EXPERT OPINION



# Ulcerative proctitis: an update on the pharmacotherapy and management

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***Introduction:*** Ulcerative colitis (UC) presents as proctitis in approximately a quarter of the patients. It may progress into left-sided or extensive colitis in up to 50% of cases upon long-term follow-up.
***Areas covered:*** Currently available data on ulcerative proctitis are summarized and critically reviewed. Extensive literature search (MEDLINE) was performed to identify relevant articles up to March 2014.
***Expert opinion:*** The short-term goal of the treatment in UC is to induce remission, whereas long-term goals are to maintain remission and prevent disease progression. Topically administered 5-aminosalicylates (5-ASA) and corticosteroids are effective in the treatment of proctitis, although they seem to be underused in everyday practice. Locally administered 5-ASA preparations are more effective than oral compounds. The combination of topical and oral 5-ASA and steroids should be considered for escalation of treatment. Refractory patients should be re-evaluated to exclude for compliance failures, infections or proximal disease extent. True refractory or steroid-dependent patients may require immunomodulators or biological therapy. Alternative medicine can be used complementarily, while experimental approaches are reserved for patients failing conventional medication. Proctocolectomy may be the last resort of treatment. Upon long-term, 5-ASA maintenance treatment is indicated in all UC cases to prevent relapse and disease progression.

**Keywords:** azathioprine, infliximab, steroids, therapy, ulcerative colitis, ulcerative proctitis, 5-aminosalicylates

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## 1. Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are the two main types of chronic inflammatory bowel diseases (IBD). UC is considered to develop due to a dysregulated immune response against the commensal gut microflora in a genetically predisposed individual [1]. Although, the precise trigger of the disease is unknown, the common final pathway is a vicious circle of mucosal inflammation and disrupted epithelial barrier function [1]. UC is characterized by colonic inflammation limited to the mucosa. It typically involves the rectum and may extend proximally in a continuous fashion. Depending on disease extent, UC can be classified as proctitis (E1, inflammation limited to the rectum), left-sided colitis (E2, inflammation terminating at the splenic flexure) or extensive colitis (E3) according to the Montreal classification [2]. However, some patients with proctitis or left-sided colitis may also exhibit a caecal patch of inflammation [3].

Incidence rates for UC vary from 0.5 to 24.5 per 100,000 person-years worldwide [4]. Approximately, a quarter of UC patients present with proctitis at the time of diagnosis [5]. In comparison, left-sided colitis is the initial diagnosis in half of the patients and extensive colitis in another quarter of the patients [5]. Importantly, upon 5-year follow-up proximal extension of ulcerative proctitis (UP) may



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**Article highlights.**

- The short-term goal of treatment in proctitis is to induce remission, whereas long-term goals are to maintain remission and prevent disease progression.
- In mild proctitis topical 5-ASA, in moderate-to-severe proctitis a combination of oral and topical 5-ASA preparations are considered as first-line treatment. In severe proctitis, topical and oral corticosteroids should be considered additionally.
- Patients refractory to combined topical and systemic 5-ASA and steroid therapy should be reinvestigated for other causes of therapeutic failure. In true refractory patients escalation of treatment to thiopurines and anti-TNF can be recommended.
- Proctocolectomy with ileal pouch anal anastomosis is considered as the last resort of treatment.
- Long-term maintenance therapy is recommended. The choice of maintenance treatment (topical and/or oral 5-ASA, thiopurines or anti-TNF) depends on previous disease severity and response to treatment.

This box summarises key points contained in the article.



occur in 20 – 28% of the patients, with 4 – 10% progressing to extensive colitis [6,7]. Long-term epidemiological studies show that up to half of the proctitis patients exhibit proximal disease extension 10 years after diagnosis [7-10]. Furthermore, the probability for disease progression was 53% upon 25 years of patients' follow-up [9]. Increased disease severity upon diagnosis, as indicated by both the endoscopic and total Mayo score, and corticosteroid use were associated with disease extension. Additionally, chronic, continuous and relapsing disease courses were also related to extension of mucosal inflammation [8]. Evidence suggests that prolonged oral mesalazine treatment may prevent proximal spread of rectal inflammation, while topical therapy prevents disease relapse [11,12]. Therefore, while the short-term goal of treatment in proctitis is to induce remission, long-term goals are to maintain remission and prevent disease progression.

