Rectal Treatment of Inflammatory Bowel Diseases

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Preface

A fundamental component of treatment for patients with ulcerative colitis is the topical and/or peroral administration of aminosalicylates (5-ASA or mesalazine). 5-ASA preparations always act locally in this case. As soon as 5-ASA is taken up by the body, metabolism and thus inactivation take place.

Unfortunately, 5-ASA preparations are only administered perorally to most patients with ulcerative colitis, even though, especially in the case of ulcerative proctitis and left-sided ulcerative colitis, rectal 5-ASA preparations in the form of a suppository, foam or enema are more effective than peroral 5-ASA preparations. If a rectal 5-ASA treatment is not sufficiently effective, rectal treatments containing steroids can be used. This applies both to remission induction and to treatment for remission maintenance.

Numerous studies in cohorts or larger treatment centers have shown that rectal treatments are not prescribed or administered often enough. This guide should clear up common misconceptions and give advice on how to make rectal treatment more acceptable for the patient. Once suitable information has been provided, acceptance of this type of treatment is much higher than generally expected.

The only case where topical treatment has no value is when colitis takes a severe course, since it is not sufficiently effective when the bowels are frequently emptied and it is not well tolerated by the patient. There is insufficient evidence on the use of rectal treatments for Crohn’s disease.

A rectal treatment is an essential component of successful treatment for ulcerative colitis.
Escalation therapy for ulcerative colitis

~70% of patients can be successfully treated with 5-ASA and/or steroids.
Introduction

Ulcerative colitis (UC) is an inflammatory bowel disease whose incidence is increasing worldwide, involving a continuous proximal spread of the inflammation from the rectum. In contrast to Crohn’s disease, the inflammation is limited to the mucosa.

As the inflammation is thus superficial, medications that reach the region of inflammation via the intestinal lumen are very effective. In the case of Crohn’s disease, in which all of the layers of the intestinal wall can be affected, this treatment option may be less effective.
In adults, ulcerative colitis most often presents as proctosigmoiditis or left-sided colitis (often also amalgamated under the name distal colitis; “distal” means that the affected area goes no further than the splenic flexure). Around 50–60% of ulcerative colitis patients have proctosigmoiditis, 20–30% left-sided ulcerative colitis and only around 20–25% extensive colitis (pancolitis). The term extensive applies when the disease affects an area beyond the splenic flexure.

As rectal treatment can be effective as far as the splenic flexure of the colon, up to 75% of patients can be treated with a rectally administered treatment that covers the entire affected area. But in the case of ulcerative pancolitis as well, a rectal treatment, in addition to systemic treatment, can aid with symptom control as the clinical presentation of watery and bloody diarrhea is primarily due to the inflammation in the distal colon. The most severe inflammation in the case of untreated ulcerative colitis is always found in the rectum.

75% of patients have a distal form of the disease that can be effectively treated with a rectal treatment.
**Treatment of ulcerative proctitis**

Ulcerative proctitis should primarily always be treated with 5-ASA suppositories (see fig. 1). When suppositories are administered, the active ingredient is better able to coat the rectal mucosa than with enema or foam preparations. Moreover, suppositories are generally better tolerated by the patient and are easier to administer.

In clinical studies where the treatment goal was a clinical remission of proctitis, however, all three rectal 5-ASA preparations (suppositories, foams or enemas) proved to be equally effective. Suppositories with 1000 mg 5-ASA once daily are very effective and can be recommended as the most practicable rectal treatment for ulcerative proctitis.\(^5, 6, 10, 19\)

![Treatment algorithm for ulcerative proctitis](image)

Fig. 1: Treatment algorithm for ulcerative proctitis
In around two thirds of patients with ulcerative proctitis, remission is achieved through rectal treatment with suppositories.\textsuperscript{17} A dose of more than 1 g 5-ASA daily as a suppository has no additional effect and therefore does not seem to be worthwhile.\textsuperscript{13}

A rectal 5-ASA treatment has proven to be more effective in inducing remission than a rectal steroid treatment.\textsuperscript{18} However, rectal administration of steroids is used as a second-line treatment for patients with ulcerative proctitis if they do not tolerate rectal treatment with 5-ASA or if they are intolerant (\textit{fig. 1}).

