EVOLUTION AND PROGNOSTIC PREDICTORS OF CROHN'S DISEASE & ULCERATIVE COLITIS IN HONG KONG CHINESE

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DECLARATION OF ORIGINALITY

The work contained in this thesis is completely original. It has not been submitted for any other degree. All the research work was accomplished in the Prince of Wales Hospital under the supervision of Dr. Francis KL Chan, Professor, and Dr. Joseph JY Sung, Professor and Chairman, Department of Medicine and Therapeutics, The Chinese University of Hong Kong. I was responsible for the overall design, conducting of the studies, data collection, analysis, and preparation of the manuscripts.

ABSTRACT

By: Dr CHOW Kai Lai
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Inflammatory bowel disease (IBD) is associated with lifetime morbidity and the onset of disease frequently occurs in early life. Although IBD manifests throughout all ethnic groups, there has been marked heterogeneity in its incidence, prevalence, manifestation, and outcome. We sought to study the incidence, prevalence, and survival of ulcerative colitis (UC) and to examine the evolution and prognostic predictors of Crohn's disease (CD) and UC among Hong Kong Chinese. A total of 4 studies were performed to address these issues. One longitudinal cohort study examined the incidence, prevalence, survival and phenotypic changes of UC. Two other longitudinal cohort studies evaluated the phenotypic evolution of CD. One of them specifically compared the course of disease between patients with and patients without upper gastrointestinal tract phenotype. The final retrospective study identified clinical factors that predicted the occurrence of corticosteroid dependency and refractoriness in patients with IBD. The annual age- standardized incidence rate and point prevalence of UC per 100,000 Hong Kong Chinese in 2006 were 2.1 (95% CI: 1.1-3.7) and 26.5 (95% CI: 22.6-30.9), respectively. Incidence of UC has increased 6 times over the past two decades. The overall survival of UC patients was similar to the expected survival of the Hong Kong population. Phenotypic changes in CD also occurred in Chinese patients in the same way as the white patients with respect to disease behavior, though at a slower rate. Similar to the white CD patients, the location of disease remained relatively stable over the course of disease. Chinese CD patients had more upper gastrointestinal tract phenotype which predicted the need of surgery and subsequent hospitalization. On the other hand, the rate of proximal extension of UC was less than 25% after 10 years. In CD, thrombocytosis predicted, whereas colonic disease negatively predicted corticosteroid dependency. Stricturing CD was associated with corticosteroid refractoriness. In UC, thrombocytosis and extensive colitis predicted corticosteroid dependency, whereas anemia predicted corticosteroid-refractory disease. The results of these studies are important in the planning of health service and they also assist in the formulation of treatment strategy.

(word count: 338)

CONTENTS

CAPTIONS FOR TABLES

CAPTIONS FOR FIGURES

ABBREVIATIONS

5ASA	5-aminosalicylates
CARD15	Caspase activation and recruitment domain 15
CD	Crohn's disease
CI	Confidence intervals
ERCP	Endoscopic retrograde cholangio-pancreatography
HR	Hazard ratios
IBD	Inflammatory bowel disease
INFγ	Interferon γ
MC	Montreal Classification
NFκB	Nuclear factor kappa B
NOD2	Nucleotide binding oligomerization domain 2
OR	Odds ratio
SNP	Single nucleotide polymorphism
TGFβ	Transforming growth factor β
TNF	Tumor necrosis factor
TPN	Total parenteral nutrition
UC	Ulcerative colitis
VC	Vienna Classification

PRÉCIS

Background

Crohn's disease (CD) and ulcerative colitis (UC) are the two main subtypes of inflammatory bowel disease (IBD) that are characterized by chronic relapsing inflammation of the gut resulting in complication and impaired quality of life. CD can affect the entire gastrointestinal tract from the mouth to the anus whereas UC is primarily restricted to colon. IBD causes significant morbidity and excess mortality. The onset of disease frequently occurs in early life. Medical treatment mainly consists of sulfasalazine or 5-aminosalicylates for mild-to-moderate disease, and systemic corticosteroids for moderate-to-severe exacerbations. Immunomodulators and biologics, in general, are reserved for corticosteroid-dependent or -refractory diseases since long-term use of corticosteroids is frequently associated with detrimental side effects. Those patients who do not respond to medical therapy or develop complications resort to surgery. Patients who are corticosteroid-dependent or -refractory belong to the high risk category because they are prone to develop complications, both disease- and treatment-related. Although IBD manifests throughout all ethnic groups, there has been marked heterogeneity in its incidence, prevalence, disease manifestations and outcomes. There is evidence suggesting that the incidence of IBD is rising in Asia. Yet, we have little data. One local epidemiologic study reported a three-time increase in the mean annual incidence of CD from $0.3/10^5$ in 1986-1989 to $1.0/10^5$ in 1999-2001 and the incidence of UC also increased during the same period. CD in Hong Kong Chinese is characterized by male predominance, absence of nucleotide-binding-oligomerization-domains (NOD) 2 variants, a high proportion of upper gastrointestinal tract disease (defined as any disease location proximal to the terminal ileum excluding the mouth) and a low proportion of isolated terminal ileal disease. Interestingly, our patients reported better quality of life. In contrast to CD, UC among Hong Kong Chinese is not well studied. The prevalence, survival and phenotypic data of UC are lacking.

The international working party classifies CD into different phenotypic subgroups according to the age of diagnosis, location of disease along the gastrointestinal tract and clinical behavior such as development of stricturing and penetrating disease. In white patients, phenotypic evolution has been reported with changing disease behavior over the course of disease. The phenotypic classification of CD correlates with genetic susceptibility and the natural history of the disease. Similar to CD, UC is classified into three subgroups by the maximal extent of colorectal inflammation which predict the risk of colectomy and colorectal cancer. Whether phenotypic evolution takes place among Hong Kong Chinese IBD patients and its impact on the outcome of disease remain largely unknown. Upper gastrointestinal tract disease is shown to carry excess risk of recurrence in the whites but such correlation remains unclear in Chinese. Phenotypic features can be used with other clinical markers early at diagnosis to identify high risk patients and help formulate individualized treatment strategies. Nonetheless, clinical markers which can predict the risk of progression to corticosteroid-dependent and –refractory IBD have not yet been identified.

Aims-

1. To study the incidence, prevalence and survival of UC.
2. To study the phenotypic evolution of CD and UC.
3. To study the predictors of corticosteroid-dependent and -refractory CD and UC.

Hypotheses

1. The incidence and prevalence of UC is increasing in Hong Kong Chinese.
2. There is a difference in the phenotypic evolution of CD and UC in Chinese patients.
3. Clinical markers present at diagnosis are useful in predicting the risk of progression to corticosteroid-dependent and -refractory diseases in IBD patients.

Methodology

1. UC in Hong Kong: incidence, prevalence, and survival

A longitudinal cohort study was conducted at a tertiary referral center, the IBD Clinic of the Prince of Wales Hospital which serviced a well-defined catchment population of 607,544 people in the Shatin district representing 8.9% of the total population in Hong Kong. The study comprised consecutive Chinese patients who were diagnosed with UC between 1985 and 2006 according to the criteria of Lennard-Jones. All patients were follow-up from diagnosis until emigration, death, or the end of the study (31st December 2006). Annual incidence rates were calculated based on the number of patients diagnosed and the number of residents in Shatin district. Point prevalence was calculated using the number of residents in the district on 31st December, 2006. The numerator was the number of UC patients in the cohort including those who had moved to the district after diagnosis. Age standardization was performed using the Hong Kong population weights that were released by the Census and Statistics Department in 2006. Ninety-five percent confidence intervals (CIs) of incidence and prevalence rates were estimated assuming a Poisson distribution of cases. Cumulative survival in the cohort was calculated from the date of diagnosis to the last follow-up using the Kaplan-Meier product limit method, and was compared with expected survival based on age specific mortality rates for Hong Kong population in 2005 using the log rank test. [Study 1]

2. Phenotypic evolution in the Chinese IBD patients

2.1 Phenotypic evolution of CD

A retrospective longitudinal study of consecutive Chinese CD patients was conducted. The diagnosis of CD adhered to the criteria of Lennard-Jones and had to be of at least 6 months duration. Phenotypic markers including disease behavior and location were determined by the Vienna Classification and the Montreal Classification at diagnosis and after 1, 3, 5, and 10 years of follow-up. The evolution of phenotypes and the need for major surgery, defined as either

bowel resection or stricturoplasty (excluding perianal abscess drainage or fistulotomy), were examined. [Study 2]

In study 3, clinical course of CD in Chinese patients with and without upper gastrointestinal tract (L4) disease present at diagnosis was compared as some evidence suggested that the former group of patients carried excess risk of recurrence. This cohort study included 132 Chinese CD patients (median age at diagnosis, 30.0 years, range: 14.0 - 77.0 years) who were follow-up for 770 person years. Demographic data including disease behavior and location, details of surgery and hospitalization were collected. Kaplan-Meier method was used to estimate the probabilities of further hospitalization and major surgery followed by Cox proportional hazards regression to determine if clinical variables independently predicted the endpoints.

2.2 Phenotypic evolution of UC

In study 1, all UC patients underwent colonoscopy at diagnosis for the assessment of disease phenotype which was classified as ulcerative proctitis (E1, rectal involvement only), left-sided colitis (E2, involvement up to the splenic flexure) and extensive colitis (E3, involvement proximal to splenic flexure) according to the Montreal Classification. Patients underwent follow-up colonoscopy for screening, surveillance or flare of disease during the observation period. Periodic surveillance colonoscopy with biopsies was conducted according to the international guidelines. Disease progression and regression were defined by changes in disease categories proven on colonoscopy and histologically by biopsies. The evolution of phenotypes was evaluated.

3. Predictors of corticosteroid-dependent and corticosteroid-refractory CD and UC

We sought to identify risk factors for the development of a subsequent

corticosteroid-dependent and –refractory course in patients with IBD. A total of 310 consecutive Chinese IBD patients (134 CD, 176 UC) were enrolled in a cohort study. Use of systemic corticosteroids among these patients was determined. The outcomes were corticosteroid-dependent, corticosteroid-refractory diseases and surgery among corticosteroid users. The Kaplan-Meier survival method was used to calculate the cumulative probability of reaching the outcomes subsequent to the initial course of corticosteroids. Clinical factors present at diagnosis that might potentially predict subsequent development of corticosteroid-dependent and -refractory disease were subjected to univariate analysis. Those variables with P values <0.10 were further tested as covariates in a Cox proportional-hazards model with backward stepwise regression to calculate the hazard ratios (HRs) and 95% CIs. A two-sided P value of less than 0.05 was used to denote statistical significance. [Study 4]

Results

1. UC in Hong Kong: incidence, prevalence, and survival

A total of 172 patients (51.7% male) with a median age at diagnosis of 37.0 years (range: 12.0-85.0) were recruited. The cohort was observed for a total of 1,393 person years with a median follow-up duration of 7.0 years (range: 0.5-22.0). The age-standardized incidence and prevalence rates of UC per 100,000 were 2.1 (95% CI: 1.1-3.7) and 26.5 (95% CI: 22.6-30.9), respectively, in 2006. Overall survival was similar to that expected (P=0.07). Cumulative survival among UC patients after 10 years was 95% versus 96% expected, and 94% versus 91% expected after 20 years. [Study 1, Am J Gastroenterol 2009;104:647-54]

2. Phenotypic evolution in the Chinese IBD patients

2.1 Phenotypic evolution of CD

A total of 109 patients were studied with a median follow-up duration of 4 years (range: 6 months – 18 years). CD behavior changed three years (P = 0.03) after diagnosis with an increase in stricturing and penetrating phenotypes as determined by Montreal Classification. In contrast, disease location remained stable upon follow-up in both classifications. The proportions of patients suffering from terminal ileal (L1), colonic (L2), ileo-colonic (L3) and upper gastrointestinal tract (L4) diseases did not show statistically significant change over time, even though there was a numerical trend towards an increase in proportion of ileo-colonic disease on longitudinal follow-up. Thirty-four patients (31.2%) underwent major surgery during the follow-up period. [Study 2, Inflamm Bowel Dis 2008;14:536-541]

In study 3, L4 phenotype was found in thirty (22.7%) patients at presentation. There were significantly more stricturing (46.7% Vs 18.6%) and penetrating (30.0% Vs 3.9%) phenotypes in L4 group than non-L4 group (P<0.0001). The 3-year cumulative probability of further hospitalization was 86.9% (95% CI: 73.8%-100.0%) in L4 group as compared with 49.3%

(95% CI: 39.3%-59.3%) in non-L4 group (Log-rank test, P< 0.0001). L4 phenotype independently predicted further hospitalization (adjusted HR: 2.1; 95% CI: 1.3-3.5). Cumulative probability of major surgery was significantly higher in L4 than non-L4 group (P< 0.0001). [Study 3, Inflamm Bowel Dis 2009;15:551-7; abstract was selected for poster presentation in UEGW 2008.]

2.1 Phenotypic evolution of UC

Thirty-two of 48 patients (66.7%) with initial E1 and 40 of 51 patients (78.4%) with initial E2 underwent follow-up colonoscopy. The mean duration of endoscopic follow-up and the mean number of follow-up colonoscopy were 6.7 years (range: 0.5 -21.0) and 2.4 (range: 1.0-7.0), respectively. The 5-year and 10-year cumulative rates of proximal extension were 10.5% and 23.8%, respectively. The median follow-up duration of patients with extension of disease was 7.0 years (range: 1.0-21.0). The 5-year and 10-year cumulative rates of proximal extension were 10.7% and 31.2%, respectively, for patients with E1 and 10.4% and 19.3%, respectively, for patients with E2 (log-rank test, P=0.4). Among patients with E1, the 10-year cumulative probabilities of progression to E2 and E3 were 21.8% and 11.4%, respectively. [Study 1, Am J Gastroenterol 2009;104:647-54]

3. Predictors of corticosteroid-dependent and corticosteroid-refractory IBD

3.1 Predictors of corticosteroid-dependent and corticosteroid-refractory CD

We enrolled 134 CD patients (41 females and 93 males) with a total observation period of 776 person years (median follow-up, 5.0 years; range: 0.5-20.0 years). The median age at diagnosis was 30.0 years (range: 14.0-90.0 years). Seventy-seven (57.5%) CD patients had received corticosteroids during study period. The cumulative probability of surgery was 17.8%

(95% CI: 8.6%-27.0%) at 1 year after the start of corticosteroids, whereas probabilities of progression to corticosteroid-dependent and corticosteroid-refractory diseases were 27.4% (95% CI: 16.6%-38.2%) and 20.6% (95% CI: 11.2%-30.0%), respectively. Thrombocytosis (P=0.004; HR:3.0; 95% CI: 1.4-6.4) at diagnosis predicted, whereas colonic CD (P=0.016; HR:0.3; 95% CI: 0.1-0.8) negative predicted corticosteroid dependency. Only stricturing disease (P=0.001; HR:4.5; 95% CI: 1.8-10.9) was associated with corticosteroid refractoriness using the multivariate analysis. [Study 4, Aliment Pharmacol Ther 2009;29:843-54; abstract was selected for poster presentation in DDW 2008]

3.2 Predictors of corticosteroid-dependent and corticosteroid-refractory UC

We enrolled 176 UC patients (86 females and 90 males) with a total observation period of 1364 person years (median follow-up, 7.0 years; range: 0.5-22.0 years). The median age at diagnosis was 37.5 years (range: 12.0-85.0 years). A total of 95/176 (54.0%) UC patients had received corticosteroid therapy during the observation period. The cumulative probability of surgery was 5.4% (95% CI: 0.7%-10.1%) at 1 year after the start of corticosteroids, whereas probabilities of progression to corticosteroid-dependent and corticosteroid-refractory diseases were 38.3% (95% CI: 28.3%-48.3%) and 8.3% (95% CI: 2.2%-14.4%), respectively. Thrombocytosis (P<0.0001; HR:3.9; 95% CI: 2.0-7.7) and extensive colitis (P=0.03; HR:1.7; 95% CI: 1.1-2.7) at diagnosis predicted corticosteroid dependency in UC. Presence of anemia (P=0.004; HR:10.8; 95% CI: 2.1-54.8) and initial requirement of TPN (P=0.001; HR:18.8; 95%

CI: 3.5-100.3) were associated with corticosteroid refractoriness using the multivariate analysis.

[Study 4, Aliment Pharmacol Ther 2009;29:843-54; abstract was selected for poster presentation in DDW 2008]

Conclusions

1.1 The age-standardized incidence of UC per 100,000 Hong Kong Chinese was 2.1 (95% CI: 1.1-3.7) in 2006. The mean annual age-specific incidence of UC have increased 6-fold from 0.3 (95% CI: 0-0.9) per 100,000 in the 3-year period of 1986 to 1988 to 1.8 (95% CI: 0.8-3.1) per 100,000 in 2004 to 2006.

1.2 The age-standardized prevalence of UC per 100,000 Hong Kong Chinese was 26.5 (95% CI: 22.6-30.9) in 2006.

1.3 The overall survival of UC patients was similar to the expected survival of the Hong Kong population.

2.1 Phenotypic changes in CD also occurred in Chinese patients in the same way as white patients with respect to disease behavior, though at a slower rate.

2.2 Similar to the white CD patients, the location of disease remained relatively stable over the course of disease.

2.3 Chinese CD patients had more upper gastrointestinal tract phenotype which predicted the need of surgery and subsequent hospitalization.

2.4 The rate of proximal extension of UC was not impressively high, less than 25% after ten years.

3.1 In CD, thrombocytosis predicted, whereas colonic disease negatively predicted corticosteroid dependency. Stricturing CD was associated with corticosteroid refractoriness.

3.2 In UC, thrombocytosis and extensive colitis predicted corticosteroid dependency, whereas anemia predicted corticosteroid-refractory disease.

PART I

LITERATURE REVIEW

CHAPTER 1

Epidemiology of Inflammatory Bowel Disease

1.0 Epidemiology of IBD

Descriptive epidemiology is the study of disease incidence, prevalence, and demographic factors. [Loftus 2004] The study of IBD epidemiology may yield clues to disease etiology and guide the provision of health service. However, several factors make such epidemiologic studies on IBD in Hong Kong difficult and they are as follows: mimicking infectious diseases, insidious onset of IBD with the absence of a pathognomonic test for diagnosis, ascertainment of mild or asymptomatic disease, availability of diagnostic techniques, cross-boundary referrals, absence of IBD registries, unawareness of the disease among physicians and the preference to use traditional Chinese medicine among Hong Kong Chinese.

1.1 Incidence of IBD

Although IBD manifests throughout all ethnic groups, there has been marked heterogeneity in its incidence and prevalence which is most likely due to a combination of genetic and environmental factors.

1.1.1 Incidence of CD

There was a substantial increase in the incidence of CD between 1950s and 1960s in economically developed nations including Europe and North America. [Miller 1974] However the incidence has stabilized in many of these high-incidence areas since the 1980s. (Figure 1.1) Table 1.1 illustrates the incidence of CD in Asia, North America, Europe and Africa. Incidence of CD ranged from $3.9/10^5$ to $14.6/10^5$ in North America, and from $1.6/10^5$ to $11.6/10^5$ in Europe. Interestingly, a north-south gradient of the rates of CD is observed within the United States [Sonnenberg 1991] and across Europe [Shivananda 1996] with a higher incidence of CD in the northern regions, possibly due to environmental influences and geographical affluence. Yet, exceptions to the north-south gradient exist and the most remarkable example comes from the Southern Hemisphere, New Zealand. Incidence of CD in New Zealand is amongst the highest ever reported in the white populations. The incidence rate was $16.5/10^5$ in 2004. [Gearry 2006] There is evidence suggesting that the incidence of CD is rising in the Southeast Asia, although the figures are still much smaller than that in the Western countries.

[Thia 2008] In a population-based cohort study conducted in Korea, the mean incidence rate increased from $0.05/10^5$ in the period of 1986-1990 to $1.3/10^5$ in 2001-2005. [Yang 2008] A local epidemiologic study reported a threefold increase in the mean annual incidence of CD from $0.3/10^5$ in the period of 1986-1989 to $1.0/10^5$ in 1999-2001 in Hong Kong Chinese. [Leong 2004] The increase in incidence of CD among the Southeast Asians lags behind the Caucasians. The reasons behind remain unclear but most likely multifactorial. It is speculated that urbanization and industrialization are the important factors.

Figure 1.1. Temporal trends in incidence rates (cases per 100,000 person-years) of Crohn's disease in selected geographic regions (Minnesota [Loftus 1998], Stockholm [Lapidus 1997], Scotland [Kyle 1992], Japan [Yoshida 1990, Morita 1995, Yao 2000], Korea [Yang 2008], and Hong Kong [Leong 2004])

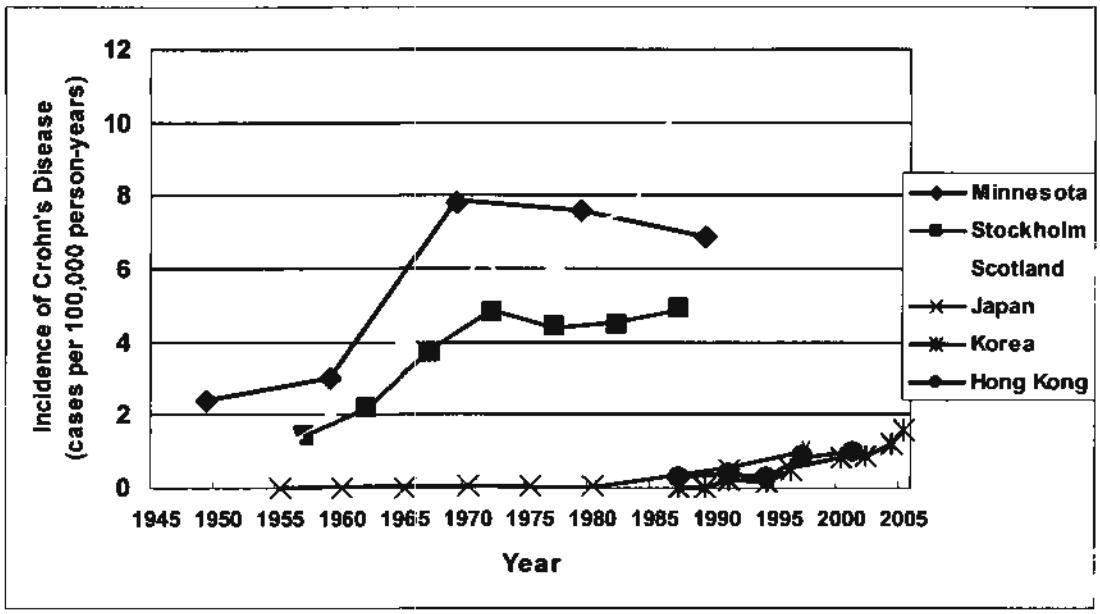


Table 1.1. Incidence and prevalence of Crohn's disease from selected registries

Study & Year of publication	Setting	Study Type	Incidence Dates	Prevalence Year	Incidence of CD*	Prevalence of CD*
Asia						
Sung et al. 1994	Hong Kong, China	Hospital	NA	1987-1992	NA	1.25
Leong et al. 2004	Hong Kong, China	Hospital	1986-2001	NA	1.0	NA
Morita et al. 1995	Japan	Survey	1991	1991	0.51	5.85
Yao et al. 2000	Japan	National registry	1998	1998	1.2	13.5
Yang et al. 2003, 2008	Korea	Population	1986-1990	NA	0.05	NA
			1986-2001	2001	0.86	5.30
			2001-2005	2005	1.34	11.24
Lee et al. 2000	Singapore	Hospital	NA	1985-1996	NA	3.6
Thia et al. 2006	Singapore	Survey	NA	2004	NA	7.2
Odes et al. 1994	Southern Israel	Population	1987-1992	1992	4.2	50.6
North America						
Pinchbeck et al. 1988	Northern Alberta	Population	1981	1981	10	44.4
Stowe el a. 1990	Rochester, NY	Hospital	1980-1989	NA	3.9	NA
Loftus et al. 1998	Olmsted County, MN	Population	1984-1993	1991	6.9	144.1
Loftus et al. 2003	Olmsted County, MN	Population	NA	2001	NA	162
Bernstein et al. 1999	Manitoba	Population	1989-1994	1994	14.6	198.5
Europe						
Munkholm et al. 1992	Copenhagen County	Population	1979-1987	1987	4.1	54
Ekbom et al. 1991	Uppsala, Sweden	Population	1965-1983	NA	7	NA
Lapidus et al. 1997	Stockholm County	Population	1985-1989	NA	4.9	NA
Rubin et al. 2000	North Tees, UK	Population	1985-1994	1995	8.3	144
Kyle et al. 1992	Aberdeen, Scotland	Population	1985-1987	1988	11.6	147
Trallori et al. 1996	Florence, Italy	Population	1990-1992	1992	3.4	40
Maté-Jiminez et al.1994	2 Spanish regions	Hospital	1981-1988	1988	1.6	19.8
Molinié et al. 2004	Northern France	Population	1988-1990	NA	5.2	NA
			1997-1999	NA	6.4	NA
Africa						
Wright et al. 1986	Cape Town, South Africa	Population	1980-1984	NA	2.6 (white) 0.3 (black)	NA

NA, not available; NY, New York; MN, Minnesota; UK, United Kingdom.

*Cases per 100,000 person-years.

1.1.2 Incidence of UC

The increase in incidence of UC preceded that of CD. Similar to CD, after a surge in the 1950s, the incidence of UC in North America and Europe has reached a plateau. (Figure 1.2) However, an opposite evolution in the incidence of CD and UC is recently reported in Northern France and Denmark. [Molinié 2004, Fonager 1997] While the incidence of CD continues to increase, incidence of UC is falling slowly. Molinié et al reported a drop in the mean incidence rate of UC from $4.2/10^5$ in the period of 1988-1990 to $3.5/10^5$ in 1997-1999 in Northern France. Table 1.2 lists the incidence of UC in Asia, North America, Europe and Africa. The incidence rates of UC ranged between $0.3/10^5$ and $6.0/10^5$ in the Southeast Asia as compared to $2.3/10^5$-$14.3/10^5$ in North America. Unlike the white populations, the incidence of UC is increasing among the Southeast Asians. Yang and his colleagues reported the mean incidence rate of UC increased from $0.3/10^5$ in the period of 1986 -1990 to $3.1/10^5$ in 2001-2005 in Korea. [Yang 2008] The highest incidence of UC among the Southeast Asian countries was reported in India. The incidence of UC in India was $6.0/10^5$ which approximated to that of

the Western countries. [Sood 2003]

Figure 1.2. Temporal trends in incidence rates (cases per 100,000 person-years) of ulcerative colitis in selected geographic regions (Minnesota [Loftus 2000], Sweden [Ekbom 1991], Cardiff [Srivastava 1992], Japan [Yoshida 1990, Morita 1995], Korea [Yang 2008], and Hong Kong [Leong 2004])

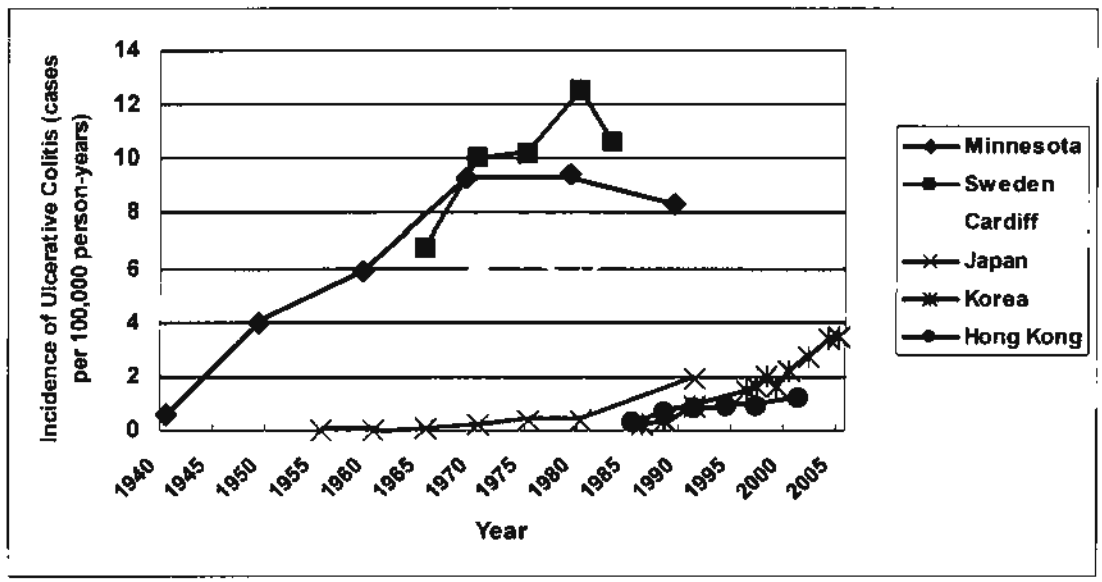


Table 1.2. Incidence and prevalence of ulcerative colitis from selected registries

Study & Year of publication	Setting	Study Type	Incidence dates	Prevalence year	Incidence of UC*	Prevalence of UC*
Asia						
Leong et al. 2004	Hong Kong, China	Hospital	1986-2001	NA	1.2	NA
Lok et al. 2008	Hong Kong, China	Hospital	NA	2006	NA	7.0
Morita et al. 1995	Japan	Survey	1991	1991	1.95	18.12
Yang et al. 2003, 2008	Seoul, Korea	Population	1986-1990	NA	0.34	NA
			1986-2001	2001	1.77	14.51
			2001-2005	2005	3.08	30.87
Lee et al. 2000	Singapore	Hospital	NA	1985-1996	NA	6.0
Sood et al. 2003	Punjab, India	Survey	1999-2000	1999	6.0	44.3
Odes et al. 1987	Southern Israel	Population	NA	1985	NA	70.6
North America						
Pinchbeck et al. 1988	Northern Alberta	Population	1981	1981	6	37.5
Stowe el a. 1990	Rochester, NY	Hospital	1980-1989	NA	2.3	NA
Loftus et al. 2000	Olmsted County, MN	Population	1984-1993	1991	8.3	229
Loftus et al. 2003	Olmsted County, MN	Population	NA	2001	NA	246
Bernstein et al. 1999	Manitoba	Population	1989-1994	1994	14.3	169.7
Europe						
Langholz et al. 1991	Copenhagen County	Population	1962-1987	1987	8.1	161.2
Ekbom et al. 1991	Uppsala, Sweden	Population	1965-1983	NA	12	NA
Rubin et al. 2000	North Tees, UK	Population	1985-1994	1995	13.9	243
Srivastava et al. 1992	Cardiff, UK	Population	1968-1977	NA	6.4	NA
			1978-1987	NA	6.3	NA
Trallori et al. 1996	Florence, Italy	Population	1990-1992	1992	9.6	121
Maté-Jiminez et al. 1994	2 Spanish regions	Hospital	1981-1988	1988	3.2	43.4
Molinié et al. 2004	Northern France	Population	1988-1990	NA	4.2	NA
			1997-1999	NA	3.5	NA
Africa						
Wright et al. 1986	Cape Town, South Africa	Population	1980-1984	NA	5.0 (white) 0.6 (black)	NA

NA, not available; NY, New York; MN, Minnesota; UK, United Kingdom.

