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The Inflammatory Bowel Disease Cohort of the Uppsala Region (ICURE)

Epidemiology and Complications

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Abstract

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The overall aims of this thesis were to investigate the incidence of inflammatory bowel disease in the Uppsala Region of Sweden, to study the clinical course and the impact of the disease with regards to complications.

Patients in Uppsala County were included in the study from the 1st of January 2005 and patients in Falun, Eskilstuna and Åland counties from the 1st of January 2007. The study was closed for all centres on the 31st of December 2009. Mean population in the study region was 305,381 in 2005–2006 and 642,117 in 2007–2009.

The mean incidence for ulcerative colitis (UC) during the time period 2005-2009 was 20.0 /100,000/year (95% CI: 16.1-23.9) and for Crohn's disease (CD) it was 9.9/100,000/year (95% CI: 7.1-12.6). The combined incidence for UC or CD in the area was thus 29.9/100,000/year (95% CI: 25.1-34.7).

Half of the UC patients relapsed during the first year. Risk factors for relapse were female gender and young age. Colectomy during the first year was uncommon (2.5%). CD patients with complicated disease had longer symptom duration before diagnosis and less often diarrhoea and blood in stools compared to patients with non-complicated disease. The risk for surgery during the first year was 12%.

The prevalence of anaemia at the time of diagnosis was 30% and after one year 18%. Anaemia was more common among newly diagnosed patients with CD compared with UC. 13% of the UC patients developed an acute severe episode. During the first 90 days 22% of these patients were subjected to colectomy. There was a significant difference between University and County hospitals in colectomy frequency (7.5% vs. 41%). The cumulative prevalence of treatment complications was 12% at the hospital with low colectomy rate versus 41% at the hospitals with high colectomy rate.

In conclusion, the incidence of UC and CD in Sweden was high compared to international studies. Colectomy frequency for UC during the first year was low. Patients with complicated CD at the time of diagnosis had longer symptom duration and less alarming symptoms compared to uncomplicated disease. Anaemia was a common trait among patients with newly diagnosed IBD and more effort is needed to treat anaemia in these patients. Severe UC can be treated safely with prolonged medical therapy instead of colectomy.

Keywords: inflammatory bowel disease, ulcerative colitis, Crohn's disease, epidemiology, incidence, colectomy, anaemia, complications, surgery, classification

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To Erika

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I **Sjöberg D**, Holmström T, Larsson M, Nielsen AL, Holmquist L, Ekbom A, Rönnblom A. (2013) Incidence and natural history of ulcerative colitis in the Uppsala Region of Sweden 2005-2009. Results from the IBD Cohort of Uppsala Region (ICURE). *Journal of Crohn's and Colitis*, 7(9):e351-357

II **Sjöberg D**, Holmström T, Larsson M, Nielsen AL, Holmquist L, Ekbom A, Rönnblom A. (2014) Incidence and clinical course of Crohn's disease during the first year. Results from the IBD Cohort of the Uppsala Region (ICURE) of Sweden 2005-2009. *Journal of Crohn's and Colitis*, 8(3):215-222

III **Sjöberg D**, Holmström T, Larsson M, Nielsen, AL, Holmquist L, Rönnblom A. (2014) Anemia in a population-based IBD cohort (ICURE). Still high prevalence after 1 year, especially among pediatric patients. *Inflammatory Bowel Disease*, 20(12):2266-2270

IV **Sjöberg D**, Karlbom U, Larsson M, Nielsen AL, Rönnblom A. (2014) Acute severe ulcerative colitis in a population based cohort (ICURE). Outcome and complications of medical and surgical treatment. *Submitted*.

Contents

Abbreviations

5-ASA	5-aminosalicylic acid
6-MP	6-merkaptopurine
A1-3	Age classes in Crohn´s disease
ASUC	Acute severe ulcerative colitis
AZA	Azathioprine
B1-B3	Behaviour of Crohn's disease
CD	Crohn's disease
CI	Confidence interval
CT	Computed tomography
E1-E3	Extent of ulcerative colitis
GI	Gastrointestinal
Hb	Haemoglobin
HR	Hazard ratio
IBD	Inflammatory bowel disease
IBDU	Inflammatory bowel disease unknown
IC	Indeterminate colitis
ICURE	IBD Cohort of Uppsala Region
IPAA	Ileal pouch anal anastomosis
IQR	Interquartile range
IRA	Ileorectal anastomosis
L1-L4	Location of Crohn's disease
MC	Microscopic colitis
MRI	Magnetic resonance imaging
MTX	Methotrexate
NS	Not significant
NSAID	Non steroid anti-inflammatory drugs
HR	Hazard ratio
PARP	Peri-appendiceal red patch
PSC	Primary sclerosing cholangitis
PUFA	Poly-unsaturated fatty acids
S0-S3	Severity of ulcerative colitis
SD	Standard deviation
TNF	Tumour necrosis factor
UC	Ulcerative colitis
UP	Ulcerative proctitis

Preface

All animal and human life is dependent on food intake and waste excretion. This is one of the most basic fundaments which evolved long before limbs and lungs, heart and brain. A healthy gut is seldom thought upon by the individual, but a gut in disorder significantly affects life physically, mentally and socially.

During my undergraduate studies at Linköping University I was intrigued by the concept of inflammatory bowel disease. Two diseases, ulcerative colitis and Crohn's disease, with both similarities and disparities, of unknown origins and relapsing nature, affecting patients in all phases of life. How could anyone not be fascinated?

Ten years later I was given the opportunity to participate in the planning of the ICURE study. The monitoring of these over one thousand patients with ulcerative colitis, Crohn's disease and microscopic colitis have made me feel like I have had one thousand patients at my own outpatient clinic. The clinical experience I personally have gathered from this project has been invaluable.

Introduction

Inflammatory bowel disease

Inflammatory Bowel Disease (IBD) is a unifying concept of several diseases affecting the gastrointestinal (GI) tract, characterized by a misdirected inflammatory response by the immune system leading to a structural damage of the bowel. The two main diseases are Ulcerative Colitis (UC), mainly affecting the rectal and colonic mucosa, and Crohn's Disease (CD), that can engage all parts of the GI tract from the mouth to the anus. The term IBD Unknown (IBDU) is used for overlapping cases where neither the UC nor CD diagnosis definitely can be set [1, 2]. In certain cases the diagnosis UC or CD cannot be declared even after a full colectomy specimen has been histopathologically examined and then the term Indeterminate Colitis (IC) is used [3].

Definition and diagnosis

The diagnosis of IBD is based on an appraisal of symptoms, laboratory findings, endoscopic and/or radiological images and histopathological changes. There are no internationally recognized criteria or scoring systems.

In 1989 Lennard-Jones presented a classification for IBD where criteria for inclusion and exclusion (*Table 1, Table 2*) as well as the distinction between UC and CD were stated (*Table 2*) [4]. In the absence of other consensus criteria, this work has had a profound impact on the classification of IBD. Furthermore UC and CD can be sub-classified in probable and definitive disease depending on the amount of evidence supporting the diagnosis [1, 2, 4].

It is crucial to set the IBD diagnosis carefully, since it results in an often life-long medication, recurring health care visits and fear of complications. Efforts must be made to distinguish IBD from other diseases also associated with bowel inflammation [5].

Table 1. Exclusion criteria for UC and CD [4].

UC	CD
Infective colitis	Infections
Ischemic colitis	Ischemia
Irradiation colitis	Irradiation
Solitary ulcer	Lymphoma/carcinoma
Abnormalities suggesting CD	
Complex anal lesion	
Granulomata	

Table 2. Structural distinctions between UC and CD [4].

UC	CD
Rectum ± colon	Mouth to anus
Continuous	Discontinuous
Mucosal	Transmural (fissure, abscess, fistula)
Muscular thickening	Fibrosis (stenosis)
Mucin depletion	Lymphoid ulcers, aggregates
Glandular damage	Granuloma

Ulcerative colitis

Symptoms associated with UC are diarrhoea, bloody stools, urgency and abdominal discomfort or pain. The endoscopic image reveals inflammation of the mucosa [6], commonly graded by the Mayo endoscopic score (*Table 3*) [7].

UC is recognized by a continuous mucosal inflammation usually starting in the rectum and spreading in oral direction, potentially affecting all of colon. Ulcerative Proctitis (UP) is UC limited to the rectum with a maximum extension of 10-15 cm from the linea dentata. Patients with left-sided UC have been shown to have an inflammation in the cecum in some cases, often as a peri-appendiceal red patch (PARP) [8] or appendicitis [9], not to be confused with CD. In certain cases appendiceal orifice inflammation can develop into UC [10].

Extensive UC can result in a terminal ileitis, so-called back-wash ileitis, which also should not be regarded as a sign of CD [11]. In some cases the inflammation in UC may be rectum sparing, often seen in patients with Primary Sclerosing Cholangitis (PSC) [12], but also during the healing process associated with rectally administered medical therapy. Even if UC is usually regarded as a disease limited to the colonic mucosa, several studies have shown signs of gastritis and increased intraepithelial lymphocytes mainly among paediatric patients [13, 14].

Table 3. Mayo Endoscopic Score [7]

Score	Endoscopic appearance
Normal (0)	Normal
Mild (1)	Erythema, decreased vascular pattern, mild friability
Moderate (2)	Marked erythema, absent vascular pattern, friability, erosions
Severe (3)	Spontaneous bleeding, ulceration

The histopathology displays goblet cell depletion, architectonic changes including crypt distortion with bifid glands, crypt atrophy and villiform surface [15-18].

Crohn's disease

Whereas UC mainly affects the colonic mucosa, CD may affect the whole GI tract. When initially described as a separate disease entity in 1932 under the term "regional enteritis" it was thought that CD only engaged the cecum and terminal ileum [19]. In the following decades jejunal [20] and colonic engagement [21] was described. CD is characterized by transmural, often discontinuous, inflammation leading in certain cases to fibrosis and/or fistulas.

The symptomatology among CD patients is far more diverse than among UC patients, mainly due to the disparate localization of the lesions. In colonic CD symptoms are similar to UC with diarrhoea (sometimes bloody), abdominal pain and urgency. When engaging the small bowel, symptoms can be less obvious such as weight loss, abdominal pain and malabsorption of vitamins or minerals. CD of the upper GI tract may cause gastroduodenal ulcers, esophagitis and strictures resulting in epigastric pain, anorexia and odynophagia. CD may also affect the perineum causing perianal abscesses and fistula.

The endoscopic image is characterized by skip lesions, longitudinal ulcers causing cobble stone pattern and aphthous erosions [6]. Rectum is usually spared. A normal vascular pattern in mucosa adjacent to bowel lesions is a sign of the segmental nature of inflammation. However, UC in healing stages may mimic segmental colitis and one should be careful not to reclassify this image as CD [22-24]. Likewise, an ischemic colitis is often rectum sparing even if the image otherwise is similar to UC [25].

Investigations such as computed tomography (CT), abdominal ultrasound and, most commonly used, magnetic resonance imaging (MRI) provides additional information apart from to the endoscopic image. These modalities can reveal small bowel involvement, intra-abdominal fistulization and abscesses, stricturing of bowel segments and mesenteric fat hypertrophy [26]. In the last decade capsule endoscopy has provided additional diagnostic yield [27].

