results in transmural (gangrenous) ischemia. On the other hand, acute occlusion of the intramural vessel(s) usually results in intramural (nongangrenous) ischemia. However, there are exceptions in both cases, depending on the severity of occlusion/hypoperfusion. As previously mentioned, the mucosa is the most metabolically active gut wall tissue layer and thus it is the first tissue layer to demonstrate signs of ischemia. The earliest form of intestinal ischemia produces changes at the tip of the intestinal villi. With ongoing ischemia ultrastructural changes begin within 10 minutes and cellular damage is extensive by 30 minutes. Sloughing of the villi tips is followed by edema, submucosal hemorrhage and eventual transmural necrosis.

The intestinal response to ischemia is first characterized by a hypermotility state. It is this intense motor activity that results in the patient experiencing severe pain, even though the ischemic damage may be limited to the mucosa at this stage. As the ischemia progresses, motor activity will cease and gut mucosal permeability will increase, leading to an increase in bacterial translocation. With transmural extension of the ischemia, the patient will develop visceral and parietal inflammation resulting in peritonitis.

An important factor often responsible for, or aggravating, intestinal ischemia is the phenomenon of vasospasm. It has been well demonstrated that both occlusive and nonocclusive forms of arterial ischemia can result in prolonged vasospasm, even after the occlusion has been removed or the perfusion pressure restored. This vasospasm may persist for several hours, resulting in prolonged ischemia. The mechanism responsible for this vasospasm is not clearly defined, but there is preliminary evidence that the potent vasoconstrictor endothelin may be involved. To date, many of the interventional techniques used in the treatment of acute mesenteric ischemia have been directed at counteracting this vasospasm.

A second factor that may be responsible for accentuating ischemic damage is reperfusion injury. This phenomenon has been well demonstrated in the laboratory, where it has been shown to be responsible for a greater degree of cellular damage than that brought about during the actual ischemic period. Parks and Granger have shown in an animal model that the injury after one hour of ischemia and three hours of reperfusion is more severe than that observed after four hours of continuous ischemia. The mechanism responsible for this reperfusion injury appears to be related to

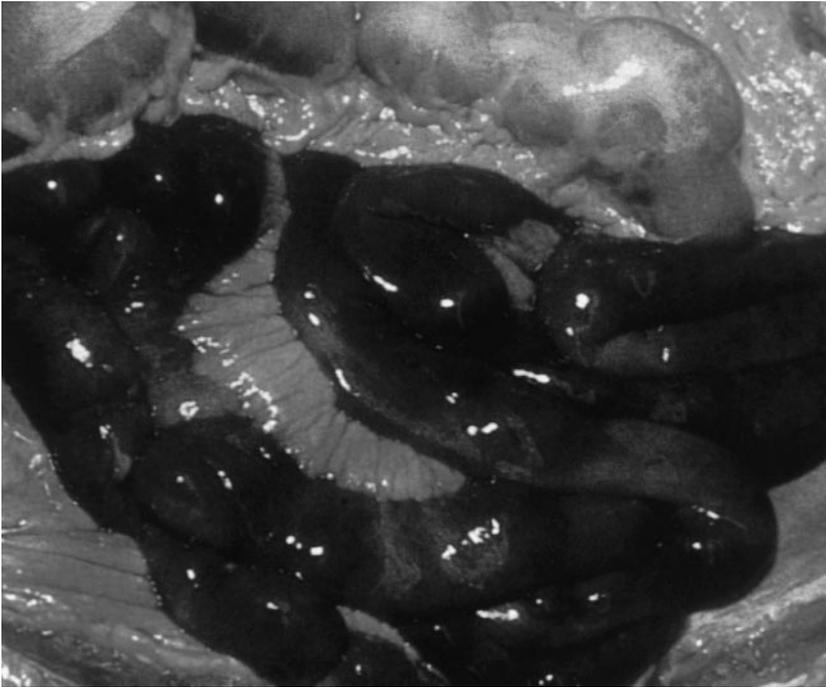


FIGURE 6. Postmortem examination of the abdominal cavity shows extensive small bowel infarction. The intestinal ischemic necrosis was secondary to proximal occlusion of the superior mesenteric artery by thrombus.

the release of harmful reactive oxygen metabolites, which are thought to be released from adhering polymorphonuclear leukocytes. It is not known what role ischemia reperfusion injury plays in humans with occlusive and nonocclusive disease.

4. ACUTE MESENTERIC ARTERIAL OCCLUSION

4.1 Clinical Presentation

Several intra-abdominal disease processes can present in a fashion identical to that of mesenteric ischemia; thus, the key to diagnosis lies in a high index of suspicion. Patients with advanced ischemia present with diffuse peritonitis, shock and severe metabolic derangements. In these patients it is clear that a catastrophic event has occurred. However, ischemia is only one of a few

possible diagnoses. In most situations these patients will come to surgery, and in those where the diagnosis was not confirmed preoperatively, the diagnosis will become obvious at the time of surgery. Often these patients can not be salvaged; the mortality is reported to be between 70 and 90% (Figure 6). It must be stressed that the patient with early ischemia is far more challenging to diagnose. Given that the mortality rate is extremely high in advanced ischemia, the best chance of successfully treating a patient with this condition depends on early diagnosis and treatment.

The typical patient is usually over 50 years of age and often has a history of cardiac and peripheral vascular disease. In the early stage of ischemia the patient complains of severe abdominal pain (due to hypermotility and spasmodic contraction of the ischemic gut) in the absence of peritoneal findings. This scenario has been described by clinicians as “pain out of proportion to the physical findings.” Other nonspecific symptoms such as nausea, vomiting and altered bowel habit may be present, but they are usually not particularly helpful in the diagnosis.

4.2 Investigation

4.2.1 LABORATORY

Unfortunately, there is no serum marker that can reliably predict early intestinal ischemia. Many studies have attempted to identify such a biochemical marker. Creatinine kinase, alkaline phosphatase, lactate dehydrogenase, diamine oxidase and inorganic phosphate are among those biochemical markers that have been examined. Although all of these will eventually become altered with advanced disease, their alteration with early ischemia is too varied to provide any clinical usefulness.

Although biochemical changes with advanced intestinal ischemia are non-specific, one can expect to find a leukocytosis. Due to third-space loss of fluid into the abdomen, electrolyte and renal function abnormalities secondary to dehydration are also often seen. Hyperamylasemia may occur secondary to amylase leaking from the infarcted bowel into the abdominal cavity, which may then enter the systemic circulation. In some situations this hyperamylasemia in the setting of abdominal pain may be misinterpreted as an indication of pancreatitis. Finally, in advanced ischemia blood gas analysis will usually show a metabolic acidosis.

