

## **EPIDEMIOLOGY**

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### ***Introduction***

Our Committee has assembled an overview of the epidemiology and economics of IBD. In this report we will review the current state of the art regarding the descriptive epidemiology, time trends of IBD epidemiology, economics of IBD and the utilization of epidemiological studies to pursue clues to disease etiology.

### ***Descriptive Epidemiology of Inflammatory Bowel Disease***

Only four North American studies have reported on the prevalence of Crohn's disease, and 3 have reported on the prevalence of ulcerative colitis (Table 1). Only two of these studies are from population-based data. The prevalence of Crohn's disease ranges from 26.0 to 198.5 cases per 100,000 persons, and the prevalence of ulcerative colitis in North America ranges from 37.5 to 229 cases per 100,000 persons. The most recent population based prevalence rates are approximately 200 per 100,000 persons for each of Crohn's Disease and ulcerative colitis (1, 2). If prevalence data from the areas with the highest prevalence are extrapolated to all of Canada and the United States (population approximately 300 million), there may be as many as 600,000 persons with Crohn's disease and 690,000 persons with ulcerative colitis in North America. Incidence rates from 11 North American studies since 1980 are shown in Table 2. Incidence rates for Crohn's disease ranged from 3.1 to 14.6 cases per 100,000 person-years, while incidence rates for ulcerative colitis ranged from 2.2 to 14.3 cases per 100,000 person-years. Using the most recent 1990s data from the US and Canada and based on an estimate of 300 million people in North America, approximately 24,000-44,000 new cases of Crohn's disease and 25,000-43,000 new cases of ulcerative colitis are diagnosed each year (1,2). These extrapolations of incidence and prevalence to Canada and the United States are crude and do not account for geographic or ethnic variation.

Within the continent there may yet exist significant geographic variation. In general, the concept of a "north-south gradient" of IBD incidence and prevalence seems to hold true. The study populations with the highest prevalence rates of IBD are located in northern latitudes (1,2). The 2 highest incidence rates for Crohn's disease were noted in Canadian locales (1,3). Hospital-based studies of U.S. military veterans and Medicare beneficiaries have also suggested a north-south gradient of IBD incidence (4, 5). However, this is not universally observed. For example, one of the highest incidence rates of Crohn's disease noted was among African-American children in Georgia (6).

The incidence of both ulcerative colitis and Crohn's disease in North America may be stabilizing. A cohort of Olmsted County, Minnesota residents diagnosed with inflammatory bowel disease between 1935 and 1993 has been studied at several points in time (2,7). Generally, rates of ulcerative colitis have plateaued prior to those for Crohn's disease. The incidence of Crohn's disease rapidly increased between the late 1950s and early 1970s and then stabilized at roughly 7 cases per 100,000 person-years (7). The incidence of ulcerative colitis in Olmsted County also rapidly increased in the post-war period, peaking in the early 1970s, with stabilization in incidence thereafter (2). Other locales with longitudinal data, such as Rochester (NY), Baltimore, and Spokane, have witnessed a rise in incidence over time (8-10). The prevalence of IBD has continued to increase. In Olmsted County, the prevalence of Crohn's disease rose 58% between 1983 and 1991 (7). The prevalence of ulcerative colitis in Rochester, MN (the county seat of Olmsted County) increased 229% between 1965 and 1991(2). The increasing prevalence may reflect a combination of previously increasing incidence and near normal life expectancy.

In most studies of Crohn's disease, there is a slight female predominance, generally in the 50% to 60% range. It is interesting to note that a male predominance of Crohn's disease exists in many regions with low incidence rates, whereas female predominance is much more common in moderate to high incidence areas. The female predominance, especially among 20 to 29 year olds, has led some to postulate that hormonal factors, either endogenous or exogenous, may be playing a role in the expression of Crohn's disease, but this remains speculative. In contrast, there tends to be a slight male predominance in ulcerative colitis, both in low and high incidence areas. Recent trends suggest a male predominance among newly diagnosed cases for both Crohn's disease and ulcerative colitis; whether changes in cigarette smoking behavior have contributed to these changes remains unclear.

