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ABSTRACT

This study investigates the evolution of abdominal surgery in treatment of Crohn´s disease (CD) in the era of immunomodulatory drugs and biologicals. It concerns risk of abdominal surgery overall and sub-categories of abdominal surgery, risk of repeat surgery and factors that affect this risk, and risk of getting a stoma. Surgical recurrence is a major clinical problem as repeat procedures are more complex and expose the patients to a higher medical risk both in conjunction with surgery and afterwards. Updated information on abdominal surgery for CD will be of use when making decisions about medical vs surgical interventions.

In a nationwide cohort of 21 273 patients with CD during the years 1990-2014, the cumulative incidence of abdominal surgery within five years of diagnosis decreased continuously down to 17.3% for patients diagnosed with CD during the last calendar period of study, 2009–2014. Ileocecal resection was the most common primary procedure. The incidence of colectomy was low in all calendar periods and continuously decreased. The incidence of proctectomy was very low even after decades with the disease, 3.0% for patients diagnosed 1990-1995 with a median follow-up of 21 years. Incidence of *repeat* abdominal surgery within five years of primary procedure decreased in the 90s down 16.0% in the 1996–2000 period with a risk of ileocolic reresection of 4.4%. After 2000, despite introduction of biologicals in 1998, no further significant decrease in repeat surgery was observed.

In a retrospective review of prospectively maintained databases at three university hospitals, the rate of surgical recurrence for 389 patients with CD who had been treated with a primary ileocecal resection between 2000-2012 was investigated. The patients were operated receiving either a temporary stoma (20%) or a primary anastomosis (80%) with a median follow-up time of 105 months. Patients selected to temporary stoma had a higher prevalence of baseline risk factors usually associated with an increased risk of recurrence such as penetrating disease behaviour. Despite this, there was no difference in long-term surgical recurrence between the one- and two-stage groups; 18% vs 16%.

In a retrospective review of prospectively maintained databases at two university hospitals, the effect of smoking cessation on rate of surgical recurrence was assessed. 242 patients were included with a median follow-up of 112 months. Surgical recurrence rate for smokers vs quitters was 16/42 (38%) vs 3/31 (10%); $p = 0.02$; risk ratio = 3.9 despite a median time for smoking exposure after the primary procedure of three years. Among the non-smokers 28/169 (17%) had a surgical recurrence at last follow-up. 8 out of 11 smoking patients who needed a second resection went on to need a third resection. Of the patients who were free of surgical recurrence at follow-up, those who had quit smoking were significantly less likely to have been put on medical therapy compared with smokers with a risk ratio of 3.2.

In an observational study of a nationwide cohort of 19 146 patients with incident CD 2002-2013 and followed through 2017, the incidence and prevalence of stoma was investigated. The cumulative incidence of stoma formation within five years was 2.4% and remained constant from 2002 and onwards although cumulative ever-use of biologicals increased and time to start with treatment with biologicals decreased. 48% of all stomas were reversed. Ileostomies encompassed about two-thirds of all stomas and risk of stoma was higher among patients with elderly-onset CD and among patients with perianal manifestations of the disease. 28% of the patients who underwent surgery with formation of a stoma had perianal disease. 0.6% of all incident patients had a permanent stoma five years after diagnosis.

**“Le doute n'est pas une condition agréable,
mais la certitude est absurde.”**

Voltaire

LIST OF PAPERS

This thesis is based on the following papers which will be referred to by their Roman numerals as follows:

I. Decrease in primary but not in secondary abdominal surgery for Crohn's disease: nationwide cohort study, 1990–2014

T. D. Kalman, Å. H. Everhov, C. Nordenvall, M. C. Sachs, J. Halfvarson, A. Ekbom, J. F. Ludvigsson, P. Myrelid and O. Olén

Br J Surg. 2020 Oct;107(11):1529-1538.

II. Temporary faecal diversion in ileocolic resection for Crohn's disease: is there an impact on long-term surgical recurrence?

R. Bolckmans, S.Singh, K. Ratnatunga, D. Wickramasinghe, K. Sahnan, S. Adegbola, D. Kalman, H. Jones, S. Travis, J. Warusavitarne, P. Myrelid and B. George.

Colorectal Dis. 2020 Apr;22(4):430-438.

III. Does Smoking Cessation Reduce Surgical Recurrence After Primary Ileocolic Resection for Crohn's Disease?

Roel Bolckmans, Thordis Kalman, Sandeep Singh, Keshara C. Ratnatunga, Pär Myrelid, Simon Travis, Bruce D. George.

Dis Colon Rectum. 2020 Feb;63(2):200-206.

IV. Probability of stoma in incident patients with Crohn's disease in Sweden 2002-2017: a population-based study

Åsa H Everhov and Thordis Disa Kalman, Jonas Söderling, Caroline Nordenvall, Jonas Halfvarson, Anders Ekbom, Jonas F Ludvigsson, Ola Olén and Pär Myrelid

Submitted 2020

ABBREVIATIONS

ADA	adalimumab
ATC	Anatomic Therapeutic Chemical classification system
aTNF	anti-tumour necrosis factor
AMP	antimicrobial peptides
AZA	azathioprine
CD	Crohn´s disease
CDAI	Crohn’s disease activity index
CRC	colorectal cancer
ECCO	European Crohn´s and Colitis Organisation
EEN	exclusive enteral nutrition
EIM	extra-intestinal manifestations
GWAS	genome-wide association studies
HR	hazard ratio
IBD	inflammatory bowel disease
IBDU	inflammatory bowel disease unclassified
IF	intestinal failure
IFX	infliximab
IMM	immunomodulators
6-MP	6-mercaptopurine
MTX	methotrexate
NPR	National Patient Register
OR	odds ratio
PDR	Prescribed Drug Register
PPV	positive predictive value
SNP	single nucleotide polymorphisms
SSSA	stapled side-to-side anastomosis
SP	strictureplasty
UC	ulcerative colitis
WP	work productivity

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BACKGROUND

CLINICAL FEATURES OF CROHN´S DISEASE

INTRODUCTION

The major inflammatory bowel diseases (IBD) in humans are Crohn’s disease (CD) and ulcerative colitis (UC). Both are characterized by recurrent flares of inflammation and share common features such as symptoms, structural damage, and therapy. In UC, the lesions usually remain superficial in the colorectal mucosa extending proximally from the rectum, whereas CD is a transmural process that can affect any part of the gastrointestinal tract. Both can affect extraintestinal sites. In a genotype association study, including almost 35 000 patients from 2016, the data however supports a continuum of disorders within IBD better explained by three groups (ileal Crohn's disease, colonic Crohn's disease, and ulcerative colitis) than by CD and UC as currently as currently defined[1]. CD and UC are associated with multiple pathogenic factors including environmental changes, susceptibility gene variants, a qualitatively and quantitatively abnormal gut microbiota and a dysregulated immune response[2].These factors cross-regulate each other in multiple ways. A common view of CD is that in this disease the immune response is directed against and induced by the intestinal microbiome and the gut inflammation is at least in part a collateral damage of this interaction[3].

EARLY DESCRIPTIONS OF THE DISEASE

The first description of CD is found in the record of an autopsy in 1612[4]. A boy had died after suffering from abdominal pain and diarrhoea. “The ulcerated cecum (was) contracted and invaginated into the ileum”. Although scarce, similar findings were reported in the following centuries. A classic paper in 1913 by Dalziel with 13 patients included, reported of “chronic interstitial ileitis”[5]. Following this paper there were in the 1920s several reports of patients with granulomatous lesions of the intestinal tract, originally identified as “hyperplastic intestinal tuberculosis”, usually involving the terminal ileum or ileocecal area[4]. The paper by Crohn et al in 1932 presenting the concept of regional ileitis gave name to the disease[6]. Speculations about what caused the disease included bacteria and impaired vascular or lymphatic circulation[7-9].

SETTING THE DIAGNOSIS OF CROHN´S DISEASE

A single reference standard for the diagnosis of CD or UC does not exist[10]. The diagnosis is based on a combination of clinical features, biochemical tests, stool investigations such as microbiological tests and faecal calprotectin, endoscopic examination, histological investigations, and cross-sectional imaging [10]. Typical clinical symptoms of CD are loose stools, weight loss, abdominal pain, and fatigue. Biochemical tests include C-reactive protein, a marker of inflammation overall (including intestinal inflammation) and faecal calprotectin, a marker for migration of neutrophils to the intestinal mucosa which can indicate intestinal inflammation. Neither of them discriminates between CD and UC[10]. Loose stools for more than six weeks make an infectious cause less probable, but stool specimens should be checked to rule out common pathogens or *Clostridium* difficile toxin. Ileocolonoscopy with biopsy is established as the first-line investigation for suspected Crohn's disease but up to 20% of patients have isolated small bowel disease proximally of the terminal ileum, beyond the reach of even complete ileocolonoscopy[11]. Endoscopic findings in CD include erythema, oedema, nodular mucosa and aphtous ulcerations[12]. No endoscopic feature is specific for CD or UC but discontinuous lesions (skip lesions), presence of strictures, fistulae, involvement of the small bowel and perianal lesions are suggestive of CD[10]. UC can however, affect the small bowel as backwash ileitis which has been shown in up to 22% [13]. Small bowel capsule endoscopy or MR enterography should be used when there is clinical suspicion of CD in combination with normal endoscopy[10]. In histological examination the features with highest diagnostic value are focal (discontinuous) chronic inflammation, focal crypt architectural distortion and granulomas not related to crypt injury[14].

DISEASE PHENOTYPES: AGE / LOCATION / BEHAVIOUR

There is a wide spectrum of disease phenotypes with a variability in disease location and behaviour. The wide clinical spectrum has prompted the development of clinical classification systems. The Vienna classification was introduced in 1998 and was based on *Age* at Diagnosis (below 40 years (A1), equal to or above 40 years (A2), *Location* (terminal ileum (L1), colon (L2), ileocolon (L3), upper gastrointestinal (L4)), and *Behaviour* (nonstricturing nonpenetrating (B1), stricturing (B2), penetrating (B3)[15] as the predominant phenotypic elements[15]. This classification was then modified within each of these categories in the Montreal classification 2005[16]. Early onset of disease was to be categorised as a new A1 category for those with age of diagnosis at 16 years or younger, A2 accounts for age of diagnosis at 17–40 years and A3 for age at diagnosis > 40 years. The change in category of age was done in recognition of new data that had shown specific serotypes / genotypes are more often found in early onset Crohn's disease[17]. The change in classification of location was done as the categories in the Vienna classification was mutually exclusive which did not allow upper GI-manifestations of CD to coexist with distal disease. L4 was added as a modifier to L1–L3 when concomitant upper gastrointestinal disease was present. To differentiate between fistulizing intestinal disease and fistulizing perianal disease "p'' was added to B1–B3. The Montreal classification is now globally accepted but the dynamic features of the early onset CD-phenotype, with change in disease location and behaviour over time and growth failure, has led to another modification for pediatric purposes, the Paris classification[18].

Genetic studies implicate that location is a biological aspect of a patient's disease, whereas behaviour is a marker of disease progression[1]. Information about the anatomic evolution of CD has been retrieved from postoperative endoscopic follow-up. The mucosal inflammation leads to the development of aphtous ulcers and longstanding transmural inflammation goes on to progressive structural damage with fibrosis and strictures in the bowel wall[19]. Disease behaviour is however both dictated by duration and location of the disease[20 21]. Patients with small bowel and anoperineal disease at diagnosis are at high risk for early stricturing and penetrating complications, ileocolonic disease has an intermediate development and colitis remains inflammatory for a long time[20].

For most patients the inflammatory behaviour predominate during the first few years[20]. Intestinal fibrosis is a dynamic process. Inflammation and fibrosis can coexist within the same stricture or region[22]. The progressive structural damage can also lead to the development of penetrating complications with enteroenteric, enterovesical, enterovaginal and enterocutaneous fistulas [19 20]. A stricture can be associated with a fistula that develops above it, or it can develop within an area with severe inflammation[23]. In the IBSEN-study; 53% of the patients had a stricturing or penetrating disease behaviour 10 years after diagnosis[24]. In a study of 2002 CD-patients seen at a tertiary centre in Paris during the years 1974-2000, the actuarial risk 5 and 20 years after diagnosis was 12% and 18% respectively for stricturing disease and 40% and 70% for penetrating disease with perianal fistulas encompassing more than half of the penetrating complications[20]. In the Rochester Epidemiology Project, a study of a comparatively small but very well-documented population in Olmsted County Minnesota, patients diagnosed with CD between 1970-1993 had a cumulative risk of *any* fistula of 33% after 10 years and of 50% after 20 years whereof *perianal fistulas* encompassed 54%[25]. This is in line with the incidence of 23% of perianal fistulas among patients with CD living in Stockholm County, Sweden, during the years of 1955–1974[26] and the cumulative probability of 28.3% at 20 years of a perianal fistula in a population-based study of patients with CD from New Zealand [27]. Perianal CD, especially when combined with anal stricture, is a risk factor for permanent stoma[28] and of severe work productivity loss[29].

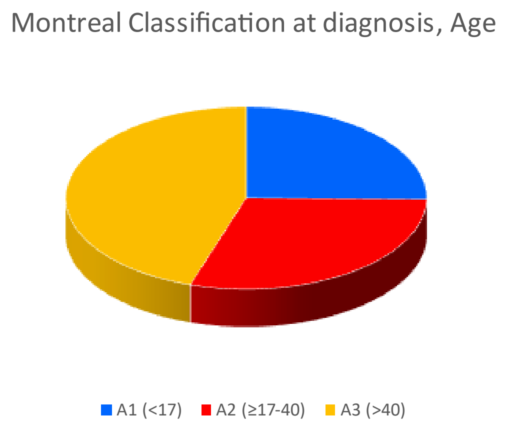
A classification into a behavioural group should however always be considered as temporary except for patients that have progressed to penetrating disease. Asymptomatic patients can still have active disease leading to progressive structural damage as disease activity does not reliably correlate with clinical symptoms[30-32].

Location of the disease is usually, but not always stable, with a higher risk of disease extension among children[21 33]. About 20% of all patients with ileal disease develop subsequent colonic lesions after 10 years of disease but extension to the small bowel develop in less than 20% of patients with colitis[19]. In the report from the EPIMAD-registry from northern France, including more than 8000 incident patients with CD during the period 1988-2008, it was shown that disease extension occurred in 31% of paediatric-onset CD while location was stable with time in more than 92% of the elderly (> 60 years) and a predominance of pure colonic disease in elderly onset CD[33]. At maximal follow-up, only 30% of the elderly patients had complicated behaviour (stricturing or penetrating) compared with more than 50% of the children[33].

DISTRIBUTION OF PHENOTYPES IN SWEDEN – SWIBREG

The Swedish IBD-quality register SWIBREG (www.swibreg.se) started in 2005 and had in April 2019 about 46 400 patients included, with patients with *CD* constituting about a *third* of the registered population, i.e. *60% of all Swedish patients with CD*[34]. The 17 624 CD-patients registered in Dec 2020 had the following distribution for age (Fig.1), localisation (Fig.2) and behaviour (Fig.3) *at diagnosis* (Of note; the A3-cohort includes all patients > 40 years of age and 23% of all CD-patients had a first diagnosis of IBD at 60 years or older[35]):

Figure 1



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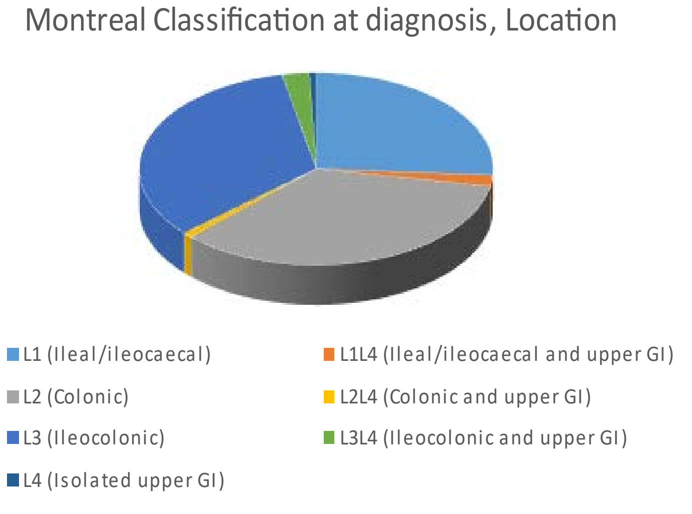
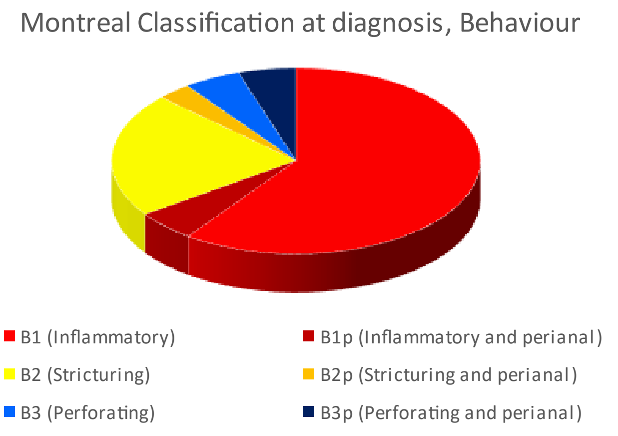


Figure 3



CHANGE IN IBD SUBTYPES

Despite careful diagnostics, studies have shown that 3% of UC patients will be reclassified as Crohn's colitis, and 0.6–3% will be reclassified to UC after an initial diagnosis of CD[36 37]. 5-15% of patients with IBD are labelled as IBD-unclassified (IBD-U) as endoscopic and histological assessments cannot distinguish between them and this is more common in paediatric care[11]. In a study of more than 44 000 patients with an IBD-diagnosis on two or more occasions in the Swedish National Patient Register 2002-2014, it was shown that 18% of the patients (17% of the adults and 29% of the children) changed IBD subtype during a median follow-up of almost four years and in the end 31% of adult cases were classified as CD, 58% as UC and 11% as IBDU[38]. Among children there was a larger proportion of IBDU [38].

LIFELONG DISEASE

The peak age for CD occurrence is 20–30 years[19 35] which is the period of life when most people start building a career and a family. Patients with CD face a lifetime of challenges to a varying degree depending on symptoms caused by the disease. In the IBSEN-study, the 10-year long follow-up of a population-based cohort of 843 new cases of IBD from South-Eastern Norway during the years 1990-1994, at least one in three CD patients had a mild to moderate course in the long term[24]. Less than half of the population developed stricturing or penetrating complications of the disease within 10 years of diagnosis and almost two-thirds were in clinical remission after this time albeit this not being synonymous of *deep remission* which is a concept that will be explained in the section about therapeutic targets [24]. There is hope that modern therapy and surveillance will be able to modify disease course, not just postpone complications of the disease, but this remains to be proven.