4.2.2 RADIOLOGICAL

Initial radiological investigations are aimed at ruling out other causes of abdominal pain and peritonitis. All patients should have an upright and supine plain film of the abdomen. Although these films may support a diagnosis of

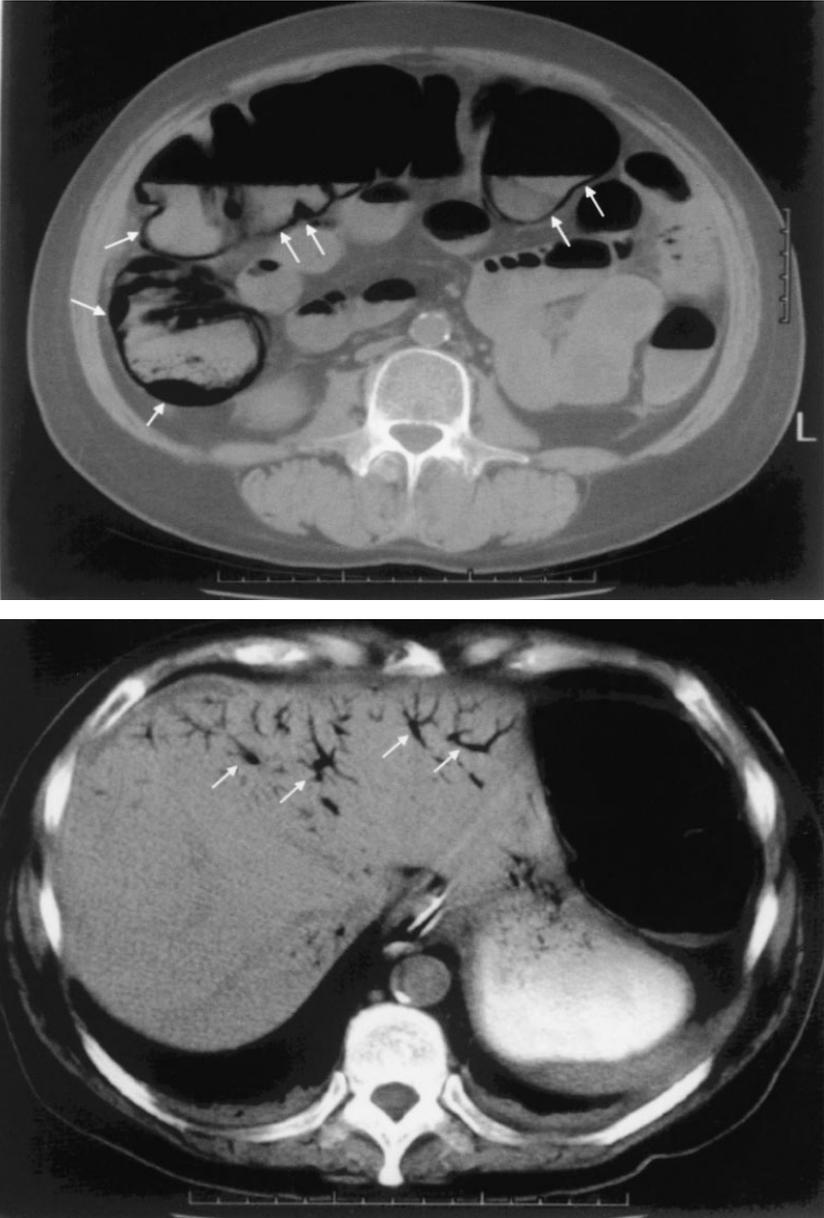


FIGURE 7 (A and B). CT scan of a patient with mesenteric ischemia secondary to acute occlusion of the ileocolic artery. Arrows point to air in the wall of the ischemic right colon (pneumatosis) (Figure 7A) and secondary accumulation of air in the portal vein system (Figure 7B).



FIGURE 8 (A and B). Mesenteric angiogram demonstrating atherosclerotic narrowing of the superior mesenteric artery (arrows in Figure 8A). Following angioplasty, the diameter of the narrowed area is significantly increased (Figure 8B).

ischemia, as indicated by bowel wall thickening and “thumb-printing,” the main purpose of the films is to rule out visceral perforation or bowel obstruction. In many centers CT scan is being used as a first-line investigation in patients with abdominal pain. Several markers of intestinal ischemia have now been described by radiologists with expertise in CT scans. These include bowel wall thickening, mucosal edema, pneumatosis (Figure 7A) and mesenteric and portal vein gas (Figure 7B). Using large injections of peripheral venous contrast, mesenteric arterial and venous occlusion can now also be identified in some patients. Of course, many of these findings are not specific, and thus we do not at present advocate the CT scan as a diagnostic test for intestinal ischemia. However, the CT scan can play a critical role in ruling out other intra-abdominal disease processes, such as pancreatitis.

Ultrasonography combined with Doppler assessment of blood flow in the splanchnic arterial and venous system is now being used in some centers to screen for mesenteric ischemia. Our personal experience with this technique is limited and the exact role this technique will play is not clearly defined. There is experimental evidence, using a rabbit model of ischemia, that magnetic resonance (MR) scanning may also be of significant use in the diagnosis of mesenteric ischemia. Certainly, both arterial and venous abnormalities as well as the extent of the collateral circulation can be identified in some patients using MR technology; however, further clinical experience is required before this technique can be completely evaluated.

Angiography remains the gold standard in the diagnosis of mesenteric ischemia (Figure 8), and, as will be discussed, it may play a significant role in

the treatment of such patients. It is our belief that all patients with suspected mesenteric intestinal ischemia should undergo angiography to confirm the diagnosis and plan treatment. Wherever possible this approach should include even those patients presenting with peritonitis. Often there is a tendency to take patients with peritonitis straight to the operating room without performing angiography. These patients need to be treated in an expedient fashion. However, the short delay to obtain an angiogram may prove to be beneficial. Not only will it identify those patients who may require embolectomy or vascular reconstruction, but it will also provide a means to treat vasospasm in the perioperative period. This type of treatment policy has two implications: First, in order for management to be effective, an invasive radiologist must be available at all times and a system must be in place that will allow the angiography suite to be functioning with a short lead time. Second, the physician must realize that an appreciable number of negative angiograms should be expected with this low angiography threshold.

The treating physician must always use clinical judgment in determining the severity of the patient's illness to decide whether or not the patient is stable enough to undergo the angiographic procedure. Also, if the patient has evidence of renal failure the risk of further renal toxicity from the angiographic dye must be weighed against the possible benefits of the procedure. In many cases these can be difficult clinical decisions.