Non-caseous epithelial cell granulomas are generally thought to be strongly indicative of CD [28]. In one study an analysis of the initial colonoscopy biopsies displayed granulomas in two-thirds of the CD cases [29]. Many of the characteristic traits associated with CD (transmural inflammation, fistula and fibrosis) cannot be evaluated in mucosal biopsies [30]. Nevertheless, several attempts have been made to create histological scores to differentiate between CD and UC [16]. Typical findings for CD are a segmental distribution of crypt atrophy and mucin depletion, mucin preservation in ulcers or crypts with surrounding neutrophils [18].

The endoscopic and histological presentation of UC in children can be especially challenging, since several studies reveal CD-like appearances including rectal sparing and patchy inflammation [31-33].

It must be appreciated that the IBD diagnoses are not based solely on one modality and that the dichotomization into UC or CD is founded on the balance between different findings. A correct diagnosis has important clinical implications, such as the effectiveness of certain medications and the need for monitoring. In order to prevent a shift towards diagnosing CD colitis instead of UC, one may regard UC as a "passive" diagnosis and CD as an "active" diagnosis, i.e. a CD colitis case has to prove itself to be more than just a UC case with positive findings indicating the CD nature.

Relapses and remissions

UC and CD are diseases renowned for their episodic behaviour, characterized by periods of relapses and remissions. This is however a slight simplification since the long-term natural course can be divided into at least four different symptomatic patterns. Patients self-reported perception of disease activity five years after diagnosis in a Norwegian study [34, 35] were as follows: decline in the severity of intestinal symptoms (UC: 59%; CD: 44%); increase in severity (UC: 1%; CD: 3%); chronic continuous symptoms (UC: 9%; CD: 24%); chronic relapsing symptoms (UC: 31%; CD: 29%). The diseases are usually more active during the first five years after disease onset [36].

Classifications

Since CD is a heterogenic spectrum with different phenotypes, much effort has been made to categorize this disease. The first classification in 1975 focused on the anatomic localization [37] with clinical implications with regards to medical and surgical therapy [38, 39]. Later on CD was divided into two distinctive behaviours (perforating and non-perforating) prognosticating both need for surgery [40] and recurrence pattern after surgery [41]. These two clinically proven and valuable parameters, together with variables regarding extent and surgical history, resulted in the Rome classification in 1991 [42].

Due to the large number of permutable groups possible in the Rome classification it was soon regarded as inappropriate for clinical use. Furthermore, the disease behaviour was insufficiently defined, resulting in only fair interrater agreement thus raising concerns regarding applicability [43]. An international working party presented the Vienna classification in 1998 [44] including age at diagnosis (A1: <40 years; A2: ≥40 years) [45-48], location (L1: Ileum; L2: Colon; L3: Ileum and colon; L4: Upper GI) and behaviour (B1: Inflammatory; B2: Stricturing; B3: Penetrating).

Stricturing disease was defined as constant luminal narrowing with prestenotic dilatation or obstructive symptoms. Penetrating disease was defined as the occurrence of intraabdominal or perianal fistulas, inflammatory masses or abscesses, including perianal ulcers. The Vienna classification has been able to predict the need for surgery and immunosuppressive therapy [49].

Table 4. Crohn's disease in Rome-, Vienna-, and Montreal classifications.

	Rome [42]	Vienna [44]	Montreal [50]
Year	1991	1998	2005
Age	-	A1: < 40 years A2: ≥ 40 years	A1: < 17 years A2: 17-40 years A3: > 40 years
Location	Stomach/duodenum Jejunum Terminal ileum Colon Rectum Perianal	L1: Terminal ileum L2: Colon L3: Ileocolon L4: Upper GI	L1: Ileal L2: Colonic L3: Ileocolonic L4: Isolated upper GI
Behaviour	-	B1: non-stricturing non-penetrating B2: stricturing B3: penetrating	B1: non-stricturing non-penetrating B2: stricturing B3: penetrating p: perianal disease modifier
Extent	Localized Diffuse	-	-
Surgical history	Primary Recurrent	-	-

A few years later, at the 2005 Montreal World Congress of Gastroenterology, a second working party of investigators reported an update [50, 51]. A new category was added for patients <17 years (A1), emphasizing the finding that certain serotypes and genotypes are more frequently found in younger patients [52-55]. In the Vienna classification each of the location groups were mutually exclusive, whereas clinical experience made it obvious that upper GI inflammation (proximal to the ileum) often coexists with ileal and colonic disease. The L4 variable was therefore changed into a modifier that could be added to L1-L3 in cases of proximal inflammation. Likewise, perianal fistulizing disease was not always associated with intraabdominal fistulizing disease [56, 57] and thus the modifier p (perianal disease) could be added to B1-B3, removing perianal disease from the B3 group.

Neither the Rome nor the Vienna classification deals with UC. Extent of the disease has practical implications with regards to medication, risk for colorectal cancer and hospitalization as well as implications in research, i.e. genetic factors predisposing extensive colitis [58]. However, extent in UC varies over time [59] and thus the maximal endoscopic extent of involvement was defined as the critical parameter [51].

Severity of relapse was identified as an important variable based on previous studies revealing an associated risk of morbidity and mortality [60, 61]. In the work of Truelove, Witt et al in 1955 [60] severe colitis was defined as six or more bowel motions per day with macroscopic blood in stools, plus signs of systemic illness: evening fever >37.5°C or a temperature of ≥37.8°C on at least two out of four days, tachycardia >90 beats/minute, anaemia ≤75% of normal haemoglobin (Hb) or elevated sedimentation rate (ESR) >30 mm. Mild colitis was defined as four or less bowel motions per day and no signs of systemic illness, whereas moderate colitis was intermediate between severe and mild. This index later became known as the Truelove-Witt criteria.

The Montreal working party integrated the severity variable into the classification of UC with minor changes of the systemic toxicity parameters (fever ≥37.5°C, tachycardia ≥90 beats/minute, anaemia Hb <105 g/L, ESR ≥30 mm) [51]. However, it was unclear whether one or all of the criteria for systemic toxicity were to be met and it has been interpreted in different ways [62].

More recently the European Crohn and Colitis Organisation (ECCO) has adopted these guidelines [1, 2, 63, 64]. The differences between these classifications (Rome, Vienna and Montreal) with regards to CD are presented in *Table 4*. A severe episode of UC was now defined as six or more bloody stools per day together with one or more of the following: temperature >37.8°C, tachycardia >90 beats/minute, anaemia Hb <105 g/L, ESR >30 mm or C-reactive protein (CRP) >30 mg/L.

A paediatric modification of the Montreal statement was proposed in 2011 and was called the Paris classification [65]. It divided the A1 subgroup in CD into A1a (0 to <10 years) and A1b (10 to <17 years) and distinguished L4 disease into L4a (proximal to ligament of Treitz) and L4b (above distal ileum and distal to ligament of Treitz). Furthermore, it allowed stricturing and penetrating disease to be simultaneously classified (B2B3) and added the variable growth failure divided into G0 (never growth failure) and G1 (growth failure at any time). For UC it added the parameter E4 describing maximum extent of inflammation proximal to hepatic flexure and whether an episode of severe colitis had ever occurred during disease course.

Incidence of IBD

Incidence, Poisson distribution and age adjustment

Epidemiology may be defined as the study of the occurrence of illness [66]. The risk of developing a certain disease for an individual within a larger group of people is described in terms of probability. The calculation is simple: the number of individuals (N) developing a certain disease in a certain population (P) during a defined time period can be described as:

$$Risk = \frac{N}{P}$$

This requires that the whole population is followed for the whole time period and the length of time must be known to interpret risk [67]. The concept of "competing risk" states that the longer the time period during which the population is studied, the higher the risk will be of people being removed from the study due to deaths or individuals moving out of the population. In such cases development of the disease may be underestimated and thereby also the estimated risk. The population at risk is thus a dynamic entity with regards to eligibility criteria. A short observation time decreases the uncertainty of the nature of the background population.

Incidence rate assess the frequency of disease onset and is defined as the number of cases of a certain disease that occur in a population (A) divided by a measure of time [67]:

$$Incidence\ rate = \frac{A}{Time}$$

Prevalence, on the other hand, defines the proportion of individuals in a population that has a disease at a given time. The prevalence is affected by the incidence rate as well as by the duration of the disease.

A cohort may be defined as a designated group of individuals that is followed over a period of time [68]. A standard requirement of the population at risk is that individuals cannot develop a disease that they currently have. It is therefore essential to exclude individuals already diagnosed with a certain disease, unless the disease is sufficiently uncommon [67]. A cohort may be either open or closed, with open meaning that individuals are allowed to be included as time passes by and closed meaning that the membership of the cohort is fixed. The closed cohort usually decreases in size over time when people die or are lost to follow-up.

Poisson distribution is a concept of probability of events occurring in a certain time period, provided that each event is independent of the last event [69, 70]. The 95% confidence interval assuming a Poisson distribution is:

$$95\%\ CI\ = 1{,}96\sqrt{\frac{a}{PT^2}}$$

where *a* is the number of cases and *PT* is person-time (the sum of the time contribution from different people) [67].

The generalizability of incidence rates measured in a certain population can be challenging (i.e. from a certain region to a nation or the world). One particular factor to adjust for is differences in the age structure of the studied population, especially if it differs from the larger population and if the disease measured is age dependant. A crude incidence rate of a disease with onset in early years measured in a young population may lead to exaggerated figures. Therefore, the study population is ideally age adjusted towards a reference population through weighting, which requires age-specific incidence rates to be calculated [71].

A Swedish perspective on IBD

Sweden has a long tradition of epidemiological studies in the field of IBD (*Figure 1*). A precondition for this is the national security numbers, a public health care system and mandatory registries of diagnoses. During the last decade electronic medical records has replaced paper records, further facilitating epidemiological research.

Most studies have been retrospective, including long time periods and retrieving data from diagnosis registries [72-79]. The strength of this approach is that uncommon diseases such as IBD can be identified in adequate numbers and temporal trends can be analysed. However, there is a risk of overestimation of the IBD incidence since the diagnosis may be prematurely set and underestimation of the incidence in cases where unspecific inflammation later develops into IBD without revision of the diagnosis.

According to these previous studies, IBD has constantly increased in Sweden since mid-1900s when the first data was presented from the county of Uppsala [75, 76]. There has been a knowledge gap regarding the development of UC incidence from the late 80s until present day. The reported increase in incidence over time from 1963 to 1987 in Örebro was attributed to better retrieval of cases with the increased availability of colonoscopy [78].

In some cases the child and adult populations have not been represented in the same study, making it difficult to apprehend the true incidence [73, 80, 81]. Despite this methodological challenge it has recently been shown that both UC and CD have increased significantly in the paediatric population of northern Stockholm County during the time period 1990-2007 [80, 82].

