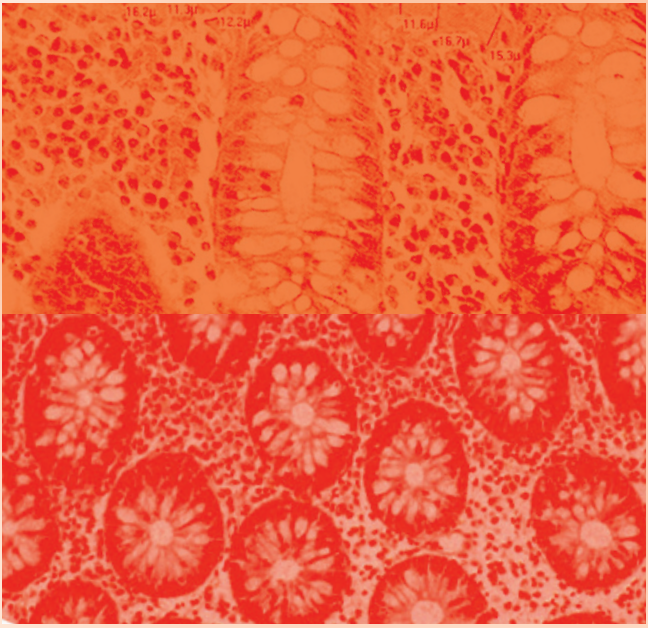
Microscopic colitis

Collagenous and lymphocytic colitis



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Contents

	Page
Introduction	5
Clinical manifestations	7
Causes and pathogenesis of microscopic colitis	10
Diagnostics	12
Treatment	15
Collagenous colitis	15
Lymphocytic colitis	18
Frequently asked questions about microscopic colitis	19

Introduction

The term *microscopic colitis* encompasses two different disorders of the colon known as *collagenous colitis* and *lymphocytic colitis.*
Both disorders are characterized by watery diarrhea and are therefore also known as watery diarrhea syndrome (Figure 1).

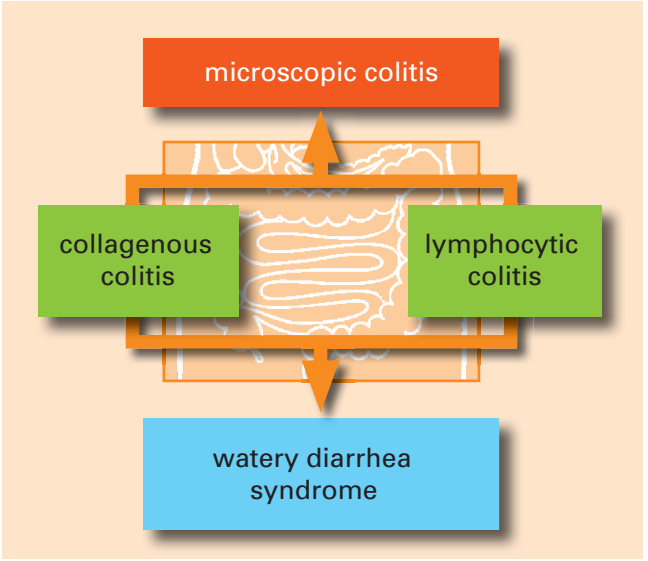

Figure 1:
Definition of microscopic colitis

The term *microscopic colitis* refers to an inflammatory disorder of the colon (colitis) which cannot be recognized with the naked eye during an endoscopy because the bowel mucosa appears normal. Small tissue samples are taken and examined under the microscope. *Microscopic colitis* can only be diagnosed microscopically.
In *collagenous colitis,* special staining of the tissue samples reveals a thickened collagen band, whereas *lymphocytic colitis* is typified by an increased number of lymphocytes, a type of white blood cell.

Since the 1980s, when *microscopic colitis* was first described, knowledge about this disorder has increased greatly. Today it is thought that the frequency of *microscopic colitis* is similar to that of the inflammatory bowel diseases Crohn's disease and ulcerative colitis.

Studies have examined various therapeutic options. To date the only drug to have been officially approved worldwide for the treatment of *collagenous colitis* is budesonide (in the form of 3 mg capsules and 9 mg granules to be taken orally). The first publications on the treatment of *lymphocytic colitis* with budesonide appeared in 2008.

