

# Diagnostic methods and drug therapies in patients with ischemic colitis

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## Abstract

**Purpose** Ischemic colitis (IC) is the most prevalent ischemic injury of the gastrointestinal tract. Clinical features of IC such as acute abdominal pain, hematochezia, and diarrhea are similar to those of acute mesenteric ischemia, inflammatory bowel disease, or infectious bowel disease, and their relative ambiguity can delay diagnosis and treatment. To comprehensively detail the current state of diagnostic methods and available drug therapies for detecting and treating IC, this review aims to provide a concise and practical summary of the corresponding literature.

**Methods** PubMed and Cochrane Library were searched to retrieve all published studies reporting the diagnostic methods and drug therapies in patients with ischemic colitis. The search strategy of drug therapy includes human and animal data.

**Results** Colonoscopy combined with histopathological biopsy is the standard of diagnosis for the IC. Most patients respond well to the conservative treatment, and surgical consultation is needed when conservative treatment is ineffective. Studies of potential drug therapy have been developed, including phosphodiesterase type 5 inhibitors, pentoxifylline, rebamipide, prostaglandin E1, and polydeoxyribonucleotide.

**Conclusion** Accurate diagnoses and effective treatments have helped reduce the mortality rate and improve prognoses for patients afflicted with IC, and corresponding drug therapies have been constantly updated as new research has emerged.

**Keywords** Ischemic colitis · Diagnosis · Drug therapy · Review

## Introduction

Ischemic colitis (IC) includes a group of clinical syndromes with existence of vascular occlusive or nonocclusive diseases, and is characterized by colonic blood supply deficiencies [1, 2]. The overall aged-adjusted and sex-adjusted incidence rates of IC in the general population were 16.3 cases per 100,000 individuals. IC is more common among individuals older than 65 years and increases in prevalence with age [3], and the incidence of colon ischemia in females is higher than in males [1]. The incidence of IC has increased nearly fourfold within 34 years, especially in relatively older patients with multiple comorbidities [3]. With the greater awareness of the impacts

of IC, a rapidly aging population, and the rising incidence of blood vessel diseases, it is estimated that the prevalence of IC will continue to increase, especially over the next few or several years.

On the basis of clinical and experimental work in the laboratory, Marston et al. firstly proposed in 1966 that IC can be divided into gangrenous, stricturing, and transient forms [4]. Brandt and Boley later classified intestinal ischemia into types according to the degree of the histopathological damage in the colonic tissue which included reversible colopathy, transient colitis, chronic colitis, stricture, fulminant universal colitis, and gangrene [5]. However, IC has emerged as the most common type of intestinal ischemia.

Thus, the goals of this narrative-based review mainly concentrate upon three aspects. Firstly, we sought to examine the hypothesis that it is necessary to timely identify the people with an increased risk of IC. Secondly, based upon examinations of the latest reference materials, we sought to provide relevant and current information regarding diagnostic methods for IC. Finally, we summarize the current states and

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efficacies of drug therapies for IC and focus on emerging drugs.

## Methods

Two independent authors (YSX, LNX) searched PubMed and the Cochrane Library to identify studies regarding the diagnostic methods and drug-based treatments for IC. The search terms used were “ischemic colitis” (MeSH terms) OR “ischemic colitis” (title/abstract) OR “intestinal ischemia” (title/abstract) AND “diagnosis” (MeSH terms) OR “diagnosis” (title/abstract) OR “diagnoses” (title/abstract) OR “Treatment” (MeSH terms) OR “Treatment” (title/abstract) OR “Therapeutic” (title/abstract) OR “therapies” (title/abstract) OR “therapy” (title/abstract) OR “Treatments” (title/abstract). Author YSX screened titles and abstracts of all initially selected potentially relevant publications, and selected the relevant abstracts. The second author (LNX) revisited the selected abstract. Any divergence between the first and second authors was resolved through discussion with a third author (YNL). Language restrictions were applied to include only English. Articles published within the last 5 years were considered as part of the prioritized list. If studies were based upon a series, or were duplicated, only the most complete and recent reports or outcomes were included.

## Observations and discussion

### Diagnostic methods

Systematic-based searches produced 3105 records after elimination of duplicates from the two databases. After initial screening and review of titles and abstracts, 74 full-text articles were included as potentially relevant for subsequent assessments.

### Identification of people at risk

Age is one of the important risk factors for IC. According to statistics, the annual incidence rate of IC ranged from as low as 1.1 per 100,000 among people under 40 years of age to as high as 107 per 100,000 for people exceeding 80.3 years old [3]. Additionally, IC is most prominent among elderly females [6]. A retrospective study from South Korea found that 78% of patients with acute nonocclusive ischemic colitis also had a variety of diseases including cancer, hypertension, coronary artery disease, diabetes, kidney disease, respiratory disease, and cirrhosis. Hypertension was the most common co-occurring diseases (46%), followed by diabetes, kidney disease, and coronary artery disease [7]. Approximately 35% of patients with segmental and non-gangrenous ischemic colitis

also had a “proven” potential source of cardiac embolism (mainly persistent or paroxysmal atrial fibrillation) [8]. Patients with acute myocardial infarction complicated with cardiogenic shock also can develop IC, and the application of vasoconstrictor in cardiopulmonary resuscitation may contribute to this process [9]. Phlebosclerotic colitis is a rare but increasingly recognized cause of IC related to venous obstruction [10]. Systemic lupus erythematosus can also be complicated by IC [11]. Thus, IC is both prevalent, and complicated by other also relatively common afflictions and diseases, which complicates its management.

