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REVIEW ARTICLE

# Asia Pacific Consensus Statements on Crohn's disease. Part 1: Definition, diagnosis, and epidemiology

# (Asia Pacific Crohn's Disease Consensus—Part 1)

Choon Jin Ooi,* Govind K Makharia,† Ida Hilmi,‡ Peter R Gibson,§ Kwong Ming Fock,¶ Vineet Ahuja,† Khoon Lin Ling,* Wee Chian Lim,** Kelvin T Thia,* Shu-chen Wei,†† Wai Keung Leung,‡‡ Poh Koon Koh,§§ Richard B Gearry,¶¶ Khean Lee Goh,‡ Qin Ouyang,*** Jose Sollano,††† Sathaporn Manatsathit,‡‡‡ H Janaka de Silva,§§§ Rungsun Rerknimitr,¶¶¶ Pises Pisespongsa,**** Muhamad Radzi Abu Hassan,†††† Joseph Sung,‡‡‡‡ Toshifumi Hibi,§§§§ Christopher C M Boey,¶¶¶¶ Neil Moran***** and Rupert W L Leong***** on behalf of the Asia Pacific Association of Gastroenterology (APAGE) Working Group on Inflammatory Bowel Disease

*Department of Gastroenterology and Hepatology, §§Department of Colorectal Surgery, Singapore General Hospital, ¶Department of Gastroenterology, Changi General Hospital, **Department of Gastroenterology, Tan Tock Seng Hospital, Singapore; ‡Division of Gastroenterology and Hepatology, Faculty of Medicine, ¶¶¶¶Department of Paediatrics, University of Malaya, Kuala Lumpur, ††††Hospital Sultanah Bahiyah, Alor Setar, Malaysia; †Department of Gastroenterology and Human Nutrition, All India Institute of Medical Sciences, New Delhi, India; §Department of Medicine, Box Hill Hospital, Monash University, Box Hill, Victoria, *****Concord Hospital, Gastroenterology and Liver Services, Sydney, New South Wales, Australia; ††Department of Internal Medicine, National Taiwan University, Taipei, Taiwan; ‡‡Department of Medicine, University of Hong Kong, ‡‡‡‡Department of Medicine and Therapeutics, Chinese University of Hong Kong, Hong Kong; ¶¶Department of Medicine, University of Otago, Christchurch, New Zealand; ***Division of Gastroenterology, Department of Internal Medicine, West China Hospital, Sichuan University, Chengdu, China; †††Department of Medicine, University of Santo Tomas, Manila, Philippines; ‡‡‡Department of Medicine, Division of Gastroenterology, Siriraj Hospital, Mahidol University, ¶¶¶Division of Gastroenterology, Department of Medicine, King Chulalongkorn Memorial Hospital, Chulalongkorn University, Bangkok, ****Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; §§§Department of Medicine, Faculty of Medicine, University of Kelaniya, Ragama, Sri Lanka; §§§§Kitasato University, Tokyo, Japan

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**Correspondence**
Professor Rupert Leong, Concord Hospital, Level 1 West, Hospital Rd, Concord 2139, Australia. Email: rupertleong@outlook.com

## Abstract

Inflammatory bowel disease (IBD) was previously thought to be rare in Asia, but emerging data indicate rising incidence and prevalence of IBD in the region. The Asia Pacific Working Group on Inflammatory Bowel Disease was established in Cebu, Philippines, at the Asia Pacific Digestive Week conference in 2006 under the auspices of the Asian Pacific Association of Gastroenterology with the goal of developing best management practices, coordinating research, and raising awareness of IBD in the region. The consensus group previously published recommendations for the diagnosis and management of ulcerative colitis with specific relevance to the Asia-Pacific region. The present consensus statements were developed following a similar process to address the epidemiology, diagnosis, and management of Crohn's disease. The goals of these statements are to pool the pertinent literature specifically highlighting relevant data and conditions in the Asia-Pacific region relating to the economy, health systems, background infectious diseases, differential diagnoses, and treatment availability. It does not intend to be all comprehensive and future revisions are likely to be required in this ever-changing field.

## Introduction

The most dramatic epidemiological changes in the incidence of inflammatory bowel diseases (IBD) have been taking place in the Asia-Pacific region over the past three-to-four decades. This region is characterized by rapidly developing economies, increasing affluence and urbanization, emergence of a middle class, Westernization of diet and culture, and decreasing exposure to infectious diseases. While the incidence of IBD has not reached the levels of Western countries, the escalating patient numbers

affect some of the most populous countries in the world, indicating an emerging high patient load. The region is also characterized by high prevalence of infectious diseases that include tuberculosis (TB) and hepatitis B virus, complicating IBD treatment with the use of immunosuppressive therapies. These and other challenges are highlighted in the consensus statements on Crohn's disease (CD) developed by the Asia Pacific Working Group on Inflammatory Bowel Disease. The aims of the statements are to raise awareness of this emerging disease, harmonize the descriptive phenotyping of CD and its investigation, advice readers the principles of management, and review the literature especially those arising from this region. Where a lack of local data was available, avenues for further research were proposed.