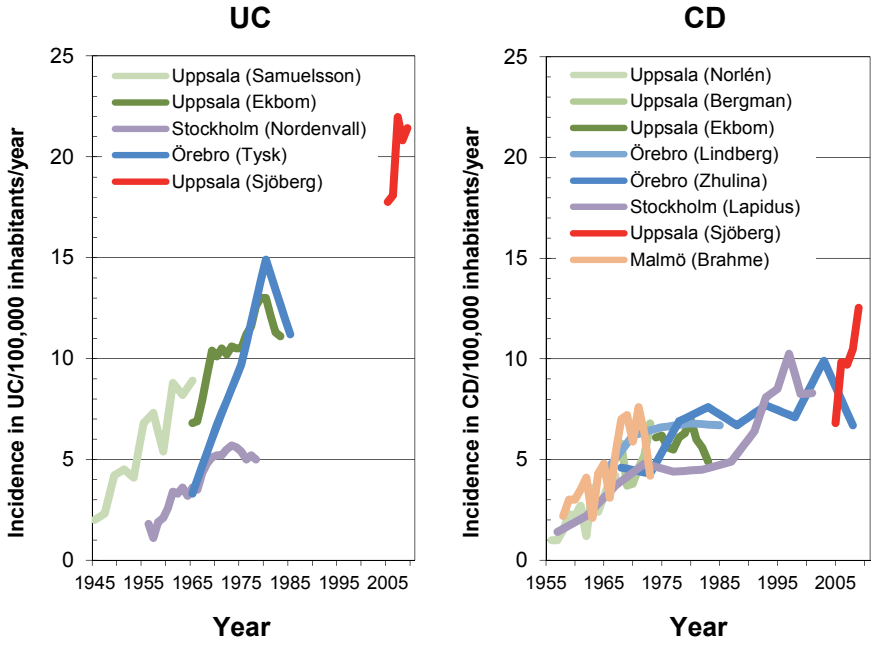

Figure 1. Incidence of UC [74, 75, 78, 83, 84] and CD [72-74, 76, 77, 79, 85-87] in Sweden 1945-2010.

IBD in a global setting

The Nordic countries have historically had a high incidence of both UC and CD compared to other European countries. During 1990-1993 a prospective population based study in south-east Norway (the IBSEN study) was conducted, setting the standard for future IBD epidemiology studies [34, 35, 47, 59, 88, 89]. Data from Iceland [90, 91], Denmark [46, 92-95] and recently Finland [96, 97] have also been published, making the epidemiology of IBD in the Nordic countries well studied both in detail and for long time periods.

In Europe and North America IBD prevalence and incidence has been high during the 20th century compared to the rest of the world. Recently data from Oceania has been presented, revealing figures of incidence comparable with Europe and North America [98, 99].

There is a shortage of well-performed population based epidemiology studies from the Middle East, Africa, South America and Asia, making the true incidence of IBD in these regions uncertain. The reasons for this are most likely multifactorial, including high prevalence of gastrointestinal infections, the low availability of health care and difficulties in ascertainment of background population. A selection of population based epidemiological studies presenting both UC and CD figures is summarized in *Table 5*.

Table 5. Selected population based epidemiological studies.

Continent	Country	Time period	IBD /10E5	UC /10E5	CD /10E5	Author
Europe	Finland	2000-2007	34.0	24.8	9.2	Jussila [97]
	Sweden	2005-2009	29.9	20.0	9.9	Sjöberg [84, 87]
	Denmark	2003-2005	22.0	13.4	8.6	Vind [92]
	Iceland	1990-1994	22.0	16.5	5.5	Björnsson [91]
	Hungary	2002-2006	20.8	11.9	8.9	Lakatos [100]
	Norway	1990-1993	19.4	13.6	5.8	Moum [47, 88]
	Spain	1998-2005	14.4	7.1	7.3	Lopez-Serrano [101]
	Netherlands	1991-2003	13.9	7.7	6.2	Romberg-Camps [102]
	Croatia	2000-2004	11.1	4.6	6.5	Sincic [103]
	Germany	2004-2006	10.5	3.9	6.6	Ott [104]
	France	2006-2007	10.1	3.4	6.7	Chouraki [105]
	Malta	1993-2005	9.2	7.9	1.3	Cachia [106]
North America	Canada	1998-2000	25.2	11.8	13.4	Bernstein [107]
	USA	1990-2000	16.7	8.8	7.9	Loftus [108]
South America	Brazil	1986-2005	5.5	4.0	1.5	Victoria [109]
Asia	Turkey	2000-2003	6.6	4.4	2.2	Tozun [110]
	Lebanon	2000-2004	5.5	4.1	1.4	Abdul-Baki [111]
	China	1986-2001	1.5	0.9	0.6	Leong [112]
Oceania	Australia	2007-2008	28.6	11.2	17.4	Wilson [99]
	New Zealand	2004-2005	24.1	7.6	16.5	Gearry [98]

Temporal trends and regional differences

IBD is a growing global health problem with increasing incidence rates over time in the majority of the studies with long-term data, recently presented in a systematic review [113]. Out of 50 studies of UC and 57 studies of CD, with temporal trends over at least 10 years, 60% and 75% respectively reported significantly increasing incidence rates. On the other hand, only 6% of the UC studies and none of the CD studies showed decreasing rates.

Notably, the ratio of UC and CD incidence varies depending on the region studied [114]. In the Nordic countries, with the world's highest incidence rates of UC, the ratio between UC and CD is usually 2:1. The opposite is true for countries such as France, Canada and New Zealand. Due to the absence of a criteria based international classification system for differentiating between UC and CD, some of the difference may be attributed to diverging diagnostic traditions. However, it is also likely that genetic and environmental factors are parts of the explanation [115, 116].

Why is IBD incidence increasing?

The significant increase in IBD in the westernized world over the last 50 years cannot be explained by genetic changes, but instead suggests environmental risk factors [117-119]. This is supported by studies describing in-

creased risk in populations migrating from low-incidence to high-incidence areas, e.g. Asia to Great Britain [120].

There are few evidence based factors affecting the risk of developing IBD. UC patients are more often non-smokers and cessation of smoking will increase the risk for UC [121-123]. In contrast, smoking is an important risk factor for developing CD as well as increasing complications to the disease [124-126]. Smoking has decreased in Sweden during the last decades, potentially explaining the increase in UC incidence but not CD [127].

Appendectomy is protective towards developing UC [128] and the incidence of acute appendicitis is declining [129, 130]. Initial findings that appendectomy increased the risk of CD [131] may however be explained by diagnostic bias [132, 133]. Hormone replacement therapy could possibly increase the risk for UC but not CD [134, 135].

Diet can affect whole populations and change over time in its composition. It is probably the most important factor affecting gut microbiota [136]. However, evaluating dietary intake retrospectively after IBD diagnosis is challenging due to recall bias [137]. Linoleic acid, a dietary n-6 polyunsaturated fatty acid (PUFA), is associated with increased risk of UC [138, 139] and there has been a concurrent rise of PUFA intake in Europe [140]. Animal protein, especially from meat and fish, also increased the IBD risk [139, 141]. Even if several studies have reported that low intake of fruit and vegetables and high intake of sugar is associated with increased onset risk, these findings could not be confirmed by similar studies [142].

Many other theories have been proposed during the last decades. Urbanization of populations has been associated with an increase of UC followed by an increase of CD [143]. The hygiene hypothesis including hot-water availability [144] and toothpaste [145] has been linked to CD incidence. A rise in refrigerator availability world-wide has led to the cold-chain hypothesis, suggesting Yersinia and Listeria species contributing to CD [146]. Recently, the increased use of emulsifiers in processed foods has been proposed to affect mucosal permeability leading to bacterial translocation and trigging of immune response [147, 148]. Even if these theories are intriguing, evidence is still lacking.

Recently, the concept of the “exposome” has been adapted from cancer epidemiology [149] to IBD research [150]. The term exposome can be used to summarize the complete environmental exposure as a complement to the risk factors provided by the genome. It acknowledges the challenge of analyzing innumerable environmental factors. Development of techniques to study the exposome as a whole is required, in analogy with genome-wide association studies (GWAS) [151].

Complications to IBD

Diarrhoea, urgency and abdominal pain are the hallmarks of IBD symptomatology. However, more uncommon complications of the ongoing intestinal inflammation are diverse and can potentially lead to severe morbidity and death. Within the framework of this thesis, two areas of complications are highlighted: anaemia and acute severe ulcerative colitis (ASUC).

Anaemia in IBD

Anaemia of chronic disease [152] is a common condition in several disorders such as rheumatic arthritis, malignancy and IBD and can be attributed to several mechanisms mediated by inflammatory cytokines [153].

Iron, inflammation and hypoxia increase the expression of hepcidin [154], resulting in reduced iron transport from enterocytes to plasma by binding to ferroportin [155]. Functional iron deficiency is mediated by IL-1 and TNF-α, causing insufficient iron delivery from the plasma to the bone marrow [153]. Bone marrow erythropoiesis is directly inhibited by interferon-γ [156]. Lastly, erythropoietin production is inhibited mainly by IL-1, IL-6 and TNF-α [157]. Together these changes result in a reduced iron uptake, a shortened red cell survival, insufficient erythropoietin response to anaemia, impaired erythroid colony forming in bone marrow in response to erythropoietin and inadequate mobilization from iron storages [158].

Iron deficiency can also be caused by loss of blood and reduced iron intake [159]. An iron deficiency develops when chronic intestinal bleeding exceeds the oral iron intake [160]. Dietary changes in IBD patients are common, resulting in lower dietary iron compared to healthy controls [161]. Cobalamin and folic acid are needed in normal erythropoiesis. A deficiency may develop due to terminal ileitis reducing uptake [162] or due to dietary changes reducing intake [163].

In a Scandinavian study in IBD outpatients the aetiology of anaemia was iron deficiency in 20%, anaemia of chronic disease in 12% and both conditions in 68% [164]. Less than 5% had cobalamin or folic acid deficiency.

Chronic anaemia results, regardless of aetiology, in chronic fatigue, impairing the patients abilities to perform daily activities [159]. A correction of iron-deficiency anaemia in IBD patients can improve quality of life [165, 166] and is currently emphasized in international guidelines [167]. Oral iron may induce oxidative stress [168] and increased disease activity [169], apart from being inhibited in its absorption [170]. The treatment algorithms calls for intravenous iron supplementation since it is more effective and better tolerated [171, 172]. In severe cases with insufficient response to intravenous iron, subcutaneous erythropoietin treatment is recommended [167].

Acute severe ulcerative colitis

The risk for UC patients of developing an episode of ASUC during their disease duration is 15-25% [61, 173, 174]. In the early 20th century, ASUC was associated with high mortality rates of 50-75% [175, 176]. With the introduction of oral prednisolone the mortality was reduced from 24% in the placebo group to 7% in the treatment group [60, 177]. Intravenous steroids further improved the prognosis with no mortality in an early case series of 87 patients [178, 179]. An audit from the United Kingdom in 2010 found an in-hospital mortality of 0.7% among 984 patients with ASUC [180]. Old age was an independent risk factor for death.

This temporal trend with reduction in mortality reflects improvement in the supportive care of UC patients rather than changes in pharmaceutical treatment [181]. The overall response rate to steroids was only 67% and the mean colectomy rate of 27% did not change between 1974 and 2006 according to a systematic review [62]. Thus, there is a need for additional medical therapy in the treatment of ASUC.

Ciclosporin reduced the risk of colectomy in steroid refractory patients from 100% in the placebo group to 18% in the treatment group in a small clinical trial from 1994 [182]. Infliximab was used in a study from 2005 including 45 patients with moderate to severe UC failing intravenous betamethasone [183]. The colectomy rate was reduced from 67% in the placebo group to 29% in the treatment group. A larger study could not find any differences in efficacy between ciclosporin and infliximab [184]. Even if these treatment options are equally recommended internationally [181], treatment traditions in Sweden prefer infliximab [185] mainly due to risk of neurological side effects associated with low cholesterol or magnesium caused by ciclosporin [181, 186].

Several studies have evaluated individual factors prognosticating steroid failure: (1) clinical markers such as stool frequency [187-189] and number of Truelove-Witt criteria [174], (2) biochemical marker such as CRP [187, 189, 190], albumin [188] and pH [191] and (3) radiological or endoscopic criteria such as colonic dilatation [188] and deep ulcerations [192].