The factors related to IC, such as including some drugs, pathogenic microorganisms, hereditary coagulative disorders, strenuous physical activity, abdominal fat accumulation, and smoking also can affect the occurrence of IC [12–14]. Drugs related to IC are known to include diuretics, antibiotics, anti-hypertensive drugs, digoxin, nonsteroidal anti-inflammatory drugs, oral contraceptives, pseudoephedrine, cocaine abuse, and interferon [1, 2, 13]. A recent application-based study from FDA’s Adverse Event Reporting System (FAERS) revealed that chemotherapeutic drugs, immunosuppressive agents, sex hormones, and anticoagulants may promote the occurrence and development of IC [13]. Likewise, influenza-fighting oseltamivir could increase the risk of IC. Patients taking baloxavirmarboxil, a novel oral anti-influenza medication, may also be at risk of developing IC with hematochezia [15]. Other possible correlated drug factors reported in recent years include rizatriptan, a cure for migraines; nintedanib, a protein kinase inhibitor; and intravitreal injections of antivascular endothelial growth factor agents; however, relative measures of their relevance require further study [16–18]. For pathogenic microorganisms, many recent clinical case reports have indicated that COVID-19 patients had small-bowel ischemia and a hypercoagulable state [19, 20].

IC is also an iatrogenic complication that can arise following surgical repairs of abdominal aortic aneurysms and after cardiovascular surgery [21]. Gangrenous IC following lung wedge resection has also been reported [22]. Even rarer have been reports of IC following colonoscopy and colonic ischemia after vaginal delivery [23, 24]. In addition, relatively young aged persons who habitually smoke are more likely to develop IC [25]. Constipation is also considered to be a risk factor for the development of IC and may be related to the decrease of blood flow caused by compression of the blood vessels as due to increased intraluminal pressures [26]. Frequent use of laxatives also may aggravate the IC and even cause associated perforations [27]. Stercoral colitis is a rare yet serious inflammatory process secondary to fecal impaction and, in rare cases, may be complicated by IC. Stercoral colitis complicated with IC can further lead to focal ulceration, perforation, peritonitis, septic shock, or even death if there is a lack of prompt diagnosis and treatment [28].

## Clinical presentation and signs

The clinical manifestations of IC largely depend upon the degree of ischemia and the site of involvement [29]. Abdominal pain, hematochezia, and diarrhea are the most common presenting symptoms. Abdominal pain is usually described as an “acutely emerged, cramping pain,” often accompanied by the urge to defecate [2]. Eating can aggravate the symptoms of abdominal pain; thus, the loss of appetite and refusal of food are common in IC-afflicted patients. Usually, bloody stools may occur within 24 h, but bleeding tends not to be severe. For patients with ischemia isolated to the right side of the colon (IRCI), abdominal pain is usually severe, accompanied by rectal bleeding, and prognoses are poor. It is noteworthy that these patients may not bleed at all [29]. In addition, the effusion of intestinal liquid, intestinal mucosal injury, and necrosis can also cause diarrhea. Other common symptoms include abdominal distention, nausea, and vomiting [26]. Symptoms in severe cases may appear as systemic inflammatory response (SIRS) including sepsis, tachypnea, and tachycardia [2].

The left side of the colon is the most frequently involved portion, followed by the distal colon, right colon, transverse colon, and pan colon [30]. Patients often have acute abdominal pain and lower gastrointestinal bleeding when the left colon is involved, and the prognosis is relatively good. When the right colon is involved, patients mostly present with acute severe abdominal pain, hematochezia, and/or diarrhea. This is mostly related to the stenosis or occlusions of the superior mesenteric artery, and most commonly seen in patients with sepsis, hypotension, shock, or chronic renal failure requiring hemodialysis. Patients with IRCI usually have worse prognoses and require a greater degree of attention to avoid delays in diagnoses and treatments [1, 29].

Upon physical examination, the majority of patients have mild-to-severe abdominal tenderness in the corresponding site of the colon ischemia [1, 31]. The most common clinical signs of gangrenous colitis include severe abdominal tenderness, rebound pain, fever, the weakening or disappearance of abdominal rumbling sounds, or even shock. In the intensive care unit, many symptoms such as abdominal pain are not obvious in patients undergoing intubation and sedation; therefore, such symptoms are easily neglected [32].

## Laboratory tests

Routine laboratory tests are of some value in assessing the degree of IC, but are limited with respect to early diagnosis. Relevant laboratory tests include complete blood count, comprehensive metabolic panel (CMP), serum lactic acid, lactate dehydrogenase (LDH), D-dimer, creatine kinase (CK), amylase, fecal culture, fecal examination, and determination of clostridium difficile toxin [1, 33]. However, these parameters

lack sensitivity and specificity. D-Lactate (D-lac), a stereoisomer of L(+)-lactic acid in serum, may be a potential biomarker for the early diagnosis of acute mesenteric ischemia (AMI) [34]. For example, the pooled sensitivity and specificity for D-lactate were 71.7% and 74.2%, respectively [35]. Plasma D-lactate levels are also considered to be a useful marker for early diagnosis of IC secondary to aortic surgery [36]. The intestinal fatty acid-binding protein (I-FABP) has value for diagnosing intestinal mucosal damage and has been widely studied as a plasma-based marker. I-FABP may be a useful diagnostic marker to identify acute intestinal ischemia in for acutely affected abdomens [37, 38]. About 72% of IC-afflicted patients also have one or more concomitant prothrombin abnormalities [39], and the risk for thrombosis should be evaluated in young and recurrent patients [1].

Single factor analysis completed by Miguel et al. suggested that the following test results are indicative risk factors for an unfavorable outcome: leukocyte  $> 15 \times 10^9/L$ , hemoglobin  $< 12$  g/dL, albumin  $< 2.8$  g/L, and additional metabolic acidosis and liver biochemical tests showing abnormal results [31]. In addition, serum procalcitonin (PCT) was found to have been correlated with the colonoscopy-based assessment of the severity of post-operative ischemic colitis (POIC) and can guide therapeutic decisions [40].

## Imaging examination

Abdominal plain film has no obvious advantages in the diagnosis of IC, but it can be used to rule out other emergencies such as organ perforations or intestinal obstructions [2]. Barium enema examinations have almost entirely been replaced by CT imaging or colonoscopy because of its low sensitivity. Barium enema examinations also can aggravate intestinal ischemia injury or even cause perforation, and contrast agent residues may influence the follow-up CT imaging or endoscopic examination [2, 26].