The effectiveness of this substance for the acute treatment and prevention of *microscopic colitis* has been confirmed in further controlled trials.

Clinical manifestations

The primary symptom of *microscopic colitis* is watery diarrhea. This can occur suddenly and mimic an infection. A large study carried out in Sweden also reported the following symptoms:

- night-time diarrhea in almost 30% of cases
- weight loss in over 40% of cases
- abdominal pain in over 40% of cases
- nausea in over 20% of cases
- flatulence in over 10% of cases

The causes of the weight loss have not yet been fully explained, but it appears likely that in a well-intentioned attempt to restrict their diet, patients eat less and lose weight as a result.
Despite frequent diarrhea, dehydration very rarely becomes a problem.
Fecal incontinence and fatigue can occur as additional symptoms accompanying *microscopic colitis* and can reduce quality of life considerably.

In *microscopic colitis,* symptoms or disorders in other organs outside the intestine occur in 30–50% of patients; these include rheumatic pain in the joints, psoriasis of the skin or thyroid dysfunction (Figure 2). Treatment is also required for these disorders.

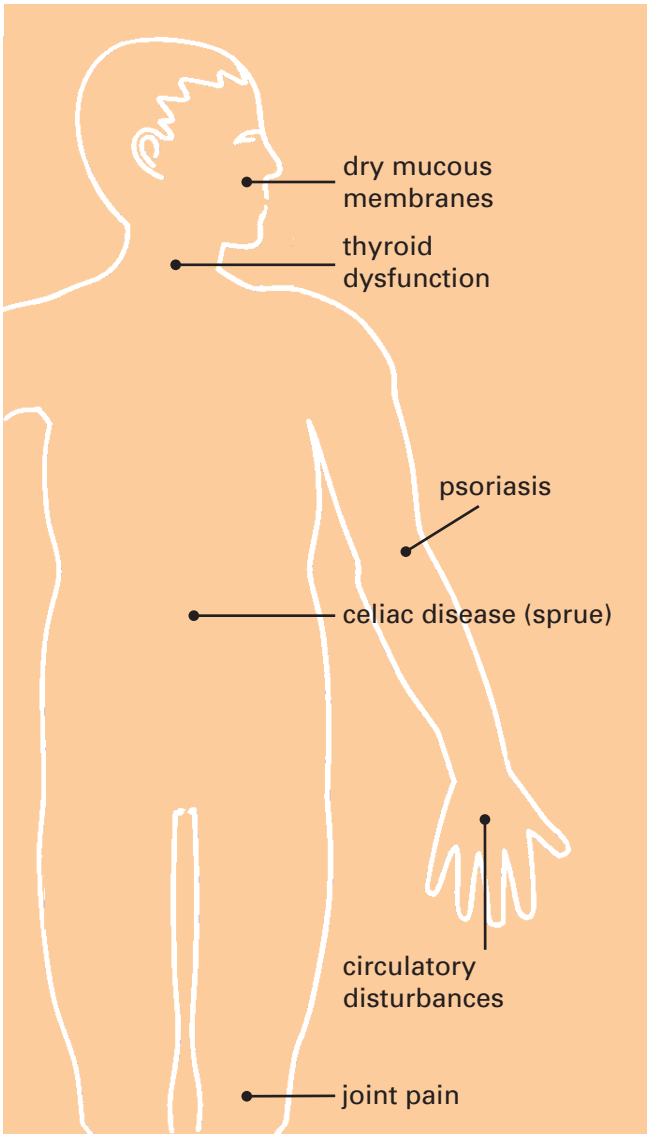

Figure 2:
Disorders that may occur concomitantly with collagenous colitis

Several studies have found that celiac disease (sprue), i.e. gluten intolerance, occurs more frequently in patients with *microscopic colitis* and vice versa. Patients with one of these disorders should therefore be examined for the other. In a recent study, the frequency of celiac disease among patients with *collagenous colitis* was reported as 12.9%.

The course of *collagenous colitis* and *lymphocytic colitis* can generally be described as benign although about 40% of patients complain of chronic – either persistent or intermittent – watery diarrhea. There is no increased risk of colorectal cancer.

