Journal of Clinical and Translational Research
10.18053/Jctres/09.202303.008

REVIEW

Acute ischemic colitis associated with oral decongestant use: a systematic review

Muhammad Hassan Naeem Goraya[1], Faisal Inayat[1]*, Sobaan Taj[2], Junaid Rasul Awan[1], Adil Mohyudin[3], Syed Hasan Ali[4], Arslan Afzal[5], Muhammad Junaid Ashraf[1], Muhammad Adnan Zaman[1], Zahra Akhtar[1], Gul Nawaz[1], Zahid Ijaz Tarar[6]

1. Allama Iqbal Medical College, Lahore, Pakistan
2. Jersey Shore University Medical Center, Neptune, NJ, United States of America
3. University of Mississippi Medical Center, Jackson, MS, United States of America
4. Dow University of Health Sciences, Karachi, Pakistan
5. Woodhull Medical Center, Brooklyn, NY, United States of America
6. University of Missouri School of Medicine, Columbia, MO, United States of America

*Corresponding author
Faisal Inayat
Allama Iqbal Medical College, Allama Shabbir Ahmad Usmani Road, Faisal Town, Lahore 54550, Pakistan.
Tel: +92 321 774 3758
Fax: +92 42 9923 1443
Email: faisalinayat@hotmail.com

Article information:
Received: August 1, 2022
Revised: August 26, 2022
Accepted: April 10, 2023

Journal of Clinical and Translational Research
10.18053/Jctres/09.202303.008

Abstract

Background and aim: Acute ischemic colitis (IC) has been linked with the use of oral decongestants. However, clinical evidence on this association remains limited. We aim to evaluate the occurrence and clinical outcomes of acute IC following over-the-counter (OTC) use of pseudoephedrine and phenylephrine.

Methods: We conducted a systematic review of the MEDLINE, Google Scholar, Scopus, and Embase databases between inception and July 20, 2022. Specific search terms were used. The inclusion criteria consisted of English-language articles describing acute IC secondary to pseudoephedrine or phenylephrine.

Results: A total of 18 case reports (level of clinical evidence: IV) fulfilled our inclusion criteria. The mean age of patients was 51.6 ± 15.3 years, with 14 (77.8%) cases reported in women. Clinical presentation was mainly related to abdominal pain 16 (88.9%), hematochezia 15 (83.3%), and/or abdominal tenderness 10 (55.6%). The medical background showed that 5 (27.8%) patients were previously healthy. In the 13 (72.2%) patients with comorbidities, hypertension 6 (46.2%), a history of tobacco use 5 (38.5%), and psychiatric illnesses 4 (30.8%) were commonly reported. Leukocytosis was encountered in 13 (72.2%) patients. Diagnostic investigations included a combination of CT scan and colonoscopy in 10 (55.6%), colonoscopy alone in 6 (33.3%), and flexible sigmoidoscopy in 1 (5.6%) patient. Colonoscopic biopsy was the mainstay of diagnosis in 15 (83.3%) patients. Treatment was based on supportive care in 18 (100%), concurrent antibiotic use in 2 (11.1%), and surgical intervention in 1 (5.6%) patient. Recurrent episodes of IC occurred in 4 (22.2%) patients.

Conclusions: Acute IC secondary to oral decongestants remains a rare but important clinical phenomenon. Clinical suspicion and imaging findings are important for early diagnosis.

Relevance to patients: In unexplained cases of IC, clinicians should specifically inquire about oral decongestants since they are OTC and patients commonly fail to reveal their usage. These drugs should be avoided for transient cold symptoms, especially in women.

Journal of Clinical and Translational Research
10.18053/Jctres/09.202303.008

Keywords: Ischemic colitis**,** Drug-induced colitis**,** Oral decongestants**,** Phenylephrine**,** Pseudoephedrine**,** Colonic ischemia

1. Introduction

Ischemic colitis (IC) is a well-known disease with an annual incidence of 16 cases per 100,000 person-years [1]. A prospective study conducted in 24 Spanish hospitals showed that IC was responsible for 1.28 per 1000 hospital admissions [2]. Colonic ischemia is predominantly caused by sudden reduction in blood flow, especially in watershed areas of the splenic flexure (Griffith's point) and rectosigmoid junction (Sudek's point), which leads to ischemic injury [3]. The underlying pathophysiology of IC stems from the colonic susceptibility to hypoperfusion in such watershed areas. It frequently affects the elderly individuals as a sequel to vascular comorbidities [3]. Among vascular disorders, non-occlusive causes are predominant (>95% of cases) compared to occlusive causes [3]. The clinical, colonoscopy, and biopsy findings are important for its detection [4]. However, the diagnosis and treatment of IC often present diagnostic and therapeutic conundrums [4]. A wide variety of etiologies have been reported to precipitate colonic ischemia. The conditions leading to mesenteric venous thrombosis, small vessel disease, hemodynamic compromise, mechanical colonic obstruction, blood dyscrasia, major vascular occlusion, iatrogenic injuries, and certain drugs have been implicated in this regard [4].

Drug-induced IC has previously been described in association with a number of drug groups [4]. Pseudoephedrine and phenylephrine are oral over-the-counter (OTC) decongestant agents. These drugs are commonly used to provide symptomatic relief from nasal congestion [5]. The arterial vasoconstriction caused by these agents can also rarely result in ischemic injuries to other organs, such as the colon [5]. However, published literature lacks organized data regarding oral decongestant-related IC. Therefore, to the best of our knowledge, this study represents the first systematic review of available clinical evidence evaluating the association between oral decongestant use and acute IC. After the Combat Methamphetamine Act (CMEA) ruling in 2005 and Health Canada's warning in 2016 on the risk of pseudoephedrine-induced IC, phenylephrine has largely replaced OTC usage of pseudoephedrine as a decongestant agent [6,7]. While this drug has a relatively lower propensity to cause vasoconstrictive complications, it may still culminate in serious adverse effects like IC. Cases of reversible IC are frequently ignored and remain undiagnosed in clinical practice. As a result, it is possible that oral decongestant-related IC has also been under-recognized. Our article may therefore help to increase

public awareness, which will aid clinicians promptly recognize this important side effect of using oral decongestants.

2. Methods

2.1. Data abstraction

In this article, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used [8]. We searched medical databases such as MEDLINE, Google Scholar, Scopus, and Embase. The published articles in the English language were considered. The latest search date was July 20, 2022. In order to identify the relevant studies, we used a specific set of medical terminologies. The search keywords, including "ischemic colitis," "colonic ischemia," "intestinal ischemia," "bowel ischemia," "acute ischemia," "colon," "drug-induced ischemic colitis," "adverse drug reaction," and "IC," were combined using the Boolean operators 'AND' and 'OR' with the terms "decongestant," "phenylephrine," and "pseudoephedrine," with all associated permutations.

