Therapy in Inflammatory Bowel Disease
To my family
Örebro Studies in Medicine 75

ANDERS GUSTAVSSON

Therapy in Inflammatory Bowel Disease
Abstract

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The aim of this thesis is to study treatment of inflammatory bowel disease with respect to an acute severe attack of ulcerative colitis and endoscopic balloon dilation in stricturing Crohn’s disease.

A retrospective follow-up was made in 158 patients who were given intensive intravenous corticosteroid treatment due a severe, moderate, or mild attack of ulcerative colitis between 1975 and 1982. After 10 years, the colectomy frequency in the severe disease group was 64%, and 49% and 28% in the moderate and mild groups, respectively. Severity of the original attack did not influence the subsequent clinical course with respect to colectomy.

In 2005, a controlled Swedish–Danish trial of infliximab as rescue therapy in an acute severe attack of steroid refractory ulcerative colitis showed that colectomy frequencies after 3 months were lower in infliximab-treated patients (29%) compared to placebo-treated patients (67%). After 3 years, a statistically significantly lower colectomy frequency remained in patients treated with infliximab (50%) compared to placebo (76%).

Between 1989 and 2009, 178 patients underwent endoscopic balloon dilation due to intestinal strictures in Crohn’s disease. Seventy-five patients, with a follow-up of 5 years or longer, underwent dilations due to symptomatic strictures only. After 5 years of follow-up, 39/75 (52%) of the patients had undergone no further intervention or one additional dilation only, and 36% had had surgery. The complication frequency was 5.3%, of which 10 patients (1.3%) required surgery. In 83 patients, we studied whether smoking at diagnosis affected the outcome after index dilation. In the group of active smokers, 31/32 (97%) underwent another intervention compared to 18/33 (55%) in never smokers (HR 2.18, 95% CI: 1.22-3.93, p = 0.01). Clinical parameters such as sex, age at diagnosis, age at first dilation, balloon size, localisation of stricture, treatment with azathioprine and treatment period did not influence outcome.

Keywords: Crohn’s disease, ulcerative colitis, rescue therapy, infliximab, stricture, endoscopic balloon dilation, smoking, surgery.

Anders Gustavsson, School of Health and Medical Sciences Örebro University, SE-701 82 Örebro, Sweden, anders.i.gustavsson@liv.se
List of papers

The thesis is based on the following papers, which will be referred to by their Roman numerals:


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### Abbreviations

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<th>Description</th>
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<tr>
<td>5-ASA</td>
<td>5-aminosalicylic acid</td>
</tr>
<tr>
<td>ASCA</td>
<td>anti-Saccharomyces antibodies</td>
</tr>
<tr>
<td>Bpm</td>
<td>Beats per minute</td>
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<tr>
<td>CDAI</td>
<td>Crohn’s Disease Activity Index</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>DCs</td>
<td>Dendritic cells</td>
</tr>
<tr>
<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>IBD</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>IBDU</td>
<td>Inflammatory bowel disease type unclassified</td>
</tr>
<tr>
<td>IIVT</td>
<td>Intensive intravenous corticosteroid treatment</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>NOD</td>
<td>Nucleotide-binding oligomerisation domain protein</td>
</tr>
<tr>
<td>OmpC</td>
<td>Escherichia coli outer membrane porin C</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PRRs</td>
<td>Pattern recognition receptors</td>
</tr>
<tr>
<td>PSC</td>
<td>Primary sclerosing cholangitis</td>
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<td>TNF</td>
<td>Tumour-necrosing factor</td>
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Endoscopic balloon dilation in treatment of intestinal strictures of Crohn’s disease

GENERAL CONCLUSION

POPULÄRVETENSKAPLIG SAMMANFATTNING

ACKNOWLEDGEMENTS

REFERENCES
Introduction

Historical remarks

We shall never know who the first patient with inflammatory bowel (IBD) disease was or who the first physician was to treat a patient with IBD. Hippocrates (460–377 BC) was aware that diarrhoea was not a single entity, although he could not distinguish between infectious and non-infectious cause.1 Aretaeus of Cappadocia, a Greek physician in the first century AD, described different types of diarrhoea, including one with “foul evacuations”. It occurred more often in women than men, and occasionally in older children. During the nineteenth century, non-contiguous diarrhoea flourished under many names, including “the flux of Sydenham”.2 The term ulcerative colitis was denominated in 1859 by Sir Samuel Wilks (1824–1911).3 He described inflammation in the distal part of the ileum and colon at autopsy of young Miss Isabella Banks, who died after a short illness of bloody diarrhoea and abdominal pain. In 1875 Wilks and his co-author Moxan described the histopathological finding of ulcerative colitis in the second edition of their Lectures on Pathological Anatomy.4 With today’s knowledge it seems reasonable that Miss Banks’s disease was not ulcerative colitis, but rather Crohn’s disease (CD).

The first physician to describe Crohn’s disease was not Burrill B Crohn; instead, the first narrative was probably made by Morgagni (1682–1771).5 He described in 1761 a deceased young man with ileal ulceration and enlarged mesenteric lymph nodes. The entity of Crohn’s disease is, however, attributed to the American surgeon B B Crohn. He published in the Journal of the American Medical Association in 1932, together with his colleagues Leon Ginzburg and Gordon D Oppenheimer, the paper “Regional Ileitis: A Pathological and Clinical Entity”.6 They meant that this disease was limited to the distal part of the ileum only, but in the forthcoming year a description of jejunal disease was made by Harris et al.7 Not until 1960, when Lockhart-Mummery and Morson described colonic Crohn’s disease, and therefore could discriminate it from ulcerative colitis, it was accepted that Crohn’s disease could affect not only the small bowel but also the colon.8 However, the paper by Crohn and colleagues was not the first adequate description of the disease. Antoni Leśniowski, a Polish surgeon, published in 1903 what may have been the earliest reports of the condition that later became known as Crohn’s disease.9 Another early report of Crohn’s disease is by the Scottish surgeon T Kennedy Dalziel in 1913.10 He described patients with ileal and colonic lesions and compared the condition with Johne’s disease in cattle, caused by Mycobacterium
paratuberculosis. In Scotland Crohn’s disease is therefore often named Dalziel’s disease.

**Epidemiology**

Epidemiology is the study of the distribution and determinants of health-related states or events (including disease), and the application of this study to the control of diseases and other health problems. John Snow, regarded as the founder of modern epidemiology, described the relationship between an outbreak of cholera and the water supply in Soho, London, in 1854.

Epidemiological studies in inflammatory bowel disease have predominantly been made in Europe and North America. Generally, the incidence has slowly increased since the Second World War for both ulcerative colitis and Crohn’s disease, and two different patterns have emerged; one describes a steady increase, while the other has an increase followed by a plateau. The highest incidence is reported from Scandinavia, the United Kingdom, and North America, and among Ashkenazi Jews. A north–south gradient has been reported both in Europe and in North America, with a 40–80% increased risk in the northern part of the continents. However, there are parts of southern Europe and North America with high incidence, and the opposite in some northern regions, which calls into question the north–south hypothesis. Instead an east-west gradient has been proposed which currently is subject of an epidemiological study (EpiCom). In Eastern Europe, the incidence of IBD seems to have increased steadily, now equivalent to that in Western European countries. The incidence in developing countries is more uncertain, due to different access to health care, different awareness of disease, and lack of diagnostic tools. The true incidence in the developing countries is probably lower than in the industrialised world. There are however, several reports of increasing incidence in Asia and the Pacific, especially in ulcerative colitis. In countries that are becoming westernised, the incidence of ulcerative colitis increases first, followed later by Crohn’s disease. It appears that certain racial groups are more prone than others to develop IBD. For instance, Indians in Southeast Asia have higher rates compared to Chinese and Malays. In North America, IBD is more prevalent in Caucasians and Afro-Americans than in those of Asian and Hispanic origin.

Crohn’s disease and ulcerative colitis are most commonly diagnosed in late adolescence and early adulthood, but diagnosis may occur in all ages. Mean age at diagnosis of ulcerative colitis is 5–10 years later than in Crohn’s disease. Some studies have shown a bimodal distribution with a major incidence peak in the third decade of life and a smaller
peak later in the fifth and sixth decades. A slight difference between male and female incidence has been found in some studies. In studies from Europe the male: female ratio was 1.2 in ulcerative colitis and the corresponding figures in Crohn’s disease were 0.8.

**Aetiology and pathogenesis**

The aetiology of these diseases is not known. However, studies have provided evidence that IBD is a result of a genetic susceptibility in combination with defect barrier function in the human gut, inappropriate mucosal inflammatory response to intestinal bacteria, together with different environmental factors.

**Genetics**

Genetics seems to play an important role in the aetiology of IBD. Several studies have shown a higher concordance in monozygotic than in dizygotic twins, especially in Crohn’s disease. The pair concordance rate for Crohn’s disease in monozygotic twins was 39% compared to 7% in dizygotic twins. The corresponding figures for ulcerative colitis were 15% and 4%, respectively. Furthermore, first-degree relatives of patients with IBD are approximately 3 to 20 times more likely to develop IBD than the general population. Not only does the risk of developing IBD increase in twins and relatives, but also the phenotype shows a high degree of concordance.

In 2001, the first susceptibility gene for Crohn’s disease was described, which showed variation of the nucleotide-binding oligomerisation domain protein 2 (NOD2) gene in chromosome 16. These NOD2 mutations have been shown to be associated with some phenotypic manifestations in Crohn’s disease, like early onset of the disease, fistulising disease, and an ileal location. NOD2 mutations are found in approximately 35–45% of the Caucasian Crohn’s disease patients, with the exception of the Scandinavian countries, as well as Scotland and Ireland. Today more than 100 independent loci on several chromosomes have been associated with Crohn’s disease. Some loci have also been associated with ulcerative colitis, but this has been much less investigated.

**Microbiota and the immune system**

There is increasing evidence that the enteric flora play a part in the pathogenesis of IBD. In germ-free animal models, inflammation does not evolve,
as long as the environment is sterile.\textsuperscript{65, 66} This is supported in humans by the observation that surgery with diversion of the faecal stream can heal an inflamed mucosa in Crohn’s disease.\textsuperscript{67, 68} Patients with IBD also have antibodies against microbial antigens (anti-Saccharomyces antibodies (ASCA), Escherichia coli outer membrane porin C (OmpC), and Pseudomonas fluorescens I2 sequence). ASCAs are present in 50–60\% of patients with Crohn’s disease, and with the highest titres in those patients who are most affected of strictures, internal perforations, and small bowel surgery.\textsuperscript{69}

The intestinal epithelium absorbs nutrient and fluid at the same time as it must function as a barrier to bacteria and dietary antigens to generate tolerance and control defence. This requires an intact epithelial layer with tight junctions in combination with a normal surface mucus layer and antimicrobial proteins to limit bacterial exposure to the epithelial cells.\textsuperscript{70, 71} In IBD, an activation of inflammatory cells and cytokines occur in the bowel. In Crohn’s disease, the major cytokines arise from of T-helper-1 (Th1) and Th17 differentiation and consist of interferon-\(\gamma\) and interleukin (IL)-17/IL-22. In ulcerative colitis, an atypical Th2 response is essential, which results in expansion of natural killer T cells, producing IL-13 and IL-5.

Environmental factors
Numerous environmental factors have been hypothesised to affect the risk of IBD. Smoking is most studied, and there is a negative correlation of smoking and ulcerative colitis.\textsuperscript{72-76} Current smokers are 40\% less likely to develop ulcerative colitis compared to those who have never smoked.\textsuperscript{77} Some studies have shown that former smokers have an increased risk of ulcerative colitis compared to those who have never smoked.\textsuperscript{75, 78, 79} In what way smoking protects against ulcerative colitis is not known. Trials with transdermal nicotine patches have not influenced the risk.\textsuperscript{80, 81} Interestingly, smoking has the same protective effect in primary sclerosing cholangitis (PSC) and pouchitis.\textsuperscript{82-85} This suggests a systemic protective effect and not a local effect in the bowel.