When making a diagnosis, other disorders with similar symptoms must be considered and excluded.
Typical bowel ailments with diarrhea but without weight loss are irritable bowel syndrome (diarrhea-predominant) and various forms of food intolerance such as widespread lactose intolerance (reduced ability to digest the sugar in milk).

Inflammatory bowel diseases (Crohn's disease and ulcerative colitis) can usually be clearly differentiated because in these disorders, colonoscopy reveals typical changes in the bowel mucosa and the presence of ulcers. If the colon is affected, as is often the case, the diarrhea usually contains blood.

Causes and pathogenesis of microscopic colitis

The precise causes of both diseases are not yet known, but various theories are under discussion.

Some studies suggest that *collagenous colitis* may be caused by increased use of certain drugs; these include the group known as non-steroidal anti-inflammatory drugs (NSAIDs), which are usually given to treat joint pain. Drugs used to treat raised cholesterol levels or to inhibit blood clotting may be under a cloud.

Case reports suggest that proton pump inhibitors (such as omeprazole, esomeprazole and lansoprazole) may exert an influence on the development of *microscopic colitis.* The connection is not yet fully understood. It is also possible that proton pump inhibitors themselves elicit watery diarrhea and that the diagnosis of *microscopic colitis* is accelerated as a result, even though its occurrence is independent of the drug treatment.

In a recently published case-control study, the proportion of smokers was significantly higher among patients with *collagenous colitis* than among controls. This study is the first to provide evidence of a potential influence of nicotine on the development of *collagenous colitis.* In this connection, it is worth noting that nicotine also increases the permeability of the bowel mucosa.

It is also conceivable that an increase in the permeability of the bowel mucosa (the cause of which is unknown) may allow constituents of the partly-digested food (chyme) to enter the bowel wall and trigger disturbances of bowel function.
A recent study found differences between patients with *microscopic colitis* and healthy people with regard to the composition of the intestinal microbiota.

About half of patients with *lymphocytic colitis* are found to possess antibodies directed against their own body, in this case against the bowel, so this disorder may belong to the group known as autoimmune diseases.

In *collagenous colitis,* antibodies to certain bacteria are often found, even though the bacteria themselves are not. This could suggest that an inflammation caused by these pathogens has come to an end, or it could result from an increase in the permeability of the bowel wall leading to the formation of antibodies to the pathogens (e.g. Yersinia).

It is not yet clear how these phenomena lead to a thickening of the collagen band in *collagenous colitis,* or the increased occurrence of immune cells (lymphocytes) in the bowel mucosa in *lymphocytic colitis.*
However, it is known that the collagen formation in *collagenous colitis* does not result from over-production of collagen but instead from a reduction in collagen breakdown.

Interestingly, a colostomy leads to complete normalization of the collagen band in the sections of the bowel below the colostomy, and thus to the disappearance of the disorder.

Diagnostics

Colonoscopy has proved successful for confirming the diagnosis of *microscopic colitis* in patients who have had watery diarrhea for more than 4 weeks; in cases where the mucosa is endoscopically normal and no changes are visible to the naked eye, samples should also be taken from the bowel mucosa. The diagnosis is then made on the basis of microscopic examination. A diagnosis of *microscopic colitis* is made in about 10% of patients with watery diarrhea lasting more than 4 weeks and without endoscopic abnormalities. It is always important to take samples from the whole colon because, in about a quarter of cases, *collagenous colitis* is found only in the ascending part of the colon.

Microscopic examination of tissue samples from the bowel provides very characteristic results for the two disorders.
Using specific staining methods, a thickened collagen band is visible in the bowel mucosa of patients with *collagenous colitis* (Figure 3).

