

TOPIC HIGHLIGHT

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Ischemic colitis: Clinical practice in diagnosis and treatment

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Abstract

Ischemic colitis is the most common form of ischemic injury of the gastrointestinal tract and can present either as an occlusive or a non-occlusive form. It accounts for 1 in 1000 hospitalizations but its incidence is underestimated because it often has a mild and transient nature. The etiology of ischemic colitis is multifactorial and the clinical presentation variable. The diagnosis is based on a combination of clinical suspicion, radiographic, endoscopic and histological findings. Therapy and outcome depends on the severity of the disease. Most cases of the non-gangrenous form are transient and resolve spontaneously without complications. On the other hand, high morbidity and mortality and urgent operative intervention are the hallmarks of gangrenous ischemic colitis.

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INTRODUCTION

Ischemic colitis (IC), first described by Boley *et al*, is the most common form of ischemic injury to the gastrointestinal tract representing more than half of the cases with gastrointestinal ischemia^[1,2]. The incidence of IC is underestimated because it often has a mild and transient nature. Moreover, many cases are misdiagnosed as suffering from other diseases such as inflammatory bowel disease or infectious colitis.

An acute, self-limited compromise in intestinal blood flow which is inadequate for meeting the metabolic demands of a region of the colon is the underlying pathophysiology^[3]. Colonic blood flow may be compromised by changes in the systemic circulation or by anatomic or functional changes in the local mesenteric vasculature. The original insult precipitating the ischemic event often cannot be established, but frequently occurs in the elderly patient with diffuse disease in small segmental vessels and various co-morbidities. Approximately 90% of cases of colonic ischemia occur in patients over 60 years of age although younger patients may also be affected^[4].

IC presents either as an occlusive or a non-occlusive form. In most cases no specific occlusive lesion is recognized on angiography, and patients are referred to as suffering from non-occlusive colon ischemia.

The aim of this review is to transfer the current knowledge on diagnosis and management of ischemic colitis into daily clinical practice.

RISK FACTORS

A plethora of conditions may predispose to IC: Mesenteric artery emboli, thrombosis, or trauma may lead to occlusive vascular disease and impaired colonic perfusion^[5]. Hypo-perfusion states due to congestive heart failure, transient hypotension in the perioperative period or strenuous physical activities and shock due to a variety of causes such as hypovolemia or sepsis can result in IC^[3]. Mechanical colonic obstruction due to tumors, adhesions, volvuli, hernias, diverticulitis or prolapse may also infrequently cause IC^[3]. There is a long list of medications that predispose to colon ischemia. Major classes of pharmacologic agents known to be associated with IC include the following^[6]: antibiotics, appetite suppressants (phentermine), chemotherapeutic agents (vinca alkaloids and taxanes), constipation inducing medications, decongestants (pseudoephedrine), cardiac glucosides, diuretics, ergot alkaloids, hormonal therapies, statins, illicit drugs,

immunosuppressive agents, laxatives, nonsteroidal anti-inflammatory drugs, psychotropic medications, serotonin agonists/antagonists and vasopressors. Iatrogenic causes may result in IC. Ischemic colitis follows aortic reconstruction with an incidence of 2% to 3% and is higher after abdominal aortic aneurysm repair^[7,8]. IC may be a complication of coronary artery bypass surgery or a rare complication of colonic surgery or colonoscopy^[3].

A state of increased coagulability, although not extensively investigated, has been raised as a significant factor in the pathogenesis of IC. Some cases of IC have been reported to be associated with genetic defects such as deficiencies of protein C, protein S, and antithrombin III^[9-11], factor V Leiden (FVL) mutation^[12,13], and prothrombin 20210G/A mutation^[14], as well as acquired factors such as antiphospholipid antibodies^[15]. Protein Z deficiency has also been reported in IC patients^[16]. A thrombophilic tendency in the majority of patients was shown in a study of comprehensive thrombophilic screening in colon ischemia^[17]. The most significant associations were found with the antiphospholipid antibodies and the FVL mutation^[17]. These results were confirmed by another recent study in which thrombophilic disorders were found in 28% of patients studied^[18].