## Methods

A modified Delphi process[1] was adopted to develop the consensus statements according to their clinical importance within the Asia-Pacific region. A steering committee (CJO, RWL, GKM, IH) generated a list of statements and circulated it electronically to Consensus Group members. The statements were grouped into the following topics: definition and diagnosis, epidemiology, and management of CD. These statements were presented to the Consensus Group panel for discussion, revision, and voting. A password-secured website was populated with relevant literature assembled by the literature review team (CJO, RWL, KLL, KT, WCL, VA, GKM, IH, SCW, KPP). A systematic literature review was conducted to identify and grade the available evidence to support each statement. The literature search was conducted in the English language publications indexed in the MEDLINE, EMBASE, and the Cochrane Trials Registry databases, and limited to those in human subjects. Regional and international consensus statements and guidelines on CD were also examined. Relevant literature from the Asia-Pacific region was of particular interest.

The categorization of evidence, classification of recommendation, and voting schema were according to the Canadian Task Force on the Periodic Health Examination (Table 1).[2] Consensus was achieved when 80% or more of votes were either accepted "completely" or "with some reservation." A statement was refuted when 80% or more of voting members rejected a statement "completely" or "with some reservation." Every statement was then graded to indicate the level of evidence available and the strength of recommendation.

***Membership of the consensus group.*** Voting members of the Consensus Group were selected using the following criteria:

1. Demonstration of knowledge and expertise in IBD through publication/research or participation in national or regional guideline development.
2. Geographical representation of the Asia-Pacific countries.
3. Diversity of views and expertise in healthcare system (including colorectal surgeon, pathologist, pharmacist, nurse practitioners, patient support group representatives). Voting was limited, however, to clinicians.

**Table 1** Quality of evidence, classification of recommendation, and voting on recommendation

| Category and grade | Description |
|---|---|
| Quality of evidence | |
| I | Evidence obtained from at least 1 randomised controlled trial |
| II-1 | Evidence obtained from well-designed control trials without randomization |
| II-2 | Evidence obtained from well-designed cohort or case-control study |
| II-3 | Evidence obtained from comparison between time or places with or without intervention |
| III | Opinion of respected authorities, based on clinical experience and expert committees |
| Classification of recommendation | |
| A | There is good evidence to support the statement |
| B | There is fair evidence to support the statement |
| C | There is poor evidence to support the statement but recommendation made on other ground |
| D | There is fair evidence to refute the statement |
| E | There is good evidence to refute the statement |
| Voting on recommendation | |
| a | Accept completely |
| b | Accept with some reservation |
| c | Accept with major reservation |
| d | Reject with reservation |
| e | Reject completely |

Statement for which more than 80% of participants voted a and b are accepted.

Representative countries included Malaysia, Thailand, Sri Lanka, India, China, Hong Kong, Taiwan, Philippines, Indonesia, Australia, New Zealand, Japan, South Korea, Vietnam, and Singapore.

***Voting, Delphi process, and general organization of the consensus.*** Voting was conducted anonymously at all times. The first vote was conducted by the entire Consensus Group electronically by email. Relevant literature was then made available on a secured website for review by all voters, and a second round of voting was undertaken, during which members could modify their first-round selections, if required. A face-to-face meeting of the entire Consensus Group was then held to discuss any suggested modifications to the wording of the statements and to openly discuss the evidence for and against each specific statement. A third vote was held thereafter. Statements that could not reach consensus were discussed and either modified or rejected. Each statement was graded to indicate the level of evidence available and the strength of recommendation by using the Canadian Task Force Guidelines on the Periodic Health Examination.[2] The full Consensus Group meeting was held in August 2011 in Singapore organized by the IBD Centre from Singapore General Hospital. Representatives attended from Asia-Pacific countries that included Australia, Hong Kong, India, Malaysia, Philippines, Singapore, Sri Lanka, Taiwan, and Thailand.

## Results

### *Part A: Definition and diagnosis of CD*

Statement 1

*The diagnosis of CD is based on a combination of clinical, endoscopic, radiological, and histological features and, where appropriate, the exclusion of an infectious etiology.*

Level of agreement: (a) 94%, (b) 6%, (c) 0%, (d) 0%, (e) 0%.
Quality of evidence: III.
Classification of recommendation: C.