The so-called "bimodal" distribution of age at diagnosis of IBD typically refers to a peak in incidence in the 2<sup>nd</sup> or 3<sup>rd</sup> decades of life followed by a smaller peak later in life, typically the 6<sup>th</sup> or 7<sup>th</sup> decade. However, a "unimodal" distribution, with a peak incidence in the 2<sup>nd</sup> or 3<sup>rd</sup> decades followed by a gradually diminishing incidence thereafter, is actually more commonly seen, especially in Crohn's disease and in more recent studies. Whether this change represents better diagnostic awareness of Crohn's disease and other segmental colitides or it represents a real change in the age of onset of Crohn's disease is unclear. A frequently observed age distribution of ulcerative colitis diagnosis in recent studies shows divergence between males and females. In men, new cases of ulcerative colitis peak in the 4<sup>th</sup> decade of life, but new cases are frequently seen in the 5<sup>th</sup>, 6<sup>th</sup>, and even 7<sup>th</sup> decades of life. In women, new cases peak in the 4<sup>th</sup> decade of life as well, but incidence drops off rapidly in later decades of life. Some have theorized that these differences may be related to gender differences in rates of current and former cigarette smoking, but this remains unproved.

Historically, IBD was thought to occur much less frequently in minority groups as compared to Caucasians. However, studies over the past 2 decades suggest that the distribution of IBD among ethnic and racial groups continues to be dynamic. For example, the difference in IBD incidence and prevalence among Caucasians and African-Americans appears to have diminished. A study from a southern California health maintenance organization showed that hospitalizations rates for Crohn's disease were similar between Caucasians and African-Americans, while the overall prevalence of Crohn's disease in African-Americans was about two-thirds that of Caucasians (11). More recently, a study of Georgia children suggested that both ulcerative colitis and Crohn's disease were equally common among African-Americans and Caucasians (6). Americans of Hispanic origin appear to have a much lower prevalence of Crohn's disease than Caucasians. The North American study with the lowest prevalence of Crohn's disease examined a population that was 31% Hispanic (11). In this study, the prevalence of Crohn's disease among Hispanics was one-tenth that of Caucasians (4.1 versus 43.6 cases per 100,000 persons) (11). Asian-Americans appear to have a low risk of IBD, similar to that of Hispanics (11). In a Canadian study, Aboriginal or First nations peoples had very low prevalence rates, particularly for Crohn's disease (14).

### ***Future needs***

Continued periodic monitoring of IBD incidence and prevalence will allow more up-to-date measurements of the overall burden of illness. More rigorous descriptive epidemiology of special populations, such as pediatric patients and minority populations, is warranted. There is a great need to establish more extensive population-based data within the United States to avoid the biases of data from specialized referral centers. Ultimately defining populations at greatest and least risk and trends may help to identify potential environmental contributors to disease etiology.

### ***Time Trends of Inflammatory Bowel Disease***

The epidemiology of ulcerative colitis and Crohn's disease are both characterized by marked temporal variations (15). Such variations point at the existence of environmental influences that must be shaping the occurrence of both types of inflammatory bowel disease. Although similar time trends are observed in all morbidity parameters of inflammatory bowel disease, the mortality data of the vital statistics offer several advantages for the analysis of the temporal trends. In comparison with other statistics, the vital statistics cover the longest time periods, they are available for many different countries alike, and they include the entire population without being subjected to various types of selection bias. When plotted against the period of birth, the age-specific mortality data of ulcerative colitis form a clear-cut hyperbola with its peak located around 1890 (16, 17). Such birth-cohort patterns in the time trends of ulcerative colitis can be confirmed in the vital statistics of most western countries (18). A birth-cohort pattern suggests that exposure to the relevant risk factors for ulcerative colitis occurs during early life between the prenatal period and adolescence. The risk factors must exert their effect within a short time period, and the amount or type of exposure must be changing with time.