A true intolerance to rectal 5-ASA preparations is rare, however. Even if the patient is intolerant to oral 5-ASA, an attempt can thus be made to administer it rectally. In the case of intolerance to a rectally administered 5-ASA preparation, a different preparation may be perfectly tolerated. If symptoms persist despite adequate topical monotherapy with 5-ASA, a rectal steroid may be combined with rectal 5-ASA preparations (\textit{fig. 1}). If this measure is ineffective, it should be combined with an oral treatment (\textit{fig. 1}).\textsuperscript{8, 23}

\textbf{A 1 g 5-ASA suppository daily is just as effective as three 500 mg suppositories daily.}
Left-sided ulcerative colitis

Left-sided ulcerative colitis should initially be treated with rectal and oral 5-ASA\(^6\) (see fig. 2). Foam preparations or enemas can be used here. The initial rectal dose should be at least 1 g 5-ASA per day. Enemas are available in doses of 1, 2 and 4 g of 5-ASA, and foam preparations in doses of 1 g per administration.

When selecting a dose, the volume to be administered should be taken into account. The higher the volume, the worse the tolerance of the treatment normally is. Greater volumes result in a more urgent need to use the toilet, meaning that enemas must often be discontinued after a short time. The apparent advantage of greater coverage as a result of the greater volume is then lost.

Fig. 2: Treatment algorithm for left-sided ulcerative colitis
The volume administered in rectal treatments is between 30 ml for foam preparations and up to 100 ml for some enemas. Volumes above 60 ml are associated with worse patient adherence. The volume of the substance administered in topical treatment should therefore always be considered. The more severe the colitis is and the more inflamed the mucosal tissue, the more likely a higher volume is to cause discomfort and the urge to defecate. This means that to provide the patient with optimal treatment, it is important to know the volume administered during rectal treatment!

**The manner of administration is also important.**
The success of the treatment depends on proper information. An enema should be administered rectally while the patient is lying on their left side. This makes it easier to insert the applicator. Directly after rectal administration, the patients should lie on their left side or stomach for 20 to 30 minutes. If the patient sits or stands immediately after rectal administration, the preparation will collect entirely in the rectum and cause a strong urge to defecate. If they lie on their left side or stomach, on the other hand, the preparation can spread out in the left colon (“flow upwards”). Scintigraphic studies have shown very good distribution of rectal treatment within 30 minutes when this approach is followed.
It may be best to administer these rectal treatments primarily in the evening, as the patients are more likely to have time to lie on their stomach for 30 minutes. In principle, however, it is not necessary to keep the foam preparation or the enema in the intestine overnight. One can explain to the patient that the medication does not need to fill the intestine over the course of hours “like a reservoir”, but that the intestinal mucosa merely needs to be sufficiently coated.

Since the medication is administered in a mostly liquid form, many patients are afraid that they will become incontinent while they are asleep and leak liquid or stool in their bed. This causes the patient to become tense and sleep badly and therefore to be unsatisfied with the treatment. For many patients who receive rectal treatment, it is thus more practical to go to the toilet in the evening and evacuate the remaining liquid before they go to bed.
Many patients who can only retain the rectal treatment in the bowel for a short period of time will benefit from taking loperamide 30 minutes before the administration of a foam preparation or enema. This seems to improve tolerance of rectal treatment (although it has not been proven by studies).

If symptoms persist despite adequate rectal 5-ASA monotherapy, patients with left-sided ulcerative colitis should receive the rectal treatment combined with a rectal steroid treatment (budesonide foams, budesonide enemas or hydrocortisone foam) (*fig. 2*). If the combination of these rectal preparations is unable to induce remission, oral 5-ASA should be added to the rectal treatment. The combination of treatment with oral and rectal 5-ASA increases the odds of achieving remission.

The combination of treatment with oral and rectal 5-ASA makes sense not only for distal colitis, but also for extensive ulcerative colitis. For patients with distal ulcerative colitis, the combination leads to a significant improvement of symptoms in 88% of patients, while only 54% of sufferers see improvement with the rectal administration of 4 g 5-ASA alone. In the case of extensive ulcerative colitis, the administration of 2.4 g of oral 5-ASA alone is markedly less effective and can only bring about this outcome in around 30–40% of cases.