IC might also spontaneously appear in apparently healthy individuals. In these cases no clear cause for the ischemia is identified. This idiopathic or "spontaneous" form is generally thought to be related to localized non-occlusive ischemia of the bowel^[5]. In younger patients a predisposing cause is more easily recognized. Vasculitides, estrogens, cocaine and methamphetamine use, psychotropic drugs, sickle cell disease, long-distance running and heritable disorders of coagulation should be considered^[19-24]. In a recent study^[25], the frequency of the 506 Q allele of the factor V (FV) 506 RQ (Leiden) mutation and the mutant 4G allele of plasminogen activator inhibitor (PAI) polymorphism were found to be significantly higher in young patients with IC compared with healthy controls.

PATHOPHYSIOLOGY

The colon is predisposed to ischemia by its relatively low blood flow and its less developed microvasculature plexus compared with the small bowel. Two major arteries supply most of the blood to the colon: the superior mesenteric artery (which supplies the ascending and transverse colon) and the inferior mesenteric artery (IMA) (which supplies the descending and sigmoid colon). The internal iliac arteries supply the rectum.

The colon is protected from ischemia by a collateral blood supply *via* a system of arcades connecting the two major arteries. The anatomy is highly variable, however, and certain areas are more vulnerable in some people^[26]. The splenic flexure and sigmoid colon are regions where two circulations meet each other (so-called watershed areas), have more limited collateral networks and therefore ischemic damage is more common in these areas. The marginal artery of Drummond is one of the collateral vessels supplying the splenic flexure; 5% of the

population has a diminished or absent marginal artery of Drummond^[27]. These patients are at particular risk of ischemia. The right colon may be vulnerable in systemic low-flow states, as the marginal artery of Drummond is poorly developed here in 50% of the population^[28]. The vasa recta are smaller and less developed in the right colon compared to the left colon. Collateral flow between the IMA and the internal iliac arteries occurs *via* the superior and middle/inferior rectal (hemorrhoidal) vessels. Ischemic damage of the rectum is rare because of its dual blood supply from the mesenteric and iliac arteries.

Classification

Clinically, ischemic colitis may be classified into gangrenous and non-gangrenous forms. The latter can also be subdivided into transient and chronic forms.

According to the classification of Brandt and Boley the following types are suggested^[29]: (1) Reversible ischemic colonopathy; (2) Transient IC; (3) Chronic ulcerative IC; (4) Ischemic colonic stricture; (5) Colonic gangrene; and (6) Fulminant universal.

The non-gangrenous form accounts for 80%-85% of cases^[26]. The disease is transient, and reversible in about 50% of cases. Chronic forms, presenting either as chronic segmental colitis or strictures, occur in 20%-25% and 10%-15% of cases, respectively^[26,29]. Predictive factors of the chronic form are older age, longer elapsed time from the onset of illness to the termination of subjective symptoms, and a prolonged period until normalization of the white blood cell count or the erythrocyte sedimentation rate^[5]. Gangrene occurs in about 15% of patients and requires laparotomy as soon as possible^[26]. Fulminant pancolitis is rare, occurring in only 1% of cases^[26].

A worse prognosis has been reported in elderly patients. There are conflicting results with regard to the relationship between the medical history of patients and the severity of IC. High blood pressure, history of cancer, diabetes mellitus, aortic surgery, peripheral vascular disease and involvement of the right side of the colon have been suggested by some authors to be predisposing factors for a worse evolution of the disease^[30-32]. In the study by Anon *et al.*^[33], factors predicting poor prognosis in ischemic colitis were the absence of hematochezia, tachycardia and peritonism, anemia, hyponatremia and colonic stenosis.

