

# ACG Clinical Guideline: Epidemiology, Risk Factors, Patterns of Presentation, Diagnosis and Management of Colon Ischemia (CI)

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## **Introduction**

This clinical guideline was designed to address colon ischemia (CI) including its definition, epidemiology, risk factors, presentations, methods of diagnosis, and therapeutic interventions. Each section of the document will present key recommendations or summary statements followed by a comprehensive summary of supporting evidence.

A search of MEDLINE (1946 to present) and EMBASE (1980 to present) with language restriction to English was conducted using the search terms ischemic colitis, ischaemic colitis, colon ischemia, colonic ischemia, colon ischaemia, colonic ischaemia, colon gangrene, colonic gangrene, colon infarction, colonic infarction, rectal ischemia, rectal ischaemia, ischemic proctitis, ischaemic proctitis, cecal ischemia, cecal ischaemia, ischemic colon stricture, ischaemic colon stricture, ischemic colonic stricture, ischaemic colonic stricture, ischemic megacolon, ischaemic megacolon, colon cast, and colonic cast. The references obtained were reviewed and the best studies were included as evidence for guideline statements or in the absence of quality evidence, expert opinion was offered.

The GRADE system (Grading of Recommendations Assessment, Development, and Evaluation) was used to evaluate the quality of evidence and strength of recommendations (1,2). The level of evidence ranged from “high” (implying that further research was unlikely to change the authors’ confidence in the estimate of the effect) to “moderate” (further research would be likely to have an impact on the authors’ confidence in the estimate of effect) to “low” (further research would be expected to have an important impact on the authors’ confidence in the estimate of the effect and would be likely to change the estimate) to “very low” (any estimate of effect is very uncertain). The strength of a recommendation was graded as “strong” when the desirable effects of an intervention clearly outweighed the undesirable effects and as “conditional” when there was uncertainty about the tradeoffs between the desirable and undesirable effects of an intervention. Of note, in this clinical guideline there are several sections focusing on factors associated with prognosis in CI. Because the GRADE system currently is not designed to rate the quality of the literature for these topics, we have preceded each of these sections with “summary statements” that detail the most important concepts regarding each area, but without a GRADE rating.

## **Risk Factors**

### **Summary Statements (GRADE system not applicable)**

1. Comorbid cardiovascular disease and diabetes mellitus should increase consideration of CI in patients with typical clinical features (14,15,20)
2. A history of IBS and constipation should be sought in patients suspected to have CI (8,13,15)
3. Selective cardiology consultation is justified in patients with CI, particularly if a cardiac source of embolism is suspected (134)
4. Chronic kidney disease is associated with increased mortality from CI (7,24,25)
5. Evaluation for thrombophilia should be considered in young patients with CI and all patients with recurrent CI (26–28)
6. Surgical procedures in which the inferior mesenteric artery (IMA) has been sacrificed, such as abdominal aortic aneurysm repair and other abdominal operations, should increase consideration of CI in patients with typical clinical features (14,29,30)
7. In patients suspected of having CI, a history of medication and drug use is important, especially constipation-inducing medications, immunomodulators, and illicit drugs (9,15,31)

## **Clinical Presentation**

### **Recommendations**

1. The diagnosis of CI is usually established in the presence of symptoms including sudden cramping, mild, abdominal pain; an urgent desire to defecate; and passage within 24 h of bright red or maroon blood or bloody diarrhea. (Strong recommendation, very low level of evidence) (7,9,17)
2. A diagnosis of non-isolated right colon ischemia (non-IRCI) should be considered when patients present with hematochezia. (Strong recommendation, very low level of evidence) (7,9,17)

