

What Are the Unanswered Questions and Unmet Needs in Inflammatory Bowel Disease Management in Asia?

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It has been more than 100 years since ulcerative colitis (UC) was first described in the mid-1800s,^[1] and nearly 90 years from 1932 when Crohn's disease (CD) was first reported.^[2] Based on the explorations of disease pathogenesis, epidemiology, and emerging new targets of treatment, the goal of therapy has now shifted from symptom control to altering the natural history in order to prevent bowel damage and disability. In Asian countries, an increasing incidence and prevalence of inflammatory bowel disease (IBD) have been witnessed during the past decades.^[3,4] Our team has reported the age-adjusted incidence for IBD as 1.77 per 100,000 population in northern region of China in 2013.^[5] Although it is lower compared with that of the Western countries, the incidence and prevalence are rapidly increasing and following the steps of which Western countries had undergone 50 years ago. Therefore, there are more and more gastroenterologists dedicating in IBD subspecialty in Asia. Although guidelines and knowledge are on hands and regularly renewed, there remain to be unanswered questions and unmet needs in IBD management in Asia.

DISEASE MONITORING: WHAT IS THE OPTIMAL MEASURES FOR DISEASE MONITOR, A COMBINATION OF CLINICAL INFORMATION, BIOMARKERS, AND IMAGING?

IBD, particularly CD, is a disease entity evolving through time like a shifting target. Uncontrolled disease with recurrent inflammation will accumulate to bowel damage described as stenosing and/or fistulizing disease. In addition, the extensive involvement of gastrointestinal tract adds complexity for accurate monitoring of bowel damage and depicting disease panorama. To date, several instruments have been utilized

in measuring disease burden. Biomarkers for instance C-reactive protein and fecal calprotectin are widely used to evaluate the inflammatory burden. Endoscopy-based scoring systems including CD Endoscopic Index of Severity as well as Simple Endoscopic Score for CD are used to evaluate the severity of mucosal appearance and mucosal healing. Ultrasonography, computed tomography, and magnetic resonance (MR) enterography are mainly responsible for evaluating bowel wall damage and disease extent. In 2015, Lémann index was introduced to measure cumulative structural bowel damage in patients with CD.^[6] Further validation and sensitivity assessment are imperative for its expansion. However, needs for comprehensive, accurate, and dynamic measures which integrate the assessment of inflammation, structural damage, and disease extent are still unmet.

TREATMENT STRATEGY: TO EXECUTE THE "TREAT-TO-TARGET" STRATEGY, HOW TO STRATIFY PATIENTS PRECISELY BASED ON PREDICTORS FOR DISEASE PROGRESSION?

Not only phenotypes differ in IBD patients, but also disease progression is highly variable from patient to patient. Predicting factors of disabling disease currently in use is from analysis of patients who underwent bowel surgery

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which was considered more progressive.^[7] For instance, preoperative corticosteroid use and hypoalbuminemia were found to be risk factors for short-term postoperative complications in patients with UC.^[8] While, as to an individual patient, precision medicine requires a different type of clinical trial that focuses on individual, not average, responses to therapy. Precise individualized stratification is an unmet need. A comprehensive predicting model using a combination of clinical, genetic, microbiotic factors and biomarkers will ideally resolve this unanswered question. Therefore, early introduction of disease-modifying anti-IBD drugs to patients with progressive predictors might bring greater chance to reach the target and prevent progression to bowel damage and disabling disease.

TREAT-TO-TARGET STRATEGY: HOW TO TARGET THE RIGHT MEDICINE TO THE RIGHT PATIENT?

There is a huge potential for variation in inflammatory response from patient to patient and within a single patient over time and then in response to different treatments. Moreover, patients enrolled in randomized controlled trials do not represent the IBD patient population due to strict inclusion criteria.^[9] These uncertainties emphasize the need for an individualized patient-based approach based on an integrated “omics” approach incorporating genetic, microbiotic information with clinical and environmental data. In patients with stricturing CD, inflammation and fibrosis always coexist. Recently, Bouhnik *et al.* reported an easy-to-use predictive score based on clinical and magnetic resonance imaging (MRI) features to predict the success of adalimumab therapy in treating stricturing CD.^[10] Another study reported that the levels of granzyme A and integrin αE gene mRNAs in colon tissues can identify patients with UC who are most likely to benefit from etrolizumab.^[11] With thorough understanding of the pathogenesis of IBD as well as the emerging era of artificial intelligence, we are going to be capable of precisely targeting the right drug to the right patient.

SPECIAL SITUATION: WHAT ARE THE OPTIMAL OUTCOME MEASURES AND TREATMENT STRATEGY FOR PERIANAL CROHN'S DISEASE?

The complexity and impairment of quality of life of perianal CD predisposes the multidisciplinary management. In the past decade, little progress was made with regard to available medical and surgical treatment options for perianal CD. Current knowledge is largely based on retrospective series, expert opinion, and subanalysis of randomized controlled trials. A comprehensive classification, which integrates all elements that are important for medical and surgical management, is unmet. A reliable classification of the perianal fistulizing CD should comprise endoscopy, magnetic resonance imaging (MRI) and/or endoanal ultrasound, and examination under anesthesia to provide necessary and comprehensive information.^[12] Outcome measures include subjective assessment of symptoms' improvement and objective

assessment of fistula healing. Deep tissue healing (i.e., deep remission of fistulizing disease) can only be determined by repeated MRI, although a sensitive, reliable, and validated scoring system is awaited. To date, randomized clinical trials with a primary objective of treating perianal CD are limited. For optimizing management, validated end points for clinical trials are needed, which could also lead to standardized diagnosis, treatment, and follow-up of Crohn's fistulas.

QUALITY OF CARE: HOW TO IMPROVE AND DISTRIBUTE THE STANDARD CARE OF INFLAMMATORY BOWEL DISEASE ACROSS ASIAN COUNTRIES?

The quality of medical care is highly variable across Asian countries and mostly depends on the local economy and physicians' knowledge of IBD. For the Asian Organization for Crohn's and Colitis (AOCC) education committee, it is a great responsibility to conduct and spread standard knowledge to young physicians in Asia. Many educational workshops held by the AOCC EduCom and the Chinese Youth Club for Crohn's and Colitis have been carried out in China during the past years, with inspirations and positive feedback from the audience. Dissemination of standard and advance care of IBD across Asian countries still remains to be an unsolved question. Moreover, in this era of increasing complexity of care, education of patients to involve them in a well-informed decision-making process should also be encouraged. To improve the quality of care of patients with IBD, there are several steps to follow: (1) define the standards of care for IBD, (2) develop an implementation program to measure and deliver this care, (3) perform continuous evaluation and refinement of this process, and (4) measure and improve the impact on patient outcomes.

Finally, although there are many unanswered questions and unmet needs in IBD management in Asia, looking back from where we set off, we are on a journey to better and greater.

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