

East Meets West: The Increasing Incidence of Inflammatory Bowel Disease in Asia as a Paradigm for Environmental Effects on the Pathogenesis of Immune-Mediated Disease

Q2 Yunsheng Yang,¹ Chung Owyang,² and Gary D. Wu³

¹Chinese PLA General Hospital, Beijing, China; ²Division of Gastroenterology, University of Michigan, Ann Arbor, Michigan; ³Division of Gastroenterology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Many diseases have increased dramatically in incidence over the past few decades in parallel with global industrialization. Diseases such as asthma, eosinophilic esophagitis and other atopic diseases, metabolic syndrome, obesity, and inflammatory bowel disease (IBD), to name a few, have become much more prevalent over the past 60 years beginning in Western societies, followed by Asian countries such as Japan and Korea, and now involving China and India. Using IBD as an example of a multifactorial disease with genetic and environmental elements involved in disease pathogenesis, it is clear that environmental factors are predominately responsible for the increasing incidence of these diseases. However, the exact nature of these environmental factors remains ill-defined. Given the fundamental role that the intestinal microbiota plays in immune regulation and the pathogenesis of IBD, it is reasonable to speculate that microbial and dietary alterations may be playing a central role in rising IBD prevalence. On April 7, 2016, the Chinese Society of Gastroenterology and the American Gastroenterological Association jointly sponsored a symposium in which experts from a diverse spectrum of disciplines met to compare and contrast Asian versus Western aspects of epidemiology and clinical phenotypes, as well as genetic and environmental factors as a first step toward understanding the factors that may be playing a role in the increasing incidence of IBD in Asia.

Epidemiologic Trends in IBD

Siew Ng opened the session by describing the changing epidemiology of IBD in Asia. The recent prospective ACCESS-IBD (Asia-Pacific Crohn's and Colitis Epidemiology Study) cohort provides, for the first time, detailed incidence and natural history data for IBD in East and Southeast Asia. The incidence of IBD across Asia was 1.37 per 100,000, with China having the highest incidence at 3.4 per 100,000 individuals. Across Asia, the incidence of IBD varies from 0.5 to 3.4 per 100,000 people, and seems to be greater in highly urbanized countries. Although lower than the West, the rapid increase in incidence over the past decade is consistently observed, particularly in Japan, Korea, Hong Kong, and mainland China. Ulcerative colitis (UC) appears first, followed by Crohn's disease (CD). The UC to CD ratio is 2.0 in Asia, but this gap is narrowing over time. Complicated CD is as common in Asia as in the West and the evolution of disease phenotype over time is similar to that in the West.

Ashwin Ananthakrishnan described the epidemiologic trends of IBD in the West. Population-based data from 1990 to 2000 from the Olmsted County cohort in the United States estimated the age-adjusted incidence of CD and UC to be 8 and 8.8 per 100,000, respectively. Similar estimates have been reported from population-based cohorts in North America, Europe, and New Zealand with some estimates of incidence of CD and UC being even higher at 15 and 14.5 per 100,000, respectively, from Manitoba, Canada. However, consistent across most population-based cohorts in the West, there has been a significant increase in incidence of IBD over the past 4 decades, with some studies suggesting a continued increase, while others demonstrate this continued increase only in the pediatric age groups. Within established high-incidence countries, north-south gradients in incidence with higher incidence in northern latitudes have been reported from Europe and North America. Variations in diet, lifestyle, and ultraviolet exposure may contribute to this gradient. However, even within a region, there may be significant small area variation influenced by rural-urban divide and ethnicity, among other factors. Immigrant populations may provide important insights into the relative contributions of genes and environment in the disease pathogenesis. Immigration to a high-incidence region from low-incidence countries is associated with an increase in risk of IBD in the second-generation offspring; however, this increase in risk may not be uniform across all ethnicities and countries of origin. The discussion at the conclusion of the session proposed reasons for the dramatic increase in the incidence in previously low-incidence countries, including a changing diet with adoption of a "Westernized" lifestyle, potential contribution of urbanization, environmental pollution, and changes in lifestyle.

Clinical Phenotypes of IBD and Approach to Treatment in Western versus Asian Countries

The second session compared the clinical characteristics and natural history of IBD in Eastern and Western

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populations. Professors Jiaming Qian and Kaichun Wu presented data about the phenotype and natural history of IBD from 2 large cohorts in China and Professor Dong Soo Han presented data from population-based cohorts in Korea. Ashwin Ananthakrishnan contrasted the observations in Asia with that observed in population-based cohorts describing the natural history of IBD in Western countries. Available national estimates suggest considerable burden of CD and UC in Asia, with an estimated 155,116 and 39,799 cases of UC and CD, respectively, in Japan and 32,026 UC and 18,242 and CD cases in Korea. The peak age of onset in Asia is in the third, fourth, and fifth decades of life, consistent with the pattern observed in Western countries. The distribution of disease location and behavior is similar between Asia and the West with an ileocolonic predominance affecting approximately 50% of cases. Perianal involvement was noted more commonly in Japan and Korea, affecting as many as 40% to 50% of CD patients, compared with the 26% rate of involvement at 20 years reported in cohorts from the West.

