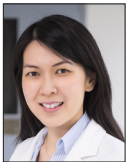


ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

Emerging Trends of Inflammatory Bowel Disease in Asia



Siew C. Ng, MBBS, PhD
Associate Professor
Department of Medicine and Therapeutics
Institute of Digestive Disease
State Key Laboratory of Digestive Disease
Chinese University of Hong Kong
Sha Tin, Hong Kong

G&H What is the incidence of inflammatory bowel disease in Asia?

SN The incidence of inflammatory bowel disease (IBD) in Asia is estimated to be less than 5 per 100,000 people. In ACCESS (Asia-Pacific Crohn's and Colitis Epidemiology Study), which my colleagues and I conducted from 2011 to 2013 across 8 countries in Asia, the incidence of IBD in each country ranged from 0.5 to over 3 per 100,000 people.

In addition, we found that the incidence of ulcerative colitis was approximately 1 per 100,000 in Asia, while the incidence of Crohn's disease was slightly lower, at approximately 0.5 per 100,000 people.

G&H How do these rates compare with the incidence of IBD in the Western world?

SN IBD is more common in the Western world, with higher rates of incidence and prevalence. According to various papers published in the literature, the incidence of IBD in the Western world is between 20 and 30 per 100,000 people. As part of ACCESS, my colleagues and I also examined the incidence of IBD in Australia, which is considered to be a Western counterpart, over the same time period that we examined 8 Asian countries. We found that the overall incidence of IBD in Australia was approximately 21 per 100,000 people, the incidence of ulcerative colitis was approximately 10 per 100,000 people, and the incidence of Crohn's disease was

approximately 12.5 per 100,000 people. Thus, the incidence of IBD is higher in the West than in Asia, although we have seen increasing trends in Asia over time.

G&H Could you describe the recent trends of IBD in Asia?

SN Several countries in Asia, although not all, have population-based data on the incidence of IBD over time. For example, Japan has over 200,000 cases of IBD according to its national insurance health care system, which has recorded IBD cases since the 1970s, and this number has increased from 30 years ago. According to Hong Kong's registry system, the age-adjusted incidence of IBD has increased from 0.1 per 100,000 in 1985 to more than 3 per 100,000 in 2014. There was a 6-fold increase in the incidence of Crohn's disease over this time period. Other countries in Asia, including Korea and Taiwan, also have data showing an increasing trend of IBD over the past decade.

However, the rate of the increase in IBD does not appear to be uniform. It seems that some countries (such as China) are experiencing a more rapid increase than other countries, mostly due to rapid urbanization and industrialization. It will be important to follow these countries and monitor their epidemiologic and incidence trends over the next 20 years. Health care resources and providers will need to address the consequences (both medical and economic) of the impact of IBD in these countries.

G&H Could you further explain why IBD is increasing in these countries?

SN The increase is most likely due to changes in environmental factors and triggers that have occurred in Asia over the past several decades. Disease emergence in developing nations suggests that epidemiologic evolution is related to westernization of lifestyle and industrialization.

G&H Are the environmental risk factors for IBD in Asia the same as those in the Western world?

SN The strongest environmental associations that have been identified are cigarette smoking and appendectomy, although neither alone explains the worldwide incidence of IBD. Urbanization, which is associated with changes in diet, antibiotic use, hygiene status, microbial exposures, and pollution, has been implicated as a potential environmental risk factor for IBD. In a recent case-control study in Asia consisting of over 400 incident cases of IBD and over 800 matched controls in the Asia-Pacific region, my colleagues and I noted several important findings. The most striking finding was that breastfeeding for more than 12 months was markedly protective (>90%) for the development of Crohn's disease and ulcerative colitis. This finding is quite consistent with study findings from New Zealand and Denmark. We also found that westernization of diet, including higher juice and cereal intake, appears to be a risk factor for the development of Crohn's disease and ulcerative colitis, when compared with controls.

We also found that the consumption of tea and coffee, which may contain antioxidants, seems to have a protective effect for IBD. In addition, having pets at a young age (ie, the hygiene hypothesis) appeared to be a protective factor for Crohn's disease. Both of these findings have also been seen in IBD patients in other parts of the world.

The main difference between our study findings and literature in the Western world is that antibiotics have a protective effect in Asia for Crohn's disease and ulcerative colitis. In contrast, many of the studies in the West have shown that the use of antibiotics in childhood is a risk factor for the development of IBD. The use of antibiotics in Asia may represent a surrogate marker of exposure to gastrointestinal infections, and antibiotic use may be a marker of more frequent childhood infections that may lead to intolerance.

G&H Do genetic risk factors for IBD differ between Asia and the Western world?

SN It appears that they do differ. Many of the genes that have been consistently reported in the Western literature

for their association with IBD, for example *NOD2* and *ATG16L1*, are not present in people with Crohn's disease in Asian countries. It appears that there is some genetic heterogeneity. In Asians, there are more patients with *TNFSF-F15*. Differences between IBD in Asia and the West may be driven by the magnitude of effect or differences in allele frequency. I work closely with the International IBD Genetics Consortium, and we recently published the results of a study in *Nature Genetics* that identified 38 novel loci associated with IBD in a transethnic cohort. Some, but not all, of these loci overlapped with those of the white cohort.

The role of family history of IBD is also different in Asia. Having a family history of IBD is more common in the West than in Asia. For example, only 3% of IBD patients in studies from Asia have reported having a family history of IBD, whereas this rate is as high as 15% in studies from the West. I expect that the prevalence of family history of IBD will increase in Asia as the disease becomes more common.