EXTRA-INTESTINAL MANIFESTATIONS (EIM)

Both CD and UC are associated with chronic inflammatory conditions that affect other organ systems than the GI-tract. These other inflammatory conditions encompass iritis, uveitis, primary sclerosing cholangitis, arthritis/ arthralgia, ankylosing spondylitis, erythema nodosum, pyoderma gangrenosum and Sweets syndrome. They are all collectively viewed as EIMs. Their disease courses run independently of the course of the intestinal disease[39]. In a study of IBD prevalence in Sweden 2010, more than 18 000 patients with CD were identified and in this population 26% had a diagnosis of EIM registered[40] which is remarkably high compared to the population-based study from Manitoba where only 5.5% of the patients with CD had a diagnosis of EIM registered[39]. In accordance with Swedish data is the report from Taiwan in 2016 where 26% of the CD-patients had a diagnosis of an EIM after 14 years of follow-up with a constant predominance of peripheral arthitis[41]. The most common manifestations among the Swedish CD-patients were rheumatic (11%) and hepatobiliary (9%)[40] whereas the most extra-intestinal complications in the Manitoba population were iritis and uveitis. In another Swedish nationwide cohort study of patients with IBD; primary sclerosing cholangitis was more common in pediatric patients (5%) than in adults (2%) and elderly (1%) 5 years after diagnosis[35]. In a joint study of national cohorts of patients with CD in Sweden 1969-2017 and in Denmark 1977-2011, incidence of PSC was 1,86%[42].

INCREASED RISK OF CANCER

A higher risk of colorectal cancer (CRC) for patients with CD has long been well-known, but the studies have had methodological weaknesses and do not reflect risk in the biological era. In a recent national Danish-Swedish study of more than 47 000 patients with CD, the data showed an overall adjusted HR of 1,74 for CRC and an increased risk of CRC mortality with a HR of 1,42 [42]. The increased mortality was observed although tumour stage did not differ between the patients with CD and the reference population (p=0,27). The strata with increased risk of CRC were patients with disease onset at a younger age than 40, concomitant PSC and colonic disease[42]. A study of more than 6800 patients with IBD seen at two tertiary hospitals in Massachusetts has, however, shown that recent colonoscopy (within 36 months) is associated with a reduced incidence of CRC in patients with IBD and lower mortality rates in those diagnosed with CRC. This can indicate that modern management with tight control and regular endoscopies of individuals at risk may decrease the risk of CRC and CRC mortality [43].

Patients with CD have an increased risk of other malignancies. These include small bowel adenocarcinoma, with a factor of 18, but this is still a rare disease[44]. They also have an increased risk of lymphoma, with twice as high incidence as the reference population, even in immunosuppression-naïve CD patients[44]. HR of squamous-cell carcinoma / basal-cell carcinoma is 1,48 which partly can be caused by medication with IMM making the patient sun-sensitive[44]. In addition to this, the risk of upper-GI cancer, bladder cancer and lung cancer is also increased with standardized incidence ratios ranging between 2.03-2.87[44] . Part of the explanation of the increased risk for the two last cancer diseases is probably the strong association with smoking which in turn increases the risk of developing CD[45].

Summary: CD is a chronic remitting, relapsing pan-enteric disease with a very variable course that sometimes is combined with extra-intestinal manifestations and an increased risk of malignancy. It often strikes at a young age and can periodically[46] have a significant effect on health-related quality of life.

EPIDEMIOLOGY

INCIDENCE

The epidemiology of IBD emerged in the 1950s. The first population-based studies were published in the 1970s[47 48]. The report on residents with CD in Stockholm county 1955-1974 was the first true population-based study of the natural history of the disease[49]. The incidence increased during the following decades particularly in the Western hemisphere, including Australia and New Zealand[50]. The incidence among adults in the Western world has then plateaued during the last decades but has continued to rise among children[33 51 52]. In 2012 the incidence of IBD in the Western world was reported to be ranging from 10 to 30 per 100,000 with a prevalence of 0.5% in the general population[50 40]. The incidence of IBD is characterized by a north–south gradient in Europe with a higher incidence in the northern countries and an east-west gradient with a higher incidence in the Western world compared to Asia[53].

IBD is now a global disease with a two- to threefold increase of incidence in several countries in Asia[54 55] as well as in other newly industrialized countries[50 56 57]. Differences in incidence/ prevalence can partly be explained by differences in environmental exposures, consequences of these exposures and differences in distribution of susceptibility genes. The detection of IBD is also increasing as advances in technology such as colonoscopy, improved access to health care and disease surveillance are implemented[58]. In a newly industrialized country sigmoidoscopy is usually introduced as the economy grows and access to health care improves and cases of UC is diagnosed (UC almost always involves rectum and distal colon). As access to colonoscopy increases, milder cases of CD that do not require surgery are detected. The effect is that after an initial emergence of UC follows rising incidence of CD[58].

PREVALENCE

IBD is most commonly diagnosed in adolescence or in young adults[59]. In IBD, positive influences on prevalence will outweigh negative influences as mortality is low. In a Swedish study the prevalence of IBD was estimated to be 0,65% and the prevalence of CD 0.19% in 2010[40]. The prevalence of IBD formerly increased over two to three generations in high-income countries, but in only one generation (the past 25 years) in much of the newly industrialized world[60]. There was almost a 16-fold increase in patients with CD during the first 10 years of the millennium in China and cases of UC in Hongkong tripled during the same period[61].

COMPOUNDING PREVALENCE

The rising incidence leads to the epidemiological phenomenon compounding prevalence. Newly diagnosed patients with IBD will every year expand the number of prevalent cases leading to an exponential increase in the number of patients with IBD. The number of patients with IBD in newly industrialized countries might approximate that in the Western world in 2025 owing to rising prevalence and rapidly growing populations. Compounding prevalence will also result in an exponential increase in the number of patients with IBD living in the Western world over the next decade[58]. In addition to this increase, the increase in expected life span in the Western world will lead to an ageing IBD population with complex comorbidities and some of them living many years with immune suppression from immunomodulators and biologic agents.

AETIOLOGY

A DYSFUNCTIONAL INTESTINAL MUCOSA

The complex microbiome in our bowels contains as many “bugs” as there are cells in our bodies and our mucosal barrier must be protected from invasion[62]. Barrier dysfunction is the common denominator of all IBD sub types, and one pathophysiologic mechanism is believed to be a defective crosstalk between immunity and the mucosal barrier[62] – or, in other words, the two important components in the immunopathogenesis of CD is an increase in gut permeability accompanied by an abnormal immune response to luminal antigens[2].

THE MUCUS BARRIER

The first barrier between microbiota and the bowel wall is the mucous layer produced by goblet cells. The mucous layer is composed by an inner sterile layer and an outer more permeable layer populated by commensal microbes[2]. The microbes and the mucus have a reciprocal relationship. It has been shown in animal studies that different microbes have different effects on properties of the colon mucus barrier including penetrability[63]. Altered gut microbiota leads to altered production of microbial metabolites which can damage the mucus layer by increased degradation. In experiments with Muc2 knockout mice (mucin MUC2 is of importance for the colonic mucus layer) vs heterozygous mice vs wild-type mice, the knockout mice developed a histologically more serious colitis when challenged with dextran sulphate sodium, a colitis-inducing agent[64].

THE CHEMICAL AND PHYSICAL BARRIER

The mucosal barrier consists of a layer of epithelial cells which are connected by tight junctions. The intestinal epithelium separates the luminal content from the mucosal immune system and works as an important defensive line to protect the homeostasis of the gut microbiota and minimize intestinal inflammatory responses. The cells in the mucosal barrier secrete antimicrobial peptides (AMPs) and mucus who serve as an extra-cellular protection[62]. The function of the mucus is both bacterial killing, through the AMPs forming a chemical barrier, and to serve as a physical barrier. The AMPs are secreted by all epithelial cells as well as inflammatory cells such as granulocytes when exposed to microbes[62]. The Paneth cells are in the base of the intestinal crypts and reside predominantly in the small intestine with a dual function of secretion of trophic factors supporting the stem cell niche of columnar cells and production of the key antimicrobial peptides called alpha-defensins, keeping the crypts sterile, and controlling the local microbiome[3]. Adherent-invasive *E*. coli associated with CD are resistant to these defensins[65]. A possible contributing factor to the disease could also be Paneth cell dysfunction with a relative defensin deficiency, leading to defective antibacterial activity[66]. The Paneth cells also seem to be an important source of tumour necrosis factor (TNF)[67], a major inflammatory cytokine and a therapeutic target when treating CD. One of the successes of genetic linkage mapping of CD was the identification of CARD15 gene which codes for the pathogen recognition receptor NOD2[68]. NOD-2 genotype affects ileum-associated microbiota[69]. Paneth cells are the most prominent cells expressing NOD2 in normal and CD-affected intestinal tissue[70]. Apart from polymorphisms in NOD-2 genotype having an influence, it has also been shown that environmental factors known to increase risk of CD, such as smoking[71] and antibiotics[72], have an impact om Paneth cell function.

CYTOKINES AND IMMUNE CELLS

Inflammatory innate and adaptive immune cells are produced in the bone marrow. Circulating monocytes transform into antigen-presenting macrophages in the gut and these cells together with granulocytes and antigen-presenting dendritic cells in the gut-associated lymphoid tissue are activated providing non-specific immunity as soon as invading bacteria are present[73]. Then follows an antigen-specific activation of the same cells which results in antigen-directed responses from T and B cells[73]. T cells and monocytes/macrophages that are activated may exit the bloodstream and traffic to the mucosal tissue to evoke inflammation. Faecal calprotectin is an established biomarker reflecting migration of activated neutrophils and monocytes to the bowel and it correlates with the inflammatory activity in IBD.

Cytokines are a family of proteins and polypeptides secreted by many different cells types that can have a pro-inflammatory or anti-inflammatory function and are required for, among other things, immune function, cell growth and tissue repair. CD is associated with elevated pro-inflammatory cytokines and a disturbed balance between pro- and anti-inflammatory cytokines[74]. The cytokines exert many of their effects through their actions on a group of immune cells known as helper or CD4+ T lymphocytes[74]. CD is associated with a T-cell mediated response and tissue destruction, and the hallmark of pathogenesis is transmural inflammation, which is facilitated by increased pro-inflammatory cytokines such as for example the early and potent cytokine TNF[75]. In Crohn's disease mucosal T cells are resistant to apoptosis, which normally is a way to avoid the risk of antigen-activated T cells causing a prolonged and potentially damaging immune response[76], and mucosal T cells cycle faster and expand more compared with normal control mucosal T cells indicating a state of hyperreactivity compatible with loss of tolerance[77]. Mucosal injury and damage are associated with dysbiosis, which can perpetuate the inflammatory cascade with luminal microflora stimulating a proinflammatory immune response[75].

Summary: Whether the first event is a primary host defect with a damaged barrier, or a primary bacterial penetration is unclear. It is also unclear if it is a primary defective reaction of the immune system to the microbiome or if this comes after breakdown of the epithelial barrier[62 78]. The pathophysiology of CD is complex and far from completely elucidated. It is assumed to be the effect of an interplay between genetic, environmental, and intestinal microbial factors which interact together with the immune system, resulting in pathological auto-inflammatory response directed towards the intestine[79].

EVIDENCE FOR ROLE OF THE MICROBIOME

FIRST CONCEPT OF FAECAL STREAM AS A PATHOGENIC FACTOR

Description on how to perform of diversion of the faecal stream in cases of "regional ileitis" were published as early as in 1939 and in the following discussion a representative from the Mayo Clinic clinic already then described a two-stage procedure with a temporary stoma[80]. Van Patter et al suggested in 1954 that the causative agent of CD could be found in the faecal stream[81]. The concept of this as an important factor in the pathogenesis of CD did however not gain wide acceptance before Rutgeerts et al in a study 1991 could show that surgical diversion induced remission in diseased segments *distal* to the diversion[82]. The importance of the faecal stream was also shown in a study in 1992 where it was reported that recurrent ileal disease after ileocolonic resection with side-to-end anastomosis involved the ileum adjacent to the colon, but spared ileum in the blind pouch[83].

DEVELOPMENT OF THE MICROBIOME

The microbiome develops and stabilises over time from immediately after birth and at least until the preadolescent phase with inter-individual variations according to diet and intestinal transit time[84]. The microbiome is shaped by environmental exposures[85]. Gut microbial colonization is important for the maturation of the immune system with the goal of establishing a symbiotic relationship of tolerance and protective immunity[86]. Immune regulatory pathways are stimulated by both pathogens, parasites and commensals[87].

DYSBIOSIS

Most of intestinal bacteria belong to 4 phyla: *Firmicutes; Bacteroidetes; Proteobacteria*; and *Actinobacteria*. In healthy adults the two first phyla predominate[88]. Breast-feeding has been shown to lead to an increased abundance of *Firmicutes* and *Actinobacteria* compared with formula-fed infants[89] and breast-feeding is protective against the development of IBD[90]. The microbiome in patients with IBD differs from healthy patients with a *decrease in diversity, less stability, and a reduced number of anti-inflammatory taxa*[91 92 93]. There is evidence in animal studies that an episode of infectious gastroenteritis can trigger an abnormal immune response in mice with *a baseline susceptible gut microbiota profile*, i.e., mice colonised with an adherent-invasive *E*. coli isolated from a patient with CD *before* the infection[94]. About 30% of CD-patients harbor adherent-invasive, pro-inflammatory *E*. coli in their mucosa and this is contrasted by decreased abundance of the protective commensal group *Clostridiales* including, *Faecalibacterium* prausnitzii[62]. This can be interpreted as showing the impact of ecology at the mucosal site with a healthy balance between aggressive and more defensive species. Patients with CD have a predisposition for developing antibodies towards microbial antigens, of which none have been shown to have a pathogenic potential, but the more numerous they are and the higher the titre is, the more severe is the clinical disease activity[95].The proportion of increased and decreased taxa correlates with disease activity and when therapy induces response, the microbiome changes into a less dysbiotic state[62].

There is, however, a large degree of inter-individual variation in microbiota composition normally encountered in different people. The reduced diversity is not as a general phenomenon specific for IBD; the microbial metabolic shift of diabetes type II is similar to IBD[62]. In a study on microbiota differences in two long-term Swiss IBD cohorts, it was shown that the differences attributable to CD or UC, or to the different lifestyle or therapeutic factors, were *far less* than those engendered by age or body habitus[84].

Whether the dysbiosis associated with CD is a primary causative phenomenon or a result of inflammation and / or treatment is unclear[92]. The microbiota is influenced at least in part by the host's genotype[96] and there is clinical and experimental evidence showing that infections, antibiotics, drugs and diet can induce dysbiosis[97]. Inflammation can in itself disrupt gut microbiota and promote preferential bacterial growth[98]. CD is associated with a more altered and unstable gut microbial composition than UC[99].

METHODOLOGICAL PITFALLS

A weakness in some of these studies have been the method of analysis of microbiota in faecal samples compared to mucosal samples. The alterations described above are not always the same in these different methods of sampling[100]. Other methodological pitfalls are a lack of having recent treatment with anti- or probiotics stated as a criterion for exclusion and lack of standardization of bowel preparation before examination, as all these factors affect the composition of microbiota as well [101]. Another problem may be that the sample reveals *functional potential* but that it does not necessarily reveal actual *functional activity*.

SUPPORT FOR ROLE OF THE MICROBIOME / DYSFUNCTIONAL RESPONSE TO THE MICROBIOME IN THE PATHOGENESIS OF CD

Some of the important findings in animal studies have been:

A. genetically susceptible mice do not develop colitis in a germ-free environment [102]
B. inflammation can be induced by transfer of proinflammatory bacteria from mice, with the disease, to healthy mice[103] (but faecal transfer from humans with IBD to healthy humans does not induce colitis[62])
C. colitis can be induced by transfer of naive CD41 lymphocytes from mice without colitis, into mice that do not have T and B lymphocytes [104]
D. differences in composition of gut microbiota in healthy mice decide degree of susceptibility to colitis that can be induced by transfer of naive CD41 lymphocytes[105]
E. intestinal microbiota from donors with IBD exacerbates colitis in mice by changing immune responses[106]

Of note are observations from several studies with genetic mouse models of intestinal inflammation that mice *do not develop disease after germ-free rederivation*[102 107] (mice that are rederived have either *no pathogens* and are referred to as germ-free, or they have a *specific, defined flora*). Further, *T cell lines specific for bacterial antigens*, but not when non-specifically activated, can *induce intestinal inflammation*[108 109].

Support for the role of microbiome in human studies[91 62]:

A. disease activity is most prominent in areas where there are large bacterial populations or where there is relative stasis of faecal material (colon, terminal ileum, and rectum)
B. surgical diversion leads to remission in the mucosa of distal bowel and recurrence when continuity is restored[82]
C. antibiotic therapy can sometimes induce remission[110]
D. antibiotics given in early life increases the risk of IBD[111]
E. specific microbes have an impact on degree of inflammation, response to therapy and risk of recurrence[84 112 113]
F. genetic markers (for example NOD2 and ATG16L1) associated with IBD are related to engagement of the immune system with the microbiota[114]
G. luminal / mucosal microbiota is abnormal in IBD[93]
H. reduced anti-bacterial activity in the intestinal mucosa in CD-colitis [115].
I. the cellular and humoral immunity in CD-patients is directed against bacterial, not cellular antigens[62]

EVIDENCE FOR GENETIC BACKGROUND

FAMILIAL CLUSTERING AND TWIN STUDIES

The first report of familial clustering of IBD in 1909[4] was regarded as a coincidence but the concept of heritability gradually gained acceptance. Studies of twins have been an important instrument to show the relative weight of inherited and environmental factors in CD. In a Swedish study of 126 twins, pair concordance in monozygotic twins was 19% for UC and 50% for CD[116]. This is in line with earlier studies from England[117] and Denmark[118]. The concordance for homozygous twins of 50%, but not higher, highlights the important role of the environment in pathogenesis of CD[119]. The ratio of risk of siblings of IBD-patients to develop IBD to the reported population prevalence of IBD, *the genetic risk ratio for IBD,* is in the range of 15-42 for CD and 7-17 for UC - showing a stronger genetic influence for CD than UC[119]. There is also a high degree of concordance regarding age at diagnosis, disease location at diagnosis and disease behaviour within families[116 120] and high concordance rates concerning EIMs in CD[120]. Specific serotypes or genotypes are more frequently found in early-onset CD[121 122].