Otherwise successive generations could not exhibit rapidly varying rates of disease occurrence. As the exposure changes over time, consecutive generations, that is birth-cohorts, come to reflect its varying influence on the risk of developing the disease. Epidemiological data also show that in many countries alike, ulcerative colitis and duodenal ulcer exhibit resembling birth-cohort patterns that affect exactly the same generations with a peak occurring around 1890 (19). The close similarity between duodenal ulcer and ulcerative colitis is especially striking, because it is confined to these very two diseases and does not involve, for instance, gastric ulcer or gastric cancer. The similarity indicates that the etiologies of ulcerative colitis and duodenal ulcer may share a common pathway and that this pathway relates to some environmental exposure before or during childhood. The trends of Crohn's disease reveal yet another peculiar pattern. Ever since its first introduction as a separate diagnostic code into the International Classification of Diseases (ICD) in 1950 the occurrence Crohn's (as revealed by various morbidity parameters) increased until about 1970 and then started to decrease again. In the vital statistics, it appeared as if mortality associated with Crohn's disease failed to continue its rise above the level of mortality associated with ulcerative colitis. This pattern is discernible in each age group, in each gender, and in many different countries alike (16, 20). Overall, these trends mean that in the near future both diseases will affect more elderly patients and that the overall incidence of inflammatory bowel disease will decrease.

### ***Future needs***

Research of time trends in inflammatory bowel disease should strive to better characterize these temporal patterns in various types of health statistics and, eventually, try to establish a relationship between disease trends and environmental risk factors that would shed light on the yet unknown etiology of inflammatory bowel disease.

### ***Epidemiological Approaches to Determining the Etiology of Inflammatory Bowel Diseases***

Despite extensive research, the etiology of inflammatory bowel disease (IBD) remains largely unknown. There is evidence that both Crohn's disease (CD) and ulcerative colitis (UC) are immunologically-mediated and that intrinsic genetic factors play a role. However, it has also been postulated that extrinsic factors such as dietary, toxic or infectious exposures play an important role in their pathogenesis (21). Much support for the etiologic role of extrinsic factors is drawn from descriptive epidemiology. It has been observed that the incidence of both conditions has increased considerably within the past several decades and that the incidence varies substantially in different populations worldwide (22). In particular, it has been observed that the prevalence of both CD and UC tends to be higher in northern latitudes, that the onset of disease is usually in the 2<sup>nd</sup> or 3<sup>rd</sup> decade of life, and that there tends to be an increased incidence among females for CD, but not for UC (23). However, beyond supporting the notion that there are important extrinsic factors, these general epidemiological observations are not sufficient to elucidate new clues to the etiology of IBD. Therefore, if epidemiology is to make an

important contribution to understanding the causes of IBD, then new approaches must be taken that are more likely to yield specific etiological hypotheses.

### ***Epidemiological Investigation – Standard Approach***

It is the general nature of epidemiological inquiry to move from the general to the specific. In this regard, the general pattern of investigation of a disease is: 1) describe the overall burden and temporal changes in disease (incidence and/or prevalence), 2) describe the population distribution of disease (according to geography, demography, etc.), 3) formulate and test etiological hypotheses. The first two steps generally use descriptive epidemiology, whereas the third step relies on analytical study methods such as case-control and cohort studies. This approach still holds much promise for IBD research, and should be pursued more vigorously. This means strengthening the specificity of descriptive epidemiological research, and explicitly linking analytic research to findings of the descriptive research both conceptually and with respect to the population to which it is applied.

### ***New Approaches***

In addition to the standard approach, new epidemiological paradigms should be explored. A few suggested approaches are:

1. ***Investigate Emerging Epidemics*** – Although the epidemics of CD and UC are well-established in many European and North American populations, they are still emerging in others. Since newly emerging epidemics are most likely due to environmental changes, a detailed analysis of the patterns of emergence, and a search for temporal environmental changes might reveal new etiological clues. It has been observed that in many populations, UC emerges before CD, so in circumstances where there is a substantial excess in the prevalence of UC over CD might be in the early phases of an emerging epidemic (24). Emerging epidemics of IBD can be sought within certain cultural or ethnic groups, such as recent migrants or those undergoing rapid social and environmental change. As an example, this pattern is now seen in some Aboriginal populations of North America, where ulcerative colitis is more prevalent than Crohn's disease (14). Other examples of emerging epidemics might be found within populations where certain demographic groups or birth cohorts experience an increasing incidence of disease. This type of analysis has been demonstrated by Delc6 and Sonnenberg. They showed a strong birth cohort effect for IBD mortality that was prominent for birth cohorts around the turn of the last century (i.e. late 1800s and early 1900s) in some Western societies (18). More recent examples should also be examined closely. There is evidence in some populations that there has been an increase in the incidence of IBD for recent birth cohorts, and that this might be affecting males more than females (1).