Any part of the colon may be affected but the left colon is the predominant location in approximately 75% of patients^[5]. Splenic flexure is involved in approximately one-quarter of patients^[5] and isolated right colon ischemia (IRCI) in about 10% of cases^[29]. In a recent biopsy-proven study, IRCI accounted for 26% of cases^[34]. Its clinical presentation was found to be different in patients who presented more commonly with abdominal pain without bloody diarrhea. IRCI has been reported to be associated with hemodialysis and chronic renal failure and in patients with shock. It is associated with severe colitis and patients have a worse outcome than those with colon ischemia involving other regions, including

a five-fold need for surgery and a two-fold increase in mortality^[34]. Patients on hemodialysis who develop IRCI have a particularly unfavorable outcome^[34]. Insufficient collateralization and blood flow to the right side of the colon is believed to be the reason for the poor prognosis in these patients. Alternatively, it is possible that the presence of an acute superior mesenteric artery occlusion and thus its outcome reflects that of acute mesenteric ischemia.

Clinical presentation

The clinical presentation varies, depending on the severity and extent of the disease. None of the symptoms and signs is specific. Most patients present with a sudden onset of crampy abdominal pain, diarrhea and an urge to defecate. The pain is mild, located over the affected bowel, usually to the left side of the lower abdomen and hypogastrium, followed by mild rectal bleeding within 24 h. The blood may be bright red or maroon, frequently mixed with the stools. Rectal bleeding is usually minimal. Significant hematochezia accompanied with hemodynamic instability or the need for blood transfusion suggests a different diagnosis. The presence of an associated ileus may be manifested by anorexia, nausea and vomiting.

Clinical examination of the abdomen reveals mild to moderate tenderness over the affected area of the colon. Rectal examination shows heme-positive stools. Fever is unusual while the white cell count is generally raised. In cases of severe ischemia with transmural infarction and necrosis, marked tenderness with peritoneal signs may be present on physical examination accompanied by metabolic acidosis and septic shock.

DIAGNOSIS

Given that the presentation of colon ischemia is not specific and is highly variable, diagnosis and management is clinically challenging. Diagnosis requires a high index of clinical suspicion. The chronology of symptoms and the clinical situations upon which these symptoms appear must be taken into account.

Special attention must be paid to the presence of conditions that predispose to the disease, such as strenuous physical activity, dehydration, illicit drugs, thrombophilic tendency, aortic surgery or cardiac bypass, vasculitis, major cardiovascular episode accompanied by hypotension or an obstructing lesion of the colon.

The presence of diarrhea, abdominal pain and tenderness as well as mild lower gastrointestinal bleeding, even in the absence of any risk factor, should prompt consideration of IC as a cause. Early and repeated clinical evaluation in addition to radiological and endoscopic assessment is necessary to avoid complications. Common clinical conditions should be excluded. The differential diagnosis includes infectious colitis, inflammatory bowel disease, pseudomembranous colitis, diverticulitis and colon carcinoma. Severe forms may be difficult to distinguish from acute mesenteric ischemia.

All patients with clinical suspicion of IC should have

stool cultures for *Salmonella*, *Shigella*, *Campylobacter* and *Escherichia coli* O157:H7^[35]. The latter organism has been implicated in causing colonic ischemia. Infection with parasites or viruses such as cytomegalovirus should also be excluded.

Laboratory tests

Various laboratory markers of ischemia have been investigated such as: lactate, LDH, CPK, amylase levels, leucocytes, alkaline phosphatase, inorganic phosphate, intestinal fatty acid binding protein and alfa-glutathione S-transferase^[36]. These markers have been studied mainly in acute bowel ischemia, and none has been found to be sufficiently specific to diagnose IC. They are uncommon in mild ischemia and only increase with advanced and severe ischemic damage, late in the course of the disease.

Imaging techniques

Plain abdominal radiography can reveal nonspecific findings such as thumbprinting, air-filled loops, colonic aperistalsis, mural thickening and exhausted bowel in up to 21% of patients^[3]. It is a useful examination for excluding colon infarction^[37]. When intra-abdominal air secondary to perforation, air within the bowel wall, or air in the portal vein, is demonstrated by plain radiography, an emergency exploratory laparotomy is indicated.