*Cases per 100,000 person-years.

1.2 Prevalence of IBD

1.2.1 Prevalence of CD

The prevalence of CD ranged from $1.3/10^5$ to $13.5/10^5$ in the Southeast Asia, and from $44.4/10^5$ to $198.5/10^5$ in North America. (Table 1.1) In Korea, prevalence of CD increased more than twofold, from $5.3/10^5$ in 2001 to $11.2/10^5$ in 2005. [Yang 2003, Yang 2008] In Olmsted County, Minnesota, the prevalence of CD increased from $144.1/10^5$ in 1991 to $162/10^5$ in 2001. [Loftus 1998, Loftus 2003] The prevalence of CD increases in Asia as the incidence of CD increases. However, in North America where the incidence remains stable, the prevalence also increases. This is presumably due to a near-normal life expectancy of CD patients.

1.2.2 Prevalence of UC

The prevalence of UC ranged from $6.0/10^5$ to $44.3/10^5$ in the Southeast Asia, and from $37.5/10^5$ to $246/10^5$ in North America. (Table 1.2) Similar to CD, the prevalence of UC is also increasing in the globe because of a normal life expectancy of UC patients. In Korea, the prevalence of UC increased by twofold, from $14.5/10^5$ in

2001 to 30.9/10^5 in 2005. [Yang 2003, Yang 2008] In Olmsted County, Minnesota, the prevalence of UC increased from 229/10^5 in 1991 to 246/10^5 in 2001. [Loftus 1998, Loftus 2003]

1.3 Mortality of IBD

1.3.1 Mortality of CD

Increased mortality was reported in CD patients compared with the general population in the past. (Table 1.3) CD patients had increased risks of dying from infectious diseases, gastrointestinal and liver diseases, small intestinal cancer and respiratory diseases. [Jess 2006, Wolters 2006, Hutfless 2007] Nonetheless, with the introduction of new treatment strategies, this observation might change. Increased mortality in CD patients 10 years after diagnosis was reported in a European-wide population-based cohort. [Wolters 2006] Yet, not all the other studies revealed similar findings. [Ishibashi 1999, Jess 2006, Palli 1998] CD patients have an increased risk of dying from gastrointestinal cancer. [Jess 2006] However, whether CD patients have a higher risk of dying from colorectal cancer remains inconclusive. (Table 1.3) The use of 5-aminosalicylates (5ASA), immunomodulators, and corticosteroids did not correlate with mortality in patients with CD. [Hutfless 2007] The survival of CD was reported to be similar to the expected survival of the general population in Japan. [Ishibashi 1999]

Nevertheless, in contrast to the Western countries, long-term survival analysis of patients with CD is sparse in Asia.

Table 1.3. Mortality of Crohn's disease from selected registries

Study & Year of publication	Setting	Study Type	Study period	SMR (95% CIs)
Asia				
Ishibashi et al. 1999	Fukuoka, Japan	Population	1971-1994	1.75† (0.15-5.75)
North America				
Jess et al. 2006	Olmsted County, MN	Population	1940-2004	1.2† (0.9-1.6)
				4.7¶ (1.7-10.2)
Hutfless et al. 2007	Northern California	Population	1996-2003	1.4† (1.2-1.6)
				1.9‡ (0.9-3.7)
Europe				
Persson et al. 1996	Stockholm County,	Population	1955-1984	1.51† (1.29-1.75)
	Sweden			0.30‡ (0.01-1.66)
Ekbom et al. 1992	Uppsala, Sweden	Population	1965-1986	1.6† (1.4-1.9)
				1.7‡ (0.5-3.9)
Palli et al. 1998	Florence, Italy	Population	1978-1996	1.36† (0.9-2.0)
Jess et al. 2002	Copenhagen County	Population	1962-1997	1.3† (1.01-1.56)
Wolters et a. 2006	12 European countries	Population	1991-2004	1.85† (1.30-2.55)

† All causes; ‡ Colorectal cancer; ¶ Gastrointestinal cancer.

SMR, standardized mortality ratio; CI, confidence intervals; MN, Minnesota.

1.3.2 Mortality of UC

In the past, mortality of patients with UC according to the population-based cohort studies varied. (Table 1.4) In a recently published European-wide population-based cohort study, patients with UC were not found to have increased mortality 10 years after disease onset. [Höie 2007] A study conducted by Jess et al in North America also demonstrated similar findings. [Jess 2006] Patients who were older than 50 years and suffered from extensive colitis at diagnosis had an increased risk of dying within the first 2 years after diagnosis, because of the colitis-associated postoperative complications and comorbidity. [Winther 2003] Mortality due to respiratory disease among patients with UC increased [Höie 2007] but the risk of cardiovascular death decreased. [Jess 2006] Data on mortality due to colorectal cancer in UC patients were inconsistent. (Table 1.4) The use of immunomodulators was associated with a 50% reduction of mortality in patients with UC but not 5ASA or corticosteroids. [Hutfless 2007] In Japan, patients with UC had an overall normal life expectancy. However, they had a higher risk of dying from colorectal cancer. [Ishibashi 1999]

Table 1.4. Mortality of ulcerative colitis from selected registries

Study & Year of publication	Setting	Study Type	Study period	SMR (95% CIs)
Asia				
Ishibashi et al. 1999	Fukuoka, Japan	Population	1971-1994	0.94† (0.09-4.50)
				9.93‡ (4.67-17.3)
North America				
Jess et al. 2006	Olmsted County, MN	Population	1940-2004	0.8† (0.6-1.0)
				2.2¶ (0.7-5.2)
Hutfless et al. 2007	Northern California	Population	1996-2003	1.0† (0.9-1.2)
				1.6‡ (0.9-2.8)
Europe				
Persson et al. 1996	Stockholm County,	Population	1955-1984	1.37† (1.20-1.54)
	Sweden			2.85‡ (1.59-4.69)
Ekbom et al. 1992	Uppsala, Sweden	Population	1965-1986	1.4† (1.2-1.5)
				4.4‡ (3.2-5.9)
Palli et al. 1998	Florence, Italy	Population	1978-1996	0.6† (0.4-0.8)
Winther et al. 2003	Copenhagen County	Population	1962-1997	1.05† (0.92-1.19)
				0.91‡ (0.39-2.86)
Höie et al. 2007	12 European countries	Population	1991-2004	1.09† (0.86-1.37)

† All causes; ‡ Colorectal cancer; ¶ Gastrointestinal cancer.

SMR, standardized mortality ratio; CI, confidence intervals; MN, Minnesota.

CHAPTER 2

Pathogenesis of Inflammatory Bowel Disease

2.0 Pathogenesis of IBD

It is widely accepted that IBD results from an inappropriate response of a defective mucosal immune system to the indigenous flora and other luminal antigens. [Baumgart 2007] There is good evidence suggesting that genetic factors play a substantial contribution to disease susceptibility in IBD. Variation within genetic determinants and interaction between genetic and environmental factors probably determine phenotypes of the disease. [Gaya 2006]

2.1 Genetics of IBD

CD and UC are likely to be polygenic disorders which share some, but not all, susceptibility loci with variable penetrance. The strength of evidence is greatest in the Western populations. According to the large European studies, the combined concordance rates in monozygotic twins are 36% and 16% for CD and UC, respectively; whereas the combined concordance rate in dizygotic twins is 4% for CD. [Tysk 1988, Orholm 2000, Thompson 1996, Russell 2004] The genetic effect is weaker in UC than in CD, suggesting a stronger environmental component affecting the susceptibility of UC. [Russell

2004] Studies on familial IBD in relatives of affected patients are also widely reported. [Lashner 1986, Monsen 1991, Probert 1993, Orholm 1991, Park 2006] Interestingly, ethnic and geographical variation is observed in the prevalence of familial IBD. In the Western countries, familial contribution ranged from 2% to 22% among patients with CD. A greater risk is noted in siblings when compared with other family members. [Peeters 1996, Satsangi 1996] In Korea, a positive first-degree family history of IBD is reported in 1.5% of CD patients and 2% of UC patients. The risk is higher in offspring than in siblings. The lowest risk is reported in parents. [Park 2006] A low familial aggregation rate, ranged between 1.5% and 5.6%, is also reported in Chinese UC patients. [Jiang 2002, Wang 2007] Yet, the familial aggregation rate of IBD among the Southeast Asians might increase as the prevalence of IBD continues to increase. With the advancement of genome-wide association analyses using microsatellite markers for the detection of susceptibility loci, more definitive and well-replicated genetic association in IBD is identified. A list of definitive susceptible genes or loci associated with IBD is shown in table 2.1. Table 2.2 depicts

the genes or loci that are possibly associated with IBD. Both positive and negative studies are listed here for reference. More genetic studies in different populations are eagerly awaited to validate these findings.

2.1.1 CARD15/NOD2 gene

From linkage study to the identification of CARD15/NOD2 gene by positional cloning, Hugot and colleagues discovered the association between allelic variants of the CARD15/NOD2 gene and CD. [Hugot 1996, Hugot 2001] Three common variants were found to be associated with the susceptibility of CD including two missense mutations, Arg702Trp and Gly908Arg, and a frameshift mutation Leu1007fsinsC. (Figure 2.1) Ogura and colleagues identified the frameshift mutation in CARD15/NOD2 gene and its association with CD. [Ogura 2001] They further investigated the expression and function of CARD15/NOD2 gene which suggested that CARD15/NOD2 were expressed predominantly in cells of the monocyte-macrophage lineage and were involved in the activation of the transcription factor NFκB. [Ogura 2001]

CARD15/NOD2 protein shares a tripartite domain structure which includes a leucine-rich repeat (LLR) domain that is involved in ligand recognition, a central NOD domain that has ATPase activity and facilitates self-oligomerization, and the caspase activation and recruitment domain that interacts with downstream adapter molecules resulting in activation of the NFκB and apoptosis. (Figure 2.1) It belongs to a wider family of genes called the CARD transcription enhancer, R (purine)-binding, pyrin, lots of leucine repeats (CATERPILLER) family. [Harton 2002] Most disease-associated CARD15/NOD2 mutations in CD affect the LLR region of the gene. [Lesage 2002] Muramyl dipeptide which is a structural motif of peptidoglycan, a component of both gram-positive and –negative bacterial cell walls, enters the cytosol via the transporter protein, hPepT1, and interacts with the LLR region of CARD15/NOD2 protein. [Tanabe 2004, Vavricka 2004] The greatest concentration of CARD15/NOD2 mRNA is noted in the Paneth cells of the small intestine. [Lala 2003] Paneth cells play an important role in innate intestinal defense by producing antimicrobial protein, α-defensin, which regulates the microbial

density. [Elphick 2005] Patients with ileal CD are found to be deficient in α-defensin, in particular, those CD patients with CARD15 /NOD2 variants. [Wehkamp 2004] CARD15/NOD2 mutations are associated with reduced activation of NFκB. Nevertheless, CD is characterized by increased activation of NFκB and downstream cytokine production. [Neurath 1998, Chamaillard 2003] Data from murine models and human studies remain discrepant. [Kobayashi 2005, Watanabe 2004, Maeda 2005] The controversy of whether CARD15/NOD2 mutations lead to a gain or a loss of function is unresolved. Most would support the theory that CARD15/NOD2 mutations impair signaling in the innate immune response to pathogen, leading to less efficient clearing of pathogen by the intestinal epithelium. As a result, chronic intestinal inflammation occurs.

The contribution of CARD15/NOD2 varies between different populations. The prevalence of CARD15/NOD2 mutations in Asian CD is negligible (~0%) in the Chinese, Japanese and Korean populations. [Leong 2003, Guo 2004, Inoue 2002, Yamazaki 2002,

Croucher 2003] Contribution of CARD15/NOD2 to susceptibility of CD is lower in the northern Europe than elsewhere in Europe. [Bairead 2003, Idestrom 2005, Cuthbert 2002, Lesage 2002, Ahmad 2002] The carriage of CARD15/NOD2 variants between Jewish descent Caucasians and non-Jewish descent Caucasians also differs. [Zhou 2002, Abreu 2002] The three common CARD15/NOD2 variants have different effects on the susceptibility of CD. [Economou 2004] The heterozygous carriage of CARD15/NOD2 increases the risk of CD by 2.4 times. The homozygous or compound heterozygous carriage of CARD15/NOD2 risk alleles confers 17.1 times increase in risk of CD. However, less than 10% of those CARD15/NOD2 homozygote/ compound heterozygote carriers would manifest CD. [Brant 2007, Hugot 2007] Carriage of at least one risk allele increases the risks of familial disease, stricturing behaviour, and small bowel disease. [Economou 2004]

Table 2.1. Definitive susceptible genes and loci in inflammatory bowel disease

Gene or Locus	References	Genomic location	Contributing alleles/region	Function	Association	Phenotypic association
CARD15/NOD2	Hugot et al. Ogura et al. Nature 2001	16q12	Arg702Trp Gly908Arg Leu1007fsinsC	It encodes a intracellular protein which activates NFκB and mitogen-activated protein kinase pathways in response to stimulation by components of peptidoglycan (muramyl dipeptide) which present in the cell wall of bacteria [Bonen 2003, Cho 2007]	**CD** *Not found in CD patients in Hong Kong, [Leong 2003] and Janpan [Inoue 2002, Yamazaki 2002]	1. Earlier-onset of CD [Bairead 2003] 2. Ileal CD [Ahmad 2002] 3. Fibrostenosing CD [Ahmad 2002, Lesage 2002, Abreu 2002] 4.Fistulizing CD [Radlmayr 2002] 5. Surgery [Kugathasan 2004]
IL23R	Duerr et al. Science 2006	1p31	Arg381Gln	The functional IL23 receptor is heterodimeric, comprised of the IL23R and IL12RB1 subunits. IL23 cytokine is also heterodimeric and it consists of p19 and p40 subunits. IL23 activates innate cells to produce inflammatory cytokines including IL6, TNFα and IL17 which further stimulate cytokine ad chemokine production by activated macrophages and endothelial cells, leading to neutrophil recruitment.	**CD and UC** *Not found in Japanese CD patients [Yamazaki 2007]	No phenotypic association [Tremelling 2007]
IBD5	Rioux et al. Nat Genet 2001	5q31	OCTN1 (SLC22A4 C/T) OCTN2 (SLC22A5 G/C)	The organic cation transporter genes (OCTN 1 and OCTN2) are within a single haplotype block. Functional difference was shown in fibroblasts transfected with a mutant gene. [Peltekova 2004] Yet, no change in function or expression of	**CD and UC** *No association found in Japanese CD patients [Negoro 2003, Tosa 2006,	1. Earlier-onset of CD [Torok 2005] 2. Ileal CD [Newman 2005] 3. Colonic CD [Torok 2005]

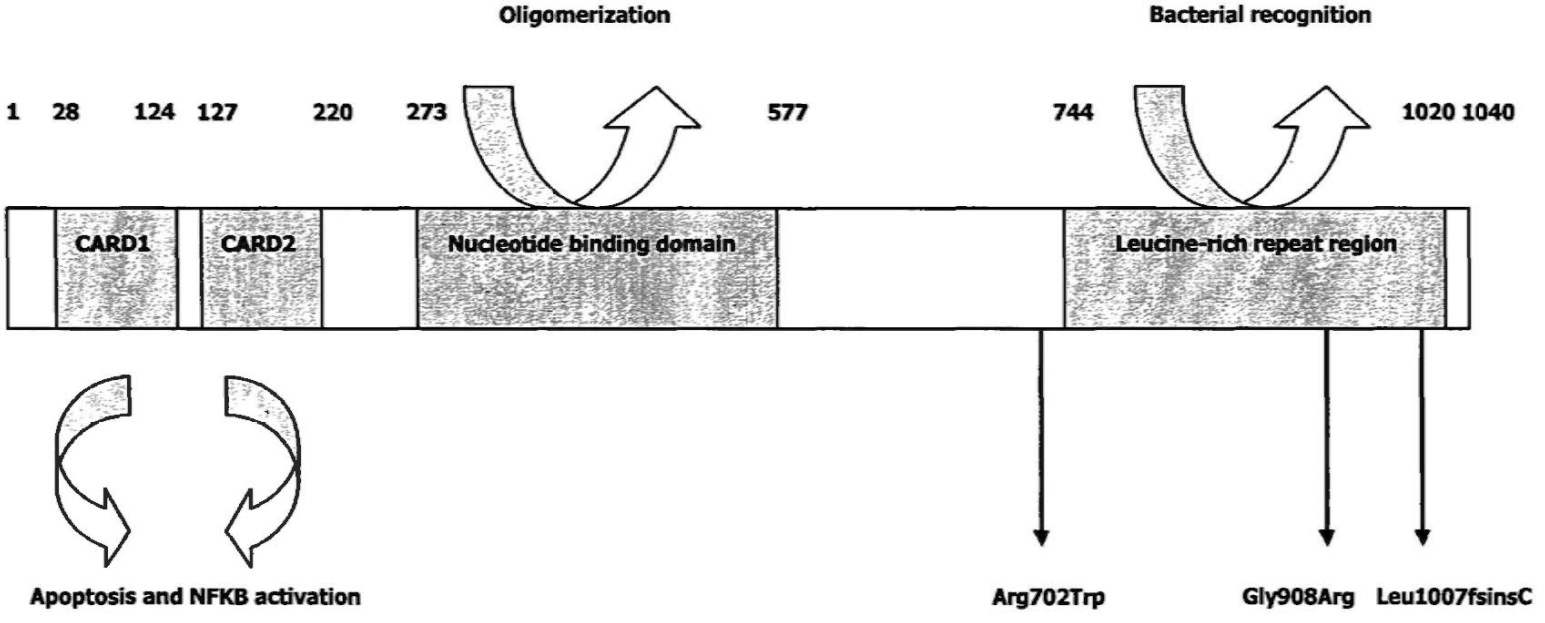
				OCTN 1 and OCTN2 was noted in tissue from affected patients. [Peltekova 2004]	Yamazaki 2004]	4. Conflicting data on perianal CD [Vermeire 2005, Newman 2005]] 5. Surgery in CD [Noble 2005, Russell 2006]
ATG16L1	Hampe et al. Nat Genet 2007	2q37	Ala197Thr	It involves in the autophagosome pathway and implicates in the intracellular bacteria processing	**CD**	Unknown
MHC region	Futami et al. Dig Dis Sci 1995 Stokkers et al. Gut 1999 Silverberg et al. Inflamm Bowel Dis 2003	6p21	DRB1*0103 DRB1*1502 DRB3*0301	The major histocompatibility complex region is a highly polymorphic and gene-dense region with complex patterns of linkage disequilibrium. The strongest association with IBD is observed in the HLA class II genes which encode cell-surface glycoproteins. Those glycoproteins are expressed on the antigen-presenting cells.	**CD and UC**	1. DRB1*0103 associates with colonic CD and UC. [Silverberg 2003] 2. DRB1*1502 associates with UC, in particular, intractable UC requiring total colectomy in Japanese. [Futami 1995,Yoshitake 1999, Masuda 1994] 3. DRB3*0301 associates with CD [Stokkers 1999]
IRGM gene region	Parkes et al Nat Genet 2007 McCarroll et al Nat Genet 2008	5q33	SNP: rs4958847	Immunity-related GTPase protein type M is an autophagy gene and it involves in the regulation of intracellular bacteria. [Singh 2006]	**CD**	1. Fistulizing behavior and perianal fistula [Latiano 2009]
IL12B	Parkes et al Nat Genet 2007	5q33	IL12/23p40 subunit	IL12B (p40) is a subunit of the IL23 cytokine. IL23 activates innate cells to produce inflammatory cytokines.	**CD**	Unknown

Table 2.2. Possible susceptible genes and loci in inflammatory bowel disease

Gene or Locus	References	Genomic location	Function	Association	Positive studies	Negative studies
MDR1/ABCB1	Satsangi et al Nat Genet 1996	7q	The multidrug resistance 1 (MDR1) gene, also known as ATP-binding cassette, subfamily B, member 1 (ABCB1) gene, encodes P-glycoprotein 170 which functions as an ATP-dependent efflux transporter pump and is widely expressed on epithelial surfaces, especially in the gut. [Thiebaut 1987]	**UC**	1. Ho et al. Gastroenterology 2005 2. Brant et al. Am J Hum Genet 2003 3. Schwab et al. Gastroenterology 2003	1. Croucher et al. Gastroenterology 2003 2. Glas et al. Gastroenterology 2004 3. Lee et al. Korean J Gastroenterol 2006
TLR4	Franchimont et al. Gut 2004	9	Toll-like receptor (TLR)-4 gene encodes receptors that are expressed on intestinal epithelial cells and recognize lipopolysaccharide which is the major component of the outer membrane of gram-negative bacteria. [Kopp 2003]	**CD and UC**	1. Ouburg et al. Gut 2005 2. Torok et al. Clin Immunol 2004 3. Gazouli et al. World J Gastroenterol 2005	1. Arnott et al. Genes Immun 2004 2. Guo et al. Postgrad Med J 2005 3. Lakatos et al. World J Gastroenterol 2005
DLG5	Stoll et al. Nat Genet 2004	10q23	Drosophila gene discs large homolog 5 is a member of the membrane-associated guanylate kinase family of scaffolding proteins which are important in the signal transduction and epithelial-cell integrity. [Baumgart 2007] Mutation within this gene is linked to increased gut permeability. [Peeters 1997]	**CD**	1. Daly et al. Eur J Hum Gen 2005 2. Newman et al. Hum Mutat 2006	1.Torok et al. Gut 2005 2.Vermeire et al. Gastroenterol 2005 3.Noble et al. Gut 2005 4.Yamazaki et al. J Hum Genet 2004

CARD4/NOD1	Satsangi et al. Nat Genet 1996	7p14	It encodes proteins that are intracellular peptidoglycan sensors expressing in the intestinal epithelial cells and recognizing gram-negative peptidoglycan derivative of invasive gram-negative bacteria. CARD4/NOD1 activates NFκB via receptor interacting protein 2 and inhibitor of κB degradation. [Inohara 2000, Chamaillard 2003, Kim 2004]	**CD and UC**	McGovern et al. Hum Mol Genet 2005	Zouali et al. Gut 2003
TNFSF15	Yamazaki et al. Hum Mol Genet 2005	9q32	It functions as a ligand for TNFRSF25 (tumor necrosis factor superfamily receptor). It is induced by the stimulation of monocytes and dendritic cells. [Prehn 2007] Protein of TNFSF15 is upregulated in macrophages and CD4+/CD8+ lymphocytes of the intestinal lamina propria of CD patients. [Bamias 2003]	**CD**	1. Yang et al. Am J Gastroenterol 2008 2. Thiebaut et al. Am J Gastroenterol 2009	Picornell et a. Inflamm Bowel Dis 2007

Figure 2.1. Structure of the CARD15/NOD2 gene and the locations of three variants which are associated with the susceptibility of Crohn's disease.



CARD, caspase activation and recruitment domain.

2.2 Environmental risk factors for IBD

2.2.1 Cigarette smoking

Cigarette smoking is a risk factor for CD. [Somerville 1984, Tobin 1987] According to a meta-analysis, smokers are two times more likely to develop CD. [Calkins 1989] Exsmokers are also at risk, but the magnitude is less than that for current smokers. [Cosnes 1999] Smokers with CD are more likely to have ileal disease and to require immunomodulators. [Lindberg E 1992] Smoking correlates with recurrence of disease following surgically-induced remission in a dose-dependent manner. [Sutherland 1990] However, the association between smoking and CD may not apply to all ethnic groups such as Jews [Reif 1995] and Hong Kong Chinese. [Leong 2004] The detrimental effect of nicotine in CD might be related to the influx of neutrophils into the intestinal mucosa. [Cosnes 2004]

On the contrary, current smokers have a significant risk reduction of developing UC. They are only 40% as likely to have UC as those who never smoke. [Calkins 1989] The protective effect of smoking against UC has been replicated in Japanese and Chinese cohorts.

[Morita 1995, Jiang 2007] Furthermore, cigarette smoking may influence the course of UC. UC patients who quit smoking are more prone to hospitalization for the flare-up of disease and to require corticosteroids or azathioprine. [Boyko 1988, Beaugerie 2001] They even have a higher risk of colectomy compared with those who never smoke or those current smokers. [Boyko 1988] The mechanism behind this interesting association between tobacco and UC remains unclear. It may be related to the effect of nicotine on rectal blood flow, colonic mucus and production of cytokines. [Rubin 2000, Cosnes 2004] Controlled trials were conducted to examine the efficacy of transdermal nicotine for induction of remission in active UC and maintenance of remission. [Pullan 1994, Sandborn 1997, Thomas 1995] However, they failed to show any beneficial effects.

2.2.2 Appendectomy

Appendectomy is associated with a future risk of CD. [Andersson 2003] The mechanisms behind remain largely unknown. It has been postulated that the removal of appendix may influence the mucosal

immune system in such a way that it increases the risk of CD.

By contrast, appendectomy appears to protect against the development of UC, with a 69% reduction in risk. [Koutroubakis 2002] Appendectomy before the age of 20 years and appendectomy for appendicitis or mesenteric lymphadenitis are found to be negatively associated with UC. [Andersson 2001] In Japan, UC patients who had appendectomy prior to diagnosis are less likely to develop recurrent symptoms; [Naganuma 2001] whereas in the Western countries, patients are less likely to require colectomy. [Radford-Smith 2002, Cosnes 2002]

2.2.3. Hygiene

The "Hygiene" hypothesis is proposed to explain the occurrence of IBD, in particular, CD. It is based on the observation that persons who were brought up in large and poor families had a lower risk of CD. Epidemiologic studies are conducted to examine the association between hygiene in infancy, childhood antigen and infection exposure, and the development of IBD later in life. A crowded living

environment, consumption of contaminated foods, absence of tap water or hot water early in life are the protective factors. It is possibly due to the enhancement of the maturation of immune system. As a result, immune tolerance towards all those environmental antigens is induced during early exposure in infancy or childhood. [Ekbom 1990, Gent 1994, Hampe 2003] On the contrary, excessive sanitation might limit the exposure to environmental antigens. Hence, functional maturation of the mucosal immune system is impaired. A lack of immune tolerance leads to the inappropriate immune response upon re-exposure to those antigens later in life.

