Epidemiology of Inflammatory Bowel Disease and Overview of Pathogenesis

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Crohn's disease (CD) and ulcerative colitis (UC) are believed to affect approximately 1.4 million people in the **United States** (US).[1] In many industrialized and developing parts of the world the incidence is rising. Both genetic and environmental factors are believed to contribute to this rise. However, people of all ages, ethnic, socioeconomic, and racial backgrounds are affected.

Incidence

Incidence is defined as the number of new cases of a disease in a defined population occurring within a specified period of time. Population-based studies conducted in the US and designed to evaluate the incidence rate of IBD have been limited. Between 1990 and 2000 the incidence rate of UC and CD in Olmsted County, MN was estimated to be 8.8 and 7.9 per 100,000 person-years, respectively.[2] In 2003, the population of the US and Canada was approximately 320 million people. Loftus et al. determined that between 7000 and 46,000 residents of the US and Canada are newly diagnosed with UC each year. In addition, 10,000 to 47,000 residents of the US and Canada are diagnosed with CD annually.[1] (Table 1)[2-18]

Prevalence

Prevalence is defined as the total number of cases of a disease in the population at a given time. Similar to incidence, data are limited on the prevalence of IBD. Loftus et al. found 214 cases of UC and 174 cases of CD per 100,000 person-years in Olmsted County, MN, on January 1, 2001.[2] An estimated 780,000 people have UC and 630,000 have CD in North America.[1] (Table 2) [2,6,9-11,13,16-20]

Geographic Characteristics

The highest rates of IBD are found in northern, industrialized countries. North America, United Kingdom and Scandinavia have the highest prevalence of IBD.[21] Historically, IBD has been rare in much of Asia, Latin America and Af-

Table 1: Incidence Rates for studies conducted in North America

Authors	Setting	Case Ascertainment	Incidence Dates	Incidence of UC (cases per 100,000 person years)	Incidence of CD (cases per 100,000 person years)
Garland et al.	15 cities USA	Hospital	1973	3.5	4.5
Nunes et al.	Spokane, WA	Hospital	1981	N/A	8.8
Caulkins et al.	Baltimore, MD	Hospital	1977-1979	2.2	3.1
Pinchbeck et al.	Northern Alberta, Canada	Population	1981	6	10
Hiatt et al.	Northern California	HMO	1980-1981	10.9	7.0
Stowe et al.	Monroe County, NY	Hospital	1980-1989	2.3	3.9
Kurata et al.	Southern California	HMO, Outpatient	1987-1988	N/A	3.6
		HMO, Hospital	1988	N/A	5.4
Loftus et al.	Olmsted County, MN	Population	1984-1993	8.3	6.9
Ogunbi et al.	Georgia	Pediatric African-American Population	1986-1995	5.3	8.8
Bernstein et al.	Manitoba, Canada	Population	1989-1994	14.3	14.6
Blanchard et al.	Manitoba, Canada	Population	1987-1996	15.6	15.6
Kugathasan et al.	Wisconsin	Pediatric Population	2000-2001	2.14	4.5
Bernstein et al.	British Columbia Alberta Saskatchewan Manitoba Nova Scotia	Population	1998-2000	9.9 (BC) 11 (Alb) 10.4 (Sas) 15.4 (Man) 19.5 (NS)	8.8 (BC) 16.5 (Alb) 13.5 (Sas) 15.4 (Man) 20.2 (NS)
Herrington et al.	Northern California	HMO	1996-2002	12	6.3
Loftus et al.	Olmsted County, MN	Population	1940-2000	8.8	7.9
Lowe et al.	Quebec, Canada	Population	1998-2000	N/A	20.2

Adapted from Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease. *Gastroenterol* 2004; 126:1504-17.

rica. However, there are reports of increasing rates of IBD on these continents, highlighting the fact that IBD is a dynamic process.[1, 22-26]

Demographic Characteristics

Gender. CD is marginally more common in females (female to male ratio 1.3).[10,11,16] Studies of UC have found either no gender preference or a slight predilection for males. A higher instance of UC in males is seen after age 40.[10,11,16,27]

