**REVIEW**

**The Asia-Pacific consensus on ulcerative colitis**

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**Key words**

Asia Pacific, biologic agents, consensus statements, Delphi, diagnosis, epidemiology, inflammatory bowel disease, leukocytapheresis, management, ulcerative colitis.

Accepted for publication 9 December 2009.

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**Abbreviations**

5-ASA, amino-salicylic acid; AZA, azathioprine; CsA, cyclosporin; IFX, infliximab; 6MP, 6 mercaptopurin; TB, tuberculosis; TNF, tumor necrosis factor; UC, ulcerative colitis.

**Abstract**

Inflammatory bowel disease (IBD) is increasing in many parts of the Asia-Pacific region. There is a need to improve the awareness of IBD and develop diagnostic and management recommendations relevant to the region. This evidence-based consensus focuses on the definition, epidemiology and management of ulcerative colitis (UC) in Asia.

A multi-disciplinary group developed the consensus statements, reviewed the relevant literature, and voted on them anonymously using the Delphi method. The finalized statements were reviewed to determine the level of consensus, evidence quality and strength of recommendation.

Infectious colitis must be excluded prior to diagnosing UC. Typical histology and macroscopic extent of the disease seen in the West is found in the Asia-Pacific region. Ulcerative colitis is increasing in many parts of Asia with gender distribution and age of diagnosis similar to the West. Extra-intestinal manifestations including primary sclerosing cholangitis are rarer than in the West. Clinical stratification of disease severity guides management.

In Japan, leukocytapheresis is a treatment option. Access to biologic agents remains limited due to high cost and concern over opportunistic infections. The high endemic rates of hepatitis B virus infection require stringent screening before initiating immune-suppressive agents. Vaccination and prophylactic therapies should be initiated on a case-by-case basis and in accordance with local practice. Colorectal cancer complicates chronic colitis.

A recent increase in UC is reported in the Asia-Pacific region. These consensus statements aim to improve the recognition of UC and assist clinicians in its management with particular relevance to the region.

**Introduction**

Inflammatory bowel disease (IBD) is uncommon in Asia but the recent literature has shown that the disease is increasing in both incidence and prevalence. 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 (APAGE) with the goal of coordinating research and raising awareness of IBD in the region. The aim of this Consensus Group was to develop recommendations for the diagnosis and management of ulcerative colitis (UC) with specific relevance to...
the Asia-Pacific region and provide some updates on the IBD Consensus drafted in Sanya, China, in 2005.1

Method

A modified Delphi process was adopted to develop the consensus.2 The issues are determined according to perceived clinical importance particular to the Asia-Pacific region. A planning group panel (CJO, RWL, KKM, KMF) generated a list of statements and circulated it electronically to Consensus Group members. The statements were divided into the topics of: definition and diagnosis, epidemiology, and management of UC. These statements were proposed 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, KKM, IH). Systematic literature reviews, with defined inclusion and exclusion criteria, were conducted to identify and grade the available evidence to support each statement. Literature searches were conducted in English language publications in MEDLINE, EMBASE and the Cochrane Trials Register in human subjects. All national and international guidelines on Ulcerative Colitis were solicited. Relevant literature from the Asia-Pacific region was of particular interest.

Categorization of evidence, classification of recommendation and voting schema is modified from the Canadian Task Force on the Periodic Health Examination [Barkun] (Table 1). Consensus was considered to be achieved when 80% or above of voting members indicated ‘accept completely’ or ‘accept with some reservation’. A statement was refuted when 80% or above of voting members ‘reject completely’ or ‘reject with some reservation’. Every statement was then graded to indicate the level of evidence available and the strength of recommendation.

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

<table>
<thead>
<tr>
<th>Category and grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>Quality of evidence</td>
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<tr>
<td>I</td>
<td>Evidence obtained from at least 1 RCT</td>
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<tr>
<td>II-1</td>
<td>Evidence obtained from well-designed control trials without randomization</td>
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<tr>
<td>II-2</td>
<td>Evidence obtained from well-designed cohort or case-control study</td>
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<tr>
<td>II-3</td>
<td>Evidence obtained from comparison between time or places with or without intervention</td>
</tr>
<tr>
<td>III</td>
<td>Opinion of respected authorities, based on clinical experience and expert committees</td>
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</table>

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.