The definition of CD was made according to accepted international guidelines and is similar to definitions adopted by other major gastroenterological associations.[3–5] The diagnosis relies on a combination of compatible clinical history and typical endoscopic and histological findings, recognizing that there is no single gold standard for the diagnosis. It is particularly important to exclude an infectious etiology in patients presenting with symptoms compatible with CD. Additionally, Behcet's disease and vasculitis need to be considered in this cohort.

Statement 2

*Ileocolonoscopy is the preferred diagnostic investigation. During ileocolonoscopy, multiple biopsies from at least five sites in the colon and terminal ileum should be taken and include endoscopically normal and abnormal areas.*

Level of agreement: (a) 50%, (b) 44%, (c) 6%, (d) 0%, (e) 0%.
Quality of evidence: III.
Classification of recommendation: C.

Ileocolonoscopy (with multiple mucosal biopsies) is the first-line investigation for the diagnosis of CD.[6] Ileoscopy is considered essential in phenotyping CD.[7–9] Although there is a paucity of data regarding the optimal number of biopsies required, the Working Party recommends biopsies from at least five sites with at least one from the terminal ileum and four from the colon (such as, the ascending colon, transverse colon, sigmoid colon, and rectum).

Statement 3

*Biopsies for* Mycobacterium tuberculosis *should be taken from patients living in countries where TB is endemic.*

Level of agreement: (a) 83%, (b) 17%, (c) 0%, (d) 0%, (e) 0%.
Quality of evidence: III.
Classification of recommendation: C.

When ileocolonoscopy shows ileocecal disease, biopsies should be taken for appropriate testing of *M. tuberculosis*. Frequently utilized microbiological studies include tissue staining for acid-fast bacilli, TB culture, or TB polymerase chain reaction (PCR), alone or in combination, depending on availability. However, the sensitivity and specificity of many PCR-based studies may be suboptimal.[10] Where available, interferon gamma releasing assays such as Quantiferon Gold (Cellestis/Qiagen, Carnegie, Australia) and TB Spot (Oxford Immunotec, Marlborough, MA, USA) may be employed.

Statement 4

**1** Evaluation for small bowel disease should be considered in patients with CD.
**2** Computed tomography (CT) or magnetic resonance (MR) enterography/enteroclysis is the preferred investigation.

Level of agreement: (a) 64%, (b) 24%, (c) 12%, (d) 0%, (e) 0%.
Quality of evidence: (a) II; (b)III.
Classification of recommendation: (a) B; (b) C.

The small bowel should be evaluated in CD. CT and MR imaging techniques can establish disease extent and activity based on wall thickness and contrast enhancement. These changes, along with the presence of edema and ulceration, allow assessment of disease activity and severity. This recommendation reflects the current standards for multidisciplinary small intestine assessment.[11,12] CT and MR have similar diagnostic accuracy for the detection of small intestine inflammatory lesions.[13,14] CT is more readily available and less time consuming than MR. Nonetheless, the radiation burden from CT should be considered, particularly when serial investigation is necessary.[15] Double balloon enteroscopy is superior to radiological investigations for the detection of aphthous erosions and small bowel ulcers of the ileum in CD. It can also retrieve retained wireless capsule endoscopy (WCE) capsule lodged within CD strictures.[16]

Statement 5

*Upper gastrointestinal endoscopy is advisable in subgroups of CD patients: (i) pediatric age group and (ii) IBD-undifferentiated (IBD-U).*

Level of agreement: (a) 44%, (b) 50%, (c) 6%, (d) 0%, (e) 0%.
Quality of evidence: II-3.
Classification of recommendation: C.

In the initial descriptions by Halme *et al.*[17] and Oberhuber *et al.*,[18] focally enhanced gastritis was observed in gastric biopsies obtained during upper gastrointestinal endoscopy in 76% of *Helicobacter pylori*-negative patients with CD and in 0.8% of controls and was therefore considered suggestive of a diagnosis of CD. A Korean study,[19] however, found a 30% rate of focally enhanced gastritis in 22% of ulcerative colitis (UC) and 11% in non-IBD controls ($P = 0.324$). Lin *et al.*[20] also reported these lesions in 29% of patients with UC. Similar reports have shown that CD involving the upper gastrointestinal tract is almost invariably accompanied by small or large bowel involvement.[21–23] In the pediatric age group, upper gastrointestinal involvement has been reported with a greater frequency (up to 70% of cases).[24–27] European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN's) Porto working group has recommended routine upper endoscopy at initial presentation to aid in the diagnosis of pediatric IBD.[28] Despite the paucity of data, upper gastrointestinal endoscopy is recommended in the assessment of pediatric CD and in adult patients with IBD-undifferentiated to aid differentiation between UC and CD.