2.2.4 Breastfeeding

Breastfeeding seems to protect against the development of IBD even though inconsistent data are shown in a meta-analysis. [Klement 2004] In the subgroup analysis of high quality studies, the pooled OR is 0.5 (95% CI: 0.3-0.8) for CD and 0.6 (95% CI: 0.4-0.8) for UC.

2.2.5 Infectious gastroenteritis and irritable bowel syndrome

An episode of infectious gastroenteritis increases the risk of IBD with an OR of 1.4 (95% CI: 1.2-1.7). The risk is slightly higher for CD compared with UC. [Porter 2008] Nevertheless, no single species is exclusively causative. [Swidsinski 2002; Garcia 2006] A higher prevalence of adherent-invasive Escherichia coli in the ileal mucosa of CD patients is reported. [Darfeuille-Michaud 2004] In addition, mycobacterium avium paratuberculosis which gives rise to granulomatous inflammation of the intestine in cattle, Johne's disease, is identified in the tissues and blood samples of IBD patients. [Chiodini 1984, Greenstein 2003] However, a 2-year prospective trial of anti-mycobacterial therapy with clarithromycin, rifabutin, and clofazimine, failed to show a sustained response in patients with CD. [Selby 2007] Patients who have a prior diagnosis of irritable bowel syndrome have a 5-time increase in the risk of IBD compared with those who do not. Adverse life events, depression and psychological stress seem to increase the likelihood of relapse in patients with IBD. [Mawdsley 2005]

2.2.6 Non-steroidal anti-inflammatory drugs, oral contraceptives, diet and attenuated live measles, mumps, and rubella vaccination

Non-steroidal anti-inflammatory drugs are implicated in the flare-up of IBD. [Felder 2000] More data on drug safety regarding the use of selective cyclooxygenase-2 (COX-2) inhibitors in IBD is warranted, although no clinically significant exacerbation of IBD is reported from a small retrospective cohort study. [Mahadevan 2002] There is a weak association between oral contraceptive use and CD. [Timmer 1998, Godet 1995] The evidence of association between diet and IBD is inconsistent. [Reif 1997, Riordan 1998, Geerling 2000, Sakamoto 2005] It is because most of the dietary studies suffer from methodological shortcomings which make the interpretation of findings difficult. So far, there is no convincing evidence to suggest that the attenuated live measles, mumps, and rubella vaccination causes IBD. [Thompson 1995, Feeney 1997, Morris 2000, Robertson 2001, Davis 2001]

2.3 Immunobiology of IBD

New insight is shed on the immunobiology of IBD with the advancement of molecular studies. It is believed that IBD results from an inappropriate response of a defective mucosal immune system to the indigenous flora and other luminal antigens. [Baumgart 2007] Several pathways interplay and result in inflammatory cascade in the intestine which can be divided into 3 categories – dysbiosis, defective mucosal barrier function and microbial killing, and deficient immunoregulation. [Sartor 2008]

Dysbiosis

(i) Changes in the composition of mucosal microbiota are observed in patients with IBD. Majority of the studies show a decrease in microbial diversity in active IBD with an increased proportion of Enterobacteriaceae and a decreased proportion of Firmicutes. [Bibiloni 2006, Swidsinski 2002, Manichanh 2006] However, it is uncertain whether these changes are primary or secondary events. In addition, data on the differences between microbial

populations in active and inactive diseases are inconsistent. [Swidsinski 2002, Darfeuille-Michaud 2004]

(ii) Adherent-invasive Escherichia coli strains are specifically associated with ileal mucosa in CD. [Darfeuille-Michaud 2004] This particular strain adheres to and invades epithelial cell. It also expresses virulence factors. Adherent-invasive Escherichia coli strains persist and replicate within the macrophages leading to the secretion of large amount of tumor necrosis factors (TNF). [Glasser 2001]

Defective mucosal barrier function and microbial killing

(i) Leaky epithelial barrier with lowered epithelial resistance and increased tight junction permeability of the intestinal mucosa is found in patients with CD. [Soderholm 2002] The defect precedes the onset of CD in individuals with a familial risk. [Irvine 2000] First-degree relatives of CD patients with a CARD15/NOD2 mutation also demonstrate

an increase in intestinal permeability. [Buhner 2006]

(ii) Mutation in ATG 16L1 gene which mediates autophagy gives rise to a defective innate immunity in patients with CD. [Hampe 2007, Rioux 2007] Bacterial clearance is hampered because of the deficient processing and killing of intracellular bacteria. In addition, variants of the IL23R gene are linked to IBD via the mechanism of altered innate immunity. [Duerr 2006] (Figure 2.2) IL23 is produced by activated myeloid cells including macrophages and dendritic cells following bacterial stimulation [Becker 2003] or via CD40 signalling. [Uhlig 2006] IL23 activates innate cells to produce inflammatory cytokines including IL6, IL17, TNFα and interferon γ which further stimulate cytokine and chemokine production by activated macrophages and endothelial cells, leading to neutrophil recruitment. Hence, an autocrine loop within the innate immune system is formed and eventually results in intestinal inflammation. [McGovern 2007]

(iii) Epithelial innate immunity is disrupted due to an over-expression of membrane-associated toll-like receptor 4 (TLR4) [Cario 2000] and upregulation of NOD2. [Berrebi 2003] (Figure 2.3) By contrast, healthy intestinal epithelial cells constitutively express TLR3 and TLR5. On recognition of specific lipopolysaccharide, TLR4 associated with its coreceptor, CD14, trigger inflammatory cytokine cascade via the activation of the transcription factor NFκB. [Rakoff-Nahoum 2004, Cario 2004] NOD2 proteins are expressed in the cytosol of antigen-presenting cells which are exposed to micro-organisms that contain peptidoglycan. (Figure 2.3) An upregulation of NOD2 in epithelial cells might compromise the ability of the host to eliminate pathogens and hence, resulting in chronic inflammation.

(iv) Commensal bacteria are mistaken for pathogens because of the dysfunctional antigen-presenting cells. Dendritic cells from IBD patients show an aberrant response to microbial surrogate stimuli such as lipopolysaccharide.

[Baumgart 2005] This might contribute to the repeated activation of certain memory T cells or failure to delete them over the reactive T-cell populations resulting in loss of tolerance and inflammation perpetuation. [Steinman 2002, Papadakis 2005] Among patients with IBD, a greater number of mature, activated dendritic cells are observed in inflammed mucosa; [Baumgart 2004, Hart 2005] whereas immature dendritic cells that are potentially tolerogenic are found to be scarce in the circulation. [Baumgart 2005]

(v) The production of antimicrobial peptides is impaired in patients with CD. Patients with ileal CD have reduced α defensin 5 production. In colonic CD, less β defensin 2 is observed. [Wehkamp 2005, Fellermann 2006, Nuding 2007]

Deficient immunoregulation

(i) Atypical antigen-presenting cells become potent effector-T-cell activators and epithelial cells acquire an

activated phenotype with increased histocompatibility molecule expression in the presence of inflammatory cytokines. [Cruickshank 2004]

(ii) Due to a failure of central and peripheral tolerance, activated T cells persist and do not undergo apoptosis in patients with CD. [Ina 1999]

(iii) Imbalance between regulatory and effector T cells is observed in patient with IBD that leads to a decrease in TGFβ and IL10. (Figure 2.4) TGFβ determines the balance between proinflammtory Th17 and anti-inflammatory T-helper cell responses. [Mangan 2006] As a result, naïve T cells (Th0) preferably differentiate into effector Th1 cells mediated by the transcription factor T-bet and IL23. [Martin 2004, Neurath 2002, Langrish 2005] Effector T cells produce inflammatory cytokines and stimulate macrophages to release IL1, IL6 and TNFα in patients with CD. Similarly, an increase in the numbers of active natural

killer T-cells is noted in patients with UC that produce IL13 and IL5 to perpetuate inflammation. [Fuss 2004]

The migration of inflammatory cells from systemic circulation to the intestinal mucosa results in intestinal inflammatory responses. The accumulation of metabolites including nitric oxide, oxygen radicals, and matrix metalloproteinases leads to tissue damage, collagen secretion and stricture formation. [Keshavarzian 2003, Leeb 2003, Theiss 2005, Kirkegaard 2004]

Figure 2.2. Signaling pathway of IL12/23

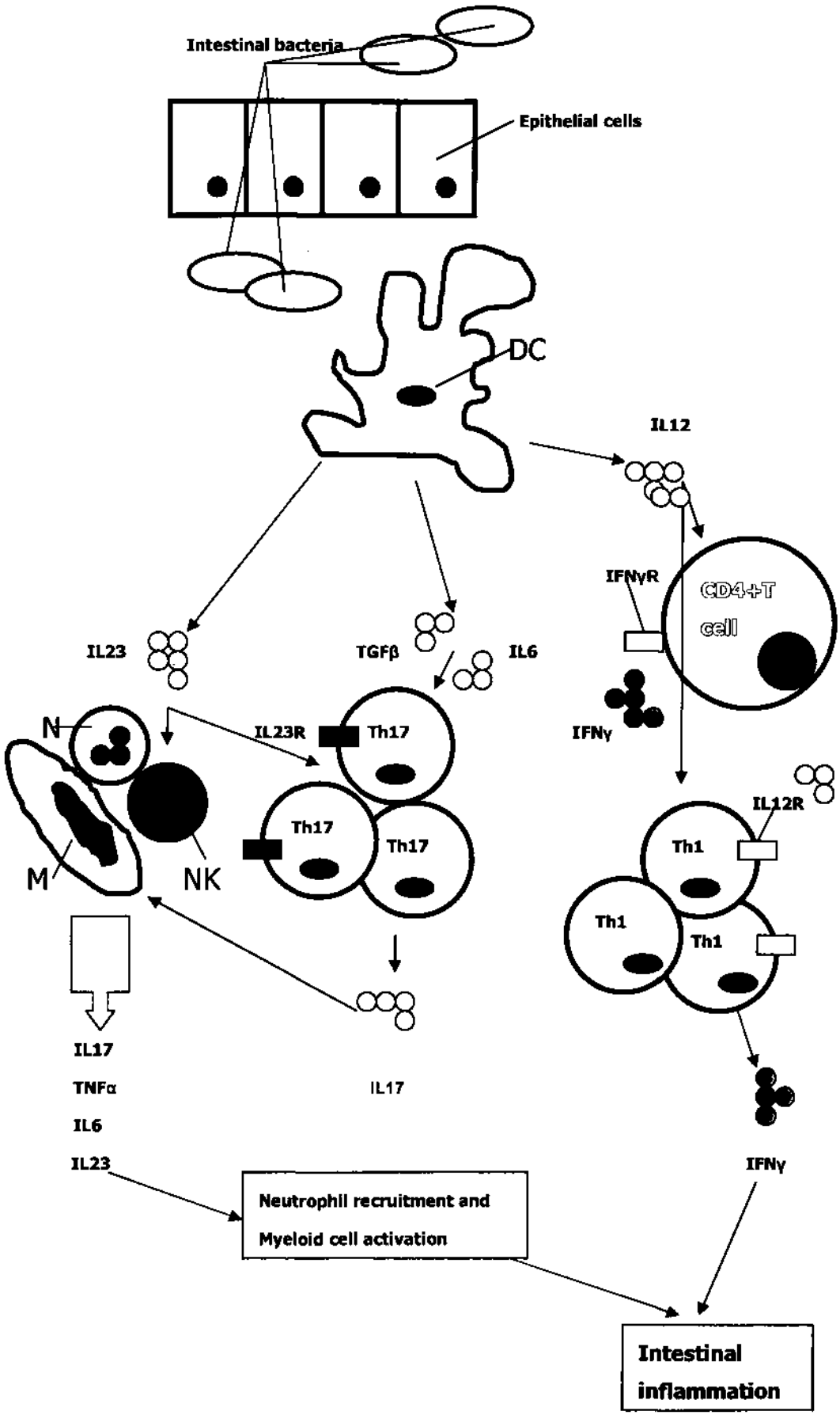


Figure legends:

DC, dendritic cells;

IL, interleukin;

IL12R, interleukin-12 receptor;

IL23R, interleukin-23 receptor;

INFγ, interferon γ;

INFγR, interferon γ receptor;

M, macrophage;

N, neutrophil;

NK, natural killer cell;

TGFβ, transforming growth factor β;

Th1, T helper type 1 cell;

Th17, interleukin-17-producing CD4+ T cell;

TNFα, tumor necrosis factor α.

Figure 2.3. Signaling pathways of NOD and TLR proteins

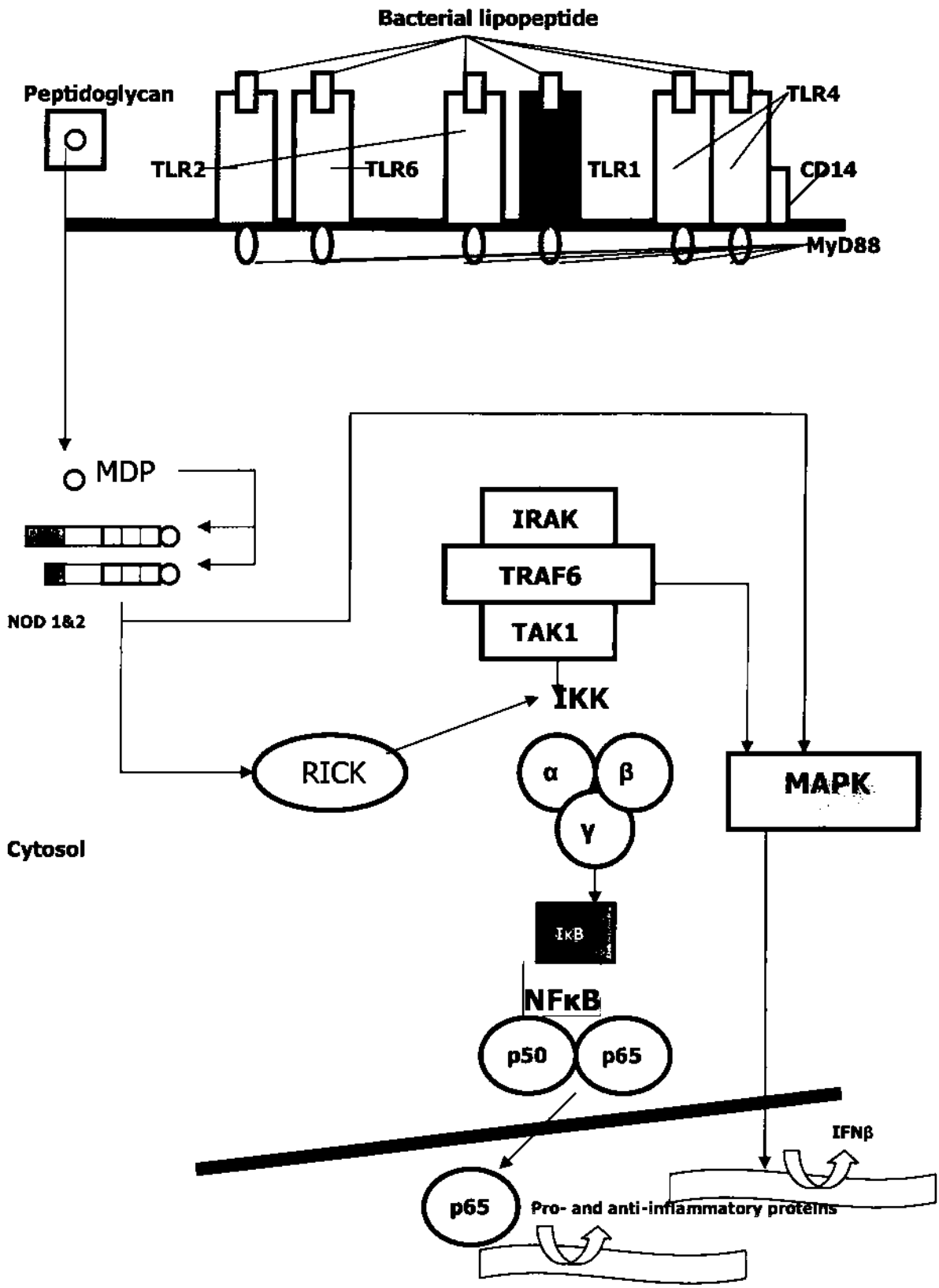


Figure legends:

IFNβ, interferon β;

IKK, inhibitor of NFκB-kinase;

IκB, inhibitor of NFκB;

IRAK, interleukin 1-receptor-associated kinase;

MAPK, mitogen-activated protein kinases signal transduction pathway

MDP, muramyl dipeptide;

MyD88, myeloid differentialtion primary response protein 88;

NFκB, (transcription factor) nuclear factor kappa B;

RICK, receptor-interacting serine/threonine kinase;

TAK, transforming growth factor-β-activated kinase;

TLR, membrane-associated toll-like receptor;

TRAF6, TNF-receptor-associated factor 6.

Figure 2.4. Deficiency in immunoregulation

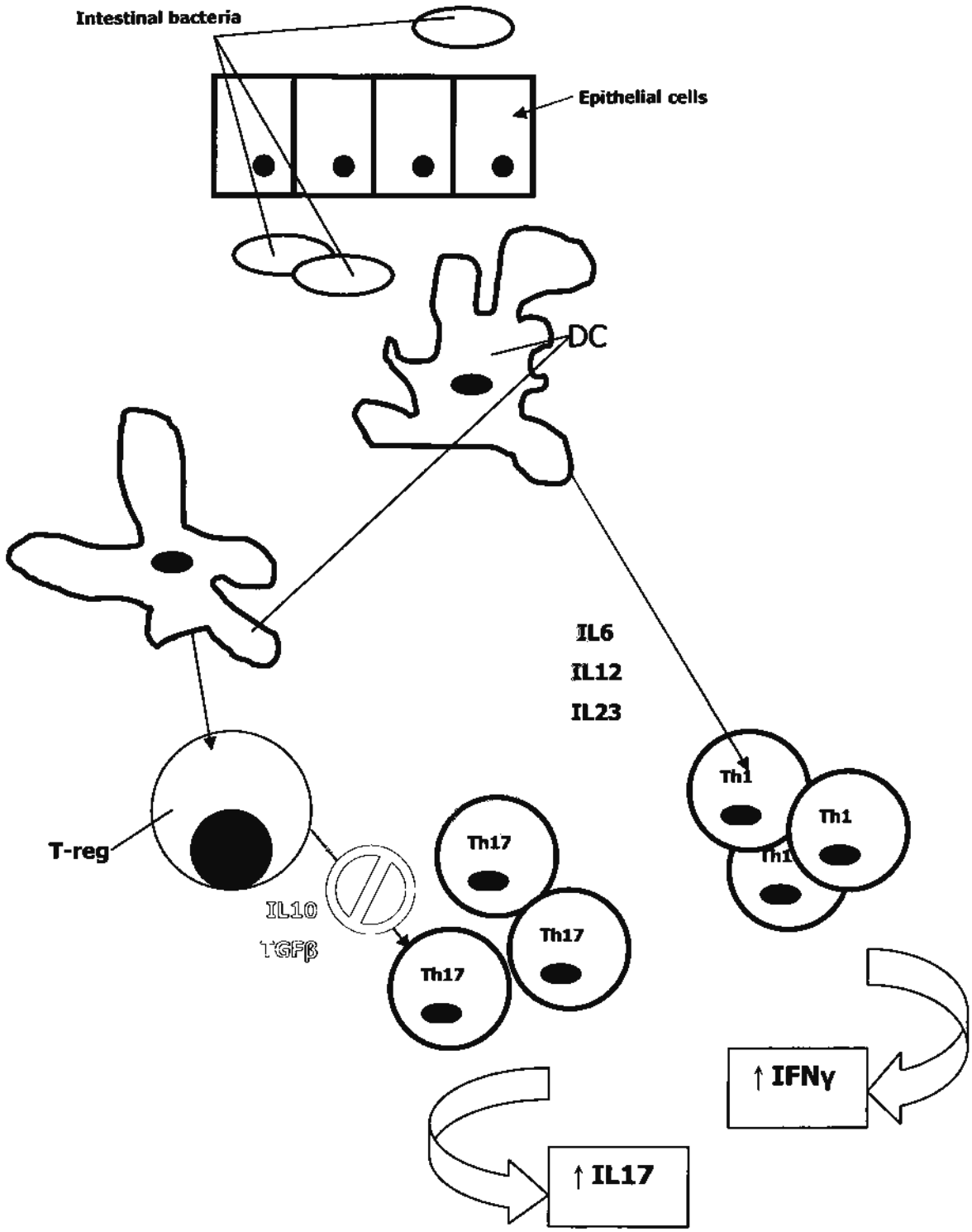


Figure legends:

DC, dendritic cells;

IL, interleukin;

INFγ, interferon γ;

TGFβ, transforming growth factor β;

Th1, T helper type 1 cell;

Th17, interleukin-17-producing CD4+ T cell;

T-reg, regulatory T cell.

CHAPTER 3

Clinical Features of Inflammatory Bowel Disease

3.0 Clinical features of IBD

IBD is characterized by chronic relapsing inflammation of the gut resulting in complication and impaired quality of life. CD can affect the entire gastrointestinal tract from the mouth to the anus whereas UC is primarily restricted to colon. The onset of IBD is typically insidious and frequently occurs in early life. The manifestations of IBD are heterogeneous. Apart from the bowel and systemic symptoms (such as diarrhoea, abdominal pain, rectal bleeding, fever and weight loss), patients can present with extraintestinal symptoms which affect the eyes, skin or joints. Occasionally, fulminant presentations due to complications of disease occur.

3.1 Clinical features of CD

3.1.1 Phenotypic classification of CD

Despite CD is heterogeneous with variable manifestations and outcomes, definable phenotypic features have been used to predict the natural history of disease, assist correlation with genotype, and to evaluate complications and outcomes. As a result, dedicated strategies can be derived to manage subtype-specific disease. In

1998, an international working party classified CD according to the age of diagnosis, location of disease along the gastrointestinal tract and clinical behavior – the Vienna Classification (VC) system. [Gasche 2000] (Table 3.1) A new classification, the Montreal Classification (MC), [Silverberg 2005] (Table 3.2) was developed in 2005 for better categorization of CD phenotypes. First, pediatric CD, when the age of onset is 16 years old and below, is separated from adult CD due to the inherent phenotypic differences. [Polito 1996, Meinzer 2005, Cuffari 1997, Heyman 2005, Kugathasan 2003] Second, when CD involves the upper gastrointestinal tract (L4) which is defined as any disease location proximal to the terminal ileum excluding the mouth, co-localization with other diseased intestinal segments is allowed. Third, behavior classification is changed so that perianal disease is no longer classified as an independent criterion for penetrating phenotype (B3) in MC. Instead, it becomes a disease modifier. This is important because perianal CD is recognized to have a different natural history from intestinal penetrating disease with respect to disease progression and outcome. The frequency of surgery is shown to be significantly

higher in those progressing to intestinal penetrating disease as compared to perianal disease. [Smith 2004] Furthermore, the evidence of association between perianal disease and internal fistulization is inconsistent among patients with isolated ileal disease. [Sachar 2005] Last but not least, CD behavior has a tendency to change with time indicating that CD is a dynamic process in evolution. [Louis 2001, Freeman 2003, Papi 2005] An increasing proportion of patients develop fistulizing and stricturing complications upon longitudinal follow-up. Hence, behavior category is considered "interim" until a prespecified time has elapsed from the time of diagnosis. [Silverberg 2005]

Table 3.1. The Vienna classification of Crohn's disease [Gasche 2000]

Age at diagnosis	A1	Less than 40 years
	A2	40 years or older
Location	L1	Terminal ileum
	L2	Colon
	L3	Ileocolon
	L4	Upper gastrointestinal tract*
Behavior	B1	Non-stricturing non-penetrating
	B2	Sricturing
	B3	Penetrating

*Upper gastrointestinal tract (L4) phenotype is defined as any disease location proximal to the terminal ileum excluding the mouth.

Table 3.2. The Montreal classification of Crohn's disease [Silverberg 2005]

Age at diagnosis	A1	16 years or younger	
	A2	17-40 years	
	A3	Over 40 years	
Location	L1	Terminal ileum	L1+L4
	L2	Colon	L2+L4
	L3	Ileocolon	L3+L4
	L4*	Upper gastrointestinal tract	-
Behavior	B1#	Non-stricturing non-penetrating	B1p†
	B2	stricturing	B2p
	B3	penetrating	B3p

*Upper gastrointestinal tract modifier (L4) allows for the co-classification of location L4 with L1 to L3. Upper gastrointestinal tract phenotype is defined as any disease location proximal to the terminal ileum excluding the mouth.
†Perianal disease modifier (p)
#B1 category should be considered "interim" until a prespecified time has elapsed from the time of diagnosis.

3.1.2 Clinical features of CD in the Southeast Asia

Male predominance of CD is a common feature of the Southeast Asians [Leong 2004, Morita 1995, Yang 2008] and it contrasts with female predominance in the whites. The age of diagnosis in Asians is similar to that of the whites. The peak age of diagnosis is in the early 20s. A younger age of diagnosis is associated with a greater number of flare-up of disease and with requirement for immunomodulators among Asians. [Thia 2006] In white CD patients, a younger age of diagnosis also predicts subsequent disabling course. [Beaugerie 2006]

Unlike the white CD patients in whom terminal ileal disease and colonic disease are the two predominant phenotypes, majority of CD patients in the Southeast Asia have concurrent ileocolonic disease. [Louis 2001, Bjornsson 2000, Yang 2008, Oriuchi 2003, Leong 2004] Isolated small bowel disease is found in approximately one fifth of the Asian patients. Disease behavior of CD patients in Asia largely resembles the phenotypic expression in the white CD patients. Nonetheless, data on phenotypic evolution of CD are

lacking among Asians.

According to a local study, [Leong 2004] 25% of CD patients have at least 1 extraintestinal manifestation and the figure is similar to the Western series. [Greenstein 1976, Rankin 1979] None of the CD patients in the cohort has primary sclerosing cholangitis. Among the Southeast Asians, the frequency of extraintestinal manifestations ranges between 19% and 25%. Primary sclerosing cholangitis is found in <1% of Asian CD patients. [Jiang 2006, Hilmi 2006]

3.1.3 Surgery in CD patients

In the white CD patients, the 10-year cumulative surgical rate is 37.9% according to a recently published population-based cohort study from Norway. [Solberg 2007] Approximately 80% of CD patients require at least one surgical resection by 20 years of disease. [Munkholm 1993] A substantial proportion of CD patients have at least two surgeries. Long-term outcome study of CD is sparse in Asia. The 5-, 10- and 15-year cumulative surgical rates of 38%, 60%, and 74%, respectively, are reported from a Japanese

hospital-based CD cohort. [Oriuchi 2003] In Hong Kong, the cumulative rate of major surgery (stricturoplasty or bowel resection) is 29% by 10 years. [Leong 2004]

3.2 Clinical features of UC

3.2.1 Phenotypic Classification of UC

Similar to CD, phenotypic classification of UC has implications for medical therapy and prognosis of disease, such as requirement for colectomy and colorectal cancer risk. In 2005 Montreal World Congress of Gastroenterology, classification of UC as defined by endoscopic appearance and by the maximal extent during follow-up was proposed. [Silverberg 2005] The three subgroups of UC are as follows:

(i) Ulcerative proctitis (E1): involvement limited to the rectum i.e. proximal extent of inflammation is distal to the rectosigmoid junction

(ii) Left-sided UC (E2): involvement limited to the portion of the colorectum distal to the splenic flexure

(iii) Extensive UC (E3): involvement extends proximal to the splenic flexure

The risk of colectomy is lower in proctitis patients as compared to patients with extensive colitis. The 5-year colectomy rates range

between 2% and 9% for proctitis patients versus 30% to 35% for extensive UC patients. [Ritchie 1978, Lennard-Jones 1983, Langholz 1992] The risk of colorectal cancer correlates with histologic inflammation [Gupta 2007] and the extent of UC. The 30-year cumulative risk of colorectal cancer is less than 5% for left-sided UC patients compared with 12% to 32% for extensive UC patients. [Ekbom 1990, Eaden 2001] Furthermore, both progression and regression of the proximal extent of inflammation are frequently reported in longitudinal studies of UC cohorts. [Langholz 1996, Ayres 1996, Meucci 2000]

3.2.2 Clinical features of UC in the Southeast Asia

There is no gender difference observed for UC in the Southeast Asia. [Leong 2004, Yoshida 1990, Yang 2000] The peak age of diagnosis is in the early 30s. An older age upon diagnosis is associated with a milder disease and a tendency for distal disease involvement. [Fujimoto 2007]

A population-based cohort study from Korea reveals that ulcerative

proctitis is the commonest UC phenotype. [Yang 2008] However, in central China, left-sided UC is found in 70% of patients. [Jiang 2006] In the southern part of China, Hong Kong, ulcerative proctitis and extensive UC are the two predominant phenotypes. [Lok 2008] Extensive colitis is more common than left-sided UC and ulcerative proctitis in Japan. [Fujimoto 2007] In the Western countries, ulcerative proctitis and extensive UC are the predominant phenotypes. [Ekbom 1991, Loftus 2000]

The frequency of extraintestinal manifestations among UC patients ranges between 6% and 14% in the Southeast Asia. [Wang 2007, Jiang 2006, Ling 2002] UC patients diagnosed with primary sclerosing cholangitis are rarely found (0-1%) in this part of the world. [Wang 2007, Jiang 2006, Park 2007, Oshitani 2002]

Approximately 50%-60% of UC patients in the Southeast Asia have a relapsing-remitting pattern of disease. [Fujimoto 2007, Ling 2002] Progression of disease is reported in 28% to 46% of UC patients. [Hiwatashi 1991, Ling 2002, Park 2007] The 1-, 3- and 10-year

cumulative probabilities of relapse for Korean patients are 30%, 59% and 88%, respectively. [Park 2007] Data of colorectal cancer among UC patients in Asia are lacking. According to a retrospective cohort study from India, the estimated risk of colorectal cancer is 5.8% after 20 years. [Venkataraman 2005] The lower risk of colorectal cancer among UC patients in Asia compared with that of the white UC patients might be related to a shorter duration of disease and a lower risk of sporadic colorectal cancer in the population.