Four authors independently screened the results of the initial search for relevant studies. Moreover, the abstracts from major gastroenterology and endoscopy scientific meetings and conferences were searched without the application of specific date and geographic filters. The bibliography lists were also manually screened. The initial search of the databases and reference lists resulted in a total of 214 articles.

2.2. Eligibility and inclusion in analysis

In order to determine eligibility, 3 authors independently reviewed all retrieved studies. Only the articles based on human subjects over 18 years of age were included. The reports based on non-English, redundant, duplicate, bench research, and pediatric data were excluded. The eligibility conflicts were resolved with mutual consensus. The final inclusion was made after consultation with the senior author. A total of 13 articles were included in the final comparative analysis.

2.3. Data Collection and Statistical Analysis

The data was validated by 2 authors who independently re-reviewed the full-text versions of the included papers. Patient demographics, hospital admission parameters, the clinical course of the illness, and clinical outcomes were studied and summarized. The PRISMA flow diagram outlines our

search strategy for data synthesis and comparative analysis **(Figure 1).** The descriptive patient data were presented as mean with standard deviation, range, or percentage, as applicable. The odds ratios were calculated to determine the recurrence risk in patients who were exposed to an oral decongestant agent and developed IC.

3. Results

3.1. Patients demographics

A total of 18 case reports (clinical evidence level: IV) of acute IC were identified in association with the use of pseudoephedrine and phenylephrine [9-21]. The reports were dated from 1995 to 2021. The culprit agents included pseudoephedrine in 15 (83.3%) and phenylephrine in 3 (16.7%) cases. The mean age of the patients was 51.6 ± 15.3 years, ranging from 23 to 81 years. It was notable that 14 (77.8%) patients were below the age of 60. A clear female gender predominance was noted, as 14 (77.8%) cases were reported in women. Information on racial background was available in 13 cases. Of these, 6 (46.2%) patients were White, 3 (23.1%) were Caucasian, 3 (23.1%) were East Asian, and 1 (7.7%) was African American. With regard to geographical distribution, all cases were reported from 3 countries, including the United States 13 (72.2%), Korea 3 (16.7%), and Australia 2 (11.1%).

3.2. Comorbidities

The medical background showed that 5 (27.8%) of 18 patients were previously healthy, with no prior underlying medical conditions. In the remaining 13 (72.2%) patients, hypertension was reported in 6 (46.2%), history of tobacco use in 5 (38.5%), psychiatric illnesses in 4 (30.8%), respiratory allergies in 4 (30.8%), sinusitis in 2 (15.4%), and lipid disorders in 2 (15.4%) patients. Notably, 6 (33.3%) of 18 patients were peri- or post-menopausal women. Hormone replacement therapy was reported in 2 (11.1%) patients. Pertinently, 17 (94.4%) patients had normal bowel habits before the current presentation. Only 1 (5.6%) patient experienced drug-related constipation following tramadol usage. Therefore, none of the patients had a positive history of irritable bowel syndrome in the published physician reports. Case-to-case variations were commonly noted with regard to the OTC products. The patients included in our review often used products like Sudafed, Nucosef, Claritin-D, DayQuil LiquiCaps, and Allegra-D.

3.3. *Presentation patterns and diagnosis*

Major clinical presentations were related to abdominal pain 16 (88.9%) and/or hematochezia 15 (83.3%). Other presenting symptoms included abdominal cramps 5 (27.8%), nausea 3 (16.7%), vomiting 3 (16.7%), diarrhea 3 (16.7%), dizziness 1 (5.6%), and/or sweating 1 (5.6%). Common clinical signs included abdominal tenderness 10 (55.6%), orthostatic changes 3 (16.7%), and abdominal distension 2 (11.1%). Laboratory data were available for 14 (77.8%) patients. In blood workup of these patients, leukocytosis 13 (92.8%) was the most common finding. Diagnostic investigations included a combination of CT abdomen and pelvis and colonoscopy in 10 (55.6%), colonoscopy alone in 6 (33.3%), and flexible sigmoidoscopy in 1 (5.6%) patient. Colonoscopy revealed involvement of different segments of the colon: the descending 9 (50%), sigmoid 8 (44.4%), and/or splenic flexure 7 (38.9%). Colonoscopic biopsy was the mainstay of diagnosis. The tissue diagnosis confirmed IC in 15 (83.3%) patients **(Table 1).**

3.4. Causality assessment

The Naranjo score was used for causality assessment in these patients. Our analysis revealed a mean value of 7.5 ± 1.3. The score ranged from 6 to 11. We examined the individual characteristics of each case to assess whether these patients were correctly diagnosed with decongestant-induced IC. A temporal relationship was noted between the onset of colitis symptoms and oral decongestant use, denoting the potential association. The mean onset delay was 7.56 ± 7.05 days, ranging from 1 to 30 days. Furthermore, a clear dose–effect relationship and resolution of symptoms after drug cessation further supported decongestant use as the etiology of IC in these patients. The exclusion of alternative etiologies is important for the detection of drug-induced acute IC. In our review, the exclusion of probable causes was performed in all the patients.

3.5. Clinical Management and Outcomes

All patients received initial supportive treatment. It included intravenous fluids, antidiarrheal drugs, analgesics, and bowel rest. Two (11.1%) patients also required concurrent antibiotic therapy. The empirical antibiotics included metronidazole and ciprofloxacin [10]. Surgical intervention was reported in 1 (5.6%) patient. Klestov et al. reported the case of a patient with recurrent IC who underwent right

hemicolectomy in her first hospitalization and then ileocolic resection in her second hospitalization [11]. The clinical outcomes were favorable. The length of the hospital stay was variable. The mean duration of hospitalization was 5.6 ± 2.8 days (range, 3–10 days). The mean follow-up duration was 17.5 ± 28.2 months (range, 1-96 months) **(Table 2).**

3.6. *Recurrence Risk*

The overall recurrence rate was 22.2%. A forest plot was used to assess the effect size (odds ratio) of factors associated with recurrence of IC following oral decongestant usage. We report that patient age, female gender, prior conservative therapy had a lower association, and increased dose of oral decongestants and prior sigmoid colon involvement had a higher association with acute IC recurrence, without statistical significance **(Figure 2).**

4. Discussion

To our knowledge, this is the first systematic review evaluating an association between oral decongestants and acute IC. It illustrates that clinicians should consider pseudoephedrine and phenylephrine-induced IC among the differentials in patients presenting with unexplained colitis symptoms.