4.3 Treatment

4.3.1 RESUSCITATION AND ASSESSMENT

It must be strongly stressed that if a diagnosis of mesenteric ischemia is being questioned, the subsequent investigation and management must proceed in an efficient and aggressive fashion if morbidity and mortality are to be reduced. Initial management of all patients consists of resuscitation. The degree of resuscitation required varies widely with the degree and extent of ischemia. Patients with early ischemia will require very little resuscitation, whereas those with infarcted intestine may require admission to a critical care unit for invasive monitoring. Insertion of a Swan-Ganz catheter with central pressure monitoring can be very useful in resuscitating the shocked patient with underlying cardiac disease. It must be kept in mind that in patients with extensive and advanced infarction, complete "stability" may never be obtained and thus investigation and treatment should proceed without extensive delay. However, ongoing patient "instability" is no doubt an ominous sign. As a general rule vasopressors to support blood pressure should be avoided, as they may further increase the degree of intestinal ischemia. The role of antibiotics is not clear-cut. Our policy is to administer broad-spectrum antibiotic coverage as soon as

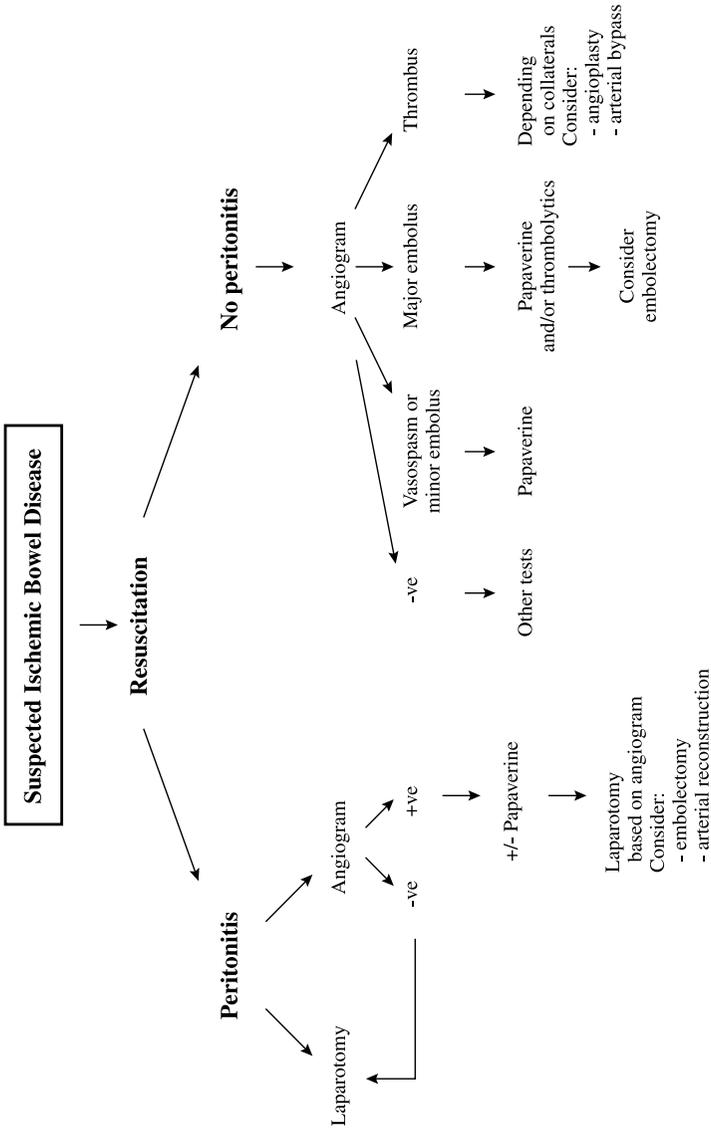


FIGURE 9. Algorithm for the treatment of acute mesenteric ischemia.

possible to those patients presenting with peritonitis. In those without peritonitis, antibiotics are used in the perioperative period, should surgery be required.

The treatment algorithm we recommend is outlined in Figure 9. Essentially, patients are divided into two groups: those with peritonitis and those without. Although all patients with peritonitis will require laparotomy, the exact treatment plan for both groups of patients will be dictated by the angiographic findings. Angiographic findings fall into four major categories:

Thrombotic occlusion. This finding is usually identified with an aortic flush of contrast dye; however, it can sometimes be difficult to differentiate from a proximal arterial embolus. The other pitfall with this finding is that sometimes it represents a chronic obstruction that is not necessarily related to the patient's present symptoms and findings. In most cases, these patients require arterial reconstruction, although the final treatment plan will be based on the exact vascular anatomy and degree of collateral circulation. Patients with peritonitis will almost always require a bowel resection.

Major embolus. Major emboli are usually located in the proximal portion of the superior mesenteric artery. The majority of these patients should be referred to surgery for consideration of embolectomy regardless of the presence or lack of peritoneal findings. In those patients requiring surgery, intra-arterial papaverine infusion could be used in the perioperative period in an attempt to reduce ongoing vasospasm. Recently, thrombolytic therapy (streptokinase and urokinase) has been used in a selected group of patients with intestinal ischemia secondary to a mesenteric embolus. Data, however, are limited since the literature contains only a handful of case reports describing this technique. Accordingly, the therapeutic efficacy and the potential complications of thrombolytic therapy are unknown at this time.

Minor embolus. These emboli are limited to the branches of the superior mesenteric artery or to that portion of the vessel distal to the origin of the ileocolic artery. Unless peritoneal signs are present, these patients should be managed conservatively or with intra-arterial infusion of papaverine. There may also be a role for intra-arterial thrombolytic therapy in selected patients.

Vasospasm (nonocclusive ischemia). This finding may occur in response to a mechanical arterial obstruction; however, when it represents the sole finding it is diagnostic of nonocclusive ischemia. The recommended management is essentially the same as for patients with minor emboli with the exception that there would be no role for thrombolytics in this group.

4.3.2 MEDICAL TREATMENT: INTRA-ARTERIAL INFUSION THERAPY

Intra-arterial infusion therapy has been used in the management of selected patients with intestinal ischemia. Two classes of pharmaceuticals have been

employed: smooth-muscle relaxants (papaverine) and thrombolytic agents (streptokinase and urokinase). Although we support the use of these agents, it must be stressed that their efficacy has not been absolutely proven in proper clinical trials. In order to administer intra-arterial therapy, a radiologist skilled in mesenteric angiography must selectively guide a catheter through the femoral artery into the trunk or a branch of the affected mesenteric artery. Once the catheter is properly placed and secured, the chosen pharmaceutical can then be administered. This procedure is not without risk. Complications include injury to the femoral artery, dislodgement of atherosclerotic plaques with embolic accidents in the lower extremities, and the formation of a false femoral artery aneurysm after the catheter is removed.