2. ***Investigate “Epidemiologically Odd” cases of IBD*** – For diseases such as CD and UC which are multifactorial, the search for etiological factors is likely to be more fruitful if it is focused on epidemiologically odd cases. Epidemiologically odd cases are those which do not fit the usual risk factor profile for IBD. The rationale for this approach rests on both practical and statistical considerations. From a practical point of view, etiological clues may be more readily discernible in the absence of generally accepted risk factors (such as ethnicity, family history, residence in northern latitudes, etc.). There are also statistical considerations. Observed risk factor associations for specific exposures as measured by relative risks (i.e. on a multiplicative scale) will be larger among those who have few risk factors. Therefore, a systematic and detailed inquiry focusing on those cases that are unusual might yield important new etiological clues.
3. ***Analyze Small Area Variations*** – Although the methods for studying small area variations are still being developed, and there are certainly many potential pitfalls, the epidemiology of IBD is characterized by large geographical variations in incidence. Thus far, most analyses in this regard have focused on differences between relatively large geographic regions (25). However, there is some emerging evidence of substantial small area variations as well (14). The use of geographic information systems and the application of new spatial techniques for data analysis should be employed to study small area variations more systematically, and in a variety of geographic settings.

### ***Future Needs***

Epidemiology is an important and often neglected tool for determining disease etiology. It has been applied in a number of interesting ways to attempt to better understand risk factors for IBD, but more research is necessary. A particular constraint in this regard is the lack of good epidemiological databases or disease registries that cover large populations. The creation and maintenance of such databases or disease registries would provide many new opportunities to apply standard and innovative epidemiological techniques to support the effort to discover the etiology of IBD.

### ***Understanding the natural or ‘drug altered’ history of IBD***

An advantage of population-based databases is the ability to evaluate outcomes for the broad range of IBD patients and not just those who present at a tertiary referral centre. For instance most gastroenterologists at a specialty IBD clinic likely consider that 80-90% of IBD patients are on some form of therapy at any one time and that the majority have been treated with corticosteroids at some time. In fact using population based data it has recently been shown that in 1997 only 65% of Manitobans with IBD were using a drug of the alimentary class (26). It has also been shown that only approximately 40% of IBD patients in Olmsted County have used corticosteroids (27). Defining, on a population-basis, the numbers of patients who ultimately develop cancer, deep venous thromboembolism or fractures can help put into perspective the magnitude of risks for these complications and help develop approaches to which IBD patients at real risk for

these complications can be defined (28-30). In fact the fracture data (an increased risk of only 40% over the general population) should temper the rapidly evolving enthusiasm for widespread bone density testing and bisphosphonate prescribing to many IBD patients. This is one example where epidemiological data can affect clinical practice.

Having large population based databases can allow pursuit of genetic epidemiology, that is, defining the prevalence of newly discovered IBD-specific genes across an unselected group of IBD patients. Research registries can help define the phenotypes of patients who are more likely to respond to one type of therapeutic intervention versus another. Ultimately these Registries can deliver subjects with well characterized genotypic and phenotypic data and hence allow for better subtyping of IBD patients. Perhaps, this will allow for the ultimate description of multiple disease patterns that are currently lumped as Crohn's disease or ulcerative colitis.

### ***Future needs***

Research registries that are population based that can deliver genotype and phenotype data can help identify subgroups of IBD that make sense. Subgroups that have greater rationale or commonality than, for instance, simply being a segmental inflammation (and hence being lumped in as a type of Crohn's disease). These Registries or other administrative databases can be analyzed to determine trends in surgery and mortality and extraintestinal complications. This can not only allow for better patient education, and risk stratification but also for health care planning from a delivery and economic point of view.

### ***Health care utilization***

The detailed use of health care services by persons with IBD, including Crohn's disease and ulcerative colitis, is essential to understanding the resources needed to treat this medically complex condition affecting individuals in their prime productive years. Where possible, a population-based analysis of health care services utilization, in general, helps policymakers to identify areas of apparent unmet need and to make decisions that may expand or restrict the services provided. An understanding of the use of health care services by IBD patients, therefore, should identify problems of access to care or service availability and appropriateness of therapeutic decisions by age, gender, time-period of diagnosis, socio-economic status and geographic residence.