This article aims to review and evaluate available data on the management of UP. Of note, only few data are available exclusively on the treatment of UP. Studies usually include patients with proctitis and distal colitis without clear distinction between the two subgroups [13]. In addition, patients with proctitis only were excluded from biological studies focusing on UC, such as the ULTRA trial on adalimumab, the PURSUIT trials on golimumab or the GEMINI trial on vedolizumab [14-17].

## 2. Management of ulcerative proctitis

### 2.1 Active proctitis

#### *2.1.1 Formulation and delivery*

Rectally administered topical agents represent the first-line therapeutic option in proctitis, as they directly target the site of inflammation when sufficient contact time is allowed to reach effective mucosal drug concentration. In addition, side effects are uncommon, as they are rarely associated with significant serum concentrations. Drug formulations such as suppository, foam and enema enable optimized delivery to the affected mucosa. Suppositories seem to be more appropriate than enemas in the treatment of proctitis, as although the latter may reach the splenic flexure, its maximum spread is localized from 11 to 40 cm from the anal verge [18,19]. Liquid and foam mesalazine enemas seem to be equally effective in the treatment of left-sided colitis and proctitis [20].

Delivery systems of oral 5-aminosalicylate (5-ASA) compounds can be divided into azo-compounds, controlled release, pH-dependent (either pH6 or pH7) and composite (pH-dependent combined with controlled release) types [21]. Although data are abundant on different delivery systems, yet evidence for difference in efficacy is weak.

#### *2.1.2 5-Aminosalicylates*

Topical 5-ASA-induced remission in active proctitis and distal colitis was 31 – 80% (median 67%) compared with 7 – 11% in patients given placebo in a meta-analysis of 11 trials including 778 patients [22]. Single dose of mesalazine suppository 1 g daily was shown to be equally effective and better tolerated than mesalazine 500 mg suppository twice (b.i.d.) or thrice daily (t.i.d.) [23,24]. Daily dose of 1 g mesalazine suppository seems optimal, and no dose response has been observed with regard to topical treatment [25]. According to a recent multicentre, randomized, double-blind, placebo-controlled study, endoscopic remission rates after 4 weeks of treatment with 1 g mesalazine or placebo suppository were 83.8% versus 36.1% ($p < 0.0001$) [26]. The percentage of patients without rectal bleeding was significantly higher already after the third day of treatment [26]. In comparison with topical steroids, topical mesalazine proved to be more effective in terms of clinical symptoms (OR = 2.42, 95%CI: 1.72 – 3.41), endoscopy (OR = 1.89, 95%CI: 1.29 – 2.76) or histology (OR = 2.03, 95%CI: 1.28 – 3.20) [27].

Oral 5-ASAs are less effective than topical 5-ASAs in treating proctitis, which may be due to the rapid transit and decreased contact time with the inflamed mucosa, and the relatively low concentration of the drug reaching the rectum [28,29]. However, oral 5-ASAs seem to be associated with better patient compliance. A recent Cochrane review showed that mesalazine exhibits the same therapeutic benefit in UC as its prodrug, sulfasalazine, in inducing remission and is better tolerated by patients [30]. The rate of adverse events was 29% in the sulfasalazine-treated patients compared with 15% in the mesalazine-treated patients (relative risk 0.48, 95% CI 0.37 – 0.63) [30]. Sulfasalazine is associated with side effects such as nausea, vomiting, abdominal pain, fever, skin rash, neutropenia, male infertility, folate deficiency, neuropathy, autoimmune haemolysis and rarely with nephrotoxicity, hepatotoxicity or pancreatitis. Once-daily dosing of 5-ASA (2 g/day) was shown to be as efficacious as conventional dosing and may also result in improved adherence [30,31]. In

mild-to-moderate UC, 2.4 g/day of delayed release oral mesalazine (Asacol) appeared effective for induction. However, patients with moderate disease activity may benefit from a higher dose of 4.8 g as shown by the ASCEND trials [32-34].

There have been no dedicated trials to evaluate combination therapy of topical and oral mesalazine in proctitis. However, combination therapy induces faster relief of symptoms and significantly greater change in the Disease Activity Index than either topical or oral mesalazine alone for colitis extending no more than 50 cm from the anal verge [35].

