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Inflammatory Bowel Disease: Epidemiology

Sumant S. Arora and Talha A. Malik

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Abstract

Inflammatory bowel disease (IBD) is characterized by two partially distinct alimentary disease processes, namely Crohn's disease (CD) and ulcerative colitis (UC), affecting genetically predisposed individuals. CD and UC were first described in 1932 and 1859, respectively. It is estimated that 1.5 million in North America and 2.5 million persons in Europe have IBD. The peak incidence of CD and UC is between 20–30 years and 30–40 years of age, respectively. Both incidence and prevalence of CD and UC are similar across males and females. However, several studies suggest a female predominance in CD and a male predominance in UC. The pathogenesis of IBD is attributed to an uncontrolled immune-mediated inflammatory response to an unrecognized environmental trigger that interacts with the intestinal flora. Various determinants of IBD include the following: peculiar environmental triggers, intestinal immune mechanisms, heritable factors, gut flora, diet, mesenteric fat, medications, nicotine, infectious agents, immunization, hygiene, pregnancy, breastfeeding, stress and lifestyle. Predominant complications in IBD are surgery, malnutrition, disease exacerbations and cancer. Patients with CD have a higher mortality compared to general population. Epidemiological studies continue to expand our understanding of the distribution, determinants and mechanisms of IBD. This has enabled us to recognize safer and effective approaches to management.

Keywords: inflammatory bowel disease, Crohn's disease, ulcerative colitis, epidemiology, incidence, prevalence

1. Introduction

Inflammatory bowel disease (IBD) is an idiopathic chronic inflammatory disorder of the alimentary tract that encompasses two major closely related yet heterogeneously distinct disease entities—Crohn's disease (CD) and ulcerative colitis (UC). IBD is characterized by

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chronic or relapsing uncontrolled immune activation and inflammation in genetically predisposed individuals to a yet unknown environmental trigger that interacts with the gut flora and primarily affects the digestive tract [1–7]. Historically, Dr. Burrill Crohn, Dr. Leon Ginzburg and Dr. Gordon Oppenheimer first described CD in 1932 as regional or terminal ileitis—inflammation of terminal ileum [8–10]. In 1859, Dr. Samuel Wilks recognized UC as a discrete entity, but it was Sir Arthur Hurst, who described its endoscopic pattern and distinguished it from the more common bacillary dysentery [8, 9, 11]. Pathologically, CD usually consists of transmural inflammation (all layers from mucosa to serosa) and may discontinuously involve any part of the alimentary tract from mouth to anus, whereas UC is characterized by submucosal inflammation limited to the colon [6]. Approximately, one and a half million residents in the USA and two and a half million in Europe have IBD, with about half represented in each of the two discrete IBD subgroups [2, 12].

2. Incidence, prevalence and distribution

Though now recognized worldwide, traditionally IBD was considered a condition that primarily affected Caucasians across Europe, North America and Australia [1]. Hence, most of the available epidemiologic data on CD and UC have been derived from population-based studies conducted in these geographic regions [1]. The incidence and prevalence of CD and UC have stabilized in the aforementioned regions; however, it is still higher than in the rest of the world [1]. Further, the incidence and prevalence of IBD, predominantly CD, have increased in the developing world particularly in the Middle East, Southeast Asia and the Asia Pacific Region [7, 12, 13]. Meanwhile, South America and Africa have significantly low incidence and prevalence rates, albeit anecdotal reports have hinted an increase in incidence [14, 15].

Even in the West, IBD has become increasingly recognized among minority populations [1]. The most significant rise in incidence has occurred in second-generation immigrants from low-risk geographic regions to Western countries, that is, high-risk regions. This supports the concept of an equal if not higher contribution from environmental influences compared to genetic predisposition [1, 16]. Also, has been noted a higher incidence of IBD among immigrants and their families who migrated from socioeconomically backward regions [1]. Moreover, compared to minorities in the West, recent immigrants tend to have a milder disease course [1].