Statement 6

*WCE is not indicated in all patients with CD. It is indicated if suspicion of CD still remains despite a negative ileocolonoscopy and CT or MR enteroclysis.*

Level of agreement: (a) 63%, (b) 37%, (c) 0%, (d) 0%, (e) 0%.
Quality of evidence: II-2.
Classification of recommendation: B.

Wireless capsule endoscopy (WCE) is a sensitive and non-invasive technique to detect mucosal abnormalities in the small bowel. In a prospective study of 17 patients with known or suspected CD with WCE, CT enterography (CTE), colonoscopy with ileoscopy, and small bowel follow-through (SBFT), the diagnostic yield, defined as the number of patients with evidence of CD over the number of patients studied, was 71% with CE, 65% with ileoscopy, 53% with CTE, and 24% with SBFT. Due to the small sample size, the study did not reach statistical significance. This study was further limited by a lack of specificity as any erosion or ulcer seen on capsule endoscopy or ileoscopy was classified as CD.[29] A meta-analysis found WCE to have a superior diagnostic yield in patients with suspected and established small-bowel CD compared with imaging techniques of small bowel radiography, CTE, push enteroscopy, and colonoscopy with ileoscopy.[30] WCE resulted in management changes in the majority of cases of symptomatic CD.[31] WCE may detect lesions compatible with small bowel CD in almost one third of patients displaying symptoms highly suggestive of CD in the absence of a conclusive diagnosis using conventional imaging techniques.[32] A normal WCE examination has a high negative predictive value in excluding small bowel CD. However, WCE findings alone are insufficient to establish a new diagnosis of CD as healthy subjects may also demonstrate small bowel mucosal breaks and erosions. Another study found the sensitivity of WCE for active CD to be 83%, 82% for CTE, 74% for ileocolonoscopy, and 65% for SBFT. The specificity of CE, however, was 53%, which was significantly lower than all other modalities. Therefore, the usefulness of WCE in cases suspicious for small bowel CD is limited by a lack of specificity.[33]

Statement 7

*Serum anti-*Saccharomyces cerevisiae *antibody (ASCA) and anti-neutrophil cytoplasmic antibody (ANCA) have a limited role in diagnosing CD, particularly in differentiating IBD-U.*

Level of agreement: (a) 39%, (b) 44%, (c) 11%, (d) 0%, (e) 6%.
Quality of evidence: II-3.
Classification of recommendation: B.

Serum biomarkers such as ASCA and anti-nuclear cytoplasmic antigen with a peripheral staining pattern (pANCA) have been proposed to play a role in the differentiation of CD from UC. A tandem Australian and Hong Kong study identified pANCA to have greater sensitivity in Caucasian than Chinese patients with UC, and ASCA IgG detection to be similar between Caucasian and Chinese patients with CD. ASCA IgA, however, has a low yield in Chinese CD.[34] However, in clinical situations, their diagnostic role is limited. Zhou *et al*. evaluated the prevalence and diagnostic value of pANCA and ASCA in patients with IBD in China.[35] The study included 260 patients with IBD (UC, $n = 152$; CD, $n = 54$), 60 patients with other gastrointestinal diseases, and 80 healthy controls. The sensitivity, specificity, positive and negative predictive values, and positive likelihood ratio of pANCA for differentiating UC from healthy controls were 43%, 96%, 96%, 47%, and 12%, respectively; corresponding values for ASCA to differentiate CD from healthy controls were 46%, 96%, 89%, 73%, and 12%, respectively. The detection of pANCA and ASCA may be useful in confirming the diagnosis of IBD, but the combination of pANCA and ASCA did not result in a greater diagnostic yield compared with either test alone. Indeed, a Canadian study concluded that ASCA and pANCA have low sensitivity and are not specific in the identification of UC and CD.[36]

Statement 8

*Genetic testing is not routinely recommended in the work-up of CD patients.*

Level of agreement: (a) 95%, (b) 5%, (c) 0%, (d) 0%, (e) 0%.
Quality of evidence: III.
Classification of recommendation: C.

Genome-wide association studies (GWAS) and meta-analyses have identified over 140 CD susceptibility loci in Caucasians.[37] There are currently no genetic tests that are routinely recommended for the diagnosis or follow-up of CD patients.[38]

Statement 9

*It is important to differentiate CD from intestinal TB (ITB). Behçet's disease should be excluded in areas of high prevalence.*

Level of agreement: (a) 63%, (b) 37%, (c) 0%, (d) 0%, (e) 0%.
Quality of evidence: III.
Classification of recommendation: C.