#### 2.1.3 *Corticosteroids*

Rectally administered corticosteroids are also effective in inducing remission in UP [36]. Rapidly metabolizing corticosteroids with low systemic bioavailability result in reduced adrenal suppression compared to prednisolone enemas [37]. Budesonide enemas were significantly more effective than placebo and comparable to 5-ASA enemas in inducing remission [36,38]. Other high glucocorticoid potency and low bioavailability steroids, such as beclomethasone dipropionate enemas showed similar efficacy to prednisolone and to topically administered 5-ASA in improving the symptoms and inducing remission [37,39].

Combination of topical mesalazine and steroid treatment may be of benefit. Beclomethasone dipropionate (3 mg) and mesalazine (2 g) enemas produced significantly better clinical, endoscopic and histological results than either agent alone [40]. Patients who fail to improve on a combination therapy of topical and oral 5-ASA and topical corticosteroids should be treated with oral prednisolone (40 mg/day for 1 week, reducing 5 mg/day every week) [41-43]. In patients with persisting active UC after oral steroid and 5-ASA treatment, remission was achieved within a week in 90%, by intensive intravenous steroid treatment [44]. Methylprednisolone 60 mg/24 h or hydrocortisone 100 mg four times daily are used as intravenous corticosteroids for a maximum of 7 – 10 days [43]. Although systemic corticosteroids have been widely used in the treatment of UC for the past 60 years, no studies evaluated their application in proctitis.

Interestingly, despite all convincing evidence for topical treatment of proctitis, it seems to be underused in everyday practice. In a Swiss cohort, only 39% of patients received topical therapy with 5-ASA or corticosteroids either in monotherapy or in combination with systemic treatment for remission induction [45].

## 3. Re-evaluation

In patients who fail to respond to topical and systemic 5-ASA and topical and oral corticosteroids, alternative causes of therapy failures should be investigated prior to escalation of therapy. Non-adherence to therapy was reported by 38.9% of IBD patients and was irrespective of medication type or disease activity [46]. Colitis due to hypersensitivity to 5-ASA may also mimic a flare and is difficult to distinguish. Proximal disease extension and superinfections predisposing to that, such as *Clostridium difficile* and cytomegalovirus (CMV) should be ruled out. Alternative explanations may also include inappropriate diagnosis, such as irritable bowel syndrome, CD, mucosal prolapse or cancer. Other rare causes including proctitis cystica profunda or sexually transmitted infections, such as herpetic, gonococcal or syphilitic proctitis should also be considered.

## 4 True therapy-refractory and steroid-dependent proctitis

True therapy-refractory cases can be extremely challenging to manage. Options mainly include thiopurines and anti-TNF agents. Salvage medical therapies may also include intravenous or oral cyclosporine or oral or rectal tacrolimus [47]. If not acutely ill, the patient may benefit from alternative therapies, whose efficacy is based on small open-label trials.

### 4.1 Thiopurines

There are no prospective dedicated trials to evaluate the effect of thiopurines in UC. A recent retrospective study, however, indicated that in steroid-dependent patients administration of azathioprine (AZA) resulted in significantly higher therapeutic success (71.2%) compared to patients with AZA intolerance (25.0%, $p < 0.001$) upon long-term follow-up [48]. Additionally, a recent trial randomized moderate-to-severe UC patients to receive AZA (2.5 mg/kg), infliximab (regular dosing regimen) or AZA and infliximab combination therapy. Corticosteroid-free remission at week 16 was achieved by 39.7% of patients receiving combination therapy compared with 22.1% receiving infliximab ($p = 0.017$) and 23.7% receiving AZA monotherapy ($p = 0.032$) [49].

### 4.2 Anti-TNF

In the ACT 1 and 2 trials on infliximab, 55% of patients had left-sided or distal colitis [13]. Although no separate subgroup analysis was carried out, two-thirds of UC patients failing 5-ASAs, steroids or thiopurines responded to regular infliximab dosing regimen [13]. A recent small retrospective cohort focusing on the efficacy of infliximab in therapy-refractory proctitis patients showed that infliximab-induced clinical response in 69% and remission in about 30% of patients [50]. Notably, patients with UP were excluded from most anti-TNF prospective randomized controlled trials [14-17]. Therefore, currently infliximab has the most available evidence on anti-TNF treatment of proctitis.

