The natural history of inflammatory bowel disease in an Australian community cohort: investigating the aetiology, clinical course, predictors of severe disease and healthcare cost.

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Inflammatory Bowel Disease (IBD), including Crohn’s Disease (CD), Ulcerative colitis (UC) and IBD undifferentiated (IBDU), are chronic disorders of the gastrointestinal tract that exert a major impact on an individual’s quality of life and result in very high usage of health care resources. The aetiology of IBD remains unknown. Clinical course can vary from mild to severe and debilitating, and it remains unclear at diagnosis what disease progression will be. Identifying early clinical prognostic factors that predict a severe course is important, thereby enabling early medical therapy to minimize complications of disease. In recent years there has been greater emphasis on intensive therapy and disease monitoring. The greatest impact has been the introduction of biological therapy. However, it remains unclear if these advances are translating into better disease outcomes in the community and at what cost.

A population based inception cohort study of patients with IBD was set up in Barwon, Victoria. The aims of the study were to validate the previously reported high incidence, to identify environmental exposures that are associated with disease aetiology, to assess the early course of disease as measured by objective markers such as surgery and hospitalization rates, to identify early clinical prognostic factors associated with severe disease and to determine the health care cost early in the course of IBD.

Incident cases from 2007/2008 and 2010-2013 in a well-defined geographical area were prospectively identified through a multifaceted approach to ensure complete capture. Cases were subsequently enrolled into the IBD registry that was used as a basis to collect outcome data on the disease progression, environmental exposures and health care cost.

A number of environmental exposures were found to be associated with increased risk of CD included smoking, frequent fast food intake and childhood events such as tonsillectomy and chicken pox infection. In UC, the risk factors
included smoking, childhood chicken pox infection as well as frequent fast food. In UC, high caffeine intake was protective (a novel finding), while frequent fruit intake and pets as a child reduced the risk of UC.

Objective clinical outcomes were measured for a median of 18 months from diagnosis (range 12-60 months) for 252 patients comprising 146 CD, 96 with Ulcerative colitis UC and 10 IBDU. Immunomodulators (IM) were prescribed in 57% of CD patients, and 19% with UC; biological therapy in 13% of CD patients. A third of all CD patients were hospitalised, the majority (77%) in the first 12 months. Risk factors for hospitalisation included penetrating, perianal and ileocolonic disease. A quarter of UC patients were hospitalized, most within the first 12 months. Resective surgery rates were 13% at 1 year in CD, and 26% at 5 years. Risk factors at diagnosis included penetrating, stricturing and ileal disease. Colectomy rates in UC were 2% and 13% at 1 and 5 years. High CRP at diagnosis was associated with colectomy. Health cost analysis in the first year of disease showed that per patient cost was higher in CD than UC; and that there has been a shift from inpatient to outpatient resources driving the majority of health cost in IBD compared to older studies. This was primarily due to the expense from medications.

This first Australian population based study of an inception cohort confirms a high incidence of IBD in Barwon, Victoria that has remained stable over 6 years. A number of environmental risk factors associated with an increased risk of IBD were identified, as well as protective factors, of which high caffeine intake is a novel finding. Disease progress in this cohort was optimistic, compared to historical cohorts, with low rates of intestinal surgery. This was associated with high rates of IM and biological therapy. Early clinical predictors of severe disease were identified that can be used in clinical practice to tailor therapy. Health cost analysis in the first year shows a shift from inpatient to outpatient resources, with medications and investigations contributing the most.
Publications and Presentations

Publications arising from this research


3) Siew C Ng, Zhirong Zeng, Ola Niewiadomski, Whitney Tang, Sally Bell, Michael A et al on behalf of the Asia-Pacific Crohn’s and Colitis Epidemiology Study (ACCESS) Group. Early Course of Inflammatory Bowel Disease in a Population-based Inception Cohort from 8 Countries in Asia and Australia. *Gastroenterology*. September 2015 (accepted). DOI:10.1053/j.gastro.2015.09.005.


**Presentations**

Niewiadomski, O et al. The first prospective Australian population-based study of newly diagnosed IBD identifies frequent use of immunomodulators, low surgery rates and high cost from medications and investigations. *Journal Crohn’s Colitis*. 2015; 9(s5): S1-S17. Oral presentation and *Recipient of the Young Investigator’s Award*: European Crohn’s Colitis (ECCO) meeting (Barcelona 2015).

Niewiadomski O et al. The first prospective Australian population-based study of newly diagnosed IBD identifies outpatient resources as the major cost driver, including medications and investigations. *Journal Gastro and Hep*. 2015; 30 (S3). Oral presentation at the Australian Gastroenterology Week, Brisbane, 2015.


Niewiadomski O and Studd C et al. Preliminary Paediatric Natural History Results from the GECCO study (Geelong Epidemiological Crohn's Colitis Ouctome Study). Oral presentation at the St Vincent's IBD symposium 2012.
Declaration

This thesis contains no material that has been previously submitted for the award of any other degree or diploma in any university. To the best of my knowledge, this thesis contains no material previously published or written by another person except where due reference is made in the text. This thesis reflects work done during the period of candidature and the text is less than 100,000 words in length.
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Table of Contents

Chapter 1  Literature Review ................................................................. 1
  1.1 Introduction ......................................................................................... 1
  1.2 Inflammatory Bowel Disease- Overview ............................................. 3
    1.2.1 Crohn's Disease ............................................................................. 3
    1.2.2 Ulcerative Colitis ......................................................................... 4
    1.2.3 IBD Undifferentiated .................................................................... 4
  1.3 Epidemiology and Aetiology of IBD .................................................. 5
    1.3.1 Incidence and Prevalence ................................................................ 6
    1.3.2 Aetiology of IBD .......................................................................... 7
      1.3.2.1 Genetics ................................................................................. 7
      1.3.2.2 Gut Microbiota ...................................................................... 10
      1.3.2.3 Dysregulated Immune Response ............................................ 11
      1.3.2.4 Environmental Factors ............................................................ 12
  1.4 Clinical Manifestations ....................................................................... 24
  1.5 Differential Diagnosis ........................................................................ 26
    1.5.1 Diagnosis ..................................................................................... 29
      1.5.1.1 Laboratory Examinations ....................................................... 31
      1.5.1.2 Endoscopy ............................................................................... 31
      1.5.1.3 Imaging .................................................................................. 32
      1.5.1.4 Biomarkers ............................................................................. 33
    1.5.2 Disease Classification and Activity Assessment Tools ................... 34
      1.5.2.1 Montreal Classification of IBD ................................................ 34
      1.5.2.2 Disease activity assessment scores .......................................... 36
  1.6 Therapeutic Strategies in IBD ............................................................ 37
    1.6.1 Induction of Remission in CD ...................................................... 39
    1.6.2 Maintenance Therapy in CD ......................................................... 42
    1.6.3 Induction of Remission in UC ....................................................... 42
    1.6.4 Maintenance Therapy in UC ......................................................... 43
    1.6.5 Real Life Outcomes of Therapeutic Strategies in CD ..................... 44
    1.6.6 Real Life Outcomes of Therapeutic Strategies in UC ..................... 46
  1.7 Disease course in IBD ................................................................. 47
    1.7.1 Progression of Phenotype in CD ................................................... 48
    1.7.2 Progression of Phenotype in UC ................................................... 50
    1.7.3 Predictors of Disabling CD ............................................................ 51
    1.7.4 Predictors of Disabling UC ............................................................ 53
    1.7.5 Hospitalization Rates in CD .......................................................... 54
    1.7.6 Hospitalization Rates in UC .......................................................... 55
    1.7.7 Intestinal Surgery in CD ................................................................. 55
    1.7.8 Colectomy in UC ......................................................................... 58
    1.7.9 Mucosal Healing in CD ................................................................. 59
    1.7.10 Mucosal Healing in UC ............................................................... 60
    1.7.11 Mortality and Malignancy in CD .................................................. 61
    1.7.12 Mortality and Malignancy in UC .................................................. 64
  1.8 Clinical Predictors of Disabling Disease .......................................... 65
  1.9 Health Cost Associated with IBD ...................................................... 65
  1.10 Conclusion ......................................................................................... 68
  1.11 Aims of this Research ..................................................................... 69

Chapter 2  Methodology .......................................................................... 70
  2.1 Study design ...................................................................................... 70
  2.2 Case Ascertainment .......................................................................... 70
  2.3 Registry ............................................................................................. 72
Chapter 3  Incidence, Disease Course and Clinical Predictors of Severe Disease in Inflammatory Bowel Disease

Chapter 4  Influence of Environmental Exposures on the Risk of Developing Inflammatory Bowel Disease

Chapter 5  Health Cost Analysis

Chapter 6  Conclusion and Future Directions

Chapter 7  References
Chapter 1   Literature Review

1.1 Introduction

Inflammatory bowel disease (IBD) is a chronic immune mediated inflammatory condition that primarily affects the gut but may also display extra-intestinal manifestations. There are two main types of IBD: Crohn’s disease (CD), Ulcerative colitis (UC), with a small proportion of patients not fulfilling the criteria for either diagnosed with a third type, IBD unspecified (IBDU). These chronic incurable disorders tend to affect young adults and exert a major impact on an individual’s quality of life. The aetiology of IBD remains unknown.

Considerable variation in the epidemiology of IBD has been observed around the world, with the highest incidence and prevalence in developed countries of Europe and North America. In the last 5 decades, the incidence rate has rapidly risen in these areas without a clear cause (1). Countries that are becoming more westernized in recent years, such as Asia and Eastern Europe, have had a very low incidence rate in the past but new evidence suggests it is also rising (2,3). Australian epidemiological research done in Barwon (Greater Geelong) (4,5) showed one of the highest incidence and prevalence of IBD in the world (6-10) This makes it an ideal setting to carry out future epidemiological studies. The epidemiological trends described above suggest that environmental factors must play a role in disease aetiology. Further research is needed to further explore this.

In the last decade there have been many recent advances in both the diagnostic tools and therapies available in managing an IBD patient. These include advanced imaging such as MRI enterography and pelvis (11,12) biomarkers including faecal calprotectin (13,14)and drug optimization strategies through the measurement of drug levels(15-17). The greatest impact on IBD management
in the last 2 decades has been the introduction of biological therapy (18-20). However, it remains unclear if the introduction of the new diagnostic and therapeutic tools, in particular biological therapy, translates into better disease outcomes in population-based cohorts and at what cost to the community.

Population based studies are the best means to answer these important questions, since hospital based studies can introduce bias and may not represent the true disease spectrum (21). However, population studies done to date have shown differing results in the objective disease outcomes such as surgery and hospitalisation rates (22). As an example, hospitalization rates have fallen in most developed countries while in North America rates have increased. Also, in most of these studies, the impact of biological therapies on these outcomes has not been clear, since patient recruitment pre-dated widespread adoption of anti-TNF antibodies use. Also, the cost associated with the use of biologics is likely to impact on the health care cost of IBD in general, and very few recent studies have addressed cost since the widespread use of this therapy.

This study was designed to answer some of these unresolved issues in a population based inception cohort study of patients with IBD in a well-defined regional geographical area (Barwon, Victoria). In particular, the focus was to assess environmental factors associated with disease aetiology; to determine the disease course of IBD in Australia in an era of recent advances; to identify early clinical markers associated with a severe disease course and to analyse the health care cost of managing IBD from time of diagnosis.
1.2 Inflammatory Bowel Disease- Overview

There are two main types of IBD: Crohn’s disease (CD), Ulcerative colitis (UC), with a small proportion of patients not fulfilling the criteria for either being diagnosed with a third type, IBD unspecified (IBDU) or Indeterminate colitis (IC). These are chronic, inflammatory and idiopathic conditions with both overlapping and distinct clinical and pathological features. They primarily affect the gastrointestinal tract but may also manifest in other organs including the skin, joints, liver and eyes. The natural history tends to be that of chronic and/or relapsing inflammation that can lead to irreversible bowel damage and need for intestinal surgery. Most patients are diagnosed in adolescence and as young adults, though there is a smaller peak in later years. A diagnosis of IBD has a great potential to result in disability and reduced quality of life.

1.2.1 Crohn’s Disease

CD is characterized by chronic and/or relapsing inflammation that can occur anywhere in the gastrointestinal tract from mouth to anus. In CD, inflammation can involve all layers of the bowel and so is termed as trans-mural, and it can affect segmental sections of the gastrointestinal tract, typically resulting in ‘skip lesions’. The most common sites of disease are the ileum and colon (23) with disease occurring in ileum alone, colon alone or both ileum and colon in equal proportions of patients (24). About 10-15% of patients have upper gastrointestinal lesions, such as the mouth, oesophagus, stomach or proximal small bowel.

Due to the trans-mural nature of the inflammation, patients with CD can develop complications of disease including intestinal obstruction, fistulas and abscesses. The fistulae can occur between loops of bowel (entero-enteric fistulae), between the anorectum and perineal skin (perianal fistula) or between the bowel and any neighboring organ or structure (25).
The histopathological features of CD include inflammatory cell infiltrate, mainly composed of lymphocytes and plasma cells. Progression leads to infiltration into crypts, forming crypt abscesses and destruction. Noncaseating granulomas are characteristic of CD, though only present on 15-35% of biopsy specimens (23,26).

1.2.2 Ulcerative Colitis

UC is characterized by superficial and continuous inflammation in the rectum, and extending proximally in a continuous fashion to involve all or part of the colon (27). It does not affect the small intestine, apart from a very short segment of ileitis without granuloma known as “backwash ileitis” which affects 10-15% of patients with UC with pancolitis.

UC causes superficial continuous ulceration of the colon that involves mucosa and sub mucosa only (23,27). Patients with UC are therefore not at risk of the same complications as CD. Toxic megacolon is a rare but potentially life-threatening complication of UC, characterized by dilatation of the colon (25) with risk of perforation, seen in the setting of acute severe disease. UC is also associated with an increased risk of colorectal cancer (25) especially in those with concomitant PSC.

The histological features of UC involve the mucosa and sub mucosa and include crypt infiltration particularly with neutrophils, mucus depletion from the goblet cells, Paneth cell metaplasia, cryptitis with crypt abscesses and disturbed crypt architecture. The crypt changes are not specific to UC and can be seen in chronic CD (23,26).

1.2.3 IBD Undifferentiated

Up to 10-15% of cases are diagnosed as IBD-undifferentiated (IBDU) because a clear assignment of CD or UC is not possible using established diagnostic criteria at diagnosis (26). For the majority of patients, this is considered a provisional diagnosis as follow up studies have shown that up to 80% of these patients are eventually reclassified as CD or UC (28). Additional information can be gained by the use of serological markers to increase diagnostic accuracy in categorizing these patients as CD or UC. The pANCA (perinuclear antineutrophil cytoplasmic
antibodies) and ASCA (anti-saccharomyces cerevisiae antibodies) serological tests have been shown to delineate the IBD phenotype for 66 and 90% respectively (29). ASCA can be detected in 35-50% of patients with CD but in <1% of patients with UC. A positive pANCA is 73% sensitive and 83% specific for the diagnosis of UC. Also, capsule endoscopy has emerged as a useful tool to identify small bowel ulceration and so confirming a diagnosis of CD (28).

However, a small subset of patients exists in which IBDU still remains the most accurate diagnosis during long term follow up, and it is likely that such patients represent a separate clinical entity (28,29). Very little is known about the clinical course of these patients. Historically it has been assumed these patients are more similar to UC than CD, but it has also been reported that when compared to UC, the IBDU patients have a more aggressive disease course with higher risk of relapses, as well as higher rates of colectomy. Those patients who require a colectomy with ileal pouch-anal anastomosis, the rate of post-operative complications is higher than in UC, in particular the rate of pouch failure (30) (31) (32).

1.3 Epidemiology and Aetiology of IBD

The study of epidemiology has contributed important knowledge to understanding IBD so far. It is through the study of incidence and prevalence that it became apparent there was a rapid rise in IBD in only a few decades, suggesting the importance of environmental changes in disease aetiology. Ongoing assessment of incidence will confirm if this rise is continuing as well as providing valuable information about the burden of illness for future health policy and resource planning. Epidemiological studies have confirmed a wide spectrum of disease severity between patients from mild symptoms to severe disease requiring surgery, and have also identified particular differences between groups of patients in relation to prognosis and disease severity, such as paediatric versus adult onset.
1.3.1 Incidence and Prevalence

The incidence of IBD has been on the rise in many developed regions such as North America, Europe and Australia for the last five decades, but appears to have stabilized in most of these areas over the last few years (1) (7) apart from the paediatric group which continues to show an increase in CD (33). These countries have the highest rates of IBD globally ranging from 24 to 29.6 per 100,000 (34) (4,8) (35) (6), with Australia among the top of these (4). The highest incidence of IBD is in the Faroe Islands, at a rate of 81.5 per 100,000 (34). In comparison the rates in Eastern Europe and Asia have historically been lower (< 5 per 100,000) but as these countries become have adopted a westernized diet and lifestyle, the rate of IBD is increasing, with recent studies documenting an incidence rates that range from 5.1-23 per 100,000 in Eastern Europe and 0.5-3.4 per 1000,000 in Asia (3) (2) (36). The highest incidence is reported in the highest urbanized areas of Asia such as Hong Kong and Macau (3). These epidemiological observations suggest recent environmental factors play a role in disease aetiology as the genetic pool is unlikely to change in this time period.

The ratio of CD to UC has considerable geographical variation, and has been shown to change over time in the same region. In many countries as the incidence of IBD begins to rise, UC is more common initially but as time goes on, CD usually equals or overtakes the incidence of UC. Currently in Australia, New Zealand and most of Europe, CD is more common than UC (8) (5) (33) (4). On the other hand, Nordic and Eastern European countries show a predominance of UC over CD (6) (2) (34). In North America, the gap between CD and UC is closing as CD becomes more common and UC rates drop (7). The variation in ratios of UC and CD between countries might reflect differences in environmental risk but genetic predisposition may also play a role (37).

Prevalence of disease is defined as the number of people living with the condition at any one particular time. The prevalence of IBD has increased alongside the rise of incidence. It is approximately 15 to 20 fold higher than the incidence rate, ranging from 344 to 388 per 100,000 in most developed countries (5) (7,38), while in parts of Canada the prevalence is approaching close
to 500 per 100,000 (35). The prevalence is likely to continue to rise in most of the regions described above due to longer life expectancies and this has been confirmed in Olmsted County in the US (38).

### 1.3.2 Aetiology of IBD

The aetiology of IBD remains unknown. The current working hypothesis is of a dysregulated mucosal immune response to intestinal bacteria (commensal and/or pathogenic) in a genetically susceptible individual (40-44). Environmental exposures are thought to play a major role in these processes, and the gene-environmental interaction is almost certainly be central and underlie the complexity of the disease phenotype (44). No matter what the trigger or the immune defects, ultimately the disease process is inevitably channeled into a common immunological pathway comprised of T helper and regulatory cells and T cell mediated cytokines (40). The cytokines drive (non infectious) inflammation of the gut. CD has been associated with excess IL-12/IL-23 and IFN-γ/IL-17 cytokine production, and in UC, it is an excess of IL-13 production (40). Both CD and UC have excess production of tumour necrosis α (TNF α) (45).

The major components of the working hypothesis, including the dysregulated mucosal immune system, gut microbiota (intestinal bacteria), genetics and environmental exposures will now be reviewed in more detail. Particular emphasis is placed on environmental factors here, as a field that is constantly evolving through ongoing epidemiological research.

#### 1.3.2.1 Genetics

A role for genetic factors in IBD was first suggested by epidemiological studies showing family aggregation and by twin studies that reported greater concordance for disease in monozygotic twins compared to dizygotic twins(46-48). First-degree relatives of affected CD individuals have a relative risk of 5-35% and in UC that risk is lower at 10-15% (49).

The major focus of recent genetic research in IBD has been the identification of disease-susceptibility genes. The pace of gene discovery in complex disease
genetics such as IBD has increased rapidly in recent years due to the advent of genome-wide association (GWA) studies. This has culminated in the discovery of 163 published susceptibility loci/genes in IBD, of which 110 are associated with both CD and UC (50). This is substantially more than reported for any other complex disease. Interestingly, seventy per cent of the 163 loci are shared with other autoimmune complex diseases or traits, such as ankylosing spondylosis, psoriasis and type 1 diabetes mellitus (44). Only in a handful of these 163 susceptibility genes/loci is the causative mutation known (44) and much work remains to be done on translating these gene discoveries including whether they are loss or gain of function genes. Most of the evidence to date relating to possible causal genes points to an essential role of these genes in the interaction between host mucosal immune systems and microbes, highlighting the importance in maintaining intestinal immune homeostasis (see Figure 1).

Figure 1- inflammatory bowel disease pathogenesis- genes and pathways involved. (*) denotes IBD susceptibility genes. Adapted from (51)

A clear emerging theme in CD pathogenesis is the central role of defective processing of intracellular bacteria. Among genes involved in this process is the
NOD2 gene, as well as the ATG16L1 and IRGM genes, through their role in innate immunity and autophagy (51,52). It remains unclear if NOD2 mutations represent a ‘loss-of-function’ or ‘gain of function’ phenotype (51). The NOD2 gene also has the most convincingly replicated association with disease phenotype. Mutations in this gene have been associated with disease involvement of the terminal ileum, fibrostenosing disease of the small bowel, shorter time to and need for surgery (53,54). There are 3 mutations of this gene associated with CD, with 10-30% of patients being heterozygote for one of these (compared to 8-15% of health controls) and 3-15% of patients with CD being either homozygotes or compound heterozygotes (55). However, NOD2 penetrance must be dependent on other factors as well, possibly related to additional genetic and environmental influences, as shown in a family study of 5 children. Two of 5 children homozygous for the mutation developed CD at a young age, but 2 others also had the same mutation with no symptoms of CD (55).

Other genetic IBD pathogenesis pathways that have been confirmed by genome wide association studies (GWAS) include those involved in the barrier function, the role of T cell subsets and cytokine-cytokine receptor signaling (56). The timing of the IL23R gene discovery for example, coincided with murine studies showing the critical role of interleukin-23 (IL 23) pathway in innate immune pathology and bacteria-induced intestinal inflammation (51). IL-23 is secreted by activated dendritic cells, monocytes and macrophages and supports the development of the Th17 subset of inflammatory T cells. Therefore IL-23 plays a crucial role in intestinal inflammation via sustained adaptive and innate immune mechanisms (51), and is an example of a key pathway in IBD pathogenesis.

It is important to note while the biology and relevance of many genes within confirmed susceptibility loci is rapidly emerging, there remains translational work to be done. For example, IBD-genetic variants are present in many individuals without disease, suggesting the impact of other factors as well. These other factors could include the heterogeneous effects of the IBD pathways when activated in different cell types resulting in different biological phenotypes (56). Also, some of the pathways, like the IL-23-Th17, are highly influenced by the
environment. These are some of the challenges that complicate the linkage between genotype and phenotype.

1.3.2.2 Gut Microbiota

The human body is colonized by a vast array of microbes, which form communities of bacteria, viruses and fungi. These microbes are collectively known as the human microbiota (57). Accumulating evidence suggests that the dynamic balance between the gut microbiota and host defensive responses at the mucosal frontier has a pivotal role in the initiation and pathogenesis of IBD. In humans, the first demonstration of gut microbiota playing a role in IBD was shown through clinical experiments in postoperative patients who had diversion of the faecal stream. There was recurrence of intestinal inflammation after infusion of intestinal luminal contents into excluded ileum (58). Another study showed improvement in symptoms from inflamed mucosa following faecal diversion (59).

Shifts in the gut microbiota have been associated with IBD. Dysbiosis is the term used to describe these shifts or imbalances (56,60). In IBD, these include alterations in relative abundance of approximately a dozen bacterial taxa as well as a decrease in the diversity of communities (61,62). Patients with IBD have fewer bacteria with anti-inflammatory properties and more bacteria with proinflammatory properties (63). Several studies have now reported that commensal bacteria members of the Firmicutes and Bacteroidetes phyla are reduced in CD and UC, respectively (64-70). Among the Firmicutes, *Faecalibacterium*, which is a major butyrate producer and exhibits anti-inflammatory properties, is reduced in patients with CD (61). Reduction of *Bacteroides fragilis* might also contribute to inflammation as this genus has shown to be protective against colitis in animal models. In CD, there have also been studies showing a greater abundance of Enterobacteriaceae, mostly *Escherichia coli*, on both mucosal-associated microbiota and fecal specimens (61). Such pathogens with virulence factors may allow a possible breach of intestinal mucosa and induction of chronic inflammation (63).
It remains unclear if gut dysbiosis is the cause of, or the response to, disease. For example, dysregulation of innate and adaptive immunity can induce dysbiosis as has been shown in mice models. Dysbiosis can also arise from dense bacteriophage communities, which are viruses that infect bacteria and likely exert a strong influence on bacterial diversity (71). Dysbiosis may also be caused by colonization by an enteric pathogen, or from host-mediated inflammatory responses, or a combination of both.

In summary, the diversity and composition of gut microbiota are major factors influencing gut homoeostasis. An imbalance in composition of the gut microbiome (dysbiosis) has been associated with IBD. However, a causal link between specific changes in the microbiota and IBD has not been established as yet. Therefore more detailed studies are needed in large well-characterized and homogenous populations to define clearly what the role of the gut microbiota is in disease pathogenesis, and whether alterations in gut microbiota can be used as therapy in IBD.

1.3.2.3 Dysregulated Immune Response

The final process to play a role in the pathogenesis of IBD is a dysregulated mucosal immune response. This occurs through defects in the intestinal epithelial barrier function, immune deficiencies and defects in the T and B-lymphocytes.

CD is associated with excess production of cytokines such as IL-12/IL-23 and IFN-γ/IL-17 which affect the small bowel and colon resulting in full thickness inflammation and ulceration. In UC, there is an excess production of IL-13 production, which primarily affects the colon. In both CD and UC, there is an excess production by T cells and macrophages of the pro-inflammatory cytokine tumour necrosis factor α c(45). The TNF cytokine induces cell proliferation and differentiation, and can up-regulate adhesion molecules as well as regulating gene expression (72). TNF promotes an inflammatory response not only in IBD, but other conditions including rheumatoid arthritis, ankylosing spondylitis and psoriasis.
There is evidence that the pro-inflammatory cascade is set in motion by the presence of gut microbiota, which was shown in both inflamed gut mucosa from patients as well as in animal models (40). There is also evidence from animal models of immune defects such as the lack of IL-10 and down-regulated toll-like receptor response. As already discussed in the genetics section, the NOD2 gene is an example of how a susceptibility gene is linked to an excessive innate immune system response towards components of the gut microbiota. These defects in the innate immune system lead to the facilitation of the adaptive immune response to one or more antigens and production of antibodies as well as T cell responses (40).

1.3.2.4 Environmental Factors

There is considerable epidemiological evidence that environmental factors must play a role in the aetiology of IBD. Firstly, there has been a rapid global rise in incidence in the last few decades (1), with a recent rise in incidence among regions where IBD was previously uncommon, such as Asia and Eastern Europe (2,3). This has coincided with a transition to a more ‘westernized’ lifestyle in these regions (73). Another clue is the ratio of CD and UC as it has considerable geographical variation. Nordic and Eastern European countries show a predominance of UC over CD (6) (2) (34), but this is the reverse in Northern Europe, Australia and New Zealand (4,8) (33). Finally, it has also been shown that migrants will adopt the risk of IBD of their new country in the first generation of migrating over (74). These rapid changes over a few decades are unlikely to be explained by genetic susceptibility and suggest an environmental impact.

It remains unclear how exactly environmental factors play a role. It has been postulated that dietary change, antibiotics and infections may result in dysbiosis of the gut flora resulting in dysregulation of the immune system in a genetically predisposed individual. The westernized lifestyle has been implicated in bringing about changes in environmental exposures, through improved sanitation, dietary changes and widespread medical intervention in the form of medications, vaccinations and surgery (such as appendicectomy and tonsillectomy). Improved sanitation conditions are likely to reduce childhood
exposure to infectious and colonizing bacteria, viruses and helminthes, which in turn has a detrimental effect on T regulatory cells (the hygiene hypothesis) (75).

A westernized diet includes increased consumption of refined sugar, fast food and reduced consumption of fruit, vegetables and fibre (69). These dietary changes are likely to have a significant impact on the composition and metabolic behaviour of gut microbiota (43, 75).

**Smoking**

Of all these factors, smoking and appendicectomy are the strongest environmental associations that consistently have been shown in studies to be associated with IBD. Smoking is unique in its polarizing effect on UC and CD. It is inversely associated with risk of developing UC (OR 0.58 in favour of smokers) and positively influences the course of disease, with smokers experiencing less active disease, reduced hospitalization rates and a reduced risk of colectomy (76) (77). Cessation of smoking is associated with the onset of UC. Conversely, smoking is a risk factor for CD, and former smokers remain at risk (76) (78).

There is some data to suggest it may influence disease location, with a higher prevalence of ileal as compared to colonic disease (79). Furthermore, patients with CD who continue to smoke are more likely to have a complicated disease course with more frequent flares, stricturing/penetrating disease, higher risk of surgery and are more likely to develop post operative recurrence (79) (80) (77) (81). The risk of post operative recurrence is higher in those who are heavy smokers (>15/day) (79). However, it is also important to point out inconsistencies in the link between CD and smoking: countries such as Asia and Africa have one of the highest rates of smoking (up to 65% of adult males) with a very low incidence of CD; also there is no association between smoking and CD in patients from Israel (82).