Barium enema may suggest colon ischemia in up to 75% of patients with thumbprinting being the most common finding. Ulcers, ridges, edema, eccentric mural deformity, succulation and strictures may also be seen. Findings are non specific^[38]. Barium enema should be avoided in cases where there is a suspicion of gangrene or perforation. Barium enema also makes the later use of angiography or endoscopy more difficult because of residual contrast agent.

Computed tomography (CT) is often used as the initial diagnostic test when assessing patients with nonspecific abdominal pain. It may suggest the diagnosis and location, exclude other serious medical conditions, narrow the differential diagnosis possibilities and illustrate the complications. Although intrinsic colonic abnormalities cannot be used to diagnose or predict the development of infarction^[39].

In non-transmural IC, the initial bowel wall thickening, thumbprinting, and pericolonic stranding, with or without peritoneal fluid, can be seen on CT images. In these cases, CT usually demonstrates the double halo or target sign. After reperfusion of the ischemic bowel wall, the sign may be produced by edema in the submucosa and appear as low attenuation or by hemorrhage and appear as high attenuation. If there is total vascular occlusion without reperfusion (infarction), the colonic wall remains thin and unenhancing, associated with dilatation of the lumen. In these cases, CT may demonstrate a thrombus in the corresponding mesenteric vessel. If ischemia is transmural, strictures may form. Occasionally, a toxic megacolon develops. Pneumatosis and/or gas in the mesenteric veins are ominous signs when associated with bowel wall thickening and are due to bowel infarction.

Pneumatosis coli or pneumatosis intestinalis can be diagnosed by demonstrating air bubbles in the colonic or intestinal wall. The gas bubbles are arranged in a linear fashion and are best visualized with the window settings for bone or lung^[40].

Mesenteric angiography usually has no role in the evaluation and management of IC because at the time of symptom onset, colon blood flow has returned to normal. Damage from hypoperfusion is often at the arteriolar level, whereas mesenteric vessels and arcades are patent. There are two exceptions where angiography may have some utility: when acute mesenteric ischemia is considered and cannot be clearly distinguished from IC by clinical presentation, or when there is isolated involvement of the right side of the colon, suggesting superior mesenteric artery occlusion.

Sonography is a sensitive technique for the early detection of changes in the colon wall resulting from ischemia, and it can suggest this cause in the appropriate clinical setting. Location and length of the involved colonic segment, colon wall thickening, bowel wall stratification and abnormal echogenicity of the pericolic fat and peritoneal fluid are some of the findings on sonography^[41].

Color Doppler sonography may be useful in the differentiation between inflammatory and ischemic bowel wall thickening^[42]. Sonography may provide data for identifying patients who will develop necrosis. In one study, altered pericolic fat or the absence of improvement in sonographic follow-up studies were factors associated with transmural necrosis^[41]. Nevertheless, overlying bowel gas, operator-dependent quality and poor sensitivity for low flow vessel disease limit its use.

Scintigraphy has recently been used in the diagnosis of ischemic colitis. In-111 or Tc-99m-labeled leukocyte scintigraphy has been studied and has demonstrated successful imaging of bowel infarction while Tc-99m(V) DMSA was recently found to have no role in the detection and diagnosis of IC^[43-45].

Colonoscopy

In recent years, colonoscopy has replaced barium enema as the most common diagnostic method and the gold standard for confirmation of IC. It is more sensitive and allows visualization of colonic mucosa and histological analysis of biopsies. However, with the exception of colonic gangrene, neither endoscopic nor histological findings are specific^[29] and highly depend on the duration and severity of ischemic injury. Diagnosis requires early colonoscopy (< 48 h). Serial studies in connection with the clinical setting are necessary to establish the diagnosis.