Several studies have reported results supporting a disturbed interaction between microbiota and mucosal immune response in healthy first-degree relatives to patients with IBD[123 124]. In a study exploring if subclinical mucosal inflammation exists in healthy twin siblings of patients with IBD, *increased neutrophil activity* (traced by immunohistochemistry showing markers of inflammation/neutrophil activity) was observed in *both monozygotic and dizygotic discordant pairs with IBD*[124]. Twin pairs can either be concordant, i.e., both twins in each pair suffer from the disease, or discordant, i.e., only one of the twins in each pair is affected. 73% of healthy siblings in discordant pairs with CD had an increased level of nuclear factor kappa B and 67% had an increased level of myeloperoxidase[124]. This at the same time as 94% of the twin siblings in discordant pairs with CD were histologically normal[124]. The influence of shared environment during childhood and adolescence is equal in monozygotic and dizygotic twin pairs in contrast to the influence of genetics that is more pronounced in monozygotic pairs. These results *point toward the importance of environmental factors in addition to genetic factors.*

GENOME-WIDE ASSOCIATIONS STUDIES (GWAS)

The initial studies of the genetic determinants of CD were performed using linkage mapping. When genes are close together on the same chromosome they are *linked*. The alleles, gene versions, already together on one chromosome will be inherited as a unit more frequently. There are limitations to linkage analysis such as requiring access to a large set of affected siblings and there are difficulties encountered in trying to identify genes of weak effect and the studies often produced weak or inconsistent signals[125]. The development of genome-wide association studies (GWAS), a search strategy involving the analysis of several hundred thousand markers distributed across the whole genome, led to the discovery of many CD susceptibility single nucleotide polymorphisms (SNPs)[79]. SNPs are the most common type of genetic variation among people and represent a difference in a single DNA building block, a nucleotide. The novel genotyping and sequencing technologies have led to the discovery of 242 common susceptibility loci associated with CD[126]. The CD-associated SNPs are supposed to mark a region of the human genome that may influence the risk of developing the disease. Many of the GWAS hits are, however, only *proxies* for the true causal variant(s) at each locus with which they are inherited[126]. So far the vast majority of GWAS studies in IBD have been performed in Caucasian populations but a recent trans-ethnic GWAS incorporating 86 640 individuals highlighted a shared genetic risk across European and non-European cohorts for most IBD risk loci, although genetic heterogeneity was observed[79]. The identification of disease-associated variants have so far exceeded our ability to characterize their functional effects why we still have a very limited knowledge of the biological consequences[79].

Most of these loci increase the risk of both CD and UC, and many of them also alter susceptibility to other immune-mediated diseases[126 127]. Most of the identified loci individually confer very modest risk odds-ratios, mostly between 1.11 and 1.29[128].

GENETIC VARIANTS ASSOCIATED WITH CROHN´S DISEASE

Several of the genetic mutations associated with IBD are related to interactions between the immune system and the microbiome (the community of microbes within the human gut) leading to the defective microbial processing associated with IBD[91]. Some of the risk alleles are associated with bacterial sensing at the mucosal level. One of the successes of linkage mapping was the identification of CARD15 gene which codes for the pathogen recognition receptor NOD2[68]. It encodes an intracellular pattern recognition receptor that interacts with peptidoglycan of gram-positive and gram-negative bacteria and is involved with regulation of both pathogenic and commensal bacteria. Mutations in NOD2 lead to decreased levels of anti-inflammatory cytokines, such as IL-10, and an increase in mucosal bacteria[91] and affects particularly the ileal microbiota[69]. Then followed the identification through GWAS of an association of CD with variants in ATG16L1 and IRGM, two genes involved in autophagy and thus the inflammatory response to microbes[2]. NOD2 also interacts with ATG16L1 during autophagosome formation[79]. Autophagy gene products regulate a vast number of immune activities[2]. Increased intestinal permeability has been reported in IBD, which is associated with abnormal expression of tight junction proteins. Autophagy regulates intestinal barrier function *via* inducing lysosomal degradation of the tight junction protein thus increasing epithelial permeability[129]. Reduced ATG16L1 expression has also been shown to be associated with Paneth cell dysfunction. Both mutation in NOD2 and ATG16L1 interferes with bacterial clearance and antigen presentation. NOD 2 is associated with ileal disease and thereby risk of surgery as ileal disease is more often treated with surgery compared to other disease locations[79]. Other associated genetic variants are for example in IL-23R and IL-12B who are important in T-cell differentiation and modulators of inflammatory response[78].

GENETIC HETEROGENEITY

However, as mentioned earlier, IBD risk loci vary between different populations. Differences in presence of susceptibility genes to CD and phenotypic features of CD between Asian and Western populations have been reported[130 131]. Interleukin-23 receptor and autophagy-related 16-like 1 (ATG16L1) genes have been shown to be associated with CD in the Caucasian population[54] but NOD2 and autophagy variants are not associated with CD in Asian populations[54 79]. This shows that *different genetic factors predispose to IBD through different inflammatory pathways*[2]. But despite *genotypic differences* among various populations, the *clinicopathologic phenotype* is similar, as is the overall response to therapies[132].

Genetic risk does not explain the fluctuations in temporal trend analyses of incidence over the past century. It does not seem unreasonable to ascribe an important part of the increasing incidence to environmental factors. Migrant studies have demonstrated that immigrants, and particularly the 2nd generation from regions with low prevalence of IBD, acquire a similar risk of IBD as the local population[97]. The risk of developing an IBD is highest among children that migrate before the age of 15 years[133]. Part of the explanation for this acquired susceptibility can be early environmental exposures affecting intestinal microbial colonization which is important for the maturation of the immune system[86]. An example of this is childhood asthma. Epidemiological data has shown that childhood asthma is inversely associated with Helicobacter pylori colonization[134]. This has been interpreted as indicating that loss of microbes commonly found in humans impairs immune education and predisposes to immune-mediated diseases[2].

EVIDENCE FOR ROLE OF ENVIRONMENTAL BACKGROUND

EFFECTS OF URBANIZATION

An environmental contribution to disease risk is implied by the fact that incidence and prevalence of IBD are increasing with time and in different regions where industrialization is increasing and occurs more commonly in urban versus rural regions[50 135]. Moving to urban regions have resulted in an evolution of lifestyle behaviours such as a more sedentary life and obesity, increase in smoking, exposures such as pollution, changes in diet and less breastfeeding [58]. Human breast milk is microbially diverse. Studies have shown that breast-feeding is protective against the development of IBD, especially with a period of breast-feeding longer than 12 months[90]. Many of the environmental risk factors that have been identified for IBD have an influence on the microbiome which differs from the microbiome in healthy patients both quantitatively and qualitatively[91].

EFFECT OF DIET

Diet is believed to be important in microbiome composition. Drastic dietary changes can alter the intestinal microbiome in as quickly as 24 hours[136]. The increase of IBD in countries that are industrialized may be in part caused by people adopting a “Western diet” with a high intake of protein and animal fat and less plant-based foods and fiber. A systematic review of studies evaluating association between diet and risk of IBD, encompassing 2600 individuals with IBD and 4000 controls, has shown that high dietary intakes of total fats, polyunsaturated fatty acids, omega-6 fatty acids, and meat are associated with an increased risk of CD and UC[137]. High fiber and fruit intakes were associated with a decreased risk of CD, and high vegetable intake was associated with a decreased risk of UC[137]. A decrease in the abundance of the member of the *Firmicutes* phylum called *Faecalibacterium* prausnitzii, a taxa with anti-inflammatory effects by producing an anti-inflammatory protein, has been associated with CD[138]. Animal-based diets have been shown to result in a decrease in the *Firmicutes* phylum[139].

Except for enteral nutrition, there is limited data regarding the impact of diet on disease course. Only extreme elimination diets have shown significant effects on gut microbiota composition and disease course. Exclusive enteral nutrition is as effective as corticosteroids for children with CD[140] but the effect only persists as long as the treatment continues and there is no evidence for this treatment strategy when treating adults[141].

Despite these findings, epidemiological investigations of dietary factors have been disappointing, mostly because data is retrospective. Some of the problems are the effect of confounding factors such as differential recall between cases and controls, the time-varying nature of diet with difficulty in remembering diet through childhood and adult life and influence of pre-diagnosis symptoms on diet resulting in false associations.

HYGIENE HYPOTHESIS

The hygiene hypothesis claims that for developing a healthy adaptive immune response, humans need to be exposed to a range of microbes during childhood. The hypothesis was based on the fact that the decrease in overall infection frequency was negatively correlated with a considerable rise in the frequency of allergic and autoimmune diseases observed in industrialized countries over the past decades[87]. The urbanization of societies seems to parallel the temporal and geographic incidence of IBD. Smaller family size, less crowded living conditions, increased sanitation, refrigeration of food, reduced consumption of fermented food products and delayed exposure to mucosal infections could all have effects on development of the microbiome. Less exposure to microbes may lead to infections later in life triggering an abnormal host immune response. It has also been shown in experimental models that the occurrence of autoimmune disease is prevented by infection with defined pathogens[142 143].

In a study from England in 1994 it was shown that CD was more common in subjects whose first houses had a hot-water tap with an odds ratio of 5.0[144]. Lipopolysaccharide levels, an ever-present bacterial product with potent immunoregulatory actions, are lower in dust samples from houses where children with IBD live than from the houses of healthy controls[145]. Furthermore, epidemiological studies in the Western world have shown an increased incidence of IBD associated with use of antibiotics[111 146 147]. Antibiotics can change the human gut microbiota by decreasing taxonomic richness and diversity. In a study of more than 500 000 Danish children the relative risk of developing CD was 3,41 after treatment with antibiotics which may indicate that this risk is of extra importance in early life[111]. In a Spanish study using the General Practice Research Database, 43 000 adult patients with an episode of acute infectious gastroenteritis, and from the same source, a matched control group of 50 000 patients without gastroenteritis, were identified and followed for 3,5 years. In this study exposure to infectious gastroenteritis among adults resulted in a HR of 2,4 to developing IBD in the first year after the infection and a HR of 6,6 of developing CD during the same period without any specific findings of mechanism of action[148]. Possible explanations could be treatment of the infections with antibiotics, or that patients who later developed IBD might have had this susceptibility from the beginning and the infectious process trigged a pathological autoinflammatory response. Results of the ACCES-study contradict to some degree both the hygiene hypothesis and the suspected link between antibiotics and risk of IBD. This case-control study across nine countries/regions in Asia-Pacific region, with 442 incident cases of IBD and 940 controls included, showed that flush toilets and antibiotics in childhood were negatively associated with UC and former use of antibiotics was negatively associated with CD (adjusted OR 0,19(Cl 0,07-0,52))[149].

EFFECT OF SMOKING

Exposure to tobacco smoking constitutes the best evidence-based environmental factor associated with the development of CD[150 151]. Cigarette smoking has a complex interaction with the bowel with protective effect against UC but negatively affecting the course of CD[152]. The occurrence of UC among *former* smokers was first reported in a thesis from Uppsala 1976[153]. The strong association between CD and smoking was shown as early as 1984 in a British study[45]. Smoking has been shown to be associated with a worse prognosis with an increased risk of recurrent disease and abdominal surgery[154-156].

Smoking cannot, however, be the only environmental influence. In a recent WHO-report it was estimated that the South-East Asia region had total tobacco use rates of around 47% in 2000[157], the highest average rate for any WHO region, and still a comparatively low rate of CD[135]. The incidence of CD is high in some populations with a much smaller proportion of smokers such as Canada, 27% smokers, and Sweden, 12% smokers in 2012[158 50 97]. The risk of CD associated with smoking is modified by genetics and ethnicity with studies showing no, or at least less, influence on risk of disease in Asian and Jewish populations[159 160].

VITAMIN D

Another potential environmental risk factor is low level of vitamin D which is an important regulator of mucosal immunity. Vitamin D deficiency in IBD is well recognised but is generally assumed to be consequence of the disease, not a cause. Availability of vitamin D depends on ingestion and on sunlight. Low sunlight exposure could therefore be part of an explanation of the higher incidence of CD in Northern Europe and Canada[161 162].

SUMMARY OF RISK-INCREASING AND RISK-DECREASING FACTORS

In a recent umbrella review of meta-analyses of *environmental risk factors* for IBD the following nine were identified: smoking (CD – odds ratio 1,76), urban living (CD and IBD), appendectomy (CD), tonsillectomy (CD), antibiotic exposure (IBD – odds ratio for CD 1,74), oral contraceptive use (IBD - oestrogen has anti-inflammatory and immune mediator properties), consumption of soft drinks (UC), vitamin deficiency (IBD), and non–Helicobacter pylori–like enterohepatic Helicobacter species (IBD)[159]. Concerning appendectomies, the association may be biased by unnecessary appendectomies performed in patients with incipient CD and when it comes to tonsillectomies antibiotic exposure may be a confounder.

Seven *risk-decreasing factors* were also identified: physical activity (CD), breastfeeding (IBD), bed sharing (CD), tea consumption (UC), high levels of folate (IBD), high levels of vitamin D (CD), and H pylori infection (CD, UC, and IBD)[159]. Evidence for association does not equal causality. Studies on tea consumption have only been done on Asian populations and has the weakness of recall bias. However, the effect of physical activity has a biological plausibility as experimental studies in animals have shown that physical activity can rescue defective autophagy and reduce proinflammatory cytokines[159].

MEDICAL TREATMENT OF CD

INTRODUCTION

When regional ileitis first was described in 1932 the only effective treatment available was intestinal resection. The medical alternatives during the first decades were digestive rest, specific diets and use of sedatives and antispasmodics. Treatment with steroids was introduced during the 1950s; immunosuppressants / immunomodulatory drugs during the early/mid 1980s with widespread use being implemented in the 1990s; and since 1998 continuing development and introduction of biologicals for adults. Since 2006 biologicals have also been accepted in pediatrics although it was used earlier than this in severe cases.

STEROIDS

Steroids induce synthesis of anti-inflammatory proteins and have an indirect suppressing effect on the synthesis of inflammatory proteins such as IFN-γ and TNF-α [163]. They are used to induce remission but cannot maintain remission as they cannot achieve mucosal healing and thereby are inefficient in affecting long term outcome[164]. An early start of corticosteroid-sparing therapy is important as side-effects can develop even after short-term and low-dose use such as bone loss, metabolic complications (glucose intolerance), glaucoma and serious infections[11].

ENTERAL NUTRITION

Enteral nutrition (EEN) is also used as a medical treatment. Exclusive EEN is based on the administration of a liquid formula as the only source of nutrition for a period of usually six to eight weeks. Exclusive enteral nutrition is as effective as steroids in inducing remission in pediatric patients with luminal CD[140], but not in adults, with the added benefit of optimizing nutrition and thereby promoting growth. Partial enteral nutrition is sometimes used as in additive in preoperative optimization of adults who have lost weight caused by disease activity. The efficacy is not correlated to the type of formula used (polymeric versus elemental)[165] or to the route of administration[101]. Exact mechanism of effect is unknown but one proposed consequence is a positive shift of altered microbiota[101]. The liquid formula with absence of dietary fiber results in reduction in the exogenous carbohydrate available for fermentation, and/or an increase in intestinal transit time, which may both independently reduce microbial mass. A frequently reported effect is a *reduction* in microbiota diversity, reversible when patients return to a normal diet[166]. The reduction in diversity and richness seem paradoxical as these reductions are what characterizes the microbiota in CD-patients from the start. It has been suggested that it could be a suppressing effect on bacterial growth and metabolic activity that constitutes the therapeutic effect rather than an effect on the microbial pattern[101]. It is also to be remembered that even though bacterial changes can be of importance when explaining the efficacy of EEN, the effect on specific bacteria has been very variable and not consistent in the different studies[101].

IMMUNOMODULATORY AGENTS

Immunomodulatory drugs (IMM) were introduced in the 1970s with widespread use implemented in the 1990s. The drugs that are used are thiopurines, such as azathioprine (AZA), 6-mercaptopurine (6-MP) and methotrexate (MTX) if the patient is intolerant to AZA. AZA and 6-MP are not effective in induction of remission but may be effective in the maintenance of remission[11] although the recent recommendations from ECCO suggest against using them as monotherapy[167]. Whether MTX can be used in combination with steroids to induce remission is debated but can be tried when other alternatives are not possible[167]. MTX must be given as injections as bioavailability is very variable [11]. All three drugs have both an immunomodulatory effect and an anti-proliferatory effect[168]. The cytotoxicity is mediated by incorporation of 6-thioguanine instead of guanine during DNA-replication in target cells leading to incomplete repair in the mismatch repair system leading to cell death instead of recovery[44]. A plateau in clinical improvement is reached within 12 to 16 weeks[169]. Adverse drug reactions are unfortunately frequent. Up to 15% of patients discontinue use in clinical trials because of dose-independent reactions such as skin rash, fever, pancreatitis and dose-dependent events such as malaise and myelotoxicity – the latter especially if the patient has a low TPMT-activity (catabolic enzyme thiopurine S- metyltransferase) which is routinely checked before initiation of therapy – and hepatotoxicity which can be both dependent and independent on dosing[170]. If the patients achieve long-time remission on IMM continued use is recommended but when the long-time remission is achieved by combination therapy with biologicals, switching to monotherapy with biologicals is preferred[167]. Use of thiopurines is associated with increased risk of some cancers such as non-melanoma skin cancer (life-long use of sun protection is recommended), HPV-related cancer of uterine cervix, acute myeloid leukemia, urinary tract cancer and lymphomas[44].

BIOLOGICALS

An important development in medical treatment of CD was the discovery of biologicals in the end of the 90s. Biological therapy refers to *monoclonal antibodies against inflammatory immune mediators.* They act as antagonists of adhesion molecules or various inflammatory cytokines. There are three main classes of biologics:

1. antibodies against tumour necrosis factor (TNF-alpha or TNF-a) given as infusions. TNF-a is a major pro-inflammatory cytokine, a key mediator, involved early in the inflammatory cascade. The TNF-a inhibitors (infliximab (IFX), adalimumab (ADA), certolizumab pegol and golimumab) are fast-acting and can induce and maintain remission[167 171] and are of particular use in perianal CD[167]. However, up to 30% of the patients are primary non-responders and up to 50% will lose clinical benefits within a year necessitating dose escalation or change of therapy[75]. There are probably several contributing factors to this such as metabolism of the drug and development of antidrug antibodies[75]. Use of concomitant immunomodulators reduces the problem with development of antibodies[75] and combination therapy with thiopurines is recommended in moderate-severe CD[167 172]. There are also problems with intolerance. About 20% develop infusion reactions within 1-2 hours such as itching, flushing and chest pain and 2% of the patients experience delayed reactions such as fever, myalgia, and arthralgia[75] and all these reactions can necessitate withdrawal of therapy.
2. anti-integrin monoclonal antibody / integrin a4b7 inhibitors (natalizumab and vedolizumab) – blocks white blood cells from migrating to the gut.
3. inhibitor of pro-inflammatory cytokines IL-12 and IL-23 (ustekinumab).

Category 2 or 3 are used if the patients fail on TNF-inhibitors (anti-TNF or aTNF)[167].

