

Hospitalisations and surgery in Crohn's disease

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ABSTRACT

Hospitalisation and surgery are considered to be markers of more severe disease in Crohn's disease. These are costly events and limiting these costs has emerged as one rationale for the cost of expensive biologic therapies. The authors sought to review the most recent international literature to estimate current hospitalisation and surgery rates for Crohn's disease and place them in the historical context of where they have been, whether they have changed over time, and to compare these rates across different jurisdictions. It is in this context that the authors could set the stage for interpreting some of the early data and studies that will be forthcoming on rates of hospitalisation and surgery in an era of more aggressive biologic therapy. The most recent data from Canada, the United Kingdom and Hungary all suggest that surgical rates were falling prior to the advent of biologic therapy, and continue to fall during this treatment era. The impact of biologic therapy on surgical rates will have to be analysed in the context of evolving reductions in developed regions before biologic therapy was even introduced. Whether more aggressive medical therapy will decrease the requirement for surgery over long periods of time remains to be proven.

INTRODUCTION

Crohn's disease is mostly an outpatient disease. The diagnosis is typically first made in adults in the outpatient setting, whereas in children it is often still first diagnosed in an inpatient setting. Occasionally first presentations of the disease involve bowel obstruction, perforation or massive bleeding, and patients are hospitalised at the time of diagnosis. With these types of presentations, patients may undergo surgery, at which time the diagnosis is made. Some patients present as if they have acute appendicitis, undergo emergency surgery and in fact are discovered intraoperatively to have Crohn's disease.^{1–3} In recent years, these cases have become far less common. In clinical practice, in clinical trials and in studies using administrative datasets, hospitalisations for active disease and surgeries have served as measures of more severe disease activity and markers of poor outcomes. In general, healthcare providers want to keep patients as outpatients, and patients in general want to avoid surgery. There is no question that well-timed surgical interventions for limited disease can lead

to prolonged periods of disease remission with accompanying enhanced quality of life.⁴ A reduction in the frequency of these outcomes over time has been used as evidence of improved medical management.⁵

Our aim in conducting this review was to explore whether rates of hospitalisation and surgery have changed over time, and to compare these rates across different jurisdictions. It is in this context that we could set the stage for interpreting some of the early data and studies that will be forthcoming on rates of hospitalisation and surgery in an era of more aggressive immunological therapy, including the use of biological agents.

In the last 20 years there has been enhanced use of immunosuppressive therapy in managing Crohn's disease, and in the past decade anti-tumour necrosis factor α (anti-TNF- α) therapy has been implemented with great improvement in disease course for some.⁶ It stands to reason, then, that hospitalisation and surgery rates should be declining. Being armed with the data on both current rates of hospitalisation and surgery in Crohn's disease, and the extent to which they have changed over time, may help providers impart realistic estimates for these milestones while discussing expectations with patients.

HOSPITALISATION

Europe

Between 1962 and 1987, 83% of patients with Crohn's disease in a population-based study in Copenhagen County, Denmark, were admitted at least once within the first year after diagnosis, and then admissions decreased over the next 5 years to a steady rate of about 20% per year⁷ (table 1). However, the local treatment policy in effect at the time encouraged hospitalisation for more expeditious diagnosis and management, and so hospitalisation in that era had a different implication than of a more recent era, where much of the diagnostic work-up is undertaken in the outpatient setting (Pia Munkholm personal communication, September, 2011).