### 4.3 Salvage therapy

Intravenous cyclosporine (2 – 4 mg/kg/d) is also effective in patients failing intravenous corticosteroids; however, its use is limited by side effects [47]. Cyclosporine enema was not more efficient than placebo in active left-sided colitis [51]. Two pilot studies evaluated the effect of locally administered tacrolimus ointment, suppository or enema in UP and distal

colitis [52,53]. Two-thirds of the patients had clinical improvement after 4 – 8 weeks of topical tacrolimus treatment. In a large retrospective chart review, which included 18 patients with proctitis, oral tacrolimus was efficient in steroid-refractory cases [54]. However, in contrast to potential toxicity of systemic administration, tacrolimus trough levels were low after local administration and side effects were reported by none of the patients [53]. Topically administered infliximab was also shown to be effective in a refractory case previously unresponsive to intravenous induction treatment [55].

### 4.4 Experimental treatment

Rebamipide, an agent suppressing neutrophil function and stimulating epithelial cell regeneration, induced significant clinical, endoscopical and histological improvement when administered as enemas in patients with proctitis or distal colitis [56]. Case series have shown that elective appendectomy can be associated with clinical improvement or complete resolution of symptoms [57,58]. Additionally, several topical agents have been investigated, such as epidermal growth factor, ecabet sodium, butyrate, arsenic, ropivacaine, bismuth subsalicylate and thromboxane [59-61]. Although some of these agents show encouraging preliminary results, most compounds were not evaluated in greater patient numbers, and therefore, solid evidence is still lacking to suggest their use in everyday practice.

### 4.5 Complementary and alternative medicine

Complementary alternative medicine (CAM) has been popular by tradition in Asia [62]. In a recent systematic review including 14 trials on UC, aloe vera gel, *Triticum aestivum* (wheat grass juice), *Andrographis paniculata* extract (HMPL-004) and topical Xilei San (a Chinese herbal medicine with anti-inflammatory effect) were superior to placebo in inducing remission or response [63]. Additionally, curcumin was superior to placebo in maintaining remission, while *Boswellia serrata* gum resin and *Plantago ovata* seeds were as effective as mesalazine [64]. Although initial results with CAM seem to be encouraging, further trials are needed to confirm their efficacy in large patient numbers and to encourage their use in daily practice.

## 5. Surgery

Colectomy in proctitis (without disease extension) is considered in exceptional cases. The outcome of total proctocolectomy with ileal pouch anal anastomosis (IPAA) formation is good. In 263 patients who had a restorative proctocolectomy, 27 patients had surgery for distal disease and all but one patient were satisfied with the results and most patients wished that they had had surgery sooner [65]. However, complications, such as cuffitis may develop, where rectal bleeding is a characteristic feature. Mesalazine suppository 500 mg b.i.d. was effective in reducing clinical, endoscopical and histological activity in cuffitis [66]. A recent cohort examined the long-term course of cuffitis in patients after IPAA. After a median follow-up of 6 years, 33.3% of patients had 5-ASA/steroid-responsive cuffitis. In patients with 5-ASA/steroid-dependent or -refractory cuffitis, 32.8% was diagnosed with CD of the pouch and 24.1% had surgical complications [67].

## 6. Maintenance treatment

Only a small percentage of patients are able to discontinue long-term therapy without disease relapse. As disease extension and relapse can be prevented by maintenance therapy, patients are encouraged to adhere to maintenance therapy. The length of the recommended maintenance therapy in patients with long-term clinical remission is, however, conflictive. Of note, data from a US database showed that maintenance therapy is not continued in the majority of proctitis cases. Seventy per cent of UP patients who were initially treated with mesalazine suppositories, and even 40 – 50% of those patients who began oral or systemic glucocorticosteroid, did not take further medication after remission induction [68].

Traditionally, oral 5-ASA and sulfasalazine were used for maintenance treatment in UC. A recent Cochrane review reported that sulfasalazine was superior in the maintenance setting [69]. A recent meta-analysis including seven randomized-controlled trials (n = 555 patients) showed that topical mesalazine was effective in preventing relapse of distal UC [12,70]. In the study, 500 mg mesalazine b.i.d. seems to be the most efficient therapeutic regimen for maintenance with a cumulative relapse rate of 10% at 12 months (95% CI: 0 – 21) [71]. However, even intermittent topical treatment is more efficient maintenance treatment than placebo [72,73].