There have been several randomized controlled trials showing reduced risk of abdominal surgery for patients treated with aTNF[173-175] and real-world studies supporting the efficiency[176]. In a Swedish national cohort of 1856 patients treated with aTNF for the first time from 2006 and onwards, and who had not had surgical treatment earlier, this could however not be corroborated[177]. Rate of bowel surgery were similar between patients who discontinued use of aTNF after treatment for less than 12 months compared to patients that who did not stop. A possible explanation could be that the treatment was initiated too late, mean disease duration before start of treatment was eight years.

There have been concerns for an increased risk of serious infections as treatment with biologicals makes the patients immunocompromised. When analysing data from the CD TREAT registry (Crohn's Therapy, Resource, Evaluation and Assessment Tool Analysis – an observational registry that was designed to examine the long-term outcomes of various treatment regimens, including IFX, used in the management of CD in North America) on more than 3000 patients on aTNF therapy, multivariate analysis did not demonstrate a significant increased risk of infection. On the contrary, odds ratio for a serious infection was

0.99 (95% CI 0.64–1.53) after controlling for factors such as disease duration, severity, and concurrent use of steroids or IMM[178]. In a follow-up study on long-term data from the same registry encompassing more than 6000 patients, neither treatment with IFX or IMM were associated with increased risk of mortality[179]. Independent risk factors for serious infections were moderate to severe disease activity (HR=2,24, p<0,001), use of narcotics for analgesia (HR=1,98, p<0,001), prednisone treatment (HR=1,57,p<0,002) and treatment with IFX (HR=1,43, p<0,006), i.e. treatment with aTNF being the weakest[179].

There has also been a concern for aTNF therapy increasing the risk of malignancy as TNF is suppressed. TNF exerts necrotizing effect on tumour cells in vitro. There is however not sufficient evidence supporting an increased risk caused by aTNF agents alone and current data, on the contrary, suggest that *monotherapy* with aTNF does not cause a significantly increase overall long-term risk of cancer[44].

However, when treating patients with prior malignancy a delay of starting therapy with biologicals with at least two years after cancer cure is recommended with a delay of five years for cancers with a comparatively high risk of recurrence such as malignant melanoma, breast, or renal cancer[11]. Studies on patients with IBD or transplant recipients (both groups exposed to immunomodulatory treatment) have produced divergent data regarding risk of recurrence of cancer, but, according to ECCO-statement in 2015 regarding IBD and malignancies, IBD-patients with a history of cancer have a two-fold risk of recurrence[44].

Biosimilars have been added to the armamentarium the last years as patents on the biologicals have expired. Biosimilars are biologic medical products very similar to the biologics that have been tested and approved earlier and generate a much lower cost.

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SURGICAL TREATMENT OF CD

INDICATIONS FOR ABDOMINAL SURGERY

A good medical alternative to intestinal resection did not appear until the introduction of steroids in the 1950s. Common indications for surgery in CD are stricturing or penetrating complications of the disease or active inflammation refractory to medical treatment. In these situations, there is a well-established consensus about the importance of *preoperative optimization* and *deferred surgery* to lower the risk of complications. Less common indications for surgery are multifocal dysplasia or focal dysplasia that cannot be treated endoscopically or CD in combination with colorectal cancer.

ILEOCECAL RESECTION / SMALL BOWEL RESECTION

The most common indication for surgery is distal ileal stenosis caused by longstanding ileitis or inflammatory distal ileitis refractory to medical treatment. Consequently, the most frequently performed surgical procedure is ileocecal resection[24 180]. The method of choice is laparoscopic resection with a side-to-side stapled anastomosis. Laparoscopic surgery to allow for quicker recovery, to minimise formation of adhesions and risk of hernias, which is of extra importance for this group of patients with risk of needing repeat surgery, and to minimise cosmetically disturbing scar formation[181-185]. It is often possible to do a laparoscopic ileocolic re-resection if the patient develops a recurrence not amenable to medication or dilatation[186]. There have been several meta-analyses during the last decade of outcomes of handsewn end-to-end vs stapled side-to-side anastomoses (SSSA). Stapled small-bowel or ileocolic SSSA are associated with lower rates of overall postoperative complications, clinical recurrences, and reoperations than end-to-end anastomoses for patients with CD[187-189]. The diameter of the anastomosis likely plays a role - a wider anastomosis will have a lower rate of clinical and surgical recurrence caused by narrowing of the lumen. There is an ongoing discussion about other ways of modifying the surgical technique to reduce the risk of recurrence such as including more of the mesentery in the resection[190] and a novel type of constructing an anastomosis, the so-called Kono-S anastomosis. It is an antimesenteric, end-to-end, hand-sewn ileocolic anastomosis where longitudinal enterotomies are created on the antimesenteric sides to allow a transverse large lumen of approximately seven centimetres with the hypothesis that this type of construction, which increases the diameter of the anastomosis and theoretically better preserves the integrity of the circular muscle, will better maintain functional peristalsis and thereby reduce the risk for faecal stasis and recurrent disease[191 192].

STRICTUREPLASTY

Strictureplasty (SP) is a way to preserve bowel length both in primary strictures and when recurring disease causes stenosis of an anastomosis[193]. However, when perforating disease is present, i.e., co-existing phlegmone /abscess / fistula, the primary strictured segment should be resected[169]. The preferred method is the Heineke-Mikulicz SP for strictures less than 8 cm in length in the small bowel[188]. The risk of site-specific recurrence is 3-7%[194 195].

ENDOSCOPIC BALLOON DILATATION

Another way of preserving bowel length is endoscopic balloon dilatation for strictures which was introduced in the 80s[196]. It is primarily used for strictures that are less than five centimetres in length in the distal ileum[188]. It is often used for anastomotic strictures but can also be used for primary ileal strictures. In an analysis of more than 3000 endoscopic balloon dilatations; primary success rate was 80.8% for clinical efficacy [symptom-free at completion of follow-up) but 73.5% of the patients underwent re-dilatation within 24 months and 42.9% eventually required surgical resection[197].

SEGMENTAL / SUBTOTAL COLECTOMY

It is not a recommended to do a SP in colon as there is a risk of missing a colorectal malignancy[193 198 199]. When a single colonic segment is involved, a segmental colectomy is enough which gives a better functional outcome and reduces risk of future short bowel syndrome[200]. When multiple colon segments are involved a (sub)total colectomy is the preferred approach[188].

COLECTOMY WITH ILEOSTOMY VS TEMPORARY DEFUNCTIONING STOMA

In an acute setting with severe refractory colitis, colectomy with formation of an ileostomy is the best alternative. In a less pressing situation a better choice might be a defunctioning ileostomy to allow the patient to recuperate and to allow time to test a new medical agent[188]. A defunctioning stoma used to lead to remission before the era of biologicals but remission rate is now less predictable and the chance of restoration of bowel continuity is especially low in the presence of refractory perineal disease[188 201].

RESTORATION OF BOWEL CONTINUITY

Restoration with an ileorectal anastomosis after colectomy can be tried in the absence of refractory proctitis or severe perianal disease. If the patient is suffering from persisting rectal disease but *without any signs of disease in the small bowel or in the perianal region (anal ulcers, anal stenosis, perianal fistulas) over a longer period*, restoration with ileal pouch anal anastomosis is an alternative for a few select patients[188]. For patients with *isolated colonic CD* the rate of failure is not higher than for patients with UC but function is worse with twice as high rate of urgency and incontinence[202].

PROCTOCOLECTOMY

Proctocolectomy is the method of choice for patients with CD and multifocal high-grade dysplasia or colorectal cancer[193,203]. If the patient is considered high risk for surgery segmental resection or colectomy with ileorectal anastomosis can be considered but this demands a close endoscopic surveillance for years to come[193].

PROCTECTOMY

Proctectomy in patients with CD is not common. The preferred approach, to symptomatic rectal and/ or perineal disease refractory to medical treatment, is defunctioning with a stoma. Indications for proctectomy are severe symptoms *despite* defunctioning or if endoscopic surveillance of rectum is impossible because of stenosis. The procedure can be technically demanding for the surgeon and very trying for the patient as delayed healing and development of a chronic perineal sinus is not uncommon. This is more common in young patients if there is extensive anorectal disease and if extra-sphincteric dissection is needed[204]. In a series of 136 patients with CD undergoing proctectomy 1995-2012, 63% healed within 12 weeks but delayed healing occurred in 26% and in 21% there was non-healing[205]. In the presence of fistulizing disease the procedure and healing can be optimised by first performing defunctioning with a stoma plus pre-treatment with biologicals continuing into the postoperative period[205].

TEMPORARY STOMA

Formation of temporary stoma can be used as a risk-minimizing procedure when operating on patients who are immunocompromised by medication such as steroids or by preoperative weight loss, and in patients with risk factors for intra-abdominal septic complications such as abscesses and fistulas[206,207,208,209]. There is ample evidence for the benefit of a temporary stoma in lowering the risk of intra-abdominal complications in patients with a high risk for anastomotic insufficiency[188,210,211,212]. Avoiding risks associated with an anastomosis is however a choice associated with stoma-specific complications such as prolapse, hernia (incidence of 3-10%[188]) and most serious of all; renal insufficiency caused by high-output (incidence of 5-9%)[188,213,214].

A temporary stoma is also used when trying to avoid a resection altogether. Defunctioning can be a method of “buying time” while waiting for a new medical regimen to have effect or when aiming at a more limited resection. The data in support of using a temporary stoma to avoid resection is, however, less persuasive. Before the biologic era temporary stoma led to initial remission rates of up to 90%[188,215]. In more recent reports success rate is lower in the range of 50–80%, especially for patients with complex perianal disease, and the chance of *enduring remission* after stoma reversal is low as these patients often have already tried optimizing medication[188,213].

Whether temporary stomas can have an effect long-term *surgical recurrence* after resection is not known. The frequently performed ileocecal resections have been reported to have a risk of surgical recurrence of 19-35% at 10 years when the bowel is in continuity[216 217]. A possible way of improving the course of the disease could be manipulation of the microbiota. In a small study in the 90s it was shown that postoperative therapy with metronidazole had a modest effect on the severity of recurrence in neoterminal ileum after resection[218]. We know from other trials with antibiotic therapy in CD that it can have an effect especially on penetrating complications of the disease (B3) but that there is a risk of serious side effects, especially with prolonged courses[11]. It has also been shown that gut microbiome function may predict responses to IBD therapy as it has been shown in a trial of treatment with integrin inhibitor that, if taxonomically, there was relative abundance of R. inulinivorans and Burkholderiales at baseline, this was predictive of remission at week 14 after start of treatment[112].

Diversion at least temporarily achieve a change in microbiota and whether this has a long-term effect and changes time to surgical recurrence has not been studied, thus giving us reason to perform study II.

PERMANENT STOMA

Disease-related worries are an important part of perception of quality of life when living with a chronic disease such as CD. When measuring this in a Swedish and in a Norwegian study, generally considered to be a part of the world where stomas are more easily accepted, worrying about getting a stoma was a top concern for patients both when having active disease and when being in remission[219 220]. The social impact of having a stoma can be for some patients be severe with body image concerns and sexual difficulties[221]. In previous reports the cumulative incidence of permanent stoma has been reported to be 10% overall in CD[19] and *30-50% for patients with complex perianal disease*[28 222].

Very symptomatic rectal and/ or perineal disease (anal ulcerations, anal stenosis, perianal fistulas), permanently refractory to medical treatment, is often handled by formation of a stoma. In a meta-analysis of studies of faecal diversion for the management of perianal CD in 556 patients, two-thirds reported a regress of symptoms but in the end only 17% had their bowel continuity restored with no difference between pre-biological and biological era, probably because of selection bias[223]. There have been several studies reporting on incidence of stoma formation in the biologic era but few population-based studies with a known incidence of the disease vs incidence of stomas, and even fewer with data about association between type of surgery and formation of stomas. This lack of reliable data in combination with the importance patients ascribe to risk of stoma gave us reason to perform study IV.

RATES OF ABDOMINAL SURGERY AND INFLUENCE OF BIOLOGICALS

During the last 25 years there has been a change in therapeutic strategy with the of use of IMM and biologicals and healthcare costs are now mainly driven by medication use[224]. To what extent this has changed disease course and risk of surgery has been, and is, debated, with studies showing decreasing vs unchanged rates of surgery[180 225 226]. A review and meta-analysis of studies from 1980-2016 stated that treatment with aTNF reduced surgery compared to placebo with an OR of 0.23[227]. Trials with biologics have, however, usually not been designed to specifically measure effect on surgical rates and limitations in this meta-analysis were a small number of eligible randomised controlled studies, a significant proportion of the patients were treated with biologics and concomitant therapy with IMM /

steroids and comparative efficacy was assessed primarily through indirect comparisons to placebo[227]. The results from the prospective observational UK-wide PANTS-study (personalised aTNF therapy in Crohn's disease) published in 2019, showed that aTNF treatment failure is common, mediated in part by immunogenicity (anti-drug antibodies), with non-remission at week 54 in 63% of more than 1200 assessable patients[228]. The recently reported long-term results from the LIR!C-study, comparing primary ileocecal resection vs treatment with IFX, supports resection as a valid treatment option for CD-patients with limited disease (<40 cm) in terminal ileum. 48% of the 65 patients in the IFX-group needed a resection during the follow-up of in median five years, and the remaining 52% maintained, switched, or escalated their aTNF therapy whereas *none* of the patients who had a primary resection had a surgical recurrence and 26% were started on aTNF[229].

Large-scale population-based research on incidence of abdominal surgery overall in CD, and even more so, studies concerning incidence of subcategories of abdominal surgical procedures, are scarce in the era of modern anti-inflammatory therapies and earlier studies have conflicting results. This gave us reason to perform the study in paper I.

TREATMENT TARGETS

CLINICAL RESPONSE VS DEEP REMISSION

Treatment target in studies and clinical practice in CD has historically been to induce and maintain symptomatic remission to improve health-related quality of life and to reduce incidence of abdominal surgery and with this the inherent risk of stoma and short bowel. There is, however, a poor correlation between endoscopic and symptom-based disease activity in CD leading to a risk of undertreatment if therapy only aims at reducing symptoms[31]. Undertreatment increases the risk of progressive structural damage.

During the last decades there has been an evolution in treatment targets with the introduction of disease-modifying agents, especially aTNFs. From *clinical response* to '*deep remission'*, which is defined as reaching *both symptomatic and endoscopic remission* (no ulceration at ileocolonoscopy)[230]. If endoscopic healing is achieved it has been shown that this leads to reduced need of corticosteroids, hospitalisation, and surgery[30 231]. The "treat to target" approach is a pro-active management regime involving tight control and treatment adjustments on demand aiming at achieving mucosal healing, biomarker normalization and/or radiographic improvement[232 233]. Regular assessments of patient-reported outcome and endoscopy are needed, as are measurement of CRP, faecal calprotectin and eventually cross-sectional imaging[234]. Proactive therapeutic drug monitoring appears to be associated with better long-term outcomes[235]. Mucosal healing is an accepted major target, but this goal is not without unresolved uncertainties such as what time interval between assessments is appropriate, how to deal with interobserver variability, the costs of endoscopy and the not negligible risk that is associated with the endoscopic procedure, i.e., the risk of perforation even if this fortunately is very uncommon.

THERAPEUTIC WINDOW OF OPPORTUNITY

In 2010 the concept of "a therapeutic window of opportunity" for early intervention was introduced in the discussion about therapeutics for CD. The *aim of therapy was redefined* as to stop the biological progression of the disease before onset of bowel damage[236]. Instead of traditional stepwise escalation of treatment, a "top-down-strategy" with early use of biologics eventually in in combination with immunomodulators for patients with an aggressive disease course or factors associated with a poor prognosis, has been put forward [11 237]. In the SONIC trial mucosal healing rate at week 26 was 44% for patients treated with a combination of IFX and azathioprine, vs 30% (IFX) and 16% (AZA) when using these agents as monotherapy[172]. Some of the clinical features raising concern for poor prognosis and need of top-down strategy are young age at diagnosis, need for steroids to control index flare, perianal fistulas and complex disease with stenosis and fistula at presentation[238]. However, the predictive power of these clinical features is limited and penetrating disease as a risk factor has been questioned[239].

RISK OF OVERTREATMENT

10-30% of patients with CD have a benign disease course and risk over-treatment which raises concerns for long term effects of the medication [24 240]. As an example, albeit rare, hepatosplenic T-cell lymphomas can be mentioned. They occur almost only in young males under the age of 35 treated with thiopurines in combination with aTNF and it has been shown that the risk for developing this disease can be reduced by limiting combination therapy to a period shorter than two years[44].

Medical therapy for IBD is rapidly evolving and to what extent this has modified disease course is debated[241]. Even though several studies have reported a reduced need of surgery there is a concern that some patients are subjected to a stepwise increase in medication with side-effects and that delaying surgery through sequential attempts of conservative therapy might be harmful when the disease is refractory to medication. This can lead worsening of the patient´s clinical status, development of complications resulting in more demanding surgery and consequently, a higher rate of formation of stomas[242].

Apart from medication improving quality of life for some patients with CD in terms of less problems with loose stools, abdominal pain, fatigue, perianal disease, and reduced risk of hospitalization - ***a reduced risk of repeat surgery and reduced risk of getting a stoma*** *would show an important* ***disease-modifying effect*** *of modern therapeutic strategy*

DIRECT AND INDIRECT COSTS OF IBD/ CD

DIRECT COSTS

Direct health costs of CD are generated by medical treatment and hospitalisation with or without surgical procedures. The proportions have changed with the development of new therapeutics. Direct health care costs were in a study from the Netherlands 2014 mainly driven by the biologicals accounting for 64%, hospitalisation for 19% and surgery for 1% of the direct total cost [224]. Health care cost for CD was three times higher than for UC[224]. There is a chance that biosimilars will drive down the costs and in a Canadian study published 2019 the costs for the use of prescription drugs accounted for 42% of direct costs[243]. In a study of a Danish inception cohort of IBD-patients 2003-2004 and followed until 2015, the cost-benefit effects of biologics on the direct costs were assessed indicating a ‘moderately-strong’ correlation between the increased costs of biologics and the falling costs of direct expenses, excluding biologics[244]. In the Epi-IBD cohort, a community-based, prospective inception cohort of unselected patients with IBD diagnosed in 2010 at centres in 20 European countries plus Israel and followed for five years, there was during follow-up a continuing increase in expenditure for biologicals for patients with CD accounting for 73% of the cost year 5 with a mean yearly budget for biologicals in CD being 6-fold the cost in UC[245].

Apart from expensive biologicals, more frequent monitoring of the patients for achievement of stricter endpoint of disease control together with rising prevalence of the disease will probably cause a continued rise in direct costs.