The reason that smoking has an opposite effect in CD and UC remains obscure. Smoking appears to have different effects on different targets in the gut- the mucous layer, cytokine production, macrophage function and microvasculature. In UC, the colonic mucous layer is significantly thinner or absent, whereas in CD it is thicker (79). Nicotine appears to increase the mucous thickness in UC as well
as in rabbit models. However, this benefit was not seen by the use of transdermal nicotine as a therapy (77). Secondly, cytokine production can be affected by smoking. Nicotine appears to abolish the production of IL-1β and TNFα in mouse colonic mucosa, which would be beneficial in IBD. In man, nicotine decreases mucosal eicosanoids and other proinflammatory cytokines such as IL2, TNFα and IL-8. Smokers with IBD have a reduction in these cytokines as well, specifically the reduction of IL-1β and IL8 in UC and a reduction in IL8 in CD. Lastly, nicotine has an effect on intestinal motility due to release of nitric oxide, as well as having an impact on microcirculation as well as causing transient ischemia through the action of carbon monoxide. In CD, where there already are abnormalities in microvasculature, smoking may amplify the impairment in vasculature. There have been some mouse models of colitis which have shown that nicotine can have opposite effects depending on dose and duration of exposure (79).

**Appendicectomy and tonsillectomy**

Appendicectomy prior to diagnosis has been shown to be protective in UC in several epidemiological cohort studies (38,83-85). The meta-analysis of 17 case-controlled studies showed an overall odds ratio of 0.312 (95% CI 0.261-0.373) in favour of appendicectomy. Interestingly a large Swedish case-control study of more than 200,000 patients showed the benefit of appendicectomy in reducing the risk of future UC was only seen in those who had the surgery under the age of 20, with confirmed inflammation of the appendix (appendicitis or lymphadenitis), and not in those who had it done for non specific abdominal pain. In addition to studies showing the reduction of incidence of UC in those who had an appendicectomy for appendicitis, there is some evidence to suggest that patients diagnosed with UC after the appendicectomy had a more benign course of UC, including fewer relapses, limited extend of disease, less likely to need immunosuppression and colectomy when compared to patients with UC with an intact appendix (86-88). Studies of histological specimens following a colectomy have demonstrated frequent discontinuous inflammation of the appendix (e.g. an inflamed appendix in a patient with left sided colitis only) (89).
and this is seen at endoscopy as well. A small pilot study was designed to look at therapeutic benefits of appendicectomy for refractory UC but it did not show a clear benefit (90). Putting this all together, it appears that early appendicectomy modifies the intestinal immune response to protect against the development of UC, but how this happens exactly remains unclear. The appendix may have a role in activating T cells, which play a pivotal role in the inflammation in UC, though it does not explain why the protective effect of appendicectomy in CD is not as clear. An Australian study found appendicectomy to be protective against CD (87) but other studies have not (91). A meta-analysis found an increased risk of CD post appendicectomy but this risk diminished after 4 years from time of operation, suggesting that the increased risk probably reflects diagnostic problems in patients with incipient CD (92).

Previous tonsillectomy has also been associated with IBD, though the evidence behind this is not as strong. Its possible role is thought to be secondary to the role of tonsils as an immunological organ. The lymphoid tissue of the tonsils shows histological similarity to that of Peyer’s patches in the intestine, and both belong to the mucosa-associated lymphoid tissue (MALT) system (83,93). Previous studies have shown conflicting results, with some showing a protective effect (83) while others found a higher rates of tonsillectomy among CD but not patients with UC (91,94). Overall, the association appears stronger in CD however but this is based on a small number of small and retrospective studies, therefore further research into this field is needed.

The hygiene hypothesis

The hygiene hypothesis is thought to play a role not only in IBD but also other diseases caused by immune dysregulation such as type 1 diabetes, multiple sclerosis, asthma and allergy (81,95). This hypothesis links well with epidemiological studies that show an increase in incidence of IBD in countries that become more ‘westernized’ and have improved sanitation as well as refrigeration. Improved sanitation conditions are likely to reduce childhood exposure to infectious and colonizing bacteria, viruses and helminthes, which in turn has a detrimental effect on T regulatory cells. In recent years the hypothesis
has been revised to reflect that it is more likely exposure to the colonizing or commensal bacteria (saprophytic bacteria, lactobacilli and bifidobacteria), helminthes and viruses, rather than conventional pathogens, that is beneficial to the immunoregulatory pathways in the host. These organisms cause little harm and have been part of the human microecology for millennia ('old friends'); but are now less frequent or even absent in the human environment of westernized societies (41,95). The ‘old friends’ variant of the hygiene hypothesis suggests that these organisms are recognized to be harmless by the innate immune system (through pattern-recognition receptors such as the CARD15 and Toll-like receptor 2) and cause dendritic cells to mature into regulatory dendritic cells that drive regulatory-T-cell polarization. This ongoing process can provide a continuous background bystander regulation (38,95,96). In IBD, there have been a number of aberrant immune responses shown in both the innate and adaptive immunity that are beyond the scope of this review, and among these, there has been recognition of a deficiency in regulatory T cell activity which strongly supports the role of the hygiene hypothesis (41).

**Diet**

Diet has also been shown to possibly play a role in the pathogenesis if IBD. The rising incidence of IBD in some regions has coincided with a shift in dietary patterns. In particular, increased consumption of refined sugar and fast food and reduced consumption of fruit, vegetables and fibre (69). The mechanism by which dietary changes are associated with risk of IBD may be multi-factorial. Food can act as an antigen to the gut immune system, or have direct contact with the colonic mucosa contributing to the chemical composition of the gut mucosa, and it also has been shown to have an impact on the composition and metabolism of gut microbiota by acting as a substrate (43,75,97).

However, diet is difficult to study as an aetiological factor in IBD. This is due to methodological limitations inherent in dietary studies that rely on retrospective assessment of diet. Studies in IBD are limited to a retrospective recall of a pre-illness dietary history and therefore the possibility of a subconscious alteration
in dietary habits with the onset of symptoms prior to diagnosis. The method used by the majority of studies to assess diet is a recall questionnaire administered after diagnosis, asking about dietary habits prior to disease onset. The main variation between studies is how long after diagnosis this was done and if the questionnaire was self-administered by the participant (67,87,98-100) or done through a standardized interview by a trained professional which may provide more detailed information but possibly introduce bias (39,93) (101,102). In recent years, standardized questionnaires have been developed, such as the country-specific Food Frequency Questionnaire (FFQ) which have been validated against 24 hour recall questionnaires as well as urinary tests of nutrients (103,104). The International Organisation of Inflammatory Bowel Diseases (IOIBD) included a dietary history as part of the environmental questionnaire and grouped nutrient groups based on several screening questions, for example, high sugar intake was based on sugar intake with tea/coffee, on breakfast cereal and soft drink intake (105). This method of diet assessment has the benefit of being general enough to use across different dietary backgrounds and has been used by some of the most recent studies (105,106). Once dietary information is collected from participants, it then needs to be converted into a standardized energy and nutrient assessment. The majority of studies focused on the main nutrient groups (carbohydrates, protein, fat, fibre), with some also focusing on specific new ‘western’ dietary influences such as soft drink consumption and fast food (100). Studies varied in how much detail was assessed as part of the food groups, for example, total fat intake compared to polyunsaturated and saturated fat. Due to the heterogeneous methods that have been used in the literature, it can be difficult to draw firm comparisons between studies. Despite these methodological limitations, some interesting findings have evolved from epidemiological studies.

Fat intake has been hypothesized to play a role in disease aetiology through a number of possible mechanisms including by increasing bowel permeability through its direct effect on gut microbiota (64,69). Not only total fat, but also types of fat have been studied, including monounsaturated (MUFA) and polyunsaturated fatty acid (PUFA). MUFA and PUFA’s are defined biochemically
by having at least one (mono) or more than one (poly) carbon to carbon double bond. PUFA's are further divided into n-3 and n-6 fatty acids. N-6 fatty acids are found in nuts, most vegetable oils and cereals, while n-3 fatty acids are predominantly found in oily fish. There has been a push in the general population over the last few decades to substitute saturated fat intake with unsaturated fat (MUFA and PUFA) due to the association of saturated fats with an unfavourable lipid profile and cardiovascular disease (69). Therefore, at the same time that the incidence of IBD has risen, intake of unsaturated fats has increased, especially in westernized regions with high cardiovascular disease rates. A small retrospective study of 43 UC and 43 controls found that high MUFA and PUFA intake was associated with an increased risk of UC (64,102). A similar association was found in a study of 54 patients with UC, with high intake of all fat groups (PUFA, MUFA, total fat and animal/saturated fat) (39,107). However, these findings have not been collaborated in larger studies. A large prospective cohort study of over 280,000 people (139 incident cases of UC) only found a very marginal increase risk of UC with PUFA intake (OR 1.19, 95% 0.99-1.43) (103). Another large prospective study of over 170,000 women (338 incident cases of UC) looked at PUFA in more detail, breaking these down into n-3 and n-6 subtype. This study found that only trans-unsaturated fats was associated with UC, and a high intake of n-3 PUFA fatty acids was protective (108). There was no association between fat intake and CD (n= 269 incident cases). A large prospective cohort study in the UK of over 25,000 people (22 cases of UC) (109) confirmed the protective mechanism from n-3 intake in UC. The association between CD and fat intake appears not as well studied, though one small study did show a correlation between CD and consumption of both n-3 and n-6 PUFA (107). Plausible biological mechanisms to explain the protective effect of n-3 PUFA on UC have been hypothesized. The n-3 PUFA's are present in cell membranes as predominantly eicosapentaenoic acid and docosahexanoic acid, and the n-6 PUFA's as arachidonic acid. Both of these molecules can be metabolized to prostaglandins, thromboxanes and leukotrienes, but it is the metabolites of arachidonic acid that have the most pronounced immunostimulatory effect resulting in aggregation, chemotaxis and release of lysosomal enzymes from neutrophils (110-112). Therefore a high intake of n-6 PUFA's
could result in a pro-inflammatory processes predisposing to colitis. The n-3 PUFA’s are not as potent in their pro-inflammatory signals compared to n-6 and act as a competitive substrate for n-6 metabolism. They have also been shown to have some anti-proliferative effect in lymphoid cells, as well as a possible effect on gene expression for inflammatory mediators (109).

Fibre intake has been associated with reduced risk of IBD, and the strongest correlation is in CD. Fermentable fiber is metabolized by intestinal bacteria to short-chain fatty acids (SCFA), such as acetate, propionate and butyrate which have been shown to have immunoregulatory properties (113,114). A novel study demonstrating this process was recently published comparing the microbiota between European children and those from an African cohort (Burkin Faso) who consumed twice as much fibre (43). This study showed a very different microbiota population between the two populations, with the African children exhibiting an abundance of bacteria from the Prevotella and Xylanibact genus, which were completely lacking in the European children. These bacteria are efficient at hydrolysis of cellulose and xylan, both of which are found in high fibre foods. The African children also had much higher levels of short-chain fatty acids (SCFA) found in the faeces due to the high fibre. In the African population the pathogenic intestinal microbes such as Shigella and Escherichia were significantly underrepresented when compared to the European children, and it was hypothesized in the study that the gut microbiota had evolved in such a way to maximize energy intake from fibers while also protecting from inflammation and infection, possibly due to the high SCFA levels. There have been a number of studies that have confirmed a reduced risk of CD with high fibre intake (84,98, 116), including a large prospective cohort study that specifically identified fibre from fruit as being beneficial in CD (106,117) and a smaller study pointing towards a possible benefit of vegetable intake in CD, though only significant on univariate analysis (101,118). On the other hand, other studies that not show a decreased risk of IBD with high fibre intake(99,102,107). There is also a suggestion based on small studies of maintenance of remission in UC with a high fibre diet (125,126). Some of the disparity between studies may be due to lack of sub-classification of fibre components: soluble, highly fermentable by colonic
bacteria producing SCFA which is possibly beneficial as compared to insoluble, barely fermentable fibre. A standardized approach to studying fibre intake is needed to further assess the associated between fibre and IBD.

Protein consumption has also been studied in relation to risk of IBD but no clear pattern has yet emerged on its impact in the aetiology of disease. In a large prospective cohort of French participants that identified 77 incident cases of IBD from over 60,000, high total protein, and specifically animal protein, was associated with risk of disease (127). It was consumption of meat and fish, but not dairy and eggs, that was associated with risk, but this may have been due to insufficient power of the study. This is the only study that showed a significant association between protein intake and CD, where as 4 other studies did show an increased risk that did not reach statistical significance and 1 study showed a non significant trend to decreased risk (64). A temporal relationship has also been shown between the rising incidence of CD in Japan and increasing dietary animal protein (101). In UC, there have been 6 studies in total that analyzed protein intake as a risk factor. Of 2 large prospective cohort studies, only the French one described above found a significantly increased risk with protein intake (127), where as a similar size prospective cohort study from the UK, with double the number of UC cases (n=139), did not find an association. A retrospective study of 104 UC newly diagnosed patients showed an association with high protein intake (99). The postulated mechanism behind protein intake and IBD is the formation of hydrogen sulfide (by bacterial fermentation of sulfur amino acids found in animal protein byproducts) that reaches the colon. Hydrogen sulphide can impair use of short- chain fatty acids and have direct toxic effects (64). However, there has also been research to suggest an anti-inflammatory effect of hydrogen sulfide, linking it with mucosal healing (64).Other byproducts such as phenolic compounds, amines and ammonia have also been implicated (67).

The intake of refined sugars has been on the rise in recent decades among most westernized countries. The US per capita intake was 55.5kg in 1970 and increased to 69 kg in 2000 (69). Also in the past thirty years, the qualitative
features of refined sugar consumption has changed, such as the introduction of high-fructose corn syrup (69). Some of the first studies of diet and risk of IBD showed a link to high sugar and refined carbohydrate intake (64) but since these initial papers, no consistent findings have been found. A retrospective Japanese study identified consumption of sweets increased the risk of UC (OR 2.86, 95% CI 1.24-6.57) and CD (OR 2.83, 95% CI 1.38-5.83), as did the consumption of sugars and sweeteners in CD (OR 2.12, 95% CI 1.08-4.17) (107), but suffered from the shortcomings of recall bias in this cohort of patients who were questioned up to 3 years after diagnosis. Another retrospective study of 150 cases each of UC and CD in Sweden identified high sucrose intake (defined as more than 55gm/day) as a risk factor for CD (OR 2.6, 95% CI 1.4-5) (98). A Danish study also showed an association between high sugar consumption and risk of CD as well as UC (83). In contrast, a study of over 120 patients failed to find a significant impact from sugar intake (128) as did a study of nearly 500 paediatric cases with IBD (84). An Italian study of just over 100 patients found that high total intake of carbohydrate, starch and refined sugar was higher in CD and UC (99). However, in contrast to these smaller retrospective studies, large prospective cohort studies did not show any significant association in UC (103,127) or in CD (127). Therefore there is no consistent association between IBD and carbohydrate or refined sugar intake from the current available data.

Other dietary patterns that have been studied include frequent fast food. A retrospective study of over 300 IBD patients showed that fast food more than twice a month was associated with an increased risk of CD (RR 3.4, 95% CI 1.3-9.3) and UC (RR 3.9, 95% CI 1.4-10.6). Biologically plausible reasons for this are not known though the study suggested the intake of chemically modified fat such as margarine, frying or cooking fat as a possibility (98). Further study into this is necessary.

A novel approach to studying the impact of diet on microbiota and colitis was recently published in Nature (129). Instead of focusing on the various nutrients in food, the authors studied the role of food additives, in this case dietary emulsifiers. They found these had an impact on murine gut microbiota,
promoting both colitis and the obesity/metabolic syndrome. Dietary emulsifiers are detergent like molecules helping to hold food together and are a ubiquitous component of processed food, such as ice cream, mayonnaise, sauces, salad dressings and margarine. It was shown in the study that emulsifiers disrupted the mucus-bacterial interactions in the gut, resulting in inflammation of the gut. The addition of food additives such as emulsifiers has steadily risen in the last half century, along with the steady rise of IBD and obesity worldwide, therefore this area requires further study.

Dietary intake as an infant, in particular breastfeeding, has attracted some attention. It has shown to be protective in other immunological conditions such as asthma (130), atopic dermatitis (131), allergic rhinitis (132) and type 1 diabetes mellitus. These effects are due to immunomodulating properties of human milk. Breastfeeding has been shown to impact the establishment of neonatal microbiota in the gut in mouse models (133) and human children, in particular in the predominance of Bifidobacteria (134). There has been much research done epidemiologically into the effect of breastfeeding on future risk of IBD. A meta-analysis has summarized 17 of these studies in which the primary or secondary goal was to evaluate the association between breastfeeding and CD and UC as separate entities (115). The studies showed heterogeneous results. The pooled odds ratio for CD was 0.67 (95% CI 0.52-8.86) and 0.77 for UC (95% CI 0.61-0.96). When only the highest quality studies were included, this improved marginally in both groups. The authors concluded that breastfeeding is associated with a lower risk of both CD and UC, but that the current evidence is limited and further research using better methodology, in particular duration of breastfeeding and exclusivity of it early in life, as well as larger sample size, are required. Since the review, a large prospective study of over 400 IBD patients in the Asia-Pacific area showed that breastfeeding for longer than 12 months was protective for both CD and UC though the breastfeeding history was susceptible to recall bias (106).

In summary, dietary patterns have been studied for a number of decades now in relation to possible impact on IBD aetiology. High fat and low fibre intake
emerge as consistent risk factors, with prolonged breastfeeding likely to be protective. A novel possible risk factor is the role of food additives found in processed foods. However, diet is difficult to study as an aetiological factor in IBD for reasons explained above. Improved methodology, and more prospective studies are needed to further assess the impact of diet on disease aetiology, as well as further work to determine possible biological mechanisms.

**Exposure to medication**

Medication use has also been implicated as a possible environmental factor playing a role in disease aetiology, in particular, antibiotic use due to its potential to alter the intestinal microbiota (118). This is thought to be particularly important in the first year of life as this is the period when commensal gut flora are established in the infant (120). A small paediatric case control study assessed antibiotic use in the first year of life, using pharmaceutical data from a state based drug programme therefore negating recall bias, and found an association between early antibiotic use and risk of paediatric IBD (OR 2.9, 95% CI 1.2-7) (121). A large adult study from the same area, Manitoba, again using direct pharmaceutical data, confirmed the association between antibiotic use 2 years prior to diagnosis and risk of both CD and UC, as well as illustrating a dose-dependent relationship (123). A large paediatric prospective cohort study confirmed an increased risk of IBD for antibiotic users (RR 1.84), with the strongest association for CD (RR 3.41), and frequent antibiotic use (RR 7.32 for > 7 courses) (124). Individual analysis did not find an increased risk of UC. These results support the hypothesis of antibiotic use altering the gut microbiota and thereby impacting on the risk of IBD. However, as these are all association studies it is important to consider other factors that necessitate the need for antibiotic use that may contribute to the development of IBD, such as early gut symptoms misdiagnosed as infectious disease. Also, it remains unclear if the effect of antibiotics on gut microbiota is long lasting, and if not, what the significance is of short-term changes. Finally, it is possible that antibiotic exposure during certain life stages is more important rather than overall exposure, for example, during early childhood when the gut microbiome and immune responses are being established.
Other medications that have been studied in the past include the oral contraceptive pill (OCP), as well as various vaccinations. Evidence for both of these is conflicting. Many of these studies have been small with methodological limitations. A meta-analysis of the major studies analyzed the effect of OCP on risk of IBD and showed a small positive association in CD (RR 1.46) and UC (1.28), with a reduced effect after discontinuation (119). The biological mechanism for OCP use and risk of IBD is not known. Concern regarding vaccinations, in particular measles, was originally based on a single study (125) but since has been refuted (135,136).

The extensive data presented here strongly suggests that the increased frequency of IBD globally is explained by environmental factors. Many of these are likely to exert their effect through changes in the gut microbiota. There has been much work done to determine which environmental factors are most important in disease pathogenesis. There are unexplained aspects such as which has the greatest impact and whether the timing of these exposures in one’s lifetime is important. Risk factor epidemiology in the absence of concurrent biologically plausible mechanisms can yield conflicting results; therefore it is important to also address potential biological reasons for associations. However, epidemiology studies can enrich the understanding of disease pathogenesis of IBD by addressing the clues offered by the changing epidemiology, particularly in areas of increasing or high incidence.

### 1.4 Clinical Manifestations

IBD is a chronic, intermittent disease for most patients, though a small proportion of patient exhibit continuous symptoms (137). During a relapse, symptoms may range from mild to severe and resolve completely or reduce during remission. In general, the symptoms will depend on the segment of bowel involved. Colonic disease is more likely to present with bleeding and diarrhea as well as tenesmus and urgency, compared to small bowel disease that is frequently associated with abdominal pain.
In CD, the most common symptoms related to bowel inflammation are abdominal pain and diarrhea (85%), with other symptoms including urgency, blood in stool, fever, weight loss, fatigue and nausea/vomiting (23) (25). Oesophageal involvement is rare and presents with dysphagia, odynophagia and heartburn. Gastroduodenal involvement is uncommon and presents with upper abdominal pain, nausea, vomiting and rarely, haematemesis. If a patient presents later in the disease course once complications have developed, symptoms may include those of bowel narrowing and obstruction (vomiting, distension, unable to pass stool); bowel perforation; fistulizing disease (perianal pain/discharge, pneumaturia and recurrent urine infections, passage of air or faecal material through the vagina) or massive bleeding from the gut (25) (26).

Typical symptoms in UC include bloody diarrhea, mucous in stool, abdominal pain, urgency, frequency and tenesmus. Patients with more extensive disease may have more systemic symptoms such as fever, night sweats, weight loss and nausea. In disease limited to the rectum, constipation may be the primary symptom (25) (23). Rarely, patients with UC present very unwell with systemic symptoms due to toxic megacolon (bowel dilatation) that can be life threatening and represents a medical emergency.

IBD is associated with extraintestinal manifestations in up to 25% of cases at some stage during the disease course (25). Mono or polyarthritis is the most common of these, usually involving 2 or 3 medium-sized joints and is typically related to intestinal inflammatory activity but can appear long before clinical manifestations of the gut (26). Arthralgia (pain with no swelling of the joint) is more frequent than arthritis, usually involves the large joints and can be associated with tendon inflammation. Neither of these conditions results in joint damage. Sacroiliitis on the other hand, does not correlate with intestinal inflammation and the majority of patients with radiologic evidence are asymptomatic (26).

Other extraintestinal manifestations include cutaneous involvement, of which erythema nodosum is the most common, occurring in up to 15% of CD and 4% of patients with UC over the lifetime. Other cutaneous manifestations include
pyoderma gangrenosum and orofacial lesions (the latter which occur mostly in CD). Ophthalmologic manifestations include episcleritis, scleritis and uveitis. They are uncommon occurring in <10% of patients and have predominance in CD. Uveitis does not parallel intestinal inflammation, and though uncommon, its consequences often are more severe including loss of vision. Symptoms include eye pain, blurred vision, photophobia and headaches. Biliary and liver manifestations can also occur, including minor fatty liver degeneration, cholelithiasis, granulomatous hepatitis and primary sclerosing cholangitis (PSC). PSC has an estimated incidence of 2-8% among IBD patients, but affects UC more than patients with CD. Though usually asymptomatic, diagnosis is highly relevant for patients as it is associated with risk of cirrhosis, hepatocellular carcinoma, cholangiocarcinoma and colorectal cancer (26).

1.5 Differential Diagnosis

The leading symptom of IBD is diarrhea, however as a symptom it is unspecific and compatible with extensive differential diagnosis (see Table 1 - Adapted from (26)). Infectious agents cause the most diagnostic confusion as not only clinical but also endoscopic features may mimic IBD. The typical culprits include Salmonella, Shigella and Campylobacter. Stool cultures and short duration of illness should aid in the differentiation. Clostridium difficile can cause pseudo membranous colitis, which may mimic IBD clinically, but is also associated with a typical endoscopic appearance and usually a history of antibiotic exposure. Proctitis can be caused by sexually transmitted infections such as Neisseria gonorrhoea, Herpes simplex virus and Treponema pallidum, as well as CMV but history again may aid the diagnosis. Intestinal tuberculosis and ischemic colitis are more difficult to diagnose. In these cases, place of origin, detection of acid-fast bacilli and endoscopy can be helpful. Tuberculosis is important to consider with the emergence of IBD in Asia and India, and in Australia due to the large migration from these areas. Intestinal ischemia is also a differential especially in the elderly. Atypical findings on histology may be useful but also a careful history of post-prandial symptoms is important, as well as vascular imaging studies.
The extensive differential diagnosis becomes very important when studying IBD epidemiology, as it is imperative that validated case definitions are used when recruiting patients into these studies.
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Disease</th>
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<tbody>
<tr>
<td>Non bloody diarrhea</td>
<td>Irritable bowel syndrome</td>
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<tr>
<td></td>
<td>Lactose intolerance</td>
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<tr>
<td></td>
<td>Infectious colitis:</td>
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<tr>
<td></td>
<td>Viral infection (rotavirus, noravirus)</td>
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<td></td>
<td>Helminths (strongyloides, schistosomiasis)</td>
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<tr>
<td></td>
<td>CMV infection</td>
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<tr>
<td></td>
<td><em>Yersinia enterocolitica</em></td>
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<td></td>
<td><em>Mycobacterium tuberculosis</em></td>
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<tr>
<td></td>
<td>Colorectal cancer</td>
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<td></td>
<td>Diverticular colitis</td>
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<td></td>
<td>Celiac disease</td>
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<tr>
<td></td>
<td>Pancreatic insufficiency</td>
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<td></td>
<td>Bacterial overgrowth of the small intestine</td>
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<td></td>
<td>Autonomic dysfunction (e.g. diabetes mellitus)</td>
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<td></td>
<td>Hyperthyroidism</td>
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<td></td>
<td>Eosinophilic gastroenteritis</td>
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<td></td>
<td>Microscopic colitis</td>
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<tr>
<td></td>
<td>Endocrine active tumours (e.g. carcinoid)</td>
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<td></td>
<td>Amyloidosis</td>
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</table>
1.5.1 Diagnosis

There is no single gold standard test for IBD, rather it is confirmed by a combination of clinical, endoscopic and histological findings. This is an important consideration for identifying incident cases of IBD in population-based cohorts, as no single diagnostic test can solely be used to identify these patients. The clinical findings include a comprehensive physical exam and review of patient’s history, taking into account the clinical manifestations and differentials listed above. It is imperative that as part of the diagnostic process, these differential diagnoses are excluded, in particular, an infective cause.

There have been a number of diagnostic criteria proposed over the years based on the combination of the various clinical and diagnostic components. These include the Lennard-Jones criteria defined in the 1980’s (138) but which has
since been shown to have poor sensitivity with up to 50% of patients being missed (139). Other criteria include the WHO definition seen in Table 2 and the Copenhagen criteria seen in Table 3. The WHO criteria focused on diagnostic testing criteria, where as the Copenhagen criteria also used clinical symptoms. In paediatric cases, the Porto criteria was proposed and revised to incorporate advances in the diagnosis of disease by incorporating the use of serum (ASCA and pANCA) and fecal biomarkers (faecal calprotectin), as well as small bowel imaging techniques such as MRI and capsule endoscopy (discussed in detail below) (63,140). Of all these, the Copenhagen Diagnostic Criteria is the most user friendly, with both a focus on symptoms as well as investigations, incorporating the most recent advances such as radiology in the assessment of small bowel. These features make it a useful tool in epidemiological studies and it has been validated in a number of these (6) (9,141,142,143). In clinical practice, the ECCO guidelines conclude that the current view is that diagnosis is established by a non-strictly defined combination of clinical presentation, endoscopic appearance, radiology, histology, surgical findings and more recently serology (144). The next section focuses on some of these aspects of diagnosis.

Table 2- WHO diagnostic criteria of CD, adapted from (145)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Clinical</th>
<th>Radiological</th>
<th>Endoscopy</th>
<th>Biopsy</th>
<th>Resected Specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Discontinuous or segmental lesions</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
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<tr>
<td>2. Cobblestone appearance or longitudinal ulcer</td>
<td>+</td>
<td>+</td>
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<td>+</td>
<td></td>
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<tr>
<td>3. Transmural inflammation</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>4. Non-caseating granulomas</td>
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<td></td>
<td>+</td>
<td>+</td>
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<tr>
<td>5. Fissures and fistulas</td>
<td>+</td>
<td>+</td>
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<td></td>
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<tr>
<td>6. Perianal disorders</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3- Copenhagen diagnostic criteria for CD and UC (9)

<table>
<thead>
<tr>
<th>Infectious and neoplastic GI diseases ruled out</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn’s disease (min of 2)</td>
</tr>
<tr>
<td>History of abdominal pain, weight loss and/or diarrhea for more than three months</td>
</tr>
<tr>
<td>Characteristic discontinuous colonoscopic lesions of ulceration (aphtous lesions, snail track ulceration) or cobblestoning or radiological features of stricture or cobblestoning</td>
</tr>
<tr>
<td>Histology consistent with Crohn’s disease (epitheloid granuloma of Langhans type or transmural discontinuous focal or patchy inflammation)</td>
</tr>
<tr>
<td>Fistula and/or abscess adjacent to affected bowel segments</td>
</tr>
<tr>
<td>Ulcerative colitis (all 3 needed)</td>
</tr>
<tr>
<td>History of diarrhea and/or rectal bleeding and pus for more than one week or repeated episodes</td>
</tr>
<tr>
<td>Characteristic continuous colonoscopic lesions in rectum of ulceration, vulnerability or granulated mucosa</td>
</tr>
<tr>
<td>Histology consistent with Ulcerative colitis (neutrophils within epithelial structures, cryptitis, crypt distortion, crypt abscesses)</td>
</tr>
</tbody>
</table>

1.5.1.1 Laboratory Examinations

There are no specific blood tests diagnostic of IBD. Elevated white cell and thrombocyte count as well as inflammatory markers such as C-reactive protein (CRP) are frequently elevated in extensive disease, but may be normal in limited left colon disease. Albumin may be low with active inflammation. A full blood examination will identify anemic patients, which is not uncommon in IBD, as will iron studies.

Stool examination for exclusion of infectious colitis is imperative at diagnosis as this remains one of the main differentials. Also, IBD patients are more susceptible to gastrointestinal infections and so may have a concomitant infection.