Membership of the consensus group

Voting members of the Consensus Group (Appendix 1) 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, nurses, practitioners, patient support group representatives). Voting was limited, however, to clinicians.

Representative countries were Malaysia, Thailand, Sri Lanka, India, China, Hong Kong, Taiwan, Philippines, Indonesia, Australia, New Zealand, South Korea, 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 web site for review by all voters. Modification of first round votes after access to the literature, if required, constituted the second round of voting. 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 discuss openly the evidence for and against each specific statement. A third vote was held thereafter. Statements that could not reach consensus were discussed and 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 on the Periodic Health Examination Guidelines. A 1-day Consensus Conference was held on 31 August 2008 in Singapore organized by the IBD Centre from Singapore General Hospital. Representatives attended from Asian-Pacific countries that included Australia, Hong Kong, India, Malaysia, Philippines, Singapore, Sri Lanka, Taiwan, and Thailand.

Funding sources

Unrestricted education grants were obtained from Falk Foundation, UCB Pharma, Schering Plough Corp., and a philanthropist who chose to remain anonymous. These sponsors did not participate in the literature collection, consensus discussion, voting, or manuscript writing in any way.

Results

Definition and diagnosis of ulcerative colitis

Statement 1

The diagnosis of UC is based on a combination of clinical, endoscopic and histological features and the exclusion of an infectious etiology.
The definition of UC is similar to that adopted by the other major gastroenterological associations and is further discussed below.2–4 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 UC as infectious colitides have been reported to mimic5–13 or be associated with the onset of UC.14–17

Statement 2
In treatment-naive patients, the endoscopic features of UC are confluent inflammation (loss of vascular pattern, friability, ulceration) involving the rectum, with or without proximal continuous extension into the colon.

Level of agreement: a-100%, b-0%, c-0%, d-0%, e-0%
Quality of evidence: II-2
Classification of recommendation: B

While no endoscopic feature is specific to UC, endoscopic changes in treatment-naive patients typically begins in the rectum that may extend proximally in a characteristic continuous and confluent fashion, ending abruptly with a clear demarcation between inflamed and normal mucosa. In patients with mild to moderately active disease, endoscopic features include erythema, loss of vascular pattern, granularity, friability, erosions and superficial ulcerations while severe colitis is characterized by gross mucosal ulcerations and spontaneous haemorrhage.5,18 Deep ulceration may be seen in severe disease and is a poor prognostic sign.19 Patients with UC who have received medical therapy may develop endoscopically and/or histologically discontinuous disease and ‘rectal sparing’, mimicking the pattern seen in Crohn’s disease (CD).20–23

Statement 3
The mucosal histology in UC includes features of chronic inflammatory infiltrates with basal plasmacytosis, crypt architectural distortion, with or without active component (cryptitis, crypt abscesses).

Level of agreement: a-82%, b-18%, c-0%, d-0%, e-0%
Quality of evidence: II-2
Classification of recommendation: B

Adequate biopsies from different regions of the colon (including rectum) and distal ileum should be obtained for a reliable diagnosis of UC.24 Typical histological features of UC include basal plasmacytosis [presence of plasma cells around or beneath the level of the crypts], a diffuse and transmucosal increase in chronic inflammatory infiltrates in the lamina propria and crypt architectural abnormalities (branching, irregularity in crypt size, shape, orientation and spacing, and decreased crypt density).1,25–29 Neutrophils are not normally present in normal colonic mucosa. The presence and infiltration of neutrophils into the lamina propria, crypt epithelium (cryptitis) and crypt lumen (crypt abscesses) is a sign of active disease, with the degree of neutrophil inflammation an indication of disease activity. It is, however, also present in infectious colitis and other colitides and is not pathognomonic of UC.

Statement 4
A minority of UC patients may have cecal patch inflammation, rectal sparing (pediatric patients) or backwash ileitis.