A European multi-country referral centre prospective follow-up study over 10 years from 1991 (the European Collaborative Study Group on Inflammatory Bowel Disease (EC-IBD)), confirms that hospitalisation rates declined significantly

Table 1 Hospitalisation trends for Crohn's disease

Author	Jurisdiction	Era of incident cases	Method	No of subjects	Hospitalisation rate	Re-hospitalization rate
Munkolm 1995 ⁷	Copenhagen, Denmark	1962–1987	Population-based cohort	373	83% within 1 yr from diagnosis	20% per yr over next 5 yrs
Odes 1991 ⁸	13 European centres and an Israeli centre	1991–2001	Inception cohort study from referral centres	425	52.7% by 10 years	
Bernstein 2006 ⁹	Canada	1994–2001	Population-based cohort	33821	25% per year	4% readmitted within 1 yr 1% readmitted ≥ 2 times
Longobardi 2006 ¹⁰	Manitoba, Canada	1987–2002	Population-based cohort	203	66% at least 1 admission over 15 years, 52% admitted within 5 years	56% readmitted ≥ 1 time
Nguyen 2011 ⁵	Manitoba, Canada	1988–2008	Population based cohort	3403	1 year rates 1995–2000: 27% 2001–2008: 24% 5 year rates 1995–2000: 36% 2001–2008: 36%	
Herrinton 2009 ²⁰	Kaiser Permanente, N California, USA	1998–2005	Data from Health Maintenance Organization (16 medical centres in an integrated health plan)	2892	Hospitalization Rates \downarrow by 33% from 1998–1999 to 2004–2005	
Peyrin-Biroulet 2010 ¹³	Olmsted County, MN, USA	1970–2004	Population-based cohort	310	71% at least 1 admission admitted by 5 yrs, 71% admitted by 10 yrs	

from the second year after diagnosis.⁸ The cumulative risk of overall hospitalisation was 52.7% at 10 years from diagnosis, but with considerable differences between countries.

North America

In a population-based study from Canada in the years 1994–2001, approximately 25% of subjects with Crohn's disease were admitted annually. Only 4% and 1% were readmitted two and three times, respectively, within 1 year.⁹ The annual hospitalisation rate declined significantly from 29.2 cases per 100 000 persons to 26.9 per 100 000 over the 7 years of the study. Since the prevalence rate of Crohn's disease in Canada did not decline over the study period, the reduction in hospitalisations most likely reflected a change in the management approach, disease severity, or improved outcomes, such that fewer hospitalisations were required. Nearly half of the hospitalisations for Crohn's disease involved major surgery.⁹ In a population-based cohort from the central Canadian province of Manitoba, of 203 newly diagnosed persons with Crohn's disease in 1987 followed for 15 years, 66% were admitted at least once to the hospital for an inflammatory bowel disease specific diagnosis, and of these 56% were readmitted at some point.¹⁰ Fifty-two per cent of the patients had their admissions within the first 5 years from diagnosis.

In a recent population-based study from Manitoba of Crohn's disease subjects diagnosed between 1988 and 2008, the highest hospitalisation rates were within the first year of diagnosis and were no different among those diagnosed during 1988–1995, 1996–2000, or those diagnosed after 2001.⁵ Similar to the EC-IBD study,⁸ after the first year, hospitalisation rates declined by about 50% and plateaued over the next 5 years.

In a population-based study from Olmsted County, Minnesota, 69% of 234 residents diagnosed with Crohn's disease between 1970 and 1999 and

followed through 2001 (median follow-up, 10.9 years) were hospitalised at least once.¹¹ Surgery was performed in 39% of all hospitalisations. Thirty-five per cent were hospitalised at the time of Crohn's disease diagnosis, and 15% required surgery at the time of diagnosis. In a subset of this cohort from the pre-biological therapy era (1970–1997, n=211), the cumulative risk of hospitalisation was 32% at 1 year, 52% at 5 years and 62% at 10 years from diagnosis¹²; these data are remarkably similar to that of Manitoba.¹⁰ The median number of hospitalisations per subject was 2 (range, 1 to 22), and rehospitalization occurred in 60% within 5 years.¹¹ In an updated population-based inception cohort from Olmsted County (diagnosed 1970–2004 and followed through mid-2009), with a median follow-up of 11.8 years, 71% of Crohn's disease patients were hospitalised at least once, and the cumulative risk of any hospitalisation (medical or surgical) was 62% at 5 years and 71% at 10 years after diagnosis.¹³ Factors associated with time to first hospitalisation included ileocolonic disease, small bowel, or upper gastrointestinal extent (relative to colonic only), and stricturing or penetrating complications at baseline.