Numerous scoring systems have been introduced in order to combine two or more of these risk factors. The Oxford index predicts that 85% of the patients with either CRP > 45 mg/L plus a stool frequency of three or more per day, or stool frequency of more than eight per day on day three after admission will be subjected to colectomy [187]. The Swedish fulminant colitis index states that a value of eight or more calculated from the formula [stool frequency/day] + 0.14 x CRP mg/L predicts a colectomy in 69% of the patients [183].

It must be noted that these indices represent the actions taken from a retrospective viewpoint. There are no controlled trials randomizing ASUC cases based on a certain score to colectomy or no colectomy, due to obvious

ethical difficulties. Caution has been expressed that indices may become self-fulfilling resulting in colectomy just because criteria are met [193].

Aims

The overall aims in this thesis were to investigate the incidence of inflammatory bowel disease in the Uppsala Region of Sweden, to study the clinical course in a contemporary setting and describe the impact of the disease with regards to complications.

Specific aims in study I

- To measure the incidence of ulcerative colitis in the Uppsala region
- To evaluate the severity and extent of the inflammation at diagnosis
- To measure the colectomy frequency during the first twelve months after diagnosis
- To assess pharmaceutical therapy during the first twelve months after diagnosis
- To measure the relapse rate and the proportion of patients with chronic symptoms

Specific aims in study II

- To measure the incidence of Crohn's disease in the Uppsala region
- To evaluate the location and behaviour of inflammation at diagnosis
- To assess established bowel injury at diagnosis
- To investigate the need for surgery during the first twelve months after diagnosis
- To assess pharmaceutical therapy during the first twelve months after diagnosis

Specific aims in study III

- To measure the prevalence of anaemia in patients with IBD at the time of diagnosis and after twelve months
- To investigate the correlation between anaemia and different phenotypes of IBD
- To evaluate the use of anaemia specific treatment during the first twelve months after diagnosis

Specific aims in study IV

- To compare the treatment and outcome of ASUC at different hospitals in the Uppsala Region
- To evaluate the timing and frequency of surgery
- To assess the complications with different treatment regimens

Material and methods

Background population

The first part of the study IBD Cohort of the Uppsala Region (ICURE) was started in 2005 with the prospective inclusion of patients with IBD in Uppsala County. From the 1st of January 2005 all patients with probable IBD was registered. Invitations were sent in 2006 to gastroenterology departments at county hospitals in neighbouring counties (Sörmland, Dalarna, Åland, Västmanland and Gävleborg). Three counties (Sörmland, Dalarna and Åland) decided to participate in the project, started the registration of IBD patients on the 1st of January 2007 and completed the study.

The study was closed for registration the 31st of December 2009. Patients that initially eluded identification, but were diagnosed with IBD in the postulated timeframe (2005-2009 for Uppsala County and 2007-2009 for Sörmland, Dalarna and Åland) were allowed to be included in the study at a later time point.

The catchment area was comprised of 7 municipalities during 2005-2006 and 17 municipalities during 2007-2009 with a mean population of 305 000 inhabitants during the first time period and 642 000 during the second (*Table 6*). 81% of the population lived in urban areas (Sweden: 85%), the population density was 38 inhabitants/km^2 (Sweden: 23) and 13% were born in another country (Sweden: 14%). The participating six hospitals were Uppsala University Hospital, Enköping Hospital, Mälar Hospital, Åland Central Hospital, Falu Hospital and Ludvika Hospital. There were no private gastroenterologists in the area at the time of the study.

Table 6. Background population.

County		2005	2006	2007	2008	2009
Uppsala						
	Håbo	18 569	18 637	18 931	19 225	19 452
	Älvkarleby	9 080	9 110	9 095	9 064	9 068
	Knivsta	13 324	13 597	13 954	14 259	14 477
	Heby *			13 492	13 407	13 355
	Tierp	20 056	19 943	20 068	20 153	20 044
	Uppsala	183 308	185 187	187 541	190 668	194 751
	Enköping	38 422	38 486	38 768	38 978	39 360
	Östhammar	21 608	21 435	21 421	21 434	21 391
Södermanland						
	Eskilstuna			93 343	94 785	95 577
	Strängnäs			31 435	31 715	32 024
Dalarna						
	Gagnef			10 111	10 107	10 071
	Smedjebacken			10 715	10 734	10 758
	Falun			55 220	55 297	55 685
	Borlänge			47 756	48 185	48 681
	Säter			11 000	10 957	10 900
	Ludvika			25 425	25 522	25 650
Åland				27 153	27 456	27 734
Total		304 367	306 395	635 428	641 946	648 978

* Heby municipality was transferred from Västmanland County to Uppsala County on the 1st of January 2007.

Case identification and ascertainment

All probable cases were identified through a) gastroenterologists reporting to local investigator, b) reviewing of all colonoscopy records at the department by local investigator, and c) reviewing lists of outpatient clinic visits. A few additional cases were identified through radiology or pathology rounds. Each probable case was evaluated by at least two investigators (all experienced gastroenterologists) at different hospitals. In uncertain cases mucosal biopsies were reviewed together with an experienced pathologist.

The patients were thereafter classified as CD, UC, IBDU, lymphocytic colitis, collagenous colitis, observational cases or were excluded. All observational cases were later reviewed in order to find additional IBD cases or to dismiss the cases. The diagnosis of IBD was based on the classification criteria of Lennard-Jones [4]. This included an appraisal of patient history together with endoscopic image, physical examination, and histopathology and in selected cases radiology. Time of diagnosis was set for UC when the first diagnostic colonoscopy was performed and for CD when the first diagnostic colonoscopy, capsule endoscopy or radiology was performed.

To avoid inclusion of non-IBD patients, certain observational cases were excluded: a) patients with aphthous lesions in small bowel only and concomitant NSAID intake, b) patients with self-limiting disease and positive findings in faecal cultures and c) patients where other diagnoses were more probable (i.e. ischemic colitis, histological changes compatible with infectious disease despite negative cultures, histological changes only without patient history or endoscopic findings). Patients with positive faecal cultures but chronic histological changes compatible with IBD were classified as observational cases and were later included as IBD if they had relapsing mucosal inflammation together with negative cultures. Patients initially classified as IBDU but during follow-up reclassified as CD or UC were added to the CD or UC cohort. The number of incident cases of IBD is presented in *Table 7*.

Data collection

Registration of data was performed with a standardized form at the time of diagnosis as well as continuously during the follow-up period, at least once a year (*Table 8*).

Table 7. Number of incident cases of IBD in the region.

County	Disease	2005	2006	2007	2008	2009	Total
Uppsala	UC	56	55	69	78	74	332
	CD	21	31	36	23	36	147
Södermanland	UC			32	23	20	75
	CD			4	12	12	28
Dalarna	UC			32	30	39	101
	CD			21	30	30	81
Åland	UC			8	3	7	18
	CD			1	3	4	8
Total	UC	56	55	141	134	140	526
	CD	21	31	62	68	82	264

Table 8. Variables used in data collection.

Variable		Ulcerative Colitis	Crohn's Disease
Basic demographic data			
	Gender	X	X
	Age	X	X
	Heredity	X	X
	Smoking habits	X	X
Disease course before and after diagnosis			
	Symptoms before diagnosis		X
	Duration of symptoms before diagnosis	X	X
	Relapse during first 12 months	X	
Diagnostic modalities			
	Endoscopy	X	X
	Radiology	X	X
	Capsule endoscopy		X
	Histology	X	X
	Laboratory (Hb, CRP and liver enzymes)	X	X
Montreal classification			
	Extent	X	
	Severity	X	
	Location		X
	Behaviour		X
	Age		X
Therapy first 12 months after diagnosis			
	Pharmacological therapy	X	X
	Surgery	X	X

Study populations

A schematic flow chart of the study populations in the four papers included in this thesis is presented in *Figure 2*.

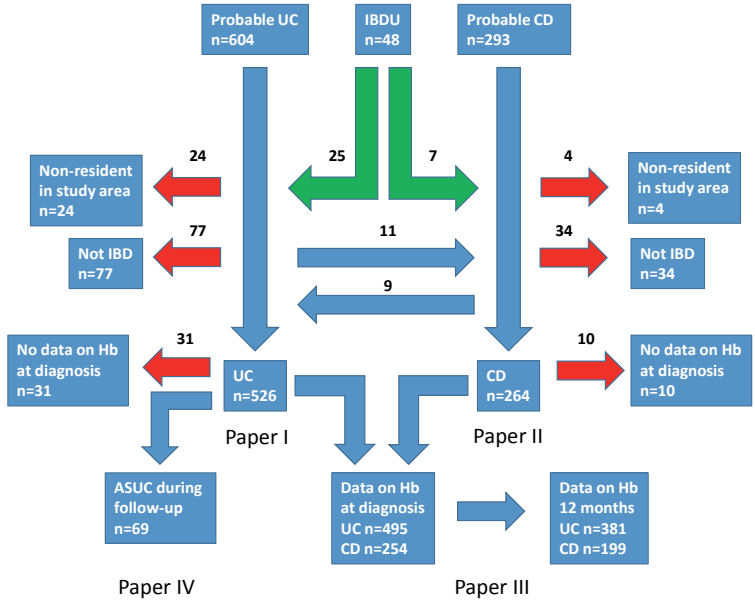

Figure 2. Flow chart of study populations.

Statistical methods

All data analysis in the thesis was performed using the statistical software STATISTICA (version 10; 2011; StatSoft Inc., Tulsa, OK). P-values <0.05 were considered to be statistically significant. All tests were two-sided.

Depending on the characteristics of the data, continuous variables are presented as means and standard deviations (SD) or medians and interquartile range (IQR) (Study I-IV). Non-parametric independent groups were compared using Mann–Whitney two sample rank sum test (Study I-IV). Parametric independent groups were compared using Student's *t*-test (Study II-III).

Data from contingency tables (Study I-IV) were analysed using $\chi 2$ test. For tables with small measured counts ($n \leq 5$) and expected counts ($n \leq 5$) Fisher's exact test was used. McNemar's $\chi 2$ test was used for paired contingency tables (Study III).

The 95% confidence intervals (CI) of incidence were calculated assuming a Poisson distribution and were age adjusted for the Swedish population for each corresponding year (Study I-II). Survival analyses were performed us-

ing Kaplan–Meier product limit methods and log-rank tests (Study I, II and IV). Cox regression analysis models were constructed for evaluating risk factors for relapse in UC (Study I) and surgery in CD (Study II).

Ethical considerations

The ICURE study was processed by the local Ethics Committee at Uppsala University (reference number 2006/173). Since no case included in the project was subjected to an intervention within the framework of the study, the research project did not require approval from the Ethics Committee according to Swedish law (3-4§§, 2003:460). An advisory statement based on the regulation for regional ethics committees (2§, 2003:616) was provided.

Registration in the main database was done by coded identification numbers in order to prevent data from patient journal records to be traceable to individual patients. The patient lists with identification numbers have been kept in a secure place and apart from the main database. Access to the database and the patient lists has been restricted to the author of the thesis and his main supervisor. In each of the four papers included in this thesis, measures have been taken when presenting data to avoid individual patients to be recognized.

Summary of results

Study I and II

Common findings

The mean incidence of UC during the time period 2005-2009 was 20.0/100,000/year (95% CI: 16.1-23.9) and of CD it was 9.9/100,000/year (95% CI: 7.1-12.6). The incidence of UC and CD each year of the time period is presented in *Figure 3*. In the subgroup of patients younger than 17 years of age, the mean incidence of UC was 8.9/100,000/year (95% CI: 3.0-14.8) and of CD it was 10.0/100,000/year (95% CI: 3.8–16.3). The combined incidence of UC and CD in the area was thus 29.9/100,000/year (95% CI: 25.1-34.7) and in children under 17 years of age the incidence was 18.9/100,000/year (95% CI: 10.2-27.4).