Globally, there remains a paucity of accurate epidemiologic data due to clinical overlap of the IBD entities with conditions such as infectious colitis and differences in the health care systems precluding reliable case estimation. The recognized IBD cases may further only represent a fraction of the actual disease burden due to diagnosis requiring invasive and expensive modalities. Moreover, at times, CD cannot be clearly distinguished from UC, especially early in the disease course before distinctive characteristics have manifested, often requiring reassignment of the IBD subgroup diagnosis [17]. Despite the aforementioned limitations, the incidence and prevalence of both CD and UC have demonstrated a distribution trend. The

incidence and prevalence data vary across the globe depending upon geographic region, environment, immigration trends, ethnicity [1–3] and even differ within the same geographic region. Moreover, a north-south distribution gradient has been observed for IBD risk across the world [18]. This has been attributed to regional differences in sunlight and vitamin D exposure with high levels of exposure inversely correlated with risk of IBD [19, 20].

The annual incidence rates of CD are comparable across most of the developed world. It is estimated to be 20.2 per 100,000 person-years, 12.7 per 100,000 person-years, 29.3 per 100,000 person-years and 16.5 per 100,000 person-years in North America, Europe, Australia and New Zealand, respectively [21–23]. In contrast, Asia has a low incidence rate of approximately 0.54 per 100,000 person-years [24]. Similarly, the incidence rates for UC in North America, Europe and Asia range from 7.6 to 19.5 per 100,000 person-years, 1.7 to 13.6 per 100,000 person-years and 0.3 to 5.8 per 100,000 person-years, respectively [4]. In the past, UC was considered to be slightly more prevalent; however, an increased incidence of CD in the past few decades has resulted in a trend reversal. Most recent estimates of prevalence of CD in North America are 25–300 per 100,000 person-years and that for UC are 170–250 and 43–294 per 100,000 person-years, respectively, in North America and Europe [21, 25, 26]. Overall, both the incidence and prevalence of CD and UC are increasing with time. This can be attributed to a number of factors including improved sanitation, diet and medication exposures, increased IBD awareness among patients and clinicians, use of improved endoscopic and radiologic diagnostic modalities and widened health care access [21, 27].

2.1. Age and gender disparity

Although IBD can occur at any age, the peak age of onset for CD and UC is generally between 20–30 years and 30–40 years of age, respectively [1, 4, 6, 21]. However, some European cohorts have suggested a second peak between 60–70 years of age, especially for UC. The most plausible explanation for this additional peak is ascertainment bias due to increased health care access and more frequent evaluation of older patients. Majority of North American population-based study has shown that the median and mean age of diagnosis of CD and UC range between 30–45 years and 40–45 years, respectively [28, 29]. Additionally, these studies especially in adults have suggested a female predominance in CD and male predominance in UC [1, 30]. This gender-based disparity may be attributed to hormonal or life-style factors. However, the variation is inconsistent, particularly in low IBD incidence regions, where CD may be more prevalent among men [25, 31]. Men tend to be diagnosed with IBD, especially UC at a later age than their female counterparts [6]. On the other hand, in the pediatric population, the trend in gender distribution is reversed with more boys having CD than girls [32].

2.2. Racial and ethnic disparity

There appears to be a marked ethnic and racial variation in the incidence of IBD. Early studies from the 1960s reported a lower incidence of IBD, specifically UC among African-Americans [33]. However, these studies were conducted in regions with predominant white populations, and more recent studies from 1990s have challenged these findings with comparable incidence

rates among Whites and non-Whites [34, 35]. Further, CD was proposed to be more aggressive with earlier age of onset in African-Americans. A recent systematic review, however, suggested that the variance in IBD severity extrapolates from socioeconomic inequalities such as health care affordability and accessibility, rather than inherent biologic or genetic dissimilarities [36, 37]. Ethnically, the Jews in particular are vulnerable to develop IBD, with incidence rates being several fold higher than in the general population across the globe. Further, IBD is more common among the Ashkenazi Jews than the Sephardic Jews in the Middle East, but this trend is reversed in the United States and northern Europe, indicating influence of environmental factors [38].

