

TITLE PAGE

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Abstract:

Ischaemic colitis (IC) is the most common form of gastrointestinal ischaemia, but may be confused with acute mesenteric ischaemia, inflammatory bowel disease or infectious colitis. This review article outlines current classification, epidemiology and risk factors, as well as approaches to diagnosis and management to guide clinical practice. It also identifies areas for further research.

Introduction:

Patients with ischaemic colitis (IC) present commonly to emergency departments and require admission to surgical wards. In fact, IC is the most common form of gastrointestinal ischaemia(1), and has an incidence of 4.5-44 cases per 100,000 person years(2). Uncertainty surrounds the diagnosis of this condition as it presents with non-specific symptoms, lacks a single diagnostic test, and has varied severity. The pathophysiology is poorly understood and there are no clear guidelines to direct evidence-based management.

Classification:

There are several classification systems of IC in the literature. These allow risk-stratification of patients to guide management, and to identify those likely to fail conservative treatment or require early surgical intervention. The simplest divides IC into gangrenous colitis, which constitutes 15-20% of presentations, and non-gangrenous colitis, 80-85% of cases(3-6). A more detailed classification system includes 6 categories based on presentation:

1. Reversible ischaemic colopathy: 3-26.1% of cases(1,6-8). This type is characterised by submucosal haemorrhage at endoscopy, with involvement of superficial mucosa. It is typically self-limiting(9).
2. Transient ischaemic colitis: the most common form at approximately 45% of cases(1,6-8). These patients present with abdominal pain, per-rectal bleeding, and full-thickness involvement of the mucosa (9).
3. Chronic segmental ischaemic colitis or chronic ulcerative ischaemic colitis: 17.9-25%

of cases(1,6,7). These patients present with persistent symptoms or recurrent episodes of pain, per-rectal bleeding, diarrhoea, and segmental colitis on imaging. Resection is often curative(10,11).

4. Ischaemic colonic stricture: 10-15% of cases(6-8). This may be detected acutely, however more frequently is found at follow-up endoscopy(10).

5. Gangrenous colitis: 9.9-19% of cases(1,6,8). This should be suspected when there is increasing abdominal pain, signs of local or generalised peritonitis, fevers or associated ileus(11).

6. Universal fulminant pancolitis: 1-2.5% of cases(1,6-8). This presents acutely with severe symptoms, progressive transmural infarction and necrosis of the entire colon, resultant sepsis and perforation with a 75 percent mortality rate (12,13). These patients present with sepsis, severe abdominal pain, peritonitis, and per-rectal bleeding(11).

Risk Factors:

A major risk factor for IC is age, with the incidence increasing from 1.1 cases/100,000 person years in individuals less than 40 years old, to 107 cases /100,000 person years in those older than 80(3). Other significant factors associated with IC are hypertension (79.5%), hyperlipidaemia (58.1%), coronary artery disease (25.9 – 50%) and diabetes mellitus (21-28.4%). Of less important are atrial fibrillation (17.9%), chronic obstructive pulmonary disease (15%, relative risk (RR) 2.62), female sex (RR 1.48), irritable bowel disease (RR 3.4), and smoking (55% in cases versus 47% in controls)(1-3,5,7,8,14-17).

IC occurring proximal to obstructing lesions, or following aortic surgery or periods of hypotension from other causes are typically excluded in trials for IC, as the pathogenesis is thought to be different(7,8,14,18).

Pathophysiology and Contributory Factors:

IC is thought to be caused by a non-occlusive acute change in colonic microvasculature leading to ischaemia(1,3,15,19). Subsequent reperfusion injury causes ongoing cellular and tissue damage(1,3-7,15,20). Reperfusion injury occurs through various mechanisms including immune cell recruitment to damaged tissues with subsequent inflammatory response and injury, injury from ischaemic molecules such as free radicals, and damage due to complications from endothelial dysfunction(21).

Multiple factors may contribute to the development of microvascular changes leading to IC. The contribution of infection in the pathogenesis of IC has been explored. *Escherichia coli* (E. Coli) is said to play a role through the production of Shiga-like toxins resulting in endothelial damage of small colonic vessels and resultant fibrin thrombi(7,22,23). Other viruses such as cytomegalovirus (CMV), which damages vascular endothelium, as well as Hepatitis B and C virus, which lead to vasculitis of vessels, may contribute(7,22).

A subgroup of approximately 15-21 percent of IC cases occur in those younger than 45 years(24-26). Causative factors in this group are skewed towards hypercoagulable states, vascular disease, long distance running and constipation(7,14,18). Constipation is an issue for 50% of young patients (<40 years) and 20% of older patients with IC (>40 years)(25).