Smoking is positively correlated with Crohn’s disease.\textsuperscript{73, 86-89} It influences the risk of developing Crohn’s disease as well as affecting the course of disease.\textsuperscript{90-92} Patients who smoke are more likely to have ileal than colonic and ileocolonic disease, and also higher risk of developing strictureing and/or penetrating disease. Patients who have not quit smoking and undergo surgery due to Crohn’s disease are more likely to have another surgery, as well as get immunosuppressive agents.\textsuperscript{93-96}

Several studies have shown that appendectomy appears to be protective against ulcerative colitis in those who undergo surgery before the age of 20
due to appendicitis or mesenteric lymphadenitis. Appendectomy seems to be associated with future risk of Crohn’s disease. Why appendectomy reduces the risk of developing ulcerative colitis and increase the risk of Crohn’s disease is not known.

Some case–control and cohort studies, but not all, have implied a weak correlation between oral contraceptives and IBD, especially Crohn’s disease. The pathogenesis behind this is not known.

Food provides a lot of dietary antigens in the bowel. It is therefore logical to hypothesise that diet could be an important factor in developing IBD. It is, however, very difficult to establish an association between dietary habits before diagnosis and the disease, due to recall bias and an unconsciousness of changing the diet when getting symptoms. Several dietary factors have been proposed to influence the developing of IBD. The most studied is the relation between increased sugar intake and especially Crohn’s disease, which probably increases the risk of the disease. High intakes of fruits and vegetables have been suggested as being protective, but data are inconsistent. Other dietary factors such as coffee, margarine, unpasteurised cheese, and fast food have been studied, but no convincing associations have been recognised. Studies of dietary intervention have not been conclusive.

**Diagnostic criteria and clinical symptoms**

The diagnosis of idiopathic inflammatory bowel disease (IBD) is established by a combination of clinical history, endoscopic appearance, and histopathological reports on intestinal biopsies. IBD comprises mainly of two different phenotypes, Crohn’s disease and ulcerative colitis. In a small group of patients the distinction between the two diseases cannot be made; this subgroup is best named as “IBD type unclassified”. The term indeterminate colitis should be preserved for pathologists to describe a colectomy specimen in which a definite discrimination of ulcerative colitis and Crohn’s disease cannot be made.

**Ulcerative colitis**

Ulcerative colitis is located solely in the colon and is classified according to the extent of the inflammation. (Table 1) In proctitis, the inflammation is limited to the rectum, approximately no more than 15 cm from the anal verge. When the inflammation is more proximal than the rectum but not proximal to the splenic flexure, it is called left-sided colitis, and if involvement is proximal to the splenic flexure, it is called extensive colitis. The
inflammation starts in the rectum and is normally continuous. In a few cases a periappendiceal involvement is seen, often in connection with left-sided colitis. Sometimes inflammation can macroscopically and/or histologically be seen in the most distal part of the small bowel. This backwash ileitis does not represent a genuine inflammatory manifestation of the disease and must not be confused with Crohn’s disease.

The symptoms of ulcerative colitis include diarrhoea, rectal bleeding, and abdominal tenderness. The combination of symptoms depends on the extent of the inflammation. In proctitis, rectal bleeding is the predominant symptom, but rectal urgency, tenesmus, passage of mucopurulent exudates, and even constipation can occur. In extensive and left-sided colitis, the main symptom is bloody diarrhoea. In severe cases, pure blood and passage of pus can occur. If rectal bleeding is missing, the diagnosis should be questioned. For most patients pain is not a major symptom, but some complain of diffuse abdominal tenderness.

Table 1. Montreal classification of ulcerative colitis

<table>
<thead>
<tr>
<th>Term</th>
<th>Localisation</th>
<th>Description</th>
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<tbody>
<tr>
<td>E1</td>
<td>Proctitis</td>
<td>Involvement limited to the rectum (i.e. proximal extent of inflammation is distal to the rectosigmoid junction)</td>
</tr>
<tr>
<td>E2</td>
<td>Left-sided</td>
<td>Involvement limited to the proportion of the colon distal to the splenic flexure</td>
</tr>
<tr>
<td>E3</td>
<td>Extensive</td>
<td>Involvement extends proximal to the splenic flexure, including pancolitis</td>
</tr>
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</table>

**Crohn’s disease**

In Crohn’s disease inflammation can develop anywhere in the gastrointestinal tract and is characterised by segmental involvement with skip lesions. The phenotype of Crohn’s disease is defined according to the Montreal classification with respect to three variables: age at diagnosis, localisation, and behaviour of the disease. (Table 2)
Symptoms of Crohn’s disease depend on localisation and behaviour of the disease. Fatigue; diarrhoea, with or without gross bleeding; abdominal pain; weight loss; and fever are common features. A pure colonic disease resembles ulcerative colitis with diarrhoea, often with blood involvement. When the inflammation is situated in the distal part of the small bowel, the dominating symptoms are abdominal pain and diarrhoea without blood, and when the upper part of the intestinal tract is affected, the clinical picture is often dominated by abdominal pain, weight loss, and malnutrition.

A stricture of the bowel is usually silent until the lumen calibre is narrow enough to cause obstructive symptoms such as postprandial pain, and may sometimes also cause a complete mechanical ileus. A fistula is an abnormal connection between the bowel and any other organ, intestine, or structure. Perianal fistulas are common in Crohn’s disease, but are not included in the classification of penetrating disease. The most common localisation of fistulas in Crohn’s disease is between the bowel and any other part of the intestine, skin, or vagina. Symptoms depend on the localisation of the fistulas.
Table 2. Montreal classification of Crohn’s disease

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>A1</th>
<th>&lt;16 years</th>
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<tbody>
<tr>
<td></td>
<td>A2</td>
<td>16–40 years</td>
</tr>
<tr>
<td></td>
<td>A3</td>
<td>&gt;40 years</td>
</tr>
<tr>
<td>Location</td>
<td>L1</td>
<td>Ileal</td>
</tr>
<tr>
<td></td>
<td>L2</td>
<td>Colonic</td>
</tr>
<tr>
<td></td>
<td>L3</td>
<td>Ileocolonic</td>
</tr>
<tr>
<td></td>
<td>L4</td>
<td>Isolated upper disease(^1)</td>
</tr>
<tr>
<td>Behaviour</td>
<td>B1</td>
<td>Non-stricturing, non-penetrating</td>
</tr>
<tr>
<td></td>
<td>B2</td>
<td>Stricturing</td>
</tr>
<tr>
<td></td>
<td>B3</td>
<td>Penetrating</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>Perianal disease modifier(^2)</td>
</tr>
</tbody>
</table>

\(^1\)L4 is a modifier that can be added to L1–L3 when concomitant upper gastrointestinal disease is present.

\(^2\)p is added to B1–B3 when concomitant perianal disease is present.

As many as 30–40% of the patients with ulcerative colitis and Crohn’s disease suffer from extraintestinal manifestations from different organs.\(^{118-124}\) Most common are musculoskeletal disorders, and in particular, arthralgia,\(^{125,126}\) but manifestations from the eye and skin are not unusual.\(^{78,120,123,127-129}\)

A serious complication of IBD is primary sclerosing cholangitis.\(^{130-132}\) It is more often associated with ulcerative colitis than Crohn’s disease.\(^{133,134}\)

The sclerosing changes affect the extrahepatic and/or intrahepatic biliary
ducts. PSC often has a subclinical course, but sometimes liver cirrhosis and cholangiocarcinoma evolve. \textsuperscript{135-138}

**Histopathology and endoscopy**

Histopathological changes of IBD are not specific for either of ulcerative colitis or Crohn’s disease. In ulcerative colitis, a diffuse lateral and vertical infiltration of the lamina propria with mononuclear cells, along with basal plasmacytosis, congested capillaries and conspicuous neutrophils forming crypt abscesses, goblet cell depletion, and architectural crypt distortion is often seen. \textsuperscript{139} In Crohn’s disease aphthoid ulcers, focal and patchy transmural inflammation with epithelioid granuloma, focal cryptitis together with segmental crypt distortion, and fissuring can be seen. \textsuperscript{139-141}

The endoscopic findings in ulcerative colitis begin in the rectum and extend proximally. In mild disease erythema, loss of vascular pattern, and a granularity of the mucosa are seen, whereas in more severe disease ulcers and spontaneous bleeding occur. The transition to normal mucosa is often distinct. Endoscopically, Crohn’s disease can be distinguished from ulcerative colitis by several factors. In early phases of the disease, aphthous ulcers often evolve, and later in the course, longitudinal ulcers forming the characteristic “cobblestone” appearance. In contrast to ulcerative colitis, Crohn’s disease often has discontinuous lesions adjacent to normal tissue, resulting in so-called “skip lesions”.

\textsuperscript{ANDERS GUSTAVSSON  Therapy in Inflammatory Bowel Disease 1  21}
Backgrounds to the studies

Clinical course/natural history – ulcerative colitis

According to the Montreal classification, ulcerative colitis is subclassified according to the extent of the inflammation in proctitis, left-sided, and extensive colitis. The extent of the disease at diagnosis varies considerably between different studies. In the Norwegian IBSEN cohort, 32% were diagnosed as proctitis, 33% as left-sided, and 35% as extensive colitis. During the first 10 years after diagnosis 28% and 14%, respectively, of patients initially diagnosed with proctitis progressed to left-sided and extensive colitis. Twenty-eight per cent of the left-sided colitis progressed to extensive colitis. These figures are supported by an Italian study in which 54% progressed after 10 years of follow-up. In the majority of the Italian patients the extension was into the sigmoid colon, and only 10% progressed proximal to the splenic flexure. The extension of the disease is part of a dynamic process; this is illustrated by the Danish study by Langholz et al., in which 76% of patients with pancolitis had regressed to a more limited extension during a follow-up of 25 years.

According to the criteria of Truelove-Witts, severity of the disease can be classified as mild, moderate, or severe (see page 29). At diagnosis the majority of patients seem to have a mild attack of ulcerative colitis. In Edwards and Truelove’s report from 1962, 54% had a mild attack, 27% had a moderately severe, and 19% had a severe attack. This was not, however, a prospective population-based cohort, but a retrospective study in which there where many patients referred from other hospitals.

Clinical course after diagnosis is showed in a Danish study, in which half of the patients were in remission every year. Twenty-three per cent had only one episode during follow-up, and 77% had a continuous or relapsing course during follow-up. The cumulative probability of a continuously active course was very low, approximately 1% after 5, and 0.1% after 25 years. These figures are almost equal to the result of a prospective cohort study from Norway, in which the cumulative relapse rate after 10 years was 83%. Fifty-five per cent were in remission or had mild intestinal symptoms after the initial activity, and 37% reported chronic intermittent symptoms.

In patients with ulcerative colitis the colectomy rate seems to have diminished in the last few years compared to 30 or 40 years ago. In the Swedish study by Leijonmarck et al. the colectomy rate was studied among 1586 patients in Stockholm County between 1955 and 1984. The 5-, 10-, and 25-year cumulative colectomy rates were 20%, 28%, and 45%, re-
spectively. The main factor affecting outcome was the extent of the disease. In patients with total colitis the cumulative colectomy rate at 25 years was 65%. In a Danish study, roughly during the same period, the 10-year colectomy rate was 24%.\textsuperscript{148} During the past years, two European prospective studies have shown considerably lower figures. In a study conducted by the European Collaborative Study Group of Inflammatory Bowel Disease, the 10-year cumulative risk of colectomy was 8.7%. The most striking feature was that the southern countries of Europe had lower risk of colectomy compared to the northern. The reason for this is not clear.\textsuperscript{150} These figures are supported by the Norwegian IBSEN study, where the 10-year colectomy rate was 9.8%.\textsuperscript{145} Initial presentation with extensive colitis, elevated erythrocyte sedimentation rate (ESR), anaemia, and fever were risk factors for later surgery. Age >50 years showed a reduced risk.