### **Summary Statement (GRADE system not applicable)**

1. IRCI is associated with higher mortality rates compared with other patterns of CI (7,17)

<b>Table 3. Drugs proposed to predispose to CI, estimate of evidence level, and postulated pathogenesis</b>		
<b>Drug</b>	<b>Evidence</b>	<b>Postulated pathogenesis</b>
<i>Moderate evidence</i>		
Constipation-inducing drugs	Predicted CI in patients with abdominal pain, 2.8 (1.1–7.1); (39) All drugs: C-CS; increased risk 0.68 (0.62–1.27); (14) Opioids: C-CS; increased risk 1.96 (1.43–2.67); (32) Nonopioids: C-CS; increased risk 1.75 (1.25–2.44); (32)	Reduced blood flow, increased intraluminal pressure (48)
Immunomodulator drugs	Antitumor necrosis factor- $\alpha$ inhibitors for rheumatoid arthritis from US FDA AERS: 17 probable, 18 possible cases; median age, 62 years <sup>a</sup> (157) Type 1 interferon- $\alpha$ for hepatitis C: 13 probable, 4 possible cases; median age, 51 years <sup>a</sup> 11 other reported cases (158) Type 1 interferon- $\beta$ for multiple sclerosis: 19 probable, 20 possible cases; median age, 56 years 10 other reported cases of interferon for hepatitis C, 8 age <55 years (159)	Cytokines affecting thrombogenesis (33)
Illicit drugs	Amphetamines: 5 reported cases; age 42–50 years (33,160) Cocaine: used by 19 of 97 (20%) CI patients at 2 inner-city hospitals; age 44–56 years; 37% right-sided and 16% small bowel disease; 26% mortality (31) Many other reported cases of multiple ischemic organs (33)	Vasoconstriction, hypercoagulation, direct endothelial injury (33)
<i>Low evidence</i>		
Antibiotics	Antibiotic-associated colitis resembles CI, usually right-sided (33) C-CS: increased risk CI, 3.3 (2.19–4.96); (32)	Altered gut microbiome, e.g., <i>Klebsiella oxytoca</i> (161)
Appetite suppressants	<i>Bitter orange</i> (resembles ephedra): 1 reported case (162) <i>Hydroxycut</i> : 1 probable case (163) <i>Ma huang</i> (mainly ephedrine): 1 reported case (164) <i>Phentermine</i> : 2 reported cases (1 with fenfluramine) (33,165) <i>Xenadrine</i> (bitter orange, ma huang, caffeine, salicin): 1 reported case (166) 3 of 5 cases age <50 years	Vasoconstriction (33)

**Table 3.** Drugs proposed to predispose to CI, estimate of evidence level, and postulated pathogenesis  
*continued*

Drug	Evidence	Postulated pathogenesis
Chemotherapeutic drugs	<i>R-CHOP</i> : 1 reported case (167) <i>Taxanes</i> : 10 reported cases (33,168–170) <i>Vinorelbine/cisplatin</i> : 1 reported case (33) C-CS: increased use of taxanes or vinca alkaloids on univariate analysis (32)	Direct epithelial toxicity, inhibited repair of vascular injury (33)
Decongestants	Pseudoephedrine: 9 reported cases, 6 age <50 years (33,171) C-CS: risk unaffected 1.1 (0.3–3.9); (10) Phenylephrine: 1 reported case (172)	Vasoconstriction (33)
Diuretics	C-CS: increased risk 1.6 (1.2–2.1); (10)	Extracellular volume deficit, lower peripheral vascular resistance, vasoconstriction (33)
Ergot alkaloids (often combined with caffeine)	20 Reported cases (33,173)	Extracellular volume deficit, lower peripheral vascular resistance, vasoconstriction (33)
Hormonal therapies	Predominance of women among young patients, (9,174) common use of female hormones by female patients (175) <i>Female hormones</i> : C-CS; increased risk 1.88 (1.30–2.73); (32) <i>Oral contraceptives</i> : C-CS; increased risk 1.05 (1.00–1.10); (15) risk unaffected 0.59 (0.28–1.33) (14); 0.7 (0.3–1.5) (10) <i>Estrogen replacement</i> : C-CS; risk unaffected 0.75 (0.67–1.19) (14) 1.0 (0.7–1.5); (10)	Hypercoagulability, endothelial injury (33)
Laxatives	<i>Osmotic agents</i> : 2 reported cases (33) <i>Bisacodyl</i> : 2 reported cases (33) <i>Bisacodyl/polyethylene glycol</i> : 1 reported case of 2 episodes (176) <i>Lubiprostone</i> : 1 reported case (177) All drugs: C-CS; increased risk 4.73 (3.71–6.02); (15)	Increased motility or rapid intravascular volume deficit, reduced perfusion (33)
Psychotropic drugs	6 Reported cases (2 with hypotension) (33,178,179) 10 cases, clinical/pathological data incomplete (180) C-CS: increased risk 3.7 (1.3–11.0); (10)	Hypotension, constipation
Serotonergic drugs	5-Hydroxytryptamine receptor agonists: 12 cases from US FDA AERS, 8 age <50 years (33,181–183) C-CS: risk unaffected 2.3 (0.8–6.9); (10) 5-hydroxytryptamine receptor antagonist: 1 case of CI/1,000 patient-years of use (35) 5-hydroxytryptamine partial agonist: 27 reported cases (drug withdrawn) (184)	For 5-hydroxytryptamine receptor agonists vasoconstriction (33); for other agents various factors (184)