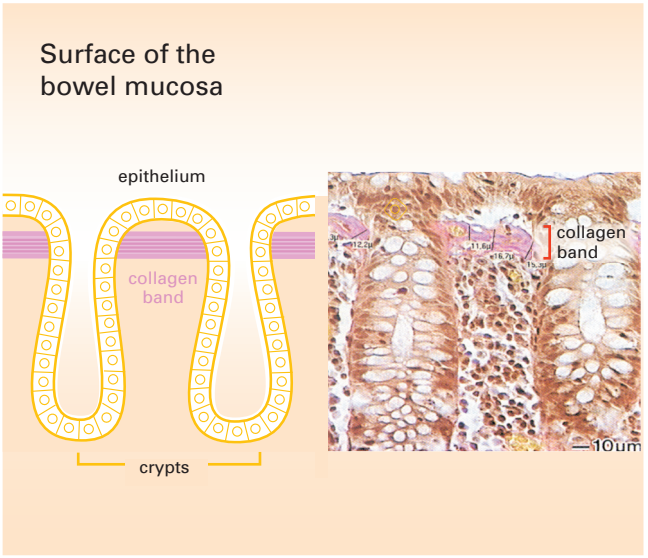

Figure 3:
Schematic illustration (left) and microscopic image (right) of the bowel mucosa in collagenous colitis. The pink-stained thickened collagen band is easy to recognize.

In the body, collagen fibers constitute a particular protein structure with a supporting function. In healthy people, this collagen band measures less than 5 micrometers (millionths of a meter), whereas in patients with *collagenous colitis,* it is at least 10 micrometers thick and is very easy to see under the microscope after staining.

In patients with *lymphocytic colitis,* examination of tissue samples reveals increased accumulation of immune cells (lymphocytes, a particular kind of white blood cell). The number of lymphocytes is about 4–5 times higher than in healthy people (Figure 4).

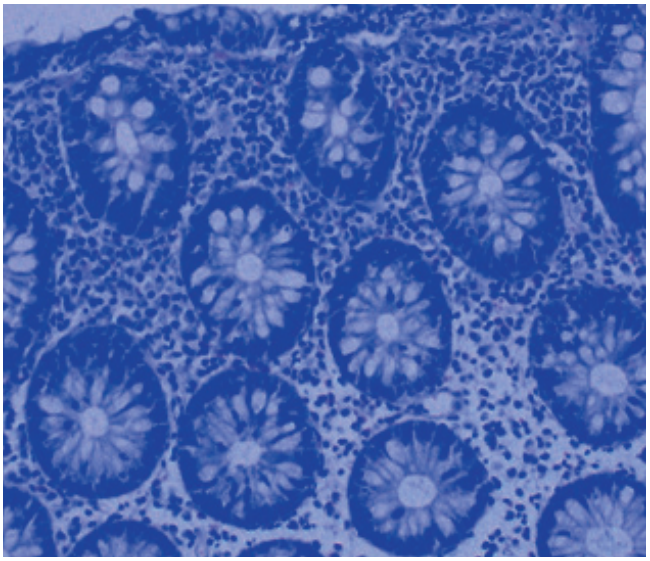

Figure 4:
Microscopic image of the bowel mucosa in lymphocytic colitis with increased number of lymphocytes

However, it is not yet clear how the thickened collagen band and the increased presence of inflammatory cells affect the development and the course of the disorder.

So far, these disorders cannot be diagnosed with a blood test.

Stool testing may reveal an increased level of calprotectin, a marker of inflammation, but this finding is not specific to *microscopic colitis.* The consequence, nevertheless, is that patients with persistent diarrhea and elevated calprotectin should always be examined endoscopically.

Treatment

As far as *controlled trials* are concerned, drug treatment is so far the best-investigated form of treatment for *collagenous colitis.* Bismuth, budesonide, prednisolone, probiotics and frankincense extract have all been used. The first controlled trial of acute treatment of *lymphocytic colitis* was published in 2008.

To date, only one drug has been officially approved worldwide for the treatment of *microscopic colitis,* namely budesonide for the treatment of *collagenous colitis.*

Collagenous colitis

Budesonide

Budesonide is a modern cortisone preparation with very good local anti-inflammatory effects on the bowel mucosa. The substance was first used as a spray in asthma treatment. In the 1990s, it began to be used to treat inflammatory bowel disease. Budesonide is taken in the form of granules or capsules; a special manufacturing process ensures that the drug is not released until it reaches the junction between the small intestine

and the ascending colon. In this area, the substance has a strongly anti-inflammatory effect on the mucous membrane; this effect is more intense than that of traditional cortisone preparations. Budesonide has the particular advantage that over 90% of the substance is metabolized directly in the liver after exerting its effect in the bowel. This means that only a small proportion of the active substance enters the body's circulation. As a result, the unwanted cortisone effects are considerably weaker than with traditional cortisone preparations. Budesonide is therefore very suitable for achieving high local effectiveness at the bowel mucosa while causing only a low rate of unwanted cortisone effects.