Health care utilization includes that of physician visits, hospitalizations, investigative tests, pharmaceutical use and complementary and alternative medicine use. There are no fully published data on physician visits, hospitalizations, and investigative tests from North America that are population-based.

Regarding prescription drug use to date, there are no US population-based data. There are data on costs and usage of prescription drugs from a large national commercial insurance carrier in both Crohn's disease and ulcerative colitis (31), from another insurance carrier in Crohn's disease alone (32), and from a single university hospital facility in Crohn's disease alone (33). Insurance carrier data are biased to reflect only those groups who

subscribe and may exclude copayments or coverages by other agencies. Hospital based data exclude ambulatory drug prescriptions and reflect the biases inherent to that center in terms of patient population and prescribing practices. One Markov model describing potential lifetime costs of certain drugs in Crohn's disease has been reported based on a population-based dataset (34). The only comprehensive population-based assessment of pharmaceutical use of Crohn's disease and ulcerative colitis including data from ambulatory patients as well as hospitalized ones from North America has been performed using the University of Manitoba database for fiscal year 1997 in the central Canadian province of Manitoba (26).

The Manitoba study found that only 7.8% used immunomodulatory drugs but these accounted for the greatest cost per IBD patient. The purine analogs (6-mercaptopurine (6-MP) and azathioprine) were significantly more prescribed in patients with Crohn's disease than in patients with ulcerative colitis ( $p < 0.05$ ). 6-MP and azathioprine were equally prescribed. 74.8% of 6-MP and azathioprine use (combined total of all purine analog prescriptions), 74.8% of methotrexate, and 36.6% of cyclosporine were prescribed for Crohn's disease rather than ulcerative colitis. This reflects that a considerable percentage of methotrexate was prescribed for ulcerative colitis and of cyclosporine for Crohn's disease, both unproven indications. After the immunomodulatory class of drugs the next most costly class of drugs used by IBD patients was 'alimentary' and these drugs were used by 64.5% of the IBD pharmaceutical user cohort. It is noteworthy that approximately one third of IBD patients were not using 'alimentary' drugs in the year of the study. It is unknown as to whether these prescribing practices in Manitoba can be extrapolated to any areas in the US. Nonetheless, they provide some insight into the extent of use of these drugs (7.8% of the population would be considered limited), and provide some insight into an estimated extent of use of these agents for unproven indications. Finally, when modeling or estimating prescription drug costs for an entire IBD population, it should be considered that up to one third of patients may not be using any alimentary or immunomodulatory drug therapy.

### *Costs of care*

In planning for adequate resource allocation for management of IBD patients it would be critical to have some data on both direct and indirect costs. Population-based direct cost data are lacking. Recently, the AGA's report on "The Burden of Gastrointestinal Diseases estimated the costs of Crohn's disease to be \$826 million compared with \$443 million in ulcerative colitis for 1998 (35). Hospital costs including physician and facility costs have been estimated at \$303 million for Crohn's disease compared with \$192 million for ulcerative colitis. National drug costs in the US in 1998 have been estimated at 105% higher in Crohn's disease (\$283 million) than in ulcerative colitis (\$138 million). The difficulty in estimating costs in the US is partially attributable to the paucity of population based estimates of disease prevalence and partially attributable to the lack of good measures of indirect costs in IBD.

In Sweden, in-hospital costs accounted for 58% of total direct costs for IBD (36). In the United States, a cost estimate analysis using a medical decision algorithm suggested that the major cost for Crohn's disease was surgical intervention along with the requisite preoperative and postoperative care. In fact these authors estimated surgery and hospitalization as accounting for as much as 70% of costs for Crohn's disease (31). Direct charges data from an American insurance company estimated that hospital expenses accounted for 55-60% of total costs for caring for IBD patients (37).