<b>Table 3. Drugs proposed to predispose to CI, estimate of evidence level, and postulated pathogenesis</b> <i>continued</i>		
<b>Drug</b>	<b>Evidence</b>	<b>Postulated pathogenesis</b>
<i>Very low evidence</i>		
Digitalis	1 Reported case (poisoning) (33) <i>Digoxin</i> : C-CS; increased risk 3.6 (2.1–6.2); (10); (atrial fibrillation not analyzed); decreased risk 0.27 (0.083–0.86); (20)	Vasoconstriction
Kayexalate	1 Reported case (185) 44 cases of colon injury with incomplete pathological data, (186)	Direct toxic effect, various nondrug factors (185,186)
NO-Xplode	1 Reported case (187)	Blood shunting to skeletal muscle, hypo- perfusion, various non-drug factors (187)
NSAIDs	Reported cases not clearly distinguishable from NSAID-induced colopathy (33) C-CS: risk unaffected 0.9 (0.6–1.2); (10); 0.68 (0.62–1.27); (188)	Inhibition of vasodilating prostaglandins, vasoconstriction (33)
Statins	2 Reported cases (33,189)	None
Vasopressors	1 Reported case (33)	Vasoconstriction
C-CS, case-control study (followed by odds ratio (95% confidence interval)); CI, colon ischemia; NSAID, nonsteroidal anti-inflammatory drug; R-CHOP, rituximab, cyclophosphamide, vincristine, doxorubicine, prednisolone; US FDA AERS, United States Food and Drug Administration Adverse Event Reporting System. <sup>a</sup> Classified by the criteria of Naranjo <i>et al.</i> (163).		

### **Laboratory Testing in CI**

#### **Summary Statements (GRADE system not applicable)**

1. Laboratory testing should be considered to help predict CI severity (17,94,107)
2. Decreased hemoglobin levels, low serum albumin, and the presence of metabolic acidosis can be used to predict severity of CI (141,142)

<b>Table 5. Recommended initial serology and stool studies for suspected colon ischemia (CI)</b>
<i>Blood tests</i>
Albumin
Amylase
Complete blood count
Comprehensive electrolyte panel
Creatine kinase (CK)
Lactate
Lactate dehydrogenase (LDH)
<i>Stool tests</i>
<i>Clostridium difficile</i> toxin assay
Culture
Ova and parasite

## **Imaging of CI**

### **Recommendations**

1. CT with intravenous and oral contrast should be the first imaging modality of choice for patients with suspected CI to assess the distribution and phase of colitis. (Strong recommendation, moderate level of evidence) (111–113)
2. The diagnosis of CI can be suggested based on CT findings (e.g., bowel wall thickening, edema, thumbprinting). (Strong recommendation, moderate evidence) (111–113)
3. Multiphase CTA should be performed on any patient with suspected IRCI or in any patient in whom the possibility of AMI cannot be excluded. (Strong recommendation, moderate level of evidence) (113,114)
4. CT or MRI findings of colonic pneumatosis and porto-mesenteric venous gas can be used to predict the presence of transmural colonic infarction. (Strong recommendation, moderate level of evidence) (115)
5. In a patient in whom the presentation of CI may be a heralding sign of AMI (e.g., IRCI, severe pain without bleeding, atrial fibrillation), and the multiphase CT is negative for vascular occlusive disease, traditional splanchnic angiography should be considered for further assessment. (Conditional recommendation, low level of evidence) (114)