4.1. Pathogenesis

The pathogenesis of drug-induced IC may be related to mechanisms like vasospasm, thrombosis, and shunting of mesenteric perfusion [22]. In a systematic review, Farooq et al. showed that drugs like cocaine, triptans, ergotamine, vasopressin and its analogs, and phenylpropanolamine can cause IC due to their strong mesenteric vasoconstrictive effects [23]. In this context, alpha-adrenergic agonists such as pseudoephedrine and phenylephrine may also precipitate IC. These drugs increase mesenteric vasoconstriction, which may trigger vasospasm and colonic ischemia in susceptible individuals. Pseudoephedrine has already been linked to marked vasoconstrictive side effects. It may even lead to myocardial infarction by causing spasm of the coronary vasculature [24]. Therefore, the likelihood of pseudoephedrine causing acute IC is higher than that of phenylephrine. This observation may be attributed to phenylephrine's poor bioavailability because of the extensive first-pass metabolism in the gut and liver [25]. Only up to 40% of phenylephrine's dose can reach systemic circulation,

compared to 90% for pseudoephedrine [25,26]. However, in a randomized controlled trial, Atkinson et al. revealed that the relative bioavailability of phenylephrine 10 mg was doubled (Fbio 2.11, 95% CI 1.89, 2.31) when used in combination with acetaminophen 1000 mg [27]. OTC products are often based on a combination of phenylephrine and acetaminophen. Therefore, this factor can have a role in the precipitation of phenylephrine-related colonic ischemia. It calls for increased pharmacovigilance for OTC products containing phenylephrine and acetaminophen.

4.2. Gender predisposition

IC commonly shows a female gender predilection [28,29]. In our systematic review on oral decongestants, 77.8% of patients with colonic ischemia were also women. The definitive rationale for this gender trend in patients with IC is still unclear. It can be attributed to the irregularities in the hypothalamic-pituitary-gonadal axis that often occur in women aged 35–50 years [30,31]. Consequently, hormonal changes culminate in a marked alteration in estrogen levels [31]. As the action of the estrogen hormone is mediated by acetylcholine or increased blood flow, it is a permissive vasodilator [32,33]. Therefore, transiently low levels of estrogen may potentiate the sensitivity to vasoconstrictors in females. Contrarily, increased levels of estrogen may contribute to a hypercoagulable state in women [34,35]. Due to hyperestrogenemia and the procoagulant properties of progestins, hormone replacement therapy may also have led to increased thromboembolic events early on in its use [36]. In our review, the rapid onset of symptoms and early improvement after decongestant cessation may point to reversible mesenteric arterial vasoconstriction as the etiopathogenesis. Dowd et al. also implicated this causal mechanism in their report on 4 cases of pseudoephedrine-related IC diagnosed in perimenopausal women [10]. However, future research is warranted to investigate the causal link between IC, female gender, and oral decongestants.

4.3. Comorbid conditions

Colonic ischemia mostly affects elderly individuals with multiple comorbid conditions. However, it was notable that 14 (77.8%) of the 18 patients in our review were under the age of 60. It indicates the possibility that drug-induced IC can also be encountered in younger age groups. Cubiella Fernández et al. conducted a retrospective, case–control study, which showed that diabetes, lipid

abnormalities, heart failure, peripheral vascular disease, and use of aspirin or digoxin were associated with the development of IC [37]. The findings in our review were mostly in line with the aforementioned results. The underlying conditions like hypertension, a history of tobacco use, psychiatric illnesses, respiratory allergies, sinusitis, and lipid disorders were reported. Notably, peri- or post-menopausal status in women is also important because it may predispose them to vasoconstrictor-related IC [10]. As constipation is a risk factor for IC, an inquiry about the daily bowel habits is imperative. In our review, prior to presenting with IC, all patients had regular bowel movements. Only 1 patient had drug-induced constipation. Traino et al. reported the case of the patient who developed pseudoephedrine-related IC and underlying tramadol-related constipation acted as a contributing factor [13].

4.4. Clinical presentation

Clinical presentation of IC is variable and nonspecific. However, a sudden-onset, cramping, lower abdominal pain and rectal bleeding are often present [38]. While colonic ischemia can present with vague symptoms, a few telltale clinical signs can point in the right direction. Such positive findings may include segmental colitis, scant diarrhea, and minor bleeding [39]. Patients often develop abdominal tenderness, particularly at the affected colonic site. No sensitive or specific laboratory markers exist for IC. However, leukocytosis is a common finding in these patients [39]. In our systematic review, the presentation patterns were in line with the above-mentioned trends. The patients with decongestant-induced IC frequently presented with abdominal pain and hematochezia. Leukocytosis was the most common laboratory finding, followed by low hemoglobin levels.

4.4. Diagnosis

The diagnosis of IC is predominantly based on clinical suspicion and the workup findings. Radiological, endoscopic, and histopathological evaluations are important in this regard [40]. Clinical suspicion may aid physicians in considering IC in patients presenting with vague clinical symptomology [40]. It is important to exclude probable causes with overlapping clinical features [41-44]. Imaging such as abdominal radiography commonly shows nonspecific gas patterns or ileus early in the disease [44]. With the progression of the disease, submucosal hemorrhage and edema occur. These may lead to focal mural thickening, often described as "thumbprinting" [44]. A CT scan can also reveal negative findings

at the beginning of the disease, but it can also help to exclude other probable etiologies [45,46]. In addition to colonic wall thickening in different segments, CT findings may often include stranding in paricolic areas [46].

Colonoscopy findings include segmental inflammation of the affected part of the colon, most commonly the descending and sigmoid parts. It is characterized by the edematous, friable mucosa with overlying exudate, erythema, erosions, friability, loss of vascularity, shallow longitudinal ulceration, and mucosal bleeding [47]. The timing of the colonoscopy in relation to the start of symptoms can also aid in determining severity of IC [47]. Early colonoscopy enables more rapid detection of ischemia stigmata, decreasing the possibility of a false positive and potentially dangerous and needless treatment [47]. In this regard, the efficacy of rapid bowel preparation with 1 L polyethylene glycol ascorbate solution can be evaluated [48]. In patients with IC, histology often shows mucosal edema and hemorrhage [49]. However, erosions, granulation tissue hypoplasia, and macrophages with hemosiderin pigmentation extend into the submucosa in more severe cases [49]. Colonoscopic biopsy is the most sensitive and specific test for the diagnosis of IC [49]. It is considered the gold standard [49]. In our review, workup findings largely validate these observations.