Ulcerative colitis seems to increase the risk of colorectal cancer.\textsuperscript{151-157} This has been recognised since the 1930s, but there has been great variation in the estimated risk. During the first 10 years after diagnosis the risk is not increased, but it seems to rise over time. Risk factors for developing colorectal cancer are concomitant primary sclerosing cholangitis, relatives with colorectal cancer, extensive colitis, severity of histological inflammation, and backwash ileitis.\textsuperscript{152, 158-163} Proctitis and left-sided colitis do not seem to, or only minimally, increase the risk. Due to the increased risk of colorectal cancer, so-called surveillance programmes have been developed to identify patients with dysplasia in colon biopsies. In general, patients with at least extensive colitis and 8–10 years of disease duration do a colonoscopy every other year, and after 20 years of disease duration every year. This can be modified due to presence of other risk factors.

The mortality in ulcerative colitis has diminished dramatically since the introduction of modern treatment principles in the 1960s. Prior to this era the natural history of untreated acute severe ulcerative colitis showed a mortality rate of 24%.\textsuperscript{164} The introduction of glucocorticosteroids in an acute severe attack of ulcerative colitis reduced the risk to approximately 7%, and in combination with the use of early colectomy the risk fell to <1%.\textsuperscript{165-169} Whether ulcerative colitis today influences the overall mortality is not clear. Some studies suggest that there is a slight increase of mortality compared to the general population.\textsuperscript{170, 171} This excess risk is explained by an increased incidence of colorectal cancer, post-operative complications, and PSC-related morbidity. Other studies have, however, failed to show this increase of mortality compared to general population.\textsuperscript{172-174}
Clinical course/natural history – Crohn’s disease

Disease location at diagnosis seems to have changed over the years from predominately a small bowel disease to one with colonic inflammation in more patients. In Stockholm County the proportion of colonic disease was increased from 15% in the period 1955–1964 to 32% in 1980–1989.175 This is in agreement with a review with patients diagnosed predominantly before 1990, in which there was an equal distribution between the three main sites of the disease, small bowel, colon, and both small and large bowel.176 The change over time is further supported by the Norwegian population-based study made at the end of the 1990s, in which there was an overweight for patients who were diagnosed with colonic disease compared to the other sites (49% vs. 27% and 23%).177 The disease location seems to be rather stable, with approximately 16% to 24% of disease pattern changing localisation over time.178, 179

Whereas disease location seems to be rather stable over time, disease behaviour appears to have changed. In an American population-based study, 81% had a non-stricturing non-penetrating disease at diagnosis, whereas 5% had a stricture disease and 14% had penetrating disease. After 20 years more than half of the patients had developed a more advanced disease.180 These data are supported by the study of Louis et al., where 45.9% changed from non-stricturing, non-penetrating disease to strictureing or penetrating disease after 10 years.179

As with ulcerative colitis, different clinical disease patterns are recognised. In the Norwegian IBSEN cohort, 43% had a decrease in disease severity, whereas 32% had a chronic relapsing, and 19% a chronic continuous course 10 years after diagnosis.177 Only 3% had a worsening in symptoms. Surgical intervention with intestinal resection is frequent in Crohn’s disease. Several Scandinavian studies have shown high resection rates of 38–71% after 10 years.177, 178, 181, 182 The recurrence risk after resection is high. New endoscopic lesions will be found in a large majority of patients as early as after one year,183, 184 that may in the subsequent course of disease cause recurrent clinical symptoms, requiring a second surgical procedure in 20–44%.185, 186

Crohn’s disease has, like ulcerative colitis, an increased risk of colorectal cancer. The magnitude of the risk is uncertain. Some studies have shown the same risk increase as ulcerative colitis,187, 188 whereas other have revealed a minor risk or no risk increase at all.189-192

There is an increased mortality among patients with Crohn’s disease, especially late in the disease course.17, 170, 193 Several studies have shown that the excessive mortality is among women, but others have older age as a negative prognostic factor.17, 194, 195
Treatment – medical
Medical treatment of inflammatory bowel disease does not provide a cure for the disease. The intention of treatment is therefore induction of remission of disease inflammation, maintenance of remission, improve health related quality of life and prevention of disease complications. A variety of treatments exist, all with different advantages and disadvantages.

Aminosalicylates
Sulphasalazine, which was developed by Nanna Svartz, the founder of the Swedish Society of Gastroenterology, was the first effective pharmaceutical preparation in IBD. 196 5-ASA, the active part of the medication, is linked with an inert carrier molecule, sulphapyridine. In the large bowel, the linkage is cleaved by the colonic flora, and the active part is delivered to the inflamed mucosa. Due to side effects caused by the sulphapyridine part, 5-ASA preparation without sulphapyridine was developed. To overcome the upper intestinal degradation, several different delivery systems evolved, a pH-dependent preparation, a slow-releasing preparation, and other carrier molecule besides sulphapyridine. 197 In ulcerative colitis, aminosalicylates had proven effective both in inducing remission and as maintenance therapy, but in Crohn’s the evidence is limited. 198-200

Glucocorticosteroids
Corticosteroids have been a cornerstone in the treatment of IBD since their introduction in the 1950s. They have been proven effective in both ulcerative colitis and Crohn’s disease to induce remission, but not as a maintenance therapy. 166, 201-206 To avoid systemic side effects, a different preparation, budesonide, with an enhanced first-pass metabolism, has evolved for treatment of ileocecal Crohn’s disease. 207-209

Thiopurine agents
The thiopurine antimetabolites azathioprine and 6-mercaptopurine are an established treatment in both ulcerative colitis and Crohn’s disease as maintenance treatment. Azathioprine is a pro-drug that is converted into 6-mercaptopurine and into a variety of different active and inert metabolites. 210-212 Cochrane reviews conclude that in ulcerative colitis, azathioprine and 6-mercaptopurine may be effective as maintenance therapy in patients who cannot tolerate aminosalicylates or in whom they have failed, and in Crohn’s disease these agents are proved to be more effective than
placebo. In induction of remission, azathioprine and 6-mercaptopurine are effective in Crohn’s disease but not in ulcerative colitis.

**Biological agents**

Tumour-necrosing factor (TNF) has a central role in the pathogenesis in both ulcerative colitis and Crohn’s disease. Infliximab is a chimeric monoclonal IgG antibody and was the first approved TNF-antibody–based treatment for ulcerative colitis. Several open-label trials have been done to evaluate the efficacy of infliximab but few placebo-controlled. In ACT 1 and ACT 2 trials infliximab was evaluated in moderate to severe, but not fulminant, active ulcerative colitis. The conclusion of the two studies was that an induction regimen of three infusions of infliximab followed by maintenance treatment every 8 weeks was superior to placebo in moderate to severe ulcerative colitis in achieving clinical response and remission and mucosal healing. An analogous study evaluating adalimumab in patients with moderate to severe ulcerative colitis was published in 2012 (ULTRA 1 and 2). Adalimumab, a fully human monoclonal antibody that binds TNF, was more effective than placebo in inducing and maintaining clinical remission. Overall rates of clinical remission at week 8 were 16.5% in patients treated with adalimumab compared to 9.3% in patients with placebo.

There are three antibodies to TNF approved in treatment of Crohn’s disease. Infliximab was first accepted for inducing remission in patients with non-fistulising disease. In the ACCENT study, 58% of the patients responded to the induction dose of infliximab, and at the end of the study, significantly more patients were in remission in the infliximab-treated group compared to those who received placebo. Infliximab has also shown effect in fistulising Crohn’s disease. In the studies by Present and Sands, it was shown that infliximab was effective in closure of draining fistulas; as well, it increased the opportunity of sustained response during maintenance therapy.

Adalimumab has shown effect in treating moderate to severe active Crohn’s disease, despite other therapies, including 5-ASA, corticosteroids, immunosuppressive therapy, or antibiotics. Unlike infliximab, adalimumab is given subcutaneously and every 2 weeks. The effect of adalimumab in treating fistulising Crohn’s disease is only evaluated in subgroup analysis, and adalimumab is therefore not indicated in treating fistulas.
Certolizumab pegol is a humanised monoclonal Fab fragment that neutralises TNF and is approved for treatment of Crohn’s disease in the United States, but not in the European Union.

No randomised controlled studies have directly compared the efficacy of the three therapies against TNF.

**Cyclosporine**

Cyclosporine is a competitive calcineurin inhibitor that normally is used as immunosuppressive therapy in patients undergoing organ transplantation. In IBD, cyclosporine has been used in acute steroid refractory ulcerative colitis as so-called rescue therapy.\(^{228-231}\)

**Treatment in a mild attack of ulcerative colitis**

Patients with mild disease according to the Truelove-Witts criteria can be treated in an outpatient manner.\(^{232,233}\) Proctitis and left-sided colitis can be treated with topical administration of 5-ASA or corticosteroids. If one of them fails, the other drugs should be tested. Sometimes a combination of the two can be tried. In extensive colitis, oral 5-ASA should be used as first-line treatment. It is important to use adequate doses, which means up to 4.8 g of mesalazine. Treatment should continue until the patient is in clinical and endoscopical remission. If patients do not respond to these regimes, oral corticosteroids should be tested, irrespective of the extension. Typically, prednisolone is used in doses of 30 to 60 mg in a tapering schedule. When the patient is in remission, 5-ASA should be continued as maintenance therapy. The doses can normally be lower than the induction therapy, which means mesalazine in doses of 1.6 to 2.4 g. Corticosteroids are not effective in maintaining remission and should not be used as maintenance therapy.

**Treatment in a moderate attack of ulcerative colitis**

Patients with moderate disease according to the Truelove-Witts criteria should be treated initially with oral corticosteroids.\(^{232,233}\) The optimal dose is not known, but usually doses of prednisolone of 30 to 60 mg are used with a tapering schedule of 5 mg every week. Normally, oral 5-ASA–based medication is added initially or during tapering of the corticosteroids. If the patient does not respond to the initiated treatment in one week, the patient should be hospitalised and treated as having a severe attack of ulcerative colitis.
Treatment in a severe attack of ulcerative colitis

According to Truelove-Witts criteria, a severe attack consists of 6 or more bloody bowel movements per day, together with one or more of the following factors: temperature >37.8°C, haemoglobin of <105 g/l, heart rate >90 beats per minute, and an ESR >30 mm/h. A patient with a severe attack should immediately be hospitalised and be evaluated by a specialist in gastroenterology and a colorectal surgeon.\textsuperscript{232–234}

A plain abdominal x-ray should be done without further notice to rule out colon dilation and perforation. In such cases, immediate colectomy should be considered. As soon as possible an endoscopy should be done to evaluate the extension and the severity of the inflammation, and this can be done in a safer manner by an experienced endoscopist.\textsuperscript{235, 236} The patients should be monitored by daily registration of blood pressure, heart frequency, abdominal status, and number of bowel movements. Blood samples such as C-reactive protein (CRP), ESR, haemoglobin, thrombocytes, and albumin should be evaluating continuously and an infectious cause should be ruled out. Parenteral nutrition is not needed to achieve optimal treatment of the inflammation, but is valuable for correcting any fluid deficit and electrolyte disturbance and is also important in order to be able to use prognostic tools described below to predict the subsequent management. Medical treatment with parenteral corticosteroids is started with or without addition of 5-ASA or corticosteroids enema. Which dose of parenteral corticosteroids to use is not properly evaluated, but often betamethasone 4 mg twice daily or hydrocortisone 100 mg four times daily intravenously is used. There is no value of oral 5-ASA preparations or antibiotics in a severe attack of ulcerative colitis.