3. Pathogenesis and risk factors

Pathogenically, IBD is believed to be due to uncontrolled immune activation and inflammation of the alimentary tract in genetically predisposed individuals. It is triggered by the interaction of an unknown environmental agent with the autoantigens believed to reside on nonpathogenic commensal bacteria of the intestinal microbiota (**Figure 1**) [7]. The primary mechanism of inflammatory insult in IBD is immune mediated. Intestinal epithelial cells in active IBD express HLA class II molecules that activate macrophages to secrete pro-inflammatory cytokines (IL-1, IL-6, IL-8, and TNF-α) and suppress the downregulatory cytokines (IL-2, IL-10, and TGF-β) in the lamina propria, thereby fostering chronic inflammation [5, 7, 12].
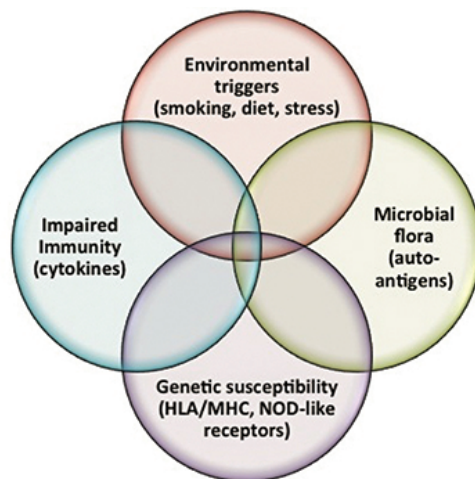

Figure 1. Factors implicated in the etiopathogenesis of IBD.

Various environmental triggers have been attributed to IBD causation. They include external antigens such as infectious pathogens (bacteria and viruses), dietary agents and autoantigens residing on the microbial gut flora [1, 6, 12]. In addition, both CD and UC tend to have genetic predisposition in about 15% cases. In regard to first-degree relative for CD and UC, the lifetime risk of developing IBD is approximately 5 and 2% among non-Jewish populations and 8 and 5% among Jewish populations, respectively [39]. The genetic predisposition is stronger for CD

than UC based on higher concordance rates (50 and 10% vs. 16 and 4%) among monozygotic and dizygotic twins, respectively [40, 41].

Dietary factors more pronounced in typical western diet have been implicated in the pathogenesis of IBD. Comprehensive review of studies involving patients with CD has suggested possible association between increased consumption of refined sugars and animal meat and risk of development of IBD [42, 43]. The aforementioned dietary components are believed to interact with intestinal flora and produce pro-inflammatory agents [44]. Individuals who consume less dietary fiber, raw fruits and vegetables tend to have higher predilection for IBD [44]. Meanwhile, molecular studies have linked adipose tissue to intestinal inflammation [45, 46]. However, it remains unclear if this translates into a causal or clinically meaningful association between obesity and CD. Regardless, obese patients with CD tend to have a rapid disease progression compared to their underweight counterparts [47, 48]. Moreover, sedentary lifestyle is associated with overall higher IBD incidence [49].

Among environmental factors, smoking has a pivotal role in IBD with divergent effects in UC and CD [1]. Both current as well as former smoking, including exposure to passive smoking during childhood, is associated with twofold increase in the risk of CD [50, 51]. Smokers with CD tend to have an earlier age of onset, more aggressive (stricturing or penetrating) disease phenotype, heightened need for steroids and immunosuppressants and overall more surgical interventions as well as higher risk of postresection recurrence [52, 53]. In contrast to CD, smoking safeguards against UC and even indeterminate colitis, with an estimated 50% risk reduction in current smokers. However, this protective effect is less pronounced in females. Further, smokers with UC tend to have milder disease course, with less frequent proximal extension of disease and decreased need for immunosuppression and surgery [53, 54].

The precise mechanisms driving these contrasting effects of smoking on the two IBD subtypes remain unclear. It is hypothesized that smoking causes polymorphisms in genes regulating nicotine metabolism and decreases heat shock protein-70 resulting in reduced protection against cellular oxidative stress, which in turn impairs endothelial function in the intestinal mucosal barrier and promotes inflammation [55–58]. On the other hand, it is proposed that smoking alters the gut flora to reduce predisposition to UC [59].