Ultrasound is a noninvasive imaging-based examination and is sensitive to the early structural changes in colonic walls caused by ischemia. Lopez et al. [41] found that the positive predictive value (PPV) of abdominal ultrasound in detection of IC was 87.5%. A retrospective study reported that the predictive model consisting of sonographic features and clinical findings could accurately predict the outcomes of IC affliction and distinguish properly between patients with mild and severe cases of IC [42]. For high-risk cases or patients with contraindications, ultrasound can be regarded as an alternative diagnostic technique for colonoscopy. However, findings from ultrasounds for colonic wall thickening are nonspecific and should be differentiated from other causes.

A prospective study proposed that magnetic resonance imaging (MRI) can be used as an alternative to invasive examinations for the diagnosis of and follow-up examinations of patients afflicted with acute IC [43]. Mesenteric angiography

examinations have proven to hold no great importance for the diagnosis of non-vascular occlusive ischemic damage, but they have obvious advantages in the detection of mesenteric vascular atherosclerosis and thromboembolism. For patients with suspected acute mesenteric ischemia or isolated right-sided ischemia disease, multiphasic CT angiography (CTA) is recommended [1, 44].

The common computed tomography (CT) manifestations of IC include colonic wall thickening, edema, thumbprinting, bowel dilatation, and effusion of intestinal circumference, sometimes with “double halo” or “target” signs [2, 26, 45]. Pneumatosis and portal venous gas are also possible manifestations, and these findings may be the results of transmural ischemia and subsequent bacterial translocation [46, 47]. The haustra of the large intestine becomes thicker and projects into the intestine at regular intervals, leading to the appearance of thumbprinting. This radiographic-based signature can also be seen in the exacerbations of inflammatory bowel disease (IBS) and infectious colitis like pseudomembranous colitis [48]. Iacobellis et al. [49] retrospectively analyzed the CT-based manifestations of 32 patients with confirmed IC afflictions at different phases (i.e., acute, subacute, and chronic). Their findings suggested that CT-based methods were able to distinguish between occlusive and nonocclusive ischemic damage by evaluating the morphofunctional alterations associated with IC, and that such methods can also be used for assessing the timing of ischemic damage.

### Colonoscopy

Colonoscopy, which can help make a definite diagnosis by directly observing the colonic mucosa and obtaining biopsy specimens, has been regarded as the gold standard method for the diagnosis of IC in recent years [1, 29]. Under the condition of hemodynamic stability and without contraindications like acute peritonitis or evidence of irreversible ischemic damage, early colonoscopies should be performed for patients with suspected IC within the first 2–3 post-onset of symptoms [1, 2]. The most frequent observations in patients with the early onset of IC are edematous, and fragile mucosa, segmental erythema, petechial hemorrhages, longitudinal ulcer, and lesions are always segmented and patchily distributed [2, 50]. “Single stripe” refers to a single line of erythema with inflammatory erosion or ulceration along the longitudinal axis of the colon, and is highly specific [1, 29]. In a few rare cases, IC lesions can form tumor-like lesions that are similar to malignant tumors [51, 52].

Intestinal mucosal biopsy-based examinations are recommended for patients with IC (except gangrenous IC). The common pathologic features of IC include mucosal and submucosal hemorrhage and edema, erosion, granulation tissue hyperplasia, gland atrophy, macrophage cells

containing hemosiderin, and inflammatory infiltration of lamina propria [1, 2, 53, 54]. Infarction and “ghost cells” are the most specific pathological manifestations, but are relatively rare [55]. Moreover, it is worth mentioning that confocal laser endomicroscopy (CLE) was able to, in real time, display the cellular and subcellular details correlating with histopathology *in vivo*, and was used to identify “ghost glands” [56].