Approximately 30\% of the patients will not respond to intravenous corticosteroids and are candidates for so-called rescue therapy. If this therapy fails, the only option is acute colectomy.

Disease activity index

The severity of a relapse of ulcerative colitis is often evaluated by a severity index, in which clinical, together with laboratory and/or endoscopical, parameters are integrated.\textsuperscript{237} Historically, the most common way to evaluate an acute attack of ulcerative colitis is using the Truelove-Witts criteria.\textsuperscript{166} (Table 3) These take into account the number of occurrences of diarrhoea and any objective signs of systemic disturbance. A mild attack is defined as fewer than four bowel movements and no signs of systemic disturbance, whereas a severe attack comprises of more than 6 bloody bowel movements with one or more signs of systemic disturbance. Another index is the Seo index, which is based on the Truelove-Witts criteria.\textsuperscript{238} It takes
into account the number of bloody bowel movements and values of ESR, haemoglobin, and albumin. Values >220 correspond to a severe attack according to the Truelove-Witts criteria, whereas values between 150 and 220 correspond to an intermediate attack, and <150 is regarded as a mild attack. In recent years the most used index is the Mayo index.\textsuperscript{239} It consists of four parameters: stool frequency, rectal bleeding, findings on endoscopy, and physician’s global assessment.

Several indices have been developed to try to identify patients at risk for emergency colectomy in an acute severe attack of ulcerative colitis. Three days after initiating intravenous corticosteroids, more than 8 bowel movements or 3-8 bowel movements and CRP >45 mg/l predicts colectomy in 85\% of the patients, and according to the “fulminant colitis index” (number of bowel movements + CRP × 0.14) at day 3, the risk of colectomy is 72\% when the result exceeds 8.\textsuperscript{240, 241}

Activity indices in Crohn’s disease are more complex and are normally used in clinical studies only. The most used indexes are the Crohn’s Disease Activity Index (CDAI) and the Harvey-Bradshaw Index.\textsuperscript{242} They take into account number of bowel movements, abdominal pain, presence of abdominal mass, any disease-specific complication, and general well-being. In CDAI, weight, haematocrit and use of antidiarrhoeic drugs are also included.
Table 3. Disease activity in ulcerative colitis, adapted from Truelove and Witts \textsuperscript{114,166}

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate “in between mild and severe”</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloody stools/day</td>
<td>&lt;4</td>
<td>4 or more if</td>
</tr>
<tr>
<td>Pulse</td>
<td>&lt;90 bpm</td>
<td>≤90 bpm</td>
</tr>
<tr>
<td>Temperature</td>
<td>&lt;37.5 °C</td>
<td>≤37.8 °C</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>&gt;115 g/L</td>
<td>≥105 g/L</td>
</tr>
<tr>
<td>ESR</td>
<td>&lt;20 mm/h</td>
<td>≤30 mm/h</td>
</tr>
<tr>
<td>or CRP</td>
<td>Normal</td>
<td>≤30 mg/L</td>
</tr>
</tbody>
</table>

**Treatment – surgery**

**Ulcerative colitis**

Colectomy is an indispensable part of treatment of ulcerative colitis. The colectomy rate in ulcerative colitis has varied much over time and depending on therapy tradition. In the early studies of ulcerative colitis, colectomy was not an option until complication occurred. A study from 1950 stated that “in the view of the unsatisfactory state of the medical treatment of the chronic form of ulcerative colitis and the high rate of relapse, it is worth considering the possible place of surgery.”\textsuperscript{166}

A major breakthrough was made in the 1960s, when the practice of early colectomy in acute severe colitis was introduced. Together with the introduction of corticosteroid treatment, this reduced the earlier high mortality to a rate less than 1%.\textsuperscript{165-169}

Indication for colectomy today is a severe attack that fails to respond to medical treatment, complication of a severe attack, chronic continuous
The most common procedure is a subtotal colectomy and ileostomy followed by a second procedure 3 to 6 months later. The second procedure can be permanent ileostomy, completion proctectomy and formation of an ileal-pouch anal anastomosis, or an ileorectal anastomosis.

**Crohn’s disease**

In spite of new medical developments, surgery is still an important therapeutic alternative in Crohn’s disease. In the early era of Crohn’s disease, radical surgery was performed in order to cure the patient. Soon it was obvious that cure was not possible, and during the following years different approaches evolved. To avoid recurrence, the practice of radical resection was introduced, with wide margins of normal non-inflamed bowel on each side of the affected part. Later it was obvious that recurrence rate was not affected by the presence of microscopic disease at the surgical margins, so this technique was abandoned, and today only grossly diseased tissue is resected.243-246

There are few randomised studies to support decisions about surgery in Crohn’s disease, and in general a multidisciplinary therapy conference precedes a decision. Today, the indication for surgery in Crohn’s disease is usually considered to be inflammation refractory to medical therapy including biological treatment or complications such as intra-abdominal abscess, haemorrhage, toxic megacolon, medically intractable fistula, and dysplasia or cancer. Fibrotic strictures can be treated with surgical resection, strictureplasty, and endoscopic balloon dilation.

After an ileocolonic resection three out of four patients have an endoscopic recurrence within 12 months, and 3 years after surgery 85% have endoscopic evidence of Crohn’s disease recurrence, and 34% have developed a symptomatic relapse.184, 247 Different surgical techniques have therefore evolved to try to diminish the risk of surgical relapse. The most common techniques are end-to-end anastomosis, end-to-side anastomosis, and side-to-side anastomosis. The anastomosis can either be hand-sewn or stapled. Clinical studies have had variable results regarding relapse. Some studies have found lower recurrence rates in stapled than hand-sewn anastomosis, whereas others have found no difference.248-251 A meta-analysis showed no difference in surgical recurrence between end-to-end anastomosis compared to other surgical techniques, but there was a significantly lower rate in anastomotic leakage in favour of side-to-side anastomosis.252
The risk of short-bowel syndrome has diminished dramatically due to an awareness of the risk and better surgical techniques.\textsuperscript{253} To further reduce this risk, the technique of strictureplasty has evolved. The Heineke-Mikulicz strictureplasty is usually used in strictures shorter than 10 cm and technique ad modum Finney is used in strictures between 10 and 25 cm.\textsuperscript{254} There are no studies comparing resection with strictureplasty, but usually strictureplasty is considered as safe and effective as resection with regard to postoperative complication and surgical recurrence.\textsuperscript{255} However, in a meta-analysis from 2006, there was a trend towards a higher surgical recurrence rate (38\% vs. 31\%) after strictureplasty compared to resection.\textsuperscript{256}

Due to the risk of recurrence after surgical resection and postoperative adhesions, a non-surgical alternative in treating intestinal fibrotic stricture has been sought. When the endoscopic technique became more available, different types of endoscopy-assisted procedures evolved, including Hegar’s dilators, Maloney’s dilators, Gruntzig balloons, and Savary dilators. However, not until the endoscopic balloon dilation with through-the-scope technique was any real achievement made. No prospective studies have evaluated when or where endoscopic balloon dilation should be used, but uncontrolled observational studies indicate that it is a safe and effective alternative to intestinal resection or strictureplasty in treating short fibrotic intestinal strictures.\textsuperscript{257, 258}
Aims

The overall aim of this thesis is to study therapy in inflammatory bowel disease, in particular, the long-term prognosis after an acute severe attack of ulcerative colitis and efficacy of endoscopic balloon dilation in treatment of intestinal strictures in Crohn’s disease.

Paper I
The aim was to describe the long-term colectomy rate in patients treated with intensive intravenous corticosteroid treatment (IIVT) prior to the immunosuppressive treatment era for a severe attack of ulcerative colitis and compare with patients treated with IIVT for a moderate or mild attack, and evaluate whether the severity of the index attack influenced the subsequent relapse rate during follow-up.

Paper II
The aim was to evaluate the 3-year follow-up results of patients who participated in the Swedish-Danish infliximab/placebo trial in acute steroid refractory ulcerative colitis, with the primary objective to determine the number of patients escaping a colectomy at follow-up.

Paper III
The aim was to report a single referral centre experience of short-term and long-term efficacy and safety of endoscopic balloon dilation in treatment of intestinal strictures in Crohn’s disease.

Paper IV
The aim of this study was to evaluate whether smoking at diagnosis, treatment with azathioprine, or other clinical variables could affect outcome of endoscopic balloon dilation in patients with stricturing Crohn’s disease, with respect to new dilations or surgery with intestinal resection or strictureplasty.
Ethics

All studies were approved by the Regional Ethics Review Board in Uppsala.

Material and Methods

Paper I

Patients

Patients in this follow-up study have earlier been described in detail. In short, during the period 1975–1982, 158 patients (89 male, 69 female) were hospitalised and treated with a standardised IIVT for an attack of ulcerative colitis. The severity of the attack was defined according to Truelove and Witts’s criteria. If unresponsive to 5–7 days of medical therapy, the patient was recommended colectomy. Patients responding to IIVT were discharged with tapering doses of oral corticosteroids for 2 months with an initial daily dose of 40 mg prednisolone. If not intolerant, the patient was recommended life-long maintenance sulphasalazine therapy 2–3 g/day.

Follow-up data

Follow-up data were searched for in the medical files in Örebro University Hospital or by contacting the current physician of patients who had left our region.

When reading the medical notes, the earlier diagnosis of ulcerative colitis was re-evaluated. The subsequent course of disease was assessed regarding time of and indication for colectomy as well as number of relapses during the observation period. The cause of death was registered from the medical notes and from the official Cause of Death Register in Sweden. The total observation time was calculated from the first IIVT until surgery, death, or this follow-up.

Clinical remission was defined as absence of bowel symptoms. Endoscopic remission refers to lack of signs of active disease such as friability, spontaneous bleeding, or ulceration. Relapse was defined as recurrence of clinical symptoms and/or an inflamed mucosa at sigmoidoscopy. Occasionally, a symptomatic patient was treated without preceding sigmoido-
scopy. Frequent relapsing disease, being an indication for colectomy, refers to a clinical judgement taking into account disease course not only after, but also prior to, IIVT.

For patients in remission after the first IIVT, relapse incidence (number of relapses per patient-month at risk) was calculated. Colectomy incidence (number of colectomies per patient-month at risk) was calculated for the periods 0–3 months and >3 months after the index IIVT.

**Paper II**

**Patients**

Patients in this follow-up study have earlier been described in detail. In short, 45 patients were hospitalised due to moderately severe or severe attack of ulcerative colitis and treated with betamethasone 8 mg/day intravenously. Patients with corticosteroid refractory disease were randomised, on day 4 according to the fulminant colitis index >8 on day 3 (n = 28), or on days 5–7 according to the Seo index >150 (n = 17), to a single infusion of infliximab (5 mg/kg) or placebo. Decision on colectomy was made on clinical grounds. Maintenance therapy with mesalazine and/or azathioprine was given according to the individual investigator’s decision.

**Follow-up data**

Three years or later after the original randomisation patients were asked to participate in a follow-up study. Clinical data and routine blood samples were collected, and a flexible rectosigmoidoscopy was performed in patients not having had a colectomy. Relapse was defined as recurrence of clinical symptoms and need for intensified medical treatment. Maintenance treatment with immunomodulators refers to treatment with thiopurines for ≥6 months.

**Papers III and IV**

**Patients**

In paper III the patient cohort comprised 178 patients with Crohn’s disease, including both patients from the primary catchment area of the hospital (n = 125) and referred patients (n = 53). In paper IV, we excluded 53 referral cases to avoid selection bias, and 42 cases that after index dilation had repeated dilations performed, due to an asymptomatic intestinal stric-
ture. Thus, the cohort in study IV consisted of 83 (39 female) patients. The patients in both papers were retrospectively identified by running the register of surgical procedures against the diagnosis register at the Departments of Medicine and Surgery at Örebro University Hospital during the period 1987, when the first dilation was performed, to 2009. Demographic data, clinical characteristics, and endoscopic and surgical procedures were searched for in the medical records at the Departments of Medicine and Surgery.