Four trials have now been completed in which budesonide was used for acute treatment of *collagenous colitis.*
They compared its effectiveness with that of a placebo. Budesonide was given at a dosage of 9 mg per day in all four studies and the treatment was continued for 6–8 weeks. Of the patients receiving budesonide, 80% showed clinical improvement and disappearance of diarrhea, a result seen in only 17% of the patients receiving the placebo. When tissue samples from the bowel were analyzed microscopically, the effect of the placebo (as indicated by a decrease in the thickness of the collagen band) was again much weaker.

No clear recommendation can yet be made for the continuing treatment procedure if diarrhea should recur after initially improving on budesonide.

In two other trials, continued treatment with budesonide (6 mg per day) for 6 months led to a considerably better result than placebo. However, relapses frequently occurred as early as 2 months after discontinuation of treatment. Up to now, budesonide has only been approved for the treatment of the acute disorder.
9 mg budesonide has also been shown to be effective in the acute treatment of *lymphocytic colitis.*

Prednisolone

Prednisolone, a classic cortisone preparation, was often used in the past to treat patients with *microscopic colitis.* In contrast to budesonide, however, prednisolone enters the blood circulation once it has been taken. Thus in addition to producing the desired therapeutic effect, it also usually leads to pronounced typical cortisone side effects such as moon face, adiposity of trunk, high blood pressure, psychological disturbances and weakening of the immune system.

Bismuth

Bismuth was the first substance to be used with *collagenous colitis* under controlled conditions, though with only limited success. This substance, which has antibiotic and anti-inflammatory properties, was not further investigated because it was not sufficiently effective. Furthermore, bismuth preparations should not be taken for more than 8 weeks because of possible accumulation in the body.

Frankincense extract

Frankincense extract also has an anti-inflammatory effect in the bowel. Initial studies have shown that it can also bring clinical improvement in *collagenous colitis.* Frankincense extract is not officially approved in most countries.

Probiotics

The effect of probiotics (lactobacillus, bifidobacterium) was examined in a 12-week placebo-controlled trial in patients with *collagenous colitis.* However, no significant difference was found between the two groups.

Other treatments

The effects of E. coli Nissle 1917, azathioprine, methotrexate and tumor necrosis factor alpha have all been the subject of open (non-controlled) trials or case reports. It may be appropriate to consider immunosuppressive therapy in cases in which patients do not respond to the standard treatment with budesonide.

Lymphocytic colitis

The first placebo-controlled trial of acute treatment of *lymphocytic colitis* with 9 mg budesonide daily for 6 weeks showed that budesonide was significantly more effective, both clinically and histologically, than placebo. On budesonide, 86% of the patients went into clinical remission as compared to only 48% on placebo.

At present, no data are available on treatment to maintain remission in *lymphocytic colitis.*

Frequently asked questions about microscopic colitis

1. How common is microscopic colitis?

Recent figures (from the USA and elsewhere) indicate that *microscopic colitis* is being diagnosed with increasing frequency (Figure 5). This increase is due not only to improved diagnostic procedures but also to a real increase in the number of cases. The figures show an annual incidence (rate of occurrence of new cases) of about 20 patients per 100,000 inhabitants.

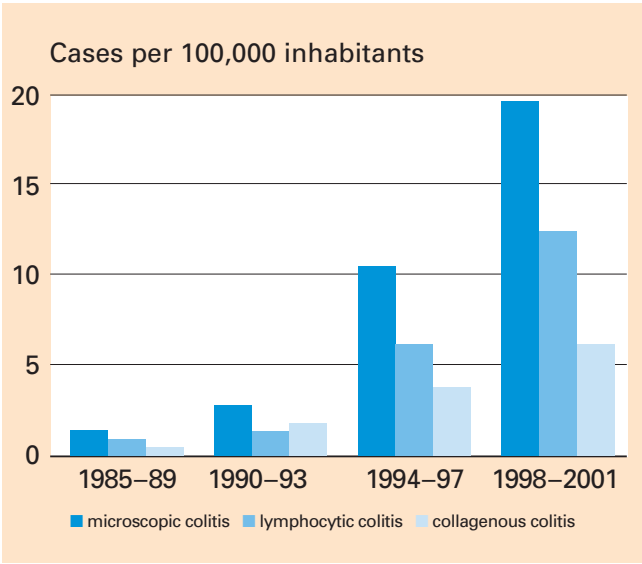

Figure 5:
Overview of the incidence rate of lymphocytic colitis and collagenous colitis (survey from the USA)

The annual incidence rate of *collagenous colitis* varies considerably between countries. In Spain, for example, it is 1–2 per 100,000 inhabitants, whereas in Sweden the annual incidence rate is reported to be 5 per 100,000 inhabitants.