### Drug therapy

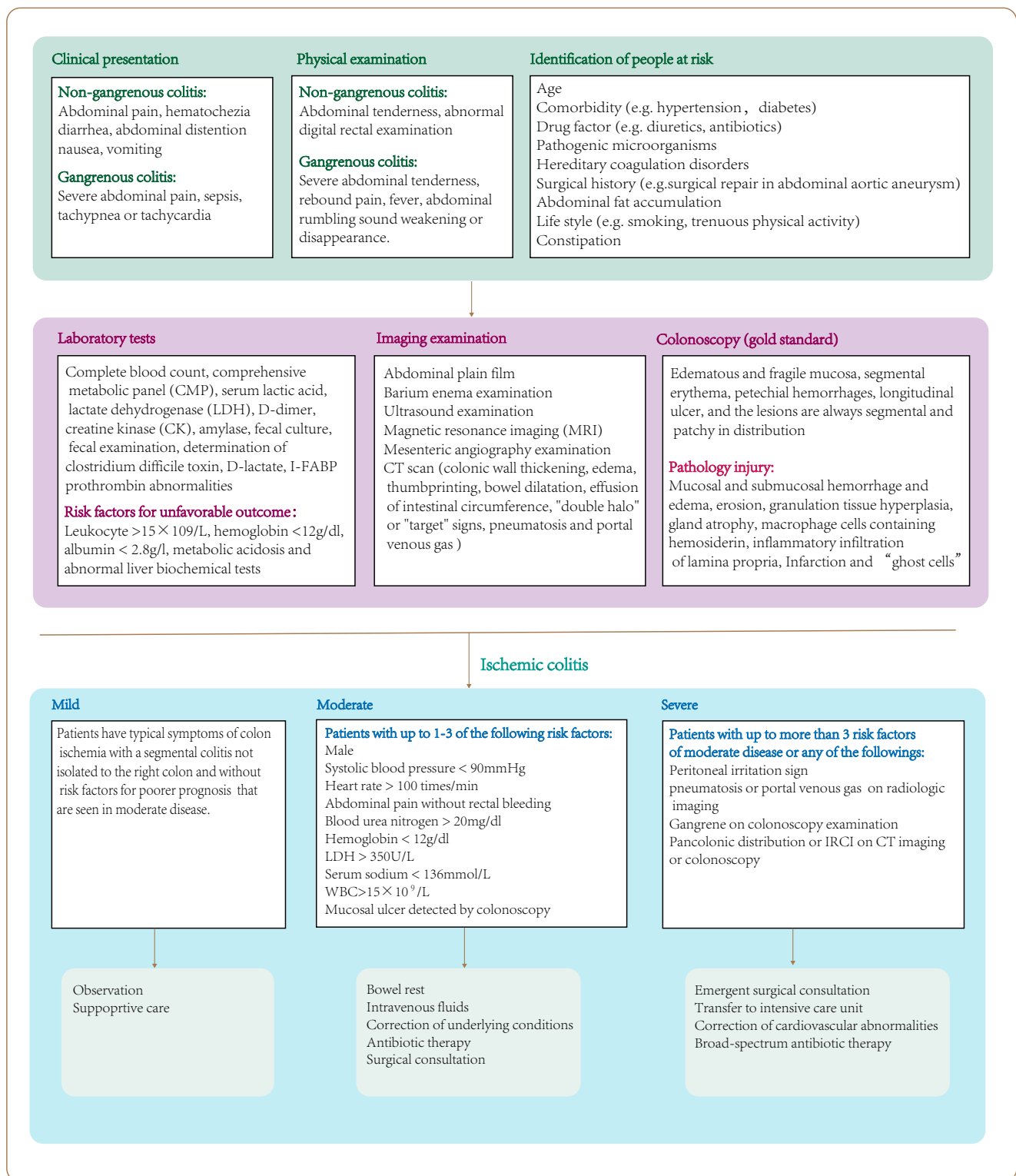
The American College of Gastroenterology (ACG) clinical guidelines suggest the redefinition of the severity of colon ischemia such as to better guide treatments [1], and corresponding diagnostic methods and severity classifications of IC are shown in Fig. 1. Patients with mild diseases such as transient ischemic colitis do not usually require special treatment, and their prognoses are good. Hospitalization is recommended in cases with more significant symptoms or signs. The major therapy measures presently employed mainly include bowel rest, intravenous fluids, correction of underlying conditions, and antibiotic therapies. For the patients with colon ischemia complicated with hypotension, tachycardia, abdominal pain without rectal bleeding, afflicted by gangrene, and or that have lesions isolated to the right side of the colon and pan colon, surgical consultation should be considered [1]. Positive surgical treatments in patients with multiple organ failure and findings of severe forms of ischemia at endoscopy are recommended [57]. In the prior decade, drugs used to treat IC have proven to be controversial; however, some new targets for medical therapy have been identified and hold promise. Some relevant insights into drug therapy and their results are presented in Fig. 2.

### General treatment

Conservative measures including fasting and bowel rest can reduce oxygen demand in the colon and help to prevent IC-related symptoms. Meanwhile, intravenous fluids, optimizing cardiac status, and supplemental oxygen are also recommended to enhance the perfusion of the large bowel [1, 26, 58]. If a protracted course of treatment is expected, administration of total parenteral nutrition may be required. Nasogastric intubation treatments should be used if patients show signs of intestinal obstruction [1]. In addition, discontinuation of IC-related drugs such as constipation-inducing medications, immunomodulators, and vasoconstrictor should be undertaken [29].

### Antibiotic

Although only based upon relatively very low levels of evidence, antimicrobial therapies have been recommended for patients with moderate or severe colon ischemia. One such



**Fig. 1** The diagnosis methods and severity classification of ischemic colitis

ACG-recommended antimicrobial regimen is an anti-aerobic antibiotic combined with agents against Gram-negative bacteria like fluoroquinolone or aminoglycoside, or, alternatively, cephalosporin of the third generation [1, 58]. Using antibiotics was found to have effectively reduced

pathogenic bacteria and bacterial translocation, and reduced overall inflammatory responses to ischemic injury [59, 60]. ACG guidelines proposed that antibiotics should be used for at least 72 h, and proposed that a 7-day course of treatment should be considered if the clinical symptoms have improved



Drugs	Suitable crowd	Mechanisms of action	Source of literature
<b>Antibiotic</b> Anti-anaerobic antibiotic combined with agents against Gram-negative bacteria	Patients with moderate or severe ischemic colitis	Reduce pathogenic bacteria Decrease the overall inflammatory response to ischemic injury. Minimize bacterial translocation and the risk of mucosal disruption.	Brandt, L.J. et al. [1]
<b>Anticoagulant and antiplatelet drug</b> Heparin prophylaxis  Iloprost	Patients with acute superior mesenteric thrombosis Patients with cardiovascular disease Patients with segmental, non gangrenous IC complicated with potential cardiac sources of embolism  Animal experiments	Prevent the formation of thrombus and embolization  Inhibite leukocyte infiltration, reduce proinflammatory cytokines, promote angiogenesis, or reduce oxidative stress and inflammatory response,	Hourmand-Ollivier, I. et al. [8] Leardi, S. et al. [62] Huguier, M. et al. [63]  Karatepe, O. et al. [64]
<b>Glucocorticosteroids</b> Combination of intravenous antibiotics and intravenous prednisolone on severe IC	Patients with severe ischemic colitis .	Reduce the damage of mucosal integrity and bacterial translocation Suppress local immune reactions	Kruis, W et al. [67]
<b>Potential drugs</b> Phosphodiesterase type 5 inhibitors (Vardenafil, Tadalafil)  Pentoxifylline  Rebamipide  Prostaglandin E1  Polydeoxyribonucleotide	Animal experiments  Animal experiments  Patients of ischemic colitis with ulcerative lesions.  Patients with ischemic colitis complicated by stricture formation  Animal experiments	Enhance the flow of blood in artery  Expand blood vessel, improve hemodynamic  Suppress free radical production and accelerating ulcer healing  Increase blood flow to the colon  Increase the expression of VEGF and inhibite inflammatory cytokines and COX-2 through enhancing the expression of A2AR	Luo, C.C. et al [59]  Luo, C.C. et al [59]  Matsumoto, S. et al. [70]  Abe, S. et al. [68]  Kim, S.E. et al. [69]

**Fig. 2** Drugs used for ischemic colitis

after 72 h. If patients have no obvious clinical effects, it is suggested to redefine the antibacterial program. But, as recommendations for antimicrobial treatment are mostly based upon animal studies and because there is a lack of basic or prospective random clinical contrast studies, the clinical value of antimicrobial treatments for IC remains to be further explored. One consideration is that increased antibiotic use could promote inflammation through the translocation of native commensal colonic microflora [61]. Therefore, further work to define the most appropriate and safe doses, frequencies, durations, and types of antibiotics used is necessary.