Diagnosis of Crohn’s disease was based on Lennard-Jones criteria. Disease location and behaviour were classified according to Montreal classification.

All patients were included in the calculations on technical success and complications. To reduce the risk of referral bias, analyses of clinical efficacy were restricted to patients from our primary catchment area.

**Stricture and endoscopic dilation**

A bowel stricture was considered to exist when passage of a standard colonoscope was not possible. A symptomatic stricture refers to a stricture associated with clinical symptoms of bowel obstruction such as postprandial abdominal pain, vomiting, and nausea. Concomitant fistula or abscesses were exclusion criteria. In most cases the stricture was documented by a small bowel follow-through or enteroclysis, or in recent years a magnetic resonance tomography of the small bowel. In patients with symptoms of bowel obstruction and a previous history of stricturing Crohn’s disease, colonoscopy was performed without prior radiological investigation.

Endoscopic dilation was generally done as an outpatient procedure using conscious sedation with midazolam and/or alfentanil, or diazepam and/or pethidine. A few procedures were done under general anaesthesia. Several different physicians with variable endoscopic skill performed the dilation procedure. Standard colonoscope and through-the-scope dilation balloons with a maximal diameter of 12 mm to 25 mm were used. The balloon was positioned under visual control in the stricture and inflated with water stepwise with a gradually increasing diameter. Inflation time varied between 1 and 3 minutes. The procedure was repeated until the colonoscope could pass through the stricture (Figure 1). Fluoroscopy was not used.
Figure 1. Intestinal stricture before, during and after endoscopic balloon dilation
Definition of smoking and medical therapy
Smoking habits, based on data in medical records at diagnosis, were classified as never smokers, ex-smokers, or active smokers. Smoking was defined as daily consumption of tobacco for at least 6 months.

Maintenance therapy with azathioprine was defined as continuous use in an appropriate dosage for at least 6 months.

Outcome
Technical success was defined as being able to pass the endoscope through the stricture after the procedure. Short-term clinical success was defined as relief of clinical symptoms of bowel obstruction during the following month after the endoscopic procedure. Long-term efficacy was assessed on cumulative proportions of patients undergoing no further procedure, one dilation, two dilations, three dilations, more than three dilations, or surgery for each year during the first 5 years after index dilation. Evaluation of clinical efficacy was made in patients from the primary catchment area only, whereas technical success was assessed in all patients, including referred patients. Surgery refers to any operation leading to intestinal resection or strictureplasty. Intervention refers to either a new dilation or surgery.

Complications such as bowel perforation, bleeding, abdominal pain, fever, or death following the procedure, and requiring hospital stay or prolonged hospital stay were assessed in all patients. Major bleeding was defined as any bleeding requiring blood transfusion.
Statistics in all papers

Data are in study I and II are presented as median (range). Time to colec-
tomy and time to first relapse was illustrated with Kaplan-Meier plot, and
differences between treatment groups and severity of index attack were
tested with log-rank test. Colectomy incidence (number of colectomies per
patient-month at risk) and relapse incidence (number of relapses per pa-
tient-month at risk) was calculated and analyzed with Poisson regression to
estimate relative risks with 95% confidence interval (95% CI). Due to
probable non-proportional hazard in study 2, we used logistic regression
analysis to adjust for potential confounders and to calculate odds ratio
(OR) with 95% confidence interval. Mann-Whitney U test was used to
analyse time to first relapse. Differences between groups were tested with
Fischer’s exact test.

In study III and IV data are presented as median and interquartile range
(IQR). Differences between groups were tested with Chi-square test, or
when appropriate, Fisher’s exact test. Time to intervention (new dilation,
bowel resection, or strictureplasty) after index dilation was illustrated with
Kaplan-Meier plot, and differences between groups were tested with log-
rank test. Cox regression was used to evaluate the association to smoking
and other clinical variables. All explanatory variables were analyzed as
categorical in Cox regression. Measures of association are Hazard ratios
(HR) with 95% confidence intervals (95% CI).
Results

Paper I

Patients
The clinical course was evaluated in 157/158 patients. In 10 patients the diagnosis had been changed to Crohn’s disease (n = 6), self-limiting colitis (n = 3), or drug-induced colitis (n = 1). In the remaining 147 patients (84 male, 63 female), the indication for IIVT was a severe attack (n = 61), a moderately severe attack (n = 45), a mild attack (n = 29), or chronic continuous disease (n = 12). Thirty-one patients were treated for a first attack of ulcerative colitis and 116 patients for relapsing disease. The median (range) age at IIVT was 36 (16–85) years. The median (range) disease duration from diagnosis to IIVT was 3 (0–42) years.

In patients not operated on (n = 68), the median (range) observation time was 214 (27–271) months.

Severe attack
Of patients treated for a severe attack 28/61 (46%) were operated on within 3 months. The colectomy rate 10 years after IIVT was 39/61 (64%). No further colectomy occurred after the first 10 years (Figure 2). Of the 33 patients who escaped colectomy during the first 3 months after index IIVT, 11 (33%) later had a colectomy. The colectomy incidence beyond 3 months was 0.002 per patient-month at risk.

Moderately severe attack
Of 45 patients initially treated with IIVT for a moderately severe attack, four patients (9%) had a colectomy within the first 3 months. During follow-up, 24/45 (54%) had a colectomy, 22 (49%) within the first 10 years of IIVT (Figure 2). Of the 41 patients who escaped colectomy during the first 3 months after index IIVT, 20 (49%) later had a colectomy. The colectomy incidence beyond 3 months was 0.004 per patient-month at risk.

Mild attack
During follow-up, 10/29 (34%) had a colectomy, 8 (28%) within the first 10 years of IIVT (Figure 2). Among the 28 patients who escaped colectomy during the first 3 months after index IIVT 9 (32%) later had a colectomy.
The colectomy incidence beyond 3 months was 0.002 per patient-month at risk.

**Relapses**
After the index IIVT, 103/135 (73%) patients achieved clinical and endoscopic remission. During follow-up, these 103 patients had 536 relapses, corresponding to a relapse incidence of 0.036 per patient-month. The relapse incidence was significantly higher in patients having a colectomy than in those escaping surgery (RR 3.7; 95% CI 3.1–4.4). Patients with a severe index attack who achieved clinical and endoscopic remission had a slightly lower relapse incidence than those with a mild attack.

**Mortality**
Twenty-six of the 147 (18%) patients died during follow-up. Three patients died postoperatively due to cardiovascular complications (n = 2) and miliary tuberculosis (n = 1). An 84-year-old woman with Alzheimer’s disease died of unresponsive disease because of reluctance to undergo surgery. The cause of death in the remaining patients was unrelated to ulcerative colitis. No patient developed colonic carcinoma or cholangiocarcinoma.
Figure 2. Kaplan-Meier graph showing probability of not undergoing colectomy in relation to disease severity for the whole study period 0-20 yr. Note that 12 patients with chronic continuous disease are included but not presented in the subgroup analysis.

**Paper II**

**Patients**

Clinical data, including on colectomy, was available in all patients for a period of 3 years or more after randomisation, with a median (range) follow-up time of 55 (36–79) months.

**Colectomy**

In addition to the 21 patients operated on during the first 3 months, another 7 patients underwent colectomy at 3 years; five had been randomised
to infliximab and two to placebo in the original study. Thus, in total 12/24 (50%) infliximab-treated patients and 16/21 (76%) placebo-treated patients had had a colectomy at 3-year follow-up (p = 0.012) (Figure 3). The difference remained after multivariate logistic regression analysis adjusting for age, sex, extent of disease, and earlier known or first attack of ulcerative colitis.

**Maintenance therapy during follow-up from 3 months to 3 years**

At follow-up, 4/16 received 5-ASA and 12/16 immunomodulators as maintenance therapy in the infliximab-treated group, whereas 3/7 and 4/7 received 5-ASA and infliximab, respectively, in the placebo treated group. Three patients randomised to infliximab also received a series of leucocytapheresis during follow-up.

![Figure 3. Kaplan-Meier plot showing probability of colectomy-free survival in ulcerative colitis, related to time after randomization.](image-url)
Papers III and IV

Demographics of all patients
During 1987 to 2009, 178 patients (94 female) underwent endoscopic balloon dilation due to bowel strictures causing obstructive symptoms. Of these, 125 (70%) resided in the primary catchment area of the hospital, and 83 patients in the primary catchment area underwent repeated dilations due to recurrent symptomatic strictures only. The median (IQR) age in all patients at diagnosis of Crohn’s disease was 29 (20–39), and at first dilation 45 (37–56) years. Demographics and clinical characteristics of all patients are shown in the original version of paper III.

Endoscopic dilation in all patients
In 178 patients, a total of 776 dilations were made; 155 (20%) were performed on de novo strictures and 621 (80%) on anastomotic strictures. Six hundred twenty-five (81%) procedures were performed in patients with symptomatic strictures, and 151 (19%) dilations in patients with strictures causing no clinical symptoms. Details of strictures and dilation procedures are shown in the original paper III. The dilation procedure was done with sedation with benzodiazepines and/or opioid analgesics in 726 (94%) procedures and general anaesthesia in 11 (1%), and in 37 (5%) procedures no sedation was given (data missing in 2 patients).

Outcome of endoscopic dilation in all patients
Technical success was achieved in 689/776 dilations (89%). Complication rate per procedure was 41/776 (5.3%), which included bowel perforation (n = 11, 1.4%), major bleeding (n = 8, 1.0%), minor bleeding (n = 10, 1.3%), and abdominal pain or fever (n = 12, 1.5%). Ten patients underwent surgery due to complications (perforation n = 8, bleeding n = 2). Significantly more complications (20/216, 9.3%) occurred with use of the largest balloon (diameter of 25 mm) compared to use of smaller balloons (diameter of ≤20 mm) (17/489, 3.5%) (p < 0.01). In four complications, the size of the balloon was not known. No difference was found between the two groups with respect to complications requiring surgery (4/216 (1.9%) vs. 4/489 (0.8%), p = 0.23). In two complications requiring surgery the size of the balloon was not known. Complications did not differ between patients dilated due to de novo (5/155, 3.2%) or anastomotic strictures (36/621, 5.8%, p = 0.20). There was no procedure-related mortality.
Outcome of endoscopic dilation in patients from primary catchment area

Of 125 patients from the primary catchment area, 83 patients underwent repeated dilations due to recurrent symptomatic strictures only. A subset of 75 patients, with a follow-up of ≥5 years, underwent 246 dilations. The cumulative proportion of patients undergoing no further intervention, repeated dilations, or surgery each year during 5 years’ follow-up after index dilation is shown in Figure 4. No further intervention or one additional dilation only was needed in 60/75 (80%) patients during the first year after the index dilation, and at 3 and 5 years corresponding figures were 43/75 (57%) and 39/75 (52%). Cumulative proportions of patients undergoing surgery at 1, 3, and 5 years were 13%, 28%, and 36%. Probability of surgery-free survival did not differ between dilations of de novo strictures compared to anastomotic strictures (p = 0.86).

![Figure 4. Cumulative proportions of patients undergoing no further invention, repeated dilations, or surgery during 5 years’ follow-up following index dilation. This analysis is restricted to 75 patients having repeated dilations only of strictures causing symptoms of bowel obstruction, and with a follow-up of 5 years or more.](image)

Smoking and medical therapy

At diagnosis, the 83 patients from the primary catchment area patients were classified as smokers (n = 32), never smokers (n = 33) and ex-smokers (n = 13). Data were missing in five patients. In total, 55/83 underwent a new intervention during follow-up. Smoking habits influenced the subse-
quent risk for new intervention after index dilation. In the group of active smokers, 31/32 (97%) underwent another intervention compared to 18/33 (55%) in the never smokers group (HR 2.18, 95% CI: 1.22–3.93, p = 0.01) (figure 5). The difference remained after adjustment for other variables.