The UC incidence was 17.8/100,000/year (95% CI: 13.0-22.5) in 2005 and increased to 21.4/100,000/year (95% CI: 16.1-23.9) in 2009. The corresponding figures for CD was 6.8/100,000/year (95% CI: 3.9-9.7) in 2005 and 12.5/100,000/year (95% CI: 9.8-15.3) in 2009.

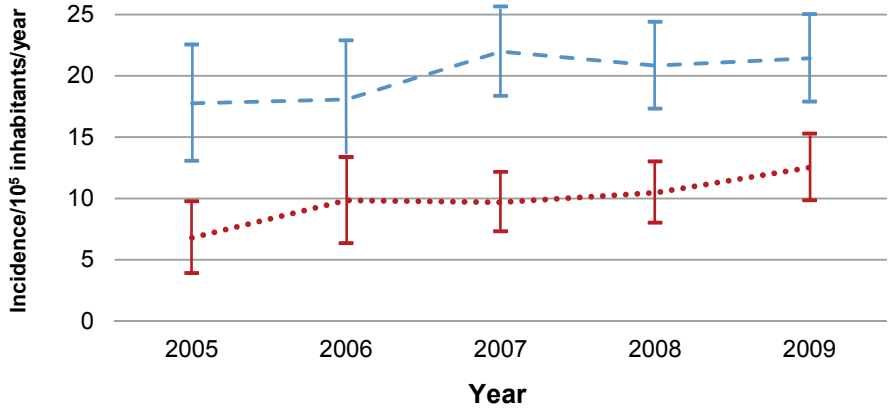

Figure 3. Incidence of UC and CD in the study area 2005-2009. UC (---), CD (···). Error bars represent 95% CI.

Patients with UC were five years older than patients with CD (median age 36.0 vs. 31.0, P=0.0006). There were no gender differences between UC and

CD patients. The Montreal criteria for both UC and CD are presented in *Table 9* and *Table 10*.

Table 9. Montreal classification of patients with UC.

		n	(%)
Extent			
	Proctitis (E1)	167	(31.7)
	Left sided colitis (E2)	161	(30.6)
	Extensive colitis (E3)	163	(31.0)
	Uncertain extent (E2 or E3)	35	(6.7)
Severity			
	Mild (S1)	269	(51.1)
	Moderate (S2)	209	(39.7)
	Severe (S3)	45	(8.6)
	Missing	3	(0.6)

Table 10. Montreal classification of patients with CD.

		n	(%)
Age			
	<17 years (A1)	50	(18.9)
	17-40 years (A2)	123	(46.6)
	>40 years (A3)	91	(34.5)
Location			
	Ileal (L1)	73	(27.7)
	Colonic (L2)	129	(48.9)
	Ileocolonic (L3)	62	(23.5)
	Upper GI (L4)	47	(17.8)
Behaviour			
	Inflammatory (B1)	204	(77.3)
	Stricturing (B2)	34	(12.9)
	Penetrating (B3)	26	(9.8)
	Perianal (p)	27	(10.2)

The use of pharmaceutical therapy in UC as well as CD patients is presented in *Figure 4*. Patients with CD more frequently received antimetabolites compared to patients with UC (112/264 [42%] vs. 61/526 [12%], P<0.0001). Furthermore, anti-TNF-alpha antibodies were used to a higher degree among CD patients compared to UC patients (29/264 [11%] vs. 25/526 [4.8%], P=0.0011). The proportion of patients treated with systemic steroids, antimetabolites or anti-TNF-alpha antibodies (or combinations of these three) during the first year was 226/264 (86%) among CD patients and 286/526 (54%) among UC patients (P<0.0001).

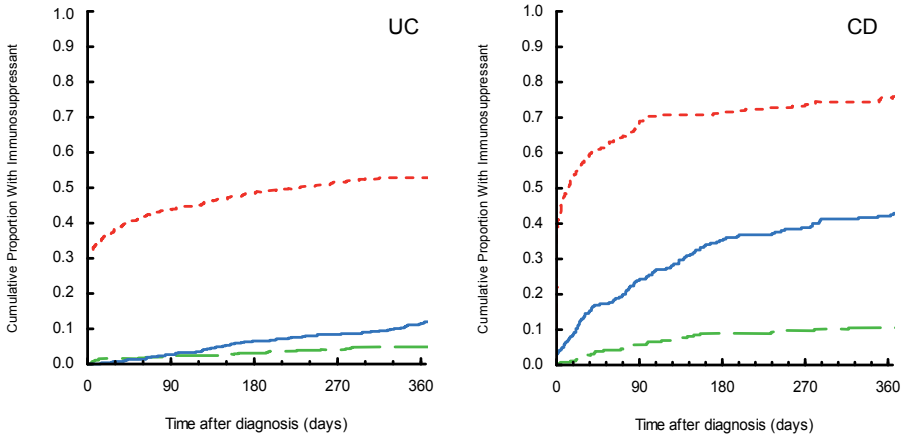

Figure 4. Introduction of immunosuppressive therapy in UC and CD patients. Steroids (•••), azathioprine/6-MP/methotrexate (——), anti-TNF-alpha antibodies (---).

Specific findings in Study I

Patients with extensive UC had a lower median age compared to patients with a more limited disease (28.5 vs. 38.0 years, P=0.0023). There were no differences in age with regard to severity of symptoms. Women had a higher proportion of proctitis as well as milder symptoms compared to men.

A relapsing course during the first 12 months after diagnosis was seen in 228/526 (43%) of the patients whereas 23/526 (4.4%) had chronic continuous symptoms without remission. Risk factors for relapse were female gender (HR: 1.37, 95% CI 1.10-1.71, P=0.0053) and age <40 years (HR: 1.29, 95% CI: 1.03-1.61, P=0.0287). Only 13/526 (2.5%) of the UC patients required a colectomy within 12 months after diagnosis and the median time from diagnosis to colectomy was short as 14.5 days. Children were not subjected to colectomy more often than adults (1/42 [2.4%] vs. 12/484 [2.5%], P=NS).

Specific findings in Study II

Patients with ileocolonic CD were significantly younger than patients with isolated ileal or colonic disease (26.0 vs. 40.6 and 35.8 years, P<0.001), whereas patients with a stricturing disease were significantly older than patients with inflammatory or penetrating disease (45.1 vs. 33.2 and 34.3 years, P=0.0100).

Patients with inflammatory behaviour (B1) had a significantly higher prevalence of diarrhoea and blood in stools compared to patients with stricturing (B2) or penetrating (B3) disease, whereas pain was a more prominent symptom among B2 and B3 compared to B1 (*Figure 5*).

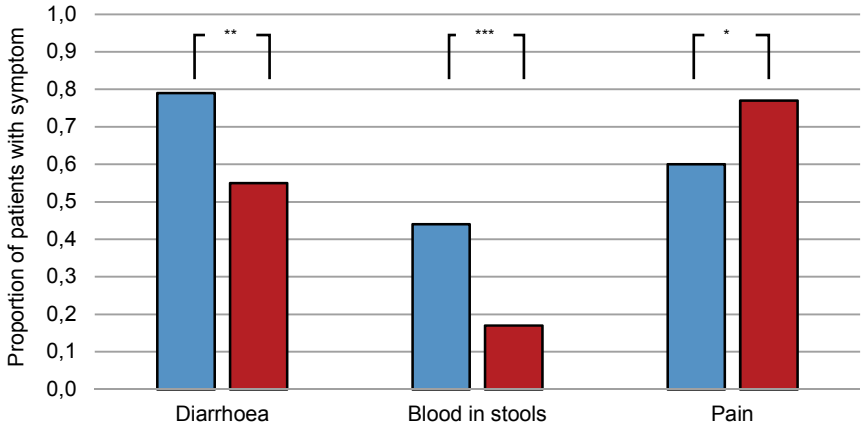

Figure 5. Symptoms before CD diagnosis. Blue bars represent inflammatory behaviour (B1), red bars represent stricturing or penetrating behaviour (B2 or B3). *P<0.05, **P<0.001, ***P=0.0001.

The median symptom duration before diagnosis was significantly longer among patients with B2 and B3 compared to B1 (12.0 vs. 4.0 months, P=0.0032). Both stricturing (HR: 10.59, 95% CI: 3.84–29.23, P<0.0001) and penetrating (HR: 36.55, 95% CI: 12.82–104.16, P<0.0001) disease were strongly associated with an increased risk for surgery. *Figure 6* illustrates both the symptom duration before diagnosis and the cumulative surgery rate (stratified by behaviour).

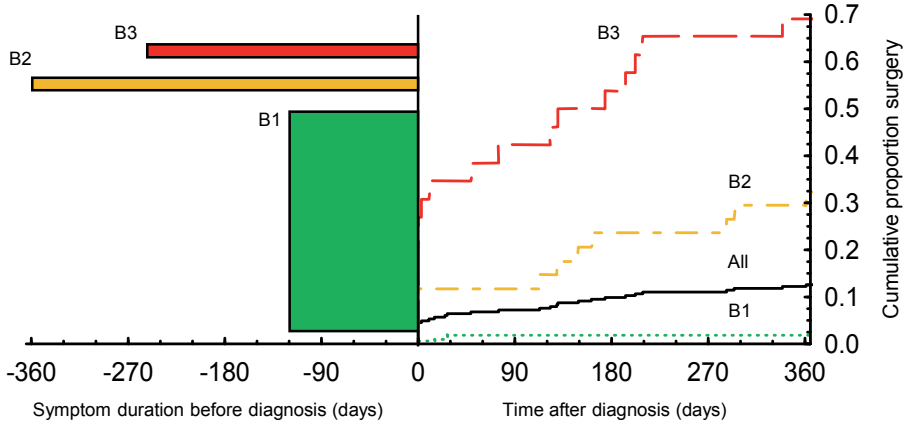

Figure 6. Left side of figure: median symptom duration before diagnosis stratified by behaviour. Area of bars correspond to proportion of patients in the cohort. Right side of figure: cumulative proportion of surgery stratified by behaviour.

Study III

From the original cohort of 790 IBD patients, haemoglobin (Hb) levels were measured in 749 patients at baseline and in 580 patients after one year. The prevalence of anaemia in the cohort was 227/749 (30%) at the time of diagnosis and 102/580 (18%) after one year. CD patients more often presented with anaemia when first diagnosed compared to UC patients (106/254 [42%] vs. 121/495 [24%], P<0.0001), but after one year this difference disappeared (35/199 [18%] vs. 67/381 [18%], P=NS). Furthermore, children were more likely to be anaemic compared to adults (diagnosis: 45/82 [55%] vs. 182/667 [27%], P<0.0001; follow-up: 20/72 [28%] vs. 82/508 [16%], P<0.05).

Only 105/230 (46%) of patients with anaemia during the first year received anaemia specific treatment, i.e. iron supplementation or blood transfusion. The extent of inflammation in UC and colonic engagement with or without ileal involvement in CD were risk factors for anaemia at the time of diagnosis (*Figure 7*).