Drug-induced IC remains a diagnosis of exclusion. Therefore, alternative causes should be systematically ruled out [40,50]. The Naranjo scoring algorithm can be used for causality assessment [51]. In our data, the score ranged are from 6 to 11, indicating that IC was a *probable* or *definitive* drug reaction following the use of pseudoephedrine and phenylephrine. Moreover, a close temporal relationship between symptom onset and oral decongestant intake and exclusion of all alternative etiologies also played an important role in establishing diagnosis.

4.5. Clinical management

A vast majority of IC cases are transient and resolve spontaneously. Therefore, the clinical management mostly consists of bowel rest, intravenous fluids, and antidiarrheal medications [52]. In most patients, the symptoms resolve within 1-2 days, with complete clinical resolution being attained within 2 weeks [52]. A nasogastric tube can be placed in selected patients with distension and ileus. Additionally, parameters like lactate levels and mixed venous oxygen saturation should be monitored,

depending on the severity of the disease. The use of antibiotics lacks consensus in mild and self-limited cases of drug-induced IC. The American College of Gastroenterology practice guidelines recommend their use in moderate to severe cases [52]. The permanent cessation of the offending drug carries paramount importance in preventing recurrent and severe episodes of colonic ischemia. Patients should be educated about this adverse drug reaction to achieve compliance.

4.6. Clinical outcomes and recurrence risk

In our review, all patients initially recovered from IC following decongestants. Due to the self-limiting nature of the disease after the offending drug cessation, the morbidity was relatively lower. Cosme et al. evaluated the five-year recurrence rate of IC, which was 9.5% [53]. Similarly, Sherid et al. showed a recurrence rate of IC of 8.5% after 6 years [54]. In patients with drug-associated IC, correct diagnosis in initial episode carries paramount clinical importance. It may save patients from severe, recurrent IC after reexposure to the similar drugs. Notably, the overall recurrence rate in our review was 22.2%. Patient age, female gender, and prior conservative therapy had a lower association, and an increased dose of oral decongestants and prior sigmoid colon involvement had a higher association with decongestant-related acute IC recurrence, without statistical significance. Most patients involved in decongestant-related IC were below 60 years of age. Females possibly had a transient presentation of IC and recovered with decongestant cessation and supportive treatment. Furthermore, increased doses of decongestants may increase their vasoconstrictive effects, which can potentiate the occurrence of severe, recurrent IC on subsequent exposure. It may point to a dose-dependency effect in gastrointestinal tolerability. However, further research is warranted in this regard.

4.7. Future directions

Mandating proper community education on the use of oral decongestants should be considered. The recognition of IC as a possible adverse effect of these drugs is clinically important. Due to the decreased efficacy of phenylephrine compared to pseudoephedrine and the control over acquiring pseudoephedrine, the chronic use of phenylephrine could increase in the following years. It may lead to an increase in systemic effects in the population. It is therefore important for policymakers to limit the OTC transactions of such medications. Moreover, clinicians should emphasize a detailed clinical

history. Specific questions regarding the OTC use of pseudoephedrine or phenylephrine-based products should be asked when a patient presents with unexplained colitis symptoms. Furthermore, in patients with a history of IC or underlying risk factors such as vascular disease or concomitant use of other high-risk drugs, the use of pseudoephedrine or phenylephrine should be completely avoided.

5. Conclusions

Acute IC following the use of pseudoephedrine and phenylephrine-based oral decongestants remains a rare clinical entity. Prompt clinical recovery can be achieved with early diagnosis and supportive treatment. A detailed clinical history specifically inquiring about the use of these medications is imperative for an early diagnosis. Moreover, a precise etiology establishment is imperative to avoid subsequent exposure and recurrence in cases of drug-induced IC. Therefore, healthcare providers should maintain a high index of clinical suspicion for oral decongestant-related acute IC in patients presenting with unexplained colitis symptoms. Even though it is uncommon, this serious complication can be avoided by limiting the use of oral decongestants for mild symptoms of common cold. After initial detection, patients should be educated to avoid phenylephrine and pseudoephedrine-containing OTC and herbal formulations.

Conflicts of interests

The authors declare that they have no conflict of interest.

References

1. Yadav S, Dave M, Edakkanambeth Varayil J, Harmsen WS, Tremaine WJ, Zinsmeister AR, *et al.* A population-based study of incidence, risk factors, clinical spectrum, and outcomes of ischemic colitis. Clin Gastroenterol Hepatol 2015;13:731-8.

2. Montoro MA, Brandt LJ, Santolaria S, Gomollon F, Sánchez Puértolas B, Vera J, *et al.* 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 2011;46:236-46.

3. Amini A, Nagalli S. Bowel Ischemia. 2021 Nov 25. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554527/ Accessed: July 05, 2022.

4. Ahmed M. Ischemic bowel disease in 2021. World J Gastroenterol. 2021 Aug 7;27(29):4746-4762

5. DynaMed. Decongestant Toxicity - Emergency Management. EBSCO Information Services. Accessed August 01, 2022. https://www.dynamed.com/management/decongestant-toxicity-emergency-management.

6. United States of America. United States Code. Combat Methamphetamine Act of 2005, 21 U.S.C. § 830. 2011.

7. Health Canada. Summary safety review—Over-the-Counter Products Containing Pseudoephedrine - Assessing the Potential Risk of Inflammation and Injury of the Large Intestine due to Insufficient Blood Supply (ischemic colitis). Ottawa, ON: Health Canada; 2016. Accessed August 01, 2022.

8. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.

9. Schneider RP. Ischemic colitis caused by decongestant? J Clin Gastroenterol 1995;21:335–336.

10. Dowd J, Bailey D, Moussa K, Nair S, Doyle R, Culpepper-Morgan JA. Ischemic colitis associated with pseudoephedrine: four cases. Am J Gastroenterol 1999;94:2430-4.

11. Klestov A, Kubler P, Meulet J. Recurrent ischaemic colitis associated with pseudoephedrine use. Intern Med J 2001;31:195–6.

12. Lichtenstein GR, Yee NS. Ischemic colitis associated with decongestant use. Ann Intern Med 2000;132:682.

13. Traino AA, Buckley NA, Bassett ML. Probable ischemic colitis caused by pseudoephedrine with tramadol as a possible contributing factor. Ann Pharmacother 2004;38:2068–70.