Level of agreement: a-82%, b-18%, c-0%, d-0%, e-0%
Quality of evidence: II-2
Classification of recommendation: B

Non-classical UC features which include cecal patch inflammation, rectal sparing and backwash ileitis have been observed in a small proportion of patients. These features should not be confused with CD.30–42 Inflammation of the peri-appendiceal cecal mucosa (‘cecal patch’) is well described in western series, particularly those with left-sided colitis.30–32 The clinical features and natural history of those with cecal patch inflammation appear to be similar to those with isolated left-sided disease.19 Similarly, cecal patch inflammation has also been described in Asian UC patients, being seen more frequently in those with less extensive disease.33–36 In one study from Japan, it has been shown to better respond to medical therapy but this observation will require confirmation in large controlled studies.37 Endoscopic and histologic rectal sparing has been observed in a small proportion of pediatric UC patients at the time of initial presentation51–53 while in adults, it may be seen after topical or systemic therapy for UC.20–21 On the other hand, ‘relative’ rectal sparing has been reported in adult UC patients at presentation.43–44 Inflammation of the distal terminal ileum, termed ‘backwash ileitis’ is seen in up to 20% of UC patients, typically in those with pancolitis although rarely ileal erosions may occur in those without cecal involvement.40–42

Statement 5
Serological tests (ASCA, pANCA) are not required for the diagnosis of UC but may occasionally be helpful in differentiation of UC from CD.

Level of agreement: a-65%, b-23%, c-12%, d-0%, e-0%
Quality of evidence: II-1
Classification of recommendation: B

Serological markers perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) and anti-Saccharomyces cerevisiae antibodies (ASCA) have been extensively studied in the Caucasian IBD population45 but less data exists for Asian IBD patients.46–55 Although pANCA and ASCA are more specific for UC and CD, respectively, their usefulness is limited by their low sensitivity and not required for the diagnosis of UC in clinical practice. In a meta-analysis, pANCA positivity alone has a 55.3% sensitivity and 88.5% specificity for UC.45 The incidence of pANCA in UC may be affected by geographical location and ethnicity, and appears to be a less useful test in the Asian than Caucasian population.55,56 The combination of pANCA+ and ASCA- test may occasionally be helpful in differentiating UC from CD, with
improved specificity to 94.3% but lower sensitivity of only 51.3%. In the pediatric population an improved sensitivity of up to 70% was observed.\textsuperscript{45}

**Statement 6**

The extent of the disease of UC in the Asia Pacific region is similar to that in the West. The extent of disease should be described as proctitis, left sided colitis and extensive colitis (Montreal classification—E1, E2, E3).

**Level of agreement:** a-94%, b-6%, c-0%, d-0%, e-0%

**Classification of recommendation:** B

Studies from the Asia-Pacific region included those from South Korea, Japan, Thailand, China, Hong Kong, Singapore and Malaysia attest to fairly similar disease presentation in terms of extent.\textsuperscript{57–63} Western data from Olmsted county(USA), Norwegian, New Zealand and Australian populations were in keeping with the presentation noted in Asia-Pacific.\textsuperscript{55,64–66} For purposes of future data collection, the group agreed that the extent of disease should follow the Montreal classification for uniformity.

**Statement 7**

Colonoscopy with ileoscopy and biopsies is preferred over barium enema in the evaluation of extent and severity of UC

**Level of agreement:** a-94%, b-6%, c-0%, d-0%, e-0%

**Classification of evidence:** II-3

Many studies showed the utility of biopsies to distinguish UC from other colitides.\textsuperscript{2,67–69} They also show the superiority of colonoscopy and biopsies in determining extent and severity.\textsuperscript{19,68,69} The group agrees with the ASGE 2006 guidelines that colonoscopy and ileoscopy with biopsies are required to evaluate IBD and are useful to differentiate UC from CD.

**Statement 8**

It is important to perform abdominal X-ray (AXR) to exclude toxic megacolon in severe UC

**Level of agreement:** a-94%, b-6%, c-0%, d-0%, e-0%

**Classification of evidence:** II-3

There was good agreement that AXR should be done to exclude the complications of toxic megacolon in severe attacks of UC.\textsuperscript{70,71} The group recognises that serial AXRs are also important in the management of acute severe attacks. Computerized tomographic (CT) scan of the abdomen may also play a role in excluding toxic megacolon.