Several studies have used US national databases to show a marked increase in the number of hospitalisations related to Crohn's disease in the USA.^{14–19} Bewtra and colleagues, using the National Hospital Discharge Survey (NHDS), showed a significant increase in hospitalisation rates for Crohn's disease from 9.3 per 100 000 in 1990 to 17.1 per 100 000 in 2003.¹⁴ Sonnenberg examined the NHDS dataset over a 35-year period and stratified the analysis by age.¹⁵ Overall, hospitalisations for Crohn's disease per million population more than doubled over the study period. In particular, hospitalisation rates for those in the 45–64-year-old and over 65 years old groups rose significantly, while rates among the under 45 years

old group remained largely unchanged. The rise in Crohn's disease hospitalisations among US minorities, including Asians and blacks, was confirmed by Sewell and coworkers' analysis of the NHDS dataset 1994–2006.¹⁶ Nguyen and coworkers used the Nationwide Inpatient Sample (NIS) to compare hospitalisation rates between 1998 and 2004 and found a 4.3% annual increase for Crohn's disease.¹⁷ Recently, Ananthakrishnan and others used updated NIS data and reported a continual rise in the number of Crohn's disease-related hospitalisations between 1998 and 2007.¹⁸ This increase was primarily seen among patients with low or intermediate disease severity not requiring surgery. Sonnenberg and colleagues analysed the Veterans Administration database to examine Crohn's hospitalisation patterns among US military veterans over a 32-year period.¹⁹ The hospitalisation rate peaked in the late 1980s, decreased through the 1990s, and remained relatively stable over the last 6 years of the study period. An increasing proportion of hospitalisations for Crohn's disease in the Veterans Administration system was among patients ≥ 45 years old in the latter part of the study period. In these national surveys, it is impossible to determine if the rise in hospitalisations is due to increased incidence rates of Crohn's disease, increasing severity of disease, or a combination thereof. As these trends differ from what was reported from Canada,⁹ it may also reflect some differences in access to care (universal in Canada, insurance-dependent in the USA); perhaps patients with Crohn's disease in the USA with suboptimal healthcare plans miss out on sufficient disease remittive and ongoing care and end up with more severe disease and ultimately in hospital.

In contrast to these studies, data from Kaiser Permanente Northern California (a health maintenance organisation) suggested that hospitalisation rates for Crohn's disease decreased by 33% between 1998 and 2005.²⁰ A reduction in hospitalisation of this magnitude would need to be corroborated in other cohorts to determine if this trend was generalisable. The decrease in hospitalisation rates in the Kaiser study and the stable rates in Manitoba (where disease prevalence rates are rising) support the possibility that more aggressive medical therapy accounts for these findings, or simply that better healthcare access for subjects in those health systems maintains their disease in a better state with a reduction in need for hospitalisations. These trends in North America will need further follow-up over time as more aggressive use of biological therapy in particular increases. However, any findings will have to be interpreted in the context of trends in disease management, disease prevalence and healthcare access.

SURGERY

Even though intestinal surgery is not curative, it has an important place in the management of Crohn's disease. First, we have gained aetiological insights from surgical procedures such as the

potential importance of colonic microflora on disease recurrence in patients who undergo primary ileocolonic anastomoses as opposed to diverting ileostomies.^{21–23} Second, surgery can be associated with long-lasting remission.⁴ Early prospective cohort studies from referral centres provided medium to long-term data on surgical rates prior to the advent of using immunomodulating therapy other than corticosteroids. Truelove and Pena first showed that of 147 patients with Crohn's disease newly diagnosed between 1938 and 1970 at Oxford, 74% required surgery.²⁴ A similar surgical rate was reported among 592 patients diagnosed at the Cleveland Clinic between 1966 and 1969.²⁵