14. Ward PW, Shaneyfelt TM, Roan RM. Acute ischaemic colitis associated with oral phenylephrine decongestant use. BMJ Case Rep 2014;2014:bcr2013202518.

15. Sherid M, Samo S, Husein H, Sulaiman S, Vainder JA. Pseudoephedrine-induced ischemic colitis: case report and literature review. J Dig Dis 2014;15:276-80.

16. Lee JM, Sun SO, Jung JO, Yoo JW, Kim JY. Cases of Ischemic Colitis Associated with Pseudoephedrine. Korean J Intern Med 2014;2014:109.

17. Ambesh P, Siddiqui S, Obiagwu C, Vincent D, Patel J, Somal N, et al. Pseudoephedrine Associated Ischemic Colitis. Am J Ther 2018;25:e604-e606.

18. Aziz M, Pervez A, Fatima R, Bansal A. Pseudoephedrine Induced Ischemic Colitis: A Case Report and Review of Literature. Case Rep Gastrointest Med 2018;2018:1-4.

19. El-Alali E, Alhmoud T. Acute Ischemic Colitis due to Oral Phenylephrine. ACG Case Rep J 2020;7:e00459.

20. Shehata A, Rajiv Mallipudi R, Khan Q, Itidiare M, Alquran L, Matin S, *et al.* Double Trouble: A Rare Case of Recurrent Ischemic Colitis Due to Pseudoephedrine. Am J Gastroenterol 2019:114;S898.

21. Goraya MHN, Awan JR, Saleem HMK, Inayat F, Tarar ZI, Akhtar Z *et al*. Acute Ischemic Colitis Secondary to Oral Phenylephrine: An Unusual Adverse Effect of a Common Drug. Am J Gastroenterol 2021;116:S777-S778.

22. Cappell MS. Colonic toxicity of administered drugs and chemicals. Am J Gastroenterol 2004;99:1175-90.

23. Farooq U, Alcantar D, Ahmed Z, Abegunde AT. Outcomes of Vasoconstrictor-Induced Non-Occlusive Mesenteric Ischemia of Colon: A Systematic Review. Clin Med Res 2022;20:164–9.

24. Wiener I, Tilkian AG, Palazzolo M. Coronary artery spasm and myocardial infarction in a patient with normal coronary arteries: Temporal relationship to pseudoephedrine ingestion. Catheter Cardiovasc Diagn 1990;20:51-53.

25. Hengstmann JH, Goronzy J. Pharmacokinetics of 3H-phenylephrine in man. Eur J Clin Pharmacol 1982;21:335-41.

26. Kanfer I, Dowse R, Vuma V. Pharmacokinetics of oral decongestants. Pharmacotherapy 1993;13:116S-128S.

27. Atkinson HC, Stanescu I, Salem II, Potts AL, Anderson BJ. Increased bioavailability of phenylephrine by co-administration of acetaminophen: results of four open-label, crossover pharmacokinetic trials in healthy volunteers. Eur J Clin Pharmacol 2015;71:151-8.

28. Sherid M, Samo S, Sulaiman S, Husein H, Sethuraman SN, Thiruvaiyaru D, *et al*. Comparison of Ischemic Colitis in the Young and the Elderly. WMJ 2016;115:196-202.

29. Yngvadottir Y, Karlsdottir BR, Hreinsson JP, Ragnarsson G, Mitev RUM, Jonasson JG, *et al*. The incidence and outcome of ischemic colitis in a population-based setting. Scand J Gastroenterol 2017;52:704-710.

30. Reame NE, Kelche RP, Beitins IZ, Yu MY, Zawacki CM, Padmanabhan V. Age effects of follicle-stimulating hormone and pulsatile luteinizing hormone secretion across the menstrual cycle of premenopausal women. J Clin Endocrinol Metab 1996;81:1512-8.

31. Santoro N, Brown JR, Adel T, Skurnick JH. Characterization of reproductive hormonal dynamics in the perimenopause. J Clin Endocrinol Metab 1996;81:1495-501.

32. Gilligan DM, Quyyumi AA, Cannon RO 3rd. Effects of physiological levels of estrogen on coronary vasomotor function in postmenopausal women. Circulation 1994;89:2545-51.

33. Hashimoto M, Akishita M, Eto M, Ishikawa M, Kozaki K, Toba K, *et al*. Modulation of endothelium-dependent flow-mediated dilatation of the brachial artery by sex and menstrual cycle. Circulation 1995;92:3431-5.

34. Wessler S. Estrogen-associated thromboembolism. Ann Epidemiol 1992;2:439–43.

35. Mishell DR, Jr. Oral contraception: Past, present, and future perspectives. Internat J Fertil 1992;37:7–18.

36. Gerstman BB, Piper JM, Tomita DK, Ferguson WJ, Stadel BV, Lundin FE. Oral contraceptive estrogen dose and the risk of deep venous thromboembolic disease. Am J Epidemiol 1991;133:32-7.

37. Cubiella Fernández J, Núñez Calvo L, González Vázquez E, García García MJ, Alves Pérez MT, Martínez Silva I, *et al*. Risk factors associated with the development of ischemic colitis. World J Gastroenterol 2010;16:4564-9.

38. Longstreth GF, Yao JF. Epidemiology, clinical features, high-risk factors, and outcome of acute large bowel ischemia. Clin Gastroenterol Hepatol 2009;7:1075-80.

39. Feuerstadt P, Brandt LJ. Colon ischemia: recent insights and advances. Curr Gastroenterol Rep 2010;12:383-90.

40. Iacobellis F, Narese D, Berritto D, Brillantino A, Di Serafino M, Guerrini S, *et al*. Large Bowel Ischemia/Infarction: How to Recognize It and Make Differential Diagnosis? A Review. Diagnostics (Basel) 2021;11:998.

41. Saleem S, Ishtiaq R, Inayat F, Aziz M, Bleibel W. Gastrointestinal and Liver Manifestations in COVID-19 Population. Middle East J Dig Dis 2021;13:281-286.

42. Rahman AU, Inayat F, Ali S, Zahid E, Charles R. The role of oral vancomycin in inducing remission for biologic-experienced ulcerative colitis with concomitant primary sclerosing cholangitis and liver transplantation. Clin J Gastroenterol 2021;14:159-164.