Azathioprine as maintenance therapy was given to 16/83 patients and was initiated before index dilation. In patients treated with azathioprine at first dilation, 7/16 underwent a new intervention compared to 48/67 of those without this treatment (HR 0.46 (0.21–1.03), p = 0.06). After adjustment for smoking, hazard ratio was 0.86 (0.36–2.09), p = 0.75) Clinical parameters such as sex, age at diagnosis, age at first dilation, balloon size, localisation of stricture, or treatment period did not influence outcome.

Figure 5. Kaplan-Meier plot showing probability of intervention-free survival after index dilation in relation to smoking habits at diagnosis of Crohn’s disease.
General discussion

Methodological considerations
The different alternatives of study design are based on the aim of the study and consideration of approaches to reduce sources of errors.

Internal validity
Intern validity is to what extent the result of a study correctly reflects the source population and defined as absence of random (chance) and systematic error (bias and confounding).

Random error
Chance is often believed to play a fundamental role in a biological phenomenon. However, in a deterministic point of view, chance is only seen as a catch-all term for our ignorance about causal explanations. If we knew all the relevant factors that would influence outcome, we could easily predict the result of the study. This is not possible in the existent world. Therefore, chance is always a potential explanation for any outcome of a study, both positive and negative. One must always consider if the observed results are realistic and in line with the a priori hypothesis and if reasonable in a biological point of view. To evaluate if the observed findings can be a result of chance; statistical tests (p-value or ratio with confidence interval) are performed. The statistical results show the probability of the results to be a true outcome of the study or not. Inability to reject the null hypothesis can be a result of chance due to a small study population. Consequently, to reduce the likelihood of a result due to chance you should increase the study population. The present studies I, III, and IV concerned single centres’ retrospective experiences of IIVT in attacks of ulcerative colitis and endoscopic balloon dilation in Crohn’s disease. The only possible way to increase the study population was to extend the retrospective inclusion periods. In study I the period was 7 years, and in studies III and IV more than 20 years. It seems, therefore, not a reasonable way to go. Another way to increase the patient population was to include patients from other hospitals. This certainly increased the number of included patients, but at the same time diminished the uniformity of treatment procedures, which lowered the significance of the study.

In the original study II, an increase of the included patients definitely would have increased the power of the results. This was not possible due to
slow recruitment, and more important, the result of the study. There was a significant difference between the active treatment and placebo, and therefore, for ethical reasons, it was not possible to continue. The follow-up study is addressed to the 45 patients who were included.

In study IV we concluded that azathioprine did not influence outcome after dilation. However, there were only 16/83 patients treated with azathioprine. In some patients treatment was initiated at the time of dilation while some had have azathioprine for a long time. Furthermore, the indication of treating these patients with azathioprine is not known. The risk of a random error seems obvious and the result should be interpreted with great caution.

The risk of association by chance should always be assessed if performing many statistical tests. When evaluated prognostic factors in study IV, we used 9 different factors that might influence the result. The risk of any association by chance seems small.

**Selection bias**

Selection bias is distortion that results from procedures used to select patients and from factors that influence participation in the study.

The risk of selection bias in studies I, III, and IV is obvious, given the retrospective design. Study I is a follow-up of the 158 patients participating in the study from 1985. All but one patient could be identified and was included in this follow-up. The risk of selection bias is therefore attributed to the original paper. In short, patients fulfilling criteria ad modum True-love-Witts for a severe attack of ulcerative colitis were all hospitalised without exception. The patients with mild or moderate attacks of ulcerative colitis and those with chronic continuous disease do not, however, represent all patients with that level of severity, due to selection criteria. The aim to describe the long-term colectomy rate in patients with a severe attack of ulcerative colitis treated with IIVT seems therefore reasonable, but the long-term comparison with the other groups is more questionable, due to lack of pre-defined criteria to join the study for the other groups.

As in study I, the selection bias in paper II is attributed to the original survey, since all patients could be followed up. It is a double blind, placebo-controlled, randomised study design. Patients rejecting participation are not showed in the original paper. The dropouts could therefore represent a group with unclear significance.

In studies III and IV, patients were recruited by running the register of surgical procedures against the diagnosis register during a study period of more than 20 years. Whether all patients undergoing balloon dilation since
1987 have been recorded in these registers is not known, since we do not know if all data was properly recorded. The Endoscopy Unit has, however, a manual backup system to register patients undergoing this procedure. Thus, it seems realistic to assume that most patient files were found. Another way to check whether the number of procedures is realistic would be to compare the incidence of dilations with those performed in other hospitals. This did not seem reasonable, since Örebro was a pioneer in this field of intervention. Selection bias could also influence whether patients were operated on or dilated. The decision as to which procedure to use was made not only by the judgement of the responsible physician but also by all gastroenterologists in the department. This would probably diminish the risk of selection bias.

In study IV we studied whether medication with azathioprine could diminish the need of additional dilations or surgery. We defined treatment as continuous use in an appropriate dosage for at least 6 months. This is a clinical definition and is not prospectively validated. The indication of medication is not evident. There is an obvious risk that patients with more severe disease are overrepresented in the group treated with azathioprine and therefore diminish the actual effect of the medication.

Confounding
Confounders are riskfactors associated both with the exposure and the outcome, but not as an intermediate step in the pathway from the exposure and the disease. Lack of information of potential confounders is always a risk in a study, especially those with retrospective design.

In study IV the risk of confounding is obvious. When looking for factors influencing the procedure and outcome of a procedure like balloon dilation one can only compensate for factors known to the investigators. We used a multivariate analysis to compensate for age at diagnosis, sex, age at first dilation, balloon size, localisation of the stenosis, and the influence of the different study periods. However, there were factors not included in the multivariate analysis due to insufficient data quality, such as the length and width of the stenosis, operation technique, the skill of the physician, the procedure time, any possible inflammatory activity, and whether medication with corticosteroids was used after dilation. Whether these factors could influence outcome is therefore not known. In previous studies evaluating endoscopic balloon dilation, these factors have not influenced outcome, although bias in these studies can be question.257, 258 In the unadjusted analysis, medical treatment with azathioprine seemed to protect against re-intervention (HR 0.46, p=0.06). In the adjusted analysis the
positive effect of azathioprine disappeared. This is entirely explained by the effect of smoking. Smoking is therefore to be considering as a confounder. In the unadjusted analysis, female gender seemed to slightly increase the risk of re-intervention, however not statistical significant (HR=1.38, p=0.23). After adjusted to other factors, the risk seemed to be less (HR=0.74, p=0.38). One can speculate if this is an effect of uneven distribution of smoking among male and females.

Recall bias
Recall bias occurs when patients in a study recall exposures as being different from the way they actually occurred. In study IV we studied the impact of smoking on the outcome of endoscopic dilation. The information on smoking habits was collected from the medical register. If information regarding smoking habits at diagnosis was collected later in the disease course, a risk of recall bias is obvious. The smoking data in our study is not validated, so are these data of smoking habit among patients with IBD reliable? In a study on smoking in IBD, a retrospective questionnaire used in 1984 was evaluated by asking the patients with ulcerative colitis to reply to the same questionnaire in 1989. Compared to the reply in the original questionnaire, a good correlation of self-reported smoking data was found. However, the patients in study IV suffered not from ulcerative colitis but from Crohn’s disease but it seem that the reported data of smoking habits in patients with IBD in our institution is reliable and probably not biased by major misclassification.

Misclassification
In studies I and II, the diagnosis in the original study was made according to the Lennard-Jones criteria. At follow-up the diagnosis was re-evaluated according the same criteria. It is a well known fact that the diagnosis of IBD can change over time, so that 10 patients in the original study I changed diagnosis is expected. In the original papers preceding studies I and II, a risk of misclassification of the severity of the attack of ulcerative colitis is possible. In both studies internationally accepted indices were use: in study I the Truelove-Witts criteria, and in study II, the Seo and the Sweden indices. The data included in the index of the original study I is retrospectively collected and in original study II, prospectively. The risk of incorrect classification is therefore bigger in study I. However, all indices were re-calculated and a good agreement was found. The risk of misclassification is therefore most likely low in both follow-up studies. In study I we
used the definition of relapse as recurrence of clinical symptoms and/or inflamed mucosa at sigmoideoscopy. Sometimes patients received medical treatment without preceding sigmoideoscopy. In these cases there is a risk of treating someone without a real relapse rather symptoms due to other causes. However, the treatment policy during the years of inclusion in original study I, was always to confirm a clinical suspicion of a relapse with a sigmoideoscopy. The rate of misclassified patients due to an inaccurate interpretation of a relapse is therefore probably minimal. In studies III and IV, the diagnosis of Crohn’s disease was re-evaluated when we scrutinised the medical notes. All patients were classified as having stricturing Crohn’s disease at follow-up.

**External validity**

External validity (or generalisability) is the possibility to generalise the observed finding to different study populations. Internal validity is a prerequisite for external validity.

In the original study I, all patients were retrospectively recruited. According to the treatment policy, all patients with a severe attack of ulcerative colitis were hospitalized but not patients with mild or moderately severe disease attack according to Truelove-Witts criteria. The conclusion that the relapse incidence not was influenced by the severity of the index attack can therefore be questioned and especially the generalisability to the entire population of patients with ulcerative colitis, seems therefore not reasonable.

In study III and IV, there are many factors impairing the external validity. All patients were identified retrospectively during approximately 20 years. However, a general written consensus of which patients to treat with endoscopic balloon dilation did not exist, but it was generally accepted, both among surgeons and gastroenterologist, to first perform an endoscopic dilation of an anastomotic stricture before surgery.

To be able to perform an endoscopic dilation the stricture must be reachable by an endoscope, no evidence of fistula, a short stricture and preferably no more than one stricture. This group of patients is therefore highly selected to be suitable for endoscopic dilation. The size of the group not suitable for dilation and underwent surgery is not known.

The impact of endoscopic dilation is very much depended of the skill of the investigator. In our study different physician with variable skills was taking part of the treatment and therefore weaken the generalisability.
Most of the strictures in study III and IV were situated in ileocolonic anastomosis. To transfer the results of dilations to other locations of the strictures is not possible.

**Treatment of a severe attack of ulcerative colitis**

An acute, severe attack of ulcerative colitis is usually defined by the criteria of Truelove-Witts. Before the era of corticosteroid therapy, therapy consisted mainly of supportive treatment such as blood transfusion to replace blood loss, parenteral therapy to overcome dehydration and electrolyte deficiencies, and a high-caloric, high-protein diet to preserve the state of nutrition. Surgery, emergency colectomy, was not an option until complication occurred. As a consequence, mortality was very high, 25–35%. Beginning in the early 1950s, ACTH was used as treatment for some time, before it was replaced by synthetic cortisone. Eventually, the Oxford model evolved as a standard treatment. It consisted of intensive intravenous corticosteroid therapy (IIVT), total parenteral nutrition, corticosteroid enema, and initially also antibiotics for 5 days. In case of unresponsiveness, early colectomy was performed. However, the response to corticosteroid treatment has been unchanged since its introduction, with response rates of approximately 60% and short-term colectomy rates of 27%. With the introduction of intravenous corticosteroids the mortality rate was reduced to 7%, and subsequently to <1% with the practice of early colectomy in unresponsive disease.