ITB and CD are chronic granulomatous disorders with similarities that make the differentiation between these two conditions challenging.[10,39–41] There is a close resemblance in the clinical, radiological, endoscopic, surgical, and histological features of CD and ITB. A misdiagnosis of ITB can result in unnecessary anti-TB therapy (ATT) and a delay in CD treatment, while treatment with steroids with or without biological therapy for CD can be disastrous in those with ITB. These scenarios highlight the need to establish the diagnosis of either CD or ITB before starting any form of empirical treatment.

Behçet's disease is a multisystem vasculitis with systemic features including mucocutaneous, ocular, articular, vascular, intestinal, urogenital, and neurologic involvement. A higher prevalence has been recorded in Middle and Eastern Asia, including Japan, Korea, and China, especially in areas along the historical "Silk Road." Although intestinal involvement is uncommon and only seen in 5–25% of Behçet's disease patients, there is a significant risk of complications including intestinal perforation, fistulization, and hemorrhage. A Korean study recently described and validated novel diagnostic criteria for intestinal Behçet's disease in patients with ileocolonic ulcers.[42] In another large study involving 110 patients with Behçet's disease and 135 patients of CD, Lee *et al*. described colonoscopic characteristics of CD versus Behçet's

disease. The most common site of involvement in Behçet's is the ileocecum with ulceration that is characteristically round, oval, and "punched-out."[43]

Statement 10

*The colonoscopic features which suggest a diagnosis of CD include anorectal lesions, longitudinal ulcers, aphthous ulcers, and cobblestone appearance. Features suggestive of ITB include transverse ulcers, involvement of fewer than four segments, and a patulous ileocecal valve.*

Level of agreement: (a) 56%, (b) 28%, (c) 6%, (d) 11%, (e) 0%.
Quality of evidence: II-2.
Classification of recommendation: B.

ITB and CD mainly involve the ileocolonic region. ITB cases often involve the ileocecum with varying degrees of contiguous large and small bowel involvement. In approximately 20% of cases, segmental colonic involvement may occur in the absence of ileocecal involvement. Skip lesions in two or more colonic sites occur in up to 44% of patients.[44] Approximately 5% of patients may present with a pancolitis indistinguishable from UC. In tuberculous colitis, the mucosa surrounding an ulcer exhibits features of inflammation, such as erythema, nodularity, or edema, but the rectum is rarely involved in ITB. Terminal ileal involvement alone with relative cecal sparing is unusual in ITB. In a Korean study, anorectal involvement, longitudinal ulcers, aphthous ulcers, and a cobblestone appearance were all significantly more common in patients with CD than in patients with ITB.[45] In contrast, patients with ITB usually have fewer than four segments involved, a patulous ileocecal valve, transverse ulcers, and more scars. A scoring system was developed comprising four endoscopic features of CD (anorectal lesions, longitudinal ulcers, aphthous ulcers, and cobblestone appearance) versus four endoscopic features of ITB (transverse ulcers, pseudopolyps, involvement of fewer than four segments, and a patulous ileocecal valve). A score of +1 was assigned to the four endoscopic parameters characteristic of CD and –1 assigned to the four parameters of ITB.[45] A diagnosis of CD was considered when the sum of the scores for the eight parameters was greater than zero, and a diagnosis of ITB was suggested by a sum less than zero. The diagnosis was regarded as indeterminate when the score equaled zero. This scoring system has a positive predictive value for CD of 95% and for TB of 89%. One of the drawbacks of this scoring system is that many patients do not show all features. The scoring system must be validated prospectively in populations with varying prevalences of both CD and ITB before it can be recommended for routine use.

Statement 11

*When granulomas are seen, features which favor ITB are necrosis (caseating), confluence, multiplicity, large size, submucosal location, and disproportionate degree of submucosal inflammation. The granulomas seen in CD are usually scant and tiny (microgranulomas).*

Level of agreement: (a) 94%, (b) 6%, (c) 0%, (d) 0%, (e) 0%.
Quality of evidence: II-2.
Classification of recommendation: B.

Both CD and ITB are characterized by granulomatous inflammation with overlapping histological features. In ITB, the classical features of caseating granulomatous inflammation and acid-fast bacilli are present in fewer than 30% of cases. A positive TB culture has a poor yield of below 20% and the diagnosis is often delayed. Retrospective studies from Southern India and South Africa have identified a number of features that may distinguish CD from ITB on histology.[46–48] ITB features include confluent granulomas, multiple granulomas, large granuloma size, bands of epithelioid histiocytes lining ulcers, submucosal granulomas, and disproportionate submucosal inflammation (i.e. submucosal inflammation that significantly exceeds mucosal inflammation). Features seen more frequently in CD include single granulomas as the only foci of granulomatous inflammation and architectural distortion distant from granulomatous inflammation.