43. Inayat F, Ullah W, Hussain Q, Abdullah HMA. Dieulafoy's lesion of the colon and rectum: a case series and literature review. BMJ Case Rep 2017;2017:bcr2017220431

44. Xu Y, Xiong L, Li Y, Jiang X, Xiong Z. Diagnostic methods and drug therapies in patients with ischemic colitis. Int J Colorectal Dis 2021;36:47-56.

45. Mehmood A, Abdullah HMA, Inayat F, Ullah W. Wolf in the sheep's clothing: intestinal angioedema mimicking infectious colitis. BMJ Case Rep 2018;11:e226682.

46. Elder K, Lashner BA, Al Solaiman F. Clinical approach to colonic ischemia. Cleve Clin J Med 2009;76:401-409.

47. Rizwan R, Feuerstadt P. Bad blood: ischemic conditions of the large bowel. Curr Opin Gastroenterol 2022;38:72-79.

48. Malik A, Inayat F, Goraya MHN, Shahzad E, Zaman MA. Severe Acute Colonic Diverticular Bleeding: The Efficacy of Rapid Bowel Preparation With 1 L Polyethylene Glycol Ascorbate Solution and Direct Endoscopic Hemoclipping for Successful Hemostasis. J Investig Med High Impact Case Rep 2021;9:2324709621994383.

49. Zou X, Cao J, Yao Y, Liu W, Chen L. Endoscopic findings and clinicopathologic characteristics of ischemic colitis: a report of 85 cases. Dig Dis Sci 2009;54:2009-2015.

50. Inayat F, Hussain Q, Shafique K, Tasleem SH, Hurairah A. Cytomegalovirus Colitis in Immunocompetent Patients. Cureus 2016;8:e869.

51. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239–245.

52. Brandt LJ, Feuerstadt P, Longstreth GF, Boley SJ; American College of Gastroenterology. ACG clinical guideline: epidemiology, risk factors, patterns of presentation, diagnosis, and management of colon ischemia (CI). Am J Gastroenterol 2015;110:18-45.

53. Cosme A, Montoro M, Santolaria S, Sanchez-Puertolas AB, Ponce M, Durán M, *et al*. Prognosis and follow-up of 135 patients with ischemic colitis over a five-year period. World J Gastroenterol 2013;19:8042-6.

54. Sherid M, Sifuentes H, Samo S, Sulaiman S, Husein H, Tupper R, *et al*. Risk factors of recurrent ischemic colitis: a multicenter retrospective study. Korean J Gastroenterol 2014;63:283-91.

Figures and tables

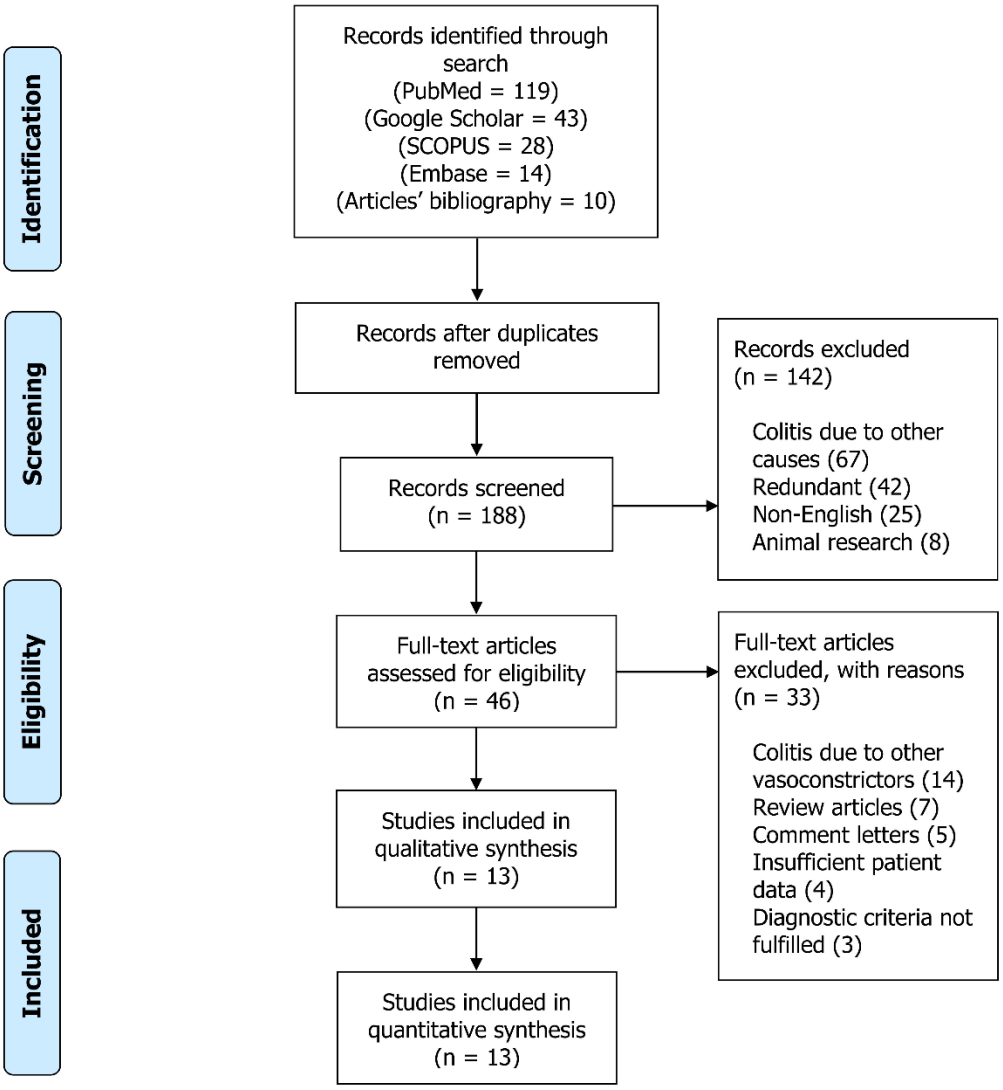

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the search methodology for data synthesis regarding acute ischemic colitis secondary to oral decongestants.