A Canadian study of direct hospital costs at a tertiary care facility using a software program that identified only direct costs exclusive of indirect facility costs reported on differences between costs for hospitalizations for Crohn's disease and ulcerative colitis, and for medical versus surgical admissions in 1994 and 1995 (38). In this study there were no significant differences in the mean cost per admission of all cases of Crohn's disease compared with ulcerative colitis. Patients treated medically were similarly costly whether they had Crohn's disease or ulcerative colitis. Surgical therapy cases accounted for 49.8% of all admissions, 57.8% of all hospital days and 60.5% of all costs. Patients treated surgically had more costly hospitalizations than those treated medically, particularly when analyzing only non-TPN cases. Notably, surgical treatment admissions were significantly more costly for ulcerative colitis admissions than Crohn's disease. There was no significant difference in cost per admission among cases admitted multiple times compared with those admitted only once. TPN cases accounted for 9.5% of cases but 27.1% of costs. TPN associated hospitalizations were more costly than non-TPN use hospitalizations but these costs were primarily driven by duration of stay rather than TPN use itself.

U.S. studies using varying methodologies have reported findings wherein indirect costs per person with IBD range from 113 USD for 1998 (35), to between 1010 USD and 1616 USD for 1990 (31). Using methods different from those used in either of the U.S. studies, a study of the cost of IBD in Sweden in 1994 had findings to suggest that the indirect cost per person was 1,481 USD (36). The range of results indicates a widespread variation at the present time over estimates of the magnitude of indirect costs of IBD.

### ***Future needs:***

There is a great need for population-based data of IBD resource utilization estimates. This can help define what is required to provide adequate service for underserved communities either in rural areas or in underinsured communities as well as what can be expected for the general IBD community. Population-based data of IBD direct costs, and estimates of indirect costs would also assist governments, insurers, and providers to understand the burden of these illnesses. In the absence of access to population-based data the US will have to rely on databases that are accessible. The VA and Medicare databases may capture a skewed sample of IBD patients (generally older, and in the case of the VA, mostly male). This leaves databases from insurers and health maintenance organizations. Data might be assembled from multiple sources to average out the utilization and costs.

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**TABLE 1. Prevalence of inflammatory bowel disease in North America.**

Study or studies (reference)	Setting	Case Ascertainment	Source Population Size	Prevalence Date	Prevalence of UC*	Prevalence of CD*
Pinchbeck et al <sup>3</sup>	Northern Alberta	Population-Based	1,295,000	12/31/81	37.5	44.4
Kurata et al <sup>11</sup>	Southern California	HMO, Outpatient	627,000	1988	NA	26.0
Loftus et al <sup>2,7</sup>	Olmsted County, MN	Population-Based	106,000	1/1/91	229	144.1
Bernstein et al <sup>1</sup>	Manitoba	Population-Based	1,140,000	12/31/94	169.7	198.5

NA, not available; UC, ulcerative colitis; CD, Crohn's disease.

\* Cases per 100,000 persons (most recent prevalence data for source population shown).

**TABLE 2. Incidence of inflammatory bowel disease in North America.**

Study or studies (reference)	Setting	Case Ascertainment	Source Population Size	Incidence Dates	Incidence of UC*	Incidence of CD*
Garland et al <sup>12</sup>	15 cities, USA	Hospital	1,070,000	1973	3.5	4.5
Calkins et al <sup>9</sup>	Baltimore, MD	Hospital	2,174,000	1977-79	2.2	3.1
Nunes et al <sup>8</sup>	Spokane, WA	Hospital	171,000	1981	NA	8.8
Pinchbeck et al <sup>3</sup>	Northern Alberta	Population-Based	1,295,000	1981	6	10
Hiatt et al <sup>13</sup>	Northern California	HMO, outpatient	156,000	1980-81	10.9	7.0
		HMO, hospital	1,700,000	1971-82	5.5	5.2
Stowe et al <sup>10</sup>	Monroe County, NY	Hospital	700,000	1980-89	2.3	3.9
Kurata et al <sup>11</sup>	Southern California	HMO, outpatient	627,000	1987-88	NA	3.6
		HMO, hospital	1,994,000	1988	NA	5.4
Loftus et al <sup>2,7</sup>	Olmsted County, MN	Population-Based	106,000	1984-93	8.3	6.9
Bernstein et al <sup>1</sup>	Manitoba	Population-Based	1,140,000	1989-94	14.3	14.6
Ogunbi et al <sup>6</sup>	Georgia	African-American children only	748,000	1986-95	5.3	8.8

NA, not available; UC, ulcerative colitis; CD, Crohn's disease.

\*Cases per 100,000 person-years (most recent incidence data for source population shown).