### Anticoagulant and antiplatelet drug

Tsimperidis et al. evaluated a variety of thrombotic factors including protein C (PC), protein S, antithrombin (AT), and resistance to activated protein C (APCR) in IC-afflicted patients. Their study proposed that the role of hypercoagulability through hereditary or as otherwise acquired was essential for the mechanisms underlying IC [14]. Acute superior mesenteric venous thrombosis (SMVT) is a cause of mesenteric ischemia disease. Some researchers have proposed that heparin prophylaxis could have a preventive effect in patients with acute SMVT [62]. Huguier et al. suggested that IC-afflicted

patients with cardiovascular disease should be treated with prophylactic anticoagulation or antiarrhythmia to decrease the risk of death from a vascular disease post-discharge [63]. Patients with segmental, non-gangrenous IC are more likely to have potential cardiac sources of embolism compared with control patients, and anticoagulant therapies are recommended for these patients [8]. Iloprost is an effective antiplatelet agent and has a protective effect in the early stage of intestinal ischemia in rats. The underlying mechanism may have been related to inhibited leukocyte infiltration, reduced proinflammatory cytokines, promoted angiogenesis, or reduced oxidative stress and inflammatory response, which ultimately resulted in decreased tissue damage [64]. However, the current roles of anticoagulant or antiplatelet therapies in the acute presentations of IC, or for the prevention of recurrence still need to be confirmed, such as through prospective clinical studies.

### Glucocorticosteroids

Glucocorticoids are not recommended for the treatment of or prevention of IC, and several studies have reported steroid-related IC or ischemic pancolitis [65, 66]. Systemic use of glucocorticoids may also exacerbate ischemic damage and cause perforation of the colon. However, Wolfgang Kruis et al. recently suggested a potential protective effect of the combination of intravenous antibiotics and intravenous prednisolone for cases of severe IC. This preliminary study may offer a new pathway for the field of study of conservative management of severe IC [67]; however, this result still needs further exploration.

### Potential drugs

Vardenafil and pentoxifylline exert positive effects upon the hemodynamics associated with vascular smooth muscle, and have proven useful as therapeutic options for rat-based models of IC [59]. In a case report, prostaglandin E1 also increased blood flow to the colon and might be a potential approach for treating IC cases complicated by stricture formations [68]. Polydeoxyribonucleotide (PDRN) is a mixture of nucleotides and is mainly found in the human placenta or such as in salmon sperm. It was reported that PDRN potentially has a therapeutic action upon IC by way of increasing the expression of VEGF and inhibiting inflammatory cytokines and COX-2 through enhancing the expression of A2AR [69]. Rebamipide, an antiulcer drug, has been reported to have ulcer-healing and anti-inflammatory effects [70]. In a rebamipide enema-treated group, left-sided IC-afflicted patients with ulcerative lesions had a shorter fasting period and reduced durations of hospitalization compared with the control group. However, there lacks sufficient evidence to fully support the potentially positive effects of sulfonapyridine,

amino salicylic acid, or fatty acid enemas for the treatment of IC [1].

### Prognosis

Sun D et al. retrospectively analyzed 22 studies including 2823 IC-afflicted patients and showed that the total rate of adverse reactions was 22.0% [71]. Male gender, tachycardia, a lack of rectal bleeding, peritonitis, arterial hypotension (< 90 mmHg), and right colon involvement are considered risk factors related to a poor prognosis for IC-afflicted patients. A novel prognostic scoring model provided a useful method for assessing the prognosis of patients, whereby the presence of tachycardia ( $\geq 90$  beats/min), shock within 24 h after admission, and endoscopic evidence of ulceration were the key predictive factors [72]. One group of researchers found that Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were more suitable for predicting gangrenous ischemic changes and mortality in patients with gangrenous IC. The absence of hematochezia, abdominal tenderness, absence of diarrhea, and albumin levels were found to have been significant predictors of IC [73]. Ange et al. prospectively analyzed 135 patients who met the criteria for definitive or probable IC according to Brandt criteria, and found that the recurrence rates were 2.9%, 5.1%, 8.1%, and 9.7% at years 1, 2, 3, and 5, respectively [74].

### Strength and limitations

This paper reviewed the diagnostic methods for IC and added new content. It is the first to summarize new progress on the currently available drug-based treatments, including for some drugs derived based upon animal experimentation. Our review also has several limitations: Firstly, we searched only two databases, albeit they are widely used, and no studies were added through other manual searches. Thus, we might have missed some relevant publications. Secondly, we focused upon the diagnostic methods and drug therapies for IC, and introduced briefly the surgical indicators. We did not discuss surgical methods for treatment and the clinical effects. Thirdly, the treatment of IC could be heterogeneous with respect to their uses across diverse subsets of different populations, and patients treated with individual regimes could improve the desired curative effects. Lastly, some low quality and moderate levels of evidence were applied and consulted. Nonetheless, further studies based upon more high-quality, large-sample randomized controlled trials will ensue, and as they do, the information can be assessed in the context of this review.