Recent studies have suggested that infectious agents, such as *Salmonella* and *Campylobacter*, impart heightened risk for IBD development [60], while *Clostridium difficile* and cytomegalovirus have been linked with IBD exacerbations [61, 62]. However, no definite causal association has been identified.

Meanwhile, poor hygienic conditions, including large family size, lack of access to running water, consumption of unpasteurized milk, early exposure to farm animals and pets, have been suggested to protect against IBD development [1, 30, 63–65]. However, these associations are derived from studies conducted in the West and they failed to be replicated in the developing world [1, 66]. On the other hand, there is no definite association between immunization and risk of IBD. Early studies have linked attenuated live measles virus vaccine with IBD occurrence; however, recent studies support the contrary thereby suggesting a protective role [67].

Several pharmacologic agents have also been implicated as potential risk factors for IBD. They include NSAIDs, oral contraceptives, hormonal replacement therapy and antibiotics [68–73]. On the contrary, studies suggesting role of nutritional factors such as vitamin D in IBD development remain equivocal [1].

With regards to pregnancy, there is no definite association between the mode of childbirth (caesarian vs. vaginal delivery) and risk of IBD [74]. However, breastfeeding may play a protective role against IBD development later in life [1]. Meanwhile, depression and anxiety have not only been linked to higher risk of development of IBD but also to increased disease severity, need for surgical intervention, reduced quality of life and diminished response to immunosuppresants [75].

4. Classification

The heterogeneity of demographic, anatomic and disease behavior characteristics in IBD warranted a systematic grouping scheme to place its various phenotypes into simple categories. The first attempt was made by the Working Party of the World Congress of Gastroenterology that met in Vienna in 1998. Their report known as the "Vienna Classification" was published in the Journal of Inflammatory Bowel Diseases in 2000. This classification attempted to stratify CD into 24 disease clusters based on age at diagnosis, disease location and disease behavior (**Table 1**) [76]. Subsequently, the Vienna classification was critiqued owing to lack of universal clinical applicability [77].

	Vienna classification	Montreal classification
Age at diagnosis	A1: Below 40 years	A1 Below 16 years
	A2: Above 40 years	A2 Between 17 and 40 years
		A3 Above 40 years
Location	L1 Ileal	L1 Ileal
	L2 Colonic	L2 Colonic
	L3 Ileocolonic	L3 Ileocolonic
	L4 Upper	L4 Upper disease modifier or isolated upper disease
Behavior	B1 Nonstricturing, nonpenetrating	B1 Nonstricturing, Nonpenetrating
	B2 Stricturing	B2 Stricturing
	B3 Penetrating	B3 Penetrating
		p Perianal disease modifier

Table 1. Vienna and Montreal classification of Crohn's disease.

The Working Party of the Montreal World Congress of Gastroenterology then met in 2005 and put forth the Montreal classification of IBD (**Tables 1** and **2**) [78]. This new scheme grouped

CD primarily based on the same variables proposed by the experts at Vienna including patient's age at diagnosis (A1, 16 years and younger; A2, 17–40 years; A3, >40 years), disease location (L1, ileal: L2, colonic; L3, ileocolonic) and disease behavior (B1, nonstricturing, nonpenetrating; B2, stricturing; B3, penetrating). In addition, it introduced modifiers for upper tract disease location (L4) and for perianal disease (*p*). Further, it extended the classification to stratify UC based on the extent and severity of the disease (**Table 2**) [78].

Class	Extent	Description
E1	Ulcerative proctitis	Proximal extent of inflammation distal to rectosigmoid junction
E2	Left-sided UC (distal UC)	Involvement limited to proportion of colorectum distal to the splenic
E3	Extensive UC (pancolitis)	Involvement extending proximal to splenic flexure

Table 2. Montreal classification of ulcerative colitis.

5. Disease course

Based on phenotype by location, of all patients with CD at the time of diagnosis, one-third of patients have ileal involvement, one-third of patients have colonic involvement and the rest have ileocolonic disease. While with regard to disease behavior, 80% of all patients with CD at the time of diagnosis have nonpenetrating/nonstricturing disease with the remaining 20% having stricturing or penetrating disease [79]. As CD evolves, of all with nonpenetrating/nonstricturing disease, up to one-third of patients progress to penetrating or stricturing complications at 5 years and about half at 20 years from diagnosis [79]. Further, in terms of disease activity, based on data from prebiologic era, about two-thirds of patients with CD tend to have a remitting and risk of CD relapsing course one-fifth remain active and about 13% enter long-term remission [80].