Papaverine infusion has been recommended as a major component of the medical therapy for mesenteric ischemia. Papaverine is a smooth-muscle relaxant and therefore it is usually used to reduce arterial vasospasm. Vasospasm can occur primarily, as seen in nonocclusive intestinal ischemia, or it may be a secondary event following acute arterial obstruction from an embolus or thrombus. Administered systemically, papaverine will nonspecifically dilate the vascular tree. However, since it is virtually completely metabolized by a single pass through the liver, selective administration into the mesenteric circulation results in very few systemic effects. This allows vasodilation in the mesenteric circulation to occur without a drop in the systemic blood pressure. Papaverine is dissolved in normal saline to a concentration of 1mg/mL, although a higher concentration can be used. Heparin should not be added to the solution, as it will crystallize. The infusion is started at 30 mg/hour and may be increased to 60 mg/hour. In most cases the papaverine infusion is maintained for 24 hours. The catheter is then flushed with normal saline for 30 minutes and the angiogram is then repeated. If vasospasm persists, the cycle should be repeated every 24 hours for a maximum of 5 days. During the papaverine infusion the patient's systemic vital signs must be monitored. A sudden drop in the blood pressure usually suggests that the catheter has slipped out of the mesenteric circulation into the aorta. The papaverine infusion should be stopped until a repeat angiogram is performed to confirm this.

It is generally believed that patients with acute mesenteric ischemia caused by a superior mesenteric artery thromboembolism should undergo surgery with possible embolectomy. However, since many of these patients are elderly and frail, thrombolytic therapy has been used in selected patients as a possible alternative to surgery. To date several case reports have indicated favorable results with either streptokinase or urokinase. Additional experience with these agents is required in order to define their exact role in the management of intestinal ischemia.

4.3.3 SURGICAL TREATMENT

The role of surgery is to evaluate the viability of ischemic bowel, to resect if necessary and if possible to alleviate or bypass a vascular obstruction. If at all possible the vascular surgery should be performed first so that its effect on intestinal viability can be assessed.

One of the most difficult decisions the surgeon has to make is to decide if the bowel injury is reversible or not. Subjective criteria such as the bowel wall color, the presence of peristalsis and the presence of palpable mesenteric pulses are often used. Unfortunately, these criteria can lead to an inaccurate assessment in over 50% of cases. This has led surgeons to adopt a second-look approach. With this approach only the most obviously infarcted gut is resected and any questionable bowel is left in situ. A second look within 24 hours is then used to decide on the necessity for further resection. Several objective measurements have been employed intra-operatively in an attempt to assess bowel viability. These include fluorescence staining, laser Doppler flowmetry, surface oximetry and intramural pH measurements. However, at present, no single technology has been widely adopted.

A second difficult situation for the surgeon is the management of patients with near-total intestinal infarction. Even with resection, the mortality rate in this group of patients is very high, and survivors will be dependent on total parental nutrition indefinitely. In elderly patients with other underlying medical problems, many surgeons would not consider a bowel resection and would treat the patient palliatively. The approach in a younger patient with a catastrophic vascular accident tends to be more aggressive, as advances in bowel transplantation surgery have created some hope for these unfortunate individuals.

4.3.4 PROGNOSIS

Over the last 35 years, over 24 case series studies of patients with acute mesenteric ischemia have been published. Most published case series studies have fewer than 100 patients and mortality rates have been reported between 24% and 96%, with an overall average of 69%. The high mortality rate is not surprising given the fact that many of these patients are elderly with significant co-morbid disease. One of the keys to improved outcome is early and accurate diagnosis. An interesting observation is that those patients with slower-developing acute symptoms will usually delay seeking medical help and as a result they have a higher overall mortality rate.

5. ACUTE MESENTERIC VENOUS OCCLUSION

Ischemia of mesenteric arterial origin is far more frequent than that of venous

disease. It is now recognized that many reported cases of mesenteric vein thrombosis in actuality represented incorrectly diagnosed cases of nonocclusive ischemia. The true incidence of mesenteric vein thrombosis is quite low. Although the etiology of acute mesenteric vein thrombosis may be idiopathic, the thrombosis is usually secondary to another disease process. Conditions that predispose to mesenteric vein thrombosis are (1) severe intra-abdominal sepsis, (2) hypercoagulable state (i.e., polycythemia vera) and (3) portal venous stasis (secondary to portal hypertension associated with hepatic cirrhosis, or to extrinsic compression of the venous system secondary to a tumor mass).

Thrombosis of the superior or inferior mesenteric vein alone is usually not sufficient to produce intestinal ischemia. However, acute thrombosis in a large mesenteric vein has the potential to cause retrograde propagation of the clot up into the venous tributaries within the bowel wall. This resultant venous occlusion within the bowel wall will usually produce ischemia, possibly with infarction. In many cases of venous intestinal ischemia the thrombosis does not begin in a large mesenteric vein. In these situations it appears that the venous thrombosis begins primarily in the small venous intramural tributaries. In either case, if the venous thrombosis becomes extensive, arterial thrombosis may follow, making it very difficult to determine the exact etiology of the intestinal ischemia.

The clinical presentation of patients with venous intestinal ischemia is often similar if not identical to that of patients with acute mesenteric artery occlusion. Accordingly, the diagnosis is often made only at the time of surgery or by the pathologist who examines the resected specimen.

The treatment of this disease is generally surgical, with the infarcted segment of intestine being resected. The surgeon should be aware that the venous thrombosis may extend beyond the limits of the gross infarction. Since any residual thrombosis has the potential to propagate, the resection should include adjacent bowel and mesentery until all grossly involved thrombosed veins are removed. It has been shown that mortality from this disease can be reduced if patients are anticoagulated as soon as possible after surgery.

6. CHRONIC MESENTERIC ISCHEMIA

Because of the extensive collateral arterial network of the gut, chronic mesenteric ischemia is relatively uncommon. It is usually related to extensive mesenteric atherosclerosis. Patients classically present with postprandial abdominal pain, "fear of eating" and weight loss. However, most patients do not present with "classic" symptomatology and are frequently misdiagnosed for other diseases. Until someone with a high index of suspicion proceeds to angiography, these patients may be treated for prolonged periods for suspected

TABLE 1. Causes of nonocclusive ischemic bowel disease

A. *Acute diminution of intramural blood flow*
1. *Small vessel disease*

Cholesterol embolus (Figure 10A)
 Diabetes
 Rheumatoid arthritis
 Chronic radiation injury (Figure 10B)
 Amyloidosis (Figures 10C and 10D)
 Systemic vasculitis
 Collagen diseases
 Allergic granulomatosis
 Behçet's syndrome

2. *Nonocclusive hypoperfusion*

Hypercoagulable states and increased viscosity

Oral contraceptives
 Polycythemia vera
 Sickle cell disease
 Acute leukemia
 Antithrombin C disease

Shock

Hemorrhage
 Hypovolemia
 Cardiopulmonary bypass
 Abdominal aortic reconstruction
 Sepsis
 Pancreatitis
 Anaphylaxis
 Cardiogenic shock
 Multiple organ dysfunction syndrome

Congestive heart failure

Portal hypertension

Medications

Digitalis
 Diuretics
 Catecholamines
 Estrogens
 Nonsteroidal anti-inflammatory agents
 Neuroleptic agents
 Verapamil overdose
 Cocaine abuse

Long-distance running

(cont'd)

TABLE 1. Causes of nonocclusive ischemic bowel disease (cont'd)

*B. Conditions compounding marginal blood flow states**1. Increased metabolic demand secondary to increased motility*

Mass lesions

Carcinoma

Diverticular disease

Obstruction

2. Compromised blood flow due to increased intraluminal pressure

Obstruction

Fecal impaction

Colonoscopy

Barium enema

C. Idiopathic (spontaneous)

peptic ulcer, functional dyspepsia, irritable bowel syndrome, etc. Unfortunately, angiographic evidence of thrombosis of large vessels is not always diagnostic, as two or even three of the major arteries may be thrombosed in apparently asymptomatic patients. Once the diagnosis is clearly established, the treatment is surgical. Many surgical procedures have been described with various results. Endarterectomy and aortovisceral bypass have been employed. More recently balloon angioplasty has appeared to provide good results with a less invasive approach (Figures 8A and 8B).