## **Colonoscopy in the Diagnosis of CI**

### **Recommendations**

1. Early colonoscopy (within 48 h of presentation) should be performed in suspected CI to confirm the diagnosis. (Strong recommendation, low level of evidence) (17)
2. When performing colonoscopy on a patient with suspected CI, the colon should be insufflated minimally. (Conditional recommendation, very low level of evidence) (69,135)
3. In patients with severe CI, CT should be used to evaluate the distribution of disease. Limited colonoscopy is appropriate to confirm the nature of the CT abnormality. Colonoscopy should be halted at the distalmost extent of the disease. (Strong recommendation, low level of evidence)
4. Biopsies of the colonic mucosa should be obtained except in cases of gangrene. (Strong recommendation, very low level of evidence)
5. Colonoscopy should not be performed in patients who have signs of acute peritonitis or evidence of irreversible ischemic damage (i.e., gangrene and pneumatosis). (Strong recommendation, very low level of evidence)

## **Severity and Treatment of CI**

### **Recommendations**

1. Most cases of CI resolve spontaneously and do not require specific therapy. (Strong recommendation, low quality of evidence) (107,108,139)
2. Surgical intervention should be considered in the presence of CI accompanied by hypotension, tachycardia, and abdominal pain without rectal bleeding; for IRCI and pan-colonic CI; and in the presence of gangrene. (Strong recommendation, moderate level of evidence) (17,107,108)
3. Antimicrobial therapy should be considered for patients with moderate or severe disease. (Strong recommendation, very low level of evidence) (107,108,140)

### **Summary Statement (GRADE system not applicable)**

1. When considering mortality risk for patients undergoing surgical intervention for acute CI, the Ischemic Colitis Mortality Risk (ICMR) factors should be utilized (141,142)

<b>Table 6. Classification of disease severity and management</b>		
<b>Disease severity</b>	<b>Criteria</b>	<b>Treatment</b>
<b>Mild</b>	Typical symptoms of CI with a segmental colitis not isolated to the right colon and with none of the commonly associated risk factors for poorer outcome that are seen in moderate disease	Observation Supportive care
<b>Moderate</b>	Any patient with CI and up to three of the following factors:	Correction of cardiovascular abnormalities (e.g., volume replacement) Broad-spectrum antibiotic therapy Surgical consultation
	Male gender	
	Hypotension (systolic blood pressure <90 mm Hg)	
	Tachycardia (heart rate >100 beats/min)	
	Abdominal pain without rectal bleeding	
	BUN >20 mg/dl	
	Hgb <12 g/dl	
	LDH >350 U/l	
	Serum sodium <136 mEq/l (mmol/l)	
	WBC >15 cells/cmm ( $\times 10^9$ /l)	
	Colonic mucosal ulceration identified colonoscopically	
<b>Severe</b>	Any patient with CI and more than three of the criteria for moderate disease or any of the following:	Emergent surgical consultation (treatment is likely to be surgical) Transfer to intensive care unit Correction of cardiovascular abnormalities (e.g., volume replacement) Broad-spectrum antibiotic therapy
	Peritoneal signs on physical examination	
	Pneumatosis or portal venous gas on radiologic imaging	
	Gangrene on colonoscopic examination	
	Pancolonic distribution or IRCI on imaging or colonoscopy	
BUN, blood urea nitrogen; CI, colon ischemia; Hgb, hemoglobin; IRCI, isolated right-colon ischemia; LDH, lactate dehydrogenase; WBC, white blood cell count.		