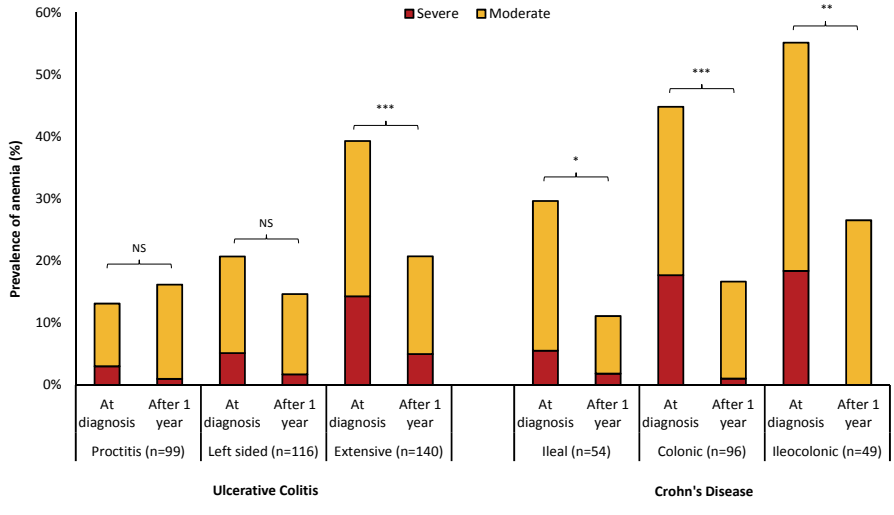

Figure 7. Prevalence of anaemia at diagnosis and after 1 year. UC (n=355), CD (n=199). UC patients with unknown extension (E2 or E3) are excluded (n=26). *P<0.05, **P<0.01, ***P<0.001. NS, not significant.

Study IV

All patients in the UC cohort (n=526) were followed for a mean time of 4.1±1.8 years. 69 patients developed ASUC (45 at the time of UC diagnosis and 24 during follow-up). 40 patients were treated at Uppsala University Hospital and 29 patients at county hospitals (Falu Hospital and Mälar Hospital). There were no differences in modified Truelove-Witt criteria [64] be-

tween cases diagnosed at the different hospitals. 50 patients were hospitalized and treated with IV betamethasone and 18 patients were treated in outpatient clinics with oral prednisolone. One patient was treated solely with infliximab.

The medical therapy was successful in 54/69 (78%) of the patients and colectomy was performed in 15/69 (22%) during the first 90 days after ASUC diagnosis. An additional three patients were subjected to colectomy due to either steroid dependency (n=2) or dysplasia (n=1), resulting in a total colectomy rate during the follow-up of 18/69 (26%). When stratifying surgery rates by university versus county hospitals, the rate of colectomy was significantly lower in Uppsala University Hospital compared to the other hospitals (3/40 [7.5%] vs 12/29 [41.4%], P=0.0006) as shown in *Figure 8*, although the use of anti-TNF antibodies was significantly lower (3/40 [7.5%] vs 11/29 [37.9%], P=0.0019).

The Clavien score [194] measuring complications to therapy was significantly higher for the colectomy group compared to the non-colectomy group (10/15 [67%] vs. 7/54 [13%], P<0.0001). The cumulative prevalence of treatment complications within 90 days was 5/40 (12%) at the hospital with low colectomy rate, versus 12/29 (41%) at the hospitals with high colectomy rate (P=0.0069). Long term outcome was good in the majority of medically treated ASUC patients. 8/54 (12%) developed a new ASUC episode, but none of these patients required colectomy. 14/54 (26%) did not have any steroid-requiring relapse.

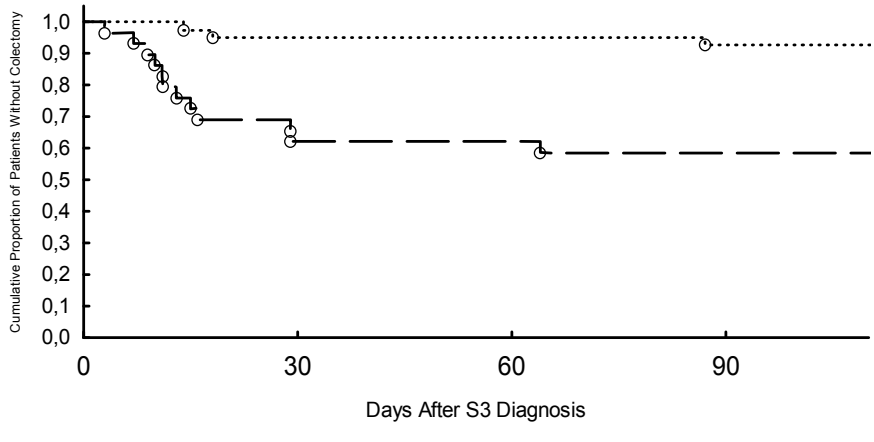

Figure 8. Kaplan-Meyer plot of colectomy free survival after ASUC diagnosis. (⋯) Uppsala University Hospital; (---) Falu Hospital and Mälar Hospital; (o) Colectomy. Log-rank test P=0.0006.

Discussion

High incidence equals high prevalence

Based on previous studies in the Uppsala region and on the results from Study I and II, it is clear that the incidences of both UC and CD have increased in the area during the last half-century. This increase may to some extent be attributed to better diagnostic modalities. However, the proportion of severe UC has not changed over time [61, 195] and the CD behaviour was similar to studies from other parts of the world [98, 100, 196]. The availability of diagnostic tools can therefore hardly explain the total increase in incidence rate.

The ICURE project was not designed to measure the prevalence of IBD in the region. But since the mean age at disease onset is low and overall mortality is similar to background population [197-200], an increase in IBD incidence will ultimately lead to an increase in IBD prevalence.

The growing number of IBD patients together with the rapid development of new pharmaceutical therapies, none providing a cure but merely keeping the inflammation at bay, will have profound implications for gastroenterologists and gastrointestinal surgeons. New treatments are often costly and it is important to continuously monitor IBD incidence in order to allocate sufficient health care resources to this group of patients.

Even if disability, unemployment and sick leave is common among IBD patients [201, 202] and health care costs are high [203, 204], efficient medical therapy may reduce work impairment, thus reducing the socioeconomic impact [205, 206]. The collective burden of IBD in Europe causes long-term disability and economic and social disadvantage. It needs to be addressed, not only by health care professionals, but by all parts of society [207]. The European Crohn's and Colitis Organisation (ECCO) launched a campaign in 2012 in order to raise public awareness of IBD [208].

Children versus adults

In Study I the proportion of children with extensive colitis at diagnosis was higher than among adults, as previously reported by other population based studies [209, 210]. There was however no increased risk of severe disease or colectomy in contrast to studies from Denmark and Hungary [209, 211]. In

Study II, the children more often had an ileocolonic disease and less often a pure ileal disease compared to adults. In a Danish cohort study, a higher proportion of ileocolonic disease could be seen among paediatric CD patients compared to adults (34% vs. 10%) [212].

The incidence of UC among children <17 years in our region (8.9/100,000/year) was higher than the incidence of 2.8/100,000/year in the neighbouring northern Stockholm County during a similar time period (2002-2007) [82]. However, the incidence of CD among children <17 years was similar in the two regions (northern Stockholm: 9.2/100,000/year; Uppsala: 10.0/100,000/year).

One explanation to the difference in UC incidence between these two areas may be that health care in Stockholm County is fragmented into several private as well as public health care providers. The paediatric gastroenterologists may not be informed of a teenage UC patient, despite current Swedish guidelines. Since there were no private gastroenterologists in Uppsala region during the study period and since all patients were included regardless of age, it is likely that the risk of underestimating UC incidence in children in the ICURE project is minimized.

Pharmacological treatment and surgery

Ulcerative colitis

The risk for colectomy in patients with UC varies significantly between different centres, suggesting differences in strategy more than actual differences in disease phenotype. The one-year risk for colectomy was 6% in Copenhagen [92] and 2.5% in the Uppsala region [84]. For UC patients diagnosed in the early 1990s the cumulative risk of colectomy was 4.0% within two years [213] and 8.7% after ten years [214]. The majority of colectomy cases are usually performed during the first two years of disease, reflecting the inability to control inflammation and induce long-term remission [59].

Even if the UC disease can be cured with a complete proctocolectomy, a large British study showed that 20 years after surgery with ileal-pouch anal anastomosis (IPAA), the mean stool frequency was six per day and two per night, 70% developed pouchitis and 40-68% experienced faecal incontinence [215]. The results from the Uppsala region suggest that outcome four years after an ASUC episode not requiring colectomy is favourable with only 12% developing new severe relapse and 26% not even requiring systemic steroid treatment.

Oral 5-ASA treatment is efficient for maintaining remission with a relative risk of 0.69 (95% CI: 0.62-0.77) for relapse compared to placebo [216]. Likewise, azathioprine reduced the proportion of relapses with a relative risk of 0.68 (95% CI: 0.54-0.86) compared to placebo [217]. The anti-TNF-alpha

antibodies are superior to placebo with a relative risk of 2.00 (95% CI: 1.52-2.62) for maintenance of remission [218]. In a recent randomized study the combination of infliximab and azathioprine was superior (40% remission) to monotherapy with infliximab (22%) or azathioprine (24%) [219]. Study I showed that 12% were treated with immunosuppressive drugs (azathioprine, 6-mercaptopurine or methotrexate) during the first year, which is far more than in the IBSEN cohort where only 1% were treated with azathioprine within five years [220].

Crohn's disease

CD was earlier thought to be best controlled by repeated extensive small bowel resections. A study from the Uppsala region in the 1960s estimated the bowel resection rate to 95% after ten years [221]. In the 1990s the surgery rate at ten years had decreased, but the need for surgery still remained on a high level at 29-38% [89, 222]. In Study II, we found a surgery rate at one year comparable with many earlier cohorts [92, 100, 213, 222]. The need for surgery in CD patients debuting with inflammatory behaviour was remarkably low of just 2%, compared to 48% in CD patients debuting with complicated disease (*Figure 6*). This suggests an incentive to early treatment.

The use of 5-ASA in CD patients has waned during the last decade since meta-analyses have failed to prove an effect on induction [223] or maintenance [224] of remission. However, some patients with CD colitis may theoretically benefit from a lower risk of colorectal cancer if the results from UC can be extrapolated [225]. The odds ratio for maintenance of remission for azathioprine has been shown to be 2.32 (95% CI: 1.55-3.49) compared to placebo [226]. Furthermore, both infliximab (RR 2.50; 95% CI: 1.64-3.80) and adalimumab (RR 2.86; 95% CI: 2.01-4.02) has been shown to be superior to placebo in maintaining clinical remission [227].

Combination therapy with one or more immunosuppressant is also efficient, i.e. infliximab + azathioprine with an odds ratio of 3.0 (95% CI: 1.7-5.5) for maintaining remission compared to azathioprine only [228]. It is clear that these data as well as current international guidelines [229] have had an impact on the CD treatment in the ICURE cohort, with 42% treated with immunosuppressant and 11% with anti-TNF-alpha antibodies within one year. When comparing once more to the IBSEN cohort with an azathioprine use of 6% [89], it is likely that long-term outcome will be more favourable than in earlier cohort studies.

The trend towards a lower frequency of surgery in IBD during the past decades has recently been the subject for a meta-analysis, evaluating the surgery risk at one, five and ten years. For UC the pooled risk of surgery was 4%, 10% and 14% respectively for incident cases after 1990. The corresponding figures for CD were 14%, 28% and 39%. Further improvement

was seen for incident cases after the year 2000 with 3% and 8% for UC and 13% and 24% for CD at one and five years [230].