## Conclusion

Clinicians usually have a low level of awareness and vigilance to the IC afflictions because of the ambiguity of symptoms and complications forming often other associated diseases. This may lead to misdiagnoses. For patients with typical clinical characteristics complicated with some underlying diseases such as hypertension and diabetes, or whom have a special history of drug use and abdominal surgery, the possibility of IC should be considered. Colonoscopy combined with histopathological biopsy is the gold standard for IC disease diagnosis. Treatment involves conservative treatment and surgical therapy. Conservative treatments mainly include bowel rest, intravenous fluids, correction of underlying conditions, and some necessary anti-infection therapies. Most patients have positive responses. Other drugs presently under evaluation include phosphodiesterase type 5 inhibitors, pentoxifylline, rebamipide, prostaglandin E1, and polydeoxyribonucleotide. Although researchers have done many useful exploration studies with respect to the development of a new therapeutic drug target, there is still a lack of evidence-based data on the appropriate drug therapy of colon ischemia.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflicts of interest.

**Ethics approval** This article does not contain any studies with human participants or animals performed by any of the authors.

## References

1. Brandt LJ, Feuerstadt P, Longstreth GF, Boley SJ (2015) ACG clinical guideline: epidemiology, risk factors, patterns of presentation, diagnosis, and management of colon ischemia (CI). *Am J Gastroenterol* 110(1):18–44 quiz 45
2. Doulberis M, Panagopoulos P, Scherz S, Dellaporta E, Kouklakis G (2016) Update on ischemic colitis: from etiopathology to treatment including patients of intensive care unit. *Scand J Gastroenterol* 51(8):893–902
3. Chang L et al (2008) Assessment of potential risk factors associated with ischaemic colitis. *Neurogastroenterol Motil* 20(1):36–42
4. Marston A, Pheils MT, Thomas ML, Morson BC (1966) Ischaemic colitis. *Gut* 7(1):1–15
5. Brandt LJ, Boley SJ (2000) AGA technical review on intestinal ischemia. *American Gastrointestinal Association. Gastroenterology* 118(5):954–968
6. Yngvadottir Y, Karlsdottir BR, Hreinsson JP, Ragnarsson G, Mitev RUM, Jonasson JG, Möller PH, Björnsson ES (2017) The incidence and outcome of ischemic colitis in a population-based setting. *Scand J Gastroenterol* 52(6-7):704–710
7. Noh M, Yang S, Jung S, Park J, Im Y, Kim K (2015) Poor prognostic factors in patients who underwent surgery for acute non-occlusive ischemic colitis. *World J Emerg Surg* 10:12
8. Hourmand-Ollivier I, Bouin M, Saloux E, Morello R, Rousselot P, Piquet MA, Dao T, Verwaerde JC (2003) Cardiac sources of embolism should be routinely screened in ischemic colitis. *Am J Gastroenterol* 98(7):1573–1577
9. Zhang R, Sun JP, Chong J, Liu B, Wang F, Yu CM (2015) Ischemic colitis as a complication of acute myocardial infarction. *Int J Cardiol* 185:50–51
10. Lo WK, Mahboobani NR, Siu Y (2017) Gastrointestinal: phlebosclerotic colitis: a rare but increasingly recognized cause of ischemic colitis with telltale imaging features. *J Gastroenterol Hepatol* 32(11):1792
11. Matsumoto Y, Wakabayashi H, Otsuka F, Inoue K, Takano M, Sada KE, Makino H (2011) Systemic lupus erythematosus complicated with acute myocardial infarction and ischemic colitis. *Intern Med* 50(21):2669–2673
12. Aoki T, Nagata N, Sakamoto K, Arai T, Niikura R, Shimbo T, Shinozaki M, Sekine K, Okubo H, Watanabe K, Sakurai T, Yokoi C, Akiyama J, Yanase M, Mizokami M, Noda M, Uemura N (2015) Abdominal fat accumulation, as measured by computed tomography, increases the risk of ischemic colitis: a retrospective case-control study. *Dig Dis Sci* 60(7):2104–2111
13. Bielefeldt K (2016) ischemic colitis as a complication of medication use: an analysis of the federal adverse event reporting system. *Dig Dis Sci* 61(9):2655–2665
14. Tsimperidis AG, Kapsoritakis AN, Linardou IA, Psychos AK, Papageorgiou AA, Vamvakopoulos NC, Kyriakou DS, Potamianos SP (2015) The role of hypercoagulability in ischemic colitis. *Scand J Gastroenterol* 50(7):848–855
15. Kanai N, Hashimoto T, Fukuda M, Shijyo T (2019) Acute ischemic colitis with hematochezia related to baloxavir marboxil treatment for influenza A. *J Infect Chemother* 25(12):1040–1042
16. Dieringer TD, Crossland DM, Mahl TC (2018) Rizatriptan-induced colonic ischemia: a case report and literature review. *Am J Gastroenterol* 113(1):148–149
17. Chandler RE (2020) Nintedanib and ischemic colitis: Signal assessment with the integrated use of two types of real-world evidence, spontaneous reports of suspected adverse drug reactions, and observational data from large health-care databases. *Pharmacoepidemiol Drug Saf* 29:951–957
18. Batteux B, Gras V, Mahboud Y, Liabeuf S, Bennis Y, Masmoudi K (2019) Ischaemic colitis associated with intravitreal administration of aflibercept: a first case report. *Br J Clin Pharmacol* 85(4):845–848
19. Norsal L, Valle C, Morotti D, Bonaffini PA, Indriolo A, Sonzogni A (2020) Intestinal ischemia in the COVID-19 era. *Dig Liver Dis*
20. Bianco F et al (2020) Acute intestinal ischemia in a patient with COVID-19. *Tech Coloproctol*:1–2
21. Arif R, Farag M, Zaradzki M, Reissfelder C, Pianka F, Bruckner T, Kremer J, Franz M, Ruhparwar A, Szabo G, Beller CJ, Karck M, Kallenbach K, Weymann A (2016) Ischemic colitis after cardiac surgery: can we foresee the threat? *PLoS One* 11(12):e0167601
22. Hayashi K, Ohshio Y, Hanaoka J (2019) Gangrenous ischaemic colitis following lung wedge resection. *BMJ Case Rep* (5):12
23. Lee SO et al (2014) Colonoscopy-induced ischemic colitis in patients without risk factors. *World J Gastroenterol* 20(13):3698–3702
24. Kim B, Tayel H, Chaput KJ (2019) Colonic ischemia after vaginal delivery. *ACG Case Rep J* 6(10):e00227
25. Kimura T, Shinji A, Horiuchi A, Tanaka N, Nagaya T, Shigeno T, Nakamura N, Komatsu M, Umemura T, Arakura N, Matsumoto A,