Statement 12

*A trial of 8–12 weeks of ATT is reasonable in patients where it is not possible to confidently differentiate ITB from CD. In patients showing no or partial symptom response at 8–12 weeks, a repeat colonoscopy should be done. To differentiate ITB from CD, a colonoscopy is suggested to document mucosal healing at the completion of anti-tuberculous therapy.*

Level of agreement: (a) 67%, (b) 33%, (c) 0%, (d) 0%, (e) 0%.
Quality of evidence: III.
Classification of recommendation: C.

The need to establish the diagnosis of either CD or ITB before starting treatment is emphasized. In the absence of a confirmatory test to differentiate ITB from CD, a therapeutic trial of ATT can be performed to assess clinical response. There are scarce data on the use of, and response to, ATT in patients with an eventual diagnosis of CD. A recent study of patients with constricting and ulcerating intestinal disease who were treated with a trial of ATT for undifferentiated ITB or CD helped to elucidate a management algorithm.[49] After 12 weeks of ATT, all ITB patients showed either complete or partial treatment response. In patients with CD, 40% showed partial or complete improvement in symptoms following 6 months of ATT, but 84% did not demonstrate any corresponding improvement in colonoscopic appearances. It is, therefore, recommended that patients who undergo a trial of ATT should undergo colonoscopy with repeat biopsies at 8–12 weeks if there is no or minimal response. Even in cases of partial or complete response to ATT, a repeat colonoscopy should be carried out at 6 months with the persistence of ulceration strongly suggestive of a diagnosis of CD. In a small case series of 25 patients, Park *et al*. also suggested that a trial of ATT for 2–3 months and colonoscopy follow-up was useful in the differential diagnosis of tuberculous colitis and IBD.[50]

Statement 13

*Starting concomitant therapy for CD and ITB should be discouraged in patients who are indeterminate for ITB and CD except in patients presenting with severe disease requiring urgent response.*

Level of agreement: (a) 59%, (b) 29%, (c) 12%, (d) 0%, (e) 0%.
Quality of evidence: III.
Classification of recommendation: C.

It is strongly discouraged to simultaneously treat for ITB as well as CD. This will create diagnostic confusion on a long-term basis. There are specific circumstances in which patients may be considered for concomitant therapy for both ITB and CD. These include: (i) patients presenting with severe disease indeterminate for ITB or CD and requiring immediate therapy; and (ii) patients with mild to moderate disease indeterminate for ITB and CD initially treated with ATT alone and with partial or no response at 8–12 weeks. Treatment options include the addition of CD therapy or a switch to CD treatment. In cases of severe but localized intestinal disease, surgical resection is a reasonable alternative.

## *Part B: Epidemiology*

Statement 14

*The incidence and prevalence of CD in Asia is lower than in Western countries but with rising prevalence and incidence trends. The incidence and prevalence of CD in Australia and New Zealand are high.*

Level of agreement: (a) 94%, (b) 6%, (c) 0%, (d) 0%, (e) 0%.
Quality of evidence: II-1.
Classification of recommendation: A.

A large prospective study investigating the incidence of IBD in the Asia-Pacific region has confirmed that the incidence of CD is much lower than in the West, with a crude annual overall incidence of 1.37 per 100 000.[51] In Japan and Korea, the incidence of CD in the period of 1998–2001 was between 1.0 and 1.34 per 100 000.[52,53] Australia and New Zealand, however, have high CD incidences of 17.4 to 23.7 and 16.5 per 100 000, respectively, some of the highest rates in the world.[51,54,55] An increasing incidence of CD is noted in the Asia-Pacific region[56] similar to that of UC.[57] Longitudinal trends support a rise in CD incidence over the last three decades,[58] especially in East Asia. The prevalence data for CD in this region also suggest a rising trend, likely due to growing incidence rates and normal to near-normal life expectancies of CD patients.[53,59,60]

Statement 15

*Unlike Western cohorts that include Australia and New Zealand with balanced or female predominance, a male predominance for CD is observed in Asia.*

Level of agreement: (a) 56%, (b) 44%, (c) 0%, (d) 0%, (e) 0%.
Quality of evidence: II-2.
Classification of recommendation: B.

In high-incidence regions, there is generally a higher proportion of females than males with CD,[61,62] in contrast with low-incidence regions where there is male predominance.[63] In Australia and New Zealand, female predominance for CD is noted, similar to other Western countries.[54,55] In Asia, a male predominance of CD has been observed with a male-to-female ratio of 1.6:1 to 2.9:1.[53,60,64–68] This may be attributable to both genetic and environmental differences.