INDIRECT COSTS

To what extent the modern treatment has affected indirect costs such as incurred by work productivity loss (absenteeism) and on-the-job productivity loss (presenteeism) has also been investigated. In the Dutch WORK-IBD study, including only patients in paid labour, overall work productivity loss was reported by 50% of the employed IBD-patients mainly caused by presenteeism and 8% had partial disability pension[29]. Active perianal disease (OR = 3.3; 95% CI, 1.3-8.1) and clinical disease activity (OR = 7.2; 95% CI, 3.8-13.4) were found to be predictors of severe work productivity loss for patients with CD[29]. Many patients with IBD need accommodations at work when working to overcome disability (the employer granting time to go to medical appointments, easy access to a suitable toilet) which was reported as difficult for almost half of the patients in a study of impact on the workplace of IBD in recent study from New Zealand[246]. In a nationwide study to assess costs of actively treated patients with CD and UC in Sweden, the societal cost of incident and prevalent patients with any of the diseases was consistently two to three times higher than the general population with more than 50% originating from productivity losses deriving from sick leave and disability pension[247].

RISK FACTORS FOR RECURRENCE AFTER ABDOMINAL SURGERY

THE SIGNIFICANCE OF RECURRENT LESIONS

The remission-inducing effect of surgery has always been accompanied by a risk of recurrent disease and repeat surgery. The anatomic evolution of CD begins with aphtous ulcers that develop into strictures or fistulas[20] which is why recurrent lesions are indicating a risk of both *symptomatic* and *surgical recurrence*. A meta-analysis of postoperative maintenance trials has shown a rate of endoscopic recurrence of 58% at a median of one year after surgery[248]. In earlier population-based studies approximately half of patients experienced clinical recurrence after surgery at 10 years[249] and 35% had a surgical recurrence after 10 years[250].

RADICAL SURGERY ACCORDING TO HISTOPATHOLOGY?

In the 1970s and 1980s several reports favoured wide margins of resection aiming at macroscopical and microscopical radical surgery to decrease the risk of recurrence[251-253]. However, frozen sections of the margins were then shown to be unreliable in predicting risk of recurrence[254] and electron microscopy studies showed mucosal architectural abnormalities of CD in macroscopically and histologically uninvolved resection margins[255]. In the only prospectively randomized study concerning resection margins by Fazio published in 1996, it was shown that recurrence of CD was unaffected by the width of the margin of resection from macroscopically involved bowel (2 or 12 cm) and by microscopic CD present at the resection margins[256]. These findings together with CD being recognised as a panenteric disease, and the emergence of a group of CD-patients with intestinal failure after repeat resections, lead to the development of a surgically conservative attitude towards the disease overall with a goal of preserving bowel length. A margin of 2 cm is now usually chosen or just removal of the section of bowel with visible disease (fat wrapping of the involved segment with thickened bowel wall)[257].

The impact of histology showing CD lesions at the proximal ileal margin of the resected specimen are still, 25 years after Fazios study, still debated. Several studies have showed an association between plexitis (the presence of inflammatory cells in the myenteric or submucosal plexi) and recurrence[258-263]. In a recent study from the Netherlands on 538 patients with CD undergoing a first ileocecal resection the results showed that microscopic involvement of the ileal margin (such as granuloma, ulcer, transmural inflammation) was an independent and significant risk factor of clinical and surgical recurrence[217]. In a recently published meta-analysis histopathological margin positivity was also associated with a higher rate of overall recurrence (odds ratio 1.7) with an even higher odds ratio of 2.3 for studies reporting plexitis[264]. A prospective multi-centres study in France of 211 patients with CD treated with ileocolonic resections between 2010-2016 showed that transmural lesions at ileal margin were correlated with both early postoperative endoscopic recurrence and long-term clinical outcome independent of other risk factors [265]. The implication of this study could be to *include histologic features of the ileal margin* when making decisions about *postoperative therapy*. A new multi-centres prospectively randomized study concerning width of margins and risk of surgical recurrence (the CERT-study, Crohn Extended Resection Trial) is ongoing involving centres in UK and Sweden.

CLINICAL FACTORS – BEHAVIOUR AND LOCATION

Preoperative disease behaviour such as *penetrating disease* have in some studies been implicated as a risk factor for recurrence[24 180 248 249 266-268] and in others not[217 239 269-271]. The presence of *perianal disease* is considered to be a risk factor with a relative risk of both clinical and surgical recurrence after surgery of 1,4 in the Stockholm study encompassing the period 1950-1989[272] and an OR of 2,2 of being treated with abdominal surgery in the study of the Sydney IBD-cohort 2015[155]. *Extensive small bowel disease* and *prior intestinal resections* are risk factors for surgical recurrence, but this might simply reflect disease activity from the beginning[11 271]. In the pre-biological French study on long-term disease evolution of CD in 2002 patients during 1974-2000, previous disease behaviour had poor predictive value regarding disease activity during the next five years[20] and previous resection was not a risk factor for endoscopic recurrence in the POCER-trial[273]. *Disease location*, however, plays a role as small bowel disease is more prone to progress to B2- or B3-disease needing surgical intervention[249]. In a European population-based inception cohort of 358 CD-patients followed for 10 years, the HR for surgery was 0,38 for patients with CD with colonic location and 1,54 for patients with upper gastrointestinal disease at diagnosis but behaviour of the disease at diagnosis (B1-B3 disease), did not play a role[274].

SMOKING

Smoking is generally considered to be the most important risk factor with 2,5-fold increase in risk of surgical recurrence at 10 years in a meta-analysis from 2008 of observational studies with more than 2900 patients included with almost half of the population being smokers[275]. In a more recent French study from the period 2010-2017; the OR for endoscopic recurrence for smokers was 2,65[271]. Even in the era of biologicals and combination therapy, the deleterious effect of smoking seems to persist. In a retrospective study of more than 3000 patients in the Spanish national Inflammatory Bowel Disease registry, smokers were found to have a significantly decreased survival free time of stricturing disease and perianal disease (HR=1.5 for both)[276].

Data on the effect of smoking is, however, not entirely consistent. In the previously mentioned Spanish study *time to surgery* for smokers and non-smokers was not significantly different[276]. In a long-term French study from the period 2010-2017 no independent effect of smoking on penetrating manifestations of the disease could be found[20] nor in the study of disease evolution in smokers vs non-smokers in the Sydney IBD cohort concerning progression to B3-disease[155]. In the Norwegian IBSEN-study there was not any significant difference in overall relapse rate in relation smoking status[24]. In the Dutch study of time to surgical recurrence after primary ileocecal resection in more than 500 patients 1998-2013, only resection margin positivity was an *independent* risk factor for surgical recurrence[217]. A confounding factor in several studies is heterogeneity in definitions of smokers vs former smokers vs non-smokers. An example of this heterogeneity in definitions is seen in a Spanish study from 2012 that compared CD-phenotype and disease evolution among non-smokers vs smokers (finding no difference) where non-smokers were defined as never having smoked or who were smoking less than 7 cigarettes per day (!)[277]. Other confounding factors may include mixing different categories of abdominal procedures and not stratifying the risk of surgery by age at diagnosis for CD for smokers vs non-smokers. In a study of risk of surgery within three years of diagnosis in a UK population of 1519 patients 1999-2009, smoking at diagnosis increased the risk of surgery if diagnosed *after* the age of 40 with a HR of 2.99 but *not* for those diagnosed *before* age 40[156]. Whether there is a dose-response effect for smoking is unclear which of course makes the varying definitions of smoking status even more problematic. In an interesting study from the Swiss IBD cohort with more than 800 CD-patients included, six SNPs associated with smoking quantity were combined into a genetic risk score which was shown to be associated with an increased risk for surgery and a shorter time to first surgery, whereas *smokers with low genetic risk scores for smoking quantity* had the same outcome as non-smokers, an example of genetics interacting with the environment[278]. Further, *smoking is associated with other life-style factors with a potential for a detrimental effect on health*. In an English study of 9000 adults, several lifestyle factors (such as consumption of fruit, vegetables[139], obesity[84], physical activity[159] – *all with the ability to affect the microbiome*) generally considered to be associated with adverse health, were compared in current smokers, never smokers and other sub-categories of smokers such as "passive smokers". 80% of the risk factors showed a significantly higher prevalence in heavy smokers than in never smokers[279]. In a French study from 2011 with more than 1000 patients with CD included, a *significant association with non-adherence to medical treatment and smoking* was found[280]. These conflicting data in combination with the heterogenous definitions of smoking status and mixed surgical panorama in earlier studies warranted a study (paper III) with more strict definitions and on a more homogenous group of patients.

AGE AND GENDER

Concerning the effect of age[155 281] and gender on recurrence, data is inconclusive. There are studies reporting male gender as a risk factor[180 271 282 283] and studies showing no influence of gender[24 155 281] and gender is currently not used as a factor in decision-making concerning postoperative prophylactic treatment[11]. There are studies on recurrent disease that have shown a protective effect of age > 40 years (HR 0.82)[274], lower risk of developing complicated disease for patients > 60 years[33] and others who have shown a higher risk of bowel surgery for patients > 60 with IBD[35].

In pediatric gastroenterology age is always of importance in decision-making as it is imperative that the disease does not cause growth failure and to minimise the effect the disease has on physiological and psychological development.

The number of risk factors plays a role independent of age with an increased risk with added risk factors - as can be expected[155 273].

TRACING AND DEFINING RECURRENT DISEASE

HETEROGENOUS DEFINITIONS

As CD cannot be cured by surgery there has been a great interest in identifying risk factors for recurrence. Recurrence can be defined as *clinical, endoscopic,* or *surgical* recurrence.

The use of the term clinical recurrence has been a source of heterogeneity in studies of treatment outcomes. Some of the different definitions that have been used for clinical recurrence have been an *increase in clinical activity indices*, *symptoms prompting an adjustment in medication*, *hospitalisation,* or the *need of a surgical procedure.* Achieving *clinical remission* in clinical scores has neither been shown to improve the natural course of disease, nor to improve outcomes such as mucosal healing in CD[31 269].

CLINICAL RECURRENCE

Clinician reported activity indices / Clinical scores: The Crohn's disease activity index (CDAI) was developed in the 1970's and has been used in a variety of clinical studies to provide supposed objective and reproducible clinical assessment. It is based on registering *clinical parameters* the week prior to consultation in combination with *laboratory tests*. Score ranges between 0 and 600 and a score <150 is associated with remission. Some of the problems with CDAI are complex structure, subjectivity and that it does not correlate well with laboratory, endoscopic and histological markers and there are confounders associated with other GI-diseases[273 284 285]. CDAI was developed in the 70s and since then it has been shown that specifically mucosal healing is associated with reduced risk of treatment with steroids, surgery, and better quality of life[12]. It is also strongly weighted by stool frequency which does not adequately reflect disease activity in proximal locations[286].

The Harvey Bradshaw Index (HBI) is a simpler disease activity score used in CD based only on *clinical parameters* (general well-being, abdominal pain, stool frequency, abdominal mass, and complications) and correlates with CDAI [287 288]. Clinical remission is considered if score is 4 points or below[288].

The Lemann score combines *clinical and endoscopic information plus imaging* into a single score and was developed to guide therapy but use of it has been limited due to time-consuming and complex interpretation[12].

Change in medication: Postoperative recurrence of symptoms may be caused by recurrent disease but can just as well be caused by problems related to defective healing of an anastomosis, bile salt malabsorption, small intestinal bacterial overgrowth, short bowel syndrome and malignancy such as lymphoma[11]. Recurrent symptoms should therefore be evaluated with for example ileocolonoscopy, sometimes radiographic disease assessment such as MR and non-invasive biomarkers, i.e., faecal calprotectin[11]. Variation in access to optimal follow-up can influence the threshold to change medication with or without the proper assessment.

ENDOSCOPIC RECURRENCE

Endoscopic scores: There are validated scores for measuring *general endoscopic disease activity* such as CD Endoscopic Index of Severity (CDEIS) and Simple Endoscopic Score for CD (SES-CD)[12]. The Rutgeerts score was developed to predict *postsurgical* CD recurrence via ileocolonoscopy usually 6-12 months postoperatively in patients having had an ileocolonic resection[12]. New lesions typically develop at the proximal side of an ileocolic anastomosis. Studies of postoperative recurrence have shown that the long-term evolution of disease behaviour in CD begins with aphtous ulcers that develop into strictures or fistulas[19]. Ileal lesions were scored at the first ileocolonoscopy as follows: i,O-no lesions: i,1 - <5 as aphthous lesions: i,2 - >5 aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions or lesions confined to the ileocolonic anastomosis (i.e., < 1 cm in length); i,3-diffuse aphthous ileitis with diffusely inflamed mucosa; i,4-diffuse inflammation with already larger ulcers, nodules, and/or narrowing [266].

Any level of endoscopic recurrence is proof of recurrent disease but an endoscopic score of 3 or more has been shown to correlate best with earlier clinical recurrence[266]. There can be a lag time of months to years between the development of recurrent lesions in the bowel and the recurrence of symptoms[289].

RECURRENCE LEADING TO HOSPITALISATION AND SURGERY

Hospitalisation as a marker for recurrent disease is influenced globally by the economic model for financing health care. It is to be expected that if there is an economic incentive to treat the patient as an inpatient, data about hospitalization can give misleading information about the gravity of the patient´s disease. In Sweden health care is tax-financed and time-trends in hospitalisation has most of all been a marker for the continuing development and improvement of hospital-based out-patient care.

Surgical recurrence can be considered the definitive evidence for recurrent disease as the knowledge of the disease being panenteric and chronic has been undisputed for decades leading to surgery only being performed when complications of the disease such as long-standing inflammation, stenoses or fistulas are not amenable to medical treatment.

SURGICAL RECURRENCE AND RISK OF INTESTINAL FAILURE / SHORT BOWEL SYNDROME

Single bowel resections followed by intra-abdominal septic complications, repeat bowel resections with or without postoperative complications and aggressive small bowel disease can lead to temporary or permanent intestinal failure (IF) for patients with CD, i.e, the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance without parenteral nutritional support[290]. In a Japanese retrospective study of 1703 patients with CD treated with abdominal surgery between 1970-2009, the cumulative risk of IF after the initial surgery was 6.1 % after 15 years with a cumulative risk of IF-related death from the time from of occurrence of IF of 8.9 % after 10 years[291]. Excluding patients treated with surgery before 1989 only marginally influenced incidence of IF; there was still an incidence of 5% after 15 years. A contributing factor to these rather grim figures can be that this was a single-centre study from a university hospital where patients with refractory CD were treated. In another smaller Japanese study of 162 patients with CD with a median follow-up of 15.5 years treated 2000-2017 at the Osaka University Hospital; the cumulative incidence of IF was 3.4% and 8.6% 10 and 15 years after diagnosis, respectively[292]. Independent risk factors were, as expected, remaining length of small bowel < 200 cm but also *non-use* of aTNF-therapy and inflammatory activity (the term used in this study is cumulative inflammation) as shown by level of CRP[292]. In a European cross-sectional survey on patients on home parenteral nutrition for IF due to benign disease, short bowel syndrome was the main mechanism accounting for about 75% of the cases among adults, whereof 29% were patients with CD[293]. In a report from a specialised intestinal failure unit in UK in 2020, it was stated that IF develops in CD primarily as a result of complications of surgical treatment with the majority having been through only one or two *planned* surgical procedures[294]. In an earlier study from the same unit three quarters of the patients with surgically induced IF consisted of patients with CD who had been through multiple *unplanned* laparotomies to control postoperative intra-abdominal sepsis[295].

Summary: patients with CD who are subject to bowel resection with postoperative intra-abdominal septic complications, repeated resections, reoperations caused by complications and with extensive disease in the small bowel are *all at risk for intestinal failure*[193]

AIMS OF THE STUDY

The objectives of this thesis were to:

I. to provide up to date estimates of primary and repeat surgery overall and according to type of primary surgical procedure in a nationwide cohort of patients diagnosed with CD during the period 1990-2014.

II. to assess whether a defunctioning ileostomy following primary resection of ileocolic CD had an impact on long-term surgical recurrence, with a secondary aim of assessing the impact of a two-stage approach on high-risk factors for surgical recurrence.

III. to assess the impact of smoking cessation on surgical recurrence in a group of patients undergoing first-time surgery for ileocolic CD.

IV. to investigate in a nationwide cohort study if the intensified biologic treatment of patients with CD during the period 2002-2013 has been accompanied by a decrease in incidence and prevalence of stoma.

PATIENTS AND METHODS

Patients and case identification

In paper I: 21 273 patients with CD were identified in the Swedish National Patient Registry (NPR) during the period 1 January 1990 to 31 December 2014 with at least *two diagnostic listings* of CD, or *abdominal surgery at the same date as the diagnosis, and* with the criteria of this being a *first-ever diagnosis* of CD / IBD as well as *no gastrointestinal surgery except appendectomies* performed before the diagnosis of CD.

In paper II: 382 patients who had undergone *primary ileocolic resection, i.e ileocecal resection (ICR), with or without defunctioning stoma, but without simultaneous other bowel procedure* for CD between 2000 and 2012, were identified from prospectively maintained databases in three university teaching hospitals (Department of Colorectal Surgery at Oxford University Hospitals, at St Mark's Hospital, London, and Linköping University Hospital).

In paper III: 290 patients identified in the same prospectively maintained databases with inclusion of all **242 patients** with *full smoking data* who underwent a *primary ICR without simultaneous other bowel procedure* between 2000 and 2012 in Oxford and Linköping (i.e the same patients as in paper II excluding the St Mark's population).

In paper IV: 19 146 patients with CD were identified in the NPR during the period 1 January 2002 to 31 Dec 2013 with the criteria of at least *two diagnostic listings of CD or ≥1 record of CD in the NPR plus a colorectal biopsy record* suggestive of IBD from the Swedish ESPRESSO Biopsy cohort *or* a *first record of CD in conjunction with intestinal surgery and* with the criteria of this being a first-ever diagnosis of CD/IBD in combination with *no gastrointestinal surgery except appendectomies* performed before the diagnosis of CD. The subcategory patients with perianal manifestations of the disease were identified by diagnostic and/ or procedural coding in NPR indicating perianal disease.

Methods

IDENTIFYING PATIENTS WITH CD AND PERFORMED SURGICAL PROCEDURES TO ESTIMATE INCIDENCE OF PRIMARY AND REPEAT SURGERY (paper I)

The personal identity number has been used since 1947 in all official registers, which enables linking of registries[296]. We used the registration of patients in the National Patient Register (NPR) by identity number and with coding of CD in the International Classification of Disease codes (ICD-9 and ICD-10). The NPR which has full national coverage of inpatient care through the Inpatient Register (IPR) since 1987[297], coverage of hospital -based outpatient surgery since 1997 and hospital-based outpatient care since 2001 – patients with CD are to a very large degree connected to specialists in IBD in hospital-based outpatient care[298]. We divided the study-population into five cohorts, 1990-1995, 1996-2000, 2001, 2002-2008 and 2009-2014.

