



# Inflammatory Bowel Disease in Asia: The Challenges and Opportunities

Pin-Jin Hu

*Department of Gastroenterology, the Sixth Affiliated Hospital, Sun Yat Sen University, Guangzhou, China  
President of the Asian Organization for Crohn's and Colitis*

The incidence and prevalence of IBD, including UC and CD, has been increasing rapidly in Asia over the last two decades.<sup>1</sup> Dilemmas are arising along with an increasing number of patients with IBD in Asia. For example, the knowledge on IBD has not been popularized in the vast area of Asia, and many IBD patients still do not receive a timely diagnosis and appropriate treatment. In addition, health care for patients with IBD has not received sufficient attention. How can these challenges be turned into opportunities? Alternatively, these challenges can be used to encourage Asian doctors and investigators to obtain more diagnostic and therapeutic skills for managing IBD. Asian researchers can use the growing IBD incidence to explore the etiology and pathogenesis of this disease.

## EPIDEMIOLOGICAL STUDY

Epidemiological data in Asia is important for exploring the etiology of IBD. The increasing incidence of IBD in Japan,<sup>2</sup> Korea,<sup>3</sup> China,<sup>4</sup> Singapore, India, and other Asian countries<sup>5</sup> is closely associated with urbanization. There are huge geographic variations in the incidence and ratio of CD to UC among countries in Asia<sup>5</sup> and even among different areas within a country.<sup>4,6</sup> A recent immigrant study showed a high prevalence of IBD in United States residents of Indian ancestry.<sup>7</sup> All these observations strongly implicate the environmental influence on disease occurrence. Preliminary studies

have found that a Western style diet, hygiene, and childhood immunological factors are associated with IBD in Asia, all of which are the results of urbanization.<sup>8,9</sup> Studies in Asia have started to link environmental factors with changes of the gastrointestinal microbiota.<sup>9,10</sup> The fundamental aspects of the pathogenesis of IBD are correlated with the abnormal mucosal immune response to antigenic stimulation from the gut microbiota secondary to environmental influence, with the background of genetic susceptibility. It has been suggested that the low incidence of IBD in the Asian population may be due to less IBD-susceptible genes compared to that in Westerners. The IBD-susceptible genes that have been firmly associated with CD in the Caucasian population such as *NOD2*, *interleukin (IL)-23R*, and *ATG16L1* showed no correlation with CD in Japanese, Korean, and Chinese Han patients with CD, except *IL-23R* had a weak association with Korean CD patients.<sup>11</sup> However, single nucleotide polymorphisms (rs3810936, rs6478108, and rs7848647) on *TNFSF15* have been identified to be more strongly associated with Asian CD patients than with Caucasian CD patients.<sup>11</sup>

To date, few epidemiological studies have been performed in Asia, because there is a lack of national registries in most Asian countries. Only a few novel Asian IBD-associated genes have been identified, and the study of epigenetic alteration just recently emerged in Asia. Studies on the interaction of environmental factors, gut microbiota, and susceptible genes in Asia should be focused on in the future. Since all these challenges exist, collaborative works should also be performed. Longitudinal studies on the early occurrence of IBD in Asia and cross-sectional studies among countries or the different ethnicities in Asia will provide amazing opportunities for Asian researchers.

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Correspondence to Pin-Jin Hu, Department of Gastroenterology, the Sixth Affiliated Hospital, Sun Yat Sen University, Guangzhou, China Tel: +86-20-38254020, Fax: +86-20-38254221, E-mail: pjhumd@vip.163.com

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**DIAGNOSIS AND MANAGEMENT OF IBD IN ASIA**

The diagnostic and therapeutic patterns of IBD are quite different in Asia.<sup>12</sup> With the growing number of IBD patients, continuous education and academic activities should be encouraged throughout this continent. However, there are guidelines on IBD management in Japan, China, Korea, etc.

The disease phenotype and evolution of IBD in Asia show some differences from that in Western countries.<sup>13</sup> For example, there is a higher prevalence of IBD in the male sex and ileo-colonic CD in South-Eastern Asia. We cannot exclude the possibility that the lower incidence of colorectal cancer in patients with UC may be correlated with a short history of IBD in Asia. Thus, it should be emphasized that long-term follow-up prospective studies from multiple centers and surveillance of colorectal cancer in colonic IBD patients should never be neglected. Consistent studies have indicated that surgical rates remain much lower in Asian UC patients than in Western countries.<sup>14</sup> It is unclear whether Asian UC patients truly have a less severe disease that leads to a lower risk of colectomy or if lower colectomy rates reflect the different cultural background between the West and East. Long-term, prospective, comparative studies among Asian and Western countries are necessary to determine the true differences and outcome, especially with regard to the quality of life. The risk of complication with deep vein thrombosis in hospitalized IBD patients has been emphasized in Western guidelines, and only in a few studies in Asia.<sup>15</sup> Therefore, further studies on deep vein thrombosis are warranted in Asia.

There are special situations in the differential diagnosis of IBD in Asia, because intestinal infectious diseases that mimic IBD are still common in the Asian population. Thus, intestinal infectious diseases should always be excluded before making the diagnosis of IBD in Asian patients. The differentiation of CD with intestinal tuberculosis is important, but it is sometimes difficult. There have been many studies on this topic in Korea,<sup>16</sup> India,<sup>17</sup> China,<sup>18</sup> etc. An Asian consensus on the differential diagnosis of these two diseases will be able to be reached when there is enough evidence in this field. Behçet disease (BD) is rare in the United States and Northern Europe, but it is common in East Asia and the Middle East. Intestinal BD is difficult to diagnosis and differentiate from CD when systemic manifestations do not emerge. A novel diagnostic criterion of intestinal BD, especially for patients with ileo-colonic ulcer, has been proposed by Korean experts.<sup>19</sup> Further studies are needed to determine its impact on the therapeutic and prognostic assessment.

From the therapeutic aspect, the most different consideration is the application of anti-tumor necrosis factor (TNF) therapy in developing countries in Asia.<sup>20</sup> First, most patients with refractory IBD who would benefit from anti-TNF therapy usually cannot get therapy because of the high cost and lack of medical insurance. Immunosuppressants, exclusive enteral nutrition, some medicines with potential effects such as thalidomide, and even surgery would provide additional choices or alternatives in these situations. Studies on the effect and safety of these alternative therapies are particularly expected. Second, the cost-effectiveness should be seriously considered when using anti-TNF therapy as the first-line therapy for the treatment of IBD, especially in countries in which patients cannot afford long-term maintenance therapy. Third, the treatment risk should always be considered, because the prevalence of infectious diseases is still very high in most Asian countries (e.g., hepatitis B and tuberculosis). Screening before anti-TNF administration, prophylaxis during use, and close monitoring are necessary. It may be reasonable that dedicated IBD centers take the responsibility to maximize the benefit and minimize the risk of these drugs.

Collaboration among Asian countries is needed in order to overcome these challenges and use these opportunities in future studies. The Asian Organization for Crohn's and Colitis (AOCC) should take the responsibility to help promote this collaboration. Furthermore, the upcoming official journal of AOCC, Intestinal Research, will play an important role in our collaboration and evolution of AOCC.

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