Few data are available for *lymphocytic colitis*. In Scandinavia, the annual incidence rate is thought to be 4 per 100,000 inhabitants.
Epidemiological studies from the USA and Denmark confirm that the incidence rate has increased in these countries over the years.

2. Do certain factors promote the development of microscopic colitis?

All the studies that have so far been conducted have found that women are 5 times as likely as men to contract *microscopic colitis.*
In women over 65 years of age, especially, the risk increases considerably. This applies both to *collagenous colitis* and *lymphocytic colitis.* The reasons for this are not known.

Patients who already have certain disorders of the immune system (autoimmune disorders) also appear to be more likely to contract *microscopic colitis* than are patients who do not have an autoimmune disorder. Patients with thyroid hypofunction or celiac disease (sprue) are particularly affected. Overall, up to 40% of patients with *microscopic colitis* have a concomitant autoimmune disease.

Patients with *microscopic colitis* more frequently have celiac disease (sprue), and vice versa. The appropriate tests (anti-transglutaminase antibodies, duodenal biopsy) should therefore be carried out.

About 10% of patients also report having previously had cancer at some time. The majority of these cases involve colon, breast, prostate or lung cancer. If the frequency in these patients is compared to that in the normal population, the risk of additionally contracting *microscopic colitis* is increased, especially in women over 65 years of age.

People with diabetes mellitus may also be at increased risk. It appears that older men are more likely to be affected in this case.

In general, further research is needed with respect to a possible connection between *microscopic colitis* and the disorders named here, as well as the underlying causes.

3. What is known about the causes of microscopic colitis?

The causes of *microscopic colitis* are not known. It is striking that increased use of painkillers (such as ibuprofen and acetylsalicylic acid) is found as a possible triggering factor in a relevant number of patients.

These drugs may increase the permeability of the bowel mucosa and could thus promote the uptake of other, as yet unknown, disease-causing substances. Other drugs have also been suggested as possible triggers of *microscopic colitis,* such as simvastatin (which reduces cholesterol levels), ticlopidine (which inhibits blood clotting) and acarbose (which is used to treat diabetes mellitus).
An initial study found that patients with *collagenous colitis* included a higher proportion of smokers as compared to controls. It is not yet clear whether taking acid blockers (proton pump inhibitors) has any effect.
Smoking should be avoided because nicotine increases the permeability of the bowel wall.

Various different studies have found antibodies to Yersinia, a bacterium that can lead to infections of the bowel mucosa, in about 80% of the patients. On the other hand, numerous stool examinations have not been able to find Yersinia bacteria in the stools of patients with *microscopic colitis.*
These findings can also be understood as the result of increased permeability of the intestinal wall to Yersinia bacteria with secondary antibody formation.

In addition, there is evidence that *microscopic colitis* runs in families. It is not yet clear to what extent this can be attributed to hereditary factors.

4. How can the thickening of the collagen band in the bowel mucosa be explained?

The thickening of the collagen band in *collagenous colitis* is due to the reduced breakdown of collagen and not to *increased* collagen formation. However, the precise mechanisms leading to this reduction in collagen breakdown in the bowel mucosa have not yet been fully investigated. It is also not known whether, and how, the thickening of the collagen band is able to cause the typical symptoms of *collagenous colitis.*

5. Does microscopic colitis cause symptoms outside the bowel?

Microscopic colitis can be accompanied by a variety of different disorders that suggest a reaction of the immune system to the body's own tissue. These include rheumatic joint pain, psoriasis, celiac disease (sprue), malfunctions of the thyroid gland, circulatory disturbances and dry mucous membranes (see also Figure 2).