Algorithm for the management of patients suspected of having colon ischemia

Clinical assessment, vital signs, serology (WBC, Hgb, BUN, LDH, electrolytes)

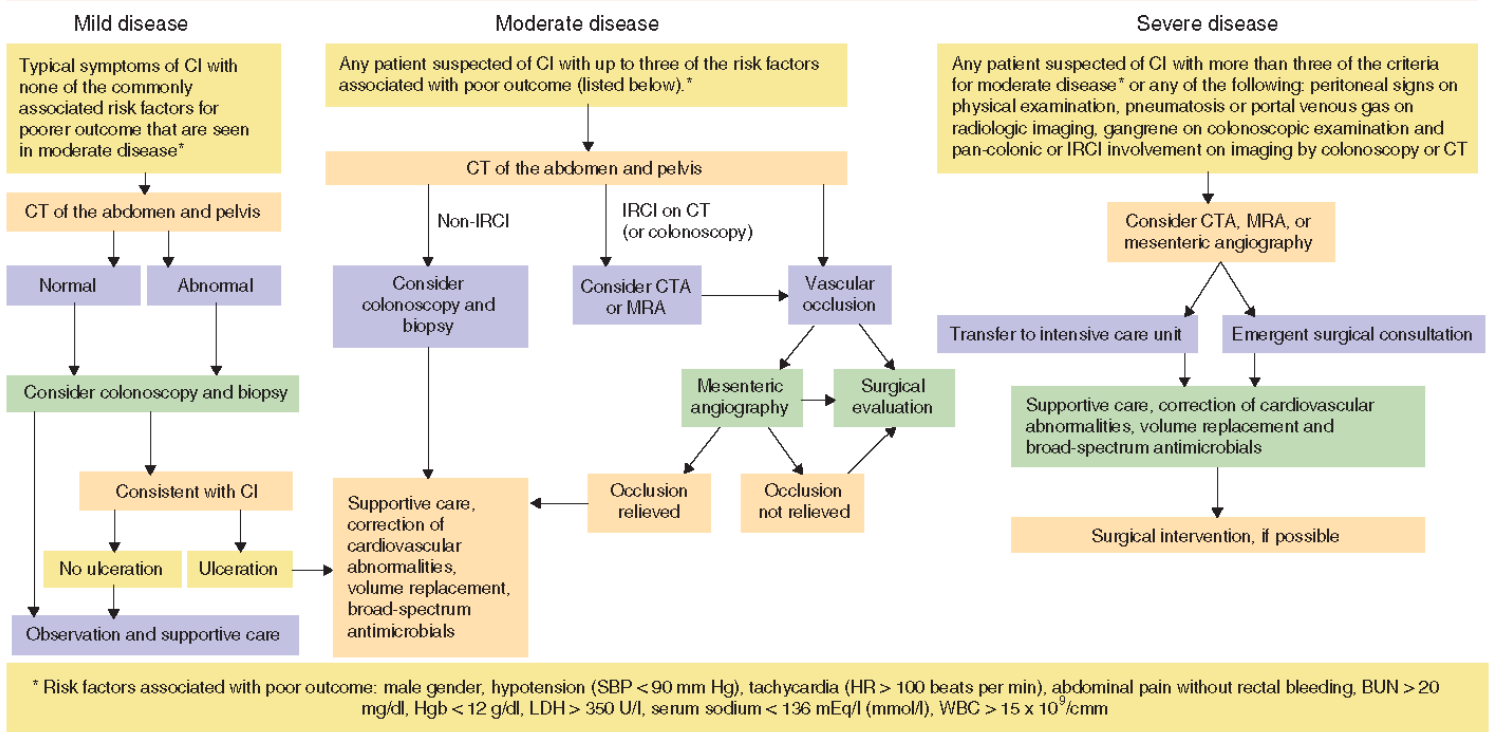


Figure 1. Diagnosis and treatment of colon ischemia (CI) based upon disease severity. BUN, blood urea nitrogen; CT, computed tomography; CTA, computed tomography angiography; Hgb, hemoglobin; IRCI, isolated right-colon ischemia; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; WBC, white blood cell count.

<b>Table 9.</b> Indications for surgery in colonic ischemia
<i>Acute indications</i>
Peritoneal signs
Massive bleeding
Universal fulminant colitis with or without toxic megacolon
Portal venous gas and/or pneumatosis intestinalis on imaging
Deteriorating clinical condition
<i>Subacute indications</i>
Failure of an acute segmental ischemic colitis to respond to treatment within 2–3 weeks with continued symptoms or a protein-losing colopathy
Apparent healing but with recurrent bouts of sepsis
<i>Chronic indications</i>
Symptomatic colon stricture
Symptomatic segmental ischemic colitis