Europe

Surgery rates were reported to be 30%, 50% and 60% at 5, 10 and 15 years, respectively, from a population-based Stockholm County cohort from 1955 to 1974.²⁶ When follow-up in this cohort was updated to 1989, surgical rates at 5 and 10 years had not appreciably changed.²⁷

A population-based inception cohort from Copenhagen County (1962–1987) was first reported in 1985 and then updated in 1993²⁸ 29 (table 2). During the first year of diagnosis 35% had surgery with surgery rates of 12% the following year, 8% the next year, with a rate of 5% per year thereafter.²⁹ The cumulative probability of surgery was 61% after 10 years and 82% after 20 years. At 15 years the cumulative risk of more than one surgery was 36%.²⁹ In an assessment of incident cases diagnosed between 2003 and 2005 in Copenhagen City and County, only 12% underwent surgery within the first year of diagnosis.³⁰ This series of Danish studies suggests that more recently surgery had been pursued less often within 1 year from diagnosis. Is this because of more aggressive medical therapy, a change in disease behaviour or could it be a change in attitude towards surgery?

In the Inflammatory Bowel South-Eastern Norway (IBSEN) population-based cohort of patients enrolled between 1990 and 1994 in southeastern Norway, the cumulative probability of surgery at 1, 5 and 10 years from diagnosis was 14%, 27% and 38%, respectively.³¹ Terminal ileal location, stricturing disease, penetrating behaviour and age younger than 40 years at diagnosis were all significant independent risk factors for surgery. Sex, the early need for systemic steroids or cigarette smoking at the time of diagnosis did not impact on the need for surgery.³¹ Of those subjects who had surgery by 10 years, 9% had at least two surgeries.

In the multi-country referral centre European EC-IBD cohort, where subjects were enrolled between 1991 and 1993, 37.2% of patients underwent surgery within 10 years of diagnosis with significant differences between countries.⁸ Surgical recurrence rates were 2.2%, 18.5% and 35.9% at 1, 5 and 10 years after the first surgery, respectively.³² In a large referral-based cohort (n=2008) from France followed from 1978 to 2002, 15% underwent surgery within the first 3 months; however, after

Table 2 Surgery trends for Crohn's disease by years from initial diagnosis

Authors	Jurisdiction	Era of incident cases	Methods	No. of subjects	Surgical rates			
					1 year	5 years	10 years	15 or 20 years
Hellers 1979 ²⁶	Sweden	1955–1974	Population-based cohort	826	–	30%	50%	60% (20 years)
Munkholm 1994 ²⁹	Denmark	1962–1993	Population-based cohort	373	35%	–	61%	82% (20 years)
Vind 2006 ³⁰		2003–2005		562	12%			
Solberg 2007 ³¹	Norway	1990–2000	Population-based cohort	237	14%	27%	38%	–
Cosnes 2005 ³³	France	1978–2002	Retrospective data from referral centre	2573	15% (3 months)	–	–	–
Odes 2006 ⁸	12 European centres and an Israeli centre	1991–2001	Inception cohort study from referral centres	425	–	–	37%	–
Ramadas 2010 ³⁴	Wales, UK	1986–1991	Population-based cohort	105	32%	59%	–	–
		1992–1997		99	25%	37%		
		1998–2003		137	19%	25%		
Lakatos 2011 ³⁷ and 2011 ³⁵	Veszprem Province, Hungary	1977–2008	Population-based cohort	506	15%	31%	52%	59% (20 years)
		2002–2006		163	10%	21%		
Nguyen 2011 ⁵	Manitoba, Canada	1988–1995	Population-based cohort	1364	16%	30%	38%	39% (20 years)
		1996–2000		920	13%	22%	29%	
		2001–2008		1119	10%	18%		
Peyrin-Biroulet 2010 ⁴⁰	Olmsted County, MN, USA	1970–2004	Population-based cohort	310	–	38%	48%	58% (20 years)
Ye 2010 ⁴¹	Korea	1991–2007	Referral centre	278	16%	25%	33%	–
Leong 2004 ⁴²	Hong Kong	1987–2003	Referral centre	80	–	–	29%	–
Oriuchi 2003 ⁴³	Japan	1965–1998	Referral centre	276	–	38%	60%	74% (15 years)

the first 3 months the annual operative rate was 3.3–7.5% with little change over 26 years.³³