IC patients will test positive for at least one type of thrombophilia in 28-72% of cases, compared with 8.4% of the general population (19,20,27,28). Thrombophilias commonly found include factor V Leiden (FVL), antiphospholipid antibodies, protein C deficiency and resistance, protein S deficiency, antithrombin III, and prothrombin gene mutations(7,19,20,27,28). Case studies

have suggested routine screening for thrombophilia and anticoagulation treatment if a prothrombotic condition is detected(7,19,28,29). No prospective or case-controlled trials of anticoagulation as treatment or prevention of recurrence have been performed.

A variety of drugs have been associated with IC in case reports and observational studies. These include digoxin, diuretics, non-steroidal anti-inflammatory drugs, cocaine, calcium channel blockers, laxatives, anti-motility medications, anti-hypertensives, neuroepileptics and others(3,14,30,31). These drugs may precipitate IC through mesenteric vasoconstriction or volume depletion(3,18,30). An association between IC and oral contraceptive pill or hormone replacement therapy use has been demonstrated in several case studies, with a RR of 6 for developing IC(32-34). IC is a rare complication from the use of these agents, and cessation of the drug will result in resolution of mild disease.

Anatomical Distribution:

IC can occur in any part of the colon from the caecum to rectum. It was previously thought that IC occurs at areas where there is tenuous blood flow, at 'watershed' zones such as the splenic flexure and rectosigmoid junction. However these areas are only involved in 3-5% and 4.8-25% of cases respectively(1,15,23). The descending colon and sigmoid colon are the most commonly-affected areas reported in 23-80% of cases(3,5,7,14). Right-sided colitis occurs at an incidence of between 4.5–26%(3,5,7,16,28).

Clinical Presentation:

Presenting symptoms of patients with IC include abdominal pain (49.4–73%), diarrhoea (14.2–68%), per-rectal bleeding that is typically self-limiting and does not require transfusion (65–76.5%), and abdominal distension (63%)(1,3,5,6,15). Patients are typically not haemodynamically unstable, unless late presentation with gangrenous IC, and these patients may be tender or show signs of peritonitis(3,5,6,14).

Investigation:

Pathology:

Pathology examination may demonstrate a number of abnormalities including leucocytosis, metabolic acidosis, elevated lactate, and renal failure. These are not specific for a diagnosis of IC and abnormalities are only present in late or severe disease(1,3,6). Stool cultures are useful to rule out infectious causes of colitis(6).

Imaging:

Abdominal X-Ray may exclude other causes of an acute abdomen, such as free gas representative of a perforated viscus, or bowel obstruction. In addition, thumb-printing from submucosal oedema, mural thickening or pneumatosis-coli may be present to suggest IC or other forms of colitis(3,28).

Computed Tomography (CT) scanning with angiography may demonstrate colitis, but is not diagnostic of or able to predict complications of IC(3,35). It may identify other diagnoses such as acute mesenteric ischaemia(3,6,7). Montoro et al present unvalidated criteria for diagnosis of IC on CT scan, interpreted in combination with the clinical picture and the presence of segmental colitis (1). These criteria include segmental wall thickening with signs of submucosal oedema such as irregular margins, mucosal enhancement, or symmetric mural thickening, with or without peri-colic

stranding(1,35). Signs that reflect gangrenous colitis include free fluid or gas, pneumatosis coli and gas within the extra or intrahepatic portal vein(1,35).

Doppler USS may be useful in the diagnosis of IC. Ripolles et al found that altered pericolic fat, absence of improvement in follow-up studies, and absence of arterial wall blood flow are indicators of a poorer outcome and progression to transmural necrosis(36).

Endoscopy:

A range of studies recommend that colonoscopy is undertaken without bowel preparation within 48hrs of symptom onset for the greatest diagnostic yield from visualisation of the mucosa and biopsies(1,3,7,15). Endoscopic appearances vary depending on the time from initial ischaemic injury, and often correlate with severity(1,5,7,37). Common early changes include segmental mucosal oedema, petechial haemorrhages, haemorrhagic submucosal nodules, pale mucosa with areas of hyperaemia, superficial ulcerations, or oedematous mucosa with a single stripe of ulceration(1,3,5-7). Cyanotic or dark mucosa, pseudomembranes, pseudopolyps, pseudotumour appearance or deep extensive ulceration indicate a more severe clinical course(1,5,7,28). Late signs (>7 days) that indicate persistence and lack of resolution include deep ulceration with a similar appearance to ulcerative colitis, which may confuse the clinical picture(7). Many authors highlight concerns regarding the risk of perforation during endoscopy in patients with active colitis, however there is no published data on the incidence of perforation at endoscopy in IC(1,7). Polter et al documents 3 cases of colonic perforation at endoscopy in patients with IC out of a total of 10,534 colonoscopies performed for any indication(38). Colonoscopy was performed in 70-94.8% of IC patients in multiple studies with no perforations reported(1,15,31,39). A number of large reviews identifying risk factors for perforation at endoscopy do not identify colitis or IC as a cause, however these studies mostly examine factors such as indications for endoscopy or symptoms and not