**Statement 9**

The assessment of UC severity is based on a combination of clinical features (fever, number of liquid stools, bleeding, abdominal pain), vital signs, functional status and objective assessment (laboratory endoscopic features).

**Level of agreement:** a-47%, b-47%, c-6%, d-0%, e-0%

**Classification of evidence:** III

Many activity indexes have been formulated to standardize methods for assessing the activity of disease. These indexes may employ clinical characteristics alone, or with laboratory and/or endoscopic information. Except for a few, many of these indexes have not been validated.\textsuperscript{22} No randomized control trials have compared the different measures of outcome for determining disease activity. In the daily course of clinical work, the group felt that a global physician impression usually prevails. Clinicians rely on an empiric global scale based on the parameters articulated by the above statement. On the other hand, formal indexes are usually employed in clinical trial settings.

**Statement 10**

Ulcerative colitis is usually characterized by relapsing and remitting idiopathic inflammation of the colon and may affect extra intestinal sites.

**Level of agreement:** a-94%, b-6%, c-0%, d-0%, e-0%

**Classification of recommendation:** B

All the studies from Asia-Pacific reflect the relapsing remitting nature of UC.\textsuperscript{57,59,63,73,74} An elegant study from South Korea documented high rates of cumulative relapse after 1, 5, and 10 years at 30%, 72%, and 88%, respectively.\textsuperscript{57} Extra intestinal sites of involvement were noted to be within 6–20% in Asia Pacific.\textsuperscript{60–63,73,74} The group recognized that older retrospective studies may have under-reported these manifestations.

**Epidemiology of ulcerative colitis**

**Statement 11**

The incidence of UC is rising in the Asia-Pacific region, with some exceptions.

**Level of agreement:** a-73%, b-14%, c-13%, d-0%, e-0%

**Classification of recommendation:** B

From the available data, UC is increasing in many parts of the Asia Pacific region.\textsuperscript{58,75–77} Exceptions include Australia and New Zealand where the disease pattern follows the other Caucasian predominant populations in Europe and America.\textsuperscript{78} There are few epidemiological regional studies and true population based registries are only available in Japan and Korea.\textsuperscript{54,75,76} The rising trend seen clearly in the Far East may not apply to all Asian countries and all ethnicities. It is also difficult to establish whether any rise in incidence is a true increase and not due to increased awareness and diagnosis. The reason for this apparent increase has not been established but is almost certainly due to environmental factors. The most likely cause is thought to be associated with the improved economic prosperity in the region and ‘Westernization’ of Asian countries leading to an increase in diseases that are common in the West but previously relatively rare in Asia.\textsuperscript{79–81}
Statement 12

The incidence and prevalence of UC is lower in the Asia-Pacific region compared to the West, with some exceptions.

Level of agreement: a-87%, b-13%, c-0%, d-0%, e-0%

Quality of evidence: II-2

Classification of recommendation: B

Available data suggest that overall, the incidence of UC in Asian countries ranges from 0.4 to 2.1 per 100,000 population. This is in contrast to the incidence rates of 6–15.6 and 10–20.3 per 100,000 in North America and North Europe, respectively. Similarly, the prevalence rates appear to be lower in Asia with rates ranging from 6 to 30 per 100,000 population compared to 37.5–229 and 21.4–243 per 100,000 population in North America and Europe, respectively. However, as mentioned previously, one of the difficulties is the paucity of data in this part of the world and the fact that very few of the studies are based on true population registries. In addition to this, the incidence may be underestimated due to lack of awareness and misdiagnosis. The incidence and prevalence of UC in Australia and New Zealand are similar to that in the West and large population studies in India also shows very similar incidence and prevalence rates to other Western countries.

Statement 13

The incidence and prevalence of UC is higher than that of CD in the Asia Pacific region, with some exceptions.