Ischemic tissue damage to the colon is thought to be a result of both local hypoperfusion during the ischemic period and reperfusion injury when blood flow returns. When the ischemic period is brief, reperfusion may be significant and accounts for most of the histologic and endoscopic damage present in IC^[2]. Reperfusion injury may be associated with the release of oxygen

free radicals which cause lipid peroxidation within cell membranes, resulting in cell lysis and tissue damage.

When the ischemic period is of long duration, hypoperfusion deprives the involved bowel of oxygen and nutrients, leading to hypoxia and direct cell death^[2]; damage progresses from the lumen outwards to the serosa (from the mucosa and submucosa to deeper layers).

In the early stages only the mucosa and the submucosa are involved. Hemorrhagic nodules may be seen at colonoscopy and represent bleeding into the submucosa. These findings parallel the “thumbprints” or “pseudotumors” found on barium studies^[5]. The purple submucosal hemorrhages usually dissipate within 48 h or are followed by ulceration. Hence, the initial diagnostic study should be performed soon after the onset of symptoms. Focal areas of pale and edematous mucosa interspersed with areas of petechial hemorrhage or superficial ulceration may also be seen in mild cases^[2,46]. Later, segmental erythema with or without ulcerations and bleeding may be observed. A single longitudinal ulcerated or inflamed colon strip represents the characteristic single-stripe sign^[47]. In more severe ischemia when transmural infarction of the bowel wall occurs, the mucosa appears gray-green or black over a significant area. Pseudopolyps and pseudomembranes may also co-exist^[5]. In chronic stages, weeks or months later, stricture, mucosal atrophy and granularity or a mucosal pattern suggestive of “segmental ulcerative colitis” may occur^[2].

Histologic changes in IC include edema, distorted crypts, mucosal and submucosal hemorrhage, inflammatory infiltration in the lamina propria, granulation tissue, intravascular platelet thrombi and necrosis. In the phase of stricture, inflammation is minimal and fibrosis predominates^[5].

Endoscopic findings which distinguish between IC and inflammatory bowel disease are the segmental distribution, rectum sparing and rapid resolution on serial examinations^[3]. Special care should be taken during colonoscopy to avoid overinflation which can lead to the risk of perforation. Distention of the bowel with room air may cause a further reduction in intestinal perfusion. Using carbon dioxide as the insufflating agent which is rapidly absorbed, and has the benefit of vasodilation and direct improvement in colonic perfusion, may minimize these risks^[26]. When signs of peritonitis are present, endoscopy should be avoided. When endoscopy reveals findings of gangrene, colonoscopy should be stopped and laparotomy performed as soon as possible.

Total colonoscopy when it is considered safe, is preferred because 30% of IC cases occur proximal to the left flexure^[3]. Given the high morbidity and mortality of IRCI and the vague presenting symptoms, early diagnosis and aggressive management is critical.

TREATMENT

Treatment depends on acuteness and severity of presentation. Most cases of IC are transient and resolve

spontaneously. Such patients do not require specific therapy. Very mild cases can be managed on an outpatient basis with liquid diet, close observation and antibiotics. Patients with more severe symptoms must be hospitalized. In the absence of colonic gangrene or perforation, general measures of supportive care are recommended. Patients should be placed on bowel rest and given intravenous fluids to resuscitate extracellular volume and reduce intestinal oxygen requirements. Parenteral nutrition should be considered for patients who need prolonged bowel rest and have major medical contraindications to surgery^[26]. Cardiac function and oxygenation should be optimized. Swan-Ganz catheterization may assist in guiding fluid status and cardiac function in hemodynamically unstable patients. Vasopressors or any medications which are associated with colon ischemia should be withdrawn if possible. Oral cathartics and bowel preparations should not be given because they can, in some cases, precipitate colonic perforation or toxic dilatation of the colon. Likewise, the use of systemic corticosteroids may potentiate ischemic damage and predispose to colonic perforation. Local corticosteroids may have a role in the treatment of patients with chronic IC although no published experience supports their use. A nasogastric tube should be placed if ileus is present. Decompression of a distended colon by use of a rectal tube may be useful. Empiric broad-spectrum antibiotics are given to cover aerobic and anaerobic bacteria and minimize bacterial translocation and sepsis which has been shown to occur with the loss of mucosal integrity^[48]. The use of antibiotics is based on several experimental studies which showed a reduction in severity and extent of bowel damage when antibiotics were given before or during an ischemic event^[2,49]. Antibiotics have resulted in prolonged survival after intestinal ischemia in rats^[49]. Although there is a lack of substantial evidence in humans, this practice is justified because of the difficulty in predicting who will progress to gangrenous colitis. In experimental studies^[5], substances such as papaverine, isoproterenol, bradykinin, histamine, serotonin, adenosine, vasoactive intestinal polypeptide and glucagon have been found to dilate colonic vasculature and improve local colonic blood flow and tissue oxygenation.