NPR provided information on date of surgery and type of surgery. Procedure codes according to National classification of procedures until 1997 when it was changed to an adapted version of the NOMESCO (Nordic Medico-Statistical Committee Classification of Surgical Procedures). Procedures were classified based on anatomical location and expected functional outcome resulting in five main categories and a sixth category of less common, miscellaneous procedures. If a patient was coded with procedures from any of the five main categories as well as a procedure code form the category miscellaneous procedures, the first five hade priority.

When investigating incidence of repeat surgery, we wanted only to capture procedures caused by recurrent disease refractory to medical treatment. We therefore excluded procedure codes for restorative procedures and procedures not primarily caused by CD. Follow-up time started the day after the patient was released from hospital after the first surgical procedure.

IDENTIFYING PATIENTS WITH CD AND TREATMENT WITH ICR (paper II)

Patients with CD who underwent a primary ileocecal resection were identified from prospectively maintained databases at three university teaching hospitals between 2000 and 2012. In the databases extent of disease and medical / surgical treatment has been registered. Patients were divided into two groups: one-stage approach (resection and primary anastomosis) or two-stage approach (resection and a diverting ileostomy and delayed anastomosis).

IDENTIFYING PATIENTS WITH CD AND TREATMENT WITH ICR (paper III)

Patients with CD who underwent a primary ileocecal resection were identified from two prospectively maintained databases at two university hospitals between 2000 and 2012 where data on smoking also is registered. Patients were divided into three groups, non-smokers, smokers, or quitters, i.e., patients that stopped smoking at varying intervals after primary surgery.

IDENTIFYING PATIENTS WITH CD WITH OR WITHOUT PERIANAL DISEASE, AND PERFORMED SURGICAL PROCEDURES WITH TEMPORARY OR PERMANENT STOMAS (paper IV)

Same criteria as in paper I for inclusion ***or*** a minimum of one record of CD in NPR combined with a colorectal biopsy record suggestive of IBD from the Swedish ESPRESSO Biopsy cohort. This database has histopathology record data from the GI-tract from 2.1 million individuals from the period 1965 – 2017[299]. Inclusion only of incident CD-patients during the period 2002-2013 - non-primary outpatient care included in NPR from 2001.

Surgical procedure codes from NPR[300] were used to verify formation of ileostomy, colostomy, or stoma of unknown location. Other procedures performed in association with stoma formation were classified into six categories as in paper I. Permanent stoma was defined as either ileostomy in combination with proctocolectomy, or non-closure of stoma within 2 years. Three cohorts, 2002-2005, 2006-2009, 2010-2013.

Perianal disease was identified by diagnostic ICD-codes for perianal manifestations of the disease and/or proctological procedure codes (NOMESCO) in NPR in conjunction with diagnosis.

When analysing cumulative use of TNF-inhibitors vs incidence of formation of stomas, other calendar periods of CD diagnosis were used as to benefit of the improved reliability of the registration of use of biologics from 2007.

IDENTIFYING USE OF MEDICATION (paper IV)

Information on drug use was taken from the Swedish quality register for IBD, SWIBREG, and from registration of ATC-codes (ATC = Anatomic Therapeutic Chemical classification system) in the Prescribed Drug register (PDR) and with the addition of all infusions of IFX in Stockholm county by being identified by the procedure code for intravenous infusion in combination with the ATC-code for IFX.

STATISTICAL METHODS (paper I-IV)

Paper I-IV: Categorical variables were described as number (n) and percentages (%), and continuous variables as mean and standard deviation (SD) when data was of normal distribution or median and interquartile range (IQR) for non-normally distributed data. A p-value of 0.05 was used as the threshold for assigning significance.

Paper I: The cumulative incidence of all primary and repeat abdominal surgery (except closure of stomas), in total and by category, was estimated using the Kaplan-Meier method.

Paper II and III: To compare numerical data, an unpaired t-test was used when dealing with normally distributed data and the Mann–Whitney *U*-test for nonparametric data. The chi-square test or Fisher's exact test was used to compare groups depending on sample size.

Paper IV: Characteristics of patients diagnosed during different calendar periods were compared using ANOVA, chi-squared test, or Wilcoxon rank-sum test. Time to stoma and stoma reversal between calendar periods were compared in a Kaplan Meier model with stratification for age of disease onset and perianal manifestations. Unadjusted differences between calendar periods were compared with the log-rank test. Cox proportional hazards model was used to estimate univariable and multivariable hazard ratios of stoma in patients with CD, for sex, age, year of disease onset, and perianal disease (yes or no). All statistical tests were two-sided. Time to stoma and stoma reversal was compared between calendar periods in a Kaplan Meier model with stratification for age of disease onset and perianal manifestations.

RESULTS

Paper I

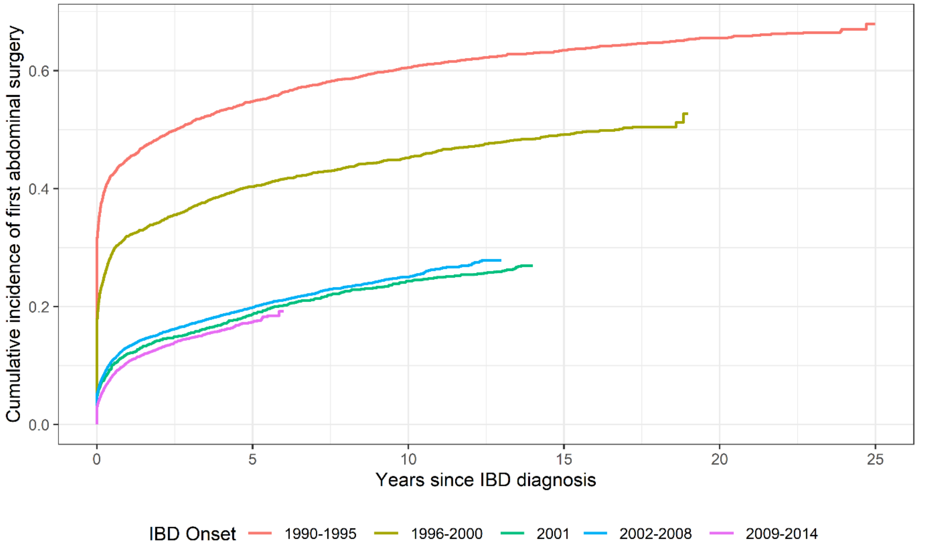
In this study the cumulative incidences of first-time and repeat abdominal surgery for CD overall and by category in Sweden during the years 1990-2014 were analysed in four cohorts encompassing five years each with the cohort only encompassing the year 2001 in between.

Two cohorts before, and two cohorts after 2001 which was the year when of inclusion of non-primary visits was added to the registration in NPR.

There was a continuing decrease in total incidence of primary abdominal surgery for CD throughout the period of the study (Fig.1a). After the introduction of biologicals in the end of the 90s the incidence of surgery within five and ten years of diagnosis was 19.8% and 25.0% in the cohort diagnosed with CD 2002-2008 and 17.3% within five years in the cohort diagnosed 2009-2014.

Figure 1a

Cumulative incidence of first abdominal surgery in relation to year of inflammatory bowel disease onset.



1990-1995 vs 1996-2000 Log-rank test p-value: < 0.001
2002-2008 vs 2009-2014 Log-rank test p-value: < 0.001

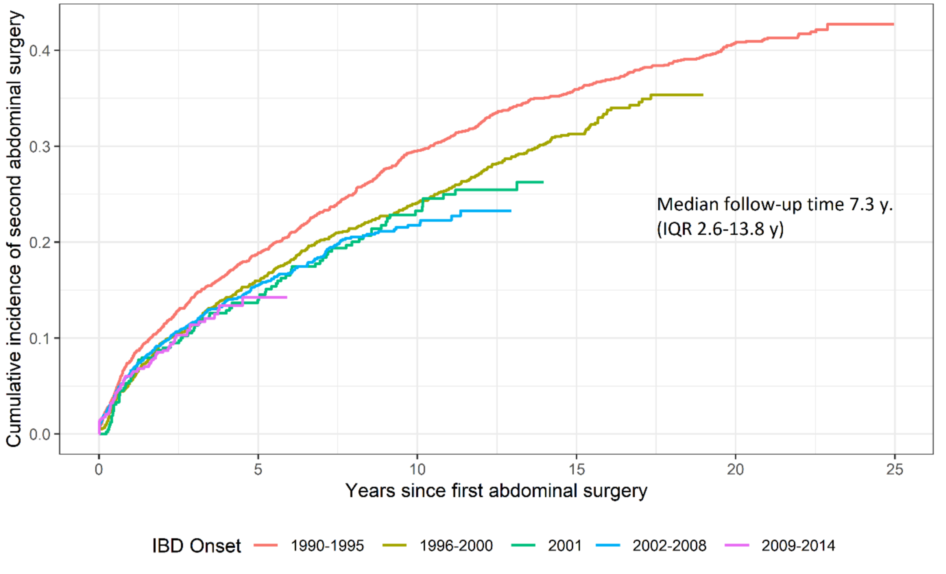
onset	type	0	5	10	15	20	25
1990-1995	at risk	3110	1319	1078	938	696	-
1990-1995	event	967	725	163	78	51	**17**
1996-2000	at risk	3184	1801	1582	1069	-	-
1996-2000	event	557	718	144	108	20	-
2001	at risk	1680	1313	1169	-	-	-
2001	event	80	231	89	36	-	-
2002-2008	at risk	7262	5545	2040	-	-	-
2002-2008	event	377	1049	280	47	-	-
2009-2014	at risk	6037	831	-	-	-	-
2009-2014	**event**	**175**	**667**	**9**	**-**	**-**	**-**

Ileocecal resection was the most common procedure performed in all cohorts encompassing almost two thirds of all primary procedures. The only subcategories with a continuous decrease across *all* time periods were resection of small bowel and colectomies - this despite reports of increasing incidence of CD with colonic location[301]. Although ileocecal resections were common, with the inherent risk of anastomotic recurrence, the incidence of ileocolic reresection was 8.8% after 10 years. Of note is also the low incidence of proctectomies of 3.0% and 1.9% respectively already in the two cohorts from the 90s with a median follow-up of 21 and 16 years.

The incidence of repeat surgery within five years decreased between the two first cohorts in the 90s, from 18.9% in 1990–1995 to 16.0% in 1996–2000 (P=0.009) (Fig.1b). After 10 years the incidence of repeat surgery was 24.1% in cohort 1996-2000. There was no significant decrease in the following time periods, i.e., in the biological era.

Figure 1b

Cumulative incidence of second abdominal surgery in relation to years after first procedure.



1990-1995 vs 1996-2000	Log-rank test p-value: 0.009
1996-2000 vs 2001	Log-rank test p-value: 0.381
2001 vs 2002-2008	Log-rank test p-value: 0.761
2002-2008 vs 2009-2014	Log-rank test p-value: 0.587

onset	type	0	5	10	15	20	25
1990-1995	at risk	2001	1474	1176	940	570	-
1990-1995	event	0	362	186	101	63	10
1996-2000	at risk	1547	1140	899	482	-	-
1996-2000	event	0	233	103	75	19	-
2001	at risk	436	302	185	-	-	-
2001	event	0	56	29	6	-	-
2002-2008	at risk	1753	1066	309	-	-	-
2002-2008	event	0	242	58	4	-	-
2009-2014	at risk	851	61	-	-	-	-
2009-2014	event	0	78	-	-	-	-

Paper II

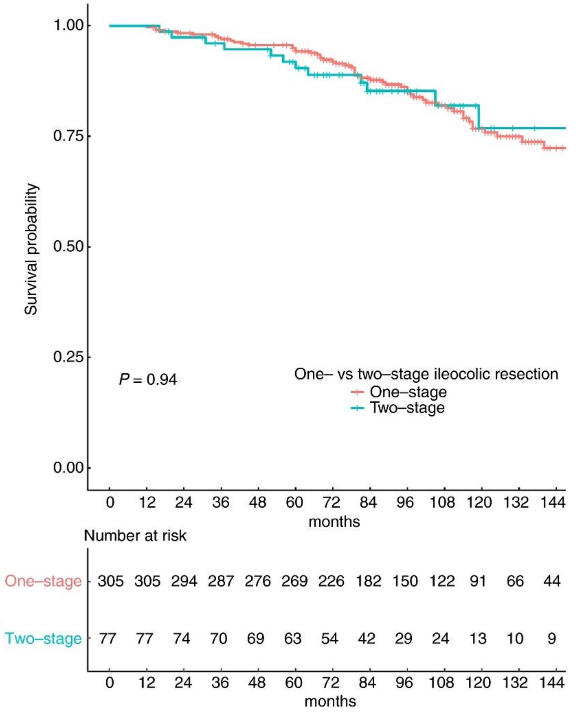
In this study we compared time to surgical recurrence for 389 patients who had undergone primary ileocolic resection (ICR) for CD, with no other simultaneous procedures, at three surgical units 2000-2012 in one-stage (80%) vs two-stage (20%) with a temporary defunctioning stoma with a median follow-up time of 105 months, i.e, almost 9 years.

All planned temporary stomas were reversed. Seven patients who leaked and required a defunctioning ileostomy were analysed separately. Time to recurrence was calculated after restoration of bowel continuity. Factors such as steroids, malnutrition or intra-abdominal sepsis were common reasons for choosing defunctioning.

There was no difference in long-term surgical recurrence between the one- and two-stage groups (18% vs 16%, p = 0.94) (Fig.2) although patients selected to temporary stoma had risk factors usually associated with a higher risk of recurrence, such as smoking (smokers 34% vs 20%; p=0.01) and / or penetrating behaviour (52% vs 28%; p<0.0001).
Time of diversion did not either have an influence on surgical recurrence nor postoperative medical prophylaxis. 23 of the 167 patients (14%) in both groups *receiving medical prophylaxis* vs 24 of the 147 patients (16%) in both groups *not receiving prophylaxis* developed a surgical recurrence, p = 0.5. Data about prophylaxis is missing for 68 patients, i.e 18%. Among the 17 smokers with B3-disease none of the ten patients who were in the two-stage group had a surgical recurrence compared with four out of seven (57%) of smoking patients with B3-disease who were in the one-stage group (p= 0.12). Of note – the only significant difference here was that 8/10 patients in this subcategory of patients in the two-stage group received postoperative medical prophylaxis compared to none of the four who recurred in the other group, p = 0.02.

Figure 2

Surgical recurrence-free survival one-stage vs two-stage.

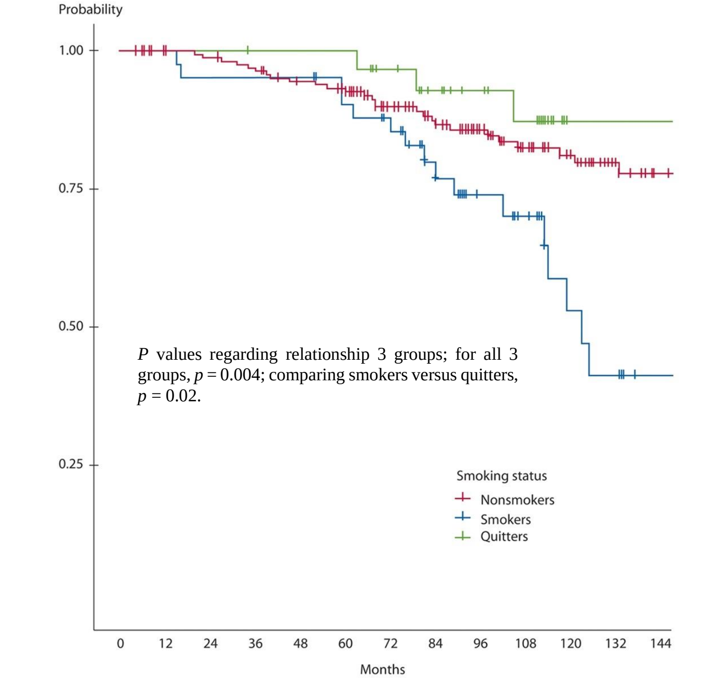


Paper III

In this study we evaluated the effect of smoking and smoking cessation on long-term surgical recurrence as primary endpoint and use of medical therapy as secondary endpoint after primary ileocolic resection for CD, with no other simultaneous procedures, at two surgical units 2000-2012. The patients were divided into three groups: smokers, non-smokers, and quitters with a surgical recurrence rate of 38%, 17% and 10% (p=0.02), respectively, with a follow-up time of in median 112 months, i.e., nine years (Fig.3). For quitters median time of smoking exposure after ileocolic resection was three years. There was a higher surgical recurrence rate for patients who continued to smoke vs quitters with a risk ratio of 3.9 (95% CI, 1–12)), i.e., a 4-fold increase in the risk of needing an additional resection and 8/11 patients who continued to smoke after a second resection went on to need a third resection. When comparing use of medical prophylaxis postoperatively there was not any significant difference between the three groups but when comparing smokers vs quitters without surgical recurrence, the latter group were significantly less likely to have been put on medical therapy, 4/28 vs 12/26; p = 0.01; risk ratio = 3.2 (95% CI, 1–9).

Figure 3

Surgical recurrence-free survival non-smokers vs smokers vs quitters.



% at risk

Smoking status	0	12	24	36	48	60	72	84	96	108	120	132	144
Nonsmokers	100	98	96	94	90	88	73	61	50	41	35	25	20
Smokers	100	100	95	95	95	88	83	64	45	38	21	17	10
Quitters	100	100	100	97	97	97	87	71	61	48	13	13	13

Paper IV

In this study we compared stoma construction and stoma closure in an observational study of all 19 146 incident patients diagnosed with CD in Sweden 2002-2013 divided into three cohorts, 2002-2005, 2006-2009, 2010-2013. Median follow-up 8.8 years. In total 3.2% of the patients underwent stoma surgery, most commonly in conjunction with an ileocolic resection or right-sided hemicolectomy (38%), followed by colectomy or partial resection of colon or rectum (28% each). The cumulative 1, 3, and 5-year incidence of stoma formation was 1.3%, 1.8%, and 2.4%, with no difference between calendar periods of diagnosis (Fig.4). In total, 48% of all patients who had a stoma later had bowel continuity restored. 58% of the patients that received an ileostomy reversed the stoma during follow-up, compared to 29% of the patients with a colostomy. Cumulative incidence of *permanent stoma* for the whole population was 0.6% within five years of diagnosis and 1.9% for patients with perianal disease already at time of diagnosis. In the first cohort, with a median follow-up of 13.4 years, 12% had a second stoma. 28% of the patients that underwent stoma surgery had perianal disease at the time of diagnosis resulting in a HR of 2.72(Cl 2.17-3.42) for stoma for patients with early perianal manifestations of CD. The crude rate of cumulative incidence of perianal disease was 11.6%. Between 2007-2009, 2010-2012, and 2013-2015 the cumulative ever-use of TNF-inhibitors increased by calendar period of CD diagnosis (p<0.001) but with no significant difference between the groups in cumulative incidence of stoma (p=0.08) (Fig.5).