Level of agreement: a-87%, b-13%, c-0%, d-0%, e-0%

Quality of evidence: II-2

Classification of recommendation: B

In countries where the overall IBD prevalence is low, UC appears to be more common than CD. In countries where the prevalence of IBD is high, CD tends to be the dominant sub-type. Generally, it is thought that in high prevalence areas, the incidence of both diseases may have stabilized but in low prevalence areas, an initial increase in UC incidence is followed by an increase in CD incidence years later. In the Asia-Pacific region, where the prevalence is generally low, a higher incidence and prevalence of UC compared to CD was seen in most countries. The temporal trends in Japan show that the incidence ratio of UC and CD has decreased over time. In New Zealand, the incidence and prevalence of CD is reported to be higher than that of UC.

Statement 14

Genetic and environmental factors are involved in the development of UC.

Level of agreement: a-94%, b-6%, c-0%, d-0%, e-0%

Quality of evidence: II-2

Classification of recommendation: B

It is generally accepted that the pathogenesis of UC is due to a combination of genetic and environmental factors. Several studies have shown genetic polymorphisms associated with UC in the Asian population, but only a few studies have looked at possible environmental risk factors in the development of UC in order to explain the rising incidence of the disease in this region. As in the West, some studies have showed that smoking has a protective effect in the development of UC. Other possible environmental factors associated with UC in the Asian population include a Western diet and a high consumption of refined carbohydrates.

Statement 15

A positive family history probably occurs at a lower rate in UC patients than in the Western population, but is a significant risk factor in the development of UC in the Asia-Pacific region.

Level of agreement: a-44%, b-50%, c-6%, d-0%, e-0%

Quality of evidence: II-2

Classification of recommendation: B

In terms of a positive family history, there appears to be a wide variation among the different studies looking at UC in Asia, with rates ranging from 0.6% to as high as 8%. However, the most reliable data comes from a Korean study, which looked specifically at the rate of positive family history among the UC subjects, but also the risk of developing UC in patients with a positive family history. The study found that although the rate of positive family history of 1.8% was lower compared to that seen in Western countries, the population relative risk of developing UC was similar in subjects with a positive family history when compared to the West.

Statement 16

The peak age of diagnosis is similar to the West.

Level of agreement: a-93%, b-7%, c-0%, d-0%, e-0%

Quality of evidence: II-2

Classification of recommendation: A

Numerous epidemiological studies from the Asia-Pacific region described similar age ranges of UC patients, which mirror those in the West. A Japanese study documented an age range of 6–92 years, supporting the notion that UC can occur at any age. Except for a Korean study that showed a second peak in the 6th to 7th decade similar to the West, the other studies from Asia-Pacific showed a single peak in the range of 30–40 years of age.

Statement 17

The male and female sex distribution in UC is approximately equal.

Level of agreement: a-93%, b-7%, c-0%, d-0%, e-0%

Quality of evidence: II-2

Classification of recommendation: B

Aside from two tertiary center cohorts which reported a male predominance among UC patients (1.5:1), all other hospital-based studies do not show a difference. Larger population based studies from Korea, Japan and New Zealand have not reported any gender differences, similar to those in the West.
Statement 18

Primary sclerosing cholangitis (PSC) associated with UC is less prevalent in the Asia-Pacific region compared to the West

Level of agreement: a-93%, b-7%, c-0%, d-0%, e-0%

Quality of evidence: II-2

Classification of recommendation: C

PSC occurs in UC patients with a prevalence of 2–7% in Western studies.\(^{57,73,85}\) There is a lack of such data on individuals in the Asia-Pacific region. From tertiary centers with a cohort size of more than 200 patients, the prevalence rate was documented to be 0–2.2%.\(^{57,73,85}\) There is a lack of such data on PSC in UC patients from Australia and New Zealand.

Statement 19

Dysplasia and colorectal cancer (CRC) are recognized complications of long-standing UC but further long-term data on the cumulative risk attributable to UC are required in the AP region

Level of agreement: a-80%, b-20%, c-0%, d-0%, e-0%

Quality of evidence: II-3

Classification of recommendation: C

The prevalence of CRC in UC patients in the Asia-Pacific region ranges from 0.3–1.8%.\(^{57,62,73,77,85,103}\) However, many of these reports have relative short duration of follow up (mean duration less than 10 years) and did not capture cumulative incidence rates. Data from UC patients in India reported the risk of CRC of 0% at 10 years, 2.3% at 20 years and 5.8% for those with UC for more than 20 years. These rates are lower than that of a Western meta-analysis, which reported rates of 1.6% at 10 years, 8.3% at 20 years and 18.4% at 30 years.\(^{104,105}\) More recently, a nationwide study conducted by members of the Korean Association for the Study of Intestinal Diseases (KASID) reviewed 7061 cases of UC and found a total of 26 cases of CRC.\(^{106}\)

Management of ulcerative colitis

Statement 20

The aims of UC treatment are to induce remission, maintain remission as well as monitor, prevent and manage complications (disease, drugs, and surgery) and improve well-being.