3.2.3 Colectomy in UC patients

The cumulative colectomy rate in a Japanese cohort is reported to be 4.1% and 6.8% in the first and second years, respectively. From the third year onwards, there is a 1%-2% increase annually. [Hiwatashi 1995] In Korea, the cumulative colectomy rate is noted to be lower, 2.0% after 1 year, 2.8% after 3 years, and 3.3% after 5 to 15 years. [Park 2007] In one study conducted in Singapore, the rate of proctocolectomy is reported to be higher in Chinese, up to 18%, as compared to 10% in Indian and 13% in Malay. [Ling 2002]

Intriguingly, a study conducted in Leicestershire reveals fewer operations and UC-related complications in the Asian migrants compared with Europeans despite similar disease distribution. [Probert 1993] The long-term colectomy rates have been reported to be 8.7% to over 20% in the white UC patients. [Langholz 1992, Leijonmarck 1990, Farmer 1993, Hoie 2007]

Notably, the risk of pouchitis after proctocolectomy is also lower among UC patients in the Southeast Asia. Cumulative risk of pouchitis is reported to be 12% at 10 years in a Japanese cohort. [Ikeuchi 2004] The cumulative risk of having one or more episodes of pouchitis reaches nearly 50% by 5 years in the white UC patients. A higher rate of pouchitis is reported among those UC patients with associated primary sclerosing cholangitis. [Penna 1996]

CHAPTER 4

Management of Inflammatory Bowel Disease

4.0 Management of IBD

4.1 Diagnosis of IBD

The diagnosis of IBD is based on a composite of clinical evaluation, radiological investigation, endoscopic and pathological findings. Importantly, infective enterocolitis such as intestinal tuberculosis, Shigella, enterotoxic E. Coli, amoeba, ova and parasites, and Clostridum difficile toxin are excluded clinically through histological examination of ileal and colonic biopsies, stool and intestinal biopsy microscopy and culture.

The measurement of fecal leukocytes and fecal concentrations of calprotectin can confirm intestinal inflammation. Elevated C-reactive protein and erythrocyte sedimentation rate which are serum acute-phase reactants can reflect inflammation in general, but they are not disease-specific. In addition, serological studies examining antibodies against Saccharomyces cerevisiae and antineutrophil cytoplasmic antibodies provide adjunctive support for the diagnosis of IBD. Recently, new serological markers namely antibodies to the outer-membrane porin C of E. Coli (OmpC), antibodies against a

Pseudomonas fluorescence-associated sequence I2 (anti-I2) and antibodies against the flagellin CBir1 (anti-CBir1) are indentified to be associated with complicated CD behavior. [Ferrante 2007] The use of genetic testing for IBD is largely reserved for research purpose.

Small bowel investigation is mandatory in CD to delineate the extent of disease. Video capsule endoscopy (VCE) is superior to barium radiography and CT enteroclysis to detect small bowel pathology in patients with established CD but not those who are suspected to have CD. [Triester 2006] It is because VCD is sensitive but the identified lesions might not be specific for CD. Importantly, the retention rate of VCD is reported to occur in up to 13% of CD patients. [Cheifetz 2006] Therefore, it is currently recommended that radiological studies (small bowel follow through, CT enteroclysis, or magnetic resonance enterography) should be performed prior to VCE in CD patients. [Spada 2007] Alternatively, a self-dissolving patency capsule should be used first.

Ileocolonoscopy is performed to confirm the diagnosis of IBD by obtaining tissue for pathological evaluation, to assess disease extent and to monitor response (mucosal healing) to therapy. [Rutgeerts 2006] Endoscopic examination of surgical anastomoses to look for mucosal lesions can also predict the likelihood of clinical relapse. [Rutgeerts 1990] Upper GI endoscopy is performed only when it is indicated to look for typical focal gastritis among symptomatic CD patients. [Parente 2000] For those CD patients who have perianal symptoms, magnetic resonance imaging, endoscopic ultrasonography, and/or examination under anaesthesia should be offered apart from colonoscopy to delineate the fistula tract and to exclude complications.

4.2 Medical treatment of CD

The goal of therapy for CD is to eliminate all disease-related symptoms, normalize the patients' quality of life, and maintain the general well-being of patients with as few side effects and long-term sequelae as possible. [Lichtenstein 2009] Owing to the "incurable" nature of CD, patient should be well educated about the natural course of the disease. Therapeutic approaches to induce and maintain symptomatic control should be emphasized. Importantly, the decision of treatment should be made in conjunction with patients. Generally speaking, disease activity, location and behavior of CD determine the treatment.

In clinical practice, disease activity is described as mild to moderate, moderate to severe, and severe to fulminant according to symptoms and signs of patients. [Baumgart 2007] Ambulatory patients who suffer from mild to moderate disease are able to tolerate oral alimentation without manifestations of dehydration, toxicity, abdominal tenderness, painful mass, intestinal obstruction or weight loss of more than 10%. Patients who suffer from moderate

to severe disease have failed to respond to treatment for mild disease. They have more prominent symptoms of fever, weight loss, abdominal pain, or intermittent nausea and vomiting without evidence of intestinal obstruction. Those with severe to fulminant disease have persisting symptoms despite treatment with systemic corticosteroids. They have high fever, persistent vomiting and the other clinical evidence of intestinal obstruction, rebound tenderness, cachexia, or evidence of an abscess. [Baumgart 2007] In clinical trials, disease activity can be measured with a variety of disease activity indices such as Crohn's Disease Activity Index (CDAI), [Best 1979] Harvey Bradshaw Index, [Harvey 1980] Crohn's Disease Endoscopic Index of Severity (CDEIS), [Mary 1989] and the endoscopic scoring system for postoperative recurrence (Rutgeerts Score), [Rutgeerts 1990] etc. The details of these indices would not be elaborated here.

Apart from disease activity, location and behavior of CD, other factors including prior response to treatment, the presence of extraintestinal manifestations or superimposed infection, and

co-morbidity should also be considered in deciding treatment. In the past five years, guidelines regarding the management of CD were published from the UK [Carter 2004], Europe [Travis 2006] and also the US [Lichtenstein 2006, Lichtenstein 2009]. The mechanisms of action of different medications and their side effects are listed in table 4.1. Treatment of CD can be divided into two phases, the induction of remission and the maintenance of remission.

4.2.1 Induction of remission

Mild to moderate CD

For patients with mild to moderate ileocaecal CD, budesonide (9mg daily) is the preferred treatment. [Greenberg 1994, Seow 2008] Budesonide is superior to 5ASA for the induction of remission in CD. [Thomsen 1998] Yet, budesonide is found to be less efficacious than prednisolone in pooled analyses. [Seow 2008] The use of 5ASA in the treatment of mild to moderate ileocaecal CD is controversial. Although mesalazine (4000mg daily) is shown to be superior to placebo, the clinical relevance of an 18-point reduction in CDAI has been questioned. [Hanauer 2004] Sulfasalazine at doses of

3000-4000mg daily is shown to be beneficial in patients with colonic CD, in particular, those with associated arthropathy. [Summers 1979, Malchow 1984] Nonetheless, its use in active CD is sometimes limited by the sulfa-related side effects. The evidence of using topical 5ASA or corticosteroids as an adjunctive therapy in left-sided or distal colonic CD is not strong. Data from controlled trials are lacking. Antibiotics such as metronidazole (10-20mg/kg/day) and ciprofloxacin (1g daily) have not consistently demonstrated efficacy in the setting of luminal CD. [Sutherland 1991, Colombel 1999] Anti-mycobacterial therapy cannot be recommended for the treatment of CD. It is because controlled trials have consistently shown a lack of benefit from anti-mycobacterial therapy among patients with CD. [Borgaonkar 2000, Selby 2007]

Moderate to severe CD

CD patients with moderate to severe disease are treated with systemic corticosteroids (prednisolone at doses of up to 1mg/kg/day or equivalent). There is good evidence suggesting that corticosteroid therapy effectively induces clinical remission in CD.

[Summers 1979, Malchow 1984, Benchimol 2008] However, a minority of patients fail to response to corticosteroids. The primary nonresponse rate ranges between 16% and 20%. [Munkholm 1994, Faubion 2001] Besides, corticosteroids are not effective for the treatment of perianal fistulas. For those corticosteroid-responders, treatment should be continued until resolution of symptoms and resumption of weight gain. Nevertheless, appropriate dose-ranging studies or standards for corticosteroids tapering are not available.

Those patients who are corticosteroid-dependent or -refractory belong to the high risk category because they are prone to develop disease- and treatment-related complications. [Faubion 2001, Toruner 2008] According to European evidence based consensus, [Stange 2006] patients who are either (i) unable to reduce corticosteroids below the equivalent of prednisolone 10/mg (or budesonide below 3mg/day) within three months of starting corticosteroids, without recurrent active disease, or (ii) who have a relapse within three months of stopping corticosteroids are regarded as having corticosteroid-dependent disease. Patients who

have active disease despite prednisolone up to 0.75mg/kg/day over a period of four weeks are regarded as having corticosteroid -refractory disease.

Thiopurines including azathioprine (2.0-3.0mg/kg) and mercaptopurine (1.0-1.5mg/kg) are effective for maintaining a corticosteroid-induced remission. [Pearson 1995, Sandborn 2000] Genotyping or determination of the activity of thiopurine methyltransferase (TPMT), the primary enzyme for the metabolism of azathioprine and mercaptopurine, is recommended by the Food and Drug Administration of the US. Yet, those tests are not readily available in Hong Kong at the moment. The carriage rate of genetic polymorphisms of TPMT is unknown in the Chinese population.

Parenteral methotrexate (25mg/week intramuscularly) is also efficacious for the induction of remission in patients with corticosteroid-dependent or corticosteroid–refractory CD. [Feagan 1995, Alfadhli 2005] The anti-TNF monoclonal antibodies [Peyrin-Biroulet 2008] including infliximab, [Targan 1997]

adalimumab, [Hanauer 2006, Sandborn 2007] and certolizumab pegol [Schreiber 2005] are effective in the treatment of CD patients who do not achieve clinical response despite adequate treatment with a corticosteroid or an immunomodulator. For selected patients in whom corticosteroids are contraindicated or not desired, anti-TNF monoclonal antibodies can be used as alternatives. The humanized monoclonal antibody to alpha-4 integrin, natalizumab, [Ghosh 2003, Sandborn 2005, MacDonald 2007] can be considered in selected patients who do not tolerate or have inadequate response to conventional corticosteroids and anti-TNF therapies. [Lichtenstein 2009]

Severe to fulminant CD

CD patients with severe to fulminant disease should be hospitalized. Surgical evaluation is warranted for patients who fail to respond to medical therapies (including parenteral corticosteroids and anti-TNF agents) or those who develop complications such as intestinal obstruction, bowel perforation or massive gastrointestinal bleeding. Drainage of abscesses should be done, either percutaneously or

surgically. Elemental feeding or parenteral nutritional support whichever is appropriate should also be considered.

Fistulizing CD

Patient with fistulizing CD should be thoroughly examined to look for any evidence of intra-abdominal or perianal abscesses and complications. Surgical drainage is indicated in patients with acute suppuration. For the treatment of perianal fistulas, metronidazole (1000-1500mg daily) or in combination with ciprofloxacin (1000mg daily), [Bernstein 1980, Brandt 1982, Jakobovits 1984] and surgical therapy including fistulotomy, placement of non-cutting setons can be recommended for symptomatic patients. Immunomodulators including thiopurines, [Pearson 1995] cyclosporine [Egan 1998] or tacrolimus [Sandborn 2003] might induce remission in patients with perianal CD. Infliximab is well demonstrated in placebo-controlled trials to be efficacious in the closure of CD fistulae. [Present 1999, Sands 2004] Adalimumab is an alternative to infliximab in the treatment of fistulizing CD. A diverting ostomy should only be considered in highly symptomatic patients who fail to respond to

medical therapy. Data from controlled trials for the treatment of internal i.e. abdominal fistula are lacking.

Extraintestinal manifestations of CD

For the treatment of peripheral arthropathy which closely relates to CD activity, therapy should be directed to control underlying disease activity. In addition, sulfasalazine is frequently used apart from physiotherapy. Infliximab, rheumatological disease-modifying agent such as methotrexate and intensive physiotherapy can be used in patients with axial arthropathy. [Caprilli 2006]

Erythema nodosum is also associated with disease activity of CD. Hence, underlying active CD should be treated. Systemic corticosteroids are usually required whereas immunomodulator and infliximab are used in resistant cases. [Caprilli 2006] On the contrary, pyoderma gangrenosum does not correlate with CD activity. Corticosteroids [Chow 1996] and infliximab [Brooklyn 2006] are efficacious for the treatment of pyoderma gangrenosum. Cyclosporine [Matis 1992] and tacrolimus [Jolles 1999, Casson 2000]

can be used in refractory cases, although the evidence is less strong.

Episcleritis responds to topical corticosteroids and to treatment of the underlying CD. Uveitis may result in loss of vision. Therefore, an urgent ophthalmological assessment is needed. Both systemic and topical corticosteroids are required for the treatment of uveitis. Immunomodulators and infliximab are reported to be useful in refractory cases.

CD patients diagnosed with primary sclerosing cholangitis are treated with ursodeoxycholic acid. It is proved to be efficacious in improving liver enzymes and liver histology. [Lindor 1997, Mitchell 2001] It may also reduce the risk of colorectal cancer. [Sjoqvist 2004] Tacrolimus can improve liver biochemistry but not histology. [Van Thiel 1995] ERCP should be considered in the treatment of biliary strictures. Liver transplantation is indicated in patients with liver failure. [MacFaul 2004]

4.2.2 Maintenance of remission

According to meta-analysis and Cochrane systematic review, there is no consistent evidence to suggest that sulfasalazine and mesalamine are efficacious for the maintenance of medically-induced remission in patients with CD. [Camma 1997, Akobeng 2005] Conventional corticosteroids are also ineffective for maintenance of remission [Steinhart 2003] whereas the benefit of budesonide is not sustained by 6 months [Sandborn 2005, Benchimol 2009] Thiopurines including azathioprine and mercaptopurine are effective for maintaining a corticosteroid-induced remission. [Prefontaine 2009, Lemann 2005] Methotrexate (15mg/week intramuscularly) is efficacious for maintaining a methotrexate-induced remission. [Feagan 2000] Regularly scheduled maintenance therapy with infliximab, [Hanauer 2002, Sands 2004, Rutgeerts 2004, Behm 2008] adalimumab, [Colombel 2007, Sandborn 2007] certolizumab pegol [Sandborn 2007, Schreiber 2007] and natalizumab [Sandborn 2005] are also effective for maintenance of remission in patients with CD. The addition of immunomodulators to biologic agent may jeopardize the

benefit-risk ratio of treatment. A rare form of hepatosplenic lymphoma was reported in young CD patients who were treated with azathioprine and infliximab concurrently. [Rosh 2007]

4.2.3 Prevention of postoperative recurrence

A 3-month course of metronidazole (20mg/kg/day) or a 1-year course of ornidazole (1000mg daily) reduces the risk of postoperative recurrence for 1 year. [Rutgeerts 1995, Rutgeerts 2005] However, the side effect of peripheral neuropathy has to be considered. Sulfasalazine (3000mg daily) is shown to be beneficial. [Ewe 1989] Data on mesalamine (3000mg daily or above) are inconsistent and its effect on the prevention of postoperative recurrence is modest. [McLeod 1995, Brignola 1995, Lochs 2000, Hanauer 2004] Azathioprine (2mg/kg/day) and 6-mercaptopurine (50mg daily) also have modest beneficial effect. [Hanauer 2004, Ardizzone 2004] A combination of 1 year of azathioprine and 3 months of metronidazole show better efficacy. [D'Haens 2008] Infliximab is recently demonstrated to be effective at preventing recurrence of CD after ileal resection. [Regueiro 2009] Last but not

least, smoking is a risk factor for clinical recurrence of CD after surgery. [Kane 2005] Hence, it is of paramount importance to emphasize smoking cessation among CD patients, especially those in surgically induced remission.

4.3 Medical treatment of UC

The goals of treatment for UC would be the same as those for CD. Patient should actively participate in the decision of therapy. Therapeutic strategies to induce and maintain symptomatic control of disease and to prevent development of complications including colorectal cancer should be emphasized. Treatment is largely determined by disease activity and location apart from prior response to treatment, the presence of superimposed infection, extraintestinal manifestations, and co-morbid illnesses.

In clinical practice, disease activity is described as mild, moderate, severe, and fulminant according to patient's symptoms and signs. [Baumgart 2007] Bowel motion of up to 4 bloody stools daily without evidence of systemic toxicity is graded as mild. Those with more frequent bowel motions (up to 6 bloody stools daily) and the presence of clinical signs suggestive of minimal systemic toxicity are regarded as moderate. Patients suffering from severe disease have bloody diarrhoea of more than 6 times a day and have clinical signs of toxicity, such as fever, tachycardia, anemia, etc. Patients who

have fulminant colitis have more profound bloody diarrhoea (more than 10 bloody stools daily). They might have significant anemia requiring blood transfusion, abdominal tenderness and also clinical evidence of colonic dilation on plain abdominal X-ray. [Baumgart 2007] In clinical trials, a large number of disease-specific activity indices have been developed such as the Truelove & Witts Severity Index, [Truelove 1955] the Mayo Scoring System, [Schroeder 1987] etc.

Guidelines regarding the management of UC were published from the UK [Carter 2004] and the US [Kornbluth 2004, Lichtenstein 2006]. The mechanisms of action of different medications and their side effects are listed in table 4.1. Similar to CD, treatment of UC can be divided into two phases, the induction of remission and the maintenance of remission.

4.3.1 Induction of remission

Mild to moderate UC

The first-line therapy for patients with mild to moderate UC is

sulfasalazine or 5ASA. The efficacy of sulfasalazine and 5ASA are comparable. [Sutherland 2006] However, 5ASA avoids the sulfa-related side effects. A dose-response is observed for 5ASA with a greater clinical response rate in dose escalation (≥3000mg daily). [Sutherland 1993, Sutherland 2006] For ulcerative proctitis or left-sided UC, rectal 5ASA is found to be effective [Sutherland 1987] and is superior to rectal formulations of budesonide and prednisolone. [Marshall 1997] Besides, combined oral and rectal 5ASA result in a better clinical response than oral 5ASA alone in patients with extensive UC of mild to moderate activity. [Marteau 2005] Patients who fail to respond to sulfasalazine or 5-ASA should be given oral corticosteroids.

Moderate to severe UC

Oral corticosteroids (prednisolone at doses of up to 1mg/kg/day or equivalent) are effective in patients with UC. [Truelove 1955] In severe UC, intravenous corticosteroids can be used. [Truelove 1974] However, long-term treatment with steroids is undesirable. Hence, initiation of therapy with azathioprine (2.0-3.0mg/kg) or

mercaptopurine (1.0-1.5mg/kg) which is shown to be efficacious is recommended to eliminate the long-term use of corticosteroids. [Jewell 1974, Ardizzone 2006] Infliximab can be used in patients who do not respond to treatment with corticosteroid alone or in combination with thiopurine. [Rutgeerts 2005] Cyclosporine, [Lichtiger 1994, D'Haens 2001, Van Assche 2003, Shibolet 2005] tacrolimus [Ogata 2006, Baumgart 2008] and infliximab [Jarnerot 2005, Lawson 2006] are all demonstrated to be efficacious in patients with severe UC who do not respond to corticosteroids.

Fulminant UC

Patients who are refractory to intravenous corticosteroids, immunomodulators and/or infliximab should be referred for surgical assessment. They should be closely monitored to look for evidence of toxic megacolon or other complications such as bowel perforation and massive gastrointestinal bleeding. Close interaction between gastroenterologists and surgeons is very important to make sure emergency colectomy is timely performed if indicated. Nutritional support through elemental feeding or parenteral hyperalimentation

whichever is appropriate should be considered.

Extraintestinal manifestations of UC

Extraintestinal manifestations of UC and their management are essentially the same as those for CD.

Management of pouchitis

Metronidazole (20mg/kg/day) [Madden 1994] and ciprofloxacin (1000mg daily) [Shen 2001] are effective for the treatment of acute pouchitis. Those patients who have chronic pouchitis or have frequent relapses require long-term maintenance therapy with antibiotics. [Mahadevan 2003, Sandborn 2004]

4.3.2 Maintenance of remission

Sulfasalazine is superior to 5ASA in the maintenance of remission among UC patients. [Sutherland 2006] There is no significant dose-response difference for maintenance therapy with sulfasalazine (2000mg daily) and 5ASA (1500mg daily). [Sutherland 1993] For patients with left-sided UC or ulcerative proctitis, rectal 5ASA can be

suggested alternatively. [Hanauer 2000] Thiopurines including azathioprine and mercaptopurine are used for maintaining a corticosteroid-induced remission although the data are inconsistent. [Timmer 2007] Infliximab is efficacious for the maintenance of remission in UC patients who are corticosteroid-dependent or corticosteroid-refractory. [Rutgeerts 2005] Evidence does not support the use of cyclosporine [Shibolet 2005] and methotrexate [Oren 1996] for the maintenance of remission in patients with UC. Data on tacrolimus are insufficient.

4.3.3 Chemoprevention

Regular use of 5-ASA (>1200mg daily) is associated with a reduced risk of dysplasia and colorectal cancer in patients with UC. [Rubin 2006] However, such an association cannot be demonstrated in those UC patients who use sulfasalazine regularly. [van Staa 2005] Pooled analysis supports a protective association between 5-ASA and colorectal cancer. [Velayos 2005] However, the optimal dosage and duration of 5-ASA for the prevention of colorectal cancer in patients with UC remain unclear.

Table 4.1. Mechanisms of action and side effects of different drugs used in the treatment of IBD

Drug	Mechanisms of action	Side effects
Sulphasalazine	Details of mechanism remain uncertain. It probably acts through the moderation of release of cytokines on epithelial cells. It also inhibits arachidonic acid metabolism and is a free-radical scavenger.	Interstitial nephritis, pancreatitis, agranulocytosis, alveolitis, Stevens Johnson syndrome, headache, nausea, epigastric pain, and diarrhoea
Mesalamine	(See sulphasalazine for mechanisms of action)	Interstitial nephritis, pancreatitis, thrombocytopenia, alveolitis, rash, headache, nausea, and diarrhoea
Conventional corticosteroids	Corticosteroids induce apoptosis of target inflammatory cells and activated lymphocytes within the lamina propria of the gut. They also suppress interleukin transcription and NFκB complex via the induction of IκB.	Prolonged use (>12 weeks) of corticosteroids is associated with acne, moon face, edema, mood disturbance, glucose intolerance, posterior subcapsular cataracts, osteoporosis, osteonecrosis of the femoral head, myopathy, adrenal insufficiency, and susceptibility to infection.
Budesonide	A corticosteroid that targets at the terminal ileum and right-sided colon in a time- and pH-dependent manner. It has extensive first-pass effect in liver. (See conventional corticosteroids for mechanisms of action)	Budesonide has fewer adverse events than conventional corticosteroids according to Cochrane systematic review. [Seow 2008] Notably, it achieves better preservation of adrenal function and bone mineral density as compared to conventional corticosteroids. [Seow 2008, Schoon 2005]
Azathioprine/ Merceptopurine	Thiopurines act through the metabolites, 6-thioguanine nucleotides, which inhibit ribonucleotide synthesis. Thiopurines induce T cell apoptosis by modulating cell signalling.	Bone marrow suppression, pancreatitis, nausea, vomiting, abdominal pain, fever, rash, arthralgia, infections, hepatic injury (including drug-induced hepatitis, cholestasis, nodular regenerative hyperplasia, and peliosis) and increased risk of lymphoma

Methotrexate	Metabolites of methotrexate inhibit dihydrofolate reductase. The exact mechanism how this drug works in CD remains undefined. It probably acts through the inhibition of cytokine and eicosanoid synthesis	Bone marrow suppression, nausea, vomiting, hepatic fibrosis, hypersensitivity pneumonitis, embryotoxic, and reversible sterility in men
Cyclosporine	A cyclic oligopeptide which inhibits the calcium-dependent transcription of IL-2 by binding to calcineurin. It suppresses the activation of T cell and immunoglobulin E receptor signaling pathway. Because of its unique pharmacokinetic profile, it warrants vigilant therapeutic drug monitoring	Paraesthesia, tremor, hypertension, hypercholesterolaemia, grand mal seizure, headache, gastrointestinal discomfort, gingival hyperplasia, hypertrichosis, nephrotoxicity, electrolyte abnormality and opportunistic infections including pneumocystis pneumonia
Tacrolimus	A calcineurin inhibitor which suppresses proinflammatory cytokine production and T cell activation. It reduces NF-κB activity by blocking the degradation of NF-κB inhibitory protein. Its therapeutic window is relatively narrow. Hence, serum tacrolimus trough level should be monitored.	Paresthesia, tremor, headache, insomnia, hot flush, alopecia, hyperglycaemia, hypomagnesaemia, hypertension, deranged liver function, nausea and other gastrointestinal symptoms, nephrotoxicity, myelosuppression and increased infection
Infliximab	A chimeric monoclonal antibody that binds with a high affinity to TNF α and induces apoptosis of inflammatory cells. TNFα is a proinflammatory cytokine playing a central role in the pathogenesis of IBD.	Infusion reaction (IgE mediated type I hypersensitivity reaction with symptoms including headache, dizziness, nausea, flushing, fever, chills, chest pain, dyspnoea, and pruritis), delayed hypersensitivity-like reaction (serum sickness-like disorder with myalgia, arthralgia, urticaria, fever, rash, pruritis, headache), bacterial infections, mycoses (histoplasmosis, coccidioidomycosis, norcardiosis, and candidiasis), and mycobacterial infections (more extrapulmonary involvement), development of antibodies to infliximab and other autoantibodies (antinuclear antibody and anti-ds DNA antibody) and drug-induced lupus reaction, increased risk of malignancy and lymphoproliferative disorder (controversial because of the concomitant use of immunomodulators and the lack of long-term data)

Adalimumab	A fully human IgG1 monoclonal antibody that binds with a high affinity and specificity to membrane and soluble TNF.	Injection-site reactions, arthralgia, pyrexia, headache, fatigue, nausea, abdominal pain, nasopharyngitis, infections, development of anti-adalimumab antibody
Certolizumab pegol	A pegylated humanized Fab' fragment of an anti-TNF monoclonal antibody with a high binding affinity for TNFα. It does not induce apoptosis of T cells or monocytes because of its absence of an Fc portion.	Injection-site reactions, headache, pyrexia, arthralgia, nausea, vomiting, abdominal pain, nasopharyngitis, infections, development of anti-certolizumab antibody
Natalizumab	A humanized IgG4 monoclonal antibody that acts against α4 integrins. α4 integrins are glycoproteins expressed on the surface of most leukocytes and they are involved in the adhesion of leukocytes to vascular endothelium and subsequent migration of leukocytes into the surrounding tissue.	Headache, dizziness, fatigue, nausea, abdominal pain, hypersensitivity-like reaction, acute infusion reaction, nasopharyngitis, infections, development of anti-natalizumab antibody, rarely progressive multifocal leukoencephalopathy

PART II

HYPOTHESES AND CLINICAL STUDIES

CHAPTER 5

Aims and Hypotheses

IBD is associated with lifetime morbidity and the onset of disease frequently occurs in early life. Corticosteroids are the mainstay of treatment for patients with moderate to severe CD and UC. Those patients who are corticosteroid-dependent or -refractory belong to the high risk category because they are prone to develop disease- and treatment-related complications. [Faubion 2001, Toruner 2008] Patients who do not respond to medical therapy or develop complications such as intestinal obstruction, bowel perforation, massive gastrointestinal bleeding, high grade dysplasia or bowel cancer, resort to surgery. Effort has been made to derive new treatment strategy - early aggressive therapy with biological agents and/or immunomodulators aiming to alter the natural course of the disease. [Lemann 2006, Hommes 2005, D'Haens 2008] In the Western countries, the total direct and indirect costs for IBD are substantial. [Feagan 2000, Odes 2006] With the advent of biological therapy, the direct cost is going to rise.