diagnosis(40,41). Some case studies identify IC developing secondary to colonoscopy (42,43). Care should be taken to avoid over-insufflation of the bowel to decrease risk of perforation, and avoid high intraluminal pressures which decrease colonic blood flow and may worsen IC(7,44). The use of carbon dioxide as an insufflation gas may be superior to the use of air due to rapid absorption of the gas and action as a local vasodilator(45). This has never been studied in human trials. It has been suggested that colonoscopy should only be performed until affected mucosa is reached to obtain a diagnosis(46).

Histopathology:

Histopathology examination is helpful in diagnosis of IC, however the changes encountered vary depending on the timeframe from symptom onset and severity. Findings such as infarction of tissue with ghost cells, mucosal and submucosal necrosis or haemorrhage with oedema and fibrin thrombus are highly suggestive of this diagnosis(5,8,28). Other pathological changes include cytologic atypia, pseudomembranes, inflammatory cell infiltration, and haemorrhage into the lamina propria with hyalinization(5,6,31,47). Full thickness or severe mucosal necrosis indicates a more severe presentation(47).

It may be difficult to differentiate between IC and inflammatory bowel disease (IBD) on histopathology alone. The clinical scenario and endoscopic appearance must be considered in combination with pathological findings. Biopsies consistent with IBD may demonstrate basal plasmacytosis of the lamina propria, crypt atrophy or architectural disruption, mucin depletion and epithelioid granulomas(47,48).

Diagnostic Criteria:

Diagnosis of IC is difficult because it presents with non-specific symptoms, can mimic conditions like infectious colitis, and has a clinical course that is often self-limiting. No clearly-defined diagnostic criteria has been published for IC. Diagnosis of IC relies on a combination of clinical history, radiographic findings suggestive of colitis, evidence of colitis at endoscopy, additional support from biopsy or pathology, and exclusion of other causes of colitis such as infective(1,8,14,23,24). This is summarised in Table 1.

Management:

Treatment of IC is determined by its severity, in that conservative medical management is possible in the majority of patients. Patients should be admitted to hospital for monitoring and regular re-evaluation for symptoms indicative of worsening disease(3,37). Precipitating factors such as sepsis, hypotension, poor cardiac function, hypovolaemia and hypoxia should be addressed, and precipitating drugs withdrawn. Fluid resuscitation with intravenous fluids, bowel rest, nasogastric tube if ileus is present, and total parenteral nutrition (TPN) if prolonged bowel rest is required, should be provided(3,7,37). Patients occasionally develop colonic dilatation which can be managed with careful insertion of a rectal tube or endoscopic decompression(28).

Antibiotic use in animal studies has demonstrated reduced duration and severity of IC, and prevention of bacterial translocation through damaged mucosa(3,10,28,49,50). A study involving dogs demonstrated reduction in vessel thrombosis and increased survival when antibiotics were administered to animals with colonic ischaemia-reperfusion(51). The role of antibiotic therapy in limiting the duration and severity of IC in humans requires further research(7).

There is no evidence available on the role of anticoagulation or antiplatelet therapy in acute presentations of IC, prevention of recurrence, or in mitigating death from vascular causes(15). Antiplatelets have an established role in limiting tissue injury in ischaemia and ischaemia-reperfusion events such as stroke and acute myocardial infarction(52). Given the similar pathophysiology of IC, further research into potential benefits of antiplatelets may be warranted. IC is associated with high rates of demonstrable thrombophilia and the role of anticoagulation of these patients has only been suggested in case studies(7,19,29). O'Neill and Yalamarthy recommend heparin prophylaxis as a component of conservative management in these patients, however there is a lack of prospective evidence for its use(15,53). Diagnosis of IC may provide an opportunity for cardio-vascular secondary prevention to mitigate their higher risk of death from vascular related causes than matched controls(15). This may include antihypertensive treatment, diabetes control, smoking cessation advice, anti-arrhythmic therapies, and cholesterol management(1,15,31).

Steroids have not been shown to improve outcomes in IC, and may mask symptoms of deterioration leading to delayed diagnosis and treatment of progressive disease(11,54).

The use of colonic vasodilatory agents in IC lacks evidence. Animal studies exist for a variety of agents including sildenafil, which results in colonic vasodilation and improved microcirculatory function, and L-arginine, a nitric oxide donor, that results in a reduction in tissue damage with accelerated healing(55,56). Intravenous infusion of prostaglandin E1 (PGE1) results in dilation of peripheral vessels and increased colonic blood flow in animal models of IC, and has been used for ischaemic strictures in case studies(57,58). No studies explore the role of arterial vasodilation with papaverine for IC, despite its use in acute occlusive mesenteric ischaemia.