In the long-term follow-up after IIVT (study I) the short-term colectomy rate was 46% in the group treated for a severe attack. This in somewhat higher than in the systematic review by Turner et al., but there were differences in the definition of short-term, the possible inclusion of moderately active patients, doses of corticosteroids, and whether cyclosporine was used. In study I, the colectomy rate after 10 years was 64%. In comparison with other studies, the follow-up time is a very long. Dr Bojic et al. have reported the Oxford experience of the 1992–1993 cohort, in which 49 patients were treated due to a severe attack of ulcerative colitis. Forty-six could be followed up, and in total, 30/46 (65%) patients came to colectomy during follow-up of a median 122 months. These figures are almost identical to those of study I and emphasise the serious prognosis of an acute severe attack of ulcerative colitis in the long run. In study I, we were also able to show that the colectomy rate beyond 3 months was not influenced by the severity of the index attack for which IIVT had been given. It
seems therefore logical to use “rescue therapy” to try to avoid colectomy when conventional corticosteroid treatment fails.

The first successful rescue therapy was cyclosporine. It is a calcineurin inhibitor derived from the fungus *Tolypocladium inflatum*. The efficacy in acute steroid refractory ulcerative colitis was first demonstrated in 1994 by Lichtiger et al., when 9/11 patients receiving intravenous cyclosporine 4 mg/kg responded versus 0/9 in the placebo group. Subsequent studies have reached a similar conclusion, with response rates of 70–80%. Cyclosporine is also proven effective as monotherapy in comparison to intravenous corticosteroids. There are, however, concerns about toxicity of cyclosporine with respect to seizures, hypertension, impaired renal function, opportunistic infection, and even death. Due to the toxicity, cyclosporine has not been accepted as rescue therapy worldwide, especially not in Scandinavia. To minimise concerns about toxicity, the use of lower doses of cyclosporine (2 mg/kg) iv has been investigated, as has an oral micro-emulsion formula. There seems to be no difference in efficacy between the high (4mg/kg) and low dose (2 mg/kg) and the other formulas. Unfortunately, it is not clear whether any difference in adverse events can be accomplished.

The other successful rescue therapy is infliximab. It was proven effective in acute steroid-refractory ulcerative colitis in 2005 by the study by Järnerot et al. Forty-five patients were randomised to receive either infliximab (5mg/kg) or placebo as rescue therapy. There was a significant difference in colectomy rate in favour of infliximab versus placebo (29% vs. 67%). The best effect was seen in patients randomised at day 5-7 according to the Seo index compared to those randomised on days 3 according the fulminant colitis index. This has been interpreted that it seems to work less well in the sickest patients. This is not correct. On day 0 there was no difference in Seo index between the two groups. The most plausible conclusion is that those patients randomised according to the fulminant colitis index are more steroid refractory than the other group, rather than more severely inflamed. There have also been several other uncontrolled studies that supported the use of infliximab as rescue therapy, while some have not shown any effect. In the original study by Järnerot et al. only one single infusion of infliximab 5 mg/kg was used, whereas in other studies a standard schedule of three infusions in weeks 0, 2, and 6 was used, or various numbers of infusions. Kohn et al. concluded that two or more infusions seemed more effective than one single infusion. As with cyclosporine, there have been concerns about toxicity. In the study by Järnerot no difference was seen between the infliximab and placebo groups, either in toxicity or in postoperative complications. There are,
however, reports of opportunistic infections and even death.\textsuperscript{275, 276} The experience of treating Crohn’s disease with infliximab suggests that the combination of infliximab, corticosteroids, and/or immunomodulators, and the underlying bowel disease is the cause of complications rather than infliximab itself.

There have been a few retrospectively designed studies comparing infliximab and cyclosporine as rescue therapy.\textsuperscript{282-284} In the Swedish–Austrian study, colectomy frequencies were significantly lower after treatment with cyclosporine than with a single infusion of infliximab at 3 months. The superiority of cyclosporine was seen within the first 15 days. The opposite was shown by Dean et al., in whose study the outcome of patients treated with infliximab was superior to cyclosporine, regarding colectomy after 3 months (21\% vs. 63\%). A randomised study evaluating the two therapies has been carried out in France, but the result has only been presented as an abstract.\textsuperscript{285} The authors concluded that there is no difference in achieving short-term remission and avoiding urgent colectomy between infliximab and cyclosporine. A British study (CONSTRUCT-study) with the same issues is ongoing and is estimated to include patients until August 2012.

A third alternative as rescue therapy is tacrolimus. Like cyclosporine, it is a calcineurin inhibitor. It has been less well studied than infliximab and cyclosporine; case studies show results similar to those of cyclosporine as rescue therapy, but the only randomised controlled trial did not reach statistical significance in showing any effect of tacrolimus.\textsuperscript{233, 286}

The “best” rescue therapy should be identified by a joint decision of the patient, physician, and surgeon. Both the patient and the physician must understand that the ultimate goal in rescue therapy in acute severe ulcerative colitis is not to save colon but to save the life of the patient. Despite having two effective rescue therapies, the choice of surgery must always be discussed early. Rescue therapy must not delay necessary colectomy, since the risk of mortality increases if surgery is delayed. There are some absolute indications for surgery, such as toxic megacolon, colonic perforation, and uncontrolled bleeding. However, if a decision is made in favour of rescue therapy, the choice between infliximab and cyclosporine must be made. If the result of the French controlled trial is accurate, the decision must be made on factors other than short-term clinical outcome, such as the risk of toxicity, post-operative complications, long-term outcome, and the familiarity of the drug by the single physician. Cyclosporine seems not to be associated with any increased perioperative complications in those patients not responding and progressing to colectomy, maybe due the short half-life of cyclosporine.\textsuperscript{287} The role of infliximab in peri- and postoperative complications is still controversial. There have been studies showing
increased risk of postoperative complications, whereas others have shown no risk. Where one rescue therapy has failed, consecutive use of cyclosporine and infliximab has been used. An American study suggests that a substantial risk of serious adverse advent, including mortality, exists. The other studies do not support this fear, but caution before using this combination is advised. Another aspect to consider when deciding which rescue therapy to use are the long-term results. Patients must be made aware that the risk of colectomy in the next 10 years is high, regardless of medical treatment. When using cyclosporine as rescue therapy, long-term follow-up has shown high colectomy rates after 7–8 years (58–88%). As maintenance therapy after successful induction of remission with cyclosporine, a combination of oral cyclosporine for 3–6 months and concomitant azathioprine is normally advised. The long-term follow-up after therapy with infliximab has been less well studied. In study II we could show that the initial benefit of infliximab persisted after 3 years, with a significant difference between the infliximab- and placebo-treated groups (50% vs. 76%). Similar results were found in a retrospective, follow-up of infliximab as rescue therapy in 211 patients. Colectomy-free survival at 3 months was 70% and at 12 months 63%. Due the high frequency of colectomy after rescue therapy with both cyclosporine and infliximab, an effective maintenance therapy is necessary. In study II, a limitation was the unequal distribution of subsequent maintenance therapy, as more patients in the infliximab-treated group than in the placebo group received azathioprine. However, patients in the infliximab-treated group, naïve to azathioprine, and receiving subsequent azathioprine as maintenance therapy, had better outcome after 3 years in respect to colectomy compared to those receiving 5-ASA as maintenance therapy (1/8 vs. 2/4). These numbers are, however, very small, the difference not statistically significant, and should therefore be interpreted cautiously. The use of maintenance therapy differed also in other studies using 5-ASA only, azathioprine or 6-mercaptopurine alone or in combination with 5-ASA, or with scheduled infliximab. According to the guidelines of the European Crohn’s and Colitis Organisation, infliximab is recommended as maintenance therapy, when responding to infliximab-induced remission. In azathioprine-naïve patients responding to infliximab induction, azathioprine is an option. These recommendations, however, are mainly based on the analysis of the ACT-1 and 2 studies and not on studies evaluating maintenance therapy after rescue therapy. Therefore, the evidence for such a recommendation in a patient successfully treated with rescue therapy in severe ulcerative colitis is limited, and the best maintenance treatment needs further study.
Mucosal healing has evolved as an important goal in therapeutic studies in IBD and is associated with increased possibility of steroid-free remission and lower rate of hospitalisation and surgery. The clinical definition of mucosal healing often refers to endoscopic evaluation of disease activity but there are several different scoring systems such as Baron and Mayo endoscopy subscore in ulcerative colitis with different parameters. In study II we could show that patients in endoscopic remission, defined as Mayo endoscopy subscore 0, at 3 months after rescue therapy had significant less risk of later undergo colectomy compared to those not in endoscopic remission (0/8 vs 7/14). This is in accordance with other studies showing that mucosal healing is associated with better clinical outcome. In ulcerative colitis; 5-aminosalicylates, corticosteroids, azathioprine, cyclosporine and anti-TNF-therapy, all have shown ability to induce mucosal healing.

In conclusion, rescue therapy in acute steroid refractory ulcerative colitis is a good alternative to surgery. But, it is evident that there is a need to evaluate the optimal dosing and treatment schedule of rescue therapy in general and infliximab in particular and what maintenance therapy to use after successful rescue therapy. This can only be done in prospective and randomised controlled studies.

**Endoscopic balloon dilation in treatment of intestinal strictures of Crohn’s disease**

Fibrotic strictures are common manifestations of Crohn’s disease and are a major cause of morbidity, hospitalisation, and surgery. Already at diagnosis of Crohn’s disease 5–27% of patients have stricture disease, and during follow-up, 10–30 years after diagnosis, 22–31% were identified as having stricture disease. The cumulative probability of bowel resection in Crohn’s disease is 38–71% within 10 years after diagnosis, and an approximately 50% risk of postoperative recurrence after 10 years.

The quantitative problem with intestinal stenosis is therefore large. Traditionally, stenosis in the bowel due to Crohn’s disease has been treated with intestinal resection, and in recent years, strictureplasty. In study III we could show that endoscopic balloon dilation is an efficacious and safe alternative to surgical resection. One year after index dilation, 60/75 (80%) patients had undergone no further intervention or one additional dilation only. At 3 and 5 years, corresponding figures were 43/75 (57%) and 39/75
Cumulative proportions of patients undergoing surgery at 1, 3, and 5 years were 13%, 28%, and 36%. That means that after 5 years, 64% escaped surgery and could manage with no further treatment or endoscopic balloon dilation only. These are figures analogous with the experience from Leuven. The authors performed 237 dilations in 138 patients. After a median follow-up of 5.8 years, 46% of the patients needed a new dilation, and 24% surgery. In the meta-analysis by Hassan et al. 58% of treated patients were surgery free after a mean follow-up time of 33 months, and 22% required two dilation procedures, while 19% required more than two dilations, ranging from 3 to 18. In our study approximately 80% of stenosis was anastomotic, and 20% were de novo strictures. The efficacy of the index dilation was comparable, regarding surgery at follow-up as well as additional dilations. Most of the previous studies have not calculated whether there are any difference between de novo and anastomotic strictures. In two small studies outcome was worse in de novo strictures.

The similar results of the Belgian study and our own work are probably due to the use of the same dilation technique and the fact that the same indication of the procedure has evolved, despite lack of controlled studies. All dilations are made under visual control and “through-the-scope” technique. The balloons used are the same and most endoscopists agree that only short (<3–5 cm) strictures should be dilated. There are, however, still differences in some aspects, for example, which sedation to use. Thienpont et al. performed most of the procedures under general anaesthesia, but we in most cases used conscious sedation. Theoretically, conscious sedation or no sedation has the advantage of allowing the patient’s discomfort to be monitored as an indicator of impending perforation during the procedure. The number of patients in our study was too small to conclude whether this is correct.