In a population-based study from Cardiff, Wales, UK, consisting of 341 patients with Crohn's disease diagnosed between 1986 and 2003 (median follow-up, 7.7 years), 148 (43%) patients underwent surgery.³⁴ The cumulative incidence of surgery was stratified by three time periods of diagnosis (1986–1991, 1992–1997, and 1998–2003). The 1-year cumulative probabilities for surgery were 32%, 25% and 19%, respectively ($p=0.1$), while the 5-year cumulative risks of surgery were 59%, 37% and 25%, respectively ($p=0.001$).³⁴ Thus, there was a significant decrease in the need for surgery over time. A multivariate proportional hazards regression analysis confirmed that even after controlling for other factors, the earlier time periods were associated with a higher risk for surgery relative to the latest time period. Early need for corticosteroids was associated with increased risk for surgery, while colonic disease (relative to ileal extent) and thiopurine use within the first year of diagnosis were protective.

A population-based study from Veszprem Province, Hungary of Crohn's disease patients diagnosed between 2002 and 2006 reported the probability of surgery was 9.8%, 18.5% and 21.3% after 1, 3 and 5 years of disease duration.³⁵ In the entire cohort (diagnosed between 1977 and 2008, with a median follow-up of 13 years) the probability of surgery was higher: 14.6%, 30.8% and 52.2% at 1, 5 and 10 years, and of these 28.2% required at least two surgeries.^{36 37} Similar to the study from Wales, there was a recent reduction in surgical rates independently associated with earlier use of immunosuppression (<1.5 or <3 years after diagnosis) in multivariate proportional hazards regression analysis and also after matching

on propensity scores in the population-based Veszprem cohort between 1977 and 2008.³⁷

North America

In a population-based inception cohort study from Manitoba of 203 newly diagnosed patients with Crohn's disease, 45% had surgery by 15 years of follow-up. Two thirds of surgical patients (or 29% overall) had their surgery within 5 years.⁹ In a recent population-based Manitoba study of subjects diagnosed between 1988 and 2008, the overall cumulative incidence rates of surgery at 1, 5, 10 and 20 years after diagnosis for the entire Crohn's disease cohort were 13%, 24%, 32% and 39%, respectively.⁵ An important trend identified in this longitudinal study was that the cumulative incidence rates of surgery decreased over time by era of diagnosis. For those diagnosed between 1996 and 2000, 1 and 5-year surgery rates were 13% and 22%, respectively, and for those diagnosed between 2001 and 2008, 1 and 5-year surgery rates were 10% and 18%, respectively. The hazard ratio (HR) for time to first surgery in the years of diagnosis after 1995 was reduced compared with those diagnosed prior to 1996 (0.72; 95% CI 0.62 to 0.84). The HR for time to first surgery in the years of diagnosis after 2000 was reduced compared with those diagnosed prior to 2001 (0.79; 95% CI 0.65 to 0.97). The rates of recurrent surgeries were not different between the three different eras of initial diagnosis.