G&H What is known regarding the progression of IBD in Asia, and how does it compare to the progression of IBD elsewhere?

SN In Asia, approximately one-third of Crohn's disease patients have complicated disease behavior at diagnosis, including strictures or penetrating disease. Data from our ACCESS incident cohort showed that approximately 5% will develop intestinal complications by 1 year. Also according to our ACCESS findings, the natural history and prognosis of Asian patients with Crohn's disease were not different from those of a Western cohort. A large proportion of patients with Crohn's disease in Asia need an operation despite increasing use of immunosuppressants, and approximately three-quarters will need surgery within the first year of diagnosis.

The main difference we found was that colectomy for ulcerative colitis was lower in Asia than in the Western world. It is not clear whether this lower rate relates to milder disease or differences in management or physician/patient threshold for surgery.

Interestingly, we also rarely encountered patients with acute severe ulcerative colitis or fulminant ulcerative colitis. I suspect that genetic differences may account for this lower rate.

G&H Are there differences in clinical manifestations of IBD between Asia and the Western world?

SN Although many of the clinical manifestations are comparable, there are several differences. One is the predominance of ulcerative colitis in Asia, although in recent

years there has been a reduction in the ratio of ulcerative colitis to Crohn's disease cases in countries in East Asia, such as Korea and Hong Kong. The ratio of ulcerative colitis to Crohn's disease is close to 1 now. Another difference is that there is a male predominance of IBD in Asia. There is also more ileocolonic disease (ie, both large bowel and small bowel disease), and a substantial proportion of patients with Crohn's disease in Asia (up to one-third) have perianal manifestations at diagnosis.

G&H Are there any differences in terms of serology?

SN There are limited data, but one study that compared IBD patients from Hong Kong with those from Australia found that whites with Crohn's disease typically had a higher antibody prevalence of certain serologies (eg, anti-*Saccharomyces cerevisiae* and perinuclear antineutrophil cytoplasmic antibodies). This suggests that serologic and immune responses may differ slightly between countries or different ethnic groups. However, further research is needed to determine whether this finding holds true in a larger group of patients.

G&H How do treatment approaches for IBD compare between Asia and the Western world?

SN Treatment approaches are quite similar, but some countries in Asia may be limited by access to specific drugs. The first line of treatment for ulcerative colitis in Asia is 5-aminosalicylic acid (5-ASA). Leukapheresis is commonly used for ulcerative colitis in Japan, and tacrolimus is commonly used in Japan, Korea, and Hong Kong. (Both of these treatments are not commonly used in the West.) Quite a large proportion of patients with mild Crohn's disease in Asia continue to be prescribed 5-ASA. At the moment, there is also increasing use of biologic agents in Asia, especially for ulcerative colitis, although these agents are still not being used as much as in the West. This is because physicians in Asia are still getting used to these extremely potent drugs, and health care resources and financial support vary among countries in Asia. Different countries have access to different biologics. For example, in Hong Kong, approved biologics include infliximab (US trade name Remicade, Janssen) and adalimumab (US trade name Humira, AbbVie), and soon vedolizumab (US trade name Entyvio, Takeda) will be available.

Thus, overall the drugs conventionally used for IBD in the Western world are also being used in Asia. However, in several countries (eg, Japan, Korea, Hong Kong), less conventional drugs are also being used, such as tacrolimus and thalidomide.

G&H Are there any particular challenges with diagnosing and managing IBD in Asia?

SN The main challenge is the risk of infection, as well as being able to exclude infections to establish the correct diagnosis. In Asia, bacterial infections (eg, tuberculosis, amebiasis, *Clostridium difficile* infection) are quite high in prevalence, so it is very important to be able to differentiate between these conditions and IBD. In my experience, differentiation of intestinal tuberculosis from Crohn's disease remains a clinical challenge and is very important, as the treatment approaches are very different. Sometimes patients require a laparotomy or even empirical therapy with anti-tumor necrosis factor drugs before a diagnosis can be made.

G&H Are there significant differences among IBD patients in different Asian countries?

SN For East Asia (ie, Japan, Korea, Hong Kong, China), the disease course, prognosis, complications, and severity are quite similar. However, for certain Asian countries such as India, there is a higher predominance of ulcerative colitis than Crohn's disease. Within Asian countries, differences in disease phenotype or course may be, in part, due to differences in ethnicity/genetic background, diet, or physician management.

G&H What lessons can the Western world learn from IBD in Asia? Why is it important to understand differences in IBD in different populations?

SN Treatment effects and risk factors differ in different populations. IBD is moving toward personalized medicine, which is targeted to a particular patient. No single drug will be appropriate for every patient with IBD. Thus, it is important to determine targets, treatment outcomes, and responses in populations with different genetic backgrounds or microbial factors.

Furthermore, comparing IBD between the Western world and newly industrialized countries may offer clues to the underlying environmental underpinnings of the disease. In addition, by identifying environmental triggers of IBD, public policy initiatives may be instituted to modify environmental exposures that prevent the disease.

G&H What are the next steps in research?

SN There are many remaining research needs. First, we need to be able to predict and define the burden of IBD in Asia so that we can understand the global needs of IBD for the next several decades. Epidemiologic research can help estimate disease burden so that we can inform health

care providers of the magnitude of the problem and how resources should be channeled into the management of this disease. Second, we need to try to identify the cause of IBD, prevent progression, and definitively determine whether early treatment can prevent some of the natural history and complications that patients develop. Third, we need to improve the standard of care for patients with IBD. Finally, we need to be able to personalize treatment.

Dr Ng has served as a speaker for Ferring, AbbVie, Janssen, and Takeda.

Suggested Reading

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