1.5.1.2 Endoscopy

Endoscopic examination with intubation of the terminal ileum is the mainstay of in the diagnosis of IBD. The endoscopic appearance of the bowel affected is able to differentiate between CD and UC in most cases. The most helpful diagnostic findings in CD are segmental inflammation, with inflamed areas alternating with normal mucosa (“skip lesions”), a “cobble-stone” appearance and aphthous ulceration. The CD ulcers can be aphthous (small punctuate lesions typically seen in the mouth or terminal ileum), small deep ulcers or longitudinal, serpingous
ulcers. CD involves the colon only in 15-25% of cases, ileocolonic in 40-50% and exclusively ileal in 25-40% (26). This forms the basis of the Montreal classification of disease phenotype, which will be discussed later. Due to the transmural nature of CD, the inflammation and subsequent attempts at healing can result in stricturing disease that can be visualized as narrowing at time of endoscopy, or in penetrating disease (defined as fistulizing or perforating disease). Gastroscopy is indicated when the patient has upper gastrointestinal symptoms.

In contrast, UC nearly always involves the rectum and can extend to involve more proximal colon. The three main patterns of disease are rectal only (proctitis), left sided (rectum to splenic flexure) and pancolitis (the entire large intestine). Approximately 30% of patients fall into each classification at diagnosis (26).

Capsule endoscopy offers an additional benefit in the diagnosis of IBD, in particular in CD, as it shows images from the entire small bowel that is not easily reached by other modalities. It is useful in patients with suspected CD but negative conventional endoscopy. The main limitation is an inability to take biopsies and the expense (25).

1.5.1.3 Imaging

Cross sectional imaging is helpful in IBD to determine disease extent, severity and assess for perforating or stricturing complications of CD. The three most common modalities include computed tomography (CT), transabdominal ultrasound (US) and magnetic resonance imaging (MRI). The latter two are preferred especially in younger patients to avoid excessive radiation (25). In the last decade, MRI advances have resulted in superior imaging of the small bowel and pelvis (11,12). MRI has the additional benefit over CT of being able to differentiate active inflammation (that will respond to medical therapy) from fibrosis and fibrostenotic lesions (which are less likely to respond) (26). This is particularly important in small bowel CD. MRI of the pelvis has become a major diagnostic tool for the detection and follow up of anorectal fistulae and abscesses.
Transabdominal ultrasound has recently become more widely used in Australia in IBD patients. It is a quick and inexpensive screening method in the diagnosis of IBD as well as in repeatedly evaluating patients with established disease. Sensitivity of detecting CD at diagnosis ranges from 75-94%, and specificity of 67-100% (26). It can detect inflammation of the small and large bowel proximal to the rectum, as well as complications such as stenosis, abscesses and fistulae.

1.5.1.4 Biomarkers

Faecal calprotectin is an emerging useful biomarker to measure at diagnosis. It is a measure of an inflammatory protein secreted by neutrophils in the feces and correlates with the excretion of Indium-111-labeled granulocytes, a sensitive marker of intestinal inflammation (13). It is therefore useful in differentiating between non-inflammatory diagnoses such as irritable bowel and IBD. It can also be measured at baseline in those with confirmed IBD as it correlates well with endoscopic disease activity in IBD and offers a non-invasive method of monitoring disease progress (13).

Serological biomarkers that are used in clinical practice include the anti-Saccharomyces cerevisiae antibodies (ASCA), which are directed against Candida albicans. These antibodies are positive in up to 40% of patients with CD and in less than 1% of patients with UC, making it useful in differentiating between the two. It is also predictive of a complicated, severe disease phenotype (146). Perinuclear antineutrophil cytoplasmic antibodies (pANCA) are found in 60-80% of patients with UC (29,38). In the small proportion of patients with CD that are pANCA positive, the phenotype is colonic.

Novel antimicrobial antibodies have been found in the serum of patients with CD, such as the CD-related protein from Pseudomonas fluorescens (anti-I2), the flagellin-like antigen (anti-Cbr1) and E Coli outer membrane porin C (anti-OmpC). However, currently the diagnostic utility of these antibodies is not routine in clinical practice (26).
1.5.2 Disease Classification and Activity Assessment Tools

Various attempts have been made over the years to address the complex issue of classification of IBD. The objective of using such a system is to incorporate clinical variables at time of diagnosis to predict future disease prognosis particularly risk of surgery, resulting in improved counseling and individualised therapy for each disease subtype.

Disease activity assessment tools on the other hand, are objective markers of disease activity, that can also be used clinically as well as in research to assess disease progression and response to therapy.

1.5.2.1 Montreal Classification of IBD

The Montreal classification of IBD (see Table 4) is the result of a Working Part of investigators in 2003 who addressed the new developments in the field since the previous Vienna classification of IBD(147). The Vienna classification was based on three main phenotypical parameters at diagnosis including age of onset, disease location and disease behaviour. The Montreal revisions made modification within each of these parameters.
<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>Crohn’s Disease</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1 &lt; 16</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>A2 17-40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A3 &gt;40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1 Ileal</td>
<td>E1 Proctitis</td>
<td></td>
</tr>
<tr>
<td>L2 Colonic</td>
<td>E2 Left sided colitis (to splenic flexure)</td>
<td></td>
</tr>
<tr>
<td>L3 Ileocolonic</td>
<td>E3 Pancolitis</td>
<td></td>
</tr>
<tr>
<td>L4 Upper gastrointestinal disease*</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Behaviour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B1 Inflammatory</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>B2 Stricturesing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B3 Penetrating</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P perianal #</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* L4 is a modifier that can be added to L1-L3 when concomitant upper gastrointestinal disease is present. # p is a modifier that can be added to B1-B3 when concomitant perianal disease is present.

With respect to age at diagnosis, the Montreal system has introduced age < 16 as an additional age bracket to the original age cut off at 40 years in the Vienna system, to reflect specific serotypes and genotypes in the younger cohort. In regards to disease location, the Vienna system did not allow for upper gastrointestinal involvement to coexist with more distal disease. It has become apparent that it is not uncommon for upper gastrointestinal to be present and therefore in the Montreal system it is no longer mutually exclusive and can co-
exist with other disease locations. Finally, in regards to disease behaviour, the Vienna system defined perianal fistulas as penetrating disease but it has been recognized that perianal disease is not necessarily associated with bowel fistulas and it should have a separate sub-classification. Some historical population based studies used the older Vienna classification and this must be taken into consideration when interpreting such studies. Inter-observer agreement using the Montreal classification has been studied with good results, though less so for the presence of upper gastrointestinal disease (148).

In UC, the location sub-classification is felt to have clear biological relevance in terms of the response to therapy and also has validity in the disease course with respect to rates of medication use, hospitalization and colectomy, as well as the risk of colorectal cancer (147).

Additional modifications have been added to the Montreal classification in the paediatric population, these have been termed as the Paris Classification (149). These were created to reflect the dynamic features of the paediatric disease phenotype. The modifications include classifying age of diagnosis between those younger than 10 years; distinguishing disease above the distal ileum as defined by the ligament of Treitz, allowing for both stenosing and penetrating disease in a patient (B2B3) and including growth failure. In UC, E4 is used to denote disease extent proximal to the hepatic flexure and S1 denoting severe disease.

**1.5.2.2 Disease activity assessment scores**

The Crohn's Disease Activity Index (CDAI) is currently the most widely used severity assessment tool in clinical and research situations. It is calculated from a composite of clinical, subjective and laboratory indices, with good reliability and reproducibility. But it can be regarded as cumbersome especially due to its reliance on physical assessment and laboratory results (150). The Harvey Bradshaw index is a well recognized assessment tool for disease activity that is easy to use and can be useful as a measure of disease progression in both a clinical and research setting (151).

In UC, Truelove and Witts were the first to attempt to quantify UC activity in 1955 by defining mild, moderate and severe disease (152). These criteria are still
used today in identifying patients with severe colitis. Since then there have been a further 12 scoring systems have been proposed in UC. The Mayo score was developed as a composite of clinical and endoscopic features (153). The simplified clinical colitis index (SCCI) has evolved as a non-invasive activity index, covering six clinical questions only and making it easy to use in a clinical setting (89,154). An age specific paediatric ulcerative colitis clinical activity index (PUCCAI) was also developed (90,155).

Even though none of the above scores have been standardized with regard to their utility in prospective epidemiological assessments, they do offer a systematic evaluation of outcomes across a patient group.

1.6 Therapeutic Strategies in IBD

The traditional step up approach to treatment in both CD and UC is illustrated in Figure 2. The therapeutic strategies are broadly similar in CD and UC, although there are some significant differences. These include a lack of response to aminosalicylates or cyclosporin in CD, response to exclusive nutrition in CD and a greater need for surgery. The initial aim at diagnosis is to induce remission. Once in remission, a maintenance agent needs to be chosen based on disease severity. Overall treatment goals are to improve and maintain well being of patients, to treat acute disease including eliminating symptoms with minimal side effects, to reduce intestinal inflammation and if possible heal mucosa, to maintain steroid-free remission and to prevent complications such as surgery and hospitalizations (25,87). In recent years the shift has been to achieve deep remission defined as clinical remission (Mayo score < 2 for UC, and CDAI < 150 for CD), with mucosal healing and cessation of steroids as this is associated with fewer relapses, surgery and hospitalization (156,157).

Coinciding with this new treatment aim, there has been a move away from a traditional step up approach towards a more aggressive either step down algorithm or an accelerated step up approach, in particular in patients with early poor prognostic features. In the first instance, it is important to know what these prognostic factors are and the challenges in determining accurate factors that can be applied to every IBD patient. This will be discussed in detail in a later
section (titled “Predictors of Disabling disease). Overall, research to date supports an accelerated step up approach in patients who are deemed as being at higher risk of an aggressive disease course (158,159). There has been a move to identify these patients early, to monitor disease aggressively with frequent objective markers of disease severity and to implement escalation of therapy early. Much of this research was done in referral based centres. There is a lack of evidence from population-based studies showing how this change in treatment paradigm has affected community-based patients. The Cardiff study, with the aim of assessing change of disease outcomes from 1986 to 2003, found that higher thiopurine use was associated with lower rates of surgery (160). The study predated regular use of biologic therapies. There is one randomized population study (published in abstract format only) comparing an accelerated step up treatment approach to biological therapy in patients who were not in remission after 4 weeks of steroid therapy. It did not show a significant improvement in outcome at 1 year as measured by the primary end point of steroid remission. However, there was a statistically significance difference in secondary end points including time to first surgery and time to complications, in favour of the accelerated treatment arm (161).

The next section summarizes the main treatments available for IBD today. Following this, there is a review of how these treatments have impacted on patient outcomes in population-based studies.
CROHN’S DISEASE  
ULCERATIVE COLITIS

Figure 2: Traditional step up approach to therapy in Crohn’s and Ulcerative colitis, starting from the least potent agents at the bottom of the pyramid. Treatment is escalated in those with more severe disease or not responding to initial treatment. GCS- glucocorticosteroids. IM- includes thiopurines and methotrexate. * Limited evidence for aminosalicylates in CD. # Exclusive nutrition therapy is primarily used in the paediatric population.

1.6.1 Induction of Remission in CD

Aminosalicylates act on epithelial cells by a variety of mechanisms to dampen the release of inflammatory cells and cytokines. They have limited evidence in inducing remission in patients with CD (162-164), showing only very minimal improvement in CD activity scores, with little clinical benefit. There was some evidence for high dose (>4g) salazopyrin in those with colonic CD.

Antibiotics, in particular metronidazole and ciprofloxacin, are effective in the treatment of perianal fistulizing disease, with more evidence for efficacy with the use of ciprofloxacin (165,166). However they are frequently used in combination.
Corticosteroids are potent anti-inflammatory agents used to induce remission in those with moderate to severe disease. They act through down regulation of inflammatory cytokines such as interleukin (IL)-1, IL-6 and tumour necrosis factor (TNF)-alpha by inhibiting the transcription of specific genes involved in their production. Steroids also interfere with NF-kB production (41,167).

Steroids are available in two oral formulations (budesonide and prednisolone), or intravenous form (hydrocortisone). Topical therapies for rectal use are also available. Budesonide is a poorly absorbed steroid with limited bioavailability and extensive first pass metabolism, resulting in less toxicity than prednisolone. It is recommended in patients with mild to moderate ileocolonic disease, unless there is significant distal colonic disease where the evidence is not as robust as it is for prednisolone, or in severe disease (CDAI>300) (168). There is evidence for the use of steroids to induce remission (167). Steroid use is limited by a long list of side effects including acne, infection, ecchymoses, hypertension, hirsutism, petechial bleeding, striae, diabetes mellitus, osteonecrosis, osteoporosis, myopathy, psychosis, cataracts, and glaucoma, particularly when used over long periods (42).

Nutritional therapy with exclusive enteral nutrition is used in the paediatric population and as effective as steroids but is generally not well tolerated in adults (169).

Thiopurines (azathioprine, 6mercaptopurine) are ineffective in inducing remission as shown by a Cochrane review of 13 randomized controlled trials (RCTs) that demonstrated no difference in clinical improvement or clinical remission when thiopurines were compared to placebo (170). There was evidence for thiopurines in acting as steroid sparing agents at induction. A review of 5 RCTs showed similar findings (171). The time to action is slow (3-6 months) and this probably plays a role in the lack of efficacy at inducing remission. The mechanism of action is inhibition of ribonucleotide synthesis and induction of T cell apoptosis. Thiopurine use may be limited by adverse events in 15-25% of patients, including allergic reactions such as fever and arthralgia, nausea and vomiting, as well as the uncommon risks of profound unpredictable leucopenia, hepatitis and rarely pancreatitis(172). There is a rare risk of
lymphoproliferative disorders, in particular lymphomas, at a relative risk of 5 times that in patients who are not exposed to thiopurines, but in real terms still represents a very low risk of less than < 1% after 10 years of use (173,174). A recent analysis compared the risk of lymphomas between population-based centres and referral based centres. This meta analysis showed a lower risk in population based studies (standardized incidence ratio, SIR, of 2.8) compared to referral based studies (SIR 9.2) (175). There is also a small increase in the risk of non-melanoma skin cancers (176).

One large study found evidence for the use of methotrexate as an induction agent CD with methotrexate with large doses of intramuscular drug (25mg/week) (177,178).

In the last decade, the introduction of biological therapies, in particular, antibodies to anti tumour necrosis factor α (anti-TNF), has revolutionized therapy for both luminal and fistulizing disease in CD. It is effective in induction of remission in both luminal (18,179-181) and fistulizing CD(182). The risks associated with these agents include increased risk of infections, including tuberculosis, opportunistic infections, autoimmunity and infusion reactions. Risk of infection increases substantially when 2 or more immunosuppressive therapies are used in conjunction with biological therapy (183). There is a risk of certain malignancies with biological therapies, though in absolute terms these are relatively rare. These include lymphoma, non-melanoma skin cancers and other solid tumours. There is an association with lymphoma in patients on combination therapy with thiopurines and biological therapy (184) but it remains unclear if this is due to the thiopurine component as these agents themselves are known to increase risk of lymphoproliferative disorders and most patients exposed to biological therapy have had previous thiopurine exposure (173,185). There have also been studies showing no increased risk of malignancy in patients treated with biological therapies compared to other therapies (186). Overall risk is considered very small as a recent meta-analysis has shown, with a rate of 6.1 per 10 000 patient years (187).
1.6.2 Maintenance Therapy in CD

There is no evidence for the use of aminosalicylates as maintenance therapy in CD (188). There is also no role for the use of steroids in maintenance due to the significant side effects and limited benefit on mucosal healing.

There is no evidence for the use of steroids to maintain remission due to the side effects listed above and limited mucosal healing with only 30% of those who achieved clinical remission demonstrating endoscopic remission, (260). Long-term use of steroids is associated with high rates of relapse, steroid dependency and significant adverse events (315).

Thiopurines are effective in maintaining remission in patients with CD, as confirmed by a Cochrane review, but efficacy is modest with a NNT of 6, and OR of 2.32 compared to placebo. There is also evidence for thiopurines based on trials of withdrawal of therapy once remission is achieved. More patients remained in remission in the group that continued azathioprine therapy (RR of failure to prevent relapse was 0.39, 95% CI 0.21-0.74) (189). There is some limited evidence for the use of MTX as maintenance therapy based on small number of patients (190).

There is good evidence from large randomized control studies for the use of biological therapies as maintenance in CD with remission rates of 39% and 45% at one year (19,191).

1.6.3 Induction of Remission in UC

Aminosalicylates are effective at inducing remission in UC (192), with higher doses of 4.8g achieving response quicker than lower doses < 3g/day (193). Topical therapies are beneficial by increasing the colonic concentration of drug and improve clinical response (194).

Oral steroids at high doses have been shown to induce remission in more patients with mild to moderate colitis compared to those on very high doses of salazopyrin (152).
Thiopurines are more effective than aminosalicylates in inducing remission in patients with UC who are steroid dependent, but based on one small study of over 80 patients (195).

Even though small studies to show some benefit of methotrexate in UC (196), this was not confirmed in those that used lower doses (12.5 mg oral) (197), and a Cochrane review concluded there was not benefit of methotrexate over placebo or other comparators in inducing remission in UC (198). Currently there are two large placebo controlled ongoing trials (METEOR and MERIT-UC) assessing the efficacy of methotrexate in active UC that may help resolve the evidence supporting the use of MTX in UC.

In UC, there is some evidence for the use of calcineurin inhibitors especially in severe acute colitis. Intravenous cyclosporine has been shown to be effective in reducing colectomy rates in severe acute ulcerative colitis, in particular in patients who are naïve to thiopurines and can be bridged to this therapy (199,200). It is associated with significant side effects, in particular nephrotoxicity and seizures, therefore long-term use is not advised. Tacrolimus, another calcineurin inhibitor, has been shown in one study to be effective in steroid refractory thiopurine naïve patients but the routine use has been limited by the risk of toxic side effects (201).

Like in CD, the introduction of biological therapies has revolutionized the management of patients with UC, with good evidence for clinical response in patients with moderate to severe disease (202,203). There is strong evidence for infliximab as salvage therapy in acute severe colitis, reducing risk of colectomy (200).

### 1.6.4 Maintenance Therapy in UC

Aminosalicylates are effective at maintaining remission in UC, as shown in a recent Cochrane review (192). There is also evidence for these agents in being chemoprotective against colorectal cancer in UC (204).

The evidence for thiopurine use in as a maintenance agent in UC is not as strong as that for CD due to the lack of studies done. A Cochrane review summarized
these studies, a total of six, with only 286 patients. It did show superiority of azathioprine compared to placebo but concluded poor study quality (205).

There is good evidence for the use of biological therapies in maintenance of remission in patients with moderate to severe UC, with up to 45% showing response at the one year follow up ((202)(203,206). Risk of adverse events is similar to those discussed for patients with CD.

Overall, the introduction of biological therapies has revolutionized medical treatment of IBD. This has primarily been shown in referral based centre studies that are likely to have patients with more severe disease. Little is known from population-based studies where the spectrum of disease is broader. It is important to assess clinical outcomes in these patients because as discussed above, introduction of these new therapies and new treatment strategies (accelerated step up or step down approach) does come at a risk of infection and uncommonly, malignancy. The next section deals with the real life outcomes of the medications already discussed. Population based data on biological therapy is lacking.

**1.6.5 Real Life Outcomes of Therapeutic Strategies in CD**

Many of the studies referenced above that support the various therapeutic strategies have used stringent patient selection and monitoring which introduces bias and is not representative of the true patient experience in the community. A discussion follows on the outcomes of the current therapeutic strategies in CD and UC based on population based studies, therefore avoiding some of these biases and reflecting more realistic outcomes for the majority of patients in the community.

Steroids as an induction medication have been shown to be effective in population-based studies such as 1994 Danish study that evaluated corticosteroids outcomes in a group of patients diagnosed between 1979-1987. It found that nearly half the patients (48%) had an initial response at day 30, 32% achieved a partial response, while 20% worsened or had no response (314). An Olmsted county study of 173 patients treated with systemic steroids
found a similar short term response, with 58% achieving complete remission within 30 days, 26% partial remission and 16% had no response (209).

However, high relapse rates have also been shown in the same studies, with half of patients (46%) who initially responded relapsing within 30 days of ceasing treatment. A substantial number (36%) were steroid-dependent or steroid resistant (314). In an Olmsted County study, at 1 year 32% had demonstrated prolonged response but this allowed for more than one course of steroids, and 28% were steroid dependent, while 38% had undergone surgical resection (209). Steroids use early in the diagnosis is associated with severe disease and poorer prognosis (137,230, 314, 316).

In recent decades, there has been a trend towards reduced steroid use (160). This coincides with an increase use of immunosuppression (IS) with thiopurines (160). The question is whether this shift has resulted in a clinical benefit to patients. The Cardiff cohort of 341 patients compared groups of patients based on year of diagnosis from 1986-1991, 1992-1997 and 1998-2003. It showed that the number of steroid dependent patients dropped over the years from 44% to 19% and there was an increased rate of immunosuppression at 5 years of follow up, from 11% in the first cohort to 45% (160). There was also a reduction in intestinal surgery between the groups, from 59% in the older cohort to 25%.

This association between in increase in IS and decline in steroid use and surgical rates is favourable and warrants further evaluation in future studies. A registry based study from the Netherlands of 476 Crohn’s patients assessed medication use in detail over a median follow up of 7 years, (238). They found steroid use to be stable, while IS use (which included thiopurines, thioguanine, cyclosporin and methotrexate) increased with time, especially in patients with ileocolonic or colonic disease. In this study, 8% of patients were also prescribed biological therapy. Whether improved outcomes were seen in those escalated to the IS medication is not clear as this study was not designed to answer this question, however, intestinal resective surgery rates were low in the first year in this cohort compared to historical cohorts suggesting this may be the case. A recent study that was designed to assess differences between countries in Europe found high use of IS in CD (57% in the first year) and 21% for biological therapies in
western Europe (9). At the 3 years of follow up there was no decline in surgical and hospitalization rates in those patients from Western Europe who had the higher IS and biologic therapy as compared to Eastern Europe (207). This is possibly due to a relatively short follow up period. Patients who require surgery early on are those who are presenting with more advanced disease including fibrosis, where medical therapy would not be as efficacious.

A Danish study that enrolled over 13,000 patients with CD from a Danish Health Register, diagnosed between 1979-2011 (with medication data available from the mid 1990s), assessed changes in medical treatment and surgery rates based on year of diagnosis (208). Use of IS was not significantly different between those diagnosed in the mid 1990’s and early 2000’s, with 32% and 39% respectively, prescribed thiopurines at 9 years. The use of biological therapies within the first 5 years of diagnosis was different between the two groups (3% and 19%, p<0.001). This coincided with a decrease in intestinal surgery rates between the two cohorts (31% versus 23% AT 9 years). Importantly, the rates of IS and biologic use, though higher to historical cohorts, are low compared to the rates prescribed today, as shown in the recent European study (9)

1.6.6 Real Life Outcomes of Therapeutic Strategies in UC

Population based studies have shown more frequent IS therapy in UC over the last two decades. In an Olmsted county study, none of the patients with UC diagnosed between 1970’s till 1990’s were prescribed IS in the first year (209); in the Norwegian IBSEN cohort of patients diagnosed in the 1990’s 4% were prescribed thiopurines over 10 years of follow up while in a Danish cohort of patients diagnosed in 2003-2004, the rate was 10 % (210,211). The most recent population based study from Western Europe showed a rate of IS of 22% and 6% of biologic therapy within the first year of diagnosis (9). There is sparse data on how this trend towards more IS therapy has impacted on objective markers of disease course. The Danish study showed that 1 year colectomy rates stayed the same among patients diagnosed in earlier years with lower rates of IS (211). Similarly the study of comparing outcomes in West and East Europe did not show short term differences in surgery or hospitalization between those patients
with higher early IS, compared to those with lower rates (207). However, as already discussed above in the CD section, early surgical rates may not be the best measure of medical therapy as these are patients who are likely to present with advanced disease. In the Danish cohort, the 10 year colectomy rate between patients diagnosed between the 1960'-1980's and the early 1990's did not change, but the IS use in all those patients was very small (1%).

The Danish study described in the Crohn's discussion included patients with UC and showed no difference in steroid use between those diagnosed in 1990s and 2000s. There were more patients with UC prescribed thiopurines within 5 years of diagnosis (10% versus 15%, p<0.001), though this difference flattened out by 9 years. Anti-TNF use was also higher in more recent years (2% vs. 9% at 9 years, p< 0.001). This coincided with a fall in colectomy rates at 1,5 and 9 years, based on calendar year of diagnosis (208). This study did not report on other objective markers such as hospitalization rates.

Further population based research is needed in recently diagnosed CD and UC, with longer follow up periods, to determine if accelerated step up therapy, with more frequent use of IS and biological therapies, results in improved outcomes as measured by objective markers including surgery and hospitalization.

1.7 Disease course in IBD

The true natural history, or disease progression, of IBD does not exist today, as almost no patients remain untreated. However, the natural history of untreated is of limited value in today's era of improved access to medical therapies. The prognosis of disease is better evaluated through the systematic approach in unbiased population-based cohorts of patients treated to current standards of therapy. These studies serve as a reference for evaluating new treatment modalities and the possible effect on the future disease course in IBD patients.

The last two decades have heralded many advances in the diagnosis, treatment and management of IBD patients. These have been discussed under the relevant sections above. To summarize these again, they have included advanced imaging (11,12); biomarkers to monitor for flares and assess response to therapy
(13,212-216) the use of metabolites and allopurinol to optimize thiopurine therapy (16,217); and anti-TNF antibody drug level measurement (15,217). The greatest impact on IBD management in the last 2 decades has been the introduction of biological therapy (18) (218). Correspondingly, there has been a shift in treatment objectives from achieving clinical remission to endoscopic remission and deep mucosal healing where possible (219) (220). However, it remains unclear if these advances are translating into better long-term disease outcomes and at what cost to the community.

The next section summarizes the evidence currently available from population-based studies on objective measures of disease outcomes, including progression of phenotype, hospitalization and surgery rates, mortality and malignancy. The focus is on how this has changed over the last 2 decades with the recent advances in management of IBD.

1.7.1 Progression of Phenotype in CD

Phenotype refers to the location and behaviour of Crohn’s disease. The Montreal classification system is a standardized framework for describing disease phenotype (see section “Classification”). Phenotype change is important in the natural history of Crohn’s disease. Disease location remains constant in the majority from time of diagnosis, with only 10-15% of patients exhibiting disease extension. Spontaneous disease regression is uncommon in CD, but more likely in those with superficial lesions especially aphtous ulcers (24). Disease behaviour is dynamic with progression from the most benign, termed as inflammatory phenotype to the complex stricturing and penetrating phenotype. Phenotypical characteristics at diagnosis can be used as predictors of future disease course. For example, small bowel involvement is more likely to progress to stenosis and obstruction if not treated. Also, phenotype predicts response to therapy. Inflammatory disease is the most likely to respond to medical therapy, where as this is less likely with stricturing disease and even less so with penetrating bowel disease. Progression of disease to these forms is also associated with need for surgery, hospitalization and other complications (221-223).
Studies to date have shown that disease location at diagnosis is remarkably similar between most cohorts, and remains stable throughout the course of disease in an individual. At diagnosis, ileal disease occurs in 27% to 45% of patients, colonic in 27% to 49% and ileocolonic is the least common at 14-20% (137) (160). Interestingly, colonic Crohn’s may be becoming more frequent in recent years, (160) and is more common among patients diagnosed over the age of 60 (224,225). In the paediatric cohort, the rate of ileo-colonic disease is much higher at 68% (33,226). Upper gastrointestinal disease is infrequent, ranging from 0.3% to 4% (36,224,226) but may be more common in the paediatric cohorts where it is generally mild.

In comparison, disease behaviour is dynamic with frequent progression from inflammatory to stricturing and penetrating disease that is associated with unfavourable disease outcomes such as surgery and hospitalization. In population based cohorts, the rate of inflammatory disease at diagnosis ranges from 73% to 80% (160)(221)(238)(317). The IBSEN cohort had a slightly lower number at 62% (137). The Olmsted County study specifically addressed the evolution of disease behaviour in a group of patients with CD diagnosed with CD between 1970 and 2004 and followed for a median of 8.4 years. At diagnosis, 14% had penetrating and 5% stricturing disease. The cumulative risk of progressing to penetrating or stricturing disease was 33% at 5 years, 39% at 10 years and 50% at 20 years (221). In a New Zealand study 31% and 25% of patients had stricturing and penetrating disease, respectively, after 10 years of disease. However, nearly a third of patients were lost to follow up for unclear reasons and this may have introduced bias, with those with more severe disease more likely to have ongoing medical care. Overall though, these studies show a more benign course of disease progression compared to referral centre based centres (88) in which half the patients at 5 years developed stricturing or penetrating complications.

The Olmsted County and New Zealand population based studies pre-dated routine use of biological therapy. It is important to determine if implementing
an accelerated step up approach to medical therapy with the addition of biological therapy when needed can alter the progression of disease behaviour and prevent stricturing/penetrating disease. A referral based retrospective review from one centre that included over 2000 patients found that despite a rise in thiopurine use, progression to stricturing and penetrating disease, as well as intestinal resection rates, did not decrease (321). A Hungarian study showed that in a cohort of patients recruited from 2002-2006, the probability of disease behaviour change from inflammatory to stricturing/penetrating was only 7% at 5 years, and this coincided with a higher rate of thiopurine use (38% at 5 years), but the use of biological therapies remained very low (222). There are currently no population-based studies with a significant number of patients on biological therapies assessing change in disease behaviour.