Frequent clinical follow up of the abdomen, careful monitoring of vital signs and serial radiographic and colonoscopic examinations are needed. Clinical suspicion of colonic infarction justifying an emergency laparotomy may arise if there are signs of clinical deterioration despite conservative therapy, such as sepsis, persistent fever and leukocytosis, peritoneal irritation, protracted pain, diarrhea or bleeding, protein-losing colopathy for more than 14 d, free intra-abdominal air, or endoscopically-proved extensive gangrene^[26].

About 20% of patients with acute IC will require surgery with an associated mortality rate of up to 60%^[31]. At laparotomy, the diagnosis is confirmed and all affected bowel resected. It is important to ensure normal surgical margins. The external appearance of the bowel may be normal during laparotomy since the serosa may be

unaffected, despite extensive mucosal damage. The extent of resection should be guided by the distribution of disease seen on preoperative studies. Some authors have reported on intraoperative techniques such as Doppler ultrasonography, intraoperative colonoscopy, evaluation of the antimesenteric serosal surface by hand-held photoplethysmography, pulse oximetry or transcolonic oxygen saturation and intravenous fluorescein for assessment of colonic viability^[49,50]. In general, the resected segment should be examined in the operating room for mucosal injury. If needed, additional colon should be removed. Questionably viable areas of colon are generally resected. A colectomy is followed by colostomy or ileostomy. Patients with left-sided IC undergo resection with a proximal stoma and a distal mucous fistula or Hartman pouch. Primary anastomosis is unusual. Rarely, an ileocolostomy may be performed in patients with right-sided IC and viable ileum and transverse colon. In a series by Longo *et al*^[51], the stoma was closed in 75% of patients with IC who underwent segmental resection *vs* only a third of those with total colonic involvement.

Fortunately, in the majority of patients, signs and symptoms of the disease resolve within 24 to 48 h and complete clinical, radiographic and endoscopic resolution occurs within 2 wk. In these circumstances no further therapy is indicated. In severe but reversible injury, when segmental ulcerative colitis exists, the colon may take 1 to 6 mo to heal^[29]. Asymptomatic patients should have frequent follow-up examinations to document healing or the development of strictures or persistent colitis. In such cases, the patient may have persistent diarrhea, rectal bleeding or repeated episodes of sepsis, which may lead to perforation. Chronic ischemia may respond to topical steroid preparations in addition to general conservative measures. Resection of the affected segment is curative and subsequent development of further ischemic disease is rare. Asymptomatic strictures should be observed, since some may return to normal within 12 to 24 mo with no specific therapy^[31]. When a stricture produces symptoms of obstruction, segmental resection is adequate while endoscopic dilation has been proposed as an alternative to surgery^[48].

CONCLUSION

The etiology of ischemic colitis is multifactorial and the clinical presentation variable. The diagnosis is based on a combination of clinical suspicion, endoscopic and histological findings. Therapy and outcome depend on the severity of the disease. Most cases of the non-gangrenous form are transient and resolve spontaneously without complications. High morbidity and mortality and urgent operative intervention are the hallmarks of gangrenous ischemic colitis.

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