The first report of requirement for surgery among Olmsted County residents with Crohn's disease examined a population-based cohort diagnosed between 1935 and 1975 with a median follow-up of about 8 years, and indicated that 41% of patients required at least one surgery.³⁸ Among those diagnosed with Crohn's disease between 1940 and 2001, 58% underwent surgery at some time to

a median follow-up of 13 years, and of these, 50% had at least two surgeries.³⁹ The cumulative risk for intestinal surgery was 24%, 49% and 64% at 1, 10 and 30 years, respectively. In the most recent update of this cohort (diagnosed between 1970 and 2004 and followed through 2009, with a median follow-up of 11.8 years), the cumulative risk of major abdominal surgery was 38% at 5 years, 48% at 10 years, 58% at 20 years and 61% at 30 years from diagnosis.⁴⁰

Other US data from 1998 to 2005 when anti-TNF therapy was emerging as a key therapeutic option, from the Northern California Kaiser Permanente (a health maintenance organisation) suggested that surgery rates did not change over that 7-year period.¹¹

Asia

In a recent Korean referral centre study of Crohn's disease patients diagnosed between 1991 and 2007, the cumulative probability of surgery after 1, 5 and 10 years was 15.5%, 25.0% and 32.8%, respectively.⁴¹ This operative rate appeared comparable with the data from a Hong Kong Chinese referral centre cohort reporting a cumulative surgical rate of 29% after 10 years of the disease.⁴² In a Japanese referral centre study of 276 Crohn's disease patients, the cumulative surgical rate from symptom onset was 37.6%, 60.4% and 74.2% at 5, 10 and 15 years, respectively.⁴³ These latter rates are much higher than that reported from Korea and Hong Kong.

Unfortunately, data describing surgical rates in Asian populations have been derived mostly from hospital-based cohorts that may include patients with a more severe spectrum of disease. However, overall surgical rates for Asian patients with Crohn's disease still appeared slightly lower than the rates experienced in most centres worldwide, and further studies are required to explore reasons behind these differences.

The impact of immunomodulatory therapy on surgery rates

There are limited population-based studies assessing the impact of biologicals on surgical rates in Crohn's disease. A population-based study from Stockholm County conducted between 1999 and 2001 where 191 Crohn's disease patients were treated with infliximab (mean, 2.6 infusions) showed that 33% of patients required some form of major surgery.⁴⁴ In the population-based Copenhagen County study, of the 209 patients with Crohn's disease diagnosed between 2003 and 2005, 12% required a surgical procedure.⁵⁰ The population-based study from Cardiff showed that the cumulative probability for surgery was 19% and 25% at 1 and 5 years, respectively, between 1998 and 2003.³⁴ These rates were lower when compared with the surgical rates in the pre-biological therapy era.³⁴ Similarly, recent reduction of surgical rates have been shown to be associated with increased and earlier azathioprine use in both a multivariate Cox analysis (HR: 0.43, 95% CI 0.28 to 0.65) and

after matching on propensity scores for azathioprine use (HR: 0.42, 95% CI 0.26 to 0.67) in a Hungarian study.³⁷

Hence, overall, it seems that in the pre-biological therapy era from population-based studies, that approximately 35–50% of subjects will have undergone surgery within 10 years from diagnosis. The Manitoba and Cardiff data suggest that more recently diagnosed patients may be undergoing surgery less frequently. The rate of surgery ranged from 18% to 25% within 5 years in the biological therapy era.

Despite a marked increase in the use of immunosuppressive drugs, the cumulative risk for surgery at 5 years remained stable in a French referral centre at 35% between 1978 and 2002, although in this study it is possible that immunosuppressive drugs might have been started too late to have impacted on surgical rates in many of the subjects.³³ While immunosuppressive drugs^{45–46} and biological agents^{47–48} have been shown to decrease hospitalisations and the need for surgery in patients with Crohn's disease, the risk of requiring surgery beyond 1 year has not been widely reported, and the long-term potential of these agents in altering the natural history of disease remains unclear. A recent population-based Manitoba study reported that users of infliximab did not have reduced rates of surgery over a 3-year follow-up when compared with patients newly using immunosuppressive drugs, patients newly using corticosteroids or those who used no immune-related medications.⁴⁹