1.7.2 Progression of Phenotype in UC

In UC, phenotype is described in relation to disease location. Distal disease involving the rectum is referred to as proctitis and denoted as E1 in the Montreal classification. Colitis involving the sigmoid and descending colon is termed as left sided diseases (E2) and when disease extends beyond the splenic flexure, it is pancolitis (E3). At diagnosis, the 30% rule tends to apply, with 30% of patients presenting with proctitis, another third with left sided disease and a third with pancolitis (24). Disease course can be more variable in UC compared to CD (24). The proximal extent of inflammation can progress such as after 20 years, about 50% of patients with proctosigmoiditis have pancolitis (227). The same study found that over 70% of those with substantial or pancolitis experienced disease regression. Disease activity also tends to decrease over time, as seen in a Danish cohort of patients who did not receive any IS, and nearly half were in prolonged remission (228).

There are a number of population-based studies that assess disease progression in detail. The IBSEN study recruited over 800 patients with UC in Norway diagnosed in the 1990s (210,229). The strength of this study was that assessment of disease progression was done endoscopically, with over 60% of the original cohort having a repeat colonoscopy at 10 years. 21% of patients with
left sided colitis progressed to pancolitis. Of those who initially only had proctitis, 28% progressed to left sided colitis and another 14% to pancolitis. Only 7% of patients were exposed to IS therapy in the form of azathioprine, as this was an older cohort of patients diagnosed in the early 1990s. This is one of the only population-based studies to publish on the progression of phenotype. It is important to compare this progression of disease in a cohort of patients diagnosed in recent years to determine if medical treatments have reversed this progression of disease.

1.7.3 Predictors of Disabling CD

The definition of disabling disease in CD remains to be clearly defined in the literature. A clear definition is necessary to be able to determine accurate predictors of disabling disease. A large referral centre study defined disabling disease by the presence of at least one of the following criteria in the first 5 years of disease: more than 2 steroid courses, >1 hospitalization, chronic symptoms of more than 12 months duration, need for immunosuppression, intestinal resection or perianal surgery (316). However, using this classification nearly 80% of their cohort were defined as having disabling disease, implying that the definition may have been too stringent. The main criticism to this definition is the inclusion of IS and perianal surgery. It does however remain one of the only definitions in the literature and has been validated in an additional referral-based study (230). In this second study, an additional definition of severe disease was introduced which included the development of complex perianal disease, any colonic resection, two or more small bowel resections (or one of more than 50cm) or the construction of a definite stoma (230).

Both these studies used the definitions to identify possible predictors of disabling disease. Beaguerie et al found that age < 40 at diagnosis, the need for steroids at diagnosis and perianal disease predicted disabling disease. Loly et al identified perianal disease, steroid at diagnosis and ileocolonic disease, but not age < 40, as predictive of disabling disease. Using the original Beaguerie criteria, Loly et al found that 58% of 361 had disabling disease. In contrast, when the second definition of disabling disease was used, 37% of patients fit the criteria
and the clinical predictors included stricturing disease and loss of weight.

There is very limited literature from population-based studies on predictors of severe disease progress. A paediatric study used the Beaguerie et al criteria with the addition of growth failure and found that 15% of patients went on to develop disabling disease (231).

In population-based studies, phenotype characteristics can predict an unfavourable disease course. Ileal and upper gastrointestinal disease has been associated with future stricturing or penetrating disease in many studies (137)(238)(317)(232). Isolated ileal disease has been associated with a 7-fold risk of future stricturing or penetrating disease compared to a patient with colonic disease, while those with ileocolonic disease had a 5 fold risk (221). Perianal disease at diagnosis has also been associated with a higher risk of progressing to complex disease behaviour (141,221).

Younger age and smoking were identified as predictors of severe disease in a prospective registry of IBD patients diagnosed in the Netherlands from 1991, which included 476 patients with CD. Younger age (< 40) at diagnosis was associated with more frequent relapses (238). The IBSEN cohort also confirmed age < 40 as risk factor. In contrast, smoking was not found to be a predictor in the New Zealand study (317) nor the Manitoba study (318).

There is limited literature on the role of serological markers in population-based studies in predicting disease severity. The Manitoba group investigated serological, genetic and psychological factors as predictors of complicated disease defined as stricturing or penetrating behaviour (318). 65% of the cohort went on to develop complicated disease at a median follow up of 9 years, with 42% proceeding to surgery. Of the panel of antibodies analyzed (which included pANCA, ASCA, anti-I2, anti-ompC and anti-CBir1), patients who were ASCA IgA and IgG positive at diagnosis were more likely to develop stricturing or penetrating disease, but on multivariate analysis, only ASCA IgG remained significant. The NOD2 gene was the only gene associated with complicated behaviour, but lost significance on multivariate analysis.
1.7.4 Predictors of Disabling UC

There has not been a published definition of disabling disease in UC, but nonetheless attempts have been made to identify clinical predictive factors of disabling disease. Colectomy is an objective surrogate marker used in these studies to define severe disease, both in the form of emergency colectomy for fulminant colitis and elective colectomy due to chronic smoldering disease or colorectal cancer (232,233).

The IBSEN population-based cohort identified younger age (< 30 years at diagnosis) to be associated with higher colectomy rates and thus predictive of a disabling course (137,210). This was verified in a paediatric cohort of patients (234). However, given the large number of patients diagnosed in their youth, this does not serve well as a differentiating early clinical predictor given a large proportion of patients will be young at diagnosis.

Extensive colitis at diagnosis has been associated with a higher future risk of colectomy (210), as has high level of inflammation at diagnosis. This includes systemic symptoms such as fever and weight loss (228,235), and elevated inflammatory markers (ESR, erythrocyte sedimentation rate) > 30, that correlates with colectomy (210). In contrast, mucosal healing has been shown to be protective against future colectomy risk (160,236).

Early hospitalization (137,237) and male sex have also been shown to be predictive of an early colectomy (238,239). Smoking has been associated with a more quiescent disease course and lower colectomy rates (240,241).

The IBSEN cohort has published in abstract only a risk matrix for prediction of colectomy in population based patients with UC. They extrapolated from their data that the risk of colectomy was 15 times higher if the patient was younger than 30 at diagnosis, had an ESR>30 and a need for corticosteroids at diagnosis (242). More recently, a prognostic index was developed in the UK and validated in 3 cohorts (two of these referral based centres), based on the presence of a high CRP > 10mg/L, haemoglobin <12.1 g/dL and extensive colitis, predicted the risk of acute severe colitis requiring hospitalization (243).
Patients most at risk of disabling disease should be identified early and monitored closely with treatment so that more progressive steps can be taken early on to prevent a disabling course. These population-based studies have made some inroads into the prediction of a disabling course of UC but early accurate identification of patients at risk remains a clinical challenge. The major limitation is the lack of a published and validated definition of disabling disease. Colectomy is the most objective surrogate marker of this but other outcomes should also been considered such as frequency and severity of relapse.

1.7.5 Hospitalization Rates in CD

Hospitalization is a surrogate marker of disease progress that is objective and reproducible. Management of IBD has shifted to a largely outpatient basis but inpatient care is still necessary in some patients. It is associated with a negative impact on a patient’s quality of life, implying severe disease. Hospitalization rates, length of stay and re-admission rates are useful parameters to measure in the assessment of disease progression.

Based on population based studies, the likelihood of a hospital admission for a Crohn’s patient over the course of their illness remains highest in the first year from diagnosis, ranging from 25% to 30% in the older studies (226) (222,223) and 19% in more recent literature (9). Most studies confirm that after the first year of disease, the risk of future hospitalization declines (224,226). A Canadian study also showed a decline in the average length of stay in recent years from 10.3 days in 1994-1995 to 9.1 days in 2000-2001, as well as a decline in the annual rate of hospitalization during this time period (226). There was no decline in the prevalence of disease over these years. In the US, hospitalization rates have in fact increased over recent years but this is the only country to report this and may be attributed to the health care system (244). Not all US studies have shown this trend, as a study of 2892 patients with CD diagnosed between 1998 to 2005 showed a decline of 33% (245). In North American studies, 10 year hospitalization rates are between 66%-71% (246). In a prospective multi-country European study a slightly lower 10-year hospitalisation rate of 52.7% was found (224). Small bowel and ileocolonic
disease increased the risk of hospitalization(222,247). All but one of the studies listed above pre-dated the regular use of biological therapies. The pivotal biological therapy clinical trials demonstrated a drop in hospitalization rates (248) and so it is hypothesized future population based studies should also show this benefit.

1.7.6 Hospitalization Rates in UC

Relatively little data are available on hospitalization rates in UC. A large database study from Canada did not show a decline in hospitalization rates between 1994 and 2001. The 7 year rate was 34% (226). A US national discharge database showed an increase in the rate of surgery between 1998 to 2007 (249). In contrast, another US study did not show such an increase between the years of 1990 to 2003 (250), and a study of nearly 6000 patients with UC showed a decline of 29% between the years of 1998 to 2005 (245). In the most recent population study from Europe, the 1 and 3 year rates of hospitalization ranged from 6-13% and 13-20%, respectively (207).

Overall there is a paucity of data on hospitalization rates in UC, in particular in the last decade. Hospitalization can be partly subjective as multiple factors may play a role, not just disease severity, but also need for diagnostic workup, as well as healthcare reimbursement policies. Nevertheless, hospitalization remains an important surrogate marker of disease progress and further research is needed to monitor this outcome over recent years.

1.7.7 Intestinal Surgery in CD

Intestinal surgery in Crohn’s disease is an indicator of a severe disease course and is the result of irreversible tissue damage. It is a consequence of medical therapy failing to achieve disease control, either due to lack of optimal therapy or advanced disease. Surgery is not curative in CD and can be associated with a negative impact on the patients’ quality of life (251) (229). The ultimate goal in the management of Crohn’s patients is to alter the natural history of disease and prevent this irreversible tissue damage requiring surgical intervention. Surgery is a reproducible objective measure of disease severity.
Most population-based studies have shown a decline in intestinal resection in the last decade (see Table 5) (6) (160) (137). Intestinal resection rates in population based studies range from 7% to 32% at 1 year, with the more recent cohorts showing a lower risk (see table 4). The rates are higher in the older studies, which included patients from the 1950’s and 1960’s, and ranged from 35 to 45%. Five-year resection rates range from 25% to 38%. Ten-year rates were higher in the 1960’s to 1980’s at 55% (141). Recent studies have shown lower 10-year surgical rates, from 29% in the European Collaborative study group in IBD, EC-IBD (232), 38% in the IBSEN cohort from Norway (137), and 50% from the Netherlands (238).

This decline in rates over recent years is encouraging suggesting that the advent of new medical therapies and management is having a positive impact. A large meta-analysis of population based studies confirmed the risk of surgery has decreased over the last 6 decades, (252). The 5 year risk was 31% in patients diagnosed after 1970, compared with 24% in those diagnosed after 2000. A number of studies addressed whether surgical rates have changed over time, such as the Copenhagen group, and showed a decline from 35% at 1 year to 12% (6,211). In Canada patients diagnosed between 1996 and 2000 had 1 an 5 year rate of 13% and 22%, respectively, whilst for those diagnosed between 2001 and 2008, the 1 year and 5 year rate dropped to 10% and 18% (223). The Cardiff group assembled data between 1986 and 2003 and observed a significant decrease in the cumulative probability of surgery at 5 years from 59% to 25% with an increase in IS (160). There is also recent evidence that there is a delay to first surgery in favour of the group diagnosed in recent years, as well as a decrease in the number of patients requiring a stoma (160). All these studies were done in the “post anti-TNF” era, but in reality the number of patients prescribed the treatment was small, such as 5-16% at 5 years.

A population based study from Hungary found an association between early azathioprine use and reduction in surgical rates, (235). A Swedish study of 191 Crohn’s patients assessed the efficacy of infliximab in a population-based cohort and included surgery as one of the clinical outcomes (253). The follow up period was very short (1 month after the first infusion in the luminal cases, and 3
months in the fistulizing ones). 14% of Crohn's patients required resective surgery despite treatment with infliximab, but as discussed before, this probably represents a group of patients who present later in the disease course with advanced inflammation/fibrosis and medical therapy will not be efficacious in those cases.

Risk factors associated with progression to surgery are important as these can be used to individualize therapy for those patients most at risk. Ileal involvement is a well established risk factor in nearly every study to assess this (137,160,238,240). Stricturing or penetrating disease has also been shown to predict surgery in some studies (137,238). Younger age at diagnosis has both been shown to be a risk factor (137) and protective (254). Medication use such as the need for steroids in the first 3 months, and the need for IS in the first year, has also been associated with a future risk of surgery (160).

Population based data on perianal surgery rates is limited, despite it being a common disease outcome. The Olmsted group found that 20% of patients with CD developed perianal fistulizing disease within 1 year, and most (71%) of these patients required surgical intervention (255). The cumulative risk of perianal fistulizing disease at 5 years was 26% and 33% at 10 years. Only 9% of patients were prescribed a thiopurine to treat the fistulas, and 2% received anti-TNF treatment. A large New Zealand study of 649 patients found that close to a third of patients developed perianal disease, and 18% of all patients had at least one perianal surgical intervention, with a median time to first intervention of 28 months (256). Risk factors for perianal surgical intervention included age younger than 17 at diagnosis and ileal disease. The morbidity with perianal disease is significant, with 294 procedures performed in 119 patients, as nearly 50% of those requiring a surgical intervention had more than one. Another study confirmed that on average 2.3 procedures are needed to heal a fistula in just over 2 years (257). There is no literature on the impact of recent medical advances on perianal surgery from population-based studies.

In summary, population based studies indicate that the rates of intestinal resections have fallen in CD over recent years. At the same time there has been
an increase use of immunosuppression and this may be the cause of lower rates of surgery. Consistently reported risk factors associated with intestinal resection include ileal disease and non-inflammatory phenotype at diagnosis. Perianal fistulizing disease is common and associated with significant morbidity but limited population based studies are available on outcomes since the use of anti-TNF agents. The number of patients exposed to anti-TNF’s in all these surgical studies remain small, and further population based studies are needed to assess the impact of these agents on long term disease outcome and surgical requirements.

1.7.8 Colectomy in UC

A large database study, mentioned in the medication section of this review, compared patients with UC from 1979 to 2011, assessed medical treatment and surgery rates over the years. It confirmed falling colectomy rates at 1, 5 and 9 years, based on calendar year of diagnosis, with the latest cohort having a rate of 9% at 9 years (208). As already discussed, this coincided with significantly increased use of IS and biological therapy. A limitation from this study was that only inpatients were considered before 1995 and from 1996, both inpatients and outpatients were included, possibly introducing the bias of more severe cases in the early recruitment.

In contrast a meta-analysis of 16 studies that included both cohort and controlled trials showed no difference in colectomy rates over 30 years, though given the mix of studies, there may have been bias introduced from the clinical trials (258).

A meta analysis of 13 population based studies reported on risk of surgery and found that it had significantly decreased over time at 1 and 10 years from of follow up (252). The cumulative risk of colectomy was 4% at 1 year, 10% at 5 years and 14% at 10 years. However, this meta analysis did not summarize medication use, so even though it has confirmed a drop in colectomy rates in the 21st century, its unclear what this could be attributed to. The authors hypothesized that apart from medical therapy, other impacts on colectomy rates include a change in practice patterns over time such as earlier diagnosis,
implementation of practice guidelines, promotion of medical education, a shift from surgical to medical care, and fewer colectomies being done for dysplasia.

A Canadian study from 1997 to 2009 showed that there was a decrease of 7% per year in elective colectomy rates but not in emergent colectomies, which tended to occur closer to the time of diagnosis (259). This coincided with a rise in thiopurine use over time period (OR 1.15, 95% CI 1.09-1.22) and anti-TNF agent use after 2005 (OR 1.68, 95% CI 1.25-2.26).

These studies demonstrating a fall in colectomy rates are reassuring for patient and clinician. However, there are gaps that should be addressed in future population based studies. This includes evaluation of surgical risk in those patients who are diagnosed when biological therapy is widely available some of the above studies either did not report this or had low rates of use.

1.7.9 Mucosal Healing in CD

Mucosal healing (MH) has been neglected as a clinical end point till recently, potentially due to inability of older therapies to achieve this and debate whether it improves clinical outcomes. Now it is considered an important surrogate end point in both clinical trials and clinical practice with data showing improved rates of sustained clinical remission, fewer hospitalizations and surgery, and reversal of paediatric growth retardation in patients with MH(156) (219) (208,220,252,258) The benefit in mucosal healing as an end point in disease assessment is its objectivity. Data from community-based cohorts is lacking.

Older therapies such as steroids do not do not correlate well with mucosal healing as only 30% of those who had a clinical response achieved a healed mucosa (259,260). Thiopurines are more effective at achieving healing in 40-50% of patients (156,261). The pivotal clinical trials for anti-TNF antibodies found that 44% of patients on maintenance treatment achieved mucosal healing at 1 year (218,219,262), and some single centre studies showed even more favourable MH rates at over 60% (263).

Its important to determine if this translates to clinical benefit and a favourable shift in the natural history of CD for the patient. Clinical trials suggest that it
does. Patients who had demonstrated mucosal healing had fewer hospitalisations, surgeries and intensive care unit stays (262) and less frequent relapses (264).

There is a paucity of population-based data on MH. A retrospective review of the IBSEN cohort is one of the few available and found that 38% of patients achieved mucosal healing at a mean time of 14 months (236). The main significant clinical outcome was that more patients in the non-healed group were taking oral steroids at the 5 year follow up and that those who had no healing of mucosa at the 1 year were also less likely to have achieved this at final follow up. There was no difference in surgery and relapse rates, and complications. There was a large drop out between the first and follow up endoscopy, with less than 50% of patients having both done.

More population-based data is needed to address whether mucosal healing is a beneficial and attainable goal in the treatment of population based CD.

1.7.10 Mucosal Healing in UC

There is evidence for the benefits of MH from referral based centre studies in UC. In the original clinical trials of infliximab, there was a decrease in surgery rates and higher rates of steroid free remission in those patients who had achieved mucosal healing at the week 8 assessment (265).

The IBSEN study is the only population based study to assess the impact of mucosal healing in UC and showed a lower risk of future colectomy at 5 years (p=0.02) in those who had healed mucosa at 12 months from diagnosis (236).

MH in UC can be achieved with 5-ASA therapy, as well as thiopurines and biological therapy (195,266). The efficacy with azathioprine is based on 2 small studies, one comparing azathioprine to 5ASA therapy. The former appears more effective, with rates of healing around 50% versus that of 20% in 5ASA’s. Biological therapy has been shown to induce MH in around 60% of patients at 2 months, with a 1 year rate of 46% (265).
As in CD there is a paucity of data from population-based literature and more research is needed in this area.

1.7.11 Mortality and Malignancy in CD

Studies on overall and cause-specific mortality in patients with CD have shown contradictory results from population-based studies, with both a large number of positive and negative studies.

The European Collaborative study group of IBD (EC-IBD) is one of the largest prospective inception cohorts to address the risk of mortality. A total of 2201 IBD patients (706 CD) across 20 centres in 12 European countries were included (232). Of this original cohort, 371 patients from 10 centres were included in a study evaluating mortality risk in CD during 10 years of follow up. The SMR (standardised mortality rate) for patients with CD was 1.85 (95% CI 1.3-2.55) compared to the normal population. The cause specific mortality risk was increased due to gastrointestinal causes that were either certainly or probably related to CD. At multivariate analysis, age over 40 remained the only independent risk factor for both total and CD related mortality causes. A limitation was the high dropout rate from the original cohort that could introduce bias of over including more severe cases.

The Olmsted County study of 314 patients is the other prospective study of an inception cohort, with patients diagnosed between 1940-2001. Median follow up was 14 years and there was a 20% increase in mortality (SMR 1.2, 95% CI 0.9-1.6)(319). The increase risk of mortality was due to deaths from gastrointestinal disease and gastrointestinal malignancies as 32% of all deaths were due to Crohn's related complications.

The other population based studies to show an increased risk of mortality in CD were dependent on database recruitment, with the advantage of a larger sample size but possibly introducing bias in particular misclassification bias from coding errors of death certificates. One of these was a Danish study of 3 consecutive population based inception cohorts that had the benefit of comparing rates between year of diagnosis (211). Cohort 1 included patients diagnosed from...
1962 to 1987, cohort 2 from 1991 to 1993 and cohort 3 from 2003 to 2004. A total of 641 patients with CD were included with a median follow up time range of 17 years in cohort 1 to 1 year in cohort 3. The overall mortality risk was increased in patients with CD (SMR 1.3, 95% CI 1.1-1.6), with the risk becoming apparent after 8 years of disease. Follow up in cohort 3 was short and hopefully a more prolonged follow up will show a reduced mortality risk in this most recent cohort to reflect the recent advances in medical management. Another Danish nation wide database cohort study done on a much larger scale (15,362 patients) confirmed an increased mortality rate shortly after diagnosis (HR 3.2, 95% CI 3.41-3.99) that declined over years but remained higher at 10 years follow up (HR 1.49, 95% CI 1.38-1.59) (320). Mortality rates were higher for paediatric cases due to the long-term risk of dying when compared to those diagnosed at age 60-79. This differs from the EC IBD study which had shown those over the age of 40 had a higher risk (232). Mortality was increased for all specific causes of death including infections, cancer, respiratory diseases and gastrointestinal disease. Finally a primary care database study (GPRD) in the UK of 5960 patients also showed an increased mortality rate of up to 70% compared with controls (HR 1.73, 95% CI 1.54-1.96) (267) but suffered from a lack of clinical data as well as including a mix of prevalence and incidence cases which may introduce bias.

There have been a number of studies that show no increase risk of mortality in patients with CD. This includes the IBSEN cohort 20 year data (one of the longest follow up periods available) that found no increase in the risk of overall mortality in patients with CD, nor an increase risk in deaths from gastrointestinal cancer or other cancers (236,268). An Australian study, also with a very long median follow up 22 years, showed no increase in mortality in CD compared to the general population (269). A Finnish prospective registry of 550 patients with CD showed no increase risk of mortality over a median follow up of 13 years (270). However, the risk of death from diseases of the digestive tract was significantly increased (SMR 5.38, 95% CI 1.42-14.61).

However, a large Finnish database study of over 5000 patients with CD diagnosed between 1987-2007 did find an increased mortality risk (SMR 1.33,
95% CI 1.21-1.46), with those within 2 years from diagnosis and more than 10 years after diagnosis at highest risk (271). There was an increased risk of cause-specific mortality, in particular gastrointestinal disease (highest in the first 3 years), intrahepatic biliary tract cancers and lymphoproliferative malignancies. There was also an elevation in pulmonary specific causes such as obstructive airways disease and pneumonia.

Given the mixed results described in all these studies, a meta-analysis is a good way to draw firmer conclusions on risk. A recent meta-analysis has been done that included 9 studies (272), some of which have been already described. Database based studies were excluded as well as selected populations (265,267). Overall pooled mortality risk was significantly increased (SMR 1.39, 95% CI 1.3-1.49). Patients with CD had increased risk of death from cancer, in particular pulmonary and cutaneous (melanoma) malignancy, though the latter was based on one study only. There was also a significant increase in mortality from chronic obstructive airway disease, genitourinary diseases and gastrointestinal diseases and infectious diseases. The high rate of pulmonary and genitourinary disease was attributed to higher rates of smoking among patients with CD. The high mortality risk from gastrointestinal but not CD related deaths was hypothesized to be due to pancreatitis, cholecystolithiasis (both previously associated with CD) or simply inaccurate coding of deaths from CD. The limitations with the study was the inclusion of only one negative study (273); and that two studies from Sweden made up nearly two thirds of the patients thus compromising the heterogeneity.

In summary, current literature remains conflicting but overall there does seem to be a small increase in all cause and cause specific mortality risk in CD. Many of the studies described above included patients diagnosed before the recent medical advances as long follow up is paramount in assessing mortality risk and so future follow up of more recent cases will be important to determine the impact of these advances.
1.7.12 Mortality and Malignancy in UC

Initial population based studies on mortality risk in UC from the 1950s-1980s showed a small increase risk of death due to elevated risk from colitis, colorectal cancer, non alcohol related liver disease and asthma (274) but since then, most studies have not.

Some of the studies described in more detail above also looked at UC mortality risk. The Olmsted county study did not show an increased risk, and in fact, demonstrated fewer cardiovascular deaths in patients with UC compared to the normal population (275). The Danish study of 3 consecutive population based inception cohorts of patients also showed no increased risk of mortality or colorectal cancer (211).

In comparison the Danish wide database study did shown an increase of 10% in mortality among patients with UC, with the risk being highest within the first year of diagnosis (276). There was an overall decrease in mortality in this study depending on year of diagnosis, with those diagnosed in the 1990’s at increased risk compared to those diagnosed from 2000-2010. All specific cause mortality followed the same pattern as overall mortality. At 10 years, there remained an increase risk of dying from cardiovascular disease, gastrointestinal disorders, infectious cause and colorectal cancer. Comparing year of diagnosis, those diagnosed later had a smaller risk of dying from colorectal cancer. The Finnish database study also showed a very marginal increase in the risk of UC (SMR 1.10, 95% CI 1.05-1.15) with slightly higher risk of death from gastrointestinal causes, pulmonary and cardiovascular disease, and cancers of the colon, rectum and biliary tract (271). Interestingly, a prospective study from Finland with a similar year of recruitment to the previous Finnish study, showed no increase risk of mortality with UC, nor was there an increase risk in mortality from colorectal cancer (270). This discrepancy in results between a retrospective database derived study and a prospective study suggests that some aspect of methodology may be responsible for the differing results. As already suggested, database studies have the advantage of large patient numbers but may suffer from inaccurate recording on death certificates and introduce bias.
Overall, the risk of mortality in UC is either equal to or only marginally increased compared to the population.

### 1.8 Clinical Predictors of Disabling Disease

It is important to identify early the sub group of patients that will go on to develop a severe disease course. These patients can then be followed intensively with earlier use of disease modifying agents such as thiopurines and biological therapy, in the hope of modifying the natural history and preventing complications such as stricturing or penetrating disease and need for surgery. Being able to predict the likely future disease pattern is also worthwhile for patient counseling and compliance.

### 1.9 Health Cost Associated with IBD

In this era of escalating health care costs and growing constraints on health care budgets, cost analysis is crucial for planning proper distribution of health care resources and novel therapeutic agents. This is especially so in lifelong incurable diseases such as IBD with long term therapy including expensive options such as biological therapy and resective surgery. The issue is made even more pertinent by the global rise in the incidence of IBD.

There is limited literature on the health care cost in population based IBD cohorts especially since the widespread introduction of biological therapy. What follows is a summary of what evidence is available.

There are certain requirements of a good cost-of-disease study, and these include the cohort being community based, the economic analysis be done from the societal perspective, and including both inpatient and outpatient costs (277). The focus of this review is to include studies that fulfill these criteria.

The total patient cost per year has been published in many studies, but it does vary between these studies whether the mean or median cost was calculated, or both. This can make comparison between studies difficult though most recent literature on the topic includes both. In IBD, the median cost tends to be lower than the mean due to the cost distribution being skewed to the right. This is as a
result of a small number of patients that contribute significant costs due to high resource utilization ('high cost outliers') (224,278-280). An older European study that recruited patients in the early 1990s and followed for 10 years found a mean annual CD cost of AUD 3617 (224) and AUD 2163 for UC, with CD cost being significantly higher (p<0.001). In comparison, the mean annual cost of a CD patient from Canada in 2005/6 was AUD 4435 and AUD 3722 for a UC, again with significantly higher cost in CD (p<0.001). Only 1% of patients in this cohort were on biological therapy. The median cost per patient was not statistically significant between CD and UC (AUD 1612 and AUD 1649, respectively) suggesting that the CD cohort had more high cost outliers. A cross sectional study from the Netherlands assessed cost in patients at a median of 16 years from diagnosis. Using the 3 month cost reported, the annual cost for patients with CD was AUD 9235 and for UC, AUD 3382, confirming statistically higher expenditure for patients with CD (p<0.01) (281). There were 23% of CD and 4% of patients with UC on biologic therapy in this cohort. A study from the Epicom group of multiple European countries found a total cost of AUD 8442 for CD and AUD 3911 for UC in the first year of diagnosis. It is likely that first year of disease is most expensive due to higher use of diagnostic resources (most patients would require endoscopy to be diagnosed) as well as higher rates of hospitalization that plateau in later years (as discussed in the hospitalization section). Cost studies have confirmed this higher cost in the first year (224,278).

It is worthwhile assessing which resources contribute most to IBD cost. Over the last two decade, there has been a shift from inpatient resources to outpatient resources being the major contributor. The EC-IBD cohort of patients diagnosed in the pre-biologic era (1991-1993) showed that inpatient costs constituted the majority of total cost (224). Medical and surgical admissions made up 63% of CD cost and 45% of UC cost. In contrast a recent trans-European study of patients diagnosed in 2010 found that in the first year from diagnosis, found that 74% of total cohort cost in IBD was due to outpatient resources (medication 36% and diagnostic tests 38%), and 26% due to inpatient cost (surgery) (282). The limitation in this study was the exclusion of medical hospitalizations. Other recent studies have confirmed this shift to outpatient resources (278,281).
It is likely that biologic therapy has contributed to this shift, as 15% of total cost was due to this therapy in one study (22% in CD and 10% in patients with UC) (282). In long standing disease, biologic therapy was even more of a substantial contributor, accounting for 64% and 31% of total cost in CD and UC, respectively (281). The Canadian study showed that the mean cost of a patient on infliximab for a year was AUD $33,000 (278), which was significantly higher than the cost of a patient requiring surgery (AUD 18,000, p<0.01). One pivotal question is whether the high cost of biologics will reduce the overall long-term cost of IBD care. These therapies have been shown to reduce hospitalizations, surgery and number of flares in controlled clinical trials. To date, population based studies have not been able to definitively answer this. A Spanish study did look at cost of infliximab patients prior to being prescribed the medication and found that these patients had higher costs earlier on in the disease process primarily due to hospitalization (283). Following the introduction of infliximab, cost remained high in these patients due to the cost of the biologic, but other costs such as hospitalization, dropped substantially. Partial and complete remission was achieved in 82%. This suggests that concurrent quality of life and disease activity measures would demonstrate cost-effectiveness of biologic therapy due to improved quality of life, but further research is needed. One study that did assess this confirmed a higher cost of infliximab use but also a higher quality of life (284).