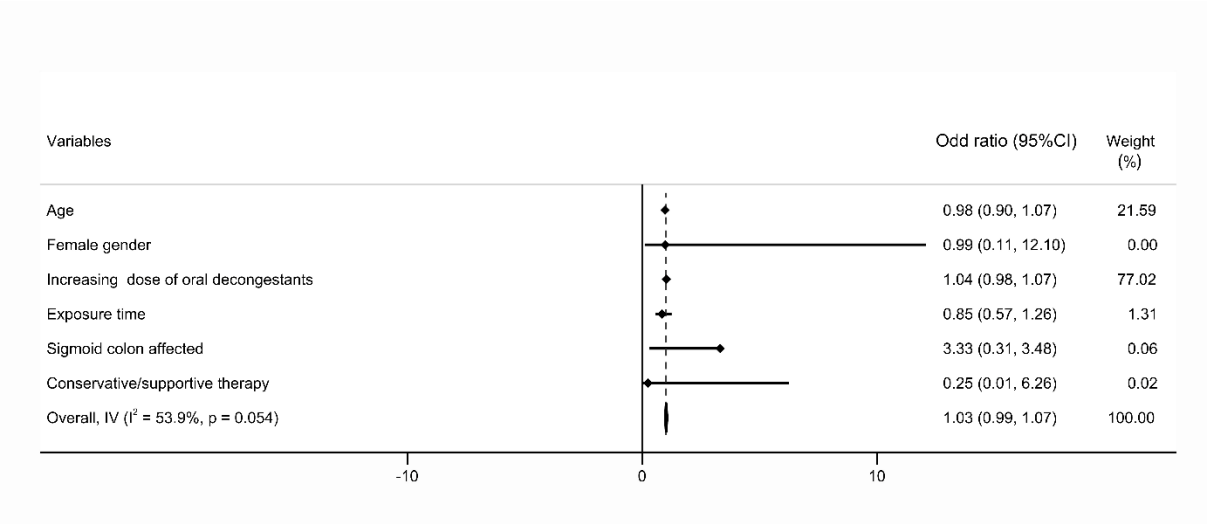

Figure 2. Forest plot showing effect size (odds ratios) of factors associated with acute ischemic colitis recurrence following oral decongestant use.

Table 1. Patient characteristics in cases of acute ischemic colitis secondary to the use of oral decongestants.

Authors, year	Age/ gender	Country, ethnicity	Clinical presentation	Comorbid conditions	Bowel habits	OTC oral decongestant containing product	Exposure time	Abnormal laboratory findings	Diagnostic investigation	Affected colon
Schneider et al. 1995 [9]	58/F	USA	Cramping abdominal pain, rectal bleeding	Previously healthy, HRT >15 years	Normal	Efidac/24 (pseudoephedrine 240 mg daily)	5 days	WBC 12,500/uL, hematocrit 43%	Colonoscopy	Upper sigmoid colon
Dowd et al. 1999 [10]	37/F	USA, White	Lower abdominal cramps, 60 episodes of bloody diarrhea	Sinusitis, depression, hypercholesterolemia, acne, former smoker, perimenopausal	Normal	Sudafed-D (pseudoephedrine 30 mg, acetominophen 500 mg) twice daily	7 days	WBC 18.7 x 10^9/L	Flexible sigmoidoscopy	20 cm from the anal verge to 8 cm into the distal transverse colon
Dowd et al. 1999 [10]	44/F	USA, White	Left-sided abdominal pain	Previously healthy, perimenopausal	Normal	Sudafed Plus Allergy (containing 30 mg pseudoephedrine) 2–3 times daily	7 days	WBC 12.0 x 10^9/L	Colonoscopy	Splenic flexure to the descending colon
Dowd et al. 1999 [10]	46/F	USA, White	Lower abdominal pain associated with bloody stools	Chronic sinusitis, allergic rhinitis, perimenopausalon HRT	Normal	Trinalin (azatadine maleate 1 mg and pseudoephedrine sulfate 120 mg)	6 days	WBC 13.3 x 10^9/L, ANA 1:40	Colonoscopy	Sigmoid to the splenic flexure
Dowd et al. 1999 [10]	50/F	USA, White	Abdominal pain and passage of nine bright red stools per rectum	Ulcerative colitis quiescent for 10 years, perimenopausal	Normal	30 mg pseudoephedrine, 500 mg acetominophen, and 2 mg chlorpheniramine maleate twice daily	7 days	WBC 15.0 x 10^9/L	Colonoscopy	Splenic flexure from 35–48 cm
Klestov et al. 2001 [11]	51/F	Australia, Caucasian	Colicky abdominal pain, vomiting, hematochezia	HTN, tension headaches, depression, left-knee osteoarthritis, right hemicolectomy	Normal	Nucosef daily (14.9 mg codeine + 60 mg pseudoephedrine) for 2 years and 900 mg daily pseudoephedrine before each hospitalizations	2 years	WBC 18.5 × 10^9/L, ESR 93 mm/h, CRP 33 mg/L	Laparotomy	Right colon and terminal ileum
Lichtenstein et al. 2000 [12]	33/M	USA	Lower abdominal cramps, diarrhea, hematochezia	Chronic asthma on albuterol and corticosteroid inhalers	Normal	Sudafed (pseudoephedrine HCl 120 mg twice daily	5 days	Not reported	Colonoscopy	Descending colon
Traino et al. 2004 [13]	46/M	Australia, White	Abdominal pain, bloody stools, dizziness, nausea, sweating	Chronic low back pain, tramadol 150 mg/day, diazepam 5 mg/day, and celecoxib 200 mg/day, smoking cessation 10 yr	Tramadol-related constipation	Pseudoephedrine HCl 30 mg, dextromethorphan hydrobromide 10 mg, guaifenesin 100 mg, and acetaminophen 250 mg	7 days	Normal results	Colonoscopy	Descending colon below the splenic flexure
Ward et al. 2014 [14]	70/F	USA, African American	Nausea, vomiting, lower abdominal pain (cramping), and hematochezia	HTN, HLD, HPT, PTX, diverticulosis, glaucoma, PTSD, Remote 5-pack-year smoking	Normal	Phenylephrine bitartrate 7.8 mg, aspirin 325 mg, and chlorpheniramine maleate 2 mg	Not reported	WBC 22.3 x 10^9/L	CT abdomen and pelvis, colonoscopy	Splenic flexure, sigmoid and descending colon
Sherid et al. 2014 [15]	49/F	USA	Abdominal pain,	Allergic rhinitis	Normal	Sudafed (Pseudoephedrine)	5 days	WBC 13.1 × 10^9/L	CT abdomen and pelvis,	Sigmoid