Figure 4

Cumulative incidence of first ever stoma in incident patients with Crohn’s disease, by year of diagnosis (log rank test, p-value = 0.15).

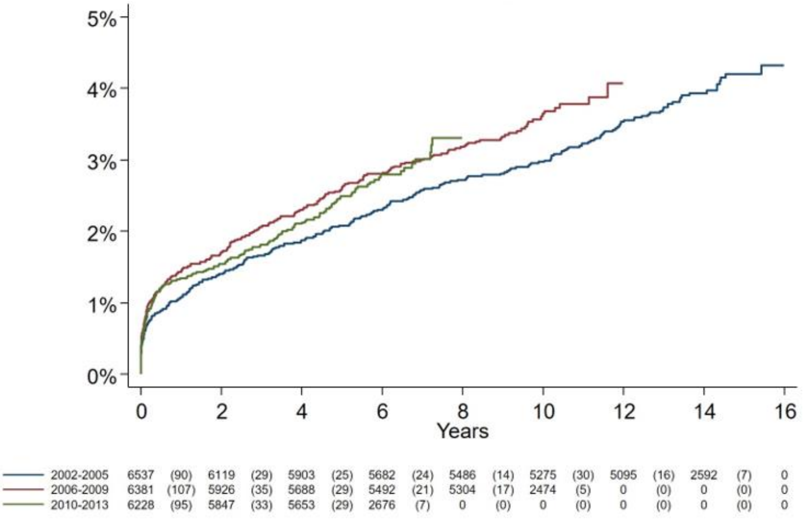
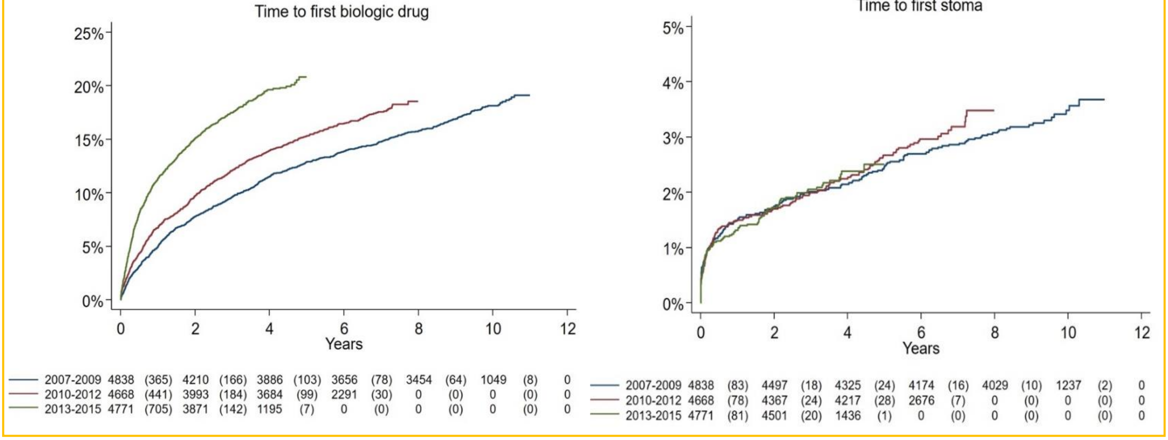


Figure 5

Cumulative use of TNF-inhibitors (log rank test, p-value<0.001) and cumulative incidence of stoma (log rank test, p-value=0.08) in incident patients with Crohn’s disease, stratified by year of diagnosis from 2007-2009, 2010-2012, and 2013-2015.



GENERAL DISCUSSION

With a nationwide cohort with a high validity of diagnostic and procedural coding we have reliable data showing a continuing decrease in primary abdominal surgery for CD throughout the period 1990-2014[302]. This decrease started during the 90s when more frequent use of IMM was implemented and has continued into the biologic era. The cumulative incidence of first abdominal surgery within five years of a diagnosis of CD was 17.3% in 2009–2014. Biologicals do not seem to have affected incidence of repeat surgery after a first decrease in the 90s and a plausible explanation for this could be that the patients that still do get selected to surgery have a more aggressive disease refractory to medication. Our data however shows a lower risk of repeat surgery than earlier reports with only 8.8% now needing an ileocolic re-resection after 10 years and in total 24% of all patients having a surgical recurrence after 10 years[302]. This information is of importance to doctors when discussing prognosis and making therapeutic decisions with the patients and for evaluation of effects of future treatment regimens.

Some comments are merited concerning the process of identifying incident cohorts of patients with CD and given surgical and medical treatment: As we strived for identification of a national cohort of patients with reasonably proven CD, one of the criteria for inclusion in study I and IV was *at least two* diagnostic listings with CD (hospitalisations or non-primary care outpatient visits) in NPR as a previous validation study has shown that this results in a positive predictive value (PPV) for any IBD in NPR of 93% (95% CI: 87–97) [303]. Using the same criteria in a study of prevalence of IBD in Sweden have resulted in stable estimates of the disease[40]. In a validation study of patients who had been treated with a biological agent between 1999-2017 recorded in the Swedish IBD Quality Register (SWIBREG), the PPV of a diagnostic listing of CD in the NPR was 97 % (96–99) [304].

In addition, patients with abdominal surgery at the same date as the first-time diagnosis of CD (producing histological evidence or macroscopical intra-abdominal findings proving the diagnosis) were included, and for *all* patients previous gastrointestinal surgery, except appendectomies, before this date lead to exclusion as the surgical procedure could have been caused by CD not yet verified. To not have previous appendectomies as exclusion criteria can be questioned as ileal or ileocecal CD can be clinically misdiagnosed as appendicitis, although the perioperative findings for most surgeons make the right diagnosis comparatively easy. A diagnosis of any form of IBD before 1 Jan 1990 was of course also a criterion for exclusion.

In study IV we added the possibility of being included in the study with only one registration in the NPR but then with the added criterion of positive histopathology, i.e., a biopsy record or an operative specimen suggestive of IBD in the ESPRESSO (Epidemiology Strengthened by histoPathology Reports in Sweden) database. In this database histopathology record data from the gastrointestinal tract from 1965 and onwards are registered to increase the sensitivity and specificity of already-recorded diseases in the national health registers (PPV of 95%, personal communication, Ludvigsson JF) [299]. In the large study of risk of colorectal cancer in CD published 2020, the additional use of the ESPRESSO database resulted in earlier start of follow-up for 34% of the patients - in median 6 months earlier[42].

It could have been of added value to investigate incidence of surgery according to clinical category in the Montreal classification system but the aforementioned validation study of NPR, using patient data from SWIBREG on patients treated with aTNF, has shown that NPR data has far less reliability for describing location and behaviour of the disease [304]. The only category of phenotype that was relatively securely identified was CD with perianal disease where the PPV was 83% (78-87%)[304]. We kept this as the only subcategory of CD in study IV as perianal disease is a known risk factor for getting a stoma[28].

There are two validation studies of coding for surgery in Sweden. Only 0.1% of surgical procedures in the NPR were found to be miscoded in 1992–1993[305] and a more recent study has shown a PPV of 96.8% for surgical procedure codes for patients with IBD [300]. We wanted to identify abdominal procedures for refractory disease or complications of the disease *only*, not procedures caused by abdominal surgery per se such as stoma closure, procedures for small bowel obstruction caused by adhesions or postoperative abdominal hernias, why codes for the latter categories were not included.

Procedures were classified into six categories based on anatomical localization and expected functional outcome. To enable us to identify as many as possible of the patients treated with radical procedures such as *colectomy or proctectomy*, both procedures with potential for great functional impact, we have in each of these groups included patients who had undergone *proctocolectomy*. An exception to this was patients treated with completion proctectomy or proctocolectomy and construction of an ileal pouch with an ileoanal anastomosis or a continent ileostomy at the same date. Knowledge of the risk of the disease extending to the small bowel, and thus less satisfactory long-term function, has for many years been well known why the threshold to use small bowel for reconstructive procedures has been, and is, high. The codes for these unusual procedures were included in category F (named "other procedures ") encompassing 51 miscellaneous surgical procedures that still do not account for being *main* procedure on more than 183 occasions during the 25 years of study.

The procedure code for strictureplasty, an important alternative to resectional surgery, could not be fully ascertained in NPR until 1997 when the classification system for procedure codes changed from National classification of procedures to an adapted version of the NOMESCO Classification of Surgical Procedure[300]. However, in the study of the well-documented CD-population in Stockholm county during the years 1955-1989 and encompassing 1936 patients, strictureplasty was employed in only five cases[272] why we believe the absence of a specific coding before 1997 is of minor importance. Furthermore, the code for strictureplasty was included in the category F of "other procedures" which as explained earlier, accounted for relatively few main procedures.

The exclusion of patients with a diagnosis of any IBD and/or registrations of gastrointestinal surgery (except appendectomies) before 1st of January 1990 enabled us to have a wash-out period of 26 years of prevalent patients as the NPR started in 1964 – however, full national coverage was not accomplished until 1987. Disease behaviour, and thereby risk of developing complications necessitating surgery, is a result of disease progression over time[20] why a *prevalent* population of patients would to a larger degree reflect older treatments of less interest for this study.

Nevertheless, although CD-patients to a very large degree were admitted to hospitals in the beginning of the investigated period, 96% of patients with CD in Stockholm County 1955-1989 were treated as inpatients[306], there was a *gradual* development of *hospital-based outpatient care*. This resulted in a peak in first-time registrations of patients with CD in 2001 in NPR[35] representing the introduction this year of inclusion of non-primary outpatient visits. Here the register then identified patients with a milder CD-disease course, so far never needing inpatient care. After this change in registration identification of patients with a mild disease as well is more reliable; a study has shown that only 3% of prevalent IBD patients in Stockholm had a primary care visit in 2013 with IBD as a main diagnosis[298].

The peak in registration when inclusion of non-primary outpatient care started does challenge the comparison of calendar periods. We divided the patients into 5 calendar periods of diagnosis: 1990-1995, 1996-2000, 2001, 2002-2008 and 2009-2014. The two first calendar periods contain patients identified through the NPR only. The 2001 cohort contains a mixture of true incident patients (identified in outpatient or inpatient care) as well as prevalent cases that appear to be incident due to no previous inpatient care. The last two calendar periods contain true incident CD cases identified in outpatient or inpatient care. Differences in cumulative incidence of first abdominal surgery was therefore compared across calendar periods *before* and *after* start inclusion of non-primary outpatient care.

The comparison of calendar periods is also challenged by different lengths of follow-up with a median time of follow-up of 9 years in the 2002-2008 cohort compared to 3 years in the 2009-2014 cohort. As we did not compare the *average* incidence rate of surgery for different calendar periods but instead compared cumulative incidence of surgery using the log-rank test, and since we have no cause to believe that the few patients with longer follow-up in the last calendar period are systematically different from the ones who are not, the problem is not one of bias, but of power.

The pronounced drop in cumulative incidence of abdominal surgery in 2001 is likely an overestimation of the decrease, partly due to a mix of prevalent and incident cases caused by the addition in NPR of patients with a mild disease, but it seems reasonable to assume that the observed decrease in cumulative incidence of primary abdominal surgery over the time periods 1990-2000 and then 2002-2014 is correct.

When comparing risk of repeat surgery the patients were *all registered as inpatients in conjunction with primary surgery*, and can be considered to be at the *same stage of disease* (having progressed to need surgical intervention), and *time to and incidence of repeat surgery could therefore be compared across all calendar periods* regardless of inclusion of non-primary outpatient care in NPR from 2001.

Earlier studies have, to a large degree, also showed decreasing incidence of abdominal surgery, with some exceptions, but several of them have methodological weaknesses. The study by Rungoe *et al*. from Denmark of 13 185 adult patients (>16 years) with CD diagnosed 1979-2011 and followed until December 2011, showed a decrease in five-year cumulative probability of surgery down to 20% for the cohort diagnosed with CD 2003-2011 which is in accordance with our results[307]. Some of the limitations were that only one diagnosis of CD was required for inclusion, which has been shown to result in lower validity [303 308] , and a lack of discussion about the selection process for which pre-study surgical procedures lead to exclusion (e.g. excision of an intra-abdominal fistula was selected to be a minor procedure and did not count towards exclusion). Furthermore, the type of surgery other than major/minor abdominal surgery was not reported and information about median time of follow-up in the last cohort, encompassing the years 2003-2011, is lacking.

The results in the study by Nguyen *et al*. of surgical treatment of 3 403 patients with CD diagnosed in Manitoba 1988-2008, is in accordance with our results showing a decrease in incidence of surgery within five years of diagnosis to a level of 18% in cohort 2001-2008[309]. Of special interest is the *lack of decrease in repeat surgery during the entire period*, whereas we found a significant decrease in the 1990s but not thereafter, and in their study a cumulative risk of repeat surgery *five* years after primary surgery of 23% compared to 22% after *ten* years in our study. The lack of decrease in repeat surgery was ascribed to the quite low use of IMM and IFX after primary surgery in all cohorts.

The study of Burr *et al*. on risk of surgery for 3 059 incident patients with CD from a UK primary care database during the years 1994-2013 also reported findings in accordance with our results[310]. They found a significant reduction in first surgery within 10 years of disease, from 44% for those diagnosed 1994-1995 to 21% for those diagnosed 2002-2003. Furthermore, they also found a significant reduction in repeat resections; 40% for those first operated in 1994 to 17% in 2003 during a follow-up period of 10 years. However, this decline in surgical rates plateaus already from the 1998–1999 cohort and the gap in size between the first small cohort and the following cohorts, combined with a not negligible loss of follow-up in all cohorts, make the results difficult to evaluate.

Finally, Beelen *et al* recently published a nationwide cohort study on the incidence of abdominal surgery in adult patients with CD in the Netherlands during the period 1991-2015[311]. In agreement with our result, they found a continuously decreasing incidence of surgery, with the most substantial decrease in the 1990s. In contrast to our result, decreasing incidence was observed for all anatomic locations and for repeat surgery during the whole period. The incidence of surgery was, however, based on an *estimated,* rather than known prevalence of CD in the Netherlands.

There are several studies contradicting our findings. A population-based study from Olmsted County 1970-2004 found no decreasing trend at all in cumulative probability of primary abdominal surgery[180]. In the last cohort, patients diagnosed with Crohn´s disease during 2000-2004, the cumulative incidence of abdominal surgery within five years of diagnosis was 35.1%. They reported on type of surgery performed in detail, which is rare in other studies. The limitation in this study was small sample size; only 310 patients.

Cosnes *et al* reported data from a tertiary centre in France 1978-2002 with 2 573 patients included and showed a steep increase in use of IMM but no change in risk of intestinal resection [226]. Another study by Lazarev *et al*, from a large tertiary centre in Pittsburgh in 1995-2007, showed no reduction in the rate of resection of small bowel despite profound changes in type of medication[312]. High loss of follow-up, referral bias and rising prevalence of Crohn´s disease may explain results from these centres.

Reports from administrative databases in Ireland 2000-2010 and USA 1988-2011 have not either demonstrated decreasing rates of surgery, but here incidence of surgery in relation to prevalence of the disease is not known and validity of coding is uncertain[313 314].

In study II the risk of, and time to, surgical recurrence after an ICR proved to be independent of one-stage or two-stage approach once the bowel continuity was restored. The two-stage group had a significantly higher proportion of smokers and more patients with penetrating disease behaviour, but still there was no difference in long-term surgical recurrence between them; 18% vs 16%, $p = 0.94$. On top of that, it was somewhat surprising to see that in the group of 10 patients with twice the burden of risk factors (both smoking and B3-disease), normally leading to an additive effect[155 273], none had a surgical recurrence in the two-stage group vs four out of seven in the one-stage group.

Risk factors for postoperative recurrence have been the focus of several studies. In Rutgeerts hallmark study from 1990 of endoscopic recurrence after surgery, the patients who underwent surgery for B3-disease and repeat surgery had a significantly higher risk of developing symptomatic recurrence (defined as an increase in diarrhoea, associated with pain, fever, or weight loss at two consecutive follow-up examinations)[266]. The definition of recurrent disease as recurrent symptoms is however not satisfactory as bile salt malabsorption, irritable bowel disease etc can result in similar complaints. In a meta-analysis of more than 2 500 patients who had undergone surgery 1988-2005 caused by perforating or non-perforating CD, an increased risk of surgical recurrence was seen in B3-disease, HR 1.50 (CI 1.16-1.93, p=0.002), but with significant heterogeneity among studies[268]. A strength of our study was the large number of patients treated with the same and the most common surgical procedure for CD, the long period of follow-up and the endpoint surgical recurrence. Differences in recurrence rates can in part be explained by different surgical interventions, for example higher risk of recurrence after a colectomy vs proctocolectomy[315], varying risk of recurrence depending on location of the disease[37 316], and varying definitions of recurrence such as clinical, endoscopic or surgical recurrence.

The lower incidence of surgical recurrence among smoking patients with B3-disease in the two-stage group can be interpreted as pointing towards a *possibility* of temporary defunctioning having an effect of modifying bacterial flora in the gut and thereby decreasing rate of surgical recurrence in this presumably high-risk group. Or, on the other hand, it can be interpreted as the good effect of given medical prophylaxis for the high-risk patients in the two-stage group. Results from the Spanish ENEIDA-registry (National Inflammatory Bowel Disease registry) do however speak against modern medical therapy being able to compensate for the deleterious effects of smoking[317] and there was furthermore no effect of medical prophylaxis on incidence of surgical recurrence when comparing *all on prophylaxis in both groups* vs *all without prophylaxis in both groups*; 23/167 (14%) vs 24/147 (16%), OR 0.8 (95% CI 0.4–1.5), p=0.5. This somewhat disappointing effect of used medical prophylaxis can maybe be explained by the findings in the POCER-study and the CALM-study. In the POCER-study patients with high risk of recurrence (smokers, B3-disease) were put on IMM after surgery and then randomized to active care with endoscopy every 6th month, with the possibility to step-up treatment if there were sign of recurrent disease, vs no endoscopy until end of the study at 18 months when everyone was evaluated with endoscopy. The results were clearly to the benefit of the patients with active care showing that *potent immune suppression adjusted to endoscopic findings* could maintain endoscopic remission in > 50% of all patients[273]. In the CALM-study it was shown that escalation with aTNF based on clinical symptoms *combined* with biomarkers in patients with early Crohn's disease resulted in better clinical and endoscopic outcomes than symptom-driven decisions alone[233].

The relevance of these results for our study is, that just starting medical prophylaxis is not enough – it must be combined with a tight control management with a preparedness for treatment escalation.