There are no dedicated studies to evaluate the efficacy of rectally administered corticosteroids for the maintenance treatment in proctitis. In the only randomized placebo-controlled trial, oral prednisone was ineffective in maintaining the remission induced by oral steroids at 6 months [74]. More importantly, cumulative doses may be associated with well-known steroid side effects.

Clinical trials showed benefit from thiopurine treatment in UC maintenance [75]. The 1-year relapse rates were significantly lower in patients taking AZA (36%) compared with placebo (59%, p = 0.04) [76]. In a recent randomized clinical trial, steroid-dependent UC patients treated with AZA (2 mg/kg/d) had a significantly higher rate of clinical and endoscopic remission, leading to steroids withdrawal in a greater percentage of cases compared with patients receiving only high-dose oral 5-ASA (53 vs 19%, p = 0.006) [77]. Finally, a randomized study suggests a favourable role of probiotics, which was comparable to mesalamine in the maintenance treatment in UC [78].

## 7. Colorectal cancer risk and surveillance

Longstanding UC is associated with increased colorectal cancer (CRC) risk. Although risks estimates vary, it is

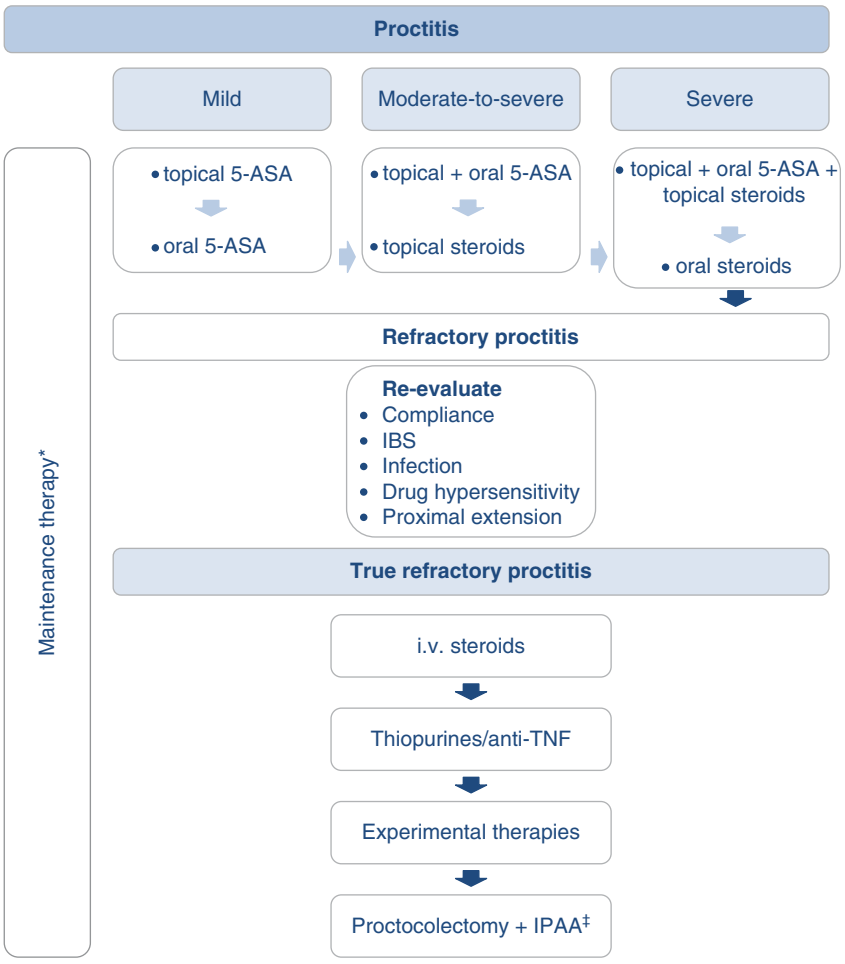


**Figure 1. Treatment algorithm for patients with ulcerative proctitis.**

*Depends on disease severity, induction agent and previous disease course: topical (or the combination of topical and oral) 5-ASA is recommended as first-line, immunosuppressives should be considered in steroid dependent cases, while immunosuppressives/anti-TNFs are recommended in refractory cases.