Many of these studies are subject to limitations. Frequently patients have been recruited through the use of databases that are dependent on administrative definitions of IBD and, importantly, lack clinical data to compare cost and disease severity. Some were performed retrospectively, thus introducing bias and difficulties in interpreting disease course and severity. Finally, some studies relied on patient-based recall of resource utilization, which introduces recall bias. Further prospective longitudinal research is needed to determine if the shift of cost to outpatient resources will result in an overall cost-benefit over the long term.
1.10 Conclusion

The above review of the literature serves as a background to this thesis. It demonstrates the rising incidence of IBD and the complexities in the diagnosis and management of these patients. While many advances in discovering the aetiology of disease have been made, there remain unanswered questions including what influence environment exposures have on the rapid rise in incidence in the last five decades. There are now new diagnostic tools as well as novel therapies in managing IBD patients and these have been beneficial for patients in clinical trials, but there is data lacking on how these advances impact on disease course and outcomes in the community based patient. Also, given the wide spectrum of disease severity, it is vital to have early clinical predictors for those patients most at risk at severe disease so therapeutic strategies can be employed early on with the aim of altering the ‘natural disease’ and preventing irreversible damage to bowel, but at the same time, not over treating those patients who are likely to have a mild course of disease. Finally, all these advances come at a significant price, but there is a paucity of health cost studies analyzing this.
1.11 Aims of this Research

The aims of this research include:

1) Prospective recruitment of new incident cases of IBD (2011-2013) into an established registry to monitor the incidence of disease in a well-defined geographical area (Barwon, Victoria) in Australia.

2) To identify the disease course and outcomes in incident cases diagnosed prospectively in 2007-2008 and 2010-2013, to assess the impact of recent diagnostic and therapeutic advances.

3) To formulate a definition of disabling disease in CD and UC and identify early clinical prognostic factors of a disabling course

4) To study environmental exposures prior to diagnosis in all incident cases to determine what role the environment may have in the recent rapid rise of IBD incidence.

5) To determine the health care cost of IBD in the first year of diagnosis from a health care system perspective.
Chapter 2  Methodology

This chapter provides an outline of the methodology chosen for each aspect of this study, including the general study design, case ascertainment methods, measurement of disease progress outcomes, interrogation of the cohort in regards to environmental exposures prior to diagnosis, the health care cost analysis methods and the statistical analysis employed.

2.1 Study design

This was a prospective observational study of a population based inception cohort (patients from time of diagnosis) followed prospectively for a minimum of 12 months.

All new cases of IBD during the specified time period in a well defined geographical area were identified through multiple sources to ensure complete capture. Each patient was asked through an opt-out consent process to participate in an established IBD registry which has previously been set up as a pilot registry and assessed to be successful in terms of feasibility and clinical validity (5). The registry served as a platform to gather longitudinal information regarding exposures prior to diagnosis, disease outcomes, quality of life and work productivity impact and health care costs.

2.2 Case Ascertainment

The geographical area chosen was the Barwon Statistical Division, details of which can be found on the Australian Bureau of Statistics website (www.abs.gov.au). This Statistical Division is an Australian Standard Geographical Classification (ASGC), representing a clearly defined geographical region. Population records are revised through the Australian Census data. The most recent total population estimate for the study region in 2011 was 293,426.

This area was chosen for the study for a number of reasons. Firstly, epidemiological IBD research has been done here since 2007 (4,5). Secondly, the
area maintains an independent infrastructure of healthcare-resources based in Geelong, the only city in the catchment area. There are 3 major hospitals (a public and 2 private), one major pathology centre utilized by most physicians, medical imaging facilities and pharmacy services. There are a dedicated group of Gastroenterologists who are located in the same clinic and work closely together. These features favour maximization of complete case ascertainment.

The cohort for this study was made up of two groups:

a) Incidence cases identified prospectively in 2007-2008 who had up to 60 months of follow up (4). These patients were enrolled retrospectively into the current study through the IBD registry.

b) Incidence cases identified prospectively from 2010-2013, including those identified by Studd et al in 20010-2011 (5). These patients had a median of 18 months follow up and were enrolled prospectively to the IBD registry.

Incident cases were identified by searching multiple health care sources to ensure complete case identification (4,5,8). This included identification of cases living within the region by the local Gastroenterologists, Paediatricians and Surgeons as well as the Gastroenterology Department at the Royal Children’s Hospital and Geelong Hospital Gastroenterology Unit. Each of these health service providers identified potential cases that were then confirmed by the principal researcher. In addition, they were all contacted on a regular 3-month basis to ensure this process remained active. The local Gastroenterologists allowed the principal researcher access to all medical records through which regular 3 monthly searches were done to ensure no case had been missed. Additionally, 3 monthly computer searches were carried out through the main hospital coding department, the primary pathology centre used by most Gastroenterologists for histology specimens (St John of God), and the local endoscopy centres, for terms of “Crohn’s disease”, “Ulcerative colitis”, “Colitis”. A computer search of the main hospital pharmacy was also done 3 monthly (which is used for inpatient and outpatient dispensing), of the terms “salazopyrin”, “mesalazine”, “azathioprine”, “mercaptopurine”, “infliximab” and
“adalumumab”. Case notes were then reviewed for each positive hit to determine if it was an incidence or prevalent case, and the treating doctor was contacted. Particular care was taken in regards to the diagnosis through the use of the Copenhagen criteria (Table 1) that includes a number of criteria including clinical symptoms as well as various diagnostic tests. These stringent criteria were used because the diagnosis of IBD is complex and multi faceted, requiring both the presence of symptoms and typical appearances on investigations. To verify the accuracy of the diagnosis, the principal investigator reviewed each patient again at 3 months to confirm the diagnosis was still valid before enrollment into the study.

Once the diagnosis was confirmed, patients were asked to participate in the IBD registry and the clinical study through the use of an opt-out consent (see Appendix 2). This form of consent is used by three quarters of the clinical registries in Australia(285). Under such an approach eligible study participants are provided with an Explanatory Statement describing the purpose and procedures of the registry. They are also provided with information to enable them to request more details about the study or to have their personal identifying information removed from the study. No consent needs to be signed and the patient needs to contact the research team to withdraw consent. No participant asked for this.

2.3 Registry

Clinical registries involve the collection and analysis of information relevant to the monitoring of and subsequent enhancement of the quality of care of patients with specific illnesses. A clinical quality registry aims to collect a standardized set of information from all patients treated for a specific illness or undergoing specific procedures (285). Data is typically restricted to a minimum set of essential data elements, with outcomes being sought. Outcome data are then sought through a number of pathways that can include review of medical records, questionnaires and/or data linkage. A group independent of those who provide the health care should undertake the management of the registry to
avoid bias. It is important that clinical groups are involved in the governance, analysis and generation of reports.

A pilot IBD registry was set up by Studd et al in the Barwon area (5). This pilot registry was further expanded in this current study to include the incidence cases from 2007-2008 and 2010-2013.

All identified cases agreed to participate in the registry, apart from one paediatric case that was deemed unsuitable due to a complex social situation. For the registry to be clinically useful, simple demographic elements were recorded, including patient name, date of birth, Medicare number, gender, address, phone number and email address. The diagnosis, treating physician and GP details were also recorded. The registry served as a backbone to collect clinical information on pre diagnosis environmental exposures, disease outcomes, therapies used, health care costs and quality of life measures. The clinical information was stored in a separate clinical database, run on Microsoft Access.

### 2.4 Clinical Database

A clinical database program was designed and implemented by the principal researcher using the Microsoft Access program, with the help of a computer programmer. This database was designed to store all de-identified clinical information on all participants in the study. Clinical information for each incident case was entered directly onto this database. There was no identifiable information on the database but each case could be linked back to the IBD registry (where all the identifiable information was kept) by a unique identifier, which was known to the principal researcher only. This was done to ensure data security. The database provided a framework in which to store clinical data and to perform queries during data analysis.

Screenshots of the clinical database are shown in Appendix 3. The pages shown include the diagnosis form, medication form and review visits forms. Other tabs were also present in the database, including a tab for investigations, surgery,
pregnancy and vaccinations. The database was populated with clinical information for each patient.

The majority of patients (those diagnosed from mid 2010) were recruited prospectively into the IBD registry and thus disease progress was also entered prospectively into the clinical database. The incidence cases identified prospectively in 2007-2008 (total number 76) were invited into the clinical part of the study retrospectively in 2012-2013. The benefit was longer follow up (median of 5 years). Disease progress for this group was assessed retrospectively from the case notes and entered into the clinical database.

The clinical information collected onto the database included age and gender, which diagnostic criteria were met, disease phenotype as based on the Montreal classification, extraintestinal manifestations, smoking status, all relevant investigations (including endoscopy results, blood tests, radiology), treatments used (date and dose at commencement, adverse events, date of cessation where applicable), disease activity at diagnosis and follow up visits (Harvey Bradshaw index and Simple Clinical Colitis Index, as described in Chapter 1), need for surgery or hospitalization, pregnancy, malignancy and mortality. All fields were regularly updated based on each subsequent visit to the treating doctor, with a minimum of 12 months required for the patient to remain in the study. Those unable to meet the 12-month prerequisite were deemed lost to follow up. Attempts were made to contact these patients and only 2 were lost to follow up.

The advantage of Microsoft ACCESS was the ability to query all stored clinical data. This is done through programming queries into the program. The principal researcher through the assistance of a computer programmer designed each query. An example of a query includes number of patients with a diagnosis of Crohn's disease who required hospitalization. Using this system the following outcomes were measured: disease activity, need for surgery, hospitalization, treatment steps used and any adverse events due to treatment, mortality and malignancy. Treatment was grouped into 5 levels of ascending potency: 5-aminosalicylates (5ASA)(oral and/or topical 5-ASA treatment +/- topical steroids), glucocorticosteroids (GCS)(oral or intravenous, immunomodulators

74
(IM) (azathioprine, mercaptopurine, methotrexate), biologicals (infliximab or adalimumab), and surgery (resective surgery or major abdominal surgery) (9). Initial treatment was defined as the highest level of treatment in the first 3 months from diagnosis. All IM's were combined into one category as over 90% of patients were prescribed a thiopurine.

2.5 Disease Outcome Measures

The following clinical outcomes were assessed at diagnosis, 3 and 12 months from diagnosis and last follow up at the end of the study:

1) Disease activity using clinical indices (described below)
2) Extraintestinal manifestations
3) Treatment steps including dose adjustments
4) Adverse events to treatment
5) Diagnostic results
   a. Serum tests - Full blood examination, electrolytes, liver function tests, C-reactive protein, vitamin d, iron studies,
   b. Radiology - abdominal xrays, CT scans, MRI scans, barium swallow +/- enema
   c. Endoscopy - gastroscopy, colonoscopy, flexible sigmoidoscopy, capsule endoscopy
   d. Biomarkers when applicable - faecal calprotectin
   e. Drug level monitoring - thiopurine metabolites
6) Hospitalization including duration
7) Surgery
8) Pregnancy
9) Malignancy
10) Mortality

2.5.1 Disease Activity

As discussed in previous sections, both CD and UC are chronic, relapsing conditions with exacerbations that may have non-specific, protean
manifestations. A clinical index is used to reliably measure disease severity, response to therapy and as an outcome measure in clinical trials is important.

In CD, the Crohn’s Disease Activity Index (CDAI) is considered the gold standard of clinical indices for evaluation of disease activity (286). However, this index is considered cumbersome for a number of reasons, including the need for a consecutive 7-day diary to be filled out by the patient, and this can be problematic with poor compliance by some patients who will do it all in one day, or not at all. The diary is also considered not sensitive enough to pick up more rapid changes in clinical state. Also, it is based on 8 clinical variables including measurements such as a blood haematocrit and body mass index, and therefore not simple enough to use at the bedside regularly by the treating physician (286). Currently it is used in Australia for 6 monthly reviews in those patients who require a biologic agent due to prescribing requirements, and given how time consuming it is, it is usually done by a specialist nurse.

For these reasons, a simplified clinical index was developed for Crohn’s disease, the Harvey Bradshaw Index (HBI) (151). It is a composite of 5 variables that can be assessed at the bedside, including general well-being, presence of abdominal pain, presence of an abdominal mass, number of liquid stools and presence of extra-intestinal manifestations (see Appendix 4A). A HBI of < 5 is defined as remission, 5 to 7 as mildly active disease, 8 to 16 as moderately active disease and ≥16 as severely active disease. It has been shown to have good correlation to the CDAI and easier to administer (151,286). It has been used in a number of prospective population based studies (9,143). It was therefore chosen as an appropriate clinical index in this study, to be used by the treating physician at regular intervals as a form of non-invasive assessment of disease progress.

In UC, the Simple Clinical Colitis Index (SCCI) was used in this study to assess disease activity (287). It is a composite of 6 clinical variables, including stool frequency during the day and night, presence of blood in stool, urgency to defecation, general well being and extra-intestinal manifestations. A score of ≤ 2 was defined as remission, 3 to 4 as mild/moderately active disease, and ≥ 5 as severely active disease.
The treating physicians used these clinical indices to assess disease activity at diagnosis and at final follow up (minimum of 1 year after diagnosis). As this had to be carried out prospectively, this tool was used in those patients recruited prospectively into the study and did not include the small proportion of patients from 2007/2008 recruited retrospectively.

### 2.6 Definition of Disabling Disease

One of the aims of this study was to formulate a definition of disabling disease in both CD and UC, and to use this definition to identify early prognostic factors of such a disease course. The definition used in this study for disabling CD was derived from the only previously definition available in the literature, discussed in details in Chapter 1 (230,288). The published definition had some limitations; 80% of patients were found to have disabling disease, which limits its clinical utility and suggests over inclusion of patients. We therefore modified the definition by excluding IM use from the criteria due to the large number of patients treated with these (>50%). IM use itself is not ‘disabling’ to the patient. Chronic relapsing symptoms were replaced with active disease at final follow up to reduce recall bias. Assessment of symptoms is subjective despite the use of indices, but important to measure as it implies ongoing disease burden and impacts negatively on patient reported outcomes (289). The final definition of disabling CD used in this study included 1 of the following criteria being present: more than 2 courses of steroids (at 12 months), further hospitalisation after diagnosis, ongoing active disease at 12 month review based on the HBI or SCCI, intestinal resection and/or perianal surgery. For the first time, an attempt was made to define UC as by using the same criteria (but excluding perianal surgery from the criteria for these patients).

### 2.7 Disease Aetiology- Environmental Exposures

A case control study was designed to explore possible aetiological environmental exposures prior to the diagnosis of IBD. To do this, incidence cases were asked to complete an environmental questionnaire at time of diagnosis. The majority of patients answered the questionnaire within 6 months of diagnosis. A small
proportion of patients (those diagnosed n 2007-2008) filled out the questionnaire 4 years after diagnosis.

The questionnaire consists of 87 questions. It was developed in 1999 by the IOIBD (International Organization of Inflammatory Bowel Diseases). It covers 25 environmental risk factors associated with IBD (Appendix 4). This questionnaire has been validated in a case control study (83) and used in multiple IBD cohorts (105,106,122). For statistical analysis items were grouped: smoking status at diagnosis, appendicectomy and tonsillectomy before age 20, use of oral contraceptives, breastfeeding during infancy, childhood infections (measles, mumps, rubella, chickenpox, pertussis and/or scarlet fever), pet ownership, vaccinations (tuberculosis, pertussis, measles, rubella, diptheria, tetanus and polio), a high sugar diet (defined as ≥ 2 of the following: sugar in coffee, sugar in tea, daily intake of soft drinks, sugar on breakfast cereal/porridge), a high fibre diet (defined as daily intake of 3 or more of the following: fruit, vegetables, wholemeal bread, ≥ 2 slices of bread, cornflakes, museli), fast food consumption (at least weekly), high intake of caffeine (≥ 2 cups of coffee or tea per day), daily physical activity, sanitation conditions (access to in-house and hot water, flush toilets, mains drainage and a separate bathroom) and IBD in a first degree relative. Poor sanitation was arbitrarily defined as answering no to two of the five sanitation questions.

If a participant did not initially return the questionnaire, a second copy was sent followed by a telephone call. An online version of the questionnaire was made available on Survey Monkey and a link emailed to the patient.

Controls were volunteers accessed through social networks and University affiliation, with no history of IBD. Family members of IBD cases were not included. Most of the controls resided in the study area of Barwon, with the remainder from greater Melbourne and is the closest major city to Barwon. A total of 103 controls, median age 47.5 (range 24-70) completed the questionnaire.
2.8 Health Care Cost Analysis

Health care cost was calculated for each patient for the first 12 months of disease including cost of diagnosis. This was done from the health care system perspective as the most complete and valid data was available on these resources. Indirect costs such as time off work and out of pocket costs to the patient were not included as it introduces recall bias (290). Therefore it was important to ensure total cost is accurate, if not slightly underestimated when compared to societal cost analysis.

Cost was calculated through the active surveillance by the principal researcher for the following IBD related health care resources utilized by each participant: diagnostic tests (including pathology, radiology, endoscopy and capsule endoscopy); medications prescribed (topical and oral aminosalicylates, 5ASA; azathioprine, mercaptopurine, methotrexate, adalimumab, infliximab); outpatient visits to the main treating specialist physician; medical and surgical hospitalization. The data on the use of these resources for each patient was available from the registry/clinical database. Outpatient visits to other health care professionals such as the General practitioner (GP), surgeon, specialist nurse or dietitian were not included. This was to ensure valid and complete cost data. Also, unpublished health economic data from the POCER study in Australia by Wright et al (291) showed that the average cost accrued by a patient visiting the GP for IBD related problems made up a very small percentage of total cost (<2%) (personal communication, Wright et al, manuscript in preparation). Similar assumptions were made regarding other health professionals (dietician, psychologist, physiotherapist) who are accessed less frequently than primary care physicians, are not reimbursed by the public healthcare system and therefore were unlikely to contribute greatly to overall cost.

Surgical admissions were defined as any admission to hospital that eventuated in a surgical procedure (intestinal and perianal) including all elective surgical admissions. This included an admission that initially required medical treatment and then progressed to surgery. The rationale of this was based on how hospital funding is allocated. It would be difficult to extract cost of surgery and surgical
care from an admission. This definition has been used in other studies (292). All hospitalizations not associated with a surgical procedure were defined as medical admissions. Hospital cost was obtained directly from the relevant hospital for each individual patient from 3 hospitals. When this was not available from the treating hospital (in a total of 10 patients), the diagnostic code and duration of stay was used to estimate the cost based on a similar admissions at a public hospital that treats a large number of IBD patients.

Private and public hospitals derive their cost based on the Department of Health and Aging Public National Round for the relevant year, which in turn are based on reports from hospitals on expenditure from previous years. In this system each hospitalization is assigned a relative cost based on the intensity of resources used. A complex coding system (DRG- Diagnoses related groups) is used nation wide in Australia to reflect the weight of resources used for each admission (Weighted Inlier Equivalent Separation, WIES). In other words, the WIES is adjusted for time spent in hospital, and represents a relative measure of resource use for each episode of care in a DRG. An average length of stay is assigned to each DRG, but if a patient extends this average, there is capacity in the system for extra payment based on outlier cost estimates. This is usually at a reduced amount per day. An example of this WIES/DRG system is a liver patient admitted for 3 days before dying is assigned a WIES of 7.51, compared to a liver transplant patient requiring an ICU stay for 40 days has a WIES of 40.21. The WIES is multiplied out by the WIES price, which is the price paid per unit of WIES by the Department of Health (e.g. the 2014/2015 WIES value was $4385).

However, the WIES system does underestimate the true cost of an admission to the hospital on an individual patient basis. On average, it encompasses between 60-80% of the cost of the admission. Therefore, most hospitals also work off the cost weights that are calculated additionally and handed in to the Department of Health as a more accurate cost estimate. Cost weights represent a relative measure of resource used foe each episode of care in a DRG, and are calculated as the ratio of the average cost of all episodes in a DRG to the average cost of all episodes across all DRG’s. Victorian cost weights are developed each year using the costs of treating patients as reported to the Department of Health by
Victorian public hospitals. Cost weights are thought to be accurate representation of each episode of patient care.

Summarizing this process, it is the cost weight that is a true reflection of a patient’s admission. The reason this is important for this study is that Barwon Health (the major Geelong public hospital where most of the patients were admitted), was only able to supply the WEIS price, not the cost price, due to local practice (most admissions only have the WEIS price assigned). Using the WEIS price only would underestimate the cost of each admission to the health care system.

To get around this limitation, the principal researcher liaised with Clinical Costing Analyst at St Vincent’s Public Hospital, located in Melbourne, with the aim to calculate the cost weight for every admission to the Barwon Health hospital. This was possible as Barwon health provided a WEIS and DRG code as well as duration of stay for every study patient who had been admitted to the hospital during the study time. By using these values, and cross-referencing with the 2014-2015 WIES Victorian cost weights table, it was possible to calculate the cost weight for each admission based on the data given. This is the technique that is used by clinical costing staff in public hospitals to calculate the cost weights based on WIES and DRG codes.

Private hospitals use a very similar system based around DRG codes to obtain funding. There are some differences depending on the private health insurance company. There were two main private hospitals used by patients in this study, and direct costing data was accessed from these hospitals for these admissions. The additional cost of physician and/or surgeon fees was added on to the hospital cost, as this is a separate payment, unlike in public hospitals. The cost for these scheduled fees was derived from the Medicare Benefits schedule (www.mbs.gov.au).

The cost of all diagnostic tests was also based on the Medicare Benefits schedule, apart from endoscopy, which was collected directly from each of the service providers. In the majority of cases, gastroscopy and colonoscopy was performed in the hospital setting as a day procedure. To ensure accuracy, each patient
record was accessed to determine the exact number of investigations done during the first 12 months. This was entered onto the clinical database, and included gastroscopy, colonoscopy, flexible sigmoidoscopy, capsule endoscopy, and radiology. This was not feasible for pathology testing however (primarily blood tests) due to the large number of tests done per patient. A standardized cost based on practice guidelines (293) was calculated for pathology testing based on disease severity and therapies used. For example, patients with mild to moderate IBD on no immunomodulator were predicted to require twice yearly baseline bloods (full blood examination, electrolytes, liver function tests and c reactive protein). Those on immunomodulator therapy had a pre-immunosuppression screen added, as well as fortnightly tests for 2 months followed by second monthly. A similar formula was used for patients on anti-TNF α therapies.

Medication cost was based on what the treating specialist prescribed, including dose and duration. The cost of each medication was calculated from the Pharmaceutical Benefits Scheme (PBS), using the dispensed price for maximum quantity (DPMQ), which was adjusted based on length of treatment. For infliximab, the additional cost of a day procedure at the relevant hospital was added into the cost of the drug.

Outpatient visits to the treating Gastroenterologist/specialist were calculated based on the Medicare Benefits schedule.

All efforts were made to adhere to the criteria set out by the Quality of Health Economic Studies (QHES) instrument and recommended methods for economic evaluation in health care (290,294).

2.8.1 Data Linkage

The section above describes how cost was calculated based on active surveillance. Active surveillance allows for more accurate health cost analysis compared to other methods such as data linkage (295). Active surveillance was possible in this study as the number of patients was reasonable. In larger studies where patient numbers are in the thousands, active surveillance is not feasible.
Data linkage is then used in such studies. During this project, consideration of data linkage was given as a possible additional method of calculating total cost per patient. The advantage would have been verification of the cost calculated via active surveillance. Unfortunately, it was not possible to obtain data linkage results within the timeframe of this study. However, it is worthwhile to discuss the process of setting up data linkage as this was successful through the Australian Institute of Health and Welfare (AIHW), and can now be accessed for future interrogation of this cohort.

Data linkage refers to using identifiable patient information, such as name, date of birth and medicare number and linking this to multiple sources through the use of a whole range of datasets. These datasets include the National Death index, the Australian cancer Database, Medicare Benefits Schedule, Pharmaceutical Benefits Scheme and Admitted Episode datasets. Such linkages are possible through the use of an accredited Integrating Authority who collect the identifiable information, link it to the relevant dataset, receive information back and then de-identifying the data before feeding it back to the requesting party. One of the disadvantages of this process is that information received cannot be linked to a specific patient. It is possible to group patients together prior to the data linkage process so that those patients are then grouped together for cost analysis, for example, dividing the Crohn’s and Ulcerative colitis patients into two groups.

For this study, the relevant datasets for health cost analysis included the Medicare Benefits schedule (for outpatient visits to specialists); the Pharmaceutical Benefits Scheme (for medications used by each patient) and the Victorian Admitted Episodes Dataset and Victorian Emergency Minimum Dataset (for all admissions for each patient state wide). The latter two datasets relating to hospital admissions can be accessed through the Victorian Data Linkage System at the state Department of Health. The datasets related to Medicare Benefits and Pharmaceutical benefits are available through the Australian Institute of Health and Welfare (AIHW), who act as the Integrating authority.
Both parties were approached to commence the process of data linkage. The AIHW required an extensive Ethics application, which was undertaken and successfully gained (number: E02013/3/29). However, after successfully being granted Ethics permission, the AIHW notified the research team that due to a Governmental change of legislation, the Medicare Benefits Schedule was no longer able to data link via the AIHW. There is a possibility of this changing in the future, and at the moment the Ethics application remains valid if this becomes the case.

The process of data linkage through the Victoria Department of Health in relation to hospital admissions was also commenced. This included submission of paperwork relating to what outcomes are to be linked. Unfortunately the process that was commenced in 2013 is still pending (May 2015) due to significant backlog with the Health Department.

The methods set up for data linkage can be used in future health cost analysis in the established cohort.

2.9 Sources of Error

Errors may occur in any study design. Most sources of error in an observational study such as this are addressed by considering the external and internal validity of a study.

Internal validity refers to whether the observed outcomes can be attributed to the exposure (or disease, such as IBD) and not due to other causes (296). Put another way, it is the ability of a study to measure what it set out to measure (297). The presence of bias undermines the internal validity of a study. To minimize the impact of selection bias in this study, great care was taken to include all new cases of IBD in the Barwon area during the study period. In IBD, one way selection bias can occur is by omitting the mildest cases because these patients are less likely to need regular medical care due to the benign nature of the disease. To avoid this, the multiple source capture methodology was to ensure complete capture of all cases. So as to avoid over inclusion of cases, the diagnosis was reviewed at 3 months from diagnosis to ensure that the original
diagnosis was still correct. Confounding is another bias possible in observational studies, but can be controlled by using a number of statistical methods, including multivariate techniques such as multivariate logistic regression which were used in the analysis of this study (297). These techniques involve mathematical modeling to examine the potential effect of one variable while simultaneously controlling for the effect of many other variables.

External validity is the ability to generalize study results to a more universal population. This is one of the advantages of a population based observational study, as it tends to be associated with high external validity given the population is a representation of the ‘real world’. The most common reason for loss of external validity is a small sample size (297). In this research, a large base population size was chosen of over 250,000 to ensure this would not be the case. The incidence of IBD identified during the study is similar to other developed parts of the world such as Europe and disease course is comparable to other cohorts (9). This points to high external validity.

2.10 Data Security

The collection of personal identifying information imposes strict obligations on the organization acting as data custodian. Data must be collected, processed, stored and released by the clinical quality registry in accordance with the Australian Code for Responsible Conduct of Research (298,299) and with any relevant legislative requirements or regulations which govern collection and storage of health-related data.

Because of the complexities in ensuring data security, registries and clinical databases must be housed in an environment with extensive experience in handling confidential personal data. Data in this study was held under strict security arrangements and with procedures in place to ensure that access to data is restricted and released only in a strictly controlled fashion. The Department of Gastroenterology at St Vincent’s Hospital fulfils these requirements.

Importantly, the registry with the patient’s identifiable information was stored separately to clinical data gathered regarding the natural history and
questionnaire responses. The clinical information was stored in a re-identifiable manner, and only the research team was able link this back to the registry.

2.11 Collaborations

Collaboration was undertaken with two separate research groups that are also studying the incidence, natural history and possible environmental aetiological in IBD.

The ECCO-Epicom (European Crohn’s and Colitis Organization’s Epidemiological Committee) study was initiated as a prospective population-based cohort of unselected incident IBD patients with the aim of studying the occurrence and disease course of IBD in eastern and western Europe (9). Collaboration with this study began in 2011 (143) and to date has resulted in one publication on the initial presentation and disease course in the first 3 months of diagnosis (143). Results are comparable to our study in regards to incidence rates and early disease progression.

The Asia-Pacific Crohn’s and Colitis Epidemiology (ACCESS) study was conducted in 20 centres, in 12 countries across the Asia-Pacific. This is also a population-based study focusing on incidence, disease progress, environmental exposures prior to diagnosis and quality of life measurement. Collaboration with this group started in 2010 by Studd et al (3) when comparison was carried out on incidence rates of IBD between Australia and Asian countries. This showed that Australia had a much higher incidence of IBD. Since then, the collaboration has continued to include a comparison of disease phenotype and outcomes at 1 year and a comparison of environmental risk factor exposure in IBD between Australia and Asia (106).

The papers that formed part of the collaboration are attached in Appendix 5.
2.12 Statistical Analysis

Incidence rates were calculated by comparing those diagnosed with IBD to the total population at risk to determine the crude incidence rate of disease. The crude rate was then directly age-standardized to the World Health Organization world standard population to enable comparison to international figures.

For the natural history part of the study, possible associations between objective outcomes (surgery, hospitalisation and biological therapy) and multiple co-variants (age, gender, disease location, disease behaviour and perianal disease in CD, smoking, initial treatment step, CRP) were analyzed by Cox regression analysis using the proportional hazard assumption, and associations were visualized using the Kaplan-Meier plots. A P value of < 0.05 was considered significant.

To determine which clinical factors were significant in predicting disabling disease univariate analysis was done using the Fisher’s test, and multivariate analysis was done by logistic regression.