Although IBD manifests throughout all ethnic groups, there has been marked heterogeneity in its incidence, prevalence, disease

manifestations and outcomes. There is evidence suggesting that the incidence of IBD is increasing in Asia. Yet, we have little data. One local epidemiologic study reported a 3-time increase in the mean annual incidence of CD from $0.3/10^5$ in 1986-1989 to $1.0/10^5$ in 1999-2001 and the incidence of UC also increased during the same period. [Leong 2004] Nonetheless, a study from another district hospital failed to demonstrate any increase in the incidence of UC. [Lok 2008] On the other hand, long-term study evaluating the natural course of the IBD in our population and the survival data are lacking.

The international working party classifies CD into different phenotypic subgroups according to the age of diagnosis, location of disease along the gastrointestinal tract and clinical behavior. In white patients, phenotypic evolution has been reported with changing disease behavior over the course of disease. The phenotypic classification of CD correlates with genetic susceptibility and the natural history of the disease. Similar to CD, UC is classified into three subgroups by the maximal extent of colorectal

inflammation which predict the risk of colectomy and colorectal cancer. Whether phenotypic evolution takes place among Hong Kong Chinese IBD patients and its impact on the outcome of disease remain largely unknown. Upper gastrointestinal tract phenotype is shown to carry excess risk of recurrence in the whites [Wolters 2006] but such correlation remains unclear in Chinese. Phenotypic features can be used with other clinical markers early at diagnosis to identify high risk patients and help formulate individualized treatment strategies. Nevertheless, clinical markers which can predict the risk of progression to corticosteroid-dependent and –refractory IBD have not yet been identified.

Therefore, a series of studies have been performed to examine the incidence, prevalence and survival of UC in Hong Kong Chinese, the phenotypic evolution of both CD and UC, and to identify predictors of corticosteroid-dependent and -refractory CD and UC. The results of these studies would be important in the planning of health service and in formulation of treatment. The aims and hypotheses of this thesis can be summarized as follows.

5.1 Aims

1. To study the incidence, prevalence and survival of UC.
2. To study the phenotypic evolution of CD and UC.
3. To study the predictors of corticosteroid-dependent and -refractory CD and UC.

5.2 Hypotheses

1. The incidence and prevalence of UC is increasing in Hong Kong Chinese.
2. There is a difference in the phenotypic evolution of CD and UC in Chinese patients.
3. Clinical markers present at diagnosis are useful in predicting the risk of progression to corticosteroid-dependent and -refractory diseases in IBD patients.

CHAPTER 6

Incidence, Prevalence and Survival of Ulcerative Colitis in Hong Kong Chinese

6.1 Longitudinal study of UC [Study 1: Am J Gastroenterol 2009;104:647-54]

6.1.1 METHODS

Population

This study was conducted at a tertiary referral center, the IBD Clinic of the Prince of Wales Hospital that serviced a well-defined catchment population of 607,544 people in the Shatin district representing 8.9% of population of Hong Kong. [Census and Statistics Department. Table 141] The residents of Shatin district were socioeconomically similar to the whole Hong Kong population. [Census and Statistics Department. Table 158] Ninety-four percent of the medical care in Hong Kong was provided by the public hospital system. Chronic diseases such as IBD incurred high cost due to the need for long-term medications and expensive investigations. As a result, most patients with IBD were followed-up in public clinics and hospitals. [Leong 2004] The gastroenterology and proctology service was provided by the medical gastrointestinal clinic and surgical Colorectal Clinic in the Prince of Wales Hospital,

the only local public hospital to provide such a service in the district. The endoscopy center in the Prince of Wales Hospital was a combined medical and surgical unit and was the only public unit to offer colonoscopy or flexible sigmoidoscopy in the district. All IBD cases were referred to the IBD clinic for further management. In addition, there was not any private gastroenterologist in the district during the observation period. Our cohort was therefore representative of the population of UC patients in the district.

UC Cohort

This cohort study consisted of all cases of UC diagnosed among residents in Shatin between 1985 and 2006. The identification and recruitment of cases have been described in detail previously. [Leong 2004] The complete medical records of all study subjects were reviewed to confirm the diagnosis of UC that adhered to the criteria of Lennard-Jones [Lennard-Jones 1989] and had to be of at least 6 months duration. Crohn's disease, indeterminate colitis, Behcet's disease, infective enterocolitis especially intestinal tuberculosis were excluded clinically through histological

examination of ileal and colonic biopsies, amoebic serology, stool and intestinal biopsy microscopy and culture. All UC patients underwent baseline ileocolonoscopy and biopsies for the diagnosis of disease and assessment of disease extent. Sigmoidoscopy had not been the preferred modality of endoscopic evaluation in our institution. The extent of disease was classified as ulcerative proctitis (E1, as defined by rectal involvement only), left-sided UC (E2, involvement up to the splenic flexure) and extensive UC (E3, involvement proximal to splenic flexure) according to the system proposed in the Montreal World Congress of Gastroenterology. [Silverberg 2005] Disease progression and regression were defined by changes in disease categories proven on colonoscopy and histologically by biopsies. Periodic surveillance colonoscopy with biopsies was offered to patients with longstanding extensive colitis in early 1990s and the practice was extended to left-sided colitis according to the international guidelines. [Eaden 2002, Itzkowitz 2005] Screening colonoscopy was performed in all UC patients 8-10 years after the onset of UC symptoms. Patients with extensive colitis or left-sided colitis who had a negative screening colonoscopy were

offered surveillance colonoscopy every 1 to 2 years. Patients who had primary sclerosing cholangitis would be offered yearly surveillance. In some cases, surveillance colonoscopy was conducted with dye-spray chromoendoscopy.

A central medical record system has been installed in all public hospitals under the Hospital Authority since late 1990s that allowed access to all inpatient and outpatient drug dispensing record, laboratory test results, radiology reports, endoscopy, and surgical operation record. This enhanced the completeness of the medical record. Baseline demographic and clinical features captured before 2001, which include sex, age, smoking history, family history of IBD, age and date of diagnosis, disease extent at diagnosis and upon any follow-up colonoscopy, details of medication and operation, were extracted retrospectively. From 2001 onwards, demographics of all newly diagnosed UC patients and clinical data, including change of disease extent calculated from findings at any follow-up colonoscopy, details of medication and operation were prospectively collected. Last follow-up date and vital status at last follow-up were

recorded. Fatality figures were based on mortality registry of the district council. Follow-up was complete to death or 31st December 2006 in 93.0%.

All patients were ethnically Chinese, of whom 70% were born in Hong Kong and 30% were emigrants from southern mainland China. They were all followed-up by the gastroenterologists in the IBD clinic. Patients with stable condition underwent periodic (usually 4 monthly) evaluations. Those with active disease would be offered frequent follow-up or even hospitalization depending on disease severity. A standard protocol of workup and management was adopted following the international guidelines. Disease activity was described as mild (up to four bloody stools daily and no systemic toxicity), moderate (four to six bloody stools daily and minimal toxicity) or severe (more than six bloody stools daily and signs of toxicity, such as fever, tachycardia, and anemia). [Carter 2004, Kornbluth 2004, Baumgart 2007] Patients received 5ASA for mild disease or as maintenance therapy. Short-term oral corticosteroid therapy has been used for episodes of worsening of symptoms in

moderate to severe UC that was usually tapered and discontinued over 2-3 months. As early 1990s, thiopurines have been used for corticosteroid-dependent or -refractory disease. Cyclosporine was introduced in late 1990s for corticosteroid- or thiopurine-refractory or intolerant disease among UC patients. Infliximab has been used in corticosteroid and/or immunomodulator refractory UC since 2006. From 2006, tacrolimus was used in some patients with moderate to severe UC. Patients who developed complications such as toxic megacolon, bowel perforation, massive gastrointestinal bleeding, high grade dysplasia or bowel cancer, underwent colectomy. Those who failed to respond to medical treatment, defined as severe disease despite systemic corticosteroid (up to 1mg/kg/day) and/or immunomodulator/infliximab had been given for at least 2 weeks, were also offered colectomy.

Analysis

The annual incidence rates with age standardization were calculated according to the Hong Kong Census figures. [Census and Statistics Department. Table 137] The year of diagnosis of UC rather than the

year of symptom onset was used to determine the incidence to avoid recall bias. Point prevalence was calculated using the total number of residents in the area on 31st December, 2006. The numerator was the number of UC patients in the cohort including those who had moved to the district after diagnosis. Prevalence rate was age adjusted using Hong Kong Census figures in 2006 as the standard. Ninety-five percent confidence intervals (CIs) of incidence and prevalence rates were estimated assuming a Poisson distribution of cases. Cox proportional hazards regression analysis that allowed simultaneous adjustment of variables was used to determine if sex, duration of UC, age at diagnosis or maximal disease extent was independent predictor of colectomy using the backward stepwise approach. Results were expressed as hazard ratios (HRs) with their 95% CIs. Cumulative survival in the cohort was calculated from the date of UC diagnosis to the last follow-up using the Kaplan-Meier product limit method, and compared with expected survival based on age-specific mortality rates for Hong Kong population in 2005 using the log-rank test. P value of less than 0.05 was used to denote statistical significance.

6.1.2 RESULTS

Demographics

A total of 172 patients were diagnosed with UC between 1985 and 2006 with a median age of 49.0 years (range: 23.0-87.0). Eighty-nine patients were men (51.7%). The median age at diagnosis was 37.0 years (range: 12.0-85.0). Figure 6.1 shows the mean annual age-specific incidence of UC in different age groups for the whole study period. A "bimodal" distribution was revealed. The peak age group of diagnosis was 25-34 years followed by a second smaller peak between 45 and 54 years. The cohort was observed for a total of 1,393 person-years with a median follow-up duration of 7.0 years (range: 0.5-22.0). Only 12 (7.0%) patients were lost to follow-up. Patients (15.1%) were ex-smokers or current smokers. One UC patient had a family history of IBD. Table 6.1 presents the demographics of Chinese UC patients. A total of 94 patients (54.7%) had received systemic corticosteroids during the observation period. Of 94 patients, 25 (26.6%) initially required corticosteroids for the treatment of first flare-up of disease. Twenty-four (14.0%), 4 (2.3%) and 4 (2.3%) patients were given

thiopurines (azathioprine or mercaptopurine), cyclosporine and tacrolimus, respectively. Two patients (1.2%) were prescribed infliximab during the study period. Upon last follow-up, 140 of 172 patients (81.4%) took oral and/or topical 5-ASA.

Incidence and Prevalence

The annual age-specific incidence rate of UC was 2.1 (95% CI: 1.1-3.7) per 100,000 in 2006. The mean annual age-specific incidence of UC have increased sixfold from 0.3 (95% CI: 0-0.9) per 100,000 in the 3-year period of 1986-1988 to 1.8 (95% CI: 0.8-3.1) per 100,000 in 2004-2006 (figure 6.2). The point prevalence of UC as determined on 31st December 2006 was 26.5 (95% CI: 22.6-30.9) per 100,000. Age-standardized prevalence peaked at the age category between 45 and 54 years for both men and women. Apart from a higher prevalence of UC in men in the category between 55 and 64 years, both gender had similar distribution (figure 6.3).

Complications

Between 1985 and 2006, one patient in our cohort had high-grade

colonic dysplasia and underwent proctocolectomy. The surgical specimen revealed moderately differentiated adenocarcinoma of cecum that invaded into the appendix without any nodal metastasis. Two patients had perforation of sigmoid colon. One patient developed fulminant colitis and two other patients had toxic megacolon. All of them underwent colectomy.

Surgery

Eleven patients underwent colectomy during the study period. Table 6.2 presents the clinical characteristics of these patients. Five patients had refractory disease despite medical treatment. The remaining six patients had operation because of disease complications. The cumulative colectomy rates were 2.4% and 7.6% at 1 and 10 years of follow-up. Figure 6.4 shows the cumulative colectomy-free survival in the Chinese UC patients. Maximum extent of disease (HR= 3.1; 95% CI: 1.0-9.5) and disease duration (HR= 1.1; 95% CI: 1.0-1.2) were found to associate with colectomy but not gender (P=0.3) or age of diagnosis (P=0.5).

Survival

A total of 8 deaths occurred in 172 UC patients, with only 1 death directly or indirectly attributable to underlying disease or its management. That male patient was first diagnosed to have extensive ulcerative colitis when he was 22 years old. He underwent proctocolectomy for toxic megacolon within 6 weeks of diagnosis. At 3 years later, he had intestinal obstruction that was complicated by extensive small bowel infarction requiring surgical resection and ileostomy. He died at the age of 26 years because of massive anastomotic hemorrhage 1 year after the small bowel surgery. For the remaining seven cases, four were women and two of them died from stroke, one died from urinary tract infection and the other died from leg ulcer and sepsis. All three men died from pneumonia. Table 6.3 presents the causes of death and figure 6.5 illustrates the observed and expected cumulative survival in the Chinese patients diagnosed with UC in 1985-2006. Overall survival was similar to that expected (log-rank test, P=0.07). Cumulative survival among UC patients after 10 years was 95% versus 96% expected, and 94% versus 91% expected after 20 years.

Table 6.1. Demographics of Chinese UC patients

Number of patients	172	
Gender (%)		
Male	89	(51.7)
Female	83	(48.3)
Mean age (yr)	48.4	
Median age (yr)	49.0	
Mean age at diagnosis (yr)	40.4	
Median age at diagnosis (yr)	37.0	
Mean duration of disease (yr)	8.1	
Median duration of disease (yr)	7.0	
Age group (%)		
15-24	4	(2.3)
25-34	27	(15.7)
35-44	30	(17.4)
45-54	54	(31.4)
55-64	35	(20.3)
65+	22	(12.8)
Country of birth (%)		
China	52	(30.2)
Hong Kong	120	(69.8)
Smoking (%)		
Ever-smoker	26	(15.1)
Never-smoker	146	(84.9)
Family history of IBD (%)	1	(0.6)
Extent of disease (%)		
Extensive colitis	73	(42.4)
Left-sided colitis	51	(29.7)
Proctitis	48	(27.9)

Table 6.2. Clinical characteristics of 11 patients with colectomy, 1985-2006

Number	Gender	Age of diagnosis (year)	Duration of disease (year)	Maximal extent	Indication of colectomy
1	F	37	1	LC	Fulminant colitis
2	M	22	0.1	EC	Toxic megacolon
3	M	51	2	EC	Refractory UC
4	M	29	12	EC	Refractory UC
5	F	30	0.5	LC	Sigmoid perforation
6	M	18	0.5	EC	Refractory UC
7	F	68	4	EC	Sigmoid perforation
8	M	45	9	EC	DALM, cecal cancer
9	M	24	6	EC	Refractory UC
10	M	22	11	LC	Toxic megacolon
11	M	18	10	EC	Refractory UC

LC, left-sided colitis; EC, extensive colitis; DALM, dysplasia-associated lesion or mass

Table 6.3. Cause of death, 1985-2006

Number	Gender	Age at death (yr)	Cause of death
1	F	52	Leg ulcer, sepsis
2	M	26	Intestinal hemorrhage
3	F	74	Stroke
4	F	87	Urinary tract infection
5	M	57	Pneumonia
6	M	82	Pneumonia
7	F	80	Stroke
8	M	72	Pneumonia

Figure 6.1. The mean annual age-specific incidence of UC in Hong Kong according to age groups, 1985-2006

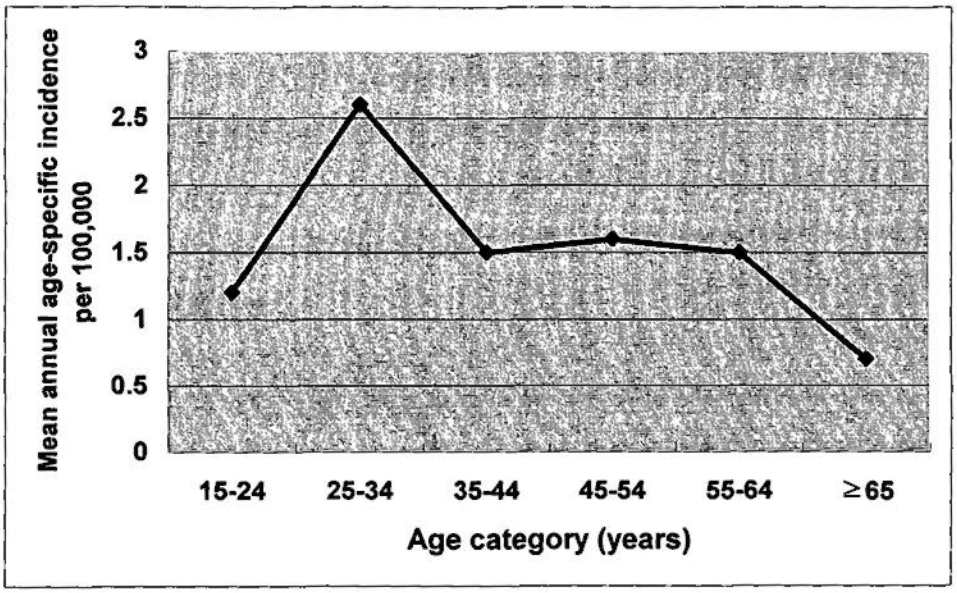


Figure 6.2. The temporal trend of mean annual age-specific incidence of UC in Hong Kong, 1986-2006

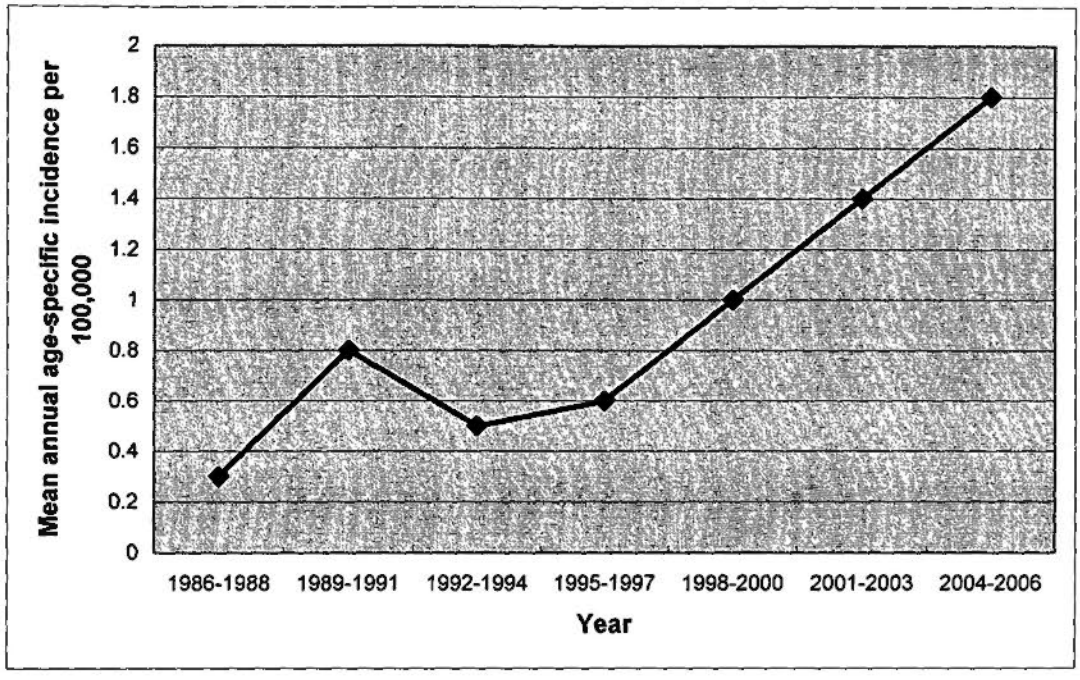


Figure 6.3. Age-adjusted prevalence of UC in Hong Kong, 2006

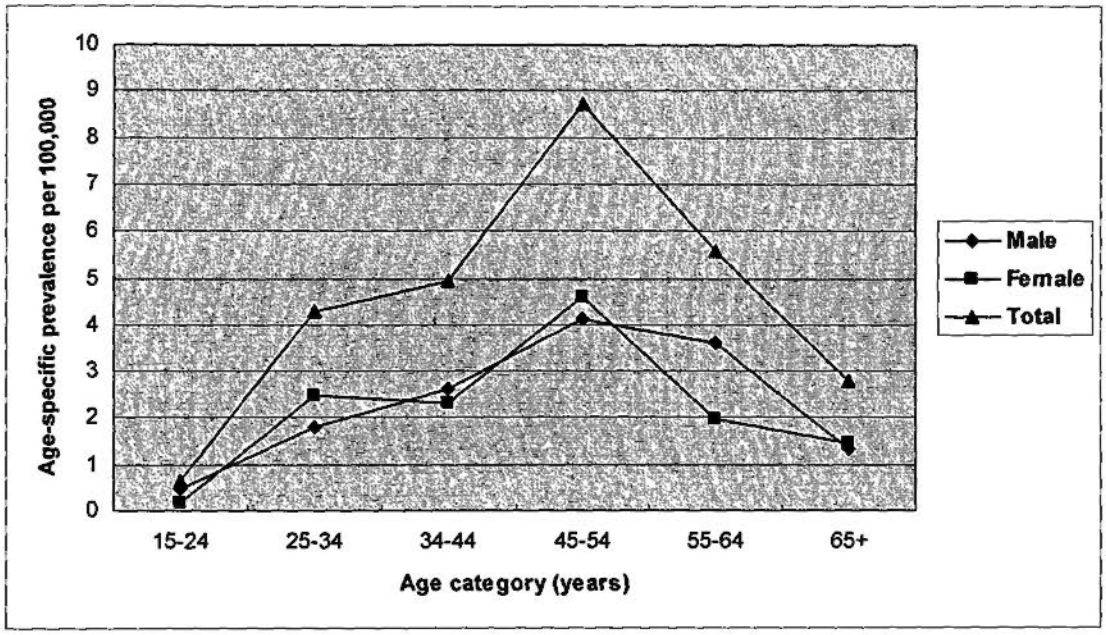
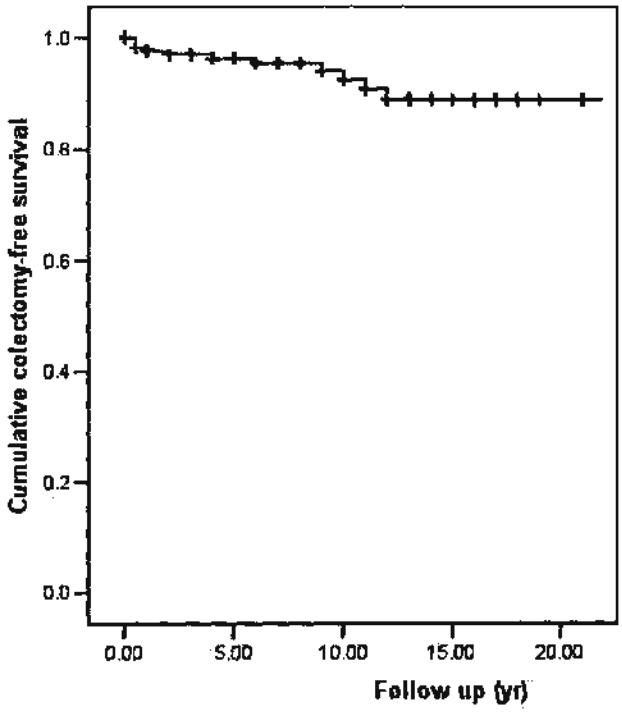
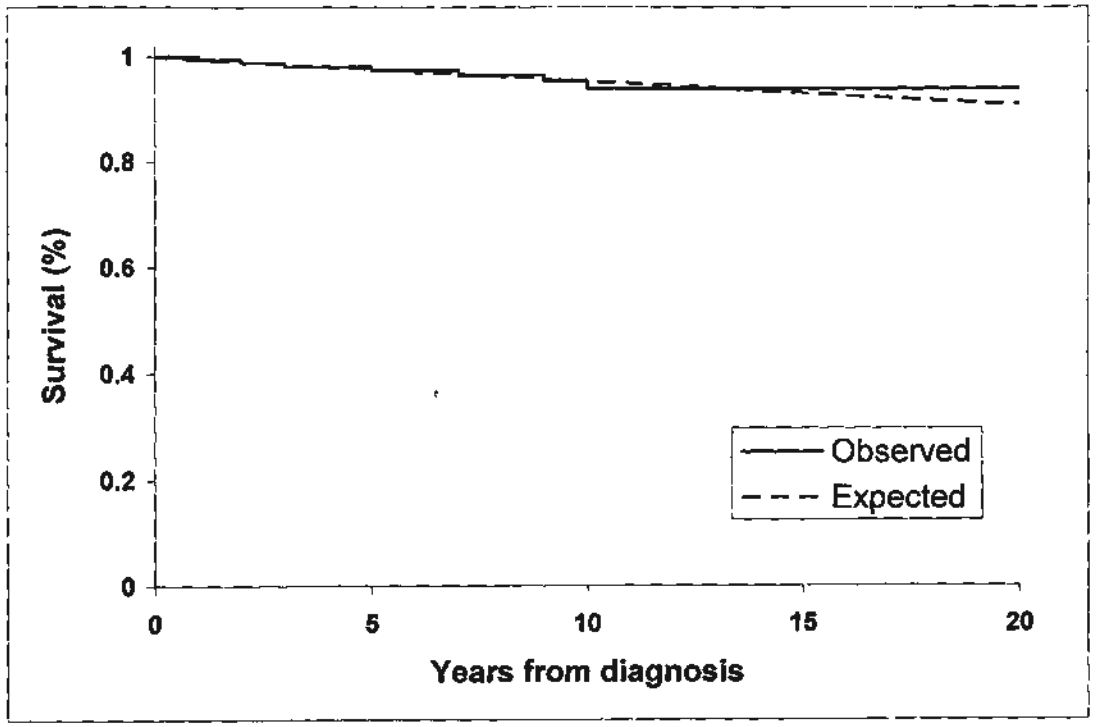


Figure 6.4. Cumulative colectomy-free survival in the Chinese UC patients



No. at risk	172	119	58	27	6

Figure 6.5. Observed and expected cumulative survival in the Chinese patients diagnosed with UC in 1985-2006 (log-rank test, P=0.07)



No. at risk	172	124	63	32	9

6.2 CONCLUSIONS

Incidence of UC in Hong Kong has increased sixfold over the past two decades. The annual age-specific incidence rate of UC was 2.1 (95% CI: 1.1-3.7) per 100,000 and the prevalence was 26.5 (95% CI: 22.6-30.9) per 100,000 in 2006. The complication, colorectal cancer, and colectomy rates were low in our locality but the figures increased with the duration of illness. The overall survival of UC patients was similar to the expected survival for the Hong Kong population.

CHAPTER 7

Phenotypic Evolution of Crohn's Disease and Ulcerative Colitis in Hong Kong Chinese

7.1 Longitudinal study of CD [Study 2: Inflamm Bowel Dis 2008;14:536-541]

7.1.1 METHODS

Consecutive ambulatory Chinese CD patients that attended the IBD clinic of Prince of Wales Hospital were recruited into a database. The diagnosis of CD was made according to the criteria of Lennard-Jones [Lennard-Jones 1989] which was based on clinical, endoscopic, histopathological, and radiological findings. All patients underwent ileocolonoscopy and biopsies and had small bowel enteroclysis. Gastroscopy was only performed when it was indicated, for instance, in the presence of epigastric pain or tarry stool. The diagnosis of CD had to be of at least 6 months duration. Ulcerative colitis, indeterminate colitis, Behcet's disease, infective enterocolitis especially intestinal tuberculosis were excluded clinically through stool and biopsy microscopy and culture and histological examination of ileal and colonic biopsies.