‡Considered in exceptional cases.

5-ASA: 5-Aminosalicylates; IBS: Irritable bowel syndrome; IPAA: Ileo-anal pouch anastomosis; i.v.: intravenous.

associated with the extent, duration and severity of mucosal inflammation. A systematic review from the previous decade reported a cumulative CRC risk of 2% at 10 years, 8% at 20 years and 18% at 30 years [79]. In contrast, in a most recent meta-analysis, the cumulative CRC risk was < 1% at 10 years, 0.4 – 2% at 15 years and 1.1 – 5.3% at 20 years [80]. The reason behind the changing trend could be multifactorial including increased surveillance, changing treatment goals (full mucosal healing) and possible chemopreventive effects of 5-ASA. A recent review on 5-ASA concluded that the ability to heal colonic mucosa as well as influencing molecular pathways of carcinogenesis may contribute to possible chemoprevention [81]. With regard to disease limited to the rectum, no increased CRC risk is reported. Therefore, according to the recent ECCO guidelines after screening colonoscopy at 6 – 8 years after the onset of symptoms, inclusion in a regular surveillance colonoscopy program is not recommended in patients without proximal extension [82].

## 8. Expert opinion

The short-term goal of treatment in proctitis is to induce remission, whereas long-term goals are to maintain remission and prevent disease progression (**Figure 1**). The first-line therapy for active proctitis should be topical 5-ASA in line with the results from meta-analyses of published trials show that topical 5-ASA is superior to placebo and conventional corticosteroids in inducing remission. One gram once daily dosing of 5-ASA suppository has been shown to be equally effective and better tolerated than b.i.d. or t.i.d. suppository. Short-term remission rates may be as high as 85%. In case of suboptimal therapeutic response to topical 5-ASA, treatment can be extended with oral 5-ASA and/or topical steroids, as the combination of rectal 5-ASA with a rectal corticosteroid or oral aminosalicylate is superior to rectal 5-ASA alone [83]. Rectally administered corticosteroid therapy with suppositories or

foam is an effective alternative for patients intolerant of or unresponsive to 5-ASA.

In moderate-to-severe UP, a combination of oral and topical 5-ASA-based therapy should be considered as first-line treatment. In severe UP, oral or intravenous corticosteroids should be applied (at a maximum dose of prednisolone 40 – 60 mg, or the equivalent of methylprednisolone).

Refractory proctitis represents a difficult clinical entity for both patients and doctors. Thus, patients failing combined topical and systemic 5-ASA and steroid therapy should be reinvestigated for other causes of therapeutic failure, such as co-existing IBS, patient compliance, drug hypersensitivity, infections (e.g.,: *C. difficile*, CMV/bacterial superinfection) and proximal disease extension. In patients with refractory disease, escalation of treatment to thiopurines and anti-TNF can be recommended [84]. UP patients with severe initial disease should be considered for more aggressive treatment from the beginning, as they are more likely to develop disease extension during the course of their disease.

The efficacy of alternative treatment options, including Chinese herbal preparation, Xilai San is conflictive and warrant further investigations. The use of other experimental therapies (e.g., elective appendectomy or infliximab and cyclosporine enemas, arsenic and tacrolimus suppositories) should also be restricted for clinical trials and exceptional cases in expert centres. Nevertheless, before these potentially promising approaches become the routine part of the therapeutic armamentarium, better understanding of their mechanism of action and solid evidence for their efficacy are needed. Proctocolectomy with IPAA may be considered as ultimate treatment in refractory proctitis cases.

Long-term maintenance treatment, especially with topical (or oral) 5-ASA therapy is recommended. However, long-term adherence is suboptimal. In mild proctitis cases with long-term clinical remission, intermittent therapy or no maintenance therapy is an option. In initially moderate-to-severe cases, combined oral (1 – 1.5 g/day) and topical 5-ASA (e.g., 1 g 5-ASA suppositories three times per week) should be the treatment of choice even for maintenance. The risk of CRC is not increased in UP; therefore, routine endoscopic surveillance is not recommended.

## Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.



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