7. NONGANGRENOUS ISCHEMIC BOWEL DISEASE

7.1 Etiology

In contrast to mesenteric ischemia, where the cause of the disease is occlusion of major vessels, in nongangrenous ischemic bowel disease the hypoxxygenation is caused by hypoperfusion of the gut wall microcirculation. Only occasionally is there secondary occlusion of intramural vessels. Many causes may precipitate this disorder. Hypoperfusion is most commonly caused by vascular diseases – e.g., collagen disease, vasculitis, diabetes, atherosclerosis – or by increased viscosity of the blood in sickle cell disease or polycythemia vera. Acute hypotension due to hemorrhage, myocardial infarct, congestive heart failure, sepsis or vasoconstricting drugs may precipitate local ischemia in patients who already have impaired local circulation. Because of an adequate collateral circulation, localization is usually segmental. The necrosis of the gut wall is rarely transmural, and

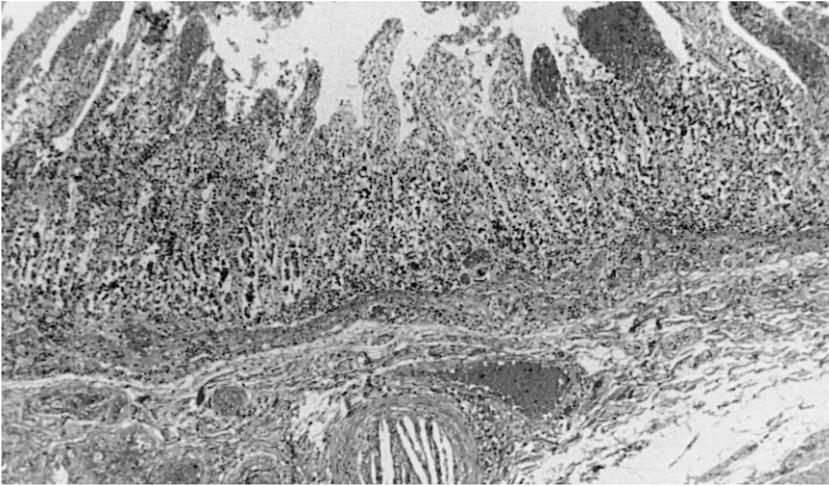


FIGURE 10 (A–D). Histopathologic examples of small vessel disease producing nonocclusive ischemic bowel disease (see Table 1).

FIGURE 10A. Cholesterol embolus. A superficial submucosal artery within the small bowel is completely occluded with atheroemboli containing cholesterol clefts. This has caused ischemic necrosis of villus tips of the overlying intestinal mucosa. (H&E stain)

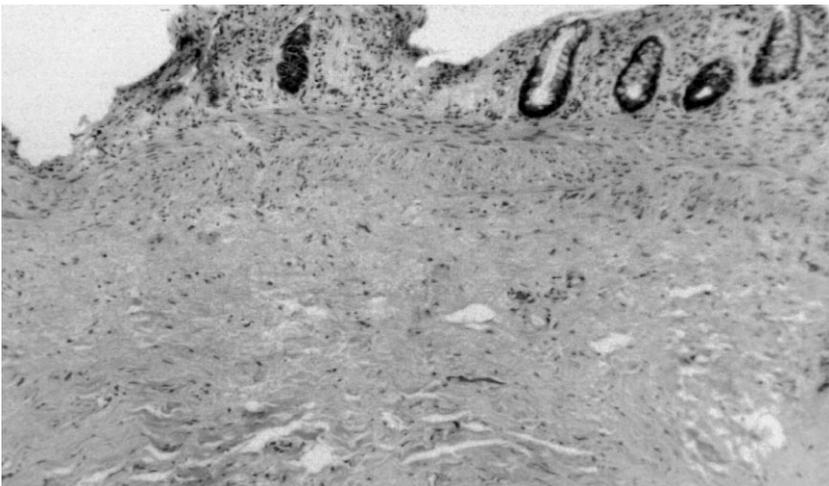


FIGURE 10B. Chronic radiation injury. Photomicrograph shows colonic mucosal atrophy and marked submucosal fibrosis. The patient had developed a colonic stricture due to the mucosal and submucosal scarring resulting from radiation-induced ischemia. (HPS stain)

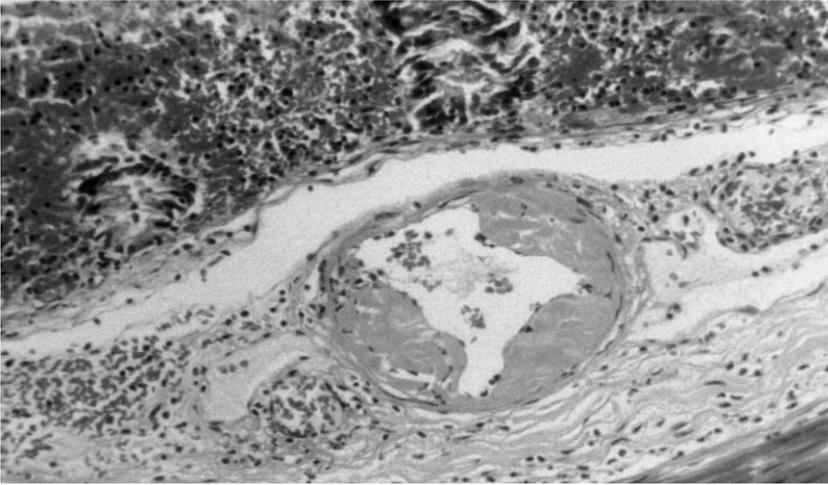


FIGURE 10C. Amyloidosis. Hemorrhagic ischemic necrosis of colonic mucosa associated with mural amyloid deposits within submucosal vessel. (HPS stain)



FIGURE 10D. Amyloidosis. Deeper leveled section of colonic tissue from Figure 10C shows positive Congo red staining of amyloid deposits within vessel wall. (Congo red stain)



FIGURE 11. Barium swallow showing a late ischemic stricture in the proximal small bowel.

as a result, peritonitis is a rare complication. In the small bowel nongangrenous ischemic bowel disease manifests as “focal segmental ischemia” and in the colon as “nongangrenous ischemic colitis.” A list of the more common causes of nonocclusive ischemic bowel disease is provided in Table 1, and the histologic appearance of some of these is shown in Figures 10A–10D.