Statement 16

*The peak age of CD is in the 20 to 30 years age group in Asia similar to the West, except that a second peak in the sixth and seventh decade is not apparent.*

Level of agreement: (a) 53%, (b) 42%, (c) 5%, (d) 0%, (e) 0%.
Quality of evidence: II-2.
Classification of recommendation: B.

The onset of CD is frequently between 20 to 30 years of age,[69] with a second peak in the sixth and seventh decade reported in Western studies, including New Zealand.[53] In the Asia-Pacific region, a similar peak age of onset is observed but generally without a second peak during older age,[65,67,68,70] except in one study in South Korea, where a bimodal age distribution in CD was seen.[71]

Statement 17

*The frequency of extra-intestinal manifestations (EIM) in the East and Southeast Asian CD patients is comparable to Western populations.*

Level of agreement: (a) 32%, (b) 58%, (c) 11%, (d) 0%, (e) 0%.
Quality of evidence: II-2.
Classification of recommendation: B.

EIM of IBD involve the joints, mouth, eye, and skin. The reported frequency of EIM is often variable due to differing case definitions, inclusion of prevalent or incident symptoms, and methods of assessment.[70] Nevertheless, the frequencies of EIM among CD patients are similar in the Asia-Pacific region and in the West at approximately 20–40%.[60,66,68,72–74]

Statement 18

*Although there is considerable variation in the distribution of disease location for CD within Asia, the most common disease location is ileocolonic.*

Level of agreement: (a) 88%, (b) 6%, (c) 6%, (d) 0%, (e) 0%.
Quality of evidence: II-2.
Classification of recommendation: B.

While CD can affect any part of the gastrointestinal tract, most studies in the Asia-Pacific region have shown that ileocolonic disease is the most common[53,58,59,68,73,75–79] (L3 Montreal classification[80]). Upper gastrointestinal involvement (L4 modifier) is diagnosed by small bowel imaging, which may not have been carried out in all suspected or established cases of CD. A few studies have focused on this uncommon location phenotype.[81,82]

Statement 19

*Similar to disease in Western populations, CD in the Asia-Pacific region tends to show progression of intestinal complications such as strictures and fistulas with time.*

Level of agreement: (a) 69%, (b) 31%, (c) 0%, (d) 0%, (e) 0%.
Quality of evidence: II-2.
Classification of recommendation: B.

CD complications frequently develop over time, with cumulative stricturing or penetrating complications reported as 19% at 90 days, 34% at 5 years, and 51% at 20 years.[83] In a study of 278 patients from Korea who were followed up for a median period of 71 months, 31% had stricturing or penetrating complications at diagnosis, and this increased to 51% at 5 years.[75] A study from Hong Kong also showed a similar progression toward stricturing and penetrating complications over time, with the proportion of patients with penetrating disease increasing from 28% to 43%, and stricturing disease from 26% to 33%, after 10 years.[68] Surgical rates in Asia-Pacific are also comparable to those in the West, ranging from 18% to 48% among the different countries across the region.[58,68,72,75,78,84]

Statement 20

*Familial CD is uncommon in Asia.*

Level of agreement: (a) 88%, (b) 12%, (c) 0%, (d) 0%, (e) 0%.
Quality of evidence: II-2.
Classification of recommendation: B.

Park *et al*. identified the rate of familial IBD in patients with CD to be lower in Korea than in the West (1.5%) but the attributable risk of developing the disease in those with a positive family history of IBD is significantly higher compared with the background population (relative risk [RR]: 15.1; 95% confidence interval [CI]: 5.4–29.7).[85] The rate of positive family history from other Asian studies ranges from 0 to 5.5%.[86] In New Zealand, 34% of the IBD cohort had a positive family history.[87]

Statement 21

*The cause for the increasing incidence and prevalence of CD in the Asia-Pacific region remains unknown. Environmental changes are likely to play a role.*

Level of agreement: (a) 47%, (b) 41%, (c) 12%, (d) 0%, (e) 0%.
Quality of evidence: III.
Classification of recommendation: C.