Study III is a retrospective review of prospectively maintained databases at two surgical units 2000-2012 (Dept of Colorectal surgery Oxford University Hospital and Linköping University Hospital) to assess the impact of smoking cessation on surgical recurrence in a group of 242 patients with full smoking data undergoing first-time surgery for ileocolic CD. The effect of smoking on flares and surgical recurrence of CD has been a topic for the last three to four decades with most of the studies, although heterogenous, converging on a deleterious effect of tobacco[275 317]. As an example of heterogeneity, the various definitions of non-smokers vs smokers be mentioned[277] and current and former smokers have often been put into the same category introducing a misclassification bias[152]. Another source of heterogeneity has been mixing different primary surgical procedures with different inherent risks of recurrence and different definitions of outcomes such as the less well-defined outcome flare of disease vs endoscopic recurrence vs surgical recurrence. The strengths of our study were the relatively uniform population of patients, all being treated in the era of biologicals, with the same primary surgical procedure, the clear-cut outcome of abdominal surgical recurrence and a long follow-up time of in median 9 years. The differences in recurrence rates, to the benefit of the non-smokers and quitters, were not unexpected. However, somewhat unexpected, the quitters stand out as a subgroup of patients where the effect of smoking seems to be the prime cause of the disease. The good result of quitting has been seen in an earlier meta-analysis of observational studies on the effect of smoking after surgery for CD with no significant difference in risk of surgical or clinical recurrence for ex-smokers compared to never-smokers[275]. Of note, this study included 2 962 patients with only 4.6% ex-smokers (137 patients). The disproportionate effect of smoking, reversed by quitting, can reflect different genotypes responding differently to tobacco smoking. In the review of Mahid *et al* of studies on CD 1966-2006, current smoking was found to be associated with late-onset CD (≥40 years old)[318]. In the study of an inception cohort of 1 519 patients with CD in UK from 1999-2009 smoking at diagnosis *increased the risk of surgery after the age of 40* to a HR of 2.99, but *not for those diagnosed before age 40*[156]. A possible interpretation of this could be that environmental factors such as smoking play an important role for patients with a late diagnosis and that genetics have a greater influence on triggering the disease among younger patients. In line with this possible influence of genetics on the effects of smoking are earlier studies showing clear ethnic differences in risk of CD for smokers[159].

The knowledge of the association between smoking and CD is well established and our result with more recurrences among the smokers is not controversial, however, it is quite remarkable that only 42% of the smokers stopped smoking after their first ileocecal resection as this for most patients must have been a stressful event in life by preceded by symptoms in form of abdominal pain etc. Whether we as healthcare professionals have done our best to use this opportunity to make the patients quit smoking can be questioned. In a study of smoking and cessations plans for 675 patients with IBD, cessation rates at and after diagnosis were equal between patients with CD and UC (despite completely opposite effects on risk of a flare)[319]. Half of the CD patients managed to stop smoking after the diagnosis leading to a lower number of current smokers in the group of patients with CD than in a control population which lead the authors to the conclusion that CD-patients seem less refractory to smoking cessation than the general population[319]. In the prospective Swiss IBD Cohort study data strongly indicated an underuse of supportive measures to achieve smoking cessation with more than 90% of the cohort claiming to never have received any support[320]. In Cosnes´ intervention study of 474 smoking patients with CD an independent factor associated with smoking cessation was the physician (the variable "physician" was dichotomised according to the impact of counselling, two groups of counsellors) with an adjusted odds ratio of 2.31, i.e. the personal relationship between the patient and the physician who gave repeated advice to quit smoking was important[321].

The results of our study once again stress the importance of advising patients with CD to stop smoking. The data about the excellent effect of quitting, even when it takes time, ought to be both persuasive and encouraging for patients and healthcare professionals.

In study IV we changed the period of study to 2002-2013 as treatment with biologicals then had been more widely implemented and these new agents had raised hopes of being disease-modifying with maybe one of the effects being a reduced risk of stoma for patients with CD. In addition, start of the Outpatient Register in 2001 made inclusion of incident patients only more straightforward. We added the diagnostic criteria of a registration suggesting IBD in the ESPRESSO database and information about use of biologicals. The PDR contains data only on all prescribed drugs dispensed from pharmacies in Sweden *from 1 July 2005*. The coverage of the register is complete for prescriptions in ambulatory care while in-hospital drug treatment is generally not recorded[322]. Use of *non-infusion* biologics is captured to 99%, such as use of ADA[323]. *Infusion* biologics, such as IFX are covered to less extent as it is given as an in-hospital treatment. Only 20% of IFX use in 2009 was found in the PDR due to varying reimbursement rules in different counties over the years[323]. Stockholm county (20% of the population of Sweden) has since 2007 close to complete coverage of IFX in NPR by all infusions of IFX being identified by the procedure code for intravenous infusion (DT016) in combination with the ATC-code for IFX [177]. According to data in SWIBREG the two biologics IFX and ADA have the same market shares well above the alternative biologicals[34] which is in accordance with the study from Stockholm county concerning effect of aTNF on risk of surgery, where 52% of included patients were prescribed ADA and 48% IFX[177].

Combining data from PDR and SWIBREG from 2005 and data from NPR from 2007 and onwards, was in this situation with incomplete registration of drug use, the most optimal way to chart the use of biologicals during the period of study. In the last validation of PDR 80% of all use of biologicals is captured but only 41% of the use of biologicals given as intravenous infusions, for example IFX and vedolizumab (*Bröms et al*, submitted manuscript) - but to this we have added the registration in SWIBREG.

Earlier studies of temporal trends concerning incidence of stoma formation have come to different conclusions and with varying degrees of external validity for the population of CD-patients in general. A report from a Swedish tertiary clinic 1970-1997 showed a clearly reduced risk for permanent defunctioning caused by Crohn´s colitis ascribed to the implementation of a surgically conservative strategy in combination with maintenance treatment with steroids and IMM[200]. An Italian tertiary clinic reported from the period 1995-2010 a reduction in incidence of permanent stoma in Crohn´s colitis from 61% pre-bio to 19% post-bio, however there was a difference in mean follow-up time of 7 years (11 years pre-bio vs 4 years post-bio)[324]. In a report from a tertiary referral IBD centre in Boston the proportion of patients with CD requiring diversion went down from 18% (26/147) 2000-2002 to 10% (72/731) in 2009-2011 at the same time as the incidence of perianal surgery procedures decreased from 27% (40/147) to 18% (131/731)[325]. The data from Iesalnieks study from a tertiary clinic in Germany was however not at all in accordance, they reported an increase in incidence of formation of an ileostomy in conjunction with surgery of ileal B3-disease from 1.4% to 18.6%, during the period 1992-2009[242]. This was associated with use of multiple drug combinations leading to a lengthening of the period of clinical deterioration preceding surgery and an increase in postoperative intra-abdominal septic complications, from 7% to 36%[242]. A large study including more than 355 000 Crohn's-related operations from the Nationwide Inpatient Sample, the largest all-payer inpatient care database in the USA, and based on a 20 % stratified sample of non-Federal hospital admissions, showed that the percentage of Crohn’s-related operations that resulted in stoma construction increased from 18% to 24% during the period 1988-2011(24-year odds ratio 1.33 (95 % CI 1.17, 1.51)), $p < 0.001$[314]. However, there is no data about incidence of CD, no data about outpatients *not* needing surgical intervention at all and it is possible that this simply reflects selection bias with the patients still needing surgery having a more severe disease. In a study of more than 20 000 US paediatric inpatients with CD 2003-2012, registered in the Kid´s Inpatient Database, a stable rate of all types of bowel resections and colostomy formation was noted. There was however an increase in post resection ileostomies, making the odds of undergoing an ileostomy creation to increase by 11% annually (from 0.8% in 2003 to 2.1% in 2012, $p < 0.001$)[326]. Of note, this figure reflects the *proportion* of inpatient surgery resulting in formation of a stoma, not the incidence of stomas in relation to incidence of the disease. A possible explanation can be the result of management strategies in the era of aTNF therapy with medicolegal aspects making surgeons more reluctant to make a primary anastomosis when the young patient has been exposed to aTNF.

There are only a few population-based studies on incidence of stoma in CD. In the study from Örebro County, encompassing the years 1963-2005, there was no difference in the five-year proportion of patients who received a permanent stoma[327]. In another population-based study from Calgary Health Zone 2002-2011, serving a population of 1.4 million inhabitants, a reduction in the overall rate of stoma formation in CD has been driven by fewer emergency stomas while rates of permanent stoma have not decreased[232].

In our population-based study of 19 146 incident patients with CD 2002-2013, a period when the use of aTNF has continuously increased, cumulative incidence of stoma formation was unchanged. Cumulative incidence of *permanent stoma* was 0.6% for the cohorts combined, and 1.9% for patients with perianal disease five years after diagnosis, which is encouraging. However, on the other hand, 42% of the ileostomies were never reversed which might indicate exclusion and loss of more functional bowel capacity than necessary – could the choice of a colostomy on any part of the colon have been an alternative? Were ileostomies always chosen because of extensive colitis or chosen as the surgical procedure with formation of an ileostomy is relatively simple and from start seems to be easy to reverse?
The data showed increased HR for stoma among male patients, patients over 40 years of age and among patients with perianal disease (HR 2.72). The lower incidence of stomas for young patients can probably in part be explained by a higher threshold for this decision as the psychosocial ramifications of a stoma are heavier for patients that have not yet established adult relations. On the other hand, the physiological consequences of an ileostomy, with inherent risk of high-output and renal insufficiency, is more difficult to evade for elderly patients with older kidneys.

The patients with perianal disease were identified by diagnostic codes (PPV in NPR of 83%[304]) and/or procedural codes for perianal complications of the disease. The proportion of the cohorts with perianal disease at *diagnosis* varied between 5.2%-7.1%, with a cumulative incidence for these patients of *any stoma* within five years of 5.2%. This might very well be an underestimation of incidence of perianal disease in all cohorts depending on the relatively short follow-up time for a disease that is lifelong and an underreporting of perianal problems that did not have clinical significance at the time of diagnosis. Using the same coding for identification *the crude rate of cumulative incidence for perianal disease* during the whole follow up period (with a median follow up of 8.8 years) was 2 221 cases in the population of 19 146 patients, i.e., 11.6%. These figures can be compared with the results from the study of patients diagnosed with CD during 1955-1974 in Stockholm County. 826 patients were identified and of this cohort 23% developed anal fistulas during a mean follow-up time of 9.4 years[26]. In the incident population of patients with CD in Olmsted County 1970-1993, the cumulative risk of developing a perianal fistula was 22% at 10 years[25]. Furthermore, in the population-based study from New Zealand of 715 patients with CD there was a cumulative probability at 20 years of *43%* for developing *any* type of perianal manifestations of the disease ranging from skin tags to abscesses and fistulas[27].

As described earlier, we know that ICD-codes of perianal disease in NPR has a PPV of 83% and to this we *added* the procedural codes for proctological surgery as a possible criterion for having CD with perianal manifestation. It seems reasonable to believe that this has resulted in a reliable identification of patients with *perianal disease of any clinical significance* and especially so in the two first cohorts 2002-2005 and 2006-2009 with a median follow-up time of 13.4 and 9.5 years respectively – both cohorts had a *crude rate of cumulative incidence of perianal disease of 12.3 and 12.1%* each. This comparably low incidence of clinically relevant perianal disease could, with some caution, be interpreted as a disease-modifying effect of modern therapeutics and/or a more aggressive step-up approach in the medical armament. The low incidence of permanent defunctioning in our study is also in contrast with earlier reports of OR of 10-33 for getting a permanent stoma for patients with perianal CD[28]. So far it is not possible to judge if this is just a matter of too short duration of disease and too short time of observation or if this data is indicating that clinically relevant perianal disease and permanent stomas are less common for patients with CD than stated by earlier reports. Our data can indicate that the need of a permanent stoma is delayed by modern care and if this is correct it would be a significant gain for patients with CD.

CONCLUSIONS

- risk of primary abdominal surgery for patients with CD has been continually decreasing during the period 1990-2014
- the cumulative incidence of primary abdominal surgery, within five years of a diagnosis of CD, was in the last calendar period of study 2009-2014, 17.3%
- ileocecal resections encompassed two-thirds of all primary procedures in all calendar periods with decreasing incidence in the 90s but no significant change after the introduction of biologicals
- the incidence of small bowel resection and colectomy continually decreased
- there was a very low risk of proctectomy during the whole period of study with a cumulative incidence of 3.0% and 1.9% in the two cohorts from the 90s with a median follow-up of 21 and 16 years respectively
- the cumulative incidence of repeat abdominal surgery within five years of primary procedure decreased in the 90s and was in the period 1996-2000 16.0%. The incidence of repeat surgery has not continued to decrease in the biological era
- the cumulative incidence of repeat ileocolic resection was 4.4% within five years of primary procedure
- there was no significant difference in surgical recurrence rate between patients who underwent primary ileocolic resection for CD with one-stage surgery / primary anastomosis vs two-stage surgery / delayed anastomosis with a temporary stoma, despite higher baseline risk factors for recurrence in the two-stage group
- surgical recurrence rate, during a follow-up time of almost nine years after primary ileocolic resection for CD, was 38% for smokers, 17% for non-smokers and 10% for patients who quit smoking after primary surgery
- risk ratio for surgical recurrence for smokers vs patients who quit smoking after primary surgery was 3.9 and risk ratio of use of postoperative medical prophylaxis was 3.2
- during the period 2002-2013 the five-year cumulative incidence of *any* stoma for patients with CD was 2.4% with no significant change between calendar periods
- the cumulative ever-use of TNF-inhibitors increased and time to start with treatment decreased by calendar period of CD diagnosis between 2007-2009, 2010-2012, and 2013-2015 but with no significant differences between these groups in cumulative incidence of stoma
- proportion stoma reversal was 58% for patients who underwent formation of an ileostomy and 29% for patients with a colostomy
- for patients with CD and perianal manifestations of the disease at diagnosis, HR for formation of a stoma was 2,7. Of all patients who underwent stoma surgery, 28% had perianal disease
- at five years from diagnosis of CD 0.6% of the patients had a permanent stoma

SVENSK SAMMANFATTNING

Den kroniska inflammatoriska tarmsjukdomen Crohns sjukdom behandlas med kirurgi när sjukdomen orsakar komplikationer som läkemedel inte har effekt på. Det kan röra sig om kroniska förträngningar på tarmen, onaturliga förbindelser / gångar, så kallade fistlar, mellan inflammationssjuka tarmavsnitt och andra tarmpartier, mellan tarm och andra bukorgan eller mellan tarm och huden. Kirurgi kan också behövas vid kontinuerligt aktiv inflammation där medicinering har otillräcklig effekt eller om sjukdomen bidragit till utveckling av cellförändringar och t. o. m cancer. Eftersom sjukdomen inte kan botas med kirurgi och ofta återkommer i områden där kvarvarande tarm skarvats ihop, är ett minskat behov av tarmresektion och ett minskat behov av anläggande av stomi vad som eftersträvas vid behandling med läkemedel.

Denna avhandling undersöker i vilken mån de förändringar som skett vad gäller handläggning och särskilt medicinsk behandling av Crohns sjukdom har påverkat i vilken utsträckning patienterna har behövt opereras i buken samt vilken typ av kirurgi de genomgått. Vi har även undersökt i vilken mån temporär stomi samt rökstopp påverkar risken för behov av ny tarmkirurgi efter operation med ileocekal resektion vilket är den vanligaste kirurgiska åtgärden för Crohns sjukdom (dvs borttagande av någon till några decimeter den nedersta delen av tunntarmen med skarvning mot höger del av tjocktarmen).

21 273 patienter med Crohns sjukdom i Sverige identifierades i Nationella Patientregistret under åren 1990 till 2014. Andelen patienter som behövde genomgå en bukoperation inom fem år efter diagnos minskade kontinuerligt och var i den sista kohorten, patienter diagnosticerade med Crohns sjukdom under perioden 2009 till 2014, nere på 17,3%. Ileocekal resektion var den vanligaste åtgärden oavsett tidsperiod. Andelen patienter som fick hela tjocktarmen borttagen minskade under hela tidsperioden och risken för att opereras med borttagande av hela ändtarmen – vilket för nästan alla patienter innebär permanent stomi – var mycket låg även för de som diagnosticerats i början av 90-talet och således har kunnat följas under upp till 20 år. Risken för en andra bukoperation inom fem år minskade mellan de två tidsperioderna 1990–1995 samt 1996–2000 från 18,9% till 16,0% men därefter skedde ingen ytterligare signifikant minskning trots introduktionen av biologiska läkemedel 1998. Risken för ileokolisk re-resektion var inom fem år var 4,4% och inom tio år 8,8% vilket kan vara prognostisk viktig information för patienter som ställs inför valet fortsatt eller utvidgad medicinering med läkemedel med systemiska effekter kontra operation med ileocekal resektion.

389 patienter som opererades med ileocekal resektion, med eller utan temporär stomi, p. g. a. Crohns sjukdom mellan åren 2000–2012 följdes upp avseende andelen som fick ett kirurgiskt återfall under en period på strax under nio år. 80% opererades med en tarmskarv direkt och 20% fick en stomi p. g. a. riskfaktorer, dvs befarad hög risk för otillräcklig läkningsförmåga vid den första operationen. En del av dessa riskfaktorer brukar tolkas som prognostiskt ogynnsamma, dvs innebära högre risk för återfall av behandlingskrävande sjukdom. Trots detta var det ingen statistiskt signifikant skillnad mellan grupperna vad gäller återfall som krävde kirurgisk åtgärd; 18% respektive 16% behövde opereras igen under uppföljningstiden.

242 patienter som opererade med ileocekal resektion under åren 2000 till 2012 följdes upp under en period på drygt nio år med avseende på effekten av rökning och rökstopp på risken för kirurgiskt återfall. 38% av de patienter som rökte fick ett återfall som krävde kirurgisk åtgärd jämfört med 17% av icke-rökarna och endast 10% av de patienter som slutade att röka

efter operationen. Rökare hade en relativ risk för ny bukoperation på 3,9 samt en relativ risk på 3,2 för att behöva läkemedel mot sin sjukdom jämfört med de patienter som slutade röka.

I en studie av alla patienter diagnosticerade med Crohns sjukdom i Sverige 2002 till 2013 identifierades 19 146 individer och utfallet i form av incidens av operationer med anläggande av stomi följdes fram till 2017. Andelen patienter som hade varit med om en operation med anläggande av stomi inom fem år var 2,4% och den kumulativa incidensen var oförändrad under hela studieperioden trots att andelen patienter som erhöll biologisk behandling ökade och tid till start med denna typ av preparat minskade. Risken för att få en stomi var högre bland patienter med sjukdomsdebut i högre ålder samt med perianal sjukdom - 28% av de patienter som fick en stomi hade perianala manifestationer av Crohns sjukdom 58% av de patienter som fick en ileostomi och 29% av de patienter som fick en kolostomi kunde sedan få denna bortopererad. Endast 0,6% av patienterna hade en permanent stomi inom fem år efter det att sjukdomen diagnosticerats.

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