A potential limitation of the technique of balloon dilation is the complication rate. The most frequent complications in our study were mild, such as minor bleeding, fever, and abdominal pain. However, serious complications requiring surgery, such as perforations and major bleeding, occurred in 1.3% of dilations. The complication rates per procedure were similar to those in other studies, with a total frequency of 5.3% for any complication requiring a hospital stay. We found that the largest balloon (25 mm) was associated with significantly greater risk of any complication compared to smaller balloons. This has previously been discussed but not confirmed. Considering that a symptomatic stricture is an indication of surgery, this complication risk seems acceptable.
The limitation of this study, consistent with other reports, is the retrospective, observational study design without a control group. The study period is very long, with a median follow-up time of 12 years. This is a strength of the study, but it also makes the data more heterogeneous. The first dilation in our hospital was done in 1987. In the early period, repeated dilations were performed in patients with recurrent strictures but without clinical symptoms of bowel obstructions, out of a belief that this might reduce the risk of surgery. Today, only patients with obstructive symptoms are referred for dilation. Over the years, the indications for referral to surgery may have changed, albeit treatment in general was discussed in a medico-surgical team. Comparing outcomes of two time periods, 1987–1998 versus 1999–2009, no significant difference was shown with respect to repeated dilation or surgery within the first year. This supports the view that changes in the medical or surgical treatment have not significantly influenced our data. Another potential limitation is that several different physicians with variable endoscopic skill performed the procedures. This, however, reflects a day-to-day clinical situation, which makes the results even more relevant.

In study IV we studied factors influencing outcome of endoscopic balloon dilation of intestinal strictures in Crohn’s disease. We found that smoking is a potent risk factor of a less favourable outcome regarding rate of new dilations or surgery after index dilation. In the group of active smokers, 31/32 (97%) underwent another intervention compared to 18/33 (55%) in the never smokers group (HR 2.18, 95% CI: 1.22–3.93, p = 0.01). The difference remained after adjustment for other factors, such as sex, age at diagnosis, age at first dilation, balloon size, localisation of the stenosis, and treatment period. This is not unexpected, since it is well known that smoking increases the risk of developing Crohn’s disease and worsens the clinical course, and increases the need for steroids, immunomodulators, and re-operations. Previous data on influence of smoking after balloon dilation are, however, sparse and inconsistent. In two studies no significant correlation between smoking and the outcome of dilation were seen.310, 311 Another showed an increased need of surgery following dilation,312 whereas a fourth study stated that smoking is a negative prognostic factor in outcome.313 We defined smoking habits at diagnosis and not at index dilation. The reason for using this definition is the strength of data quality and the well-known influence of smoking at diagnosis in the subsequent course of disease. At the Department of Gastroenterology, Örebro University Hospital, smoking habits have been recorded since the 1980s in patients at first visit, so data quality is firm. If patients ceased smoking
during follow-up, cessation may not have been recorded in the medical records.

There have been only a small number of studies, with few patients, evaluating whether medical therapy could influence the results after dilation.\textsuperscript{305, 312, 314-316} In study IV, we saw a difference, in respect to the risk of new dilations or surgery, between patients receiving azathioprine at diagnosis compared to those not receiving any treatment. The risk however, disappeared when adjusted for smoking. Only a minority of our patients was treated with azathioprine, and the indication of initiating treatment was not well known. There is therefore an obvious risk of selection bias that could influence outcome, in particular, the possibility that the severity of the disease may have influenced the treatment decision, in other words, azathioprine-treated patients represent a more severe phenotype. Thienpont et al. evaluated treatment given at first dilation. Neither 5-ASA, azathioprine, anti-TNF therapy, nor budesonide affected outcome in respect to surgical and endoscopic relapse compared to those patients not receiving any treatment. The only randomised study evaluating medical therapy after dilation is an abstract by Raedler et al.\textsuperscript{316} Thirty patients randomised to receive either azathioprine 100 mg and budesonide 9 mg or placebo after dilation were followed prospectively for 1 year. After 12 months, eight patients in the placebo group needed surgery versus three in the azathioprine/budesonide group. The difference was statistically significant.

Theoretically, all medications that are able to affect fibrosis could diminish the risk of intestinal strictures. Corticosteroids have a well-known anti-fibrotic effect of decreasing collagen synthesis. No study has evaluated oral corticosteroids as a single medication, and there are, of course, major disadvantages with long-term systemic side effects. Some studies have evaluated local injection of cortisone in the stricture with inconsistent results.\textsuperscript{306, 315, 317-319} The role of anti-TNF therapy to prevent stricture formation in general, and after dilation in particular, is not known. There have been reports with positive results in treating inflammatory stenosis with anti-TNF, but no study has evaluated anti-TNF agents after balloon dilation.\textsuperscript{320, 321} HMG-CoA reductase inhibitors (statins) and angiotensin-blocking agents have showed anti-inflammatory and antifibrotic effects both in vitro and in vivo.\textsuperscript{322} Atorvastatin have demonstrated anti-inflammatory effects in patients with Crohn’s disease, but no study has evaluated effects on intestinal strictures.\textsuperscript{95, 323, 324} Tranilast, anthranilic acid—an antifibrotic agent—inhibits keloid scarring and was evaluated in a placebo-controlled trial in which 24 Crohn’s disease patients with asymptomatic intestinal strictures was randomised.\textsuperscript{314} During follow-up, five patients in the placebo group
and one in the tranilast-treated group developed symptomatic strictures and underwent endoscopic balloon dilation. The authors concluded that tranilast “has a potential as a therapeutic modality for the prevention of the development of intestinal stricture in patients with Crohn’s disease”.

Another option to treat intestinal stricture in patients with Crohn’s disease is by inserting stents, with or without, previous dilation. Both metallic and biodegradable stents has been tried in small series with variable results.325, 326

We also searched for other factors influencing outcome in our study. Clinical parameters such as sex, age at diagnosis, age at first dilation, balloon size, localisation of the stenosis, and treatment period did not influence outcome. Several other factors were recorded in the study protocol, such as stricture length and diameter, anastomotic surgical technique, and whether the endoscopist assessed the dilation as technically successful or not. Technically successful dilation has been considered as a positive prognostic factor.327 In our study, index dilation was considered as a failure in only 6/83 patients at index dilation. It is not possible to draw any conclusion regarding the prognostic influence due to dilation result, but it seems reasonable to think that it might have a strong influence on the risk of surgery or a new dilation. Short stricture length has also been considered as a good prognostic factor,257 however, we had insufficient data due to the retrospective design, to analyse whether stricture length and width could influence outcome.

Whether balloon size could influence outcome after balloon dilation is not known. In study IV we could see no influence of balloon size of 18, 20, and 25 mm, with respect to risk of surgery and new dilations (data not shown). In the meta-analysis by Hassan et al., balloon calibre ≥20 mm versus <20 mm was not associated with dilation efficacy.257 Nor did the stepwise inflation method influence outcome compared to not using this method.

The conclusion in study III is that endoscopic balloon dilation of intestinal strictures in Crohn’s disease is an effective and safe alternative to surgical resection. An important issue is to what extent this conclusion can be generalised. Patients accepted for balloon dilation are always a highly selected group. First, only patients with a symptomatic stenosis are appropriate. Second, the stenosis must be located in reach of an endoscope, most likely in the colon or the distal ileum. Third, the stenosis must be shorter than 4–5 cm and not complicated by a fistula or abscess. In this group of selected patients endoscopic balloon dilation seems a reasonable alternative, but is it comparable to or even better than surgical resection or strictureplasty? Studies comparing the efficacy of surgical resection and stric-
tureplasty have been done, showing higher surgical recurrence following strictureplasty, but fewer postoperative complications. However, studies comparing surgical resection or strictureplasty with endoscopic balloon dilation have not been done. There has been a review of the literature by Wibmer et al., trying to compare efficacy and safety between dilation and strictureplasty. They searched in MEDLINE and found 40 papers dealing with strictureplasty and 23 with endoscopic balloon dilation. In patients operated on with strictureplasty due to Crohn’s disease-related intestinal stenosis, the median surgical recurrence rate was 24% after a median follow-up of 46 months, and the corresponding figure after dilation was 28% after a median follow-up of 21 months. The median rate of major complication after strictureplasty was 5.7%, including anastomotic leakage, intra-abdominal abscess, fistulas, sepsis, and ileus. The rate of relaparotomy was 5%. After dilation, the median of major complications was 3%, particularly bleeding and perforation. These figures are analogous to our own figures in study III. These data comparing strictureplasty and endoscopic balloon dilation can only give a rough comparison of the two methods, and firm conclusions regarding which method to use are therefore not possible. A randomised controlled trial is the only way to provide evidence for the best symptomatic treatment, both short-term and long-term, while taking into account recurrence frequencies, complications, health-related quality of life, and also health-economic aspects.
General conclusion

I. In a cohort of patients treated for an acute attack of ulcerative colitis, a 10-year follow-up showed a high colectomy rate in patients treated for a severe attack (64%) compared to patients treated for a moderate (49%) or a mild (28%) attack. Severity of the original attack did not influence the subsequent clinical course with respect to colectomy.

II. Infliximab has been shown to be an effective treatment in acute steroid-refractory ulcerative colitis, according to the Swedish–Danish infliximab/placebo trial. For three years or more, a follow-up study evaluated the long-term effect of the treatment given with infliximab. A statistically significantly lower colectomy rate in patients treated with infliximab (50%) remained after 3 years, compared to placebo (76%).

III. In a retrospectively designed study, endoscopic balloon dilation was shown to be an effective and safe alternative to surgical intervention in patients with intestinal stricture in Crohn’s disease. The complication rate was low, with a need of surgical intervention of 1.3%.

IV. Smoking at diagnosis doubles the risk of a new intervention after endoscopic balloon dilation due to intestinal stricture in Crohn’s disease. Treatment with azathioprine did not prevent a new intervention. Clinical parameters such as sex, age at diagnosis, age at first dilation, balloon size, localisation of stricture, and treatment period did not influence outcome after endoscopic balloon dilation.
De inflammatoriska tarm sjukdomarna ulcerös kolit och Crohns sjukdom är kroniska sjukdomar som förloper i skov. Orsaken är okänd men trolig utlöses sjukdomen av en kombination av ärftlig benägenhet tillsammans med olika miljöfaktorer. Svårighetsgraden av ett skov av ulcerös kolit kan delas in i milt, måttlig eller svårt. Ca 10–15% av alla patienter drabbas någon gång av ett svårt skov. Innan 1950-talet, då behandling med kortison och tidig operation med borttagande av tjocktarmen blev etablerad, var dödligheten ca 30% i ett svårt skov. Dödligheten är idag <1% men andelen patienter som måste opereras vid ett svårt skov har inte minskat utan uppgår fortfarande till ca 30%.


På 1980-talet genomfördes en undersökning av 158 patienter som vårdats på Universitetssjukhuset Örebro för ulcerös kolit och behandlats med kortison i injektionsform. Man såg då att patienter med svårt skov opererades i hög utsträckning redan inom 3 månader jämfört med dem med milt eller måttligt svårt skov. Vi har nu studerat om det på lång sikt finns någon skillnad avseende andelen patienter som blivit opererade och avseende antalet nya skov i de olika grupperna. Efter 10 år var andelen opererade i gruppen med svårt skov 64% jämfört med 49% respektive 28%, i grupperna med måttligt svårt och milt skov. Hos patienter som ej opererades de första tre månaderna, var det fortsatta kliniska förloppet avseende antalet nya skov och andelen av patienterna som blev opererade, oberoende av det initiala skovets svårighetsgrad.

2005 publicerades en vetenskaplig artikel från Örebro där läkemedlet infliximab visade sig ha god effekt vid ett svårt skov av ulcerös kolit då kortison ej fungerat. Tre år efter behandlingen kunde vi nu visa att patienterna som behandlades med infliximab hade fortsatt nytta av behandlingen. Det fanns alltjämt en skillnad efter tre år i andelen opererade mellan gruppen som fick behandling med infliximab (50%) och gruppen som fick placebo (76%).

Sammanfattningsvis har studierna visat att operationsfrekvensen vid ett svårt skov av ulcerös kolit är hög men att behandling med läkemedlet infliximab har bestående värde även tre år efter behandlingen. Vidare har vi visat att endoskopisk ballongvidgning av tarmförträngningar vid Crohns sjukdom är en effektiv och säker behandling och att rökning ökar risken för att behöva genomgå en ny vidgning eller operation.
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