On one hand, the current medical therapy often results in a better life with fewer symptoms for the patients. On the other hand, adverse events such as opportunistic infections [231], liver or kidney damage and long-term risk of malignancy such as lymphoma [232] and skin cancer [233, 234] result in extended surveillance routines and primary prophylaxis [231]. This leads to increased health care consumption and changes in risk panorama for the patient.

Implications of patient's and doctor's delay

The current natural history model of CD describes a progression from purely inflammatory disease to structural damage of the intestine, with more than 50% of the patients developing complications 20 years after diagnosis [56, 196, 235, 236]. In order to change the natural history of the disease, pharmaceutical intervention is essential [237]. The results from Study II highlight that long disease duration before diagnosis, attributed to unspecific abdominal symptoms, is associated with higher degree of complicated disease at the time of diagnosis and thus increased risk of surgery [87].

A hypothetical model over disease progression in CD is presented in *Figure 9*. All treatment results must be evaluated in the light of baseline intestinal damage and hence the need for surgery. The opposite was true for UC where patients with severe colitis had shorter symptom duration compared to patients with mild or moderate colitis, possibly explained by the velocity of inflammatory cascades (*Figure 10*).

It is important that health care professionals as well as the general population are aware of early signs of IBD. The use of laboratory methods such as faecal calprotectin may identify patients who are most likely to need endoscopy for suspected IBD [238]. An early diagnosis is crucial for changing the natural course of IBD in order to prevent bowel damage [236].

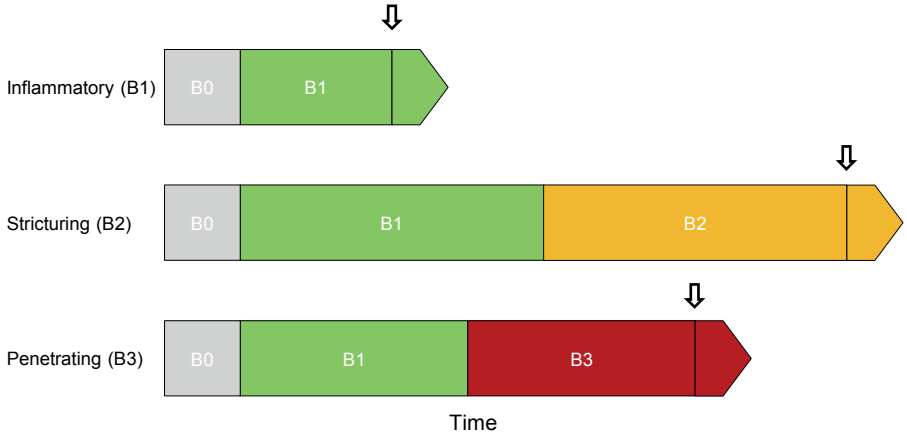

Figure 9. Hypothetical model of CD phenotypes developing different behaviour over time. White arrows indicate CD diagnosis.

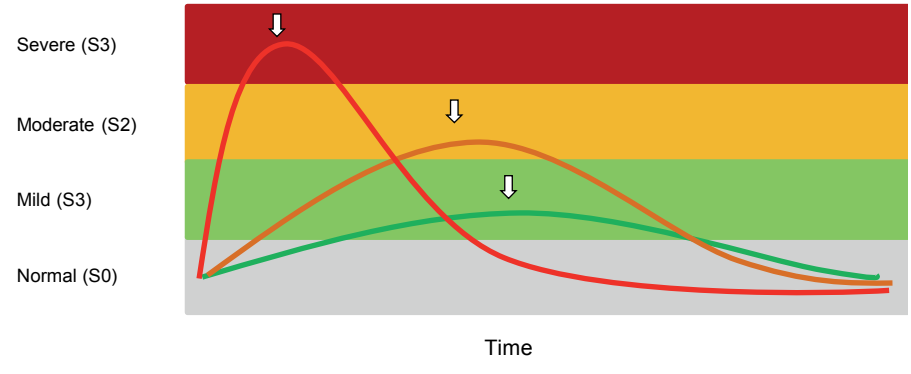

Figure 10. Velocity of inflammatory cascades as an explanation to differences in severity and symptom duration at UC disease onset. Curves represent three different hypothetical patients. White arrows indicate UC diagnosis.

Keeping an eye on complications

Anaemia

Anaemia is the most common complication to IBD, or better described as a "constant clinical feature of IBD" [159]. The ICURE cohort was treated extensively with immunosuppressive medical therapy compared to older cohorts. But despite current guidelines, Study III showed that the majority of IBD patients with anaemia did not receive anaemia-specific treatment, and that oral iron was preferred to intravenous iron. This finding is consistent with several other studies recently published [239-241].

The prevalence of anaemia in IBD (18%) can be compared to the prevalence in other chronic inflammatory disease such as rheumatoid arthritis (17-31%) [242, 243] and coeliac disease (21%) [244]. Only two previous studies have reported on anaemia in population based IBD cohorts. In a Norwegian study of IBD patients diagnosed in 1990-1993, 29% were anaemic at the time of diagnosis and 17% after one year [245], which is remarkably similar to the data in Study III. A more recent German study reported on an anaemia prevalence of 32% among IBD patients diagnosed in 2004-2009 [241].

The risk factors for anaemia (young age, colonic involvement in CD and extent of inflammation in UC) should be adequately recognized and proactive treatment as well as follow-up of anaemia should be better implemented in current practice. It is not sufficient to only treat IBD inflammation and hope that the iron deficiency will self-correct.

Severe colitis

In Study IV the cumulative risk for developing an ASUC episode was 13% during the first four years after diagnosis. A total of 18% of the UC patients developed ASUC in a hospital based retrospective material from 1938-1962 [61]. Explanations to this difference include the observations that Study IV was population based, more patients were treated with immunosuppressive drugs and follow-up time was shorter.

Patients treated at the University Hospital were less often subjected to colectomy compared to the County Hospitals. This could not be attributed to baseline differences among the two groups. The result suggests that the culture among gastroenterologists and colorectal surgeons at the University Hospital allowed for prolonged medical treatment and that this tradition resulted in fewer colectomies. Since gastroenterologists and colorectal surgeons at the University Hospital are available all days of the week, preemptive colectomy decisions does not need to be forced.

The decision to proceed with surgery is balanced between the will of preserving the colon and the normal bowel function on one hand and the risk for morbidity and mortality on the other hand. The key issue is the timing of surgery. In 1956, shortly after the introduction of steroids in the treatment of severe UC, lack of improvement within one or two weeks was regarded as an indication for colectomy [246]. Ten days of medical therapy was recommended by Goligher in 1961 [247]. However, an analysis in 1966 showed a high mortality rate of 24% among urgent colectomy patients and 0% among elective patients [248].

In a study from 1970, the outcomes during two different time periods were compared: during 1952-1963 when colectomy took place 12 to 17 days after admission and during 1964-1969 when the time was five to seven days. The operative mortality was 20% in the former and 7% in the latter [249], suggesting an advantage of early surgery.

The observation that the prognosis of severe episodes of UC could be improved with the use of intravenous steroids led to standardized protocols. In the benchmark study from Radcliffe Infirmary, Oxford, United Kingdom, the protocol prescribed intravenous steroids, fluids and electrolyte substitution during five days [178, 179]. Absence of decisive improvement after five days was considered an absolute indication for surgery.

This five-day rule influenced the practise during the forthcoming years, resulting in a fear of prolonged medical treatment. However, observations from experienced centres reported that it was possible to extend the treatment beyond these five days even if no definitive improvement had occurred and by doing so, a colectomy could in a number of cases be avoided [250, 251]. Notably, a subgroup of ASUC patients responds slowly to steroids and benefits from prolonged treatment [252].

In the recently published European guidelines regarding surgery in UC, colectomy is recommended in case of failure of a second line treatment within the timeframe of seven days [253]. Even if the words deterioration and lack of improvement are often used interchangeable, a distinction must be made when discussing patient outcome.

A second line treatment with either infliximab or ciclosporin may be beneficial for a number of patients. But if the gastroenterologist does not perceive that there has been any improvement on the basis of endoscopic images, laboratory data or clinical marker, this may trigger a colectomy decision. In Study IV endoscopic deterioration was a major indication for surgery, regardless of the patient's clinical state. It was also more common that patients at the two high colectomy hospitals received infliximab compared to the low colectomy hospital.

Complications to medical and surgical treatment of ASUC

A study from 2009 found that in eighty patients with ASUC, 27% had complications in the initial postoperative period and 60% during a five year follow-up [254]. Patients who developed major complications, defined as those prolonging hospital stay or necessitating readmission, had a longer preoperative duration of admission compared to patients who did not (8 vs. 5 days).

In Study IV the cumulative complication rate was significantly higher at the hospitals with high colectomy rates (41%) compared to the hospital with a low colectomy rate (12%). This could be attributed to the fact that complications were caused by surgery per se rather than by the disease itself.

Two deaths occurred among the 69 patients, both of which among the colectomy cases. One death occurred 19 days after surgery. On the suspicion of free gas, the patient was subjected to a secondary laparotomy where no perforation was found. Another patient developed sepsis emanating from a disconnected rectum and died more than three years after surgery. Both of these cases were elderly patients. High in-hospital mortality rates in patients with

ASUC has recently been reported among patients >60 years of age (3.5%) compared to younger patients (0.1%) [180]. The highest mortality rate was seen among patients >80 years (10.5%).

Strengths and limitations

Observational studies are associated with certain strengths, but also with certain weaknesses that need to be addressed. Even if randomized controlled trials (RCT) are widely viewed as the golden standard for medical science, there are limitations derived from the methodology, mainly the issues of external validity, time and cost [255].

Observational studies may provide valuable clinical knowledge. They allow longer follow-up periods, can detect seldom occurring events and are not hampered to the same extent as RCTs by the problem of external validity, i.e. generalizability of results. There are also ethical difficulties in performing an RCT aiming at answering certain questions, such as randomization into surgery or no surgery based on clinical or laboratory data. Observational research has improved over time, as a result of structured statements with checklists [256].

The major strength of the ICURE project is that virtually all incipient IBD cases within a certain time frame and geographic area have been identified and subsequently followed. The material collected is reasonably large, making it possible to analyse subgroups without losing statistical power. Since patients of all ages and all IBD diagnoses were eligible, the completeness of data provides valuable comparisons between subgroups (children vs. adults; UC vs. CD). In contrast to observational studies based on registries, all cases in the ICURE cohort were scrutinized by two gastroenterologists, providing consensus regarding the IBD phenotype. The prospective nature of the project allowed for the researchers to collect information initially missing from the patients at scheduled follow-up.

However, it is difficult to assess and avoid bias in observational trials. The method of randomization in RCTs allows for confounders to be evenly distributed among the intervention and comparison groups. The most significant shortcoming in observational trials is selection bias due to differences in patient characteristics [255]. Non-randomization can be met by statistical analysis such as regression or hazard models adjusting for baseline discrepancies [257, 258], even if it is only possible to adjust for known and recorded confounders.

In the ICURE cohort, these limitations apply to all four studies. For Study I and II the common exposure is IBD diagnosis and the outcome is relapse and surgery. For Study I, the risk of relapse was adjusted for age, gender, extension and severity through Cox regression analysis resulting in hazard ratio. Certain other factors could have been included in the analysis, but

missing data rendered them difficult to utilize (i.e. smoking, appendectomy and heredity). For Study II, the risk of surgery was estimated using univariate analysis for age, location, behaviour, perianal disease, upper GI disease, gender and heredity. Age, behaviour and location were significantly associated with surgery and included in the Cox regression analysis. The cut-off level of significance in the univariate analysis was conservatively set to $P<0.05$, potentially under-estimating the influence of the non-included confounders in the regression analysis.