Age at Onset. The peak age of onset is between 15 and 30 years old; a smaller peak is seen between the ages of 50 and 70 years old, although IBD can occur at any age. Ten percent of newly diagnosed cases occur among children younger than age 18.[21]

Race. IBD occurs more frequently in Caucasian than African-American, Hispanic and Asian populations; however, racial and ethnic differences seem to be decreasing. Recent studies have reported incidence and prevalence rates in African-Americans and Hispanics similar to those found in Caucasians.[12,19]

Ethnicity. The increased prevalence of IBD among the Jewish population is well established. Ashkenazi Jews (eastern European) were found to have a 5 to 8 fold increased risk of developing IBD when compared to non-Jewish populations. [28] Prevalence of IBD is less among non-Jewish Caucasians, African Americans, Hispanic and Asian populations.

Table 2: Prevalence rates for studies conducted in North America and Puerto Rico

Authors	Setting	Case Ascertainment	Prevalence Date	Prevalence of UC (cases per 100,000 person years)	Prevalence of CD (cases per 100,000 person years)
Pinchbeck et al.	Northern Alberta, Canada	Population	12/31/1981	37.5	44.4
Kurata et al.	Southern California	HMO	1988	N/A	26.0
Loftus et al.	Olmsted County, MN	Population	1/1/1991	229	144.1
Bernstein et al.	Manitoba	Population	12/31/1994	169.7	198.5
Appleyard et al.	Puerto Rico	Hospital	1/1/1996 to 12/31/2000	12.53	5.89
Bernstein et al.	British Columbia Alberta Saskatchewan Manitoba Nova Scotia	Population	7/01/00	162.1 (BC) 185.0 (Alb) 234.3 (Sas) 248.6 (Man) 247.9 (NS)	160.7 (BC) 283.0 (Alb) 263.8 (Sas) 271.4 (Man) 318.5 (NS)
Kappelman et al.	USA	33 States (Health insurance claims)	1/1/2003 to 12/31/2004	< 20 yo: 28 >20 yo: 238	<20 yo: 43 >20 yo: 201
Loftus et al.	Olmsted County, MN	Population	1-1-01	214	174
Herrington et al.	USA	9 Health Plans	1/1/1999 to 6/30/2001	191	129
Lowe et al.	Quebec, Canada	Population	1993-2002	N/A	189.7
Herrington et al.	Northern California	HMO (Health insurance data)	12/31/02	155.8	96.3

Adapted from Loftus, EV Jr. Clinical epidemiology of inflammatory bowel disease. *Gastroenterol* 2004; 126: 1504-17.

Environmental Factors

Despite numerous studies, few environmental risk factors have been established, and these factors do not completely explain the occurrence of IBD and the rising incidence of CD. Environmental and genetic factors in combination play a significant role in the development to IBD.

Smoking. Smoking is regarded as the strongest environmental risk factor for IBD. There is an inverse relationship between smoking and UC. Current smoking is considered protective against the development of UC. The relative risk for developing UC while smoking is 40% that of non-smokers. Ex-smokers are 1.7 times more likely to develop UC and to suffer a worse disease course than those who have never smoked.[1,21,29,30] In contrast, smokers are more susceptible to developing CD than nonsmokers. The relative risk for developing CD while smoking is between 1.15 and 3.9. Smokers with CD have a worse disease course than nonsmokers.[21,29,31]

Appendectomy. Appendectomy has been associated with decreased risk of UC susceptibility.[32,33] In contrast, the relationship between appendectomy and CD is arguable, with conflicting results.[34]

Oral Contraceptives. Studies to determine whether females taking oral contraceptives are at a higher risk of developing IBD have shown a weak association. A meta-analysis demonstrated that after adjusting for smoking the risk of developing IBD while taking oral contraceptives was 1.44 for CD (95% CI: 1.12, 1.86) and 1.29 for UC (95% CI: 0.94, 1.77).[35]

Diet. Diet has been extensively studied as a risk factor for both CD and UC. The most predominant risk factor identified has been intake of refined sugars,[36] although a high fat diet has also been implicated,.[37] A critical review of diet studies in IBD revealed a number of methodological flaws; at this point in time, the link between diet and IBD is inconclusive.