For the case control study looking at environmental exposures prior to diagnosis, odds ratios (OR) with 95% CIs were calculated to examine difference between those diagnosed with CD and UC and controls on relevant environmental factors. All controls were pooled together. Separate binary logistic regressions was used.

Health cost analysis was done through active collection of all resources used by the patients and summed together. Both the median and mean cost was calculated for CD and UC, respectively. The median cost is more representative of the outlay in most of the patients without introducing bias from a minority of patients with high cost. This was done as the cost is the health cost was skewed to the right. However, mean costs are also important for planning future health care budgets as they account for overall expenditure and were also included. To analyze the high cost outliers in more detail, patients were identified to be high cost by the statistically verified method (Q3+1.5IQR, where IQR is the interquartile range) (278,300). To determine which clinical variables may
predict future high IBD health cost, univariate analysis was done using the Mann Whitney rank sum due to the skewed distribution of cost. The dependent variable was total cost with the independent variables being diagnosis, age, gender, disease location, disease behaviour and perianal disease (Crohn’s only), smoking and steroid/immunomodulator at diagnosis. A threshold of p<0.2 was used to determine which variables would be incorporated into a multivariate (negative binomial) regression analysis, with manual backwards step-wise techniques employed to identify the variables independently associated with cost. All statistical tests were two-sided, with p<0.05 considered to indicate statistical significance.

Statistical analysis was performed using SPSS version 22 (IBM Corp. Armonk, NY.).
Chapter 3  Incidence, Disease Course and Clinical Predictors of Severe Disease in Inflammatory Bowel Disease

3.1 Introduction

Previous research in the Barwon area has shown a high burden of disease with crude incidence rates ranging from 24.2 to 29.1 per 100,000 (4,301). This offers an ideal opportunity to establish a registry that can be used as a platform to study the disease course of IBD in a population based cohort. As already discussed in Chapter 1, there have been many advances in recent years in both diagnostics and management of these diseases but there is a paucity of population based data about the impact of these changes on objective disease outcomes such as surgery and hospitalization rates. CD and UC can have a variable disease course, from mild to severe and debilitating, and it remains unclear at diagnosis what disease progression will be. It’s important to identify early prognostic features so those with severe disease can be managed aggressively to prevent disease complications.

Population-based studies are the best means to answer these important questions. This Chapter presents the results from a population based inception cohort study of patients with IBD, with the following aims:

1) To prospectively recruit new incident cases of IBD (2011-2013) into an established registry in a well-defined geographical area (Barwon, Victoria) in Australia.

2) To assess the early disease course through objective outcome measures such as medication use, surgery and hospitalization.

3) To identify early clinical prognostic factors associated with severe disease.
The methodology is described in detail in Chapter 2. Section 3.2 is a PDF of a paper published in *Journal of Gastroenterology and Hepatology*. This covers the bulk of the results in relation to the aims listed here. Section 3.3 discusses the results on the clinical indices that were measured in patients to assess disease progress. These were omitted from the paper published due to the word restriction. Section 3.4 will include discussion of how these additional results contribute to the overall results presented in the paper.
3.2 PDF of Paper: Prospective Population-Based Cohort of Inflammatory Bowel Disease in the Biologics Era: Disease Course and Predictors of Severity

GASTROENTEROLOGY

Prospective population-based cohort of inflammatory bowel disease in the biologics era: Disease course and predictors of severity

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Key words
Crohn’s disease, diverticular disease, epidemiology, incidence, inflammatory bowel disease, natural history, ulcerative colitis.

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Conference presentation: Australian Gastroenterology Week 2014: ECCO Vienna 2013 (poster); ECCO Barcelona 2015 (oral presentation).

Abstract
Background and Aim: We have previously found high incidence of inflammatory bowel disease (IBD) in Australia. A population-based registry was established to assess disease severity, frequency of complications, and prognostic factors.

Methods: Incident cases were prospectively identified over 4 years. Early disease severity was assessed according to need for hospitalization and rescue surgery and medication use.

Results: We report on the early outcomes (median 18 months, range 12–60 months) for 282 patients comprising 146 with Crohn’s disease (CD), 96 with ulcerative colitis (UC), and 10 IBD undifferentiated. Eighty-seven percent of CD patients had inflammatory disease at diagnosis, and this reduced to 73% at 5 years (n = 38). Immunomodulators were prescribed in 57% of CD patients and 19% with UC. A third of all CD patients were hospitalized, the majority (77%) in the first 12 months. Risk factors for hospitalization included penetrating, perianal, and ileocolonic disease (P < 0.05). Twenty-four percent of UC patients were hospitalized, most within the first 12 months. Intestinal resection rates were 13% at 1 year in CD and 26% at 5 years. Risk factors include penetrating and strictureing disease (P < 0.001) and ileal involvement (P < 0.05). Colectomy rates in UC were 2% and 13% at 1 and 5 years. High C-reactive protein (CRP) at diagnosis was associated with colectomy.

Conclusions: A high rate of inflammatory disease, frequent immunomodulator use in CD, and a low rate of surgery in both CD and UC were identified. UC ileal involvement and complex disease behavior are associated with a more severe disease course, while in UC a high CRP predicted this outcome.

Introduction
Inflammatory bowel disease (IBD), including Crohn’s disease (CD), ulcerative colitis (UC), and IBD undifferentiated (IBDU) are chronic disorders of the gastrointestinal tract that exert a major impact on an individual’s quality of life and result in very high usage of health-care resources. Disease outcomes, such as a need for surgery and hospitalization, are objective measures that can be used as surrogate markers of disease severity. Clinical course can vary from mild to severe and debilitating, and it remains unclear at diagnosis what disease progression will be. Identifying early clinical prognostic factors that predict a severe course is important, thereby enabling the option for more aggressive medical therapy to minimize structural bowel damage and complications of disease.

In recent years, there has been greater emphasis on intensive therapy and disease monitoring to reduce disease activity through the use of advanced imaging, biologics, and drug levels. The greatest impact has been the introduction of biological therapy. However, it remains unclear if these advances are translating into better disease outcomes in the community and at what cost.

Population-based studies are the best means to answer these important questions, since hospital-based studies can introduce bias. Previous studies have shown variation in disease outcome measurements, such as surgery and hospitalization rates. In most of these studies, the impact of biological therapies is not clear, since patient recruitment pre-dated widespread adoption of anti-TNF (anti-tumor necrosis factor) antibody use.

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We undertook a population-based inception cohort study of patients with IBD in a well-defined regional geographical area to investigate the disease course in Australia. The aims of the study were to validate the previously reported high incidence, to assess the early course of disease as measured by objective markers such as surgery and hospitalization rates, and to identify early clinical prognostic factors associated with severe disease.

Methods

Population and case ascertainment. Incident cases of IBD in the years of 2007–2008 and 2010–2013 in the Barwon area, Victoria (pop. 934,426),16 were prospectively identified through methods described below and asked to participate in the IBD registry through an opt-out consent. The registry was used as a basis to collect outcome data on the natural history, quality of life impact, environmental factors, and health-care cost.

Incident cases were identified by a multifaceted approach to ensure complete population case identification.15,17,19 Patients were recruited from general practitioners, specialist gastroenterologists, surgeons, pediatricians, as well as three monthly computer searches through the hospital coding department, the main pathology center (St John of God), and the local endoscopy centers. The search terms included “Crohn’s disease,” “ulcerative colitis,” and “colitis.” A computer search of the main hospital pharmacy was done of the terms “sulfasalazine,” “mesalazine,” “azathioprine,” “mercaptopurine,” “infliximab,” and “adalimumab.” Case notes for each positive hit were then reviewed to determine if it was a true incident case. From 2010 to 2013, patients were recruited prospectively into the registry at time of diagnosis. The incident cases diagnosed in 2007–200816 were recruited retrospectively into the registry in 2012 to provide a longer follow-up time as a comparison.

Classifications and definitions. The diagnosis of CD, UC, or IBDU was based on the Copenhagen diagnostic criteria.19,20 Disease phenotype was defined by the Montreal classification.11,12 Treatment was grouped into five levels of ascending potency, similar to the method described in the EpCoMo study:12 5-aminoalicyclics (SASA) (oral and/or topical SASA treatment +/− topical steroids), glucocorticosteroids (GCS) (oral or intravenous), immunomodulators (IM) (azathioprine, mercaptopurine, methotrexate), biologicals (infliximab or adalimumab), and surgery (reseuctive surgery or major abdominal surgery). All IMs are combined into one category as over 90% of patients were prescribed a thiopurine.

To identify predictive factors of a subsequent disabling course in the first year of diagnosis, we defined CD as disabling based on criteria previously identified in a hospital-based study and validated in an additional study.22,23 There is debate regarding what parameters represent disability in CD. The current definition has its limitations, including possible overinclusion of patients, as 80% of patients were found to have disabling disease in the study, which limits its clinical utility. However, this is the only published definition of disabling disease. We have modified the definition by excluding IM use from the criteria and replacing chronic relapsing symptoms with active disease at final follow-up to reduce recall bias. Therefore, definition of disabling CD was made if one of the following criteria was present at 12 months: > 2 courses of steroids, further hospitalization after diagnosis, ongoing active disease, intestinal resection, and perianal surgery. For the first time, an attempt was made to define disabling UC by using the same criteria (excluding perianal surgery).

Data collection and validity. Clinical progress was assessed prospectively from time of diagnosis for a minimum of 12 months (range: 12 months–5 years) through access to case notes, hospital records, investigations, and liaison with the treating doctor. For those diagnosed in 2007–2008, early disease progress from time of diagnosis was assessed retrospectively through the same methods. Data collected included demographics, disease classification, disease activity, medications, surgery, hospitalization, malignancy, and death.

Statistical analysis. Statistical analysis was done using STATA (version 12.1; STATA Corporation, College Station, TX, USA). Incidence rates were compared with the total population at risk to determine the crude incidence rate of disease, which was then age-standardized to the World Health Organization (WHO) standard population. Possible associations between primary endpoints (surgery, hospitalization, and biological therapy) and multiple covariates were analyzed by Cox regression analysis using the proportional hazard assumption, and associations were visualized using the Kaplan–Meier plots. A P-value of < 0.05 was considered significant. Univariate analysis for associations with disabling disease was done using the Fisher’s test, and multivariate analysis was carried out by logistic regression.

Ethical considerations. This study was approved by Barwon Health’s ethics department and was carried out according to the local regulations.

Results

Incidence. Two hundred seventy-eight patients were diagnosed with IBD in 2007–2008 and 2010–2013. The annual age-adjusted WHO incidence rate of IBD was 21.83 per 100,000, the CD rate was 11.6–17.4 per 100,000, the UC rate was 7.5–11.2 per 100,000, and the IBDU rate from 0.5 to 2 per 100,000. The incidence rate was stable over the years, with no statistically significant change.

Patient demographics. Of the 278 incident cases of IBD, 16 (6%) patients were lost to follow-up, 8 (3%) were rediagnosed as not IBD, 1 (0.4%) was not a true incident case, and 1 (0.4%) was not suitable for the study due to a complex social situation. Therefore, 252 (91%) patients were recruited to the registry. One hundred forty-six (58%) had CD, 90 (58%) had UC, and 10 (4%) had IBDU, with a median follow-up of 18 months (range 12–82 months).

Patient demographics are listed in Table 1, including disease location. Figure 1 illustrates the progression of disease behavior in CD from diagnosis until maximum follow-up of 5 years. The rate of inflammatory disease at 5 years was 76%, 16% had penetrating disease, and 8% had strictureting.
Table 1 Distribution of patient characteristics at diagnosis according to a non-disabled or disabling disease course at follow-up

<table>
<thead>
<tr>
<th>Variables</th>
<th>Clinical course during follow-up</th>
<th>Statistical univariate test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-disabling % (n = 98)</td>
<td>Disabling % (n = 48)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>54</td>
<td>29</td>
</tr>
<tr>
<td>Female</td>
<td>44</td>
<td>19</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25 years</td>
<td>36</td>
<td>42</td>
</tr>
<tr>
<td>≥ 25</td>
<td>64</td>
<td>58</td>
</tr>
<tr>
<td>Location at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ileal</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td>Ileocolic</td>
<td>31</td>
<td>25</td>
</tr>
<tr>
<td>Colonic</td>
<td>36</td>
<td>42</td>
</tr>
<tr>
<td>Upper GI</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Disease behavior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory</td>
<td>86</td>
<td>66</td>
</tr>
<tr>
<td>Strictures</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Penetrating</td>
<td>6</td>
<td>19</td>
</tr>
<tr>
<td>Periostal</td>
<td>5</td>
<td>29</td>
</tr>
<tr>
<td>GC at diagnosis</td>
<td>38</td>
<td>54</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variables</th>
<th>Clinical course during follow-up</th>
<th>Statistical univariate test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-disabling % (n = 72)</td>
<td>Disabling % (n = 24)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>33</td>
<td>63</td>
</tr>
<tr>
<td>Female</td>
<td>67</td>
<td>37</td>
</tr>
<tr>
<td>Age &lt; 25</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>Age ≥ 25</td>
<td>76</td>
<td>75</td>
</tr>
<tr>
<td>Location at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fecalis</td>
<td>33</td>
<td>29</td>
</tr>
<tr>
<td>Left-sided</td>
<td>31</td>
<td>38</td>
</tr>
<tr>
<td>Pancolitis</td>
<td>36</td>
<td>33</td>
</tr>
<tr>
<td>Steroids at diagnosis</td>
<td>28</td>
<td>38</td>
</tr>
<tr>
<td>CRP &gt; 10 at diagnosis</td>
<td>22</td>
<td>29</td>
</tr>
</tbody>
</table>

**Significant on multivariate analysis. ***No significant variables on multivariate analysis.

Protective against disabling disease.

CRP, C-reactive protein; GCS, glucocorticosteroids; GI, gastrointestinal.

Outcomes.

Therapeutic strategy. The highest level of treatment at diagnosis and at maximum follow-up is summarized in Table 2. The progression of treatment steps during the course of disease is shown in Figure 2.

Steroids were used in 108 CD patients (74%), and 23 (16%) required two courses. In UC, 60 (63%) of patients used at least one course of steroids, and 5 (5%) had two courses. IMs were prescribed in 83 CD patients (57%), 18 UC patients (19%), and in 4 BDUs (40%).

Adverse events to thiopurines occurred in 21 CD patients (25%) and 2 UC patients (11%) at a median of 1 month (range 1–24 months). The adverse events included pancreatitis 6 (6%), arthralgia 4 (4%), rash 4 (4%), headache 2 (2%), gut symptoms including nausea and diarrhea 4 (4%), allergy 4 (4%), myelosuppression 1 (1%), hepatitis 3 (3%), and another in 4 (4%). All but one patient ceased treatment. Two patients with pancreatitis were switched to mercaptopurine and had a second episode requiring cessation.

An adverse event to ASA’s occurred in 22 of the 165 patients (13%), and in the majority (73%) salicycylate was the culprit. The adverse events included rash in 5 (23%), headache 4 (18%), arthralgia 4 (18%), gut symptoms including nausea, vomiting, and diarrhea in 3 (14%), and other nonspecific symptoms in 7 (32%).
Biological therapy. Eighteen CD patients (13%) were started on a biological therapy (eight infliximab, nine adalimumab). Of these, two (11%) had stricture, five (28%) penetrating, and nine (50%) perianal disease. Until recently, biological therapy was not reimbursed in the treatment of UC, therefore it was only used in two (2%) patients. Adverse events occurred in one patient (headaches).

Cox regression analysis found that among CD patients, age < 25 at diagnosis (Hazard ratio [HR] 4.8, \( P = 0.01 \)), ileocolonic (HR 4.6, \( P = 0.03 \)), and perianal disease (HR 9, \( P < 0.001 \)) were risk factors for biological therapy.

Surgery. Twenty-seven (18%) of CD patients required resection surgery during a median follow-up of 18 months (six subtotal colectomies, one hemicolectomy). The 1- and 5-year resection rates were 13% (19 of 146) and 23% (9 of 38), respectively. Of those who had surgery, seven (26%) had strictureing disease and eleven (41%) had penetrating disease. The maximum therapy before resection included SASA’s in 1 (4%), GCS in 3 (11%), IM in 15 (56%), and biological therapy in 3 patients (11%).

Eighteen patients had perianal disease and 13 (72%) required at least one operation; four patients required two or more operations.

The colectomy rate in UC at median follow-up of 18 months was 6% (6 patients), of which 2 (2%) were in the first year. The 5-year colectomy rate was 13% (3 of 23 patients). The maximum therapy before colectomy included SASA in one patient, GCS in one patient, IM in two patients, and biological therapy in one patient.

In CD, the Cox regression analysis identified those with ileal and ileocolonic location (L2 vs L1 HR 5.1; L2 vs L3 HR 5.7; \( P < 0.001 \)), as well as strictureting and penetrating behavior (B1 vs B2 HR 10.6; B1 vs B3 HR 21; \( P < 0.001 \)) at an increased risk of surgery.

In UC, an elevated CRP (over 10) at diagnosis was associated with risk of surgery (HR 10.7, \( P = 0.04 \)). Survival plots for disease extent and risk of surgery shown in Figure 3.

Hospitalization. Fifty-three (36%) of CD patients required hospitalization, of which 32 (22%) were hospitalized in the first month and 41 (28%) at 1 year. The 5-year hospitalization rate was 37%.

Factors predictive of disabling disease. Forty-eight (33%) CD patients were classified as having disabling disease, as were 24 (25%) UC patients. Predictive factors for disabling disease in CD on univariate analysis were perianal disease (\( P < 0.001 \)), penetrating disease (\( P = 0.04 \)), and need for steroids at diagnosis (\( P = 0.05 \)). Inflammatory disease was protective (\( P = 0.05 \)). In UC, male gender (\( P = 0.010 \)) was associated with higher risk of disabling disease. Multivariate analysis found that in CD, penetrating disease (odds ratio [OR] 2.4, \( P = 0.04 \), confidence interval [CI] 2.54–4) and steroids at diagnosis (OR 2.3, \( P = 0.034 \), CI 1.06–5) were independently predictive.

Death/malignancy. Three patients died (1.2%, 2 CD, 1 UC), none of related IBD causes. The first patient died from metastatic transitional cell carcinoma, with no exposure IM or biological therapy; the second patient from esophageal adenocarcinoma diagnosed at the same time as CD and the last from an intracerebral hemorrhage on warfarin.

Discussion

This study confirmed high incidence rates of IBD in Australia. It is one of the highest in the world, along with Canada,24 Denmark,25,26 and New Zealand.27,28 CD is more common than UC in Australia. This is similar to New Zealand29,30 and Northern France.31 In contrast, in Eastern Europe, Denmark, the Netherlands, and parts of Asia, UC is more common than CD,32,33 while in Canada the rates are equal.34 The reasons for these differences are unknown but may point to different environmental etiological factors between the countries.

We have shown that early disease progression in CD is not as aggressive as previously reported. At 18 months, 80% of patients had inflammatory disease. Further follow-up over time will indicate whether this pattern of predominantly inflammatory behavior continues. It seems likely given that in the subgroup of 38 patients followed for 5 years, only 26% went on to develop strictureing or penetrating disease. A study from New Zealand found 40% of patients had complicated disease at 5 years.35 This is in contrast to a large multicenter French experience that showed that 50% developed complicated disease at 5 years.36

Hospitalization and surgery are objective surrogate markers of disease severity. Over a third of patients with CD (36%) required admission and the majority at diagnosis (22%) or within the first year (28%). Among UC patients, most hospitalizations also occurred within the first year of diagnosis (17% of the total 24%). Similar findings were shown in CD patients in North America and Europe, with annual hospitalization rates of 25%, followed by a significant decline after the first year of diagnosis.37,38 The need
for hospitalization in the first year of diagnosis suggests a more severe phenotype in a proportion of patients. The intestinal resection rates were 13% at 1 year and 23% at 5 years in Crohn’s patients, suggesting the greatest risk is in the first year of diagnosis. Strictures and penetrating disease were found to be risk factors, as was ideal disease location. In UC patients, colectomy rates were low at 2% at 1 year and 13% at 5 years and comparable to recent population-based studies.28,29,35 An elevated CRP (> 10) at diagnosis was a risk factor for colectomy, which has previously been shown at a higher level of 33.30

Our 1-year intestinal resection rates in CD are much lower to studies conducted over a decade ago with rates of 21–29%,7,28 but comparable to recent studies.31–46 Similarly, 5-year resection rates were higher in the older studies at 25–39%.7,28 A possible explanation for fall in surgery rates in our cohort is more frequent IM use and the introduction of biological therapies. A Hungarian population-based study found that decline in surgery was independently associated with early use of IM.42

A third of CD patients and 25% of UC patients suffered from disabling disease. In the absence of a universally accepted definition of disabling disease, one previously published was used.12,47 This is the first study to use the definition of disabling disease in UC patients, but no clinical factors were found predictive. The risk factors for developing disabling CD were steroid use and penetrating disease at diagnosis. Patients who present with these features should be reviewed regularly to prevent irreversible bowel damage. These patients may benefit most from a step-down approach to therapy, with early immunosuppression, but further studies are required to validate this.48

Table 2. Patient characteristics and outcomes of 252 incident IBD patients

<table>
<thead>
<tr>
<th></th>
<th>CD</th>
<th>UC</th>
<th>IBDU</th>
<th>Univariate test*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of patients (%)</td>
<td>146 (58%)</td>
<td>96 (38%)</td>
<td>10 (4%)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>No. of patients diagnosed 2007–2008</td>
<td>39 (15%)</td>
<td>23 (9%)</td>
<td>1 (1%)</td>
<td>—</td>
</tr>
<tr>
<td>Pediatric cases (age ≤ 19)</td>
<td>25 (11%)</td>
<td>12 (13%)</td>
<td>1 (1%)</td>
<td>—</td>
</tr>
<tr>
<td>Male (%)</td>
<td>68 (47%)</td>
<td>39 (41%)</td>
<td>6 (67%)</td>
<td>NS</td>
</tr>
<tr>
<td>Female (%)</td>
<td>80 (53%)</td>
<td>57 (59%)</td>
<td>4 (33%)</td>
<td>—</td>
</tr>
<tr>
<td>Age at diagnosis (range)</td>
<td>65 (11–80)</td>
<td>40 (11–90)</td>
<td>58 (18–75)</td>
<td>P = 0.04</td>
</tr>
<tr>
<td>Median time to diagnosis (range)</td>
<td>6.4 (0.5–79)</td>
<td>3 (0–73)</td>
<td>3 (1–49)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>19 (13%)</td>
<td>5 (5%)</td>
<td>0</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Former smoker</td>
<td>13 (9%)</td>
<td>17 (16%)</td>
<td>3</td>
<td>—</td>
</tr>
<tr>
<td>Disease extent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proctitis</td>
<td>—</td>
<td>31 (32%)</td>
<td>1 (10%)</td>
<td>—</td>
</tr>
<tr>
<td>Left-sided colitis</td>
<td>—</td>
<td>30 (31%)</td>
<td>4 (44%)</td>
<td>—</td>
</tr>
<tr>
<td>Pericolic</td>
<td>—</td>
<td>26 (26%)</td>
<td>4 (44%)</td>
<td>—</td>
</tr>
<tr>
<td>Disease location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1: terminal ileum</td>
<td>46 (32%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>L2: caecum</td>
<td>44 (29%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>L3: ileocecal</td>
<td>55 (38%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>+ L4: upper GI</td>
<td>17 (12%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Disease behaviour†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory</td>
<td>117 (80%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Strictureing</td>
<td>15 (10%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Penetrating</td>
<td>15 (10%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Perineal</td>
<td>18 (12%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Highest level of treatment at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>8 (5%)</td>
<td>0</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>SACSA</td>
<td>34 (23%)</td>
<td>66 (69%)</td>
<td>5</td>
<td>—</td>
</tr>
<tr>
<td>Steroid</td>
<td>53 (36%)</td>
<td>26 (27%)</td>
<td>3</td>
<td>—</td>
</tr>
<tr>
<td>Immunomodulators</td>
<td>31 (25%)</td>
<td>1 (1%)</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Biological therapy</td>
<td>1 (1%)</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Surgery</td>
<td>14 (9%)</td>
<td>2 (2%)</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Highest level of treatment during flares</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>8 (5%)</td>
<td>0</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>SACSA</td>
<td>23 (16%)</td>
<td>40 (42%)</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>Steroid</td>
<td>27 (18%)</td>
<td>31 (32%)</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>Immunomodulators</td>
<td>47 (32%)</td>
<td>17 (18%)</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>Biological therapy</td>
<td>14 (10%)</td>
<td>2 (2%)</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Surgery</td>
<td>27 (18%)</td>
<td>6 (6%)</td>
<td>0</td>
<td>—</td>
</tr>
</tbody>
</table>

*P-values are given for P < 0.05.
†At 12 months.
SACSA, 5-aminosalicylates; CD, Crohn’s disease; GI, gastrointestinal; IBD, inflammatory bowel disease; IBDU, IBD unclassified; UC, ulcerative colitis.
The early use of IM in CD patients was high in this study (57% at 18 months) compared with older studies that observed lower early use, ranging from 3% to 25% at 1 year and from 21% to 45% at 5 years.12,20,17 In UC, IM use was also more common at 19%, which is twice as high compared with previous studies (7–13%).12,20,44

This is one of the first population-based studies to have a significant proportion of CD patients on biological therapy early in the diagnosis (13%), which has only been shown in one previous study (18%).15 In comparison, earlier studies had rates of 4–10%.12,13,15,16

It is possible that the intensive therapy in our cohort, including high IM and more biological use, has resulted in a favorable disease course, with less complicated disease behavior and low surgery rates. However, due to the observational nature of this paper, other confounding factors may also play a role, such as change in surgical practice or more aggressive monitoring of patients.

An important finding of this study is the frequent adverse events to thiopurines, as 25% of CD and 11% of UC patients experienced these, necessitating cessation of therapy. This is higher than previously reported and may reflect the “real-life” use of these medications compared with clinical trials.

The strengths of this population-based study lie in a prospective recruitment of newly diagnosed incident cases in a well-defined geographical area. Follow-up was excellent at over 90%. This was an observational study and therefore represents the true community-based management of a patient with IBD outside of controlled trials. Finally, the outcomes we focused on were objective measures of disease course, such as surgery rates and hospitalization.

This study does have some limitations. By its nature, as an observational study, only associations can be made. Therefore, findings such as the increasing use of IM and biological therapies, which has also coincided with low surgery rates, suggest an association between the two, but other confounders may be at play. Also, a small proportion of the patients were recruited retrospectively.

In conclusion, this first Australian population-based study of IBD shows favorable early outcomes for CD and UC patients with predominantly inflammatory disease behavior for the former and modest surgical rates in all patients. After the first year of disease, the risk of hospitalization and surgery declines. IM and biological therapy use is common, and ongoing follow-up will determine the impact on disease course. Early clinical predictors of severe...
disease in CD include complex disease behavior and steroids at diagnosis.

References
34 Nguyen GC, Negen J, Shaw S, Bernstein CN. Outcomes of patients with Crohn’s disease improved from 1988 to 2008 and were associated with increased specialist care. Gastroenterology 2011; 141: 90–7.


### 3.3 Disease Activity Based on Clinical Indices

As discussed in the Methods chapter, the clinical indices of Harvey Bradshaw Index (HBI) and the Simple Clinical Colitis Index (SCCI) were used to assess disease activity in CD and UC, respectively. This was done by the treating physician at or close to time of diagnosis (within 3 months) and at final follow up.

Clinical index assessments were completed in 67 (62%) CD and 41 (56%) UC patients. The results are illustrated below in Figure 3.

The number of CD patients in remission as per the HBI increased from 32% immediately after diagnosis to 88% at the final follow up (median of 18 months). There was a decrease in the number of patients with moderate (39% to 4%) and severe disease activity (4% to 0%) but the number of patients with mild disease remained the same (29%).

The number of UC patients in remission as per the SCCI increased from 13% immediately after diagnosis to 73% at the final follow up. Mild/moderate disease remained relatively stable (27% to 20%) while the number of patients with severe disease decreased from 60% to 7%.
Figure 3: Disease activity as per the HBI (Harvey Bradshaw Index) in Crohn’s disease and the SCCI (Simple Clinical Colitis Index) in Ulcerative colitis. % At diagnosis - within 3 months of diagnosis; % at final follow up - median 18 months.
3.4 Discussion

The disease activity, as assessed by the HBI and SCCI, indicate a favourable disease course in this cohort, and corresponds to the other markers of disease severity reported in the paper, including low rates of intestinal surgery and low rate of progression to complex disease behaviour in CD.

There was an increase in the number of patients in remission and with mild disease at the median follow up of 18 months as compared to time of diagnosis. There was also a decline in the number of patients with moderate and severe disease activity during this time period. This was most marked in CD, with 4% of patients with moderate disease at final follow up, and none with severe disease activity. In UC, there was a decline in the number of patients with severe disease from 60% to 7%.

Around time of diagnosis 29% CD and 13% UC patients were classified to be in remission. This suggests a very quick resolution of symptoms or the presence of very mild symptoms, both of which occur with milder disease. Future longitudinal research of these mild cases will be useful to determine if these patients continue to exhibit a milder phenotype long term.

The paper in the first part of this chapter discusses other outcomes including treatment strategies, as well as hospitalization and intestinal resection rates. Predictors of the latter were identified. Of note, colectomy rates were very small in the UC patients (6 patients only). This low rate of colectomy is reassuring for patients. But as a result, further analysis to identify risk factors for colectomy was underpowered. This can be seen in Figure 3, as it displays the cumulative probability of colectomy based on disease location at diagnosis. It found that those with left sided colitis had a higher probability of colectomy compared to pancolitis (which is both counterintuitive and against previous literature). This is likely a misrepresentation due to the small number of patients undergoing surgery.