Indications for operative management include presentations with gangrenous disease, universal fulminant colitis, peritonitis, perforation, haemorrhage, mucosal necrosis at endoscopy, a

clinical course beyond 2-3 weeks, and clinical deterioration despite conservative management(3,8,15,16,18,31). Approximately 17% to 28% of IC cases require surgical resection of the ischaemic bowel to well perfused mucosa(37). On-table colonoscopy may be useful to delineate the extent of mucosal involvement. Decision regarding primary anastomosis as opposed to delayed restoration of intestinal continuity is case dependant and requires an assessment of the patient's overall status and confidence regarding vascular supply(31). Patients requiring surgery are often unstable and the majority do require a colostomy(59,60). Some patients may require second-look laparotomy if there is concern about ongoing ischemia(59,60).

Outcomes:

The available literature demonstrates that the majority of patients improve with conservative management.

Predictors of severity include evidence of shock or systemic inflammatory response (tachycardia or systolic blood pressure <100), which confers a mortality of up to 100%(17,61). Evidence of gangrenous or severe disease including signs of peritonitis (RR 23.5), evidence of ileus, and radiographic or endoscopic signs consistent with gangrene increase the risk of surgery and mortality(7,11,17,28,61). The overall mortality of IC is estimated to be 12%(14-16). Patients with right sided IC have a 5 fold increased risk of requiring surgery, and a mortality of 20.3-50%(6,7,16).

Ischemic strictures develop in 0.3-26% of patients. Most of these are asymptomatic, while a minority will present with obstructive symptoms and require surgery(3,7,62). On follow-up endoscopy, asymptomatic strictures resolve spontaneously within 12-24 months(28). Persistent

bloody diarrhoea is a feature in seven percent of patients, and one percent will develop protein-losing colopathy(62). The majority of these patients will resolve with conservative management within 6 months, however surgical resection is curative in those that persist(62). Recurrence occurs in 6.7-13% of patients within 5 years(14,15,62).

Conclusion:

IC is a common presentation requiring admission to surgical wards, however clinicians have a low index of suspicion for this disease. Diagnosis may be difficult given the non-specific presenting symptoms which may be similar to other colonic diseases, and it is important to exclude other diagnoses such as acute mesenteric ischaemia and IBD. The pathophysiology and factors contributing to the development of IC are poorly understood. Clear guidelines for the management of this condition are lacking and there are many areas that warrant further investigation such as the use of vasodilators, anticoagulation and antibiotics. Whilst the majority of patients will resolve with conservative treatment the key to managing this condition successfully is making the diagnosis and ensuring close clinical monitoring to exclude progression of disease or the development of necrosis requiring surgery. Early endoscopic visualisation is a useful diagnostic tool to exclude necrosis on presentation and subsequent progression to full thickness necrosis.

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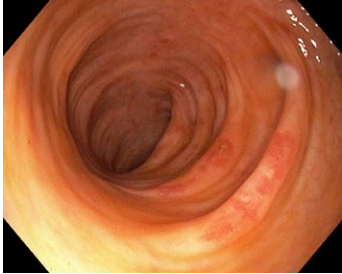
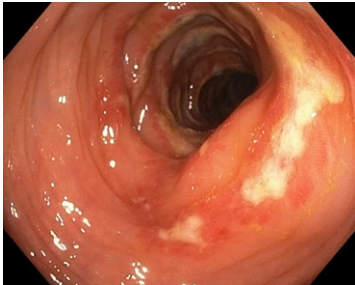
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TABLE 1:
Diagnostic Criteria for Ischaemic Colitis

Clinical	Acute symptoms suggestive of IC	Abdominal pain Diarrhoea Bloody stool
Imaging / Investigations	Evidence of colon inflammation	On endoscopy, radiographically (CT / USS), at operation or at autopsy
Endoscopy	Colonoscopy demonstrating changes consistent with IC	 Patchy mucosal oedema and erythema  Cyanotic / bluish-black mucosal nodules  Superficial ulcerations and (early) pseudomembranes  Cyanotic mucosa with deep ulceration
Histopathology	Evidence of histopathologic changes consistent with IC	From endoscopic biopsy, from surgical specimen or at autopsy
Exclusion	No history of previous or subsequent diagnosis of inflammatory bowel disease	
	Stool culture negative	For C Difficile Salmonella Shigella E Coli Campylobacter
	No history of recent antibiotic use	
	No mechanical obstruction due to any cause	Cancer Volvulus Hernia
	No recent vascular procedures	