6. Is a rectoscopy sufficient to make a diagnosis?

Rectoscopy (endoscopy of the rectum) is not sufficient for making a diagnosis because *microscopic colitis* occurs more frequently in the ascending (right-side) colon. The whole colon should always be endoscopically examined and, in the process, tissue samples should be taken from the different sections of the colon. Otherwise *microscopic colitis* can be overlooked in up to 40% of patients.

7. Does microscopic colitis promote the development of colorectal cancer?

No. There is no evidence that either *collagenous colitis* or *lymphocytic colitis* leads to increased formation of polyps or colorectal cancer.

8. Are there any concerns regarding pregnancy?

No. In terms of the disorder itself, there are no concerns regarding pregnancy.
However, when drugs are being taken, it is important to be aware of any restrictions that may apply on their behalf with regard to pregnancy and breastfeeding. In any case, the disorder tends to occur in older female patients who have already been through menopause.

9. Can certain dietary factors have a favorable effect on the course of microscopic colitis?

No firm evidence is available on a possible influence of dietary factors in triggering these disorders. It is also not known whether eating or avoiding particular foods can have positive or negative effects on the disease course.

However, because watery diarrhea is the cardinal symptom, the preliminary diagnostic process should first exclude lactose intolerance and celiac disease (sprue). If either of these two disorders is present, maintaining a lactose-free or gluten-free diet is clearly recommended.

Studies have shown that fasting can lead to a considerable improvement in the diarrhea occurring as a symptom of *collagenous colitis.* But sustained fasting is not a long-term treatment option for *microscopic colitis.*

10. Does surgery help with microscopic colitis?

Up to now, surgery has only been carried out in very severe cases of *microscopic colitis,* which are very rare. However, these cases have shown that diverting the content of the bowel to an artificial outlet in the abdominal wall (stoma) results in improvements in the remaining bowel through which the stool no longer passes. The inflammation and the thickened collagen band both disappear. This fact suggests that factors in the bowel contents could act as triggers for *microscopic colitis.*

11. Are there cases of spontaneous remission or complete recovery from these disorders?

Two studies on the long-term course of *collagenous colitis* showed that, after successful initial treatment, some patients remained symptom-free for a long time without taking further medication. In one of these studies, 23% of the patients still had no watery diarrhea after 10 years. On the other hand, up to two thirds of the patients experienced a recurrence of symptoms within 2 months after treatment was discontinued. In these cases another cycle of treatment is recommended.

12. Is it possible to improve the diarrhea by taking bulking agents?

If the diarrhea is mild it is often sufficient to increase the firmness of the stool with bulking agents or bile acid binders and thus to reduce the stool frequency. In one small study, diarrhea disappeared in over 20% of patients who took a bulking agent (e.g. psyllium seed husk, also known as plantago ovata seed shells).

13. For how long should budesonide be taken in the acute phase of the illness?

In the four treatment trials carried out with budesonide so far, daily doses of 9 mg were given for a period of 6 or 8 weeks. On this treatment regimen the majority of patients became virtually symptom-free within 14 days. Budesonide is to be taken in a single dose in the morning.

14. Is there a maintenance treatment for collagenous colitis?

After discontinuation of acute treatment of *collagenous colitis* with budesonide, diarrhea often recurs within the first 2 months and makes further treatment necessary. In two placebo-controlled trials it was shown that, after achieving clinical improvement during acute treatment with 9 mg budesonide, continuing treatment with 6 mg budesonide per day for 24 weeks led to a significant reduction of the rate of relapse.

15. Is there a confirmed drug treatment regimen for lymphocytic colitis?

Budesonide at a dosage of 9 mg per day is the only substance that has so far been tested with *lymphocytic colitis* in a controlled treatment trial. This treatment was definitely shown to be superior to placebo. However, budesonide has not yet been approved for the treatment of *lymphocytic colitis.*

Further information for patients with inflammatory bowel diseases:

- Rectal treatment for inflammatory bowel disease (S97e)
  29 pages
- Ulcerative colitis and Crohn's disease
  An overview of the diseases and their treatment (S80e)
  63 pages
- Diet and Nutrition in Crohn's Disease and Ulcerative Colitis
  Important Questions – Real Answers (S84e)
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- Crohn's disease and its associated disorders (S85e)
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