- Tanaka E (2012) Clinical characteristics of young-onset ischemic colitis. *Dig Dis Sci* 57(6):1652–1659
26. Washington C, Carmichael JC (2012) Management of ischemic colitis. *Clin Colon Rectal Surg* 25(4):228–235
  27. Seo HI et al (2017) Predisposing factors of ischemic colitis: data from 14 years of experience in a single center. *Gastroenterol Res Pract* 2017:1049810
  28. Naseer M, Gandhi J, Chams N, Kulairi Z (2017) Stercoral colitis complicated with ischemic colitis: a double-edge sword. *BMC Gastroenterol* 17(1):129
  29. Brandt LJ, Feuerstadt P (2016) Beyond low flow: how i manage ischemic colitis. *Am J Gastroenterol* 111(12):1672–1674
  30. Brandt LJ, Feuerstadt P, Blaszcza MC (2010) Anatomic patterns, patient characteristics, and clinical outcomes in ischemic colitis: a study of 313 cases supported by histology. *Am J Gastroenterol* 105(10):2245–2252 quiz 2253
  31. Montoro MA, Brandt LJ, Santolaria S, Gomollon F, Puértolas BS, Vera J, Bujanda L, Cosme A, Cabriada JL, Durán M, Mata L, Santamaría A, Ceña G, Blas JM, Ponce J, Ponce M, Rodrigo L, Ortiz J, Muñoz C, Arozena G, Ginard D, López-Serrano A, Castro M, Sans M, Campo R, Casalots A, Orive V, Loizate A, Titó L, Portabella E, Otazua P, Calvo M, Botella MT, Thomson C, Mundi JL, Quintero E, Nicolás D, Borda F, Martínez B, Gisbert JP, Chaparro M, Bernadó AJ, Gómez-Camacho F, Cerezo A, Nuñez EC, On behalf of the Workgroup for the Study of Ischaemic Colitis of the Spanish Gastroenterological Association (GTECIE-AEG) (2011) Clinical patterns and outcomes of ischaemic colitis: results of the Working Group for the Study of Ischaemic Colitis in Spain (CIE study). *Scand J Gastroenterol* 46(2):236–246
  32. Rezende-Neto JB, Rotstein OD (2013) Abdominal catastrophes in the intensive care unit setting. *Crit Care Clin* 29(4):1017–1044
  33. Azam B, Kumar M, Mishra K, Dhibar DP (2019) Ischemic colitis. *J Emerg Med* 56(5):e85–e86
  34. Memet O, Zhang L, Shen J (2019) Serological biomarkers for acute mesenteric ischemia. *Ann Transl Med* 7(16):394
  35. Treskes N, Persoon AM, van Zanten ARH (2017) Diagnostic accuracy of novel serological biomarkers to detect acute mesenteric ischemia: a systematic review and meta-analysis. *Intern Emerg Med* 12(6):821–836
  36. Assadian A, Assadian O, Senekowitsch C, Rotter R, Bahrami S, Fürst W, Jaksch W, Hagmüller GW, Hübl W (2006) Plasma D-lactate as a potential early marker for colon ischaemia after open aortic reconstruction. *Eur J Vasc Endovasc Surg* 31(5):470–474
  37. Sun DL, Cen YY, Li SM, Li WM, Lu QP, Xu PY (2016) Accuracy of the serum intestinal fatty-acid-binding protein for diagnosis of acute intestinal ischemia: a meta-analysis. *Sci Rep* 6:34371
  38. Lieberman JM, Sacchetti J, Marks C, Marks WH (1997) Human intestinal fatty acid binding protein: report of an assay with studies in normal volunteers and intestinal ischemia. *Surgery* 121(3):335–342
  39. Koutroubakis IE, Sfridakis A, Theodoropoulou A, Kouroumalis EA (2001) Role of acquired and hereditary thrombotic risk factors in colon ischemia of ambulatory patients. *Gastroenterology* 121(3):561–565
  40. Cossé C, Sabbagh C, Fumery M, Zogheib E, Mauvais F, Browet F, Rebibo L, Regimbeau JM (2017) Serum procalcitonin correlates with colonoscopy findings and can guide therapeutic decisions in postoperative ischemic colitis. *Dig Liver Dis* 49(3):286–290
  41. López E, Ripollés T, Martínez MJ, Bartumeus P, Blay J, López A (2015) Positive predictive value of abdominal sonography in the diagnosis of ischemic colitis. *Ultrasound Int Open* 1(2):E41–E45
  42. Pastor-Juan MDR, Ripollés T, Martí-Bonmatí L, Martínez MJ, Simó L, Gómez D, Revert R (2017) Predictors of severity in ischemic colitis: usefulness of early ultrasonography. *Eur J Radiol* 96:21–26
  43. Mazzei MA, Guerrini S, Cioffi Squitieri N, Imbriaco G, Chieca R, Civitelli S, Savelli V, Mazzei FG, Volterrani L (2013) Magnetic resonance imaging: is there a role in clinical management for acute ischemic colitis? *World J Gastroenterol* 19(8):1256–1263
  44. Menke J (2010) Diagnostic accuracy of multidetector CT in acute mesenteric ischemia: systematic review and meta-analysis. *Radiology* 256(1):93–101
  45. Theodoropoulou A, Koutroubakis IE (2008) Ischemic colitis: clinical practice in diagnosis and treatment. *World J Gastroenterol* 14(48):7302–7308
  46. Jung SH, Lee KM, Chung WC, Paik CN, Kim JD, Kwak JW (2010) Ischemic colitis and portal venous gas. *Gastrointest Endosc* 71(7):1302–1303
  47. Sridhar P, Fisichella PM (2016) Bowel ischemia and portal venous gas: what to do? *J Laparoendosc Adv Surg Tech A* 26(9):713–714
  48. Manatakis D (2018) Thumbprinting in ischemic colitis. *N Engl J Med* 378(24):e33
  49. Iacobellis F et al (2014) CT findings in acute, subacute, and chronic ischemic colitis: suggestions for diagnosis. *Biomed Res Int* 2014:895248
  50. Taourel P, Aufort S, Merigeaud S, Doyon FC, Hoquet MD, Delabrousse E (2008) Imaging of ischemic colitis. *Radiol Clin N Am* 46(5):909–924 vi
  51. Danakas AM, Fazili BG, Huber AR (2019) Mass-forming ischemic colitis: a potential mimicker of malignancy. *Case Rep Pathol* 2019:8927872
  52. Khor TS, Lauwers GY, Odze RD, Srivastava A (2015) “Mass-forming” variant of ischemic colitis is a distinct entity with predilection for the proximal colon. *Am J Surg Pathol* 39(9):1275–1281
  53. Fenster M, Feuerstadt P, Brandt LJ, Mansoor MS, Huisman T, Aroniadis OC (2018) Real-world multicentre experience of the pathological features of colonic ischaemia and their relationship to symptom duration, disease distribution and clinical outcome. *Color Dis* 20(12):1132–1141
  54. Zou X, Cao J, Yao Y, Liu W, Chen L (2009) Endoscopic findings and clinicopathologic characteristics of ischemic colitis: a report of 85 cases. *Dig Dis Sci* 54(9):2009–2015
  55. Mitsudo S, Brandt LJ (1992) Pathology of intestinal ischemia. *Surg Clin North Am* 72(1):43–63
  56. Zheng M, Zhang M, Li C, Wang X, Zhong N, Zuo X, Li Y (2018) Gastrointestinal: “ghost gland” in probe-based confocal laser endomicroscopy for diagnosing ischemic colitis: a novel approach. *J Gastroenterol Hepatol* 33(11):1818
  57. Moszkowicz D, Trésallet C, Mariani A, Lefevre JH, Godiris-Petit G, Noullet S, Rouby JJ, Menegaux F (2014) Ischaemic colitis: indications, extent, and results of standardized emergency surgery. *Dig Liver Dis* 46(6):505–511
  58. Misiakos EP, Tsapralis D, Karatzas T, Lidoriki I, Schizas D, Sfyroeras GS, Moulakakis KG, Konstantos C, Machairas A (2017) Advances in the diagnosis and management of ischemic colitis. *Front Surg* 4:47
  59. Luo CC, Shih HH, Chiu CH, Lin JN (2004) Translocation of coagulase-negative bacterial staphylococci in rats following intestinal ischemia-reperfusion injury. *Biol Neonate* 85(3):151–154
  60. Redan JA et al (1990) Organ distribution of radiolabeled enteric *Escherichia coli* during and after hemorrhagic shock. *Ann Surg* 211(6):663–666 discussion 666–8
  61. Knoop KA, McDonald KG, Kulkarni DH, Newberry RD (2016) Antibiotics promote inflammation through the translocation of native commensal colonic bacteria. *Gut* 65(7):1100–1109
  62. Leardi S, de Vita F, Felici S, Pietroletti R, Capitano S, Simi M (2006) Acute ischaemic colitis: outcome in elderly patients. *Chir Ital* 58(3):309–313
  63. Huguier M, Barrier A, Boelle PY, Houry S, Lacaine F (2006) Ischemic colitis. *Am J Surg* 192(5):679–684