Complicated disease at diagnosis is as common or more common in Asia with similar rates of progression from inflammatory behavior to fibrostenosing and penetrating complications. The greater frequency of complicated disease is also not explained by diagnostic delay, because the interval between onset of symptoms and establishment of diagnosis is similar in both regions. The extent of UC is comparable in both regions, although some studies from Asia have reported that as many as 68% of UC patients have left-sided colitis. Extraintestinal manifestations, particularly primary sclerosing cholangitis, are less common in Japan and Korea when compared with Western cohorts.

The rates of CD-related surgery and recurrence post-operatively are comparable between the 2 regions. In contrast, UC in the East is characterized by a mild disease course and a less frequent need for immunosuppression and for surgery. The cumulative probability of colectomy at 10 years was 10% to 20% in Western cohorts compared with 7.8% in cohorts from Asia. Cohort studies have suggested a significantly lower proportion of patients on immunomodulators and biologic therapies in Asia compared with Western countries. Such differences could reflect a milder disease course in Asia (as suggested by lower rates of colectomy in UC), patient and provider hesitation regarding long-term immunosuppression particularly in the setting of competing infectious risks, and cost and access to therapies. It is important for future studies to determine if such variations reflect different disease biology or practice variation. Limited data exist about the comparative effectiveness of immunosuppressive or biologics in Asia compared with the West. Azathioprine is frequently maintained at a lower dose in Asia compared with the West, but is associated with similar long-term outcomes, with this difference potentially being due to more favorable pharmacokinetics. However, this is also associated with higher rates of leucopenia in Asia. Emerging data from North American and European cohorts demonstrate a secular reduction in the need for surgery in both CD and UC, suggesting that current treatment practices may be beneficially modifying the

natural history of IBD. Whether a similar effect will emerge in Asia with growing use of newer therapies is unknown, but must be considered in ensuring access to such modalities.

The Genetics of IBD: Western Societies versus Asia

Judy Cho and Byong Duk Ye compared and contrasted the genetics of IBD in Western versus Asian societies. Epidemiologic studies have suggested that the development of IBD is strongly influenced by genetic predisposition. To overcome the limitations of linkage studies, "hypothesis-free" genome-wide association studies (GWAS), GWAS meta-analyses, and targeted genotyping array techniques have been performed during the past decades, and have broadened our understanding of the genetic basis of IBD. After the first GWAS in Japanese patients with CD, which revealed *TNFSF15* as a CD-susceptible gene, subsequent GWAS and ImmunoChip studies showed that some risk loci for CD are shared between East Asians and European ancestry populations, although some seem to be unique to the East Asian populations. Studies on East Asian UC patients have shown a tendency toward more extensive genetic overlap with European ancestry populations than that seen in CD. The first transethnic association study of IBD increased the number of IBD risk loci to 200, with 231 independent single nucleotide polymorphisms, with the direction and effect size being consistent in the European and the non-European ancestry cohorts for the majority of the IBD risk loci. The observed genetic heterogeneity across divergent populations at several risk loci is by differences in risk allele frequency (*NOD2*) or effect size (*TNFSF15-TNFSF8* and *ATG16L1*) or a combination of these factors (*IL23R* and *IRGM*), as previously reported. Because host genetic factors are suggested to play a role in shaping the gut microbiota in IBD patients as well as in healthy individuals, the different genetic architectures between Europeans and Asians may lead to differences in the gut microbial milieu, thereby contributing to different incidences and clinical characteristics of IBD across populations. Still, the number of genes/loci significantly associated with IBD risk in Asian populations is much fewer than that of European ancestry populations, at least partially resulting from the smaller cohorts studied thus far. Therefore, more genetic studies with larger cohorts are needed in Asia, combining analyses of genetic, microbiome, and environmental factors.

Dietary Factors in IBD Pathogenesis

Much of Asia has experienced rapid urbanization and transformation from low to middle income to urbanized, high-income countries, resulting in a massive transformation of health concerns from undernutrition to overnutrition. Data presented by Anthony Fodor and Penny Gordon-Larsen showed that dietary changes in China have occurred more rapidly than anywhere in the world, with 20-year increases in animal source foods (a key indicator of Western diet) and edible oils, declines in coarse grains and vegetables, and

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