There are a number of limitations to address regarding the use of the HBI and SCCI. Firstly, there was incomplete data. The indices need to be done
prospectively at time of clinical review and so patients diagnosed in 2007/2008 were excluded as these patients were recruited retrospectively into the registry. Also, it was dependent on the clinician finding the time to do this assessment at the review. Finally, the HBI and SCCI are simplified indices shown to have good correlation to more complex scoring systems, but this correlation is not perfect and there are limitations on how accurate they are in gauging disease activity (286).

In conclusion, the disease activity indices show an optimistic early disease course in this local population based cohort of CD and UC. This correlates to the favourable outcomes discussed in the paper in this Chapter. These outcomes included low risk of disease progression to complicated behaviour in the CD patients, low rates of intestinal surgery in both CD and UC, and hospitalization rates that plateau after the first 12 months. These outcomes have improved in comparison to historical population based cohorts and correspond to frequent IM and biological therapy. Future follow up of this cohort will determine if the disease severity will remain less severe with time.
Chapter 4  Influence of Environmental Exposures on the Risk of Developing Inflammatory Bowel Disease

4.1 Introduction

The incidence of Inflammatory Bowel Diseases (IBD) is on the rise globally and varies in different populations (1). Current understanding of the pathogenesis suggests an interplay between genetic susceptibility of the immune system to changes in microbiota, likely due to environmental exposures that trigger a dysregulated immune response, (41) (42). The changing epidemiology globally offers an opportunity to study the impact of environmental drivers on disease aetiology. The incidence of IBD has stabilized in places such as North America, Northern Europe and Australia after a marked increase over half a century (1) (7) (302), in comparison to Denmark that shows a continual rise in incidence (6). Eastern Europe and Asia have historically had much lower rates of IBD but as they become more westernized in diet and lifestyle, the rate of IBD is increasing (3) (2) (34). This rapid rise in incidence over a few decades strongly points to the environment playing a significant role in disease aetiology.

Smoking (122,303) (83) (106) and appendicectomy (38,83,304) are the strongest exposures that have been shown in studies to be associated with IBD. Dietary factors are likely to have an impact, possibly through their role on gut microbiota, but studies so far show contradictory associations. It is intuitive to study such environmental associations when the disease pattern is changing or emerging at a rapid rate. We have previously documented that the Barwon area in Australia has one of the highest incidence and prevalence rates of IBD in the world (4) (301) and it is important to employ epidemiological tools in such a population to determine possible aetiologically factors.
In this part of the study, the aim was to conduct a case control study assessing environmental exposures prior to diagnosis of IBD in a population-based cohort in Barwon, Australia.

4.2 Results

There were 132 incident cases (81 Crohn’s Disease, CD, and 51 Ulcerative Colitis, UC) from the IBD registry (53%) and 104 controls that replied to the IOIBD (International Organization of Inflammatory Bowel Diseases) environmental questionnaire. The majority replied to the questionnaire within 6 months of diagnosis, except for those diagnosed in 2007/2008 (n =21) who did so retrospectively 4 to 5 years after diagnosis. The patient characteristics are listed in Table 5.
Table 4.1- Patient characteristics of 132 incident cases of IBD who participated in the environmental case control study.

<table>
<thead>
<tr>
<th></th>
<th>CD</th>
<th>UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. Patients (%)</td>
<td>81 (62%)</td>
<td>51 (39%)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>36 (44%)</td>
<td>22 (43%)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>45 (56%)</td>
<td>29 (57%)</td>
</tr>
<tr>
<td>Age at diagnosis (range)</td>
<td>37 (11-75)</td>
<td>40 (11-76)</td>
</tr>
<tr>
<td>Median time to diagnosis in months (range)</td>
<td>6.4 (0.5-79)</td>
<td>3 (0-73)</td>
</tr>
<tr>
<td>First degree relative</td>
<td>8 (10%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Extra intestinal complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint</td>
<td>7 (9%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Skin</td>
<td>4 (5%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Eye</td>
<td>1 (1%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Disease extent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proctitis</td>
<td>-</td>
<td>15 (29%)</td>
</tr>
<tr>
<td>Left sided colitis</td>
<td>-</td>
<td>21 (41%)</td>
</tr>
<tr>
<td>Pancolitis</td>
<td>-</td>
<td>15 (29%)</td>
</tr>
<tr>
<td>Disease location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1: terminal ileum</td>
<td>30 (37%)</td>
<td>-</td>
</tr>
<tr>
<td>L2: colonic</td>
<td>16 (20%)</td>
<td>-</td>
</tr>
<tr>
<td>L3: ileocolonic</td>
<td>35 (43%)</td>
<td>-</td>
</tr>
<tr>
<td>+L4: upper GI</td>
<td>9 (11%)</td>
<td>-</td>
</tr>
<tr>
<td>Disease behaviour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory</td>
<td>62 (78%)</td>
<td>-</td>
</tr>
<tr>
<td>Stricturing</td>
<td>11 (14%)</td>
<td>-</td>
</tr>
<tr>
<td>Penetrating</td>
<td>7 (9%)</td>
<td>-</td>
</tr>
<tr>
<td>Perianal</td>
<td>15 (19%)</td>
<td>-</td>
</tr>
</tbody>
</table>
4.2.1 Family History

A total of 10% (8 patients) with CD had a first degree relative with a history of IBD. In UC, this was the case in 8% (4) patients. In the control group, there were no individuals with a first degree relative with IBD.

The rest of the environmental exposures that were found to be statistically significant between controls and incidence cases are listed next and summarized in Table 6 below.

4.2.2 Childhood Immunity and Infections

Chicken pox infection as a child was higher amongst CD patients compared with healthy controls (OR 3.9, CI 1.61-9.4), as shown in Table 6. Other childhood diseases including pertussis, measles, rubella, mumps and scarlet fever were not significant.

History of a tonsillectomy as a child was more likely in CD patients (OR 1.74, CI 1.15-2.6). History of appendicectomy and cholecystectomy were not significant in UC and CD.
Table 4.2- Comparison of childhood immunological exposures and infections in Crohn’s and Ulcerative Colitis compared to controls.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Control</th>
<th>CD</th>
<th>UC</th>
<th>CD vs. controls (p value)</th>
<th>Odds ratio (95% CI)</th>
<th>UC vs. controls (p value)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonsillectomy*</td>
<td>16 (21.9%)</td>
<td>27 (45.8%)</td>
<td>9 (22.5%)</td>
<td>0.003</td>
<td>1.74 (1.15–2.6)</td>
<td>0.943</td>
<td></td>
</tr>
<tr>
<td>Appendicectomy</td>
<td>9 (12.3%)</td>
<td>12 (21.1%)</td>
<td>4 (10.5%)</td>
<td>0.170</td>
<td></td>
<td>0.780</td>
<td></td>
</tr>
<tr>
<td>Vaccinations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCG</td>
<td>32 (76.2%)</td>
<td>16 (72.7%)</td>
<td>10 (58.8%)</td>
<td>0.683</td>
<td></td>
<td>0.187</td>
<td></td>
</tr>
<tr>
<td>Measles</td>
<td>42 (79.2%)</td>
<td>42 (89.4%)</td>
<td>31 (88.6%)</td>
<td>0.189</td>
<td></td>
<td>0.261</td>
<td></td>
</tr>
<tr>
<td>Rubella</td>
<td>48 (85.7%)</td>
<td>37 (84.1%)</td>
<td>26 (81.3%)</td>
<td>0.784</td>
<td></td>
<td>0.583</td>
<td></td>
</tr>
<tr>
<td>Diphtheria</td>
<td>46 (100%)</td>
<td>45 (93.8%)</td>
<td>29 (90.6%)</td>
<td>0.999</td>
<td></td>
<td>0.999</td>
<td></td>
</tr>
<tr>
<td>Tetanus</td>
<td>56 (98.2%)</td>
<td>50 (96.2%)</td>
<td>35 (100%)</td>
<td>0.505</td>
<td></td>
<td>0.999</td>
<td></td>
</tr>
<tr>
<td>Polio</td>
<td>50 (90.9%)</td>
<td>47 (95.9%)</td>
<td>32 (94.1%)</td>
<td>0.333</td>
<td></td>
<td>0.588</td>
<td></td>
</tr>
<tr>
<td><em>Childhood disease</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles</td>
<td>5 (38.5%)</td>
<td>20 (50%)</td>
<td>14 (46.7%)</td>
<td>0.425</td>
<td></td>
<td>0.619</td>
<td></td>
</tr>
<tr>
<td>Pertussis</td>
<td>0 (0%)</td>
<td>1 (3.3%)</td>
<td>2 (7.7%)</td>
<td>0.999</td>
<td></td>
<td>0.999</td>
<td></td>
</tr>
<tr>
<td>Rubella</td>
<td>0 (0%)</td>
<td>8 (23.5%)</td>
<td>1 (3.7%)</td>
<td>0.999</td>
<td></td>
<td>0.999</td>
<td></td>
</tr>
<tr>
<td>Chicken Pox*</td>
<td>6 (46.2%)</td>
<td>35 (87.5%)</td>
<td>23 (74.2%)</td>
<td>0.005</td>
<td>3.89 (1.61–9.4)</td>
<td>0.080</td>
<td></td>
</tr>
<tr>
<td>Mumps</td>
<td>5 (35.7%)</td>
<td>10 (27%)</td>
<td>7 (24.1%)</td>
<td>0.583</td>
<td></td>
<td>0.430</td>
<td></td>
</tr>
<tr>
<td>Scarlet fever</td>
<td>1 (7.7%)</td>
<td>3 (8.8%)</td>
<td>2 (7.1%)</td>
<td>0.880</td>
<td></td>
<td>0.950</td>
<td></td>
</tr>
</tbody>
</table>

Number refers to those who replied yes to the question. Percentage refers to those with positive reply over the total number that answered the question (not every participant replied to each question).

*Significant difference in that exposure between the groups.
4.2.3 Sanitation and the Hygiene Hypothesis

Having a pet as a child was protective against UC (OR 0.3, CI 0.1-0.7), and non significant in CD. Poor sanitation was defined as at least two exposures during childhood regarding in house and hot water, flush toilets and shared bathrooms. There was a trend towards poor sanitation being protective against UC (OR 0.45, CI 0.2-1.03), but total numbers were small in this group of questions.

Table 4.3- Comparison of childhood sanitation exposure in Crohn’s and Ulcerative Colitis patients compared to controls.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Control</th>
<th>CD</th>
<th>UC</th>
<th>CD vs. controls (p value)</th>
<th>Odds ratio (95% CI)</th>
<th>UC vs. controls (p value)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pet(s)*</td>
<td>67 (93.1%)</td>
<td>54 (84.4%)</td>
<td>36 (69.2%)</td>
<td>0.201</td>
<td>0.001</td>
<td>0.36 (0.2 – 0.79)</td>
<td></td>
</tr>
<tr>
<td>Swimming Pool</td>
<td>19 (28.8%)</td>
<td>19 (32.2%)</td>
<td>11 (29.7%)</td>
<td>0.594</td>
<td>0.953</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other #</td>
<td>16 (24.2%)</td>
<td>17 (28.8%)</td>
<td>8 (21.6%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>31 (47%)</td>
<td>23 (39%)</td>
<td>18 (48.6%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor sanitation^</td>
<td>4 (5.9%)</td>
<td>7 (11.7%)</td>
<td>9 (23.1%)</td>
<td>0.252</td>
<td>0.014</td>
<td>0.45 (0.2 – 1.03)</td>
<td></td>
</tr>
</tbody>
</table>

Number refers to those who replied yes to the question. Percentage refers to those with positive reply over the total number that answered the question (not every participant replied to each question). Key: *significant difference in that exposure between the groups. *Swimming in the lake, river and beach during childhood. ’Refers to exposure to poor sanitation, which was defined arbitrarily as answering no to 2 of the 5 sanitation questions (see methods and Appendix 3).
4.2.4 Smoking

A past history of smoking was significantly associated with both CD (OR 1.42, CI 1.0-2.02) and UC (OR 1.39, CI 1.1-1.92), as shown in Table 8. Ongoing smoking appeared to be protective against CD and UC (OR 0.58, CI 0.4-0.8 and OR 0.63, CI 0.5-0.81) but very few CD and UC patients continued to smoke after diagnosis so numbers are too small to be conclusive.

4.2.5 Dietary Factors

Eating fast food more than once a week was significantly associated with a risk of UC (OR 2.91, CI 1.54-5.58) and CD (OR 2.26, CI 1.76-4.33). Caffeine was protective against UC (UC OR 0.51, CI 0.3-0.87) and with a trend towards being protective against CD (OR 0.59, CI 0.34-1.03). Daily fruit intake was protective against UC (OR 0.59, CI 0.4-0.88) but not CD, as shown in Table 8.

Breastfeeding was not found to be protective against IBD. Rates were high in both the disease group and controls (>65%). There was poor recall regarding duration of breastfeeding. Other important negatives include high sugar intake.
Table 4.4- Comparison of pre-illness exposure to smoking, contraceptive use and diet habits in Crohn’s disease and Ulcerative colitis to healthy controls.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Control</th>
<th>CD</th>
<th>UC</th>
<th>CD vs. controls (p value)</th>
<th>UC vs. controls (p value)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past smoker*</td>
<td>24 (33.3%)</td>
<td>33 (50.8%)</td>
<td>24 (53.3%)</td>
<td>0.029</td>
<td>1.42 (1.01 - 2.02)</td>
<td>0.026</td>
</tr>
<tr>
<td>Ongoing smoker *</td>
<td>10 (15.2%)</td>
<td>2 (3.3%)</td>
<td>1 (2.4%)</td>
<td>0.023</td>
<td>0.58 (0.4 - 0.80)</td>
<td>0.029</td>
</tr>
<tr>
<td>Fruit daily*</td>
<td>77 (78.6%)</td>
<td>43 (68.3%)</td>
<td>20 (48.8%)</td>
<td>0.313</td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Vegetables daily</td>
<td>65 (92.9%)</td>
<td>57 (90.5%)</td>
<td>33 (80.5%)</td>
<td>0.600</td>
<td></td>
<td>0.059</td>
</tr>
<tr>
<td>Eggs daily</td>
<td>3 (4.3%)</td>
<td>5 (8.2%)</td>
<td>3 (7.3%)</td>
<td>0.359</td>
<td></td>
<td>0.500</td>
</tr>
<tr>
<td>Fast food*</td>
<td>7 (10.1%)</td>
<td>16 (26.7%)</td>
<td>20 (50%)</td>
<td>0.003</td>
<td>2.26 (1.76 - 4.33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High fibre</td>
<td>5 (23.8%)</td>
<td>23 (39%)</td>
<td>12 (26.7%)</td>
<td>0.247</td>
<td></td>
<td>0.805</td>
</tr>
<tr>
<td>High sugar</td>
<td>17 (23.3%)</td>
<td>24 (29.6%)</td>
<td>13 (22.8%)</td>
<td>0.350</td>
<td></td>
<td>0.949</td>
</tr>
<tr>
<td>High caffeine*</td>
<td>61 (87.1%)</td>
<td>43 (70.5%)</td>
<td>25 (61%)</td>
<td>0.031</td>
<td>0.59 (0.34 - 1.03)</td>
<td>0.002</td>
</tr>
<tr>
<td>Breastfed</td>
<td>54 (78.3%)</td>
<td>40 (74.1%)</td>
<td>21 (65.6%)</td>
<td>0.548</td>
<td></td>
<td>0.180</td>
</tr>
<tr>
<td>Contraceptive</td>
<td>31 (79.5%)</td>
<td>24 (52.2%)</td>
<td>20 (83.3%)</td>
<td>0.381</td>
<td></td>
<td>0.706</td>
</tr>
</tbody>
</table>

Number refers to those who replied yes to the question. Percentage refers to those with positive reply over the total number that answered the question (not every participant replied to each question).
*Significant difference in that exposure between the groups.
4.3 Discussion

This is the first population-based Australian cohort study to investigate the impact of environmental factors on the development of IBD in an area known to have a very high incidence of disease. Childhood immunologic events are associated with a higher risk of CD. The hygiene hypothesis may play a protective role in UC, as shown by childhood pet ownership. An important finding was the influence of diet. High caffeine intake was protective against both CD and UC, while frequent fruit intake was protective against UC. Frequent fast food intake on the other hand increased risk of both diseases. The findings support emerging theories on IBD aetiology. Firstly that early childhood exposures are important and secondly that modulation of the intestinal microbiota through immunologic, hygienic and dietary events may increase the risk of IBD in the future.

As discussed in Chapter 1, diet is difficult to study as an aetiological factor in IBD. This is due to methodological limitations inherent in studies relying on retrospective assessment of diet. Nonetheless diet has a significant impact on the composition and metabolic behaviour of gut microbiota (75). This study has shown that daily fruit intake is protective against UC, irrespective of total fibre intake. It adds to the growing evidence that there is a benefit of fruit intake on the risk of IBD (100). The biological mechanism behind the benefit is not known. It has been postulated that fruit may play a role in the clearance of reactive oxygen species (116). Enzymes belonging to the family of glutathione S-transferases are of particular interest as these are found in fruit and vegetables.
and are important detoxifying enzymes in the gut (116). In fact, a case-control study of 179 UC patients found low levels of one group of these transferases was associated with younger onset and more severe colitis (305). Fibre, a component of fruit and vegetables, has been shown in epidemiological studies to be protective against IBD (306) (83) (126). This may be through the action of short-chain fatty acids increasing blood flow and suppressing inflammation through the nuclear factor (NF) – kB pathway, (307) (64). These hypotheses require further biological explanation. Also, future studies should include a more detailed history of specific fruits.

Fast food more than once a week was associated with both CD and UC. This has previously been documented among UC patients in Eastern Europe (105). This may be related to the high levels of monounsaturated (MUFA) and polyunsaturated fatty acids (PUFA) found in these foods, which have been shown to be a risk factor for UC in a study from the Netherlands (102), as well as in a small Japanese study (107). PUFA appear to have the greatest association with UC (103), but a subtype, n-3 PUFA’s, have also been shown to have a protective association possibly due to anti-proliferative effects on lymphoid cells (108,109). Evidence for the impact of fat intake on the risk of CD is not as robust. Small Japanese studies have shown an association between Crohn’s disease and consumption of total animal fat, MUFA, PUFA and animal protein, (101) (107), and so has a paediatric cohort (116,308). A large cohort study of women did not find an association (108). Fast food is also high in animal protein which has been shown in a prospective French cohort to be associated with risk of IBD (127). Food additives that are present in fast foods may also play a role. Recently, diet
emulsifiers which are a food additive found in processed foods, was shown to both induce inflammation of the gut and obesity/metabolic syndrome in murine models (129). Emulsifiers were shown to have this effect by disruption of the mucus-bacterial interaction. Further research is needed to study the role and possible mechanisms of various components of fast food on the risk of chronic gut inflammation.

A relatively novel finding was that high caffeine intake, defined, as 2 or more cups of coffee and/or tea per day, is protective against UC and with a trend to be protective in CD. High tea intake was recently shown to be protective against CD, and both coffee and tea were protective against UC in an Asian-Pacific cohort, (106); coffee has also shown to be protective against UC in a twin study though this did not remain significant after adjusting for smoking habits, (122). A study from the Netherlands that focused on ‘modern life’ nutritional factors in the aetiology of IBD did not show a significant association with coffee or tea intake (100). No established biological mechanism is known for this association though it has been shown caffeine can ameliorate acute colitis in intestinal epithelial cells, (106). An association between coffee intake and lower levels of liver disease and fibrosis has been documented possibly through a beneficial effect on connective tissue growth factors (309), and these have a role in the repair of mucosal injury seen in IBD, (310) (311).

Childhood immunological events are likely to play a role in the development of IBD. Tonsillectomy rates were highest among CD patients in our cohort. Previous studies have shown conflicting results, with some showing a protective effect (83,94) while others found a higher rate among CD patients, (94) (91).
One study found an association between tonsillectomy and risk of ileal CD involvement. The lymphoid tissue of the tonsils shows histological similarity to that of Peyere’s patches in the intestine, and both belong to the mucosa-associated lymphoid tissue (MALT) system (93). The other significant immunological event in this cohort was chicken pox disease as a child and risk of CD. This has not been reported in previous studies and rates of infection were low in the controls (46%) compared to the general population which is estimated to be 90% (312), suggesting recall bias.

Sanitation conditions and exposure to a ‘dirty’ environment as a child has for many years been thought to play a role in not only IBD (313), but other autoimmune conditions, as explained by the hygiene hypothesis (96). In most recent years the hypothesis has been revised to reflect reduced exposure to colonizing bacteria, helminthes and viruses rather than infections, (95). Such a reduction in exposure may have a detrimental effect on T regulatory cells. In our study pet ownership, which is considered one of the possible ‘dirty’ exposures during childhood, reduced the risk of UC but not CD. This is a relatively novel finding shown previously in one small study (46), but also recently shown in an Asian cohort where it was protective against CD (106).

Smoking is an established environmental factor influencing IBD. It is unique in its polarizing effect on UC and CD. It is inversely associated with risk of developing UC (OR 0.58 in favour of smokers) and conversely, smoking is a risk factor for CD, and former smokers remain at risk (76) (78). Smoking may modulate these outcomes in CD through effects on vascular endothelium, on mucin production or through other toxic byproducts, (75). However, in Asia and
Africa, with the highest rates of smoking there is a low incidence IBD suggesting that its not the only factor at play (75). In fact, a study from Asia has shown that there was no association between CD and smoking (106). In our study, both CD and UC were associated with a history of smoking. This is consistent with what has previously been found in CD cases, but not UC. However, on closer inspection of the smoking history, nearly all UC patients ceased smoking by the time of this study. The results available from the questionnaires did not have enough information to determine if the majority ceased leading up to or after the diagnosis and this needs to be explored in greater detail. It would not be surprising that the majority would have ceased before and therefore may in fact have precipitated diagnosis given the known dampening effect of smoking on UC.

The challenge in studying the impact of environmental factors on IBD aetiology is in the recall of pre-illness behaviour. This is particularly important in diet, as dietary changes may have been subconsciously made prior to diagnosis due to the onset of symptoms. To counteract this effect in this study, the majority of patients completed the questionnaire within 6 months of diagnosis, which has not been the case in all previous studies (122) (107) (78). There were also limitations in the use of the IOIBD questionnaire, which is based on certain assumptions especially in relation to dietary history (for example, high sugar intake is represented by intake of juice and number of teaspoons of sugar in tea/coffee). However, this survey has been used in multiple studies, and therefore can be used to compare geographically varied populations (105,106). Also, the response rate was 53% and not all participants replied to every question in the questionnaire, resulting in a small number of responses for some
questions, which limited further analysis. Poor response to questionnaires is a known shortcoming, and in fact, in some studies is as low as 30% (281). This may introduce bias, though the poor response rate was similar in both the study population and the controls, and there was no significance in which questions were unanswered. Finally, the number of controls fell short of the optimum 1:1 ratio due to difficulty in the recruitment of controls. There are now strict restrictions in Australia in approaching the general population to participate in such studies such as through the electoral roll (unlike other countries where epidemiological research is rampant). It was considered best not to recruit through hospitals, as a major disadvantage of a control group selected from diseased individuals is that some of the illnesses may share risk factors with the disease under study. As a result, the number of controls did fall slightly short of the ideal ratio.

The strengths of this study are that this is a true population based cohort, without the bias found in hospital-based cohorts that include sicker patients with other co-morbidities. Patients were recruited close to time of diagnosis to minimize risk of recall bias. Also, this is the first Australian population based study to address environmental risk factors for developing IBD in an area with one of the highest incidence rates in the world, which offers an ideal platform to study culprit exposures. The results from this study can be extrapolated to other countries with a similar westernized lifestyle, such as Europe and North America.

We have identified environmental exposures including dietary patterns, pet ownership and immunological events that are associated with developing IBD.
Due to the observational nature of this study, it is not possible to establish cause and effect. Therefore these associations should be considered as clues to the aetiology of disease and as a starting point for further study. Firstly, future research should focus on greater detail regarding some of the positive exposures from this study, especially in regards to diet. This should either be done by designing a more specific questionnaire or through a more involved process such as patient interviews. The paediatric population may be most suitable to study diet in due to the young age of the patients (so a shorter dietary history) and possibly more reliable information from a second party, such as the parents. Concurrently, further work is needed to identify plausible biological mechanisms behind these exposures found here, such as the impact of them on the gut microbiota. In the meantime, intervention can be planned to reduce some of the environmental exposures associated with disease development (and encourage the protective ones such as fruit intake) in an effort to curb the rising incidence of IBD, especially in countries where the rate is still low.
Chapter 5  Health Cost Analysis

5.1 Introduction

In this era of escalating health care costs and growing constraints on health care budgets, cost analysis is crucial for planning proper distribution of health care resources and determining the cost effectiveness of novel therapeutic agents. This is especially so in lifelong incurable diseases such as CD and UC that have several expensive therapeutic options available, including anti TNF antibody therapy (biological) therapy and resective surgery. Additionally vedolizumab, an antibody against gut specific T lymphocytes, has just been released as a therapeutic option in Australia. Other therapeutic agents list are likely to become available in the coming years given the expanding research into such therapies. Also, the issue of cost is made even more pertinent by the global rise in the incidence of IBD.

There is limited prospective population based data on the health care cost of IBD in the post-biologic era. Of those available, there are limitations that are discussed in the paper in section 5.2. These include the use of retrospective cohorts, disease definition and case ascertainment through large insurance databases that lack clinical data, and no local studies done in the Australian health care system.

The aim of this prospective population based study of a well-characterized inception cohort of patients was to assess the total health care cost in the first year of diagnosis, from the health care system perspective.

The results of the health cost analysis have been published in a peer-reviewed journal, Journal of Crohn’s Colitis. The next section contains the PDF version of this paper.
5.2 PDF of paper: Health Care Cost Analysis in a Population-based Inception Cohort of Inflammatory Bowel Disease Patients in the First Year of Diagnosis


Original Article

Health Care Cost Analysis in a Population-based Inception Cohort of Inflammatory Bowel Disease Patients in the First Year of Diagnosis

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Abstract

Background: There are limited prospective population-based data on the health care cost of IBD in the post-biotherapeutic era. A prospective registry that included all incident cases of inflammatory bowel disease (IBD) was established to study disease progression and health cost.

Aim: To prospectively assess health care costs in the first year of diagnosis among a well-characterised cohort of newly diagnosed IBD patients.

Method: Incident cases of IBD were prospectively identified in 2007–2008 and 2010–2013 from multiple health care providers, and enrolled into the population-based registry. Health care resource utilisation for each patient was collected through active surveillance of case notes and investigations including specialist visits, diagnostic tests, medications, medical hospitalisation, and surgery.

Results: Of 276 incident cases of IBD, 252 (91%) were recruited to the registry, and health care cost was calculated for 242 (146 Crohn’s disease [CD] and 96 ulcerative colitis [UC] patients). The median cost in CD was higher at A$6905 per patient (interquartile range [IQR]: A$1571–A$91,324) than in UC at A$4752 (IQR: A$1488–A$68,072). In CD, outpatient resources made up 55% of all cost, with medications accounting for 32% of total cost (15% aminosalicylates, 15% biological therapy), followed by surgery [31%], and diagnostic testing [21%]. In UC, medications accounted for 39% of total cost [of which 37% was due to 5-aminosalicylates, and diagnostics 29%]; outpatient cost contributed 71% to total cost.

Conclusion: In the first year of diagnosis, outpatient resources account for the majority of cost in both CD and UC. Medications are the main cost driver in IBD.

Keywords: Inflammatory bowel disease; health cost analysis; population-based; Crohn’s disease; ulcerative colitis

1. Introduction

In this era of escalating health care costs and growing constraints on health care budgets, cost analysis is crucial for planning proper distribution of health care resources and novel therapeutic agents. This is especially so in lifelong incurable diseases such as inflammatory bowel disease [IBD] that have several expensive therapeutic
options available, including anti-tumour necrosis factor [TNF] antibody therapy [biologics] and restorative surgery. The issue is made even more pertinent by the global rise in the incidence of IBD.\textsuperscript{12,13,14} There is limited literature on the health care cost in population-based IBD cohorts, especially since the widespread introduction of biological therapy. The studies that are available have a number of limitations. Frequently patients have been recruited through the use of databases that are dependent on administrative definitions of IBD and, importantly, lack clinical data to compare cost and disease severity.\textsuperscript{15,16} Many population-based studies were performed retrospectively, thus introducing bias and difficulties in interpreting disease course and severity.\textsuperscript{17} Finally, some studies relied on patient-based recall of resource utilisation, which introduces recall bias.\textsuperscript{18,19} With the current escalating medical costs and advances in therapeutic options, there is a need for more accurate information regarding the health care cost of IBD. This prospective population-based study of a well-characterised inception cohort of all IBD patients with known disease progression, was designed to assess the total health care cost in the first year of diagnosis, from the health care system perspective.

2. Method

2.1. Study population

During a 4-year inclusion period [2007 and 2008, 2010 to 2013], incident cases of IBD from a well-defined area of greater Geelong, Victoria, were recruited to be part of this population-based prospective study. New cases were identified using the multiple source capture methodology as previously described\textsuperscript{20-22} and enrolled into an IBD registry through the use of an opt-out consent process.

A total of 278 incident cases of IBD were identified during the study period. Of these, 16 [6.5%] patients were lost to follow up, 8 [3%] were re-diagnosed as not IBD, 1 [0.4%] was not a true incident case, and 1 [0.4%] was not suitable for the study due to an unstable social situation. Th252 patients were enrolled into the IBD clinical registry, which was used as a basis to collect outcome data on the natural history, quality of life impact, environmental factors, and health care cost of IBD. Here we publish the health care costs of crohn's disease [CD] and ulcerative colitis [UC] patients [total of 242 patients; 10 cases of indeterminate colitis were excluded].