*If the effect is insufficient, rectal 5-ASA should be supplemented, not replaced, with oral 5-ASA.*
Extensive colitis, pancolitis

For patients with extensive ulcerative colitis or pancolitis, the initial treatment strategy consists of a combined treatment with oral and rectal 5-ASA\textsuperscript{21} (see fig. 3). Although the rectal treatment is unable to reach the right colon, a combination therapy is nevertheless beneficial for distal inflammation (especially in the rectum), which is primarily responsible for the symptoms of bleeding and diarrhea. However, this does not apply in all cases – patients with severe diarrhea do not tolerate rectal treatment well.

**Extensive ulcerative colitis**

Mild to moderate activity

\[
\text{rectal mesalazine + oral mesalazine (}> 2 \text{ g})
\]

\[
\text{Yes} \quad \text{Response / Remission} \quad \text{No}
\]

+ oral steroid

Fig. 3: Treatment algorithm for extensive colitis, pancolitis
If the combination of oral and rectal 5-ASA is not sufficient for patients with pancolitis, systemic corticosteroids should be used. In the case of extensive ulcerative colitis, systemic steroids should be used at an earlier stage than for left-sided colitis.\textsuperscript{6}

Severe forms of ulcerative colitis should primarily be treated with IV steroids. If the patient suffers more than ten episodes of diarrhea per day, orally administered preparations are barely absorbed. In severe forms of ulcerative colitis, a rectal treatment will also have little effect. However, it can be begun as soon as the symptoms improve and the frequency of diarrhea decreases.

If a patient can retain a rectal administration in the form of foam or an enema for more than 20 minutes, such treatments are also worthwhile for patients with ulcerative pancolitis.\textsuperscript{6} However, some reviews do not recommend a topical treatment for severe colitis, as it may aggravate the patient’s symptoms (stomach cramps, urge to defecate, diarrhea). This must be taken into account for each individual case and adapted to the patient’s situation.

\textit{A rectal treatment is also useful for patients with extensive ulcerative colitis or pancolitis, but should be dependent on the individual patient’s symptoms.}
Rectal treatment for remission maintenance

For ulcerative proctitis and left-sided colitis\textsuperscript{5,6}, rectal 5-ASA preparations are believed to be even more effective in maintaining remission than the oral administration of 5-ASA\textsuperscript{6,9} (see fig. 4, right-hand side). According to studies on remission maintenance in cases of ulcerative colitis\textsuperscript{6,9}, most patients do not need to receive rectal treatment daily. Administering the treatment once every three days appears to be sufficient for many patients. It would seem possible for the patient to receive the treatment over a period of seven to ten days, either distributed throughout the month, at the beginning of the month\textsuperscript{4} or two to three times a week.\textsuperscript{20}

Furthermore, no clear dose-response relationship could be proven for rectal 5-ASA for remission maintenance.\textsuperscript{6} 1 g rectal 5-ASA per day seems to be sufficient for remission maintenance.\textsuperscript{9,13}

In clinical practice, it is not always easy to determine the minimum dose of rectal 5-ASA necessary for maintaining remission. By definition, the minimum effective maintenance dose can only be discovered at the cost of another flare-up. Here, the patient’s wishes and preferences should be taken into account in order to ensure the highest possible adherence.
Extensive involvement

Distal involvement

Oral 5-ASA $\geq 1.5$ g/d; SASP 2 g/d

Rectal 5-ASA $\geq 3$ g/week

oral 5-ASA 3 g/d + possibly rectal 5-ASA

+ oral 5-ASA

Re-induction of remission

Re-induction of remission + immunosuppressive therapy or anti-TNF

Yes

Successful

No

Yes

Successful

No

Yes

Successful

No

Yes

Successful

No

Fig. 4: Treatment algorithm for remission maintenance
Can rectal treatment achieve mucosal healing?

Mucosal healing is a crucial objective of treatment for ulcerative colitis. Not only is it accompanied by a significantly lower rate of relapse and of colectomy, it also reduces the risk of colorectal carcinomas. The effectiveness of mucosal healing using rectal 5-ASA treatment was recently corroborated by a post hoc analysis of previously published studies.25, 27

**Fig. 5:** Normal mucosa  
**Fig. 6:** Mucosa with colitis

*A rectal 5-ASA treatment can induce mucosal healing in 50% of patients.*
Adherence to rectal treatment

Whether patients will adhere to rectal treatment for ulcerative colitis is constantly being called into question. But a series of studies have shown no disparity between rectal and oral treatment with regard to non-adherence in patients with ulcerative colitis. However, non-adherence rates for patients with ulcerative colitis can be up to 60%.16 The majority of ulcerative colitis patients who suffered a relapse or flare-up terminated the remission maintenance treatment.16

Adherence to remission maintenance treatment is fundamentally much worse than adherence to treatment for flare-ups,16, 28 which is not difficult to understand. The reasons for inadequate adherence to treatment appear complex. While in some investigations many patients simply seem to forget16 to take their medication, patients in other studies attribute their lack of adherence to the rectal administration (65%) or their “busy lifestyle” (40%).1 The midday dose in particular often seems to be a problem in remission maintenance treatment. This highlights once again the importance of instructing patients.