Breastfeeding. A meta-analysis concluded that among individuals who were

Table 3: Summary of IBD Epidemiology

Characteristic		Ulcerative Colitis	Crohn's Disease
Incidence Range (North America)		2.2-19.5	3.1-20.2
Prevalence Rate (North America)		12.53-248.6	5.89-318.5
Gender (female : male)		1.1	1.3
Age at Onset (years)		15-30 50-70	15-30 50-70
Race		Caucasians >African >Americans > Hispanic > Asian	
Ethnicity		Jewish >non-Jewish Caucasian >African American > Hispanic	
Mortality (SMR)		0.8	1.2
Environmental Factors			
	Smoking	Protective	Risk factor
	Appendectomy	Protective	No effect
	Oral Contraceptives	Slight risk	Slight risk
	Breastfeeding	Protective	Protective

Adapted from: Friedman S, Blumberg RS. Chapter 289. Inflammatory Bowel Disease. In Fauci AS, Braunwald E, et al. *Harrison's Principles of Internal Medicine, 17th Edition*.

breastfed (duration unknown) the risk of developing CD was 0.67 (95% CI: 0.52, 0.86) and 0.77 for UC (95% CI: 0.61, 0.96).[38]

Measles Infections. Measles virus has been implicated in the development of IBD; however, the literature does not support a causal association.[39] The preliminary evidence suggesting an association with CD has been strongly refuted.[40,41]

Mortality. In North America, the overall survival rate of patients with IBD is similar to that of the US White population. The standard mortality ratios for UC and CD are 0.8 and 1.2 respectively.[42]

Pathogenesis

The current hypothesis states that overly aggressive acquired (T cell) immune responses to a subset of commensal enteric bacteria develop in genetically susceptible hosts, and environmental factors precipitate the onset or reactivation of disease.[43] The hallmark of IBD is chronic, uncontrolled inflammation of the intestinal mucosa.[21]

Evidence suggests that the dynamic balance between microbes, particularly commensal bacteria, and host defensive responses at the mucosal level plays a pivotal role in the initiation and pathogenesis of IBD.[44] Tolerance to commensal bacteria is lost in IBD. Exposure to luminal microflora initiates an inflammatory response by mucosal immune cells. This leads to a chronic, destructive immune response.[21,45] Possible pathogens for UC may include epithelial antigens or functionally altered aerobes, and for CD the antigens seem to be anaerobic bacteria and cell wall bacterial components. [21]

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Overview of Pathology of IBD. Stimulation may occur from the penetration of bacterial products through the mucosal barrier, leading to their direct interaction with immune cells, especially dendritic cells and lymphocyte populations, to promote a classic adaptive immune response.[46] The innate immune system responds first when a pathogen is present in the intestine. Neutrophils infiltrate the intestinal epithelium and release substances that damage surrounding tissues. In addition, neutrophils activate other leukocytes by secreting proinflammatory cytokines TNF-á, IL-â, IL-6 and IL-8..[21,47] Antigen-presenting cells (macrophages) and dendritic cells activate the adaptive immune system. Secretion of cytokines causes the maturation of undifferentialed T cells to effector T cells. These may include TH1, TH2 and, more recently described, T_H17 cell types. [48] Activation of immune-cell populations is accompanied by the production of a wide variety of nonspecific mediators of inflammation (i.e. cytokines, chemokines). These mediators enhance the inflammatory process and tissue destruction, which result in the clinical features of IBD.[46]

Genetic Factors

UC and CD are heterogeneous polygenic disorders sharing some but not all susceptibility loci. [21] However, the presence of a mutated gene does not guarantee that IBD will develop, nor does it predict who will develop IBD .[49] The majority of patients do not have a family history or a known genetic defect,[21,50] yet having an affected family member is the single greatest risk for developing IBD. There is an increased prevalence of IBD in first and second degree relatives, and among these, a higher risk in siblings of affected individuals.[21]