64. Karatepe O, Cakir A, Unal O, Battal M, Adas G, Kamali G, Kemik A, Aydin T, Kamali S, Karahan SR, Aksoy M (2011) Iloprost reduces colonic injury in ischemic colitis in rats. *Acta Cir Bras* 26(3):220–226
65. Akar M, Koseoglu H, Solakoglu T, Kosker T, Buyukasik N, Ersoy O (2017) Steroid-induced ischemic pancolitis. *J Gastrointest Liver Dis* 26(1):7
66. Sedano Casas A et al (2013) Cholesterol emboli-induced ischemic colitis. *Med Clin (Barc)* 141(4):e7
67. Kruis W, Schiff M (2019) Combination treatment with antibiotics and glucocorticosteroids for severe ischemic colitis. *Digestion*:1–6
68. Abe S, Takayama T, Ohta H, Takimoto R, Okamoto T, Sato Y, Nikaïdo T, Takizawa K, Abe T, Niitsu Y (2004) Successful treatment with prostaglandin E1 of ischemic colitis complicated by colonic stricture. *Gastrointest Endosc* 60(1):148–151
69. Kim SE et al (2020) Polydeoxyribonucleotide exerts therapeutic effect by increasing VEGF and inhibiting inflammatory cytokines in ischemic colitis rats. *Biomed Res Int* 2020:2169083
70. Matsumoto S, Tsuji K, Shirahama S (2008) Rebamipide enema therapy for left-sided ischemic colitis patients accompanied by ulcers: open label study. *World J Gastroenterol* 14(25):4059–4064
71. Sun D, Wang C, Yang L, Liu M, Chen F (2016) The predictors of the severity of ischaemic colitis: a systematic review of 2823 patients from 22 studies. *Color Dis* 18(10):949–958
72. Chung JW et al (2010) Development and validation of a novel prognostic scoring model for ischemic colitis. *Dis Colon Rectum* 53(9):1287–1294
73. Kwak HD, Kang H, Ju JK (2017) Fulminant gangrenous ischemic colitis: is it the solely severe type of ischemic colitis? *Int J Color Dis* 32(1):147–150
74. Cosme A, Montoro M, Santolaria S, Sanchez-Puertolas AB, Ponce M, Durán M, Cabriada JL, Borda N, Sarasqueta C, Bujanda L (2013) Prognosis and follow-up of 135 patients with ischemic colitis over a five-year period. *World J Gastroenterol* 19(44):8042–8046

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