Medical notes of all patients were reviewed by a single clinician

(D.K.C.) familiar with the classifications of IBD. Disease behavior and location were determined by Vienna Classification [Gasche 2000] and the Montreal Classification [Silverberg 2005] at diagnosis and after 1, 3, 5, and 10 years of follow-up. The evolution of these characteristics and the need for major surgery, defined as either bowel resection or stricturoplasty and excluding perianal abscess drainage or fistulotomy, were evaluated. For those patients who had undergone operation, surgical assessment of the extent of disease and the pathological assessment of surgical specimens were used for phenotyping. When data were missing or unclear, the item was unclassified until more recent data became available.

Analysis

The Wilcoxon signed rank test was used to describe changes in CD behavior and location. A time-to-major-surgery curve was derived using the Kaplan-Meier method. Cox proportional hazards regression analysis that allowed simultaneous adjustment of variables was performed to evaluate whether sex, smoking, age at diagnosis, and disease location and behavior were predictive factors

for major surgery by giving the adjusted HRs and 95% CIs. Level of significance was set at $P<0.05$.

7.1.2 RESULTS

One hundred and nine consecutive patients were recruited from 1987 to 2005 (77 men and 32 women), with a median follow-up of 4 years (range, 6 months – 18 years) and a mean follow-up of 5 years. The median age at diagnosis was 30 years old. Table 7.1 and 7.2 disclose CD patients' phenotypes according to the VC and MC, respectively. Ninety-six patients (88.1%) in the cohort were non-smokers, and 13 patients (11.9%) were either smokers or ex-smokers. Only 2 of the patients had a definite family history of CD and were of a father and son relationship. Male sex predominance and low proportion of IBD familial clustering are the typical pattern in Asia. [Leong 2004] All 109 patients underwent ileocolonoscopy and biopsies, 97% had small bowel investigations (small bowel enema 69%, small bowel follow-through 17%, CT enteroclysis 21%, and gastroscopy and/ or laparotomy 36%), and a number of patients underwent more than 1 type of small bowel

investigation. There were 103, 82, 64 and 21 patients available for classification after 1, 3, 5, and 10 years, respectively, over the course of disease.

Age

Eighty-two patients (75.2%) and 27 patients (24.8%) belong to the age of less than 40 years (A1) and the age of 40 years or older (A2), respectively, using the VC. There were 2 patients (1.8%) aged 16 years or younger (A1), 80 patients (73.4%) aged between 17 and 40 years (A2), and 27 patients (24.8%) aged over 40 years (A3) as determined by the MC.

Behavior

The proportions of patients suffering from non-stricturing non-penetrating disease (B1), stricturing disease (B2) and penetrating disease (B3) at diagnosis according to the VC were 45.9%, 25.7% and 28.4%, respectively. CD behavior changed significantly 5 years after diagnosis (P=0.015) through reclassification of non-stricturing, non-penetrating disease to

stricturing and penetrating phenotypes (Figure 7.1). The proportion of penetrating disease (B3) increased from 28.4% to 42.9%, and stricturing disease (B2) increased from 25.7% to 33.3% after 10 years. Only 3 patients with stricturing disease progressed to penetrating disease during follow-up. The proportions of patients suffering from non-stricturing non-penetrating disease (B1), stricturing disease (B2) and penetrating disease (B3) at diagnosis as determined by the MC were 67.0%, 30.3 % and 2.8 %, respectively. CD behavior changed significantly 3 years ($P = 0.025$) and 5 years ($P = 0.005$) after diagnosis, with an increase in the stricturing and penetrating phenotypes (Figure 7.2). The proportion of penetrating disease (B3) increased from 2.8% to 14.3%, and stricturing disease (B2) increased from 30.3% to 42.9% after 10 years.

Location

Disease location remained stable after 10 years of follow-up in both the VC and the MC (Table 7.1). The proportions of patients suffering from terminal ileal disease (L1), colonic disease (L2), ileocolonic disease (L3), and upper gastrointestinal tract disease (L4) at

diagnosis according to the VC were 5.5%, 34.9%, 50.5% and 9.2%, respectively. When disease location was classified by the MC in our cohort, the upper gastrointestinal location of CD (L4) often coexisted with terminal ileal disease (60.0% of all L4 cases) or ileocolonic disease (40.0% of all L4 cases) but never with the colonic disease (Table 7.2).

Surgery

Thirty four patients (31.2%) underwent major surgery during the follow-up period, and the time-to-surgery Kaplan-Meier curve is shown in Figure 7.3. The stricturing (P=0.002; adjusted HR: 3.3; 95% CI: 1.5-7.0) and penetrating (P=0.03; adjusted HR: 5.8; 95% CI: 1.2-28.2) phenotypes according to the MC were predictive of the need for major surgery. Only the stricturing phenotype using the VC predicted major surgery (P=0.005; adjusted HR: 3.6; 95% CI: 1.5-8.8), but not the penetrating phenotype (P=0.8). Colonic disease as determined by the MC was found to be protective against major surgery (P=0.02; HR: 0.3; 95% CI: 0.08 - 0.8). In contrast, colonic disease did not have any predictive value for major surgery

using the VC (P=0.2). Age at diagnosis did not correlate with surgery in our cohort for either the VC (P=0.8) or the MC (P=0.8), nor was history of smoking associated with surgery (P=0.1 for VC; P=0.6 for MC).

Table 7.1. Number of patients (% in bracket) with Classification B (behavior) and L (location) at diagnosis and at different time points in the course of the disease (years) according to the Vienna Classification

	Disease duration (years)				
	0 (at diagnosis) n=109	**1 n=103**	**3 n=82**	**5 n=64**	**10 n=21**
Non-stricturing non-penetrating **(B1)**	50 (45.9%)	48 (46.6%)	30 (36.6%)	21 (32.8%)	5 (23.8%)
Sricturing **(B2)**	28 (25.7%)	27 (26.2%)	23 (28.0%)	20 (31.3%)	7 (33.3%)
Penetrating **(B3)**	31 (28.4%)	28 (27.2%)	29 (35.4%)	23 (35.9%)	9 (42.9%)
Terminal ileum **(L1)**	6 (5.5%)	6 (5.8%)	3 (3.7%)	1 (1.6%)	0 (0%)
Colon **(L2)**	38 (34.9%)	34 (33.0%)	27 (32.9%)	20 (31.3%)	7 (33.3%)
Ileocolon **(L3)**	55 (50.5%)	53 (51.5%)	47 (57.3%)	41 (64.1%)	14 (66.7%)
Upper gastrointestinal tract **(L4)**	10 (9.2%)	10 (9.7%)	5 (6.1%)	2 (3.1%)	0 (0%)

Table 7.2. Number of patients (% in bracket) with Classification B (behavior) and L (location) at diagnosis and at different time points in the course of the disease (years) according to the Montreal Classification

	Disease duration (years)				
	0 (at diagnosis) n=109	**1 n=103**	**3 n=82**	**5 n=64**	**10 n=21**
Non-stricturing non-penetrating **(B1)**	73 (67%) [B1p=26; B1=47]	68 (66%) [B1p=23; B1=45]	47 (57%) [B1p=16; B1=31]	32 (50%) [B1p=11; B1=21]	9 (43%) [B1p=4; B1=5]
Sricturing **(B2)**	33 (30%) [B2p=7; B2=26]	32 (31%) [B2p=7; B2=25]	31 (38%) [B2p=9; B2=22]	29 (45%) [B2p=8; B2=21]	9 (43%) [B2p=1; B2=8]
Penetrating **(B3)**	3 (3%) [B3p=0; B3=3]	3 (3%) [B3p=0; B3=3]	4 (5%) [B3p=0; B3=4]	3 (5%) [B3p=0; B3=3]	3 (14%) [B3p=0; B3=3]
Terminal ileum **(L1)**	12 (11%) 6/12 +L4	12 (12%) 6/12 +L4	6 (7%) 3/6 +L4	2 (3%) 1/2 +L4	0 (0%)
Colon **(L2)**	38 (35%) No L4	34 (33%) No L4	27 (33%) No L4	20 (31%) No L4	7 (33%) No L4
Ileocolon **(L3)**	59 (54%) 4/59 +L4	57 (55%) 4/57 +L4	49 (60%) 4/49 +L4	42 (66%) 4/42 +L4	14 (67%) 2/14 +L4

L4, Upper gastrointestinal tract

Figure 7.1. Evolution of disease behavior as determined by the Vienna Classification over 10 years in Chinese patients with Crohn's Disease

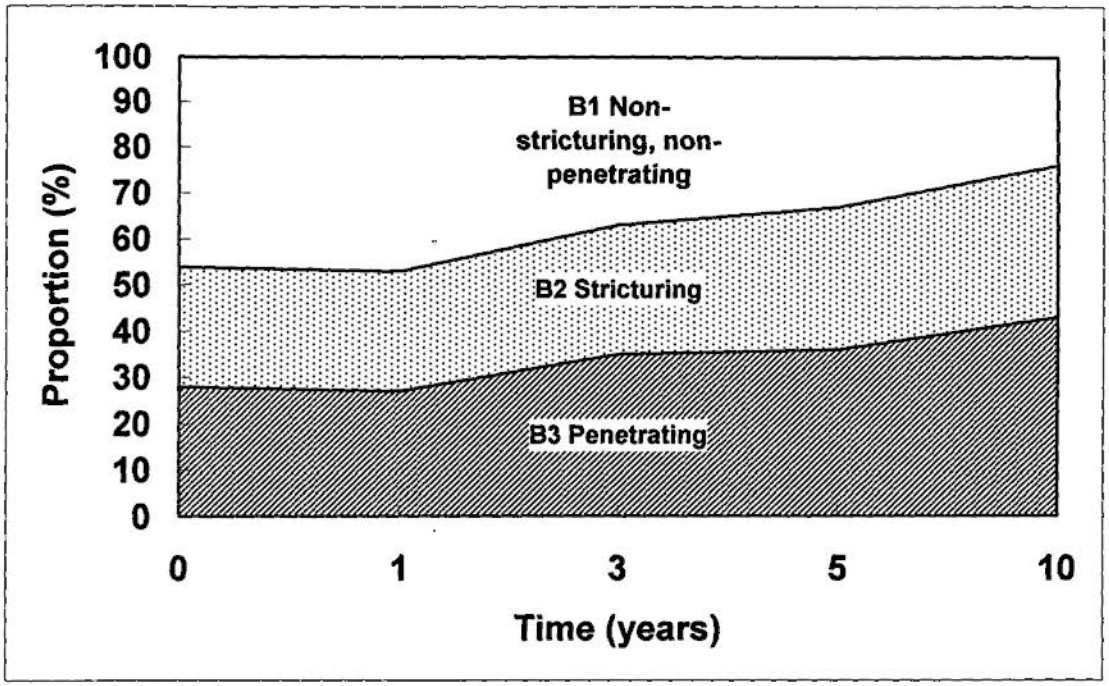


Figure 7.2. Evolution of disease behavior as determined by the Montreal Classification over 10 years in Chinese patients with Crohn's Disease

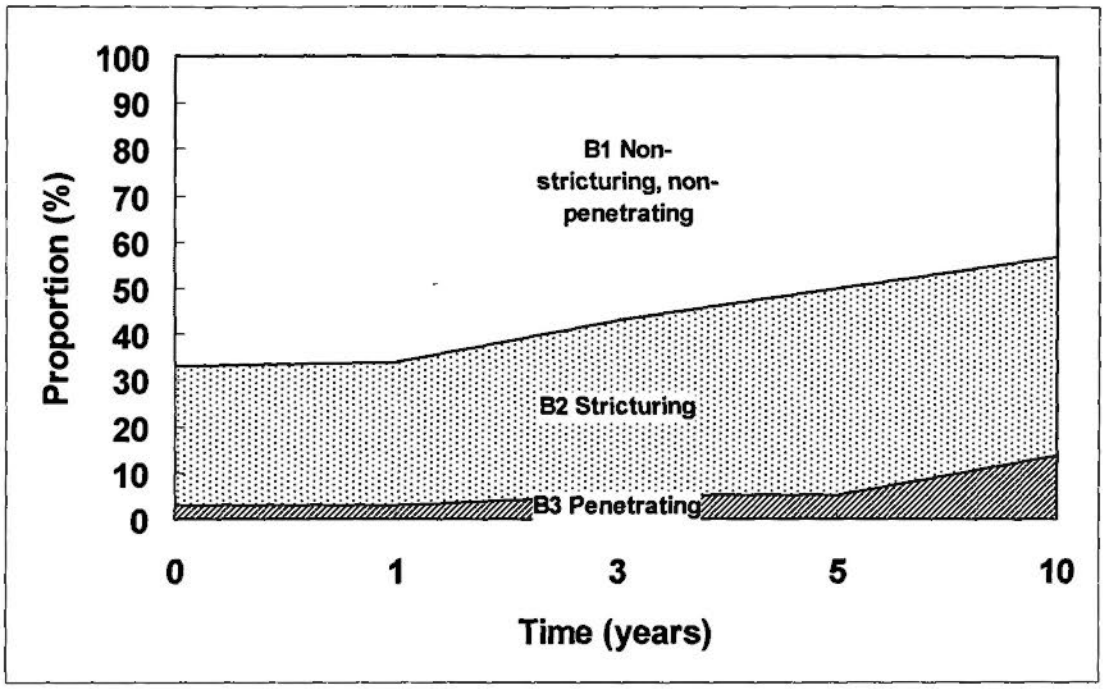
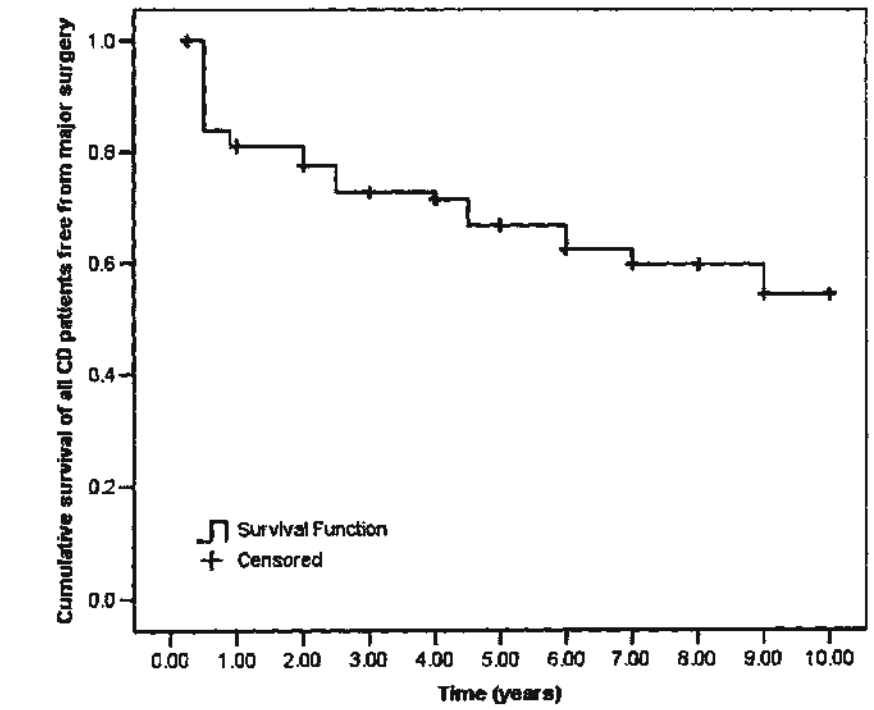


Figure 7.3. Cumulative survival of CD patients free from major surgery upon 10 years of follow-up



No. of at risk	109	85	60	42	8

7.2 Clinical course of CD in patients with upper gastrointestinal tract involvement [Study 3: Inflamm Bowel Dis 2009;15:551-7]

7.2.1 METHODS

Consecutive Chinese CD patients who attended the IBD clinic of Prince of Wales Hospital were recruited as previously described. [Leong 2004] Our former CD cohort was extended until the end of December, 2007. Diagnosis of CD had to be of at least 6 months duration. The extent of disease was assessed by ileocolonoscopy and biopsies and by at least 1 of the following small bowel investigations: small bowel enema, small bowel follow-through, computed tomography (CT) enteroclysis, or capsule endoscopy. The choice of small bowel investigation was based on the gastroenterologist's discretion and patient's preference. For those patients who had undergone operation, surgical assessment of the extent of disease and the pathological assessment of surgical specimens were used for phenotyping during the subsequent follow-up period. Gastroscopy was only performed when it was

indicated. The exclusion criteria were ulcerative colitis, indeterminate colitis, absence of small bowel investigation, and infective enterocolitis.

Demographic data including sex, age at diagnosis, duration of disease and follow-up, smoking history and family history of CD were collected. We determined phenotypes of the disease according to the Montreal Classification [Silverberg 2005] on initial presentation and subsequent follow-up visits. Clinical symptoms (abdominal pain, rectal bleeding, diarrhea, weight loss of more than 3 kg, and extraintestinal symptoms) and laboratory data on initial presentation including anemia (hemoglobin ≤10.0g/dL), thrombocytosis (platelet count ≥450x10^9/L) were recorded. We observed their clinical course according to their medications, indications for hospitalizations, requirement of TPN, and details of operation during the study period.

Treatment policy

During the observation period, patients diagnosed with CD were

followed-up by gastroenterologists at the IBD clinic. Patients in stable condition underwent evaluations every 4 months. Those with active disease were followed-up at more frequent intervals or hospitalized depending on disease severity. Patients received 5ASA or sulfasalazine for mild disease. Short-term oral corticosteroids were used for episodes of worsening of symptoms in moderate to severe CD. The latter was defined as failure to respond to treatment for mild disease, more prominent symptoms of fever, weight loss, abdominal pain, or anemia. Prednisolone 0.5-1mg/kg/day or budesonide 9mg/day was given initially and was tapered within 8 to 12 weeks. Second-line agents including thiopurines (azathioprine 2.5mg/kg or mercaptopurine 1.5mg/kg) and methotrexate (25mg per week at induction and 15mg per week for maintenance) were used for corticosteroid-dependent or -refractory disease. We defined corticosteroid-dependent as failure to reduce prednisolone below 10mg/day or budesonide <3mg/day within 3 months of starting steroid or relapse within 3 months of stopping steroid. Infliximab was used in corticosteroid and/or immunomodulator refractory CD since 2001. From 2006, tacrolimus was used in some

patients with penetrating CD. Surgery was offered to those patients who failed to respond to medical treatment or developed complications such as intestinal obstruction, bowel perforation, massive gastrointestinal bleeding, or bowel cancer.

Analysis and Study endpoints

Patients' baseline characteristics were compared with Student's t-test for parametric data, the Mann-Whitney U-test for nonparametric data, and the chi-square test for proportions. The Kaplan-Meier method was used to estimate the likelihood of reaching the endpoints, which included further hospitalization and major surgery. Further hospitalization after diagnosis was defined as care in an acute hospital setting lasting for at least 3 days for flare-up or complication of the disease. Major surgery was defined as either bowel resection or stricturoplasty. Drainage of perianal abscess and fistulotomy were excluded. The log-rank test was used for comparisons between the upper gastrointestinal tract (L4) group and the non-upper gastrointestinal tract group. Cox proportional hazards model with backward stepwise regression was used to

identify possible covariates as significant predictors of endpoint and to calculate the HRs and 95% CIs. The Cox model allows simultaneous adjustment of each variable for all the other variables in the model. A 2-sided *P*-value of less than 0.05 was used to denote statistical significance. All statistical tests were performed using SPSS 15.0 statistical software (SPSS, Chicago, Illinois, USA).

7.2.2 RESULTS

Among the 139 consecutive patients screened between 1987 and 2007, we excluded 4 patients because of incomplete medical records or loss to follow-up and 3 patients who refused small bowel investigations. A total of 132 patients with a male-to-female ratio of 2.1:1 were recruited and followed for 770 person-years (median follow-up duration: 5.0 years, range: 0.5-20.0 years). The median age at diagnosis was 30.0 years (range: 14.0 - 77.0 years). All 132 patients underwent ileocolonoscopy and biopsies and had small bowel investigations (small bowel enema 63.6%, small bowel follow-through 26.5%, CT enteroclysis 30.3%, capsule endoscopy 7.6%). Seventy-seven patients (58.3%) had gastroscopy. Thirty

patients (22.7%) were diagnosed with the upper gastrointestinal tract phenotype at presentation and 18 (13.6%), 47 (35.6%), and 66 (50.0%) patients were diagnosed with the terminal ileal disease (L1), colonic disease (L2), and ileocolonic disease (L3) phenotypes, respectively. Eighty-six (65.2%), 33 (25.0%), 13 (9.8%) and 44 (33.3%) patients were classified as non-stricturing non-penetrating (B1), stricturing (B2), penetrating (B3), and perianal diseases at diagnosis. Fifty-seven patients (43.2%) underwent major surgery in addition to 21 patients (15.9%) who were operated on for perianal abscess drainage or fistulotomy. A total of 30 patients (22.7%) underwent major surgery within the first month of disease.

Patients with and without L4 diseases

Table 7.3 shows the demographics of patients with and without upper gastrointestinal tract disease. Gender, age at diagnosis, duration of disease, smoking or family history of CD, prior appendectomy, clinical symptoms apart from rectal bleeding, anemia, thrombocytosis, medications, or TPN use were comparable between the upper gastrointestinal tract and the non-upper

gastrointestinal tract groups. Disease behavior according to the MC significantly differed between the 2 groups ($P<0.0001$). There were more stricturing (46.7% Vs 18.6%) and penetrating (30.0% Vs 3.9%) phenotypes in the upper gastrointestinal tract group compared with the non-upper gastrointestinal tract group. In contrast, non-stricturing non-penetrating (B1) (77.5% Vs 23.3%) and perianal phenotypes (35.3% Vs 26.7%) were more common in the non-upper gastrointestinal tract group than in the upper gastrointestinal tract group. Patients with upper gastrointestinal tract involvement less frequently presented with rectal bleeding than those without upper gastrointestinal tract involvement (26.7% Vs 51.0%) ($P=0.02$). There were significantly higher proportions of patients who underwent major surgery in the upper gastrointestinal tract group than in the non-upper gastrointestinal tract group (66.7% Vs 36.3%). Among those patients with upper gastrointestinal tract involvement who had an operation, 50.0% were performed within the first month of diagnosis as compared to 14.7% of those patients without upper gastrointestinal tract involvement ($P<0.0001$). Fourteen out of 15 (93.3%) patients with

upper gastrointestinal tract involvement who underwent an operation within the first month presented with acute abdominal symptoms (peritonitis 9, intestinal obstruction 4, massive gastrointestinal bleeding 1).

The 3-year cumulative probability of further hospitalization was significantly higher in the upper gastrointestinal tract group than the non-upper gastrointestinal tract group (Figure 7.4). In the Cox proportional hazards model, the upper gastrointestinal tract phenotype was an independent risk factor predicting further hospitalization (Table 7.4). Similarly, cumulative probabilities of major surgery were significantly different between the 2 groups (Figure 7.5). The 5-year cumulative probability of major surgery was higher in the upper gastrointestinal tract group than the non-upper gastrointestinal tract group. The stricturing and penetrating phenotypes independently predicted, whereas the colonic disease (L2) phenotype negatively predicted major surgery after adjustment for covariates in the Cox model (Table 7.5). The upper gastrointestinal tract phenotype was not found to be associated

with major surgery.

Progression to L4 phenotype

A total of 18/102 (17.6%) patients developed the upper gastrointestinal tract phenotype upon longitudinal follow-up. The stricturing phenotype and initial requirement of operation at diagnosis independently predicted the progression to upper gastrointestinal tract phenotype, with an HR of 5.5 (95% CI: 2.2-14.0) and HR of 4.2 (95% CI: 1.5-11.2), respectively, after adjustment for covariates including age at diagnosis and smoking using the Cox model.

Figure 7.4. Kaplan-Meier estimates of the cumulative probabilities of further hospitalization in the upper gastrointestinal tract (L4) group and the non-upper gastrointestinal tract (non-L4) group

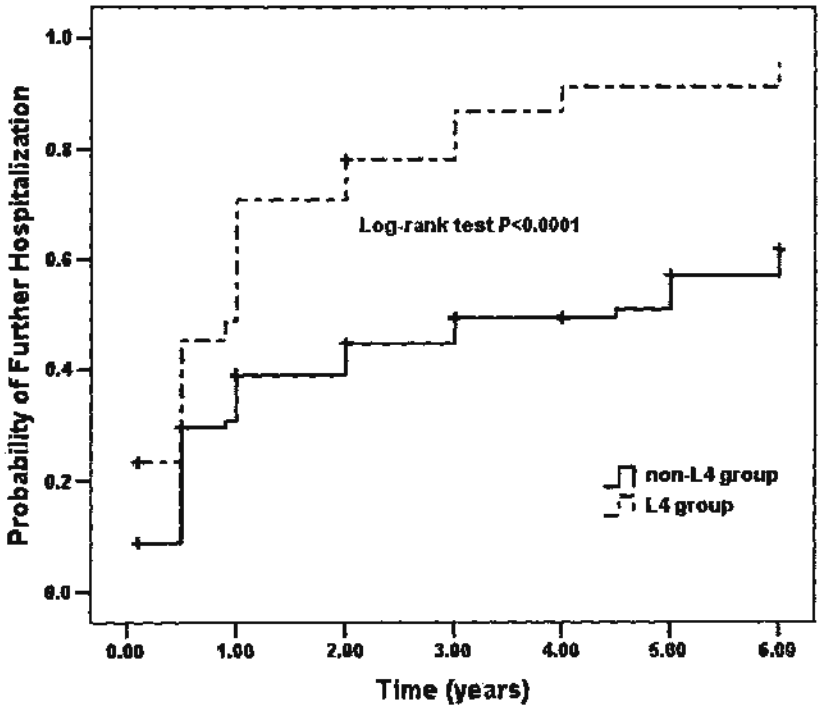


Figure 7.5. Kaplan-Meier estimates of the cumulative probabilities of major surgery in the upper gastrointestinal tract (L4) group and the non-upper gastrointestinal tract (non-L4) group

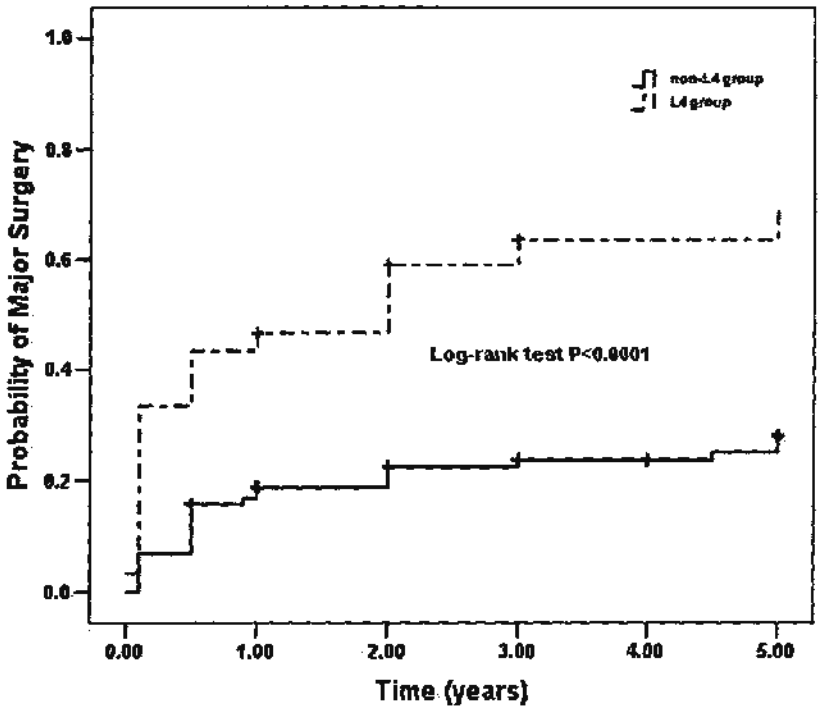


Table 7.3. Characteristics of the patients

	All CD patients n=132	Patients without L4 at diagnosis n=102	Patients with L4 at diagnosis n=30	*P* value[a]
Gender				
Female	42 (31.8)	30 (29.4)	12 (40.0)	0.27
Male	90 (68.2)	72 (70.6)	18 (60.0)	
Age at diagnosis				
<40 years	100 (75.8)	75 (73.5)	25 (83.3)	0.27
≥40 years	32 (24.2)	27 (26.5)	5 (16.7)	
Median Age at diagnosis, years	30.0	28.5	30.0	
Mean Age at diagnosis, years	32.7	32.6	33.0	0.89
Median Age, years	37.0	37.0	42.0	
Mean Age, years	39.8	39.4	41.0	0.58
Mean Duration of CD, years	7.7	7.6	8.1	0.69
Smoking History				
Non-smoker	113 (85.6)	89 (87.3)	24 (80.0)	0.32
Ever-smoker	19 (14.4)	13 (12.7)	6 (20.0)	
Family History of CD				
No	126 (95.5)	96 (94.1)	30 (100.0)	0.17
Yes	6 (4.5)	6 (5.9)	0 (0)	
Disease location at diagnosis				
L1 (Terminal ileum)	18 (13.6)	8 (7.8)	10 (33.3)	<0.0001
L2 (Colon)	47 (35.6)	44 (43.1)	3 (10.0)	
L3 (Ileocolon)	66 (50.0)	50 (49.0)	16 (53.3)	
L4[b]	30[c] (22.7)	0 (0)	30[c] (100.0)	

Disease behavior at diagnosis						
B1 (Non-stricturing non-penetrating)	86	(65.2)	79	(77.5)	7	(23.3)	<0.0001
B2 (Stricturing)	33	(25.0)	19	(18.6)	14	(46.7)	
B3 (Penetrating)	13	(9.8)	4	(3.9)	9	(30.0)	
p[d]	44	(33.3)	36	(35.3)	8	(26.7)	0.38
Operation at diagnosis[e]							
No	102	(77.3)	87	(85.3)	15	(50.0)	<0.0001
Yes	30	(22.7)	15	(14.7)	15	(50.0)	
Major operation							
No	75	(56.8)	65	(63.7)	10	(33.3)	0.003
Yes	57	(43.2)	37	(36.3)	20	(66.7)	
Prior Appendectomy							
No	117	(88.6)	90	(88.2)	27	(90.0)	0.79
Yes	15	(11.4)	12	(11.8)	3	(10.0)	
Anemia at diagnosis							
No	49	(37.1)	40	(39.2)	9	(30.0)	0.36
Yes	83	(62.9)	62	(60.8)	21	(70.0)	
Thrombocytosis at diagnosis							
No	64	(48.5)	53	(52.0)	11	(36.7)	0.14
Yes	68	(51.5)	49	(48.0)	19	(63.3)	
Abdominal pain at diagnosis							
No	21	(15.9)	19	(18.6)	2	(6.7)	0.12
Yes	111	(84.1)	83	(81.4)	28	(93.3)	
Rectal bleeding at diagnosis							
No	72	(54.5)	50	(49.0)	22	(73.3)	0.02

Yes	60	(45.5)	52	(51.0)	8	(26.7)	
Diarrhea at diagnosis							
No	50	(37.9)	37	(36.3)	13	(43.3)	0.48
Yes	82	(62.1)	65	(63.7)	17	(56.7)	
Weight loss at diagnosis							
No	60	(45.5)	48	(47.1)	12	(40.0)	0.50
Yes	72	(54.5)	54	(52.9)	18	(60.0)	
Extraintestinal symptoms at diagnosis							
No	100	(75.8)	77	(75.5)	23	(76.7)	0.90
Yes	32	(24.2)	25	(24.5)	7	(23.3)	
Initial requirement oral corticosteroids							
No	94	(71.2)	76	(74.5)	18	(60.0)	0.12
Yes	38	(28.8)	26	(25.5)	12	(40.0)	
Use of immunomodulators or biologics							
No	47	(35.6)	40	(39.2)	7	(23.3)	0.11
Yes	85	(64.4)	62	(60.8)	23	(76.7)	
Use of TPN[f]							
No	112	(84.8)	86	(84.3)	26	(86.7)	0.75
Yes	20	(15.2)	16	(15.7)	4	(13.3)	

Data are number and figures in parentheses are percent unless otherwise specified.