For Study III, an analysis of attrition was performed for patients excluded at the follow-up at one year, suggesting that patients with loss to follow-up were characterized by ulcerative proctitis and mild symptoms. This may over-estimate the prevalence of anaemia. Finally, in Study IV, the only difference between University and Count Hospitals with regards to baseline characteristics was a higher rate of naïve cases in the County Hospitals. Other non-recognized confounders might have influenced the surgery rate difference, but since all cases of ASUC were recruited from each hospital's primary catchment area, the study resembles a quasi-experimental study [259].

When comparing colectomy vs. no colectomy outcome, the only factor that differed between the groups was the albumin level, suggesting that the differences in colectomy rates were not based on these variables. Instead, site-specific traditions influenced the frequency of surgery, which seemed to be affected by the access to specialized care. Finally, the finding that colectomy cases had more complications compared to medically treated cases could arguably be due to the selection of the most favourable cases to the medical treatment group.

Conclusions

- The incidence of ulcerative colitis (UC) in the Uppsala region 2005-2009 was 20.0/100,000 inhabitants/year (95% CI: 16.1-23.9).
- The incidence of Crohn's disease (CD) in the Uppsala region 2005-2009 was 9.9/100,000 inhabitants/year (95% CI: 7.1-12.6).
- At the end of the study in 2009 the incidence of UC was 21.4/100,000/ year (95% CI: 16.1-23.9) and the incidence of CD was 12.5/100,000/ year (95% CI: 9.8-15.3).
- During the first year the colectomy rate was 2.5% for UC and the intestinal resection rate was 12.5% for CD.
- The risk of relapse in UC was increased for patients with female gender and age <40 years.
- The risk of intestinal resection in CD was increased for patients with stricturing or penetrating disease and for ages >40 years.
- Patients with complicated CD at diagnosis had longer symptom duration before diagnosis and less prominent symptoms compared to patients with pure inflammatory CD.
- The prevalence of anaemia was high at the time of diagnosis (30%) and after one year (18%).
- Children <17 years were more likely to be anaemic compared to adults.
- Anaemia was correlated to the extent of colonic inflammation in UC and the prevalence of colonic inflammation in CD.
- The risk of developing a severe episode of UC was 13% during the first four years after diagnosis.
- By letting pharmacological treatment of ASUC proceed for a longer time period, colectomy may be avoided and total burden of treatment complications reduced.
- The complication frequency <90 days was higher among patients subjected to colectomy compared to patients with pharmacological treatment only.
- Patients with medical treatment only of their ASUC episode had favourable outcome with just 12% developing a new severe relapse of which none required colectomy.

Future directions

One thing I have learned during my doctoral studies is that you should always aim for owning your data. A well-defined, well-organized database is a goldmine for future studies. For the current project this is truer than ever. The value of the ICURE cohort will continue to grow, making it more and more interesting as time goes by. The need for population based prospective cohorts in the era of new pharmaceutical therapies is urgently needed [260] and the ICURE cohort provides a potential to give future clues to the long-term outcome of these chronic diseases.

My impression when we are approaching the five-year follow-up of the cohort is that patients in the ICURE cohort have far lower surgery rates compared to earlier studies. In the following year we intend to report outcome data for both UC and CD reaching the five-year mark. Hopefully, the cohort data is still viable at the ten years follow-up shedding new light to factors such as need for surgery, medication and changes in disease phenotype.

Parallel to these cornerstone reports we intend to investigate the prevalence of associated liver diseases and celiac disease in the cohort with two manuscripts presently in the making. Another intriguing phenomenon worth pursuing is the transition between microscopic colitis and UC/CD and vice versa.

An ongoing collaboration with researchers at Oxford University further explores the possibility to prognosticate future development of ASUC among newly diagnosed UC patients through a scoring system.

We also want to report on the presence of perianal disease in the CD population together with detailed surgical data regarding fistula management. If the impression is true that CD surgery is more uncommon at five and ten year follow-up than previously reported, in-depth investigation of surgical methods could lead to better understanding of the change in strategy.

This cohort may act as a litmus test for evaluating adherence to international guidelines, i.e. vaccination before starting treatment, anaemia control, and risks associated with one or more immunosuppressive drugs.

An area not covered by this thesis is the socioeconomic applications of IBD, both for the individual and society. A report concerning sick-leave, disability and health care consumption in the present day should be of utmost importance for evaluating the burden of IBD in a Swedish population.

Long-term follow-up can tell us whether IBD patients have the same life expectancy as the background population and whether the incidences of malignancy, cardiovascular disease and osteoporosis are increased or decreased. We also seek prognostic factors at the time of diagnosis or the first few years of disease that predict long-term outcome, thus enabling us to construct scoring systems indicating which patients to focus on early in order to prevent a less favourable course of the disease.

Since the aetiology of IBD probably is multifactorial, it is unlikely that future studies will reveal a single causative risk factor explaining the majority of the cases. Much data is already available regarding the pathology on the cellular and mucosal level, which needs to be translated into the patient's phenotype and vice versa. In order to achieve this and further strengthen the value of population based IBD cohorts in the future, biological data such as blood and tissue samples needs to be collected from the patients.

As a final note, my belief is that even if IBD continues to grow in incidence and prevalence, patients will benefit from the new pharmacological therapies decreasing the number of patients with chronic or relapsing symptoms to a minimum. Surgery will become a rare treatment for only a few selected patients. It is however important that the treatment does not injure the patient more than the disease. Already, the shift in focus from discussing treatment algorithms to safety concerns regarding the medication is a noticeable development of the international gastroenterological debate.

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Sammanfattning på svenska

Inflammatorisk tarmsjukdom är ett samlingsbegrepp för flera sjukdomar, där ulcerös kolit och Crohns sjukdom är de två vanligaste. De vanligaste symtomen vid inflammatorisk tarmsjukdom är diarré (ofta blodig), buksmärta och trängningar till tarmtömning. Mindre vanliga symtom är viktnedgång och brist på vitaminer och mineraler. Båda sjukdomarna kännetecknas av återkommande skov med försämring i perioder. En mindre andel patienter besväras av kontinuerlig aktivitet.

Ulcerös kolit orsakar inflammation i ändtarmens och tjocktarmens slemhinna. Den kan kategoriseras utifrån hur utbredd inflammationen är (ändtarm, vänster sida eller hela tjocktarmen) samt hur allvarliga symtom inflammationen ger (milda, måttliga eller svåra symtom). Crohns sjukdom kan drabba alla delar av magtarmkanalen, från mun till anus. Även Crohns sjukdom kan kategoriseras i var inflammationen är belägen (tunntarm, tjocktarm eller både tunn- och tjocktarm) samt dess beteende (inflammatorisk, förträngande eller penetrerande).

Nya läkemedel har utvecklats det sista decenniet, samtidigt som gamla läkemedel används i större utsträckning än tidigare. Vid otillräcklig effekt av behandlingen eller vid komplikationer till sjukdomarna så behövs ibland kirurgi. Vid ulcerös kolit innebär det att man opererar bort hela tjocktarmen och vid Crohns sjukdom innebär det att man tar bort den del av tarmen som är inflammerad, trång och/eller där sjukdomen har penetrerat tarmväggen.

Både ulcerös kolit och Crohns sjukdom har ökat i västvärlden under 1900-talet. Befolkningarna i de nordiska länderna har tidigare varit särskilt drabbade av inflammatorisk tarmsjukdom. Det behövs nya studier som beskriver prognosen för de patienter som insjuknar idag.

Syftet med denna avhandling har varit att undersöka antalet nyinsjuknade patienter med ulcerös kolit och Crohns sjukdom i Uppsalaregionen samt att beskriva förloppet under det första året med hänsyn till behandling och komplikationer.

Alla patienter med ulcerös kolit och Crohns sjukdom under åren 2005-2009 (Uppsala) respektive 2007-2009 (Falun, Eskilstuna och Åland) registrerades. Data samlades in från patienternas journaler och bedömdes av minst två specialister i magtarmmedicin.

I studie I uppmättes andelen nyinsjuknade patienter i ulcerös kolit till 20 fall per 100 000 invånare och år, vilket motsvarar drygt 1 900 fall i Sverige årligen. Hälften av alla patienter återinsjuknade under det första året med ett

nytt skov. Risken för att drabbas av ett nytt skov var ökad hos kvinnor samt hos de med inflammation endast i ändtarmen. Endast 2,5 % av alla patienter med ulcerös kolit behövde genomgå kirurgi under det första året. Den vanligaste orsaken till kirurgi var ett svårt skov eller långvariga symtom där medicinering inte har lyckats läka inflammationen.

I studie II uppmättes andelen nyinsjuknade patienter i Crohns sjukdom till 9,9 per 100 000 invånare och år, vilket motsvarar drygt 950 fall i Sverige årligen. Patienter med komplicerad sjukdom (förträngningar eller penetrering) vid diagnos hade haft symtom under längre tid än patienter med okomplicerad sjukdom. Risken för kirurgi under det första året var 12 %.

I studie III analyserades förekomst av blodbrist hos patienterna. 30 % hade blodbrist vid diagnostillfället och 18 % efter ett år. Blodbrist vid diagnos var vanligare hos patienter med Crohns sjukdom (42 %) än hos patienter med ulcerös kolit (24 %). Efter ett år var det ingen skillnad mellan diagnosgrupperna. Endast en minoritet av patienterna med blodbrist fick järnbehandling, trots att detta rekommenderas i nationella och internationella riktlinjer.

Studie IV handlade om komplikationen svårt skov av ulcerös kolit. Sammanlagt 13 % av patienterna med ulcerös kolit drabbades av ett svårt skov. 22 % av alla svåra skov ledde till att man opererade bort tjocktarmen. Det var dock stor skillnad mellan sjukhusen. Vid Akademiska sjukhuset behövde endast 7,5 % av patienterna kirurgi och vid Falu lasarett och Mälarsjukhuset behövde 41 % kirurgi. Trots detta var risken för komplikationer i samband med det svåra skovet lägre vid Akademiska sjukhuset.

Orsaken till denna skillnad var att man vid Akademiska sjukhuset valde att avvakta effekten av den medicinska behandlingen längre innan man tog beslut om kirurgi. Fler kunde då tillfriskna utan operation. Risken för ett nytt svårt skov eller framtida kirurgi var låg i gruppen som endast fick medicinsk behandling.

Sammanfattningsvis har denna avhandling visat att risken för att insjukna med inflammatorisk tarmsjukdom i Sverige är mycket hög jämfört med internationella studier. Nästan 3 000 personer beräknas insjukna varje år i Sverige. Eftersom medelåldern när man insjuknar är låg (< 40 år) och sjukdomarna ofta är livslånga, så blir andelen av befolkningen som är drabbad hög. Detta ställer ökade krav på sjukvården men också på samhället i stort i form av läkemedelskostnader och sjukskrivningar.

Det var sällsynt att patienter med ulcerös kolit behövde kirurgi. Patienter med komplicerad Crohns sjukdom kom sent till diagnos på grund av mindre alarmerande symtom. Blodbrist är en vanlig och underbehandlad komplikation till inflammatorisk tarmsjukdom. Svårt skov av ulcerös kolit kan med framgång behandlas med mediciner. Andelen som är i behov av kirurgi kan minskas utan att komplikationerna ökar.

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