In recent years, much has been learned about the genetic and environmental determinants of disease susceptibility in IBD. Genome wide scanning using linkage mapping has identified over 30 loci in CD.[51] The first susceptibility gene identified was the NOD2/CARD15 gene, located on chromosome 16. Although the pathogenesis of NOD2 mutations in CD patients is incompletely understood, allele variants increase the risk of developing CD. In a meta-analysis of 42 case-control studies the odds ratios of developing CD compared to the general population in homozygotes or compound heterozygotes was 17, while the risk in heterozygotes with the Leu1007fsinsC, Gly908Arg, and Arg702Trp allelic variants were 4, 3, and 2 fold greater, respectively.[52] The association of NOD2 and risk of CD varies by ethnicity and race. Japanese and Asian populations do not report NOD2 mutations, while European countries report ranges between 9% and 14% in Southern Europe and 0% to 9% in Northern Europe.[53] Despite the high relative risk of developing CD with NOD2 mutations, the absolute risk of developing CD among homozygous carriers is only one in twenty-five; thus NOD2 gene mutations alone cannot explain the risk.[53] The most recent genetic studies highlight a few contributing factors to the pathogenesis of IBD; i.e., defects in innate immunity, mucosal barrier function of the gut, regulation of the adaptive immune response and a novel

process called autophagy. The latter process is implicated in recycling of damaged intracellular proteins and organelles, and in dealing with intracellular pathogens, again highlighting the importance of innate immunity in these diseases.[44]

Table 4: Gene Associations with CD and UC

Chromosome	Location (Mb)	Genes of Interest	Associated with CD	Associated with UC
1p31	67	IL23R	Yes	Yes
1q24		EMC1	No	Yes
2q37	231	ATG16L1	Yes	No
3p21	49	Multiple, including MST1	Yes	Yes
5p13	40	Intergenic, PTGER4	Yes	No
5q31	131	Multiple, including SLC22A5	Yes	Unclear
5q33	150	Multiple, including IRGM	Yes	No
5q33	158	IL12B (P40)	Yes	Yes
10q21	64	ZNF365	Yes	Unclear
10q24	101	NKX2-3	Yes	Yes
16q12	49	NOD2	Yes	No
17q21	37	Multiple, including STAT3	Yes	Yes
18p11	12	PTPN2	Yes	Unclear
		BTNL2		Yes
		HLA-DRB1		Yes
1p13	114	PTPN22	Yes	Unclear
1q23	158	ITLN1	Yes	Unclear
1q24	170		Yes	Unclear
1q32	198		Yes	Unclear
5q33	159	IL12B	Yes	Unclear
6p22	21	CDKAL1	Yes	Unclear
6q21	107		Yes	Unclear
6q27	167	CCR6	Yes	Unclear
7p12	50		Yes	Unclear
8q24	127		Yes	Unclear
9p24	5	JAK2	Unclear	Yes
10p11	35		Unclear	Yes
11q13	76	C11orf30	Unclear	Yes
12q12	39	LRRK2,MUC19	Unclear	Yes
13q14	43		Unclear	Yes
17q21	35	ORMDL3	Unclear	Yes
17q21	38	STAT3	Unclear	Yes
21q21	16		Unclear	Yes
21q22	44	ICOSLG	Unclear	Yes

Adapted from Cho JH. The genetics and immunopathogenesis of inflammatory bowel disease. *Nat Rev Immunol* 2008; 8: 458-66; and
Barrett JC, et al. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. *Nat Genet* 2008; 40: 955-62.

Conclusion

CD and UC are chronic conditions that have a substantial negative impact on patients' quality of life. Several studies have demonstrated that the incidence of UC and CD is rising in North America. Current clinical and subclinical characteristics do not adequately account for or predict the variable rate of disease progression or aggressiveness of IBD. To date, there is a lack of well-defined, prospectively evaluated, population-based studies describing IBD in the US.

The etiology of IBD is unknown. However, IBD is thought to result from a complex interaction between genetics, environmental factors, response to intestinal flora, and alterations in innate and adaptive immunity.[44] Most data support a dysfunctional immune response to normal luminal components, infection, and/or a defective mucosal barrier.[21]

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Disclosure of Financial Interests

The authors have no financial interests to disclose.

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