Level of agreement: a-94%, b-6%, c-0%, d-0%, e-0%

Quality of evidence: III

Classification of recommendation: C

The goals of management of UC are to induce remission, maintain remission, prevent complications and improve quality of life. The treatment of UC depends upon the activity of the disease (active phase, remission phase), extent of the disease (proctitis, proctosigmoiditis, left sided colitis and pancolitis), and dependency on steroid, and needs to be individualized for each patient.\(^{5,8,107}\)

Statement 21

In patients with mild distal UC, 5-ASA given topically and/or orally is the treatment of choice.

Level of agreement: a-94%, b-6%, c-0%, d-0%, e-0%

Quality of evidence: I

Classification of recommendation: A

Ulcerative colitis distal to the splenic flexure may be treated topically with suppositories, enemas, foams and gel.\(^{108,109}\) The choice of preparation depends on the extent of the colitis (for example, suppositories are suitable for proctitis and enemas can reach the splenic flexure). This route of administration delivers a higher dose directly to the affected mucosa and reduced systemic drug absorption may minimize systemic adverse effects.\(^{108–110}\) Patient preference regarding route of drug delivery should also be considered.

There is no high quality evidence for treatment choice in Asian populations, and extrapolation from Western data is necessary. 5-ASA enemas and suppositories are effective first-line therapies for patients with distal UC and ulcerative proctitis.\(^{111}\) Combined oral and topical 5-ASA is superior to oral mesalazine alone for patients with distal colitis.\(^{112,113}\) There is no dose-response to topical therapy above a dose of 1 g mesalazine daily. Clinical (and endoscopic) remission can occur in up to 64% within 2 weeks. Oral mesalazine is also effective in the treatment of active distal colitis and may be preferred for convenience and compliance.\(^{111,112,114}\) For maintenance treatment for distal colitis, oral and/ or topical mesalazine are effective.\(^{115,116}\)

Topical corticosteroids can be used as second line therapy for patients intolerant to- or failed-topical mesalazine.\(^{108,114}\) Patients who have failed to improve on a combination of oral mesalazine with either topical mesalazine or topical corticosteroids may be treated with oral prednisolone.

Statement 22

In acute severe colitis, intravenous (IV) corticosteroid is the treatment.

Level of agreement: a-94%, b-6%, c-13%, d-0%, e-0%

Quality of evidence: IIA

Classification of recommendation: B

The mainstay of treatment of acute severe exacerbation of UC is IV corticosteroids,\(^{5,117}\) at a dose of, for example, 48–60 mg/day methylprednisolone or 300–400 mg/day daily hydrocortisone.\(^{117–121}\) In Asian countries, infective enterocolitis should be excluded first. In a systematic review of 32 trials of steroid therapy for acute severe colitis involving 1991 patients, the overall response to corticosteroids was 67% (95% CI 65–69%).\(^{118}\) Higher doses are no more effective, but lower doses are less effective.\(^{5,117}\) Bolus injection is as effective as continuous infusion.\(^{122}\) Treatment is usually given for about 5 days, since extending therapy beyond 7–10 days carries no benefit but may delay definitive treatment.\(^{118,120,121,123}\)

Other measures for the management of acute severe colitis in addition to IV corticosteroids are:\(^5,124\)

- Nil orally if impending surgery.
- Nutritional support.
- Potassium supplementation and avoidance of hypokalemia.
- Avoidance of anticholinergic, anti-diarrheal agents, non-steroidal anti-inflammatory drugs (NSAID) and opioid drugs, which risk precipitating colonic dilatation.
- Stool cultures and assay for Clostridium difficile toxin.
• Exclusion of cytomegalovirus infection (CMV colitis), especially following prolonged exposure to immunosuppressive drugs.