[a] *P* for differences in proportions between CD patients with L4 disease and patients without L4 disease.

[b] Upper gastrointestinal modifier (L4) allows for the co-classification of L4 with L1 to L3.

[c] At diagnosis, there was one case of isolated L4. The remaining 29 cases had co-classification of L4 with L1-3.

[d] Perianal disease modifier.

[e] Operation at diagnosis was defined as patients who were operated on for CD within the first month of the disease.

[f] Total parenteral nutrition.

Table 7.4. Analysis of possible risk factors predicting further hospitalization using the Cox Model

	Multivariate analysis	
Covariates	Adjusted Hazard Ratio (95% CI)	*P* value
B1 phenotype	0.4 (0.3 to 0.6)	<0.0001
B2 phenotype	1.4 (0.8 to 2.3)	0.196
B3 phenotype	2.1 (1.0 to 4.6)	0.053
L1 phenotype	0.7 (0.1 to 5.6)	0.757
L2 phenotype	0.5 (0.3 to 1.0)	0.064
L3 phenotype	0.8 (0.4 to 1.4)	0.426
L4 phenotype	2.1 (1.3 to 3.5)	0.004
Age at diagnosis	0.8 (0.5 to 1.4)	0.496
Smoking	1.3 (0.7 to 2.3)	0.420

B1, non-stricturing non-penetrating

B2, stricturing

B3, penetrating

L1, terminal ileum

L2, colon

L3, ileocolon

L4, upper gastrointestinal tract

Table 7.5. Analysis of possible risk factors predicting major surgery using the Cox Model

	Multivariate analysis	
Covariates	Adjusted Hazard Ratio (95% CI)	*P* value
B1 phenotype	0.4 (0.2 to 0.8)	0.013
B2 phenotype	4.1 (2.3 to 7.5)	<0.0001
B3 phenotype	16.8 (7.7 to 36.7)	<0.0001
L1 phenotype	2.3 (0.3 to 19.2)	0.437
L2 phenotype	0.3 (0.1 to 0.7)	0.008
L3 phenotype	0.6 (0.3 to 1.3)	0.188
L4 phenotype	1.3 (0.7 to 2.5)	0.406
Age at diagnosis	0.6 (0.3 to 1.3)	0.236
Smoking	0.7 (0.3 to 1.9)	0.532

B1, non-stricturing non-penetrating

B2, stricturing

B3, penetrating

L1, terminal ileum

L2, colon

L3, ileocolon

L4, upper gastrointestinal tract

7.3.1 Phenotypic evolution of UC [Study 1: Am J Gastroenterol 2009;104:647-54]

7.3.1 METHODS (see 6.1.1 for details)

7.3.2 RESULTS

Phenotypes

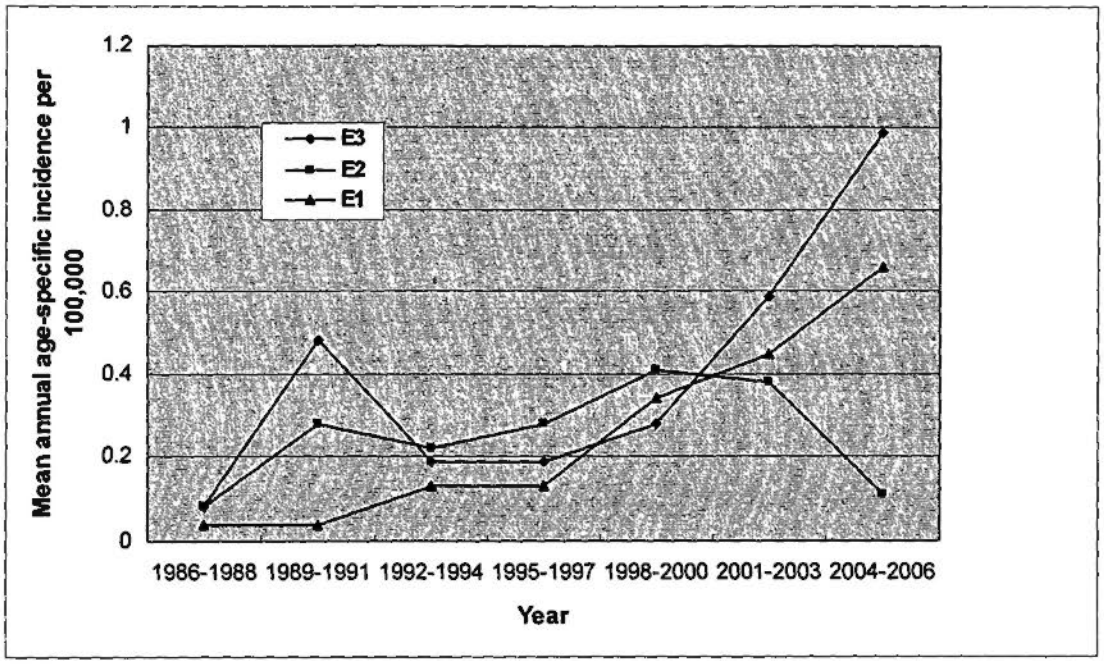
A total of 73 (42.4%), 51 (29.7%) and 48 (27.9%) patients had extensive colitis (E3), left-sided colitis (E2) and proctitis (E1), respectively, at the time of diagnosis. The incidence rates of proctitis and extensive colitis have increased approximately 15-fold and 10-fold, respectively, over the past two decades as shown in figure 7.6. The increase in the incidence of proctitis and extensive colitis occurred more dramatically in the past decade whereas the incidence of left-sided colitis increased from 1986 to 2000 but decreased afterward.

Phenotypic evolution

In total, 32 of 48 patients (66.7%) with initial proctitis and 40 of 51

patients (78.4%) with initial left-sided colitis underwent follow-up colonoscopy for screening, surveillance, or flare-up of disease during the observation period. The mean duration of endoscopic follow-up and the mean number of follow-up colonoscopy were 6.7 years (range: 0.5 -21.0) and 2.4 (range: 1.0-7.0), respectively. The 5- and 10-year cumulative rates of proximal extension were 10.5% and 23.8%, respectively. Only those patients who experienced both endoscopically and histologically confirmed disease extension were counted. Those patients who once had disease extension but the final disease extent returned to its original status were also included. The median follow-up duration of patients with extension of disease was 7.0 years (range: 1.0-21.0). The 5- and 10-year cumulative rates of proximal extension were 10.7% and 31.2%, respectively, for patients with proctitis and 10.4% and 19.3%, respectively, for patients with left-sided colitis (log-rank test, P=0.4). Among patients with proctitis, the 10-year cumulative probabilities of progression to left-sided colitis and extensive colitis were 21.8% and 11.4%, respectively.

Figure 7.6. The temporal trend of mean annual age-specific incidence of extensive colitis (E3), left-sided colitis (E2) and proctitis (E1), 1986-2006



7.4 CONCLUSIONS

Phenotypic evolution of CD also occurred in Hong Kong Chinese patients in the same way as the white patients with respect to disease behavior. Similar to the white CD patients, the location of disease remained relatively stable over the course of disease. Chinese CD patients had more upper gastrointestinal tract phenotype which predicted the need of subsequent hospitalization and surgery. On the other hand, proximal extension of disease took place in less than one fourth of patients with UC after 10 years.

CHAPTER 8

Predictors of corticosteroid-dependent and –refractory Crohn's Disease & Ulcerative Colitis

8.1 Predictors of corticosteroid-dependent and -refractory IBD: analysis of a Chinese cohort study [Study 4: Aliment Pharmacol Ther 2009;29:843-54]

8.1.1 METHODS

Study Population

This was a cohort study of consecutive Chinese IBD patients who attended the IBD clinic at the Prince of Wales Hospital between 1985 and 2007. The identification and recruitment of cases had been described in detail previously. [Study 1, 2, and 3] Potential cases of this study were categorized as having CD or UC based on all available clinical, radiographic, endoscopic, and histological evidence. By definition, an individual patient could not be counted in both categories, and there was no category of indeterminate colitis. The extent of disease was assessed by ileocolonoscopy and biopsies in all IBD patients and by at least one of the following small bowel investigations, which included small bowel enema, small bowel follow-through, CT enteroclysis or capsule endoscopy in CD patients. We determined phenotypes of the disease according to the

MC [Silverberg 2005] on initial presentation. The exclusion criteria were indeterminate colitis, absence of small bowel investigation in CD patients and infective enterocolitis.

Baseline demographic and clinical features captured before 2001, which include sex, age, smoking history, family history of IBD, age and date of diagnosis, disease extent at diagnosis, clinical symptoms (abdominal pain, rectal bleeding, diarrhea, fever, weight loss of more than 3 kg, and extraintestinal symptoms) and laboratory data on initial presentation including anemia (hemoglobin ≤10.0g/dL), thrombocytosis (platelet count ≥450x10^9/L), requirement of TPN, details of medication and operation, were extracted retrospectively. From 2001 onwards, demographics of all newly diagnosed IBD patients and clinical data, including clinical symptoms, laboratory data, requirement of TPN, details of medication and operation, were prospectively collected. Last follow-up date and vital status at last follow-up were recorded. We observed their clinical course according to the use of systemic corticosteroid therapy (type of corticosteroids, initial dose, and

duration of therapy including attempts to taper dose), and details of operation during the study period.

Treatment policy (see Treatment policy of Study 1 & 3)

Study outcomes

Corticosteroid therapy was administered as oral prednisolone or budesonide (CD patients only) and initial doses ranged between prednisolone 0.5 and 1mg/kg/day or budesonide 9mg/day that was usually tapered and discontinued over 2-3 months in those patients who were corticosteroid-responsive. The dose of prednisolone was decreased by 5mg per week, whereas dose of budesonide was tapered by 3mg every 3 to 4 weeks. Patients were classified into three clinical response categories as described previously at 30 days after start of corticosteroids: [Munkholm 1994]

Primary complete remission – total regression of clinical symptoms (≤2 bowel movements per day, no blood, pus or mucus in faeces, no abdominal pain, fever, weight loss, and extra-intestinal symptoms).

Primary partial remission – regression of clinical symptoms (≤4 bowel movements per day, blood, pus or mucus in faeces, or abdominal pain or all four less than daily and no systemic symptoms, such as fever, weight loss or extra-intestinal symptoms).

Primary nonresponse – no regression of clinical symptoms despite corticosteroids equivalent to prednisolone up to 0.75mg/kg/day had been given for ≥ 2 weeks. CD patients who were given budesonide (9mg/day) had to switch to prednisolone before they were classified as primary non-response.

After the initial requirement of corticosteroids, patients were re-classified into the following outcome categories at the last follow-up:

Prolonged corticosteroid response – maintenance of complete remission or partial remission after treatment had finished.

Corticosteroid dependence – attained initial response to corticosteroids but followed by clinical relapse at dose reduction or within 30 days after corticosteroid therapy had finished which impeded discontinuation of corticosteroid therapy.

Secondary nonresponse – attained initial response to corticosteroids

but subsequently lost response or became intolerant to corticosteroid therapy.

Surgery – either bowel resection or stricturoplasty in CD patients and colectomy in UC patients. Drainage of perianal abscess and fistulotomy were excluded.

Corticosteroid-refractoriness – both primary and secondary corticosteroid nonresponse was included.

The diagnoses of corticosteroid dependency and corticosteroid refractoriness were sustained by review of cases by senior gastroenterologists with the help of the criteria.

Analysis

Clinical factors present at diagnosis that might potentially predict subsequent development of corticosteroid-dependent or -refractory disease were subjected to univariate analysis. Variables were compared using the chi-square test. Those variables with *P* values <0.10 were further tested as covariates in a Cox proportional-hazards model with backward stepwise regression to calculate the HRs and 95% CIs. Cox model allowed simultaneous

adjustment of each variable for all the other variables in the model. A two-sided *P* value of less than 0.05 was used to denote statistical significance. The Kaplan-Meier survival method was used to calculate the cumulative probability of outcomes subsequent to the initial course of corticosteroids. The outcomes included corticosteroid-dependent disease, corticosteroid-refractory disease and surgery. Comparison of the cumulative risks of outcomes between CD and UC was made by log-rank test. All statistical tests were performed using the SPSS 15.0 statistical software (SPSS Inc., Chicago, Illinois, USA).

8.1.2 RESULTS

Study patients

Three hundred and thirty IBD patients (141 CD, 189 UC) were identified. Seven CD and 13 UC patients were excluded because of incomplete medical records or loss to follow-up. Hence, 134 CD and 176 UC patients were recruited with a follow-up duration of 2140 person-years. A total of 77/134 (57.5%) CD patients and 95/176 (54.0%) UC patients had received corticosteroid therapy during the

observation period. Table 8.1 shows the demographic characteristics of patients, the prevalence of anemia and thrombocytosis, clinical symptoms, and the prevalence of initial requirement of corticosteroids and TPN at diagnosis.

CD patients

We enrolled 134 CD patients (41 females and 93 males) with a median follow-up duration of 5 years (range: 0.5-20 years). The median age at diagnosis was 30.0 years (range: 14.0-90.0 years). A total of 77 (57.5%) CD patients had received corticosteroids during study period. Thirty-eight (49.4%) patients initially required corticosteroids for the treatment of first flare-up of disease. At 30 days, 40 of the 77 (51.9%) patients and 26 (33.8%) patients achieved primary complete response and partial response, respectively. (Figure 8.1) Eleven of 77 (14.3%) patients failed to respond to corticosteroid therapy 30 days after initiation of corticosteroids. Nine of 11 primary non-responders underwent surgery despite all of them were given azathioprine or mercaptopurine. Two patients were given methotrexate, 2 on

infliximab and 1 on tacrolimus. During the study period, 45 CD patients became corticosteroid-dependent and 21 patients maintained prolonged corticosteroid response. Ten of the 45 corticosteroid-dependent patients became secondary nonresponse. Among the secondary nonresponders, 9 of the 10 patients had surgery. Nine patients were given azathioprine or mercaptopurine, 3 patients on methotrexate, 3 on infliximab and 1 on tacrolimus.

Five factors present at diagnosis were found to be associated with the corticosteroid dependency in CD by univariate analysis which included the presence of thrombocytosis, anemia, abdominal pain, colonic disease, and proximal gastrointestinal tract disease.(Table 8.2) Nine factors that were associated with corticosteroid refractoriness by univariate analysis were the presence of anemia, weight loss, stricturing disease, proximal gastrointestinal tract disease, perianal disease, non-stricturing non-penetrating disease, prior bowel resection, initial requirement of TPN, and use of 5ASA or sulfasalazine.(Table 8.3) In multivariate analysis using the Cox proportional hazards model, thrombocytosis (P=0.004; HR:3.0;

95% CI: 1.4-6.4) at diagnosis predicted, whereas colonic CD (*P*=0.016; HR:0.3; 95% CI: 0.1-0.8) negatively predicted corticosteroid dependency. (Table 8.2) Only stricturing disease (*P*=0.001; HR:4.5; 95% CI: 1.8-10.9) was associated with corticosteroid refractoriness using the multivariate analysis.(Table 8.3) Figure 8.3 shows the cumulative probabilities of surgery in corticosteroid users. The cumulative probability of surgery was 17.8% (95% CI: 8.6%-27.0%) at 1 year after the start of corticosteroids, whereas probabilities of progression to corticosteroid-dependent and corticosteroid-refractory diseases were 27.4% (95% CI: 16.6%-38.2%) and 20.6% (95% CI: 11.2%-30.0%), respectively.

UC patients

We enrolled 176 UC patients (86 females and 90 males) with a median follow-up duration of 7 years (range: 0.5-22 years). The median age at diagnosis was 37.5 years (range: 12.0-85.0 years). A total of 95 (54.0%) UC patients had received corticosteroids during study period. Twenty-six (27.4%) patients initially required

corticosteroids for the treatment of first flare-up of disease. At 30 days, 61 of the 95 (64.2%) patients and 28 (29.5%) patients achieved primary complete response and partial response, respectively. (Figure 8.2) Six of 95 (6.3%) patients failed to respond to corticosteroid therapy 30 days after initiation of corticosteroids. All 6 primary nonresponders underwent surgery despite 1 was given azathioprine, 2 on cyclosporin, 1 on infliximab and 1 on tacrolimus. During the study period, 45 UC patients became corticosteroid-dependent and 44 patients maintained prolonged corticosteroid response. Three of the 45 corticosteroid-dependent patients became secondary nonresponders. Among the secondary nonresponders, 1 of the 3 patients had surgery. All 3 patients were given azathioprine or mercaptopurine. One patient had received infliximab after failing cyclosporine. The other patient had received tacrolimus after failing cyclosporine.

Six factors present at diagnosis were found to be associated with the corticosteroid dependency in UC by univariate analysis which included the presence of thrombocytosis, anemia, diarrhoea, weight

loss, extensive colitis and initial requirement of corticosteroids.(Table 8.4) Five factors that were associated with corticosteroid refractoriness by univariate analysis were the presence of thrombocytosis, anemia, abdominal pain, initial requirement of corticosteroids and TPN.(Table 8.5) In multivariate analysis using the Cox proportional hazards model, thrombocytosis (P<0.0001; HR:3.9; 95% CI: 2.0-7.7) and extensive colitis (P=0.03; HR:1.7; 95% CI: 1.1-2.7) at diagnosis predicted corticosteroid dependency in UC. (Table 8.4) Presence of anemia (P=0.004; HR:10.8; 95% CI: 2.1-54.8) and initial requirement of TPN (P=0.001; HR:18.8; 95% CI: 3.5-100.3) were associated with corticosteroid refractoriness using the multivariate analysis. (Table 8.5) Figure 8.3 depicts the cumulative probabilities of surgery in corticosteroid users. The cumulative probability of surgery was 5.4% (95% CI: 0.7%-10.1%) at 1 year after the start of corticosteroids, whereas probabilities of progression to corticosteroid-dependent and corticosteroid-refractory diseases were 38.3% (95% CI: 28.3%-48.3%) and 8.3% (95% CI: 2.2%-14.4%), respectively.

Table 8.1. Characteristics of the patients at diagnosis

	CD patients	UC patients
	n=134	n=176
Gender		
Female	41 (30.6)	86 (48.9)
Male	93 (69.4)	90 (51.1)
Age		
<40 years	101 (75.4)	99 (56.3)
≥40 years	33 (24.6)	77 (43.8)
Median Age at diagnosis, years	30.0	37.5
Smoking History		
Non-smoker	114 (85.1)	148 (84.1)
Ever-smoker	20 (14.9)	28 (15.9)
Family History of IBD		
No	128 (95.5)	175 (99.4)
Yes	6 (4.5)	1 (0.6)
Disease location*		
L1	17 (12.7)	
L2	50 (37.3)	
L3	66 (49.3)	
L4#	29 (21.6)	
Proctitis		50 (28.4)
Left-sided colitis		52 (29.5)
Extensive colitis ‡		74 (42.0)
Disease behavior*		
B1	89 (66.4)	
B2	33 (24.6)	
B3	12 (9.0)	
p†	44 (32.8)	
Prior Appendectomy		
No	119 (88.8)	164 (93.2)
Yes	15 (11.2)	12 (6.8)
Anemia		
No	52 (39.8)	123 (69.9)
Yes	82 (61.2)	53 (30.1)
Thrombocytosis		
No	66 (49.3)	142 (80.7)

Yes	68	(50.7)	34	(19.3)
Fever				
No	107	(79.9)	171	(97.2)
Yes	27	(20.1)	5	(2.8)
Abdominal pain				
No	23	(17.2)	107	(60.8)
Yes	111	(82.8)	69	(39.2)
Rectal bleeding				
No	72	(53.7)	16	(9.1)
Yes	62	(46.3)	160	(90.1)
Diarrhea				
No	51	(38.1)	55	(31.3)
Yes	83	(61.9)	121	(68.8)
Weight loss				
No	61	(45.5)	152	(86.4)
Yes	73	(54.5)	24	(13.6)
Extraintestinal symptoms				
No	102	(76.1)	157	(89.2)
Yes	32	(23.9)	19	(10.8)
Initial requirement of corticosteroid				
No	96	(71.6)	150	(85.2)
Yes	38	(28.4)	26	(14.8)
Use of TPN¶				
No	131	(97.8)	173	(98.3)
Yes	3	(2.2)	3	(1.7)

Data are numbers and figures in blanket are % unless otherwise specified.

*Disease location and behavior was classified according to the Montreal Classification system.

#Upper gastrointestinal modifier (L4) allows for the co-classification of L4 with L1 to L3.

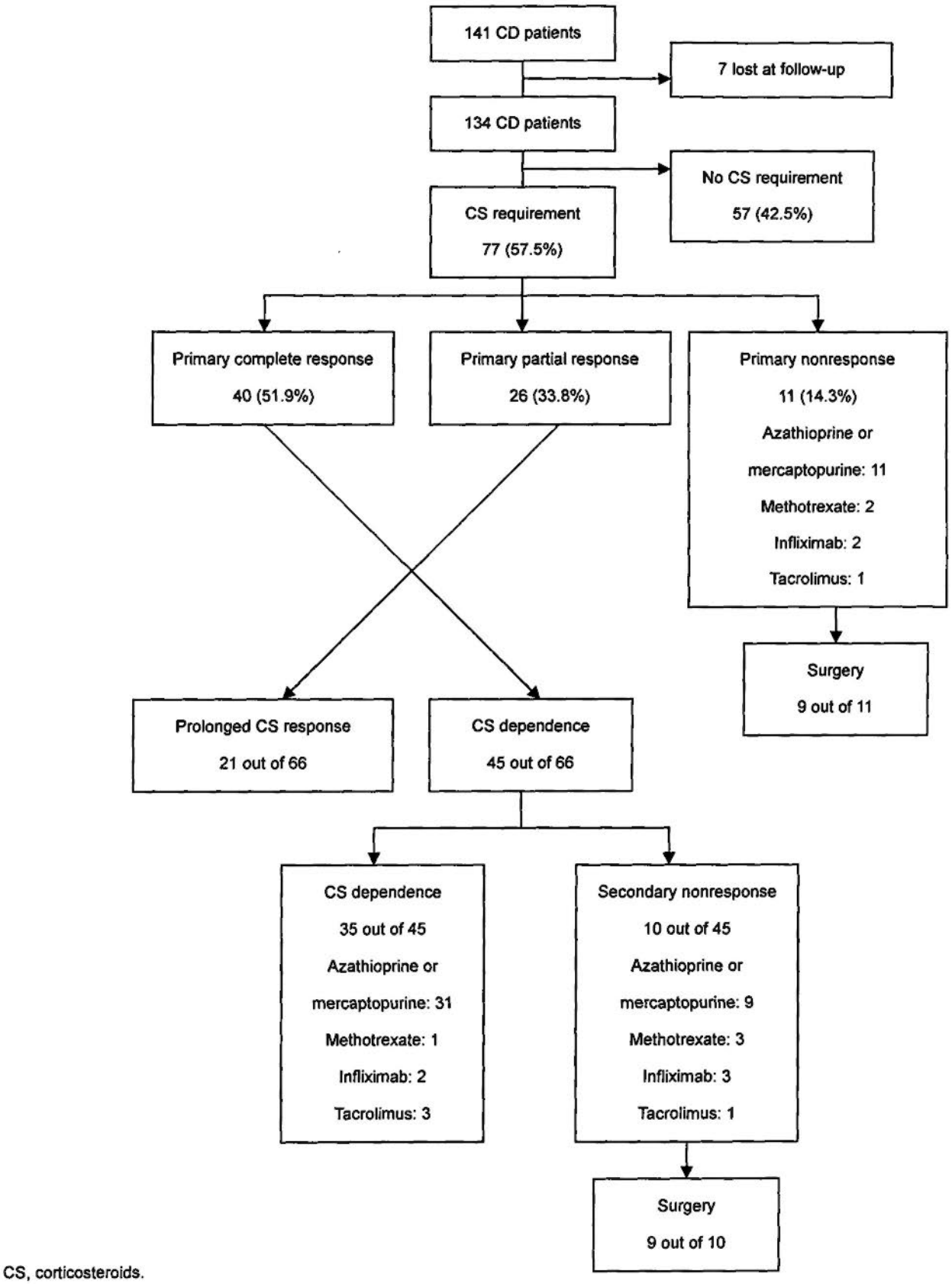
‡Involvement extends proximal to the splenic flexure.

¶ Total parenteral nutrition.

B1, non-stricturing non-penetrating disease; B2, stricturing disease; B3, penetrating disease; p†, perianal disease modifier.