7.2 Focal Segmental Ischemia of the Small Intestine

Ischemia to short segments of the small bowel results in a variable clinical course that depends on the severity of the infarct. For short segment involvement there is usually appropriate collateral circulation, and thus the disease involves only the mucosa and submucosal tissues. Limited necrosis may heal completely. Ongoing repeated injury may cause chronic enteritis, almost indistinguishable from Crohn’s disease. In some patients the necrotic ulcer may lead to late stricture formation (Figure 11). Occasionally the process may become transmural, resulting in peritonitis. Diagnosis is difficult, as the symptoms may be those of chronic recurrent abdominal pain, bowel obstruction or frank peritonitis. Unless there is complete spontaneous resolution, the treatment of strictures and persistent ulcers is usually surgical. The diagnosis is often made only on histology of the resected small bowel.

7.3 Nongangrenous Ischemic Colitis

7.3.1 PATHOGENESIS

There are two major forms of colonic ischemia: gangrenous (transmural) and nongangrenous colitis (disease contained within the colonic wall). These are in fact two different diseases, with different etiologies and clinical courses, and require different approaches to their management. Gangrenous ischemic colitis is caused by obstruction of the major mesenteric vessels and is discussed in Section 4 (see Figure 1). Occasionally, transmural gangrene may develop when nongangrenous ischemic colitis slowly progresses to transmural necrosis. The recognition and management of this complication of the originally nongangrenous disease is crucial, and as discussed below, depends on careful ongoing observation of the patient with nongangrenous ischemic colitis.

In contrast to the rarity of nonocclusive ischemia of the small bowel is the frequency of local vascular hypoperfusion of the colon. The cause of this relative frequency may be related to the following factors: In comparison to the small intestine, the colon receives less blood, has fewer vascular collaterals, has susceptible “watershed areas” and possesses an ongoing forceful motor activity. Elevated intramural pressure during increased motility in patients with constipation, diverticular disease and cancer of the colon may lead to diminished gut wall blood flow. Similarly, distention with air during colonoscopy or barium enema may temporarily reduce blood flow to the colon. The large bowel also has a different neuroendocrine control. Evidence in our laboratory has indicated that the vessels of the canine colon respond more vigorously to hypotension than those of the small intestine and that contrary to the latter, in the colon the major local vasoconstrictory substance is angiotensin.

7.3.2 CLINICAL PRESENTATION

The classic clinical presentation is characterized by a sudden onset of severe crampy abdominal pain, diarrhea mixed with bright red blood, and occasionally melena. Physical examination may reveal a distended abdomen. Bowel sounds are present and there are no signs of peritoneal involvement. The patient is usually elderly and may show signs of one of the associated diseases such as hypotension, congestive heart failure and atherosclerosis. Under specific conditions, nongangrenous ischemic colitis can also occur in the young. This is often due to iatrogenic or patient-induced causes such as contraceptive medication, nonsteroidal anti-inflammatory agents, cocaine abuse, verapamil overdose, etc. (for details see Table 1). In the elderly, the specific event that precipitated the attack occasionally cannot be determined. The early clinical presentation may be so similar to that of infectious colitis, ulcerative colitis,

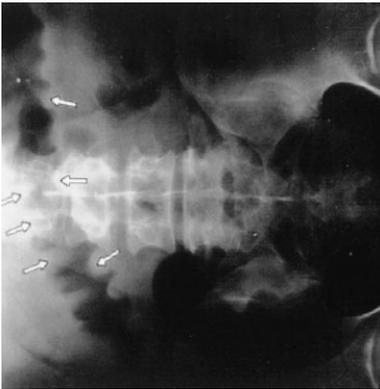


FIGURE 12. Abdominal survey film demonstrating ischemic colitis. This film was taken five hours after the onset of acute hematochezia and severe abdominal pain. Arrows point to areas of submucosal hemorrhage in the air-filled transverse colon. This appearance is often referred to as "thumb-printing."



FIGURE 13. Single contrast barium enema. To avoid increased intraluminal pressure the examination was carried out without preparation and no air was insufflated. The multiple adjacent areas of indentations provide the appearance of thumb-printing (arrows).

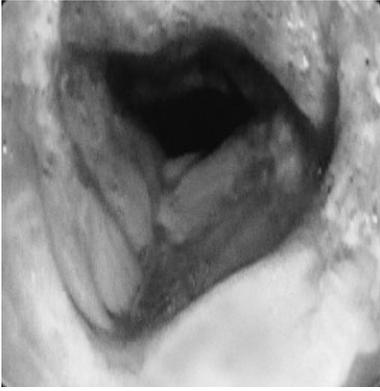


FIGURE 14. Colonoscopic view of a recent-onset ischemic colitis of the splenic flexure. Note the normal mucosa on the left and the dark hemorrhagic mucosal indentation at the right, top and bottom of the image. These blood-filled submucosal blebs in the absence of mucosal damage are diagnostic of the initial stage of ischemic colitis.

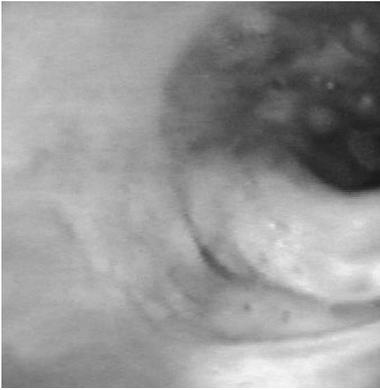


FIGURE 15. Colonoscopic view of ischemic colitis imitating Crohn's disease. Note the nodularity, erythema and petechiae of the mucosa.

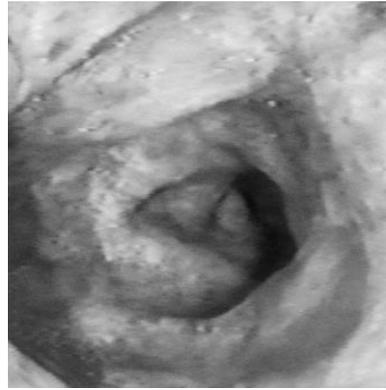


FIGURE 16. Colonoscopic view of ischemic colitis imitating pseudomembranous colitis. Note the generalized erythema and whitish plaques (pseudomembranes).

Crohn's colitis and pseudomembranous colitis that the diagnosis can be established only by exclusion of infection, including *Clostridium difficile*, and by demonstrating the classic radiographic (Figures 12 and 13) and/or colonoscopic (Figure 14) findings of ischemic colitis. Because large vessels are never involved, angiography has no place in the diagnosis of nongangrenous ischemic colitis.