			bloody diarrhea, nausea			120 mg twice daily			colonoscopy	and descending colon
Lee et al. 2014 [16]	79/F	Korea, East Asian	Colicky abdominal pain followed by hematochezia	HTN	Normal	Pseudoephedrine	14 days	Not reported	CT abdomen and pelvis, colonoscopy	Colonic ischemia
Lee et al. 2014 [16]	81/F	Korea, East Asian	Colicky abdominal pain followed by hematochezia	HTN	Normal	Pseudoephedrine	14 days	Not reported	CT abdomen and pelvis, colonoscopy	Colonic ischemia
Lee et al. 2014 [16]	53/M	Korea, East Asian	Colicky abdominal pain followed by hematochezia	Previously healthy	Normal	Pseudoephedrine	7 days	Not reported	CT abdomen and pelvis, colonoscopy	Colonic ischemia
Ambesh et al. 2017 [17]	56/F	USA	LLQ abdominal pain, hematochezia	GERD, HTN, hemorrhoids, stopped smoking 3 years ago, postmenopausal	Normal	Pseudoephedrine hydrochloride, 10 mg 4 times a day	30 days	WBC 9.7 K/mL; serum lipase 11 U/L, ALP 108 IU/L, stool hemoccult +	CT abdomen and pelvis, colonoscopy	Distal descending and sigmoid colon
Aziz et al. 2018 [18]	54/F	USA, Caucasian	Hematochezia, LLQ abdominal pain	Previously healthy	Normal	10 mg pseudoephedrine 4 times daily	1 day	Hemoglobin 11.5 mg/dl, hematocrit 34.5%, ESR 31 mm/hr, CRP 2.15 mg/dl	CT abdomen and pelvis, colosnoscopy	Sigmoid colon, descending colon and splenic flexure along with internal and external hemorrhoids
El-Alali et al. 2019 [19]	34/M	USA, White	Lower abdominal pain (cramping), hematochezia	Smokeless tobacco use, BMI 43 kg/m^2	Normal	Phenylephrine HCl 5 mg, acetaminophen 325 mg, and dextromethorphan hydrobromide 10 mg	2 days	WBC 11.9 x 10^9/L	CT abdomen and pelvis, colonoscopy	Splenic flexure, sigmoid and descending colon
Shehata et al. 2019 [20]	64/F	USA	LLQ pain, hematochezia, afebrile, normotensive	HTN, seasonal allergies, Allegra-D-related colonic ischemia	Normal	Claritin-D (loratadine and pseudoephedrine)	2 days	Hemoglobin 14.9 g/dL, WBC 15,100/mL	CT abdomen and pelvis, colonoscopy	Sigmoid area
Goraya et al. 2021 [21]	23/F	USA, Caucasian	LLQ pain, hematochezia	Previously healthy	Normal	Phenylephrine HCl 10 mg, acetaminophen 650 mg, and dextromethorphan hydrobromide 20 mg	3 days	WBC 14.3 x 10^9/L	CT abdomen and pelvis, colonoscopy	Descending colon

Abbreviations: OTC, over the counter; HRT, hormone replacement therapy; LLQ, left lower quadrant; WBC, white blood cell; BMI, body mass index; HLD, hyperlipidemia; HPT, hyperparathyroidism; PTX: total parathyroidectomy; PTSD, post-traumatic stress disorder

Table 2. Clinical outcomes of acute ischemic colitis associated with oral decongestant use.

Authors	**Biopsy-proven IC**	**Associated findings**	**Other etiologies excluded**	**Treatment**	**Rechallenge**	**Naranjo score**	**Clinical outcome, hospital stay** (days)	**Follow-up duration**	**Recurrence**
Schneider et al. 1995 [9]	Yes	Not reported	Yes	Conservative treatment	No	6	Resolved	Not reported	No
Dowd et al. 1999 [10]	Yes	LLQ cramps, tenderness, rectal blood	Yes	Empirical metronidazole and ciprofloxacin; supportive therapy	No	7	Resolved, 3 days	12 months	No
Dowd et al. 1999 [10]	No	Orthostasis	Yes	Supportive treatment	No	7	Resolved, 3 days	10 months	No
Dowd et al. 1999 [10]	Yes	Orthostasis, abdominal tenderness, guaiac-positive stool	Yes	Misdiagnosed in the first episode then treated supportively and Trinalin cessation	No	8	Resolved	12 months	Yes
Dowd et al. 1999 [10]	Yes	Abdominal tenderness, rectal blood	Yes	Conservative treatment	No	7	Resolved	1 month	No
Klestov et al. 2001 [11]	Yes	Peritonitis requiring emergency laparotomy	Yes	First hospitalization: Right hemicolectomy Second hospitalization: ileocolic resection	No	10	Resolved	10 months	Yes
Lichtenstein et al. 2000 [12]	Yes	Not reported	Yes	Conservative treatment	No	7	Resolved	10 months	No
Traino et al. 2004 [13]	Yes	LLQ tenderness, rectal blood clots, *H. pylori*-positive	Yes	Managed conservatively	No	7	Resolved, 7 days	20 months	Yes
Ward et al. 2014 [14]	Yes	Elevated BP, LLQ tenderness	Yes	Supportive therapy	No	8	Resolved	Not reported	No
Sherid et al. 2014 [15]	Yes	LLQ tenderness, rectal blood	Yes	IV hydration, bowel rest and pain control	No	8	Resolved, 4 days	Not reported	No
Lee et al. 2014 [16]	No	Not reported	Yes	Supportive therapy	No	6	Resolved, 7~10 days	Not reported	No
Lee et al. 2014 [16]	No	Not reported	Yes	Supportive therapy	No	6	Resolved, 7~10 days	Not reported	No
Lee et al. 2014 [16]	No	Not reported	Yes	Supportive therapy	No	6	Resolved, 7~10 days	Not reported	No
Ambesh et al. 2017 [17]	Yes	Nonbloody, nonbilious vomiting	Yes	IV pantoprazole, morphine, clear liquid diet	No	7	Resolved	Not reported	No
Aziz et al. 2018 [18]	Yes	LLQ tenderness, rectal blood	Yes	NPO, supportive treatment	No	8	Resolved, 3 days	Not reported	No
El-Alali et al. 2019 [19]	Yes	Distended abdomen, LLQ tenderness	Yes	Managed conservatively	No	8	Resolved	2 months	No
Shehata et al. 2019 [20]	Yes	LLQ tenderness	Yes	NPO, IV fluids, antibiotics	Yes	11	Resolved	7 years	Yes
Goraya et al. 2021 [21]	Yes	LLQ tenderness, hypoactive bowel sounds	Yes	IV fluids and antidiarrheal medication	No	8	Resolved, 4 days	2 months	No

***Abbreviations*:** IC, ischemic colitis; LLQ, left lower quadrant; BP, blood pressure; IV, intravenous; NPO, nil per os.