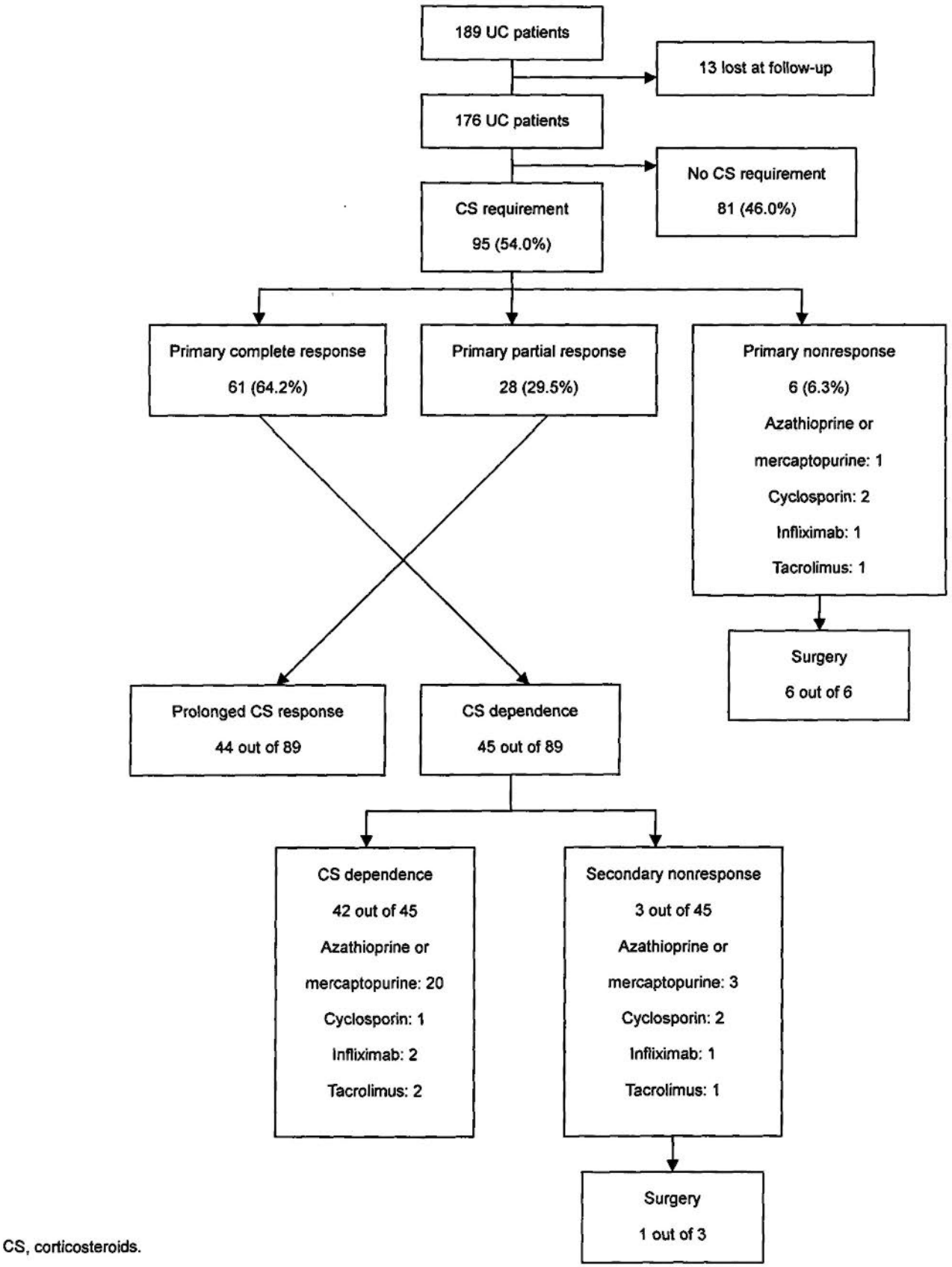
L1, terminal ileum; L2, colon; L3, ileocolon; L4, upper gastrointestinal tract (as defined by any disease location proximal to the terminal ileum excluding the mouth).

Figure 8.1. The 30-day outcome and outcome at last follow-up for CD



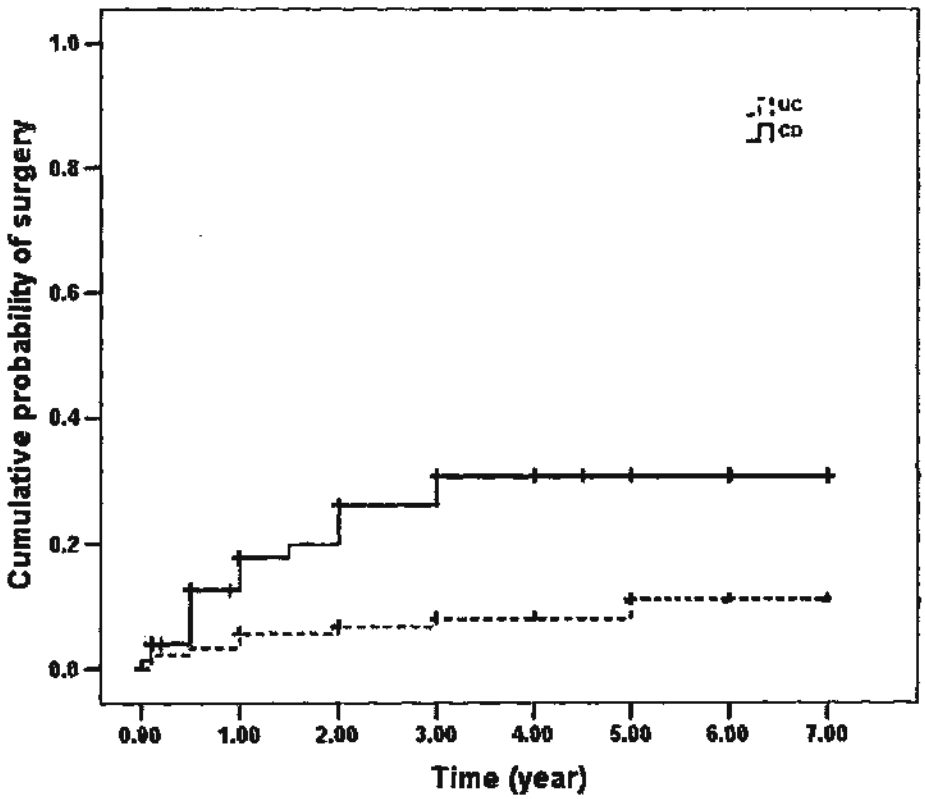
CS, corticosteroids.

Figure 8.2. The 30-day outcome and outcome at last follow-up for UC



CS, corticosteroids.

Figure 8.3. Cumulative probabilities of surgery in CD and UC patients who ever required corticosteroid therapy (P=0.002 by log-rank test)



No. at risk						
CD patients	77	47	36	30	23	14
UC patients	95	87	81	76	60	46

Table 8.2. Analysis of possible risk factors predicting corticosteroid dependency in CD

Covariates	Univariate analysis	Multivariate analysis	
	P value	Hazard ratio (95% CI)	P value
Thrombocytosis	0.004	3.0 (1.4 to 6.4)	**0.004**
Colonic disease (L2)	0.004	0.3 (0.1 to 0.8)	**0.016**
Abdominal pain	0.029	4.9 (0.6 to 36.8)	0.119
Anemia	0.008	1.9 (0.8 to 4.5)	0.171
Proximal gastrointestinal tract disease (L4)	0.016	0.9 (0.5 to 1.7)	0.737
Weight loss	0.120		
Stricturing disease (B2)	0.123		
Family history of IBD	0.136		
Initial requirement of corticosteroids	0.180		
Penetrating disease (B3)	0.195		
Age less than 40 years	0.232		
Non-stricturing non-penetrating disease (B1)	0.350		
Sex	0.466		
Use of 5-aminosalicylates or sulfasalazine	0.475		
Perianal disease	0.534		
Initial requirement of TPN	0.793		
Prior bowel resection	0.839		
Smoking	0.902		

Table 8.3. Analysis of possible risk factors predicting corticosteroid refractoriness in CD

Covariates	Univariate analysis P value	Multivariate analysis Hazard ratio (95% CI)	Multivariate analysis P value
Stricturing disease (B2)	<0.0001	4.5 (1.8 to 10.9)	**0.001**
Weight loss	0.030	2.7 (1.0 to 7.3)	0.058
Perianal disease	0.051	0.4 (0.1 to 1.6)	0.178
Initial requirement of TPN	0.001	1.8 (0.7 to 4.3)	0.190
Anemia	0.043	2.0 (0.6 to 6.3)	0.227
Prior bowel resection	0.046	1.3 (0.5 to 3.4)	0.529
Non-stricturing non-penetrating disease (B1)	0.010	1.2 (0.4-3.9)	0.746
Proximal gastrointestinal tract disease (L4)	0.042	0.9 (0.4 to 2.1)	0.830
Use of 5-aminosalicylates or sulfasalazine	0.035	1.0 (0.9-1.1)	0.836
Initial requirement of corticosteroids	0.108		
Thrombocytosis	0.112		
Colonic disease (L2)	0.164		
Family history of IBD	0.280		
Age less than 40 years	0.518		
Penetrating disease (B3)	0.576		
Sex	0.650		
Abdominal pain	0.882		
Smoking	0.929		

Table 8.4. Analysis of possible risk factors predicting corticosteroid dependency in UC

Covariates	Univariate analysis	Multivariate analysis	
	P value	Hazard ratio (95% CI)	P value
Thrombocytosis	<0.0001	3.9 (2.0 to 7.7)	**<0.0001**
Extensive colitis	0.001	1.7 (1.1 to 2.7)	**0.03**
Anemia	<0.0001	1.8 (0.8 to 3.8)	0.135
Weight loss	0.028	1.6 (0.7 to 3.3)	0.237
Initial requirement of corticosteroids	0.017	0.8 (0.3 to 1.8)	0.604
Diarrhea	0.051	1.0 (0.4 to 2.4)	0.971
Use of 5-aminosalicylates or sulfasalazine	0.100		
Abdominal pain	0.101		
Sex	0.213		
Family history of IBD	0.574		
Age less than 40 years	0.624		
Initial requirement of TPN	0.698		
Smoking	0.878		

Table 8.5. Analysis of possible risk factors predicting corticosteroid refractoriness in UC

Covariates	Univariate analysis	Multivariate analysis	
	P value	Hazard ratio (95% CI)	P value
Initial requirement of TPN	<0.0001	18.8 (3.5 to 100.3)	**0.001**
Anemia	0.001	10.8 (2.1 to 54.8)	**0.004**
Initial requirement of corticosteroids	<0.0001	2.9 (0.6 to 14.0)	0.189
Abdominal pain	0.083	1.7 (0.4 to 8.1)	0.476
Thrombocytosis	0.005	1.9 (0.3 to 12.5)	0.520
Age less than 40 years	0.100		
Sex	0.101		
Extensive colitis	0.128		
Smoking	0.180		
Diarrhea	0.380		
Weight loss	0.441		
Use of 5-aminosalicylates or sulfasalazine	0.664		
Family history of IBD	0.816		

8.2 CONCLUSIONS

Majority of Chinese IBD patients responded to corticosteroid therapy. The primary nonresponse rate at 30 days and cumulative risk of surgery at 1 year after starting corticosteroids were 14% and 18%, respectively for CD, 6% and 5%, respectively for UC. Thrombocytosis predicted, whereas colonic disease negatively predicted corticosteroid dependency in CD. Stricturing CD was associated with corticosteroid refractoriness. For UC, thrombocytosis and extensive colitis predicted corticosteroid dependency, whereas anemia predicted corticosteroid- refractory disease.

CHAPTER 9

Discussions

9.1 Incidence, prevalence and survival of UC in Hong Kong Chinese [Study 1]

The incidence of UC is rising in Hong Kong with a sixfold increase in the past two decades. The mean annual incidence rates in our study compared favorably with those reported by Leong et al. [Leong 2004] In previous study, the mean annual incidence of UC showed a 4 times increase, from 0.3 per 100,000 in 1985 and before to 1.2 per 100,000 in the 3-year period of 1999-2001.The incidence of UC continued to increase at a steady rate beyond 2001. Nonetheless, a retrospective cohort study that was conducted in another district hospital of Hong Kong, failed to reveal any increase in the incidence of UC. [Lok 2008] Only 73 patients were enrolled in that particular study despite Tuen Mun Hospital serviced two districts (Tuen Mun and Yuen Long) that amounted to 15.1% of the population of Hong Kong.[Census and Statistics Department. Table 141] Additionally, there was another regional public hospital that provided gastroenterology service jointly with Tuen Mun Hospital in the districts. Hence, patient collection might not be complete. In Lok et al [Lok 2008] study, the study period and follow-up were of shorter

duration.

The incidence and prevalence of UC in Hong Kong are comparable to the figures in Japan of 1.95 and 18.12 per 100,000 and in South Korea of 1.51 and 30.87 per 100,000 respectively. [Morita 1995, Yang 2008] India has the highest reported incidence and prevalence of UC in Asia with rates of 6.02 and 44.3 per 100,000 respectively between 1999 and 2000. [Sood 2003] Although the prevalence of UC in India was lower than the west, the incidence was similar to that of Caucasians. [Loftus 2000] Urbanization and industrialization are believed to partly account for the surge of IBD in Asia together with other unidentified factors. [Ekbom 1991, Loftus 2000, Yoshida 1990] Asthma, an example of urbanized disease, is increased in prevalence among US children from 3.6% in 1980 to 5.8% in 2003. [Health, United States, 2005] Our cohort of Chinese UC patients serves as an excellent platform for further epidemiological study of UC, in particular, the etiologic roles of the environment and genes.

Despite the low prevalence of complications, extensive colitis was

the predominant phenotype in our cohort. This was also the predominant UC phenotype in Olmsted County, USA. [Loftus 2000] In Korea and Sweden, there was a trend toward an increase in the proportion of patients with proctitis, which was the commonest phenotype, as the incidence of UC increased. [Yang 2008, Ekbom 1991] The ratio of extensive colitis, left-sided colitis and proctitis was approximately 4:3:3 in our cohort as compared to 3:2:4 in the Korean study. Although the increase in incidence was greater in proctitis than in extensive colitis, the rate of increase was the most pronounced in extensive colitis in the past 10 years. We believed that the increase in extensive colitis was genuine and it was not due to a change in diagnostic tools during the study period. It was because colonoscopy had all along been the preferred diagnostic tool in our institution, even in the early study period, but not sigmoidoscopy and/or barium enema. Yet, we could not eliminate the possibility that a minority of UC patients who suffered from mild proctitis were not referred to hospital. They might have been cared by primary physicians because the level of knowledge about UC among community general practitioners increased as the incidence

of UC in the community increased. In addition, a small number of patients with mild disease might have consulted traditional Chinese herbalists. As a result, patient collection might not be complete. However, Chinese IBD patients perceived a lower level of expertise in the management of their diseases among community general practitioners. [Leong 2004] Most of them would still go to the out-patient clinics of the public hospitals. Apparently, prospective population-based cohort studies are eagerly awaited in the Chinese population.

Despite extensive colitis being the commonest phenotype in the Chinese population, most cases were managed adequately with medications. Patients who required immunomodulator or infliximab only constituted a minor proportion. The use of corticosteroid, immunomodulator or infliximab was even less frequent among UC patients in Korea. [Park 2007] In this cohort, there were a few cases of refractory disease, fulminant colitis or colorectal cancers. This observation was consistent with the finding from the Tuen Mun group [Lok 2008] and the Korean group. [Park 2007] However, the

negligible rate of colorectal cancer in our cohort may be due to the relatively short duration of follow-up and small number of patients. According to the Danish study, the calculated cumulative colorectal cancer incidence was 3.1% after 25 years. [Langholz 1992] The incidence of sporadic colorectal cancer has been rising in the Chinese population [Hospital Authority Statistical Report 2005/2006] and this may independently increase the colorectal cancer rate in our IBD patients. Subsequent long-term outcome study is needed to validate this speculation.

The cumulative colectomy rates in the Study 1 were 2.4% and 7.6% at 1 and 10 years, as compared to 4.1% and 6.8% in the first and second years in Japanese cohort. [Hiwatashi 1995] In Korea, the cumulative colectomy rates were noted to be lower, at 2.0% after 1 year, 2.8% after 3 years, and 3.3% after 5-15 years. [Park 2007] Interestingly, a study conducted in Leicestershire revealed fewer operations and UC-related complications in South Asian migrants compared with Europeans despite similar disease distribution. [Probert 1993] In that study, the cumulative colectomy rates in

South Asians at 5, 10, and 15 years were 9%, 10%, and 10%, respectively versus 13%, 18% and 21%, respectively in Europeans. In one study conducted in Singapore, the rate of proctocolectomy was reported to be higher in Chinese, up to 18%, as compared to 10% in Indian and 13% in Malay. [Ling 2002] Whether we are seeing a less aggressive UC natural history among Asians worldwide remains to be confirmed.

9.2 Phenotypic evolution of CD and UC in Hong Kong Chinese

9.2.1 Phenotypic evolution of CD [Study 2 & 3]

Study2 revealed that phenotypic changes in CD also occurred in Chinese patients in the same way as in the white patients. [Louis 2001, Schwartz 2002] The non-stricturing, non-penetrating phenotype had a tendency to progress into stricturing or penetrating disease. This would support the concept that CD consists of a heterogeneous group of disorders that eventually result in a specific phenotypic complication.

Significant proportions of patients developed stricturing and penetrating complications. In the Chinese CD cohort, complications became statistically significant as early as three years ($P = 0.025$) after diagnosis using the MC. Nevertheless, behavioral phenotypic changes in Chinese CD still took longer to occur than in white CD, which typically changed after only 1 year. [Louis 2001] This might reflect the slower rate of disease progression in Chinese CD patients, milder disease overall, or the need for a larger sample size. On the

other hand, similar to the white CD patients, [Louis 2001] the location of disease remained relatively stable over the course of disease.

None of the B3 patients classified by the MC in our cohort developed perianal disease over the 10-year follow-up. This concurs with previous finding suggesting that perianal CD represented a distinct entity that was distinct from intestinal penetrating disease with respect to disease progression and outcome. [Smith 2004, Sachar 2005]

The proportions of patients who had surgery (31.2%) were comparable to that of the Louis et al cohort (30.4%). [Louis 2001] We found stricturing and penetrating phenotypes predicted the need for major surgery.

A high proportion of L4 phenotypes (19%) was first reported in a Chinese CD cohort by Leong et al. [Leong 2004] Nevertheless, the proportion of patients with L4 disease at diagnosis in Study 2, which

was an extension of the Leong et al study, was only 9.2%. In Study 3, approximately 23% of CD patients were found to have L4 phenotypes upon diagnosis. The reason for the fluctuating proportions of L4 phenotypes over times in this similar cohort of CD patients could be due to interobserver variation in the use of the MC of CD. Although data on interobserver variation in the application of the MC were lacking, appreciable interobserver disagreement on the location of CD according to the original VC was reported. [Oefferlbauer-Ernst 2007] If the results of histopathology were included in the evaluation of location, then the interobserver agreement increased, which was mainly a result of greater agreement on rating for L4. Importantly, the location of CD was defined as the maximum extent of disease involvement at any time before the first resection in VC. In our cohort study, surgical specimens were used for phenotyping only in the subsequent follow-up period but not at diagnosis. Hence, the high proportion of L4 phenotypes at diagnosis in Study 3 was genuine.

Although the proportions of patients diagnosed with L4 phenotype

were larger in Chinese than in Caucasians, the overall operation rate was not driven to the high side. There are a number of plausible explanations. First, the B2 and B3 phenotypes might exert greater influences on major surgery when compared to the L4 phenotype since only B2 and B3 phenotypes were independent risk factors predicting major surgery after adjusting for confounding covariates. Second, unlike colonic CD, patients with the L4 phenotype infrequently present with hematochezia (26.7%) and the symptoms might not be prominent until significant stricture or even perforation develops. Third, phenotypic progression in Chinese CD patients was slower compared to that of Caucasian patients. The slow disease progression in Chinese CD patients might partly account for the low operative rate.

In Study 3, there were more stricturing and penetrating diseases in the L4 group. Patients who had a stricturing phenotype were more prone to develop L4 disease, indicating the importance of disease location in determining its behavior. The less spacious lumen in the small intestine makes it prone to stricture formation and, as the

disease progresses, fistulalization. The pathogenesis of CD may also give us some hints on the correlation between the L4 and B2 phenotypes. The small intestine contains Paneth cells, which are specialized epithelial cells. Paneth cells play an important role in innate intestinal defense by producing an antimicrobial protein, defensin, which regulates the microbial density. [Elphick 2005] The expression of NOD2 are found to be highest in Paneth cells in the small intestine. [Lala 2003] It has been well recognized and confirmed in multiple Caucasian studies that the CARD15/NOD2 mutation was associated with stricturing behavior and small bowel phenotypes in CD. [Economou 2004] Nonetheless, the prevalence of CARD15/NOD2 mutations in Chinese CD is negligible. [Leong 2003, Guo 2004] The association of L4, B2 and B3 phenotypes in Chinese may suggest that there are as yet unknown genetic variants. Further genotypic-phenotypic correlation studies are needed to help understand the pathogenesis of this complex heterogeneous disease.

9.2.2 Phenotypic evolution of UC [Study 1]

In study 1, the cumulative rate of proximal extension of ulcerative proctitis or left-sided colitis in our cohort was less than 25% after 10 years. Our figure was lower than the rate (44.5%) reported from Korea, even though the proportions of patients undergoing follow-up colonoscopy were similar. [Park 2007] The relatively short duration of endoscopic follow-up might be a reason for the low rate of disease extension. A generally less aggressive behavior of UC in our population is speculated to be another reason.

9.3 Predictors of corticosteroid-dependent and –refractory IBD [Study 4]

The proportion of CD patients who had ever received corticosteroids, the primary corticosteroid nonresponse rate and the 1-year cumulative risk of corticosteroid-dependency in our CD cohort were comparable to the figures of the white population. [Faubion 2001, Munkholm 1994, Ho 2006] Yet, the cumulative risk of surgery at 1 year after starting corticosteroid therapy was slightly less in Chinese CD patients compared with approximately 30%-40% in white CD patients. On the other hand, the proportion of UC patients required corticosteroid therapy (54% versus 34%) and the 1-year cumulative risk of corticosteroid dependency (38% versus 22%) were slightly higher when contrasted with the study by Faubion et al. [Faubion 2001] Interestingly, primary corticosteroid nonresponse rate (6% versus 16%) and the risk of surgery at 1 year after starting corticosteroid therapy (5% versus 29%) were much lower in our UC patients compared with the white patients. A note of caution was that in Faubion et al study, the proportion of UC patients who suffered from pancolitis was up to 59%, whereas proctitis was only

3%. These might account for higher treatment failure and colectomy rates. Besides, the previous study was conducted between 1970 and 1993, whereas immunomodulators and biologics were introduced in mid to late 1990s. This might also be a reason for high colectomy rate. Alternatively, the lower incidence of corticosteroid-refractory disease among Chinese UC patients might also reflect a generally milder disease in our population. This speculation remained to be confirmed by large-scale population-based studies. Last but not least, genetic factor might play a role in determining glucocorticoid resistance and this might differ between populations. In white IBD patients, high multidrug resistance gene (MDR1) expression was observed leading to increased P-glycoprotein-mediated efflux of glucocorticord and therefore, a decrease in cytoplasmic glucocorticoid concentration. [Farrell 2000] Nonetheless, data on over-expression of MDR1 in the Chinese population were lacking.

In Study 4, thrombocytosis was associated with corticosteroid dependency in both CD and UC. Chronic inflammatory diseases such

as IBD and connective tissue disorders were well-recognized causes of reactive thrombocytosis. Indirectly, the presence of reactive thrombocytosis might signify a greater magnitude of inflammation and therefore, a more difficult-to-treat disease. In addition, iron deficiency anemia *per se* might also lead to reactive thrombocytosis. A marginally higher proportion of CD patients with ileocolonic disease had thrombocytosis when compared with other disease location. The frequencies of thrombocytosis were similar in patients with non-stricturing non-penetrating disease, stricturing or perianal diseases. Thrombocytosis was only found in one third of UC patients who had extensive colitis at diagnosis. The proportion of patients with thrombocytosis that required corticosteroids at diagnosis for disease control was not impressively high, only 40%. We believe that thrombocytosis is a true predictor of corticosteroid dependency in IBD patients, rather than a mere marker of disease phenotype or severity.

Approximately 90% of UC patients presented with rectal bleeding in this cohort but only less than one third had anemia. Those with

rectal bleeding that was severe enough to result in significant anemia (hemoglobin ≤10.0g/dL) had a higher chance to progress to corticosteroid-refractory disease. Extensive colitis which was well-proven to be associated with higher risks of colectomy [Ritchie 1978, Langholz 1992] and colorectal cancer [Brostrom 1987] had modest association with corticosteroid dependency. In CD, only stricturing phenotype was found to predict corticosteroid refractoriness. Fibrostenosing CD always posed great challenges for gastroenterologists. It was not uncommon to encounter patients with active stricturing disease failing corticosteroid therapy (41.4% in Study 4). Stricturing disease was also shown to predict surgery in Study 2. However, our findings did not concur with previous studies, which showed prior bowel resection, [Gelbmann 2002] perianal disease, [Gelbmann 2002] colonic disease, [Franchimont 1998] smoking [Franchimont 1998] and a younger age at diagnosis [Franchimont 1998] predictive of corticosteroid response in CD. We used antibiotics and/or thiopurines and/or surgical therapy to treat perianal diseases, but not oral corticosteroids. Hence, the value of using perianal disease phenotype to predict response to

corticosteroids was not high in our study. We reported a negative association between colonic phenotype and major surgery in Study 2. In Study 4, a negative association between colonic phenotype and corticosteroid dependency was also demonstrated. Yet, one drawback of Study 4 was that markers of disease activity such as CRP and CDAI were not captured for correlation analysis. Besides, Study 4 had not been designed to be population-based. The possibility of referral bias could not be eliminated even though our study was ambulatory clinic-based.

Clinical predictors help individualize treatment strategy. Ideally, early administration of aggressive medical therapy with biologics and/or immunomodulators should be reserved for selected high risk group of patients including those who are corticosteroid-dependent and –refractory because of the potentially serious adverse events. [Colombel 2004, Ljung 2004, Hansen 2007] The identification of different clinical markers in different populations deserves further large-scale prospective population-based cohort studies to validate.

CHAPTER 10

Summary

1.1 Incidence of UC in Hong Kong has increased sixfold over the past two decades, from 0.3 (95% CI: 0-0.9) per 100,000 in the 3-year period of 1986-1988 to 1.8 (95% CI: 0.8-3.1) per 100,000 in 2004 - 2006.

1.2 The annual age-standardized incidence of UC per 100,000 Hong Kong Chinese was 2.1 (95% CI: 1.1-3.7) in 2006.

1.3 The age-standardized prevalence of UC per 100,000 Hong Kong Chinese was 26.5 (95% CI: 22.6-30.9) in 2006.

1.4 The overall survival of UC patients was similar to the expected survival of the Hong Kong population.

2.1 Phenotypic changes in CD also occurred in Chinese patients in the same way as the white patients with respect to disease behavior, though at a slower rate.

2.2 Similar to the white CD patients, the location of disease remained relatively stable over the course of disease.

2.3 Chinese CD patients had more upper gastrointestinal tract phenotype which predicted the need of surgery and subsequent hospitalization.

2.4 The rate of proximal extension of UC was less than 25%

after 10 years.

3.1 In CD, thrombocytosis predicted, whereas colonic disease negatively predicted corticosteroid dependency. Stricturing CD was associated with corticosteroid refractoriness.

3.2 In UC, thrombocytosis and extensive colitis predicted corticosteroid dependency, whereas anemia predicted corticosteroid-refractory disease.

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Census and Statistics Department, the government of the Hong Kong Special Administrative Region. 2006 Population By-census. Table 158. Domestic Households by Household Composition, Monthly Domestic Household Income and District Council District, 2006.
http://www.censtatd.gov.hk/hong_kong_statistics/statistical_tables/?charsetID=1&subjectID=1&tableID=158

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PUBLICATIONS

The results of the studies used in this thesis have been published as original articles in the following peer-reviewed journals:

1. Chow DK, Leong RW, Tsoi KK, Ng SS, Leung WK, Wu JC, Wong VW, Chan FK, Sung JJ.

   Long term Follow-up of Ulcerative Colitis in the Chinese Population.

   American Journal of Gastroenterology 2009;104:647-54.

2. Chow DK, Leong RW, Lai LH, Wong GL, Leung WK, Chan FK, Sung JJ.

   Changes in Crohn's disease phenotype over time in the Chinese population: Validation of the Montreal Classification System.

   Inflammatory Bowel Diseases 2008;14:536-541.

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3. Chow DK, Sung JJ, Wu JC, Tsoi KK, Leong RW, Chan FK.

Upper Gastrointestinal Tract Phenotype of Crohn's Disease is associated with Early Surgery and Further Hospitalization.

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4. Chow DK, Sung JJ, Tsoi KK, Wong VW, Wu JC, Leong RW, Chan FK.

Predictors of Corticosteroid-dependent and Corticosteroid-refractory Inflammatory Bowel Disease: Analysis of a Chinese Cohort Study.

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