Radiographic and colonoscopic investigations have to be carried out within 24–48 hours of the onset of the disease, as the typical findings tend to disappear and are rapidly replaced by nonspecific signs, and the picture may imitate other conditions such as Crohn's disease (Figure 15). The first radiologic examination should be an abdominal survey film (Figure 12), which may demonstrate the classic intramural hemorrhage-induced thumb-printing in an air-filled segment of the colon. This finding, however, may not always be diagnostic, because occasionally it can be mimicked by mucosal and submucosal edema caused by severe inflammatory processes. Colonic involvement is usually segmental in ischemic colitis. Although any part of the colon may be affected, the "watershed" areas of the splenic flexure and of the rectosigmoid junction are most commonly involved. Thumb-printing can be demonstrated by barium enema (Figure 13), but differentiation between edema and submucosal hemorrhage can be done only by colonoscopy, where hemorrhage can be recognized as large dark red submucosal blebs (Figure 14). Because distention of the colon with air may compress intramural blood vessels and thus further decrease blood flow, barium enema is rarely used,



FIGURE 17 (A and B). Histopathologic mimickers of ischemic bowel disease.

FIGURE 17A. Photomicrograph of colonic mucosa and superficial submucosa in a patient with chronic ischemic colitis. There is focal ulceration, epithelial regeneration with polypoid mucosal areas, inflammation and distortion of crypt architecture similar to that seen in the chronic colitis of Crohn's disease. (HPS stain)

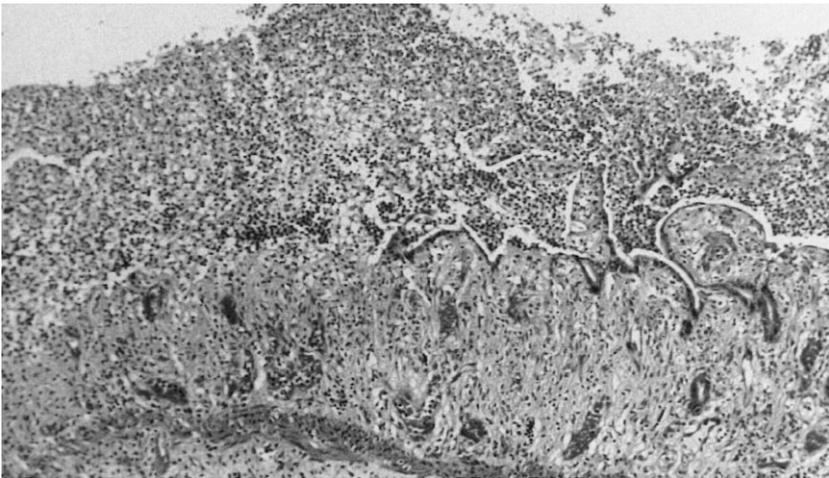


FIGURE 17B. Photomicrograph showing prominent inflammatory exudate forming a pseudomembrane that covers the colonic mucosa, which is superficially eroded. This intense inflammatory reaction was due to acute mucosal ischemic injury and mimics the histopathology of infectious pseudomembranous colitis. (HPS stain)

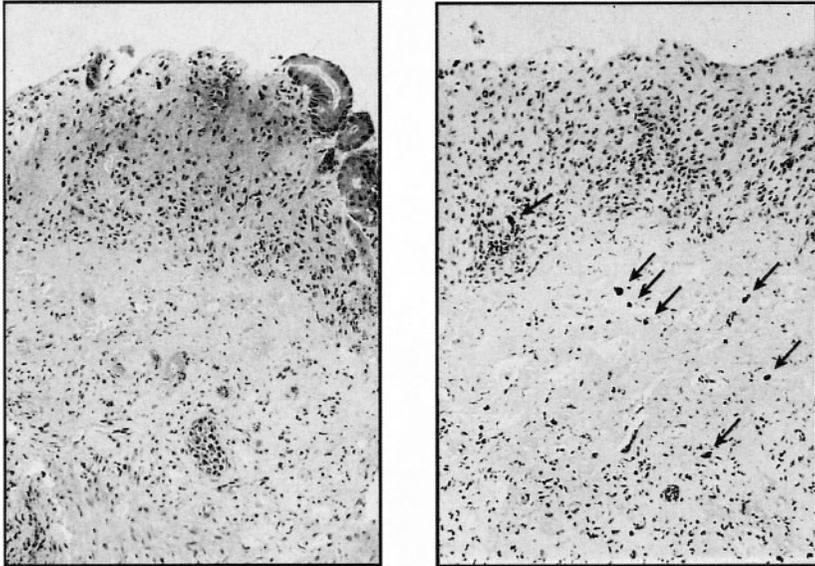


FIGURE 18. Photomicrograph of mucosal biopsy in patient with ischemic colitis taken five days after onset of disease.

- A. Routine HPS stain showing ischemic necrosis of the mucosa and submucosa.
- B. Prussian blue stain. Arrows indicate dark blue iron-laden macrophages in the mucosa and submucosa.

unless plain films of the abdomen can not provide a diagnosis and colonoscopy is not available. Colonoscopy must be carried out carefully with minimal air insufflation. After 24–48 hours, the hemorrhage resolves and the mucosa becomes necrotic. If colonoscopy is done at this stage, the endoscopist may be unable to differentiate the necrosis and ulcerations resulting from ischemic colitis from those caused by Crohn's disease (Figure 15) or pseudomembranous enterocolitis (Figure 16). The pathologist reviewing biopsies taken a few days after the onset of the disease may have similar difficulties (Figure 17). Not infrequently, only time will tell whether the patient has inflammatory bowel disease (IBD) or ischemia. It is not impossible that some elderly patients with what is thought to be late-onset IBD or young women on contraceptive medication who are thought to have Crohn's are actually suffering from ischemic colitis.

The disease can progress in four different ways (Figure 1). Mild disease may resolve spontaneously. In patients with involvement of only small

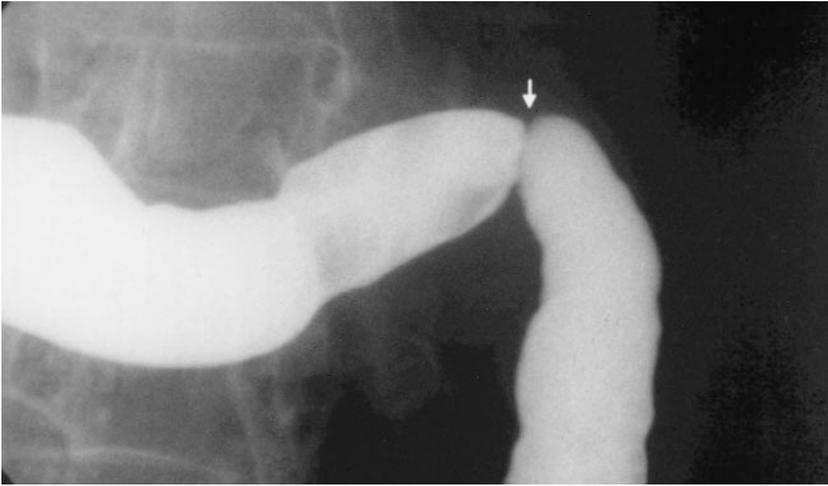


FIGURE 19. Single contrast barium enema demonstrating a late colonic ischemic stricture.