The pathogenesis of IBD involves a complex interplay between genetic polymorphisms in innate and adaptive immunity, the intestinal microbiome, as well as external environmental triggers. The rapid increase in the incidence of IBD in the Asia-Pacific region is almost certainly attributable to environmental factors. "Westernization" comprising changes in diet, urbanization, improved hygiene and affluence, may be the attributable factor but the exact pathogenic triggers remain elusive. A Japanese review suggests that the prevalence of CD and UC appeared to increase approximately 20 years after an increased daily consumption of dietary animal meat/fats and dairy products, and after a decreased consumption of rice.[88]

Statement 22

*Smoking has been shown to be positively associated with CD in the Asia-Pacific region. Smoking is also associated with increased need for surgery and hospitalization in CD and smoking cessation reduces disease progression.*

Level of agreement: (a) 33%, (b) 56%, (c) 11%, (d) 0%, (e) 0%.
Quality of evidence: III.
Classification of recommendation: C.

Minimal data on the relationship between smoking and CD in the Asia-Pacific region exist. In a population study in Canterbury, New Zealand, cigarette smoking at diagnosis was positively associated with CD (odds ratio [OR] 1.99; 95% CI: 1.48–2.68) but Leong *et al*.[66] found that, among Chinese patients, ever smoking was not a risk factor for CD. Another study by Leong *et al*.[89] found that current or previous smoking protected against the development of intestinal granulomas in CD (OR 0.16; 95% CI: 0.04–0.59). A recently completed inception cohort study in the Asia-Pacific region found that CD was associated with current smoking (adjusted OR 1.82; 95% CI: 1.02–3.25) whereas UC was associated with previous smoking history (adjusted OR 1.66; 95% CI: 1.02–2.70).[90] In Australia, a history of smoking increased the risk of CD (adjusted OR 2.14; 95% CI: 1.18–3.87) while smoking protected against the development of UC (adjusted OR 0.77; 95% CI: 0.41–0.98).[91] Surgical management of CD was required more frequently in those with a smoking history, and ever-smoking was associated with increased cumulative probability of intestinal resections ($P = 0.045$).[92] Cessation of smoking reduced the rate of progression toward complicated CD and surgery. Therefore, all CD patients should be strongly encouraged to stop smoking.[93]

Statement 23

*Genetic susceptibility in Asian CD patients differs from Western Caucasian populations. The three main predisposing mutations of NOD2/CARD15 found in Caucasian populations are absent in Asian CD.*

Level of agreement: (a) 50%, (b) 44%, (c) 6%, (d) 0%, (e) 0%.
Quality of evidence: II-2.
Classification of recommendation: B.

In 2001, CARD15 (NOD2) was the first gene reported to be associated with CD.[94,95] Three known common CARD15 (NOD2) single nucleotide polymorphisms (SNPs) (R702W, G908R, 1007fs) were confirmed independently to be positively associated with the risk of developing CD in Caucasian populations.[96] In the Australian population, all three SNPs are significantly associated with CD,[97] and a New Zealand study has shown an association with the 3020Ins polymorphism.[98] Reports from Japan,[98] Korea,[99] Hong Kong,[86] Taiwan,[100] India,[101] and Malaysia,[102] however, have not demonstrated an association between these three SNPS and CD in Asia. Other mutations in the CARD15 gene may play a role in the development of CD in Asian populations. For example, P268S was found to be positively associated among the Han Chinese[103] and Malaysian populations.[102]

Statement 24

*TNFSF15 is the common CD-associated gene in Asia, but genetic profile of CD varies between different Asia-Pacific countries.*

Level of agreement: (a) 44%, (b) 56%, (c) 0%, (d) 0%, (e) 0%.
Quality of evidence: II-2.
Classification of recommendation: B.

By using the GWAS approach, TNFSF15 (tumor necrosis factor superfamily 15, also called TNF, superfamily ligand A, or vascular endothelial cell growth inhibitor) was found to be a susceptible gene to CD in Japan.[104] It was also found to be associated with the risk of CD in Korea[105] and Taiwan.[106] At present, it seems that TNFSF15 may be the most important CD-associated gene in Asians. In addition to TNFSF15, other disease susceptibility genes have been identified similar to those reported in Caucasian populations. For example, IL23R was reported to be associated with CD in Korea;[107] ATG16L1 was associated with CD in Australia[108] and Taiwan;[106] DLG5 was associated with CD in Malaysia;[109] and DLG5 haplotype A was associated with a reduced risk of IBD in the New Zealand.[110]

## Summary

In summary, part 1 of the Asia Pacific Consensus Statements on CD highlighted the methodology in the development of the CD consensus statements, the definition and diagnosis of CD and the role of investigations. An overview of the epidemiology of CD was provided that compared and contrasted the Asia-Pacific region with that of Australia and New Zealand, two developed countries with some of the highest incidences of CD in the world. Data on the genetic and environmental risk factors of CD were summarized with emphasis on the latter being responsible for the rapidly rising incidence of CD over the past three-to-four decades in the region. Part 2 of the consensus statements highlight medical and surgical management of CD.

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