Meanwhile, for UC at the time of diagnosis, one-third of patients tend to have colonic involvement distal to rectosigmoid junction, one-third up to splenic flexure, while the remaining third have pancolitis, that is, contiguous involvement extending proximal to the splenic flexure [2]. The disease behavior is variable; 50% of UC patients with proctitis/proctosigmoiditis progress to extensive disease at 25 years [81]. While in regard to disease activity, based on data from prebiologic era, 57% of patients with UC tend to have a remitting and relapsing course, one quarter go into long-term remission, and about one-fifth remain active [39, 82].

6. IBD and morbidity

The key factors driving morbidity overlap between the two IBD subgroups—CD and UC. The predominant causes of morbidity in patients with CD are need for surgery, malnutrition followed by disease exacerbations and cancer [2, 4]. While among patients with UC, the major

burden of morbidity is due to the development of cancer followed by requirement for surgery and disease exacerbations [2, 4]. Overall, surgery remains the most common cause of morbidity in CD and a significant cause of morbidity in UC. Recently, the cumulative risk of IBD, particularly patients with CD requiring surgery has significantly decreased with rates of surgery being approximately 10–14% and 18–35% after 1 and 5 years, respectively [83–88]. This is attributed to adoption of more aggressive medical therapy in recent times [1, 2, 83, 84, 89, 90]. Based on age, location and behavior of CD, the greatest need for surgery is with ileocecal location and stricturing or penetrating/fistulizing disease phenotype [2, 86, 87]. Similarly, in UC, the likelihood of need for colectomy has decreased recently with estimated rates of 6 and 10% after 1 and 5 years, respectively [83, 91–93]. The highest probability of colectomy is in those with relatively recent diagnosis and severe disease especially pancolitis [2].

An interesting association has been observed between appendectomy and IBD [1]. While appendectomy is found to protect against future occurrence of UC, it may lead to an increased incidence of CD [94–96].

With regard to cancer as one of the drivers of morbidity, the overall risk of colorectal cancer is significantly higher in patients with IBD compared to the general population. The primary factors influencing this risk include persistent active inflammation, immunosuppression, long-standing disease, extensive disease, young age at diagnosis, family history of colorectal cancer and coexisting primary sclerosing cholangitis [2, 97]. Overall, patients with IBD have heightened risk of extraintestinal cancers such as lymphoproliferative and skin cancers [2, 98–100].

7. IBD and mortality

Whether or not having IBD confers a higher mortality remains debated. Population-based studies from 1980s to 1990s suggested a moderate increase in mortality rate in CD [101, 102]. However, recent European studies have failed to replicate these findings and indicate a comparable mortality rate in CD to the general population [103–105]. Major causes of mortality in CD include direct, such as surgical complications and malnourishment, and indirect related to smoking [101, 106–107].

Similarly, there is lack of definitive evidence to support higher mortality rate in patients with UC [105, 107–110]. However, unlike CD, most deaths in UC are due to colorectal cancer than from surgical or other complications [106, 109].

8. Conclusion

In conclusion, IBD is a condition with a unique etiopathogenesis and significant epidemiologic burden. To the present day, epidemiological studies continue to expand our understanding of the distribution, determinants and mechanisms of IBD. This has enabled us to recognize safer and more effective approaches to management and therapeutics outside of mere immunosuppression for IBD with emphasis on prevention, preemption and immunomodulation.

Author details

Sumant S. Arora[1*] and Talha A. Malik[2]

*Address all correspondence to: sumantarora@uabmc.edu

1 Department of Medicine, University of Alabama at Birmingham, Montgomery Residency Program, Montgomery, Alabama, USA

2 Department of Medicine-Gastroenterology and Department of Epidemiology, University of Alabama at Birmingham, Birmingham, Alabama, USA

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