The reasons for inadequate adherence to treatment are complex
In surveys, a clear majority of patients (80%) prefer remission maintenance treatment which is administered only orally.\textsuperscript{22} Most ulcerative colitis patients, however, accept rectal treatment\textsuperscript{14, 15} when the advantages of this are explained to them in detail.\textsuperscript{7, 15, 24} The most frequently cited reason preventing patients from continuing with a rectal treatment is the urge to defecate that this form of treatment induces. According to a Spanish study, 5-ASA suppositories are tolerated very well and most patients also find them to be well-suited for year-long remission maintenance treatments.\textsuperscript{2} For enemas, as already mentioned, it was reported that the strength of the urge to defecate is correlated with the volume of the preparation administered. This also explains why most patients in clinical practice and in studies prefer foam preparations with a smaller volume.\textsuperscript{3, 12} A review published in 2010 reported contradictory results on this subject, however.\textsuperscript{19}
In clinical practice, it has proven effective (although there are no studies to back this up) for patients to take 2 mg loperamide before the topical treatment and initially lie on their left side or stomach. This prevents the volume of the preparation administered from collecting in the rectum and also reduces stool frequency.

*Lying on the stomach or left side improves retention of the volume of the preparation.*
Do physicians observe treatment guidelines and evidence?

For successful rectal treatment of ulcerative colitis, not only must the patients adhere to treatment but the doctors treating them must also adhere to the published clinical practice guidelines for treatment and the evidence that supports these guidelines. Multiple studies have shown failures to take rectal treatment options into consideration in the treatment of colitis. A survey of Spanish gastroenterologists found that only 12–17% of respondents saw a rectal treatment as a first-line treatment for distal ulcerative colitis. Only 31% of the gastroenterologists used a combination of oral and rectal 5-ASA treatment for extensive ulcerative colitis with mild to moderate severity.

A study at a large US clinic showed that three quarters of patients did not receive adequate rectal treatment. Despite available studies that show the opposite, 31–47% of gastroenterologists believe that peroral steroids are equally as effective as rectal 5-ASA treatment. This brochure should help to provide information about the importance of rectal treatment for ulcerative colitis and to convince readers of the benefits of using it consistently.
Conclusions for clinical practice

- In mild to moderate ulcerative proctitis and left-sided ulcerative colitis, rectal 5-ASA preparations are the first-line treatment.

- For extensive colitis and pancolitis, the use of rectal 5-ASA in combination with oral 5-ASA preparations also makes sense.

- Tips on administration improve patient adherence and thus treatment success.

- If rectal treatments prove insufficiently effective, they should be supplemented but not replaced.

- A rectal treatment should be tried for EVERY patient with ulcerative colitis, in accordance with the clinical practice guidelines.
References


23. Mulder CJ, Fockens P, Meijer JW, van der Heide H, Wiltink EH, Tytgat GN. Beclomethasone dipropionate (3 mg) versus 5-aminosalicylic acid (2 g) versus the combination of both (3 mg/2 g) as retention enemas in active ulcerative proctitis. Eur J Gastroenterol Hepatol. 1996;8(6):549–53.


Further literature for specialists and patients

**Therapy algorithms**
**Crohn’s disease and ulcerative colitis**
Authors: K. Herrlinger, E.F. Stange
4 pages (S7e)

**Early symptoms and differential diagnosis of inflammatory bowel diseases**
Author: J. Schölmerich
24 pages (S29e)

**Inflammatory bowel diseases of the rectum**
Authors: H. Krammer, A. Herold
18 pages (S33e)

**Salofalk® 1g Rectal Foam**
for topical therapy of ulcerative colitis
Short monograph
8 pages (S2e)
The microbiota and intestinal diseases
Authors: B.J. Campbell, J.M. Rhodes
44 pages ($19e)

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