segments, the symptoms and physical findings subside within 24–48 hours and complete resolution can occur within two to three weeks. In some, the disease does not resolve and may progress to ongoing or recurrent chronic colitis. As the pathological response of colonic tissue to chronic injury is restricted to a very few modalities, such as infiltration with leukocytes, crypt abscess, hemorrhage, necrosis, ulceration and regeneration of crypts, the pathologist may also have difficulty in differentiating ongoing ischemic colitis from that of Crohn's disease (Figure 17A). Hemosiderin, a sign of previous bleeding, is often considered a typical manifestation of ischemic colitis (Figure 18). Unfortunately, this finding is not restricted to ischemic colonic disease, as it can be found in any type of colitis, including IBD, if hemorrhage has occurred sometime in the past.

Once ischemic colitis has become chronic, it may resolve, relapse or progress to deeper intramural inflammation and necrosis. In severe disease the patient may exhibit toxic symptoms with chills, fever, severe bloody diarrhea and abdominal distention with diminished bowel sounds. The patient may develop leukocytosis, anemia, elevated platelet count and electrolyte disturbances. In some instances the disease progresses to toxic megacolon, and if the intramural necrosis becomes transmural, acute peritonitis will ensue. This progression may take only a few hours or several days to develop, and as the patient must be surgically treated well before peritonitis develops, this process

must be detected early by careful, sometimes hourly, follow-up of the patient. If the necrosis does not progress transmurally, the process will heal first with granulation tissue that is replaced by fibrous tissue, scarring and finally a stricture (Figure 19).

7.3.3 TREATMENT

Infectious enteropathies, IBD and other precipitating causes such as diverticulitis, cancer, etc. have to be detected and appropriately treated. Therapy for ischemic colitis can be considered under the following three categories: (1) nonspecific supportive therapy, (2) specific medical treatment and (3) surgical therapy.

Nonspecific supportive therapy. Fluid and electrolyte balance must be carefully maintained. Oral intake should be restricted according to the severity of disease. Well-nourished patients can be maintained for a few days without specific nutritional support, except for what they receive in intravenous solutions. Severely undernourished patients may require enteral nutrition, or if this is poorly tolerated, total parenteral nutrition (TPN). Bleeding is rarely severe enough to require blood transfusion, but if anemia is present it may have to be corrected even in elderly patients with poor cardiovascular reserve. This requires careful balancing, so that an already precariously maintained circulation is not overloaded. Patients tend to request medication to relieve diarrhea and abdominal pain. However, the use of analgesics, antispasmodic or antidiarrheal agents is contraindicated, because they may lead to an inert bowel, which may result in a toxic megacolon.

As the patient improves, a low-residue diet may be slowly started. If this is not well tolerated, enteric feeding may be required. However, in some patients the diarrhea and abdominal pain may become worse on enteric nutrition. This may be overcome with the use of an iso-osmotic product, dilution of the solution and constant slow administration over 24 hours.

Patients have to be carefully followed to detect deterioration, as they may progress to toxic megacolon or perforation. In patients who show signs of deterioration, the use of antibiotics may be justified. If there is further progression and the patient develops increasing peritoneal signs, surgery becomes imperative, even in an elderly patient who appears to be a poor surgical risk.

Specific medical treatment. There is no need for specific therapy for mild self-limiting disease. For chronic ongoing disease there is no proven specific therapy, and no experimental data exist to assess the usefulness of any of the drugs utilized in IBD. Because of the relatively low incidence of ischemic colitis, up to now it has not been possible to design a valid prospective double-blind study to assess the efficacy of these drugs. However, patients with long-standing progressive disease have been treated with

variable results using 5-aminosalicylic acid (5-ASA) by oral and/or (depending on the location of the disease) rectal administration. For patients who do not respond to 5-ASA, a trial with oral or local steroids may be attempted. There is no experience with metronidazole or immunosuppressive agents. In contrast to acute mesenteric arterial occlusion, there is no evidence in nongangrenous ischemic colitis that vasodilators (papaverine, ACE inhibitors, nitrites) and/or fibrinolytic agents (streptokinase, urokinase) are useful. By the time the patient is seen the intramural ischemic injury has already occurred and vasodilators cannot reverse the pathological changes. Treatment of heart disease, change of digitalis to other medication, discontinuation of estrogens, management of diabetes, recognition and treatment of vasculitis, polycythemia, etc., may not necessarily alter the outcome of already established chronic disease, but may prevent future recurrences.

Surgical therapy. Indications for immediate surgery are toxic megacolon and transmural necrosis leading to peritoneal signs. Usually within six months after onset of the disease a considerable number of patients with severe ischemic colitis will develop strictures. They present with symptoms of partial obstruction. One should attempt colonoscopic dilation, but if this fails stricturoplasty or surgical resection may be necessary.

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OBJECTIVES

1. Understand the anatomy and physiology of splanchnic circulation.
2. Understand the pathophysiology of ischemic bowel disease.
3. Realize the importance of differentiating superficial (mucosal and submucosal) from deep (transmural) necrosis.
4. Be aware of the risk factors that may lead to intestinal ischemia.
5. Develop a high index of suspicion for the possibility of acute mesenteric ischemia in an emergent patient with extremely severe abdominal pain.
6. Learn to act immediately when this condition is suspected, as delay may lead to rapid necrosis of the bowel.
7. Understand the value of the different imaging techniques used in acute mesenteric ischemia.
8. Learn the methods of management of acute mesenteric ischemia.
9. Become aware of the possibility of chronic mesenteric ischemia in a certain group of patients who present with unexplained postprandial abdominal pain.
10. Learn to consider nongangrenous ischemia in localized small bowel disease.
11. Suspect nongangrenous ischemic colitis in patients with severe crampy abdominal pain and hematochezia.
12. Learn the risk factors that can lead to nongangrenous ischemic colitis.
13. Understand the differences between imaging techniques used in nongangrenous ischemic colitis and those used in acute mesenteric ischemia.
14. Learn the problems involved in differentiating nongangrenous ischemic colitis from inflammatory bowel disease or infectious colitis.
15. Understand the natural history and evolution of nongangrenous ischemic colitis.
16. Learn to be aware of possible progression of acute ongoing nongangrenous disease to toxic megacolon and occasionally to transmural necrosis.
17. Understand the problems involved in managing nongangrenous ischemic colitis during its acute and chronic phases.