Disease location and rates of surgery

Disease location and extent appears to influence the need for surgery in Crohn's disease. In a population-based Stockholm County cohort of Crohn's disease (1955–1989), patients with orojejunal, small bowel, ileocecal and continuous ileocolonic extent at diagnosis were significantly more likely to require surgery than those who presented with isolated colorectal involvement.²⁶ For persons with isolated small bowel disease and for those with ileocecal disease, the relative risks (RRs) of surgery compared with persons with colorectal disease were 3.2 (95% CIs, CI 2.5 to 4.0) and 3.2 (95% CI 2.7 to 3.6), respectively. Furthermore, those patients presenting with perianal fistulas were 20% more likely than those without to require surgery (RR, 1.2 95% CI 1.0 to 1.3). Among 907 Stockholm County residents with ileocecal Crohn's disease, 87% eventually required surgery.⁵⁰ The cumulative probability of surgery was 61% at 1 year, 77% at 5 years and 83% at 10 years after diagnosis. The presence of perianal fistula increased the risk of surgery by 60% (RR=1.6, 95% CI 1.2 to 2.3). This group reported separately on 507 subjects with isolated colorectal Crohn's disease diagnosed from 1955 to 1989, and the surgery rate at first presentation was 18%.⁵¹ The probability of major surgery in this group was 33% by 5 years and 47% by 10 years. Although the risk of needing surgery at the time of initial presentation decreased over the

study period, the 5 and 10-year risks did not change over time. The probability of surgery in isolated colorectal disease was increased with the presence of fistulas (RR, 1.7; 95% CI 1.3 to 2.2) and decreased with left sided disease (RR, 0.6; 95% CI 0.4 to 0.8).⁴⁸ Those with proximal colonic disease had the highest surgery rates. The most recent data from the IBSEN study between 1990 and 2004³¹ showed in an adjusted Cox regression model that the HRs for first surgery were 0.5 (95% CI 0.5 to 0.9) for age > 40 years, 0.3 (95% CI 0.2 to 0.6) for ileocolonic and isolated colonic localisation, and 2.3 (95% CI 1.4 to 4.1) and 5.4 (95% CI 3.0 to 9.9) for stricturing and penetrating disease, respectively.

Ileal (HR, 2.35, 95% CI 1.6 to 3.45) or ileocolonic (HR, 1.79, 95% CI 1.19 to 2.68) location compared with isolated colonic location, stricturing disease behaviour at diagnosis (HR, 4.33, 95% CI 2.95 to 6.36 vs inflammatory disease) and fistulising disease behaviour at diagnosis (HR, 3.44, 95% CI 2.33 to 5.08 vs inflammatory disease), but not perianal disease or smoking were independently associated with time to first surgery in a population-based study from Hungary.³⁷

In a study from the Cleveland Clinic of patients diagnosed from 1966 to 1969 the site of disease at surgery did not significantly impact on recurrence rates; however, their recurrence rates were impacted by the presence of an internal fistula or perianal fistula.⁵² In a prospective cohort study from Hong Kong, the cumulative probability of major surgery was significantly higher in Crohn's disease patients with upper gastrointestinal phenotype (L4) than in the non-L4 group.⁵³ The 5-year cumulative incidence of major surgery in this cohort approached 70%, and half of them under-

went surgery within the first month. Upper gastrointestinal phenotype also predicted the need for subsequent hospitalisations.⁵³

The nature of the surgery can impact on recurrence rates, although this may be dictated by the location of the disease as opposed to necessarily reflecting a 'choice' of procedures. For example, the 10-year symptomatic recurrence rates for patients with Crohn's colitis undergoing surgery were 24% for those who had subtotal colectomy with ileostomy, 37% for those who had proctocolectomy with ileostomy, 47% for those who had segmental colonic resection and 58% for those with a subtotal colectomy and ileorectal anastomosis.⁵⁰ Similarly, high rates of recurrence after subtotal colectomy with ileorectal anastomosis were reported from a British study at 58% at 10 years. In this group of patients, ultimately proctectomy with ileostomy creation was necessary in 24% after a median follow-up of 12.5 years.⁵⁴ The implication is that reoperation is lower in persons who have had their entire colons removed, but of course this involves accepting a permanent stoma. However, in an analysis of natural history studies the authors suggested that survival curves extended for longer periods show that the rates of reoperation among proctocolectomy patients may approach that of those treated with segmental resection.⁵⁵ Hence, further long-term studies on postoperative recurrence rates in large sample sizes are required to fully understand if the type of surgical resection predicts recurrence rates.