2.2. Data collection

Patient progress was assessed by the review of specialist case notes, hospital records, and pathology and radiology services, as well as liaison with the treating doctor[s]. For the majority of patients this was done prospectively, and for the smaller group diagnosed in 2007/2008 [n=41] this was done retrospectively in 2012. Patients were assessed at diagnosis, 3 and 12 months from diagnosis, and at the end of the study. A minimum of 12 months [≥12 months] follow-up was required. Audits of case ascertainment and data quality were performed 3-monthly. The clinical data collected included demographics, disease classification, disease activity, medical therapy, surgery, hospitalization, malignancy, and death.

2.3. Calculation of health care resource utilisation

Health care cost was calculated for each patient for the first 12 months of disease, including cost of diagnosis, from the health care system perspective. This perspective was chosen as providing valid and reliable cost data that can be then extrapolated to other populations, and is least likely to result in the introduction of bias seen with assessment of indirect costs. Cost is reported in Australian dollars [A$]. This was done through active surveillance for the following IBD-related health care resources: diagnostic tests [including pathology, radiology, endoscopy, and capsule endoscopy]; medications based on the treating physician's prescription [topical and oral aminosalicylates, azathioprine, mercaptopurine, methotrexate, adalimumab, infliximab]; outpatient visits to the main treating specialist [physician]; and medical and surgical hospitalisation. The cost of outpatient visits to other health care professionals such as the general practitioner [GP], surgeon, specialist nurse, or diettian was not included. Unpublished health economic data from the POCER study in Australia by Wright et al. showed that the average cost accrued by a patient visiting the GP for IBD-related problems was 13% of the cost of visiting the specialist. Therefore, this assumption was made to calculate the cost of GP visits in the analysis.

Any admission that eventuated in a surgical procedure [intestinal and perianal] was classified as a surgical admission [including all elective resection and all other hospitalisations]. The cost of hospitalisation was calculated as medical admissions.\textsuperscript{1} Hospital cost was obtained directly from the relevant hospital for each individual patient. Both private and public hospitals derive their cost based on the Department of Health and Aging Public National Round for the relevant year. In this system, each hospitalisation is assigned a relative cost based on the intensity of resources used. In a public hospital this incorporates physician fees; however, in private hospitals the physician fees are added on separately, based on the Medicare Benefits schedule.

Diagnostic costs were based on the Medicare Benefits schedule, apart from endoscopy, which was collected directly from each of the service providers. For all blood tests an estimate was calculated dependent on the therapy prescribed. Patients on no immunomodu- lator were predicted to require twice yearly baseline blood tests [full blood examination, electrolytes, liver function tests, and C-reactive protein [CRP]]. Those on immunomodulator therapy had a pre-immunosuppression screen added, as well as fortnightly tests for 2 months followed by second-monthly. A similar formula was used for patients on biological therapy.

Medication use was based on what the treating specialist prescribed, including dose and duration. The cost of each medication was calculated from the Pharmaceutical Benefits Scheme [PBS], using the dispensed price for maximum quantity [BPMQ] which was adjusted based on length of treatment. For infliximab, the additional cost of a day procedure at the relevant hospital was added into the cost of the drug.

Our patients visit to the treating gastroenterologist/specialist were calculated based on the Medicare Benefits schedule. All efforts were made to adhere to the criteria set out by the Quality of Health Economic Studies [QHES] instrument.\textsuperscript{4}

2.4. Statistics

As the health cost was skewed to the right, both median and mean costs per patient were calculated, as median cost is more representative of the outlay in most of the patients without introducing bias from a minority of patients with high cost. However, mean costs are also important for planning future health care budgets as they account for overall expenditure.\textsuperscript{5} To further analyse the high-cost outliers, these patients were identified by the statistically verified method [Q3+1.5IQR, where IQR is the interquartile range].\textsuperscript{6}

To determine which clinical variables may predict future high IBD health cost, univariate analysis was done using the Mann-Whitney rank sum because of the skewed distribution of cost. The dependent variable was total cost, with the independent variables being diagnosis, age, gender, disease location, disease behavior, and perianal disease.
2.5. Ethics
This study was approved by the Barwon Health ethics department and was carried out according to the local regulations.

3. Results

3.1. Cohort characteristics
A total of 242 patients [146 CD and 96 UC] from the IBD registry were included in the cost analysis, with a median follow-up of 18 months. This included 38 paediatric cases [15%, defined as age ≤ 19 years], of whom 25 (65%) had CD, 12 (32%) UC, and 1 IBD unclassified [BDU] [3%].

Patient demographics as well as disease classification [using the Montreal classification] are listed in Table 1. A more detailed overview of disease progression in this cohort has been described elsewhere.3,13

The total expenditure for the 242 patients in the first 12 months from diagnosis was A$2,145,585.00. This included $497,767 [23%] on investigations, A$728,897 [34%] on medications, A$321,059 [15%] on medical hospitalisation, A$544,810 [25%] on surgical hospitalisation, and A$53,050 [3%] on gastroenterologist outpa-
tient reviews. The inclusion of GP visits to the latter increased the cost to A$5,240 [3%].

The cost for the first 12 months in the CD cohort [n=146] was A$1,529,750 and for the UC cohort [n=96] was A$613,885. The median cost per CD patient was A$5905 [range A$1571-9,324] and for a UC patient was A$4752 [range A$1488-5,072] [Figure 1]. The mean CD cost per patient was significantly higher compared with UC [p<0.001, 95% confidence interval (CI) 686-1684], due to higher mean diagnosis cost [p<0.001] and specialist cost [p<0.001] [see Table 2].

3.2. Breakdown of total expenditure
The major cost driver in CD were medications at A$491,504 [32%], followed closely by surgery A$473,797 [31%, diagnostic tests A$320,693 [21%, medical hospitalisation A$214,255 [14%, and protein outpatient specialist reviews A$28,500 [3%]. The surgical cost includes intestinal resection [A$427,670, 90% of surgical cost] and perianal surgery [A$46,127, 10% of surgical cost]. Figure 2 shows the breakdown of each component of total cost, with a detailed overview of medications used; 5-ASA use accounts for 15% of total cost in CD, and biological therapy for 16%. The bulk of diagnostic testing in CD is due to endoscopy, which accounts for 18% of total cost [85% of diagnostic testing], and radiology, pathology, and cap-
sule endoscopy contributed 1% each. The majority of the endoscopy was done at time of diagnosis, with 24 additional colonoscopies [14% of total endoscopy cost] done during follow-up.

In UC patients, medications made up the bulk of the cost at A$273,393 [39%], followed by diagnostic tests at A$177,074 [29%], medical hospitalisation at A$106,804 [18%], surgery at

121

Table 1. Patient characteristics and outcomes of 242 incident IBD patients.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>CD</th>
<th>UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. patients [%]</td>
<td>146 [60%]</td>
<td>96 [40%]</td>
</tr>
<tr>
<td>No. of patients diagnosed in 2007/8/2010</td>
<td>38 [15%]</td>
<td>23 [9%]</td>
</tr>
<tr>
<td>Paediatric cases [age ≤ 19 years]</td>
<td>25 [17%]</td>
<td>12 [13%]</td>
</tr>
<tr>
<td>Male [%]</td>
<td>68 [47%]</td>
<td>39 [41%]</td>
</tr>
<tr>
<td>Female [%]</td>
<td>78 [53%]</td>
<td>57 [59%]</td>
</tr>
<tr>
<td>Median time [months] to diagnosis [range]</td>
<td>6.4 [1–7.9]</td>
<td>3 [0–7.3]</td>
</tr>
<tr>
<td>Current smoker</td>
<td>19 [13%]</td>
<td>5 [13%]</td>
</tr>
<tr>
<td>Former smoker</td>
<td>25 [17%]</td>
<td>17 [18%]</td>
</tr>
<tr>
<td>Disease extent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proctitis</td>
<td></td>
<td>31 [32%]</td>
</tr>
<tr>
<td>Left-sided colitis</td>
<td></td>
<td>31 [32%]</td>
</tr>
<tr>
<td>Pancolitis</td>
<td></td>
<td>34 [33%]</td>
</tr>
<tr>
<td>Disease location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1: terminal ileum</td>
<td>49 [32%]</td>
<td></td>
</tr>
<tr>
<td>L2: colonic</td>
<td>42 [30%]</td>
<td></td>
</tr>
<tr>
<td>L3: ileocolonic</td>
<td>55 [38%]</td>
<td></td>
</tr>
<tr>
<td>L4: upper gastrointestinal</td>
<td>18 [12%]</td>
<td></td>
</tr>
<tr>
<td>Disease behaviour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory</td>
<td>16 [8%]</td>
<td></td>
</tr>
<tr>
<td>Stereocutaneous</td>
<td>15 [10%]</td>
<td></td>
</tr>
<tr>
<td>Penetrating</td>
<td>15 [10%]</td>
<td></td>
</tr>
<tr>
<td>Perianal</td>
<td>19 [12%]</td>
<td></td>
</tr>
<tr>
<td>Treatment exposure at 1 year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>4 [3%]</td>
<td>0</td>
</tr>
<tr>
<td>S-aminosalicylates</td>
<td>82 [36%]</td>
<td>93 [99%]</td>
</tr>
<tr>
<td>Steroids</td>
<td>100 [40%]</td>
<td>53 [55%]</td>
</tr>
<tr>
<td>Immunosuppressors</td>
<td>60 [41%]</td>
<td>9 [9%]</td>
</tr>
<tr>
<td>Biological therapy</td>
<td>12 [8%]</td>
<td>1 [1%]</td>
</tr>
<tr>
<td>Surgery [primary]</td>
<td>20 [14%]</td>
<td>3 [12%]</td>
</tr>
<tr>
<td>Surgery [perianal]</td>
<td>11 [8%]</td>
<td></td>
</tr>
<tr>
<td>Medical hospitalisation</td>
<td>32 [23%]</td>
<td>17 [18%]</td>
</tr>
</tbody>
</table>

CD, Crohn’s disease; UC, ulcerative colitis; BDU, inflammatory bowel disease unclassified.

16 months. Total health care resource utilization in the first year of diagnosis.

A$70,013 [12%], and specialist outpatient visits at A$23,550 [4%].

Figure 2 illustrates the breakdown of specific medications, with 37% of the total cost stemming from use of 5-ASAs. Biologicals use in UC has not been widely available till recently. Diagnostic cost is mainly due to endoscopy, accounting for 27% of total cost [94% of diag-
nostic cost], with radiology and pathology contributing 1% each. The majority of the endoscopy was done at diagnosis in UC, with an extra 15 colonoscopies done during follow-up, accounting for 14% of the total endoscopy cost.

Outpatient resources are responsible for the majority of the cost in both CD [55%] and UC [71%], when compared with inpatient resources [hospitalisation and surgery].

3.3. High-cost outliers
High-cost outliers were identified for both CD and UC. 11% of patients [16 of 146] with CD were defined as outliers [total cost range A$24,321 to A$91,324]. These patients accounted for A$642,325 [42%] of the total cost in CD. The major cost contribu-
tors in these patients were surgery [54%] and medications [29%]. Biological therapies contributed 60% to the medication cost. On
more detailed analysis of these 16 patients, there were 5 patients whose cost primarily stemmed from complicated intestinal resections, costing a minimum of AUD30,000. This included three patients with a surgical cost of over AUD50,000 each due to prolonged admission associated with the surgery (30 days minimum). There was a delay to salvage therapy or surgery in two of the three patients with severe colonic and ileocolonic disease, respectively. The third was an 80-year-old patient with multiple comorbidities who underwent small bowel resections within 12 months, on no immunomodulator therapy despite predictors of high-risk disease. Of the remaining 11 high-cost CD patients, the major driver to cost was either biological therapy for most of the 1 year, more than one hospitalisation, or the combination of needing both rective or perianal surgery and a biological.

In UC, 10% [10] patients were classified as high-cost outliers [range AUD13,426 to AUD58,072]. These patients comprised AUD2,183,033 [36%] of the total UC cost. Medical hospitalisations accounted for 34%, surgery 33%, and medications 20%. 5-ASA use made up 75% of all the medication cost. There were two patients that had high costs due to a colectomy, with a difference between the two in the cost [AUD13,382 vs AUD7,631]. This was due to a delay in diagnosis of UC in the higher-cost patient, a young man with a concomitant gastrointestinal infection. Of the remaining high-cost UC patients, the costs of six were due to hospitalisation and one due to biologicals use.

3.4. Predictors of high cost

In CD, univariate analysis found that the following clinical variables present at diagnosis predicted high cost: perianal disease ($p=0.006$, colonic and ileocolonic location ($p=0.014$), complicated disease behaviour ($p=0.015$), and early immunomodulator [IM] use, defined as within 3 months of diagnosis ($p=0.009$). On multivariate regression analysis, colonic (incidence rate ratio [IRR] 1.49, 95% CI: 1.04–2.14) and ileocolonic [IRR 1.84, 95% CI: 1.34–2.52] location and complex disease behaviour [stratifying IRR 1.79, 95% CI: 1.14–2.82, penetrating IRR: 2.25, 95% CI: 1:43–3.53, when compared with inflammatory] remained significant [Table 3].

In UC, univariate analysis identified early IM use ($p=0.006$), extensive disease location ($p=0.001$), and a high CRP ($p=0.013$) as predictors of high cost in the first year. On multivariate regression analysis, left-sided colitis [IRR 1.53, 95% CI: 1.12–2.09], pancolitis [IRR 1.76, 95% CI: 1.23–2.47] and a CRP > 10 at diagnosis [IRR 1.79, 95% CI: 1.26–2.53] predicted high cost in the first year [see Table 4].

4. Discussion

This cost-analysis of health care in IBD during the first year of disease, including the cost of diagnosis, has identified a number of important findings. First, health care is more expensive in CD than UC. Second, outpatient resources account for more health expenditures when compared with inpatient resources, and medications contribute the largest proportion to total cost. Use of 5-ASA is not only expensive in UC but also accounts for half of the cost of medications.

The Mann-Whitney [rank sum] test was used to compare the two groups. SD, standard deviation; IQR, interquartile range. *Statistically significant.

<table>
<thead>
<tr>
<th>Table 2. Mean and median cost (AUD $) per patient in the first year of disease.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>Crohn’s disease [per patient cost AUD]</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Total cost</td>
</tr>
<tr>
<td>Mean [SD]</td>
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<tr>
<td>Median [IQR]</td>
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<tr>
<td>Medical hospitalisation</td>
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<tr>
<td>Mean [SD]</td>
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<td>Surgery</td>
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<td>Mean [SD]</td>
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<tr>
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<tr>
<td>Median [IQR]</td>
</tr>
<tr>
<td>Specialist review</td>
</tr>
<tr>
<td>Mean [SD]</td>
</tr>
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</table>

Figure 1. Box and whisker plot (using the Tukey method) illustrating the total distribution of cost in Crohn’s and ulcerative colitis patients [the top two outliers excluded here due to very wide distribution].
in CD. Despite the shift to outpatient resources, surgery costs remain high in the first year. Lastly, the distribution of cost is influenced by a small number of ‘high-cost outliers’—patients who accumulate a much higher cost in the first year of diagnosis compared with the rest of the cohort.

This prospectively recruited inception cohort of 242 patients has been followed longitudinally to assess disease progression, details of which have been published elsewhere. Early disease course was not as aggressive as has previously been reported. Disease behaviour in CD was predominantly inflammatory at 1 year (80%) and, of the CD patients (n=38) with 5-year follow up, 75% had non-penetrating non-structuring disease. Rates of intestinal resection were low in CD (13% at 1 year) and UC (2% at 1 year) compared with the pre-biologics studies but comparable to recent population-based studies from Europe. Immunomodulator use was frequent (57% at 18 months in CD; 18% in UC), and biological therapy use in CD was common (8% at 1 year; 12% at 18 months). These rates are very similar to those in Western European countries, described in the recent ECCO-EpiCom cohort, though biological therapy was lower in our cohort, especially in UC. These similarities between cohorts suggest that the health cost data from this study can be extrapolated to other regions, in particular Western Europe.

This study shows a shift from inpatient resources contributing most of the cost in IBD, to outpatient resources. This is due to medications and diagnostic testing contributing a larger percentage of the total cost when compared with historical population-based cohorts. This shift has been confirmed in other recent studies. It is likely that the gap between inpatient and outpatient resource cost will widen even more after the first year of disease, as surgical and hospitalisation rates continue to decline in later years of disease, as has been shown in recent cohort and health analysis studies.

In CD the high medication cost is driven equally by biological therapies (50%) and 5-ASA (49%). This is one of the first health cost studies to include significant biological therapy [8% at 1 year], as compared with 0.7% at 1 year in the Manitoba cohort and similarly infrequent use in other studies. A health cost study in patients with longstanding disease [median 13–16 years] also showed a high number of patients on biological therapy [22%]. In that study, biological therapies accounted for 64% of total cost in CD and 31% in UC, but patient recruitment was hospital based and was through the use of an administrative definition of IBD which may skew to
Table 2. Clinical variables at diagnosis that predict high cost in Crohn’s disease patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Count</th>
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<th>Multivariate regression</th>
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<td>Mean [IQR]</td>
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<td>Strictureing</td>
<td>35</td>
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<td>19310 ± 18217</td>
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<td>Yes</td>
<td>61</td>
<td>10485 ± 10539</td>
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<td>IM at diagnosis</td>
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<td>127</td>
<td>8196 ± 11207</td>
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<tr>
<td>Yes</td>
<td>19</td>
<td>12239 ± 13874</td>
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SD, standard deviation; IQR, interquartile range; GI, gastrointestinal.

The other cost driver are the 5-ASA’s, accounting for 15% of total cost in CD and 37% of total cost in UC. Similar results have been shown before in a US health cost study in which 5-ASA’s contributed 29% of the CD cost. In the IBD-COH cohort, mesalazine was more expensive than the cumulative cost of all other drugs.3 5-ASA’s such as mesalazine are expensive ($52 per 1g for oral and AS12 for an enema preparation), and are used widely in IBD, with 56% and 99% of CD and UC patients respectively, being prescribed this medication by the end of the first year from diagnosis in our cohort.5 Salazopyrin is not as costly but has frequent side effects and is therefore poorly tolerated by patients.5 The expense of 5-ASA’s brings into question the use of these in CD, given the limited evidence for its efficacy in these patients.5

Health care cost from CD has frequently been shown to be more expensive than UC,3,5,7 and we have confirmed this. In our study, this was due to significantly higher cost from diagnostic tests [specifically radiology] and more specialist visits in the CD population compared with UC [see Table 2].

Diagnostic tests are expensive, accounting for 18% and 27% of total cost in CD and UC respectively, and most of this cost is due to endoscopy (≤85%). However, the majority of these procedures are performed during the diagnostic process, so it is reasonable to assume that further follow-up of this cohort will show a significant reduction of endoscopy cost. A potential cost-saving approach would be to reduce the number of follow-up colonoscopies through the use of a more severe disease phenotype and introduce bias, as the definition is used for re-imbursement. As the number of patients using biological therapies in population-based studies increases, it is important to determine if the costly price tag of the therapy will be offset by reduced cost from longer disease remission, as well as less frequent hospitalisation and surgery. There have been studies done with Markov modelling to try to answer this question, one of which concluded that therapy is not cost effective; however, this was on refractory CD patients, not strictly a population-based cohort.14 A retrospective analysis of a large IBD registry in Canada found that hospitalisation and surgery rates dropped at 2 and 3 years, respectively, after initiation of infliximab compared with other drug groups in patients who had double the cost of treatment before the initiation of biological therapy—suggesting that in these patients, biological therapy was cost effective.25 The ECCO-Epicom group found more frequent anti-TNF therapy and IM use in the first year of disease in the Western European patients as compared with those in Eastern Europe, but this was not associated with a significant difference in surgery rates or hospitalisations at 3 years, perhaps due to the follow-up not being long enough to demonstrate effect. It is also possible that biological therapies will not be cost saving, as is the case with many health care interventions, but still remain cost effective through impact on quality of life and patient-reported outcomes. Future follow-up of this cohort will include quality of life and disease activity measures that will help determine the cost-effectiveness.
of faecal calprotectin to monitor treatment response and mucosal healing, rather than repeat colonoscopy.\textsuperscript{\textasciitilde,25\textendash30} In this study, 39 follow-up colonoscopies were performed after the initial diagnostic procedure, accounting for A$2,253. If all of these were replaced with a faecal calprotectin (average cost of A$50 each), a 10% saving on total diagnostic testing would be achieved.

There is a right skew in the distribution of cost among the cohort that is further exacerbated by a small number of high-cost outliers contributing a substantial burden of the cost. This has also been found in previous health-cost analyses.\textsuperscript{\textasciitilde,26\textendash30} These high-cost outliers make up 11% and 10% of patients with CD and UC, respectively, and contribute 54% and 36% of the total cost of the cohort. In CD, the cost in this outlier group was driven by surgery and surgical admissions, whereas in UC it was driven by a combination of prolonged complex medical hospitalisations, surgery, and medications. In-depth analysis of the group showed that the three most expensive patients [two CD and one UC] with surgical costs over A$50,000 each [including hospitalisation at the time of surgery] had experienced delay to either definitive therapy or to diagnosis, underlining the importance of vigilant and active treatment of unwell patients.

Several clinical variables present at diagnosis predicted high cost in the first year of disease. In CD, these were colonic and ileocolonic location and complex disease behaviour. In UC, these were left-sided and pancolitis location as well as an abnormal CRP of >10. These clinical predictors are similar to those predicting a need for surgery and hospitalisation,\textsuperscript{\textasciitilde,25\textendash26} which are both unfavourable clinical outcomes. Patients displaying such clinical variables at diagnosis should be managed aggressively to prevent complex disease behaviour with associated high cost.

There are several limitations to this study. First, we did not include the cost of outpatient visits to other health care providers due to the difficulty of capturing all such visits. However, given the overall low impact specialist visits had on total cost in this study [3%], it is unlikely that the overall cost from these service providers would be significant. Other studies that have included all outpatient visits have shown a low contribution to total cost.\textsuperscript{31} This should not be interpreted that the outpatient care provided by health professionals is not important, but simply that they are not costly. In fact, the comparative low cost of frequent contact with IBD health professionals suggests cost efficacy, as these visits have a pivotal role in assessing clinical response and achieving treatment to target goals, with a positive effect on patient compliance. The other limitation in this study is the lack of societal and patient cost assessment [indirect costs] including work productivity and absenteeism, as well as out-of-pocket costs.\textsuperscript{25} This is because the cost analysis was from a health care system perspective to optimise cost reliability and external validity to other populations. Also, the cost of medications, excluding biological therapy which is monitored strictly, may have been overestimated as non-compliance was not considered [it was based on the doctor's prescription] but, given the low cost of all other medications [apart from 5-ASA], this is unlikely to be significant. Finally, the use of biological therapies in the UC group was limited due to prescribing restrictions in Australia till recently. This is one of the only well-characterised inception cohorts of community-based patients with both clinical outcomes and health cost analysis data since the widespread use of biological therapies. This provides real-life health cost data that can be generalised to other populations and used in cost-efficacy assessment of new therapies and in the future planning of allocation of health care resources. Follow-up was excellent [over 90%] reducing risk of bias. Active
surveillance was used to capture all resources use, which has the added benefit of thorough and accurate data collection when compared with database-based searches. The study fulfilled the requirements of a good cost analysis study, providing therefore a basis for cost-utility and cost-effectiveness analysis.12,13 This health cost analysis can be extrapolated to other developed countries, given the similarities in cohort characteristics described earlier. One caveat is the dominance of CD over UC in the Australian population, which is similar to North American countries, New Zealand, and France14 but the opposite to other Western and Eastern European countries.15,16,17 For this reason, total IBD cost may differ as CD is more expensive than UC but per patient costs should remain similar. The majority of cost was public system cost in this study, and there is no difference between private and public funding for outpatient resources. Additionally, even if there are differences between health care costs between countries, the cost profile should remain the same given the comparable disease progress and treatment strategies used in these countries.

In conclusion, we have shown that health care cost is more expensive for CD than UC patients. There has been a shift in IBD health cost expenditure in the first year of disease, from inpatient driven resources to outpatient driven resources, primarily due to medications such as biological therapy and 5-ASAs. Future longitudinal follow-up of the cohort will help determine which treatment strategies induce sustained low-cost remission in patients and therefore offset the cost of treatment. Quality of life measures will aid in assessing the cost-effectiveness of current strategies.

Conflict of Interest
The authors have no conflict of interest to declare.

Acknowledgments
ON is the guarantor of this article. All authors have approved the final version of the manuscript. ON was the lead investigator for this study, and was supervised by SB as well as PD. WC was involved in the original recruitment of patients and setting up of the study, and continues to make significant contribution to the running of the study. MF was the statistician involved in the evaluation of the health economics. JM provided invaluable advice on how to set up a registry and how to run it. JW and CS were the previous researchers who recruited a significant number of the patients, and set up the registry. The remainder of the authors were involved in the recruitment of patients. The authors have no funding to declare. No open access fees were paid.

References


Chapter 6  Conclusion and Future Directions

This is the first Australian IBD population based study of an inception cohort with the majority of patients followed prospectively from time of diagnosis. It represents the true community based management of a patient with IBD outside of controlled trials, therefore offering the ideal environment to study some of the unanswered epidemiological questions regarding disease aetiology, disease progress and health cost.

The incidence and prevalence of IBD has been on the rise in developed countries over the last few decades. International literature has suggested this may now be leveling off and this study has confirmed the pattern. The incidence rates are high in comparison to other parts of the world, ranging between 20-29 per 100,000 in the years of 2007 to 2013, respectively, but are not continuing to rise, which is reassuring for the community and from a health care perspective. Ongoing recruitment of incidence cases in the Barwon area can be used to monitor the rate of disease. In contrast, countries that have recently adopted a western lifestyle such as parts of Asia, are now showing a rapid rise now. Future efforts should be made to curb this rising incidence, possibly through such avenues as studying the environmental factors responsible for the rise.

This research has addressed the environmental factors that are contributing to disease aetiology and rise in incidence. Certain environmental exposures were identified, including dietary habits. Frequent fast food was associated with an increased risk of both CD and UC, while high caffeine intake was found protective against UC, as was high fruit intake. Pet ownership was also found protective against UC and may tie with the hygiene hypothesis. Certain childhood immunological events such as tonsillectomy and chicken pox infection were found to be associated with risk of IBD. These factors should be confirmed in larger cohorts. Also, work is needed to characterize the effect of these exposures on plausible biological mechanisms, such as the gut microbiota and studies can be developed with these mechanisms in mind. Epidemiological research into disease aetiology is important as it can alert to causal mechanisms, and it should
be concentrated in areas of frequent or changing incidence, as is the case in Barwon. Also, patients who are newly diagnosed with IBD should be evaluated for confirmation of the novel environmental risk factors. In the meantime, intervention can be planned to reduce some of the exposures identified, such as changes in diet, in an effort to curb the rising incidence of IBD, especially in countries where the rate remains low.

Over the last decade, there have been changes in the management of IBD including new diagnostic tools, and a shift in the therapeutic aims from clinical remission to endoscopic and mucosal healing. Therapeutic advances have included the ability to individualize immunosuppressive therapy through drug levels and the introduction of biological therapy. This is one of the first population-based studies done since the widespread introduction of these changes. It was designed to measure objective markers of disease progress and it has confirmed favourable early outcomes for IBD patients. In CD, most patients continue to exhibit an inflammatory disease phenotype and did not progress to more complicated disease behaviour. Intestinal resection rates were modest in both CD and UC patients. Hospitalization remains common in the first year, but decline after the first 12 months. This has coincided with high levels of immunomodulator and biological therapy, suggesting a positive impact of these agents, though there were frequent side effects noted from the immunomodulator therapy. Ongoing follow up of this cohort will evaluate the long term benefits on disease course and assess the risk/benefit ratio.

Early clinical predictors of severe disease were identified, by the use of a proposed definition of disabling disease. In CD, these predictors included complex disease behaviour, ileal location and steroids at diagnosis. In UC, an elevated CRP predicted both the need for hospitalization and colectomy. Ongoing recruitment of patients into the cohort will help validate this new definition of disabling disease and longer follow up of the cohort will assess the reliability of these predictive factors. It would also be worthwhile to study other early predictors of severe disease, such as serological and genetic markers.
This is one of the first studies to prospectively analyze the health care cost in IBD during the first year of disease in a community-based cohort through the use of active surveillance of all resources used. It therefore is a valid and accurate cost analysis from a well characterized cohort that can be used for future health policy planning as well as clinical studies aiming to assess the cost efficacy associated with changes in IBD care. The results show that CD remains more expensive to treat than UC. There has been a shift in IBD health cost expenditure in the first year of disease from inpatient driven resources to outpatient, primarily due to medications such as biological therapy and 5ASA's. The cost of 5ASA therapy in CD was concerning especially given the limited efficacy this therapy has in CD. Diagnostic tests are also significant contributors to overall cost, though this may decline after the first year as the majority of cost stemmed from endoscopy (which is a prerequisite to diagnosis). Surgery costs remained high in CD in the first year but these are likely to decline as well, based on those patients with longer follow up in this study showing a decline in surgical rates after the first 18 months. Future longitudinal follow up of the cohort will help determine which treatment strategies induce sustained low-cost remission in patients and therefore offset the cost of treatment. Quality of life measures will be invaluable in assessing the cost-effectiveness of current therapeutic strategies.

The ongoing recruitment of incidence cases into this well established IBD registry and clinical database will facilitate some of the future research outlined here, as will the ongoing follow up of already recruited patients. Additional clinical measurements such as genetic and serological markers should be collected from patients so these can be correlated to disease outcomes; as well as patient related outcome measures including quality of life and work productivity indices.
Chapter 7  References


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153


Author/s:
Niewiadomski, Olga

Title:
The natural history of inflammatory bowel disease in an Australian community cohort: investigating the aetiology, clinical course, predictors of severe disease and health cost

Date:
2015

Persistent Link:
http://hdl.handle.net/11343/90884

File Description:
The natural history of inflammatory bowel disease in an Australian community cohort: investigating the aetiology, clinical course, predictors of severe disease and health cost.