SUMMARY

The most recent data on hospitalisation is from Canada and the Kaiser Permanente Northern California, and there seems to be a recent trend towards reduced hospitalisation rates. Plateaued or even rising hospitalisation rates in other administrative data from the USA may be due to a number of contributing factors. In the pre-biological therapy era, from population-based studies, approximately 40–50% of subjects will have undergone intestinal surgery within 10 years from diagnosis and the risk of postoperative recurrence may be about 50% by 10 years. The most recent data from Manitoba, Canada reported that surgery rates at 1 and 5 years have reduced between 1988 and in the post-biological therapy era of 2001–2008.⁵ Reductions in surgery rates at 1 and 5 years were evident in the most recent pre-biological therapy era (1998–2003) from Cardiff.³⁴ Figure 1 presents surgery rates over time. The rates are based on average values across studies, weighted by sample size. Studies were grouped by starting dates of incident cases and show that with successive eras rates have been falling, with obvious separation starting at 3 years of disease.

So the impact of biological therapy on surgical rates will have to be analysed in the context of evolving reductions in developed regions before biological therapy was introduced. Studies of surgical rates in the era after biological therapy was introduced are required from other jurisdictions to

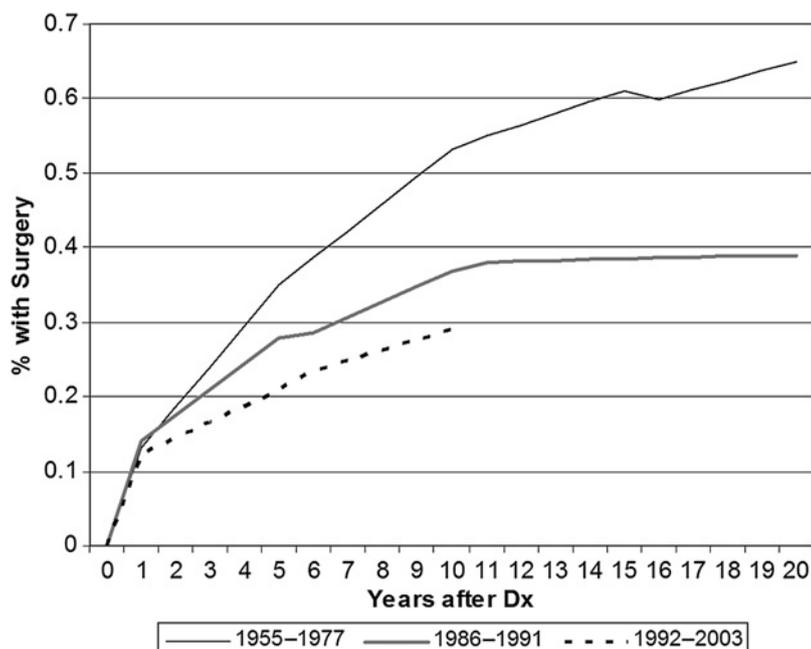


Figure 1 Surgery rates over time. The rates are based on average values across studies, weighted by sample size. Studies were grouped by starting dates of incident cases. The curves for 1955–1977 were extracted from references^{26 29 37 40 43}, for 1986–1991 from references^{5 8 31 34 41 42}, and for 1992–2003 from references^{5 30 34 35 37}.

understand if the reduction in surgery rates was a unique outcome to Manitoba and Wales or whether it reflects broader trends. Despite an increasing use of immunosuppressive drugs and biological agents, surgery is still required for many patients with Crohn's disease. Whether more aggressive medical therapy will impact on decreasing the long-term requirement for surgery remains to be proven.

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