Statement 23
Patients with acute severe UC, non-responsive to IV corticosteroids within 5–7 days are candidates for second line therapy cyclosporin [LA], anti-TNF therapy [II-3,C] and surgery [III,C].

Quality of evidence and Classification of recommendation: as above

Cyclosporin (CsA). CsA is an immunosuppressive macrolide that inhibits the production of interleukin 2 by activated T lymphocytes through a calcineurin-dependent pathway. CsA has been used to induce clinical remission in acute severe colitis refractory to IV corticosteroids. CsA commenced initially as intravenous therapy may be continued orally to bridge the gap needed for the full efficacy of azathioprine or 6-mercaptopurine, especially if thiopurine agents have not been tried previously, to prevent disease relapse.117,125

In the only randomized controlled trial published, 82% of patients with severe steroid-refractory colitis responded to IV CsA (4 mg/kg daily) compared with 0% treated with placebo.126 Low dose (2 mg/kg) intravenous induction therapy is as effective as standard dose (4 mg/kg), but has fewer adverse effects.127 The long-term outcome, however, indicates that colectomy was avoided in 12–42% patients at 7 years.128–130 In small open-label studies in Japan and India, CsA was effective in steroid-refractory UC patients.131,132 Cytomegalovirus colitis has been recognized as a complication in UC patients undergoing treatment with CsA and responds to treatment with ganciclovir.133

Antibiotics as monotherapy have not been shown to improve active ulcerative colitis.

Level of agreement: a-60%, b-40%, c-0%, d-0%, e-0%
Quality of evidence: I
Classification of recommendation: A

The benefit of antibiotics in the primary or adjunctive treatment of IBD has not been established in randomized controlled trials. Studies have been limited by poor study design, small patient numbers, high dropout rates and heterogeneity in entry criteria, concomitant therapies, and endpoints. The majority of the data do not support the use of antibiotics as primary treatment or as an adjunct to standard corticosteroid therapy of mild to moderate or severe UC. However, broad-spectrum antibiotics are reasonable to consider in patients with fulminant colitis, such as toxic megacolon at risk of perforation, especially if these patients are also receiving corticosteroids.143

Statement 26
Immunomodulators such as thiopurines [IA] or biologics [II-2,B] can be recommended for treating steroid-dependent, steroid-refractory or relapsing ulcerative colitis. There is currently only limited evidence for the use of methotrexate in ulcerative colitis [III,C]. Cyclosporine inhibitors are used short-term as a bridge to another immunomodulator such as a thiopurine [II-2,B].

Level of agreement: a-44%, b-56%, c-0%, d-0%, e-0%
Quality of evidence and Classification of recommendation: as above

Definitions. Steroid-refractory colitis is defined as active disease despite prednisolone up to 0.75 mg/kg/day over a period of 4 weeks. Whereas steroid-dependent colitis is defined as the
inability to reduce steroids below the equivalent of prednisolone 10 mg/day within 3 months of starting steroids, without recurrent active disease, or a relapse within 3 months of stopping steroids. Relapse is defined as a symptomatic flare of symptoms in a patient with established UC who is in clinical remission. Early relapse is arbitrarily defined as relapse occurring within 3 months of achieving remission. Severe colitis is defined clinically as presentation with bloody diarrhea ≥ 6/day and signs of systemic toxicity (tachycardia > 90 bpm, fever > 37.8°C, Hb < 10.5 g/dL, or an ESR > 30 mm/h). In-hospital intensive management is required for patients who present with severe colitis.\(^3\)

Azathioprine and 6-mercaptopurine. The thiopurine analogues azathioprine (AZA) and 6-mercaptopurine (6-MP) are immunomodulators that effectively induce and maintain remission in UC.\(^{144-146}\) The quality of published data on AZA/6-MP in UC is poorer than for CD, but they should still be considered as first choice of therapy in steroid-dependence and relapsing UC. In UC, thiopurines are commonly used as steroid-sparing agents and are increasingly considered early in the course treatment.\(^{146}\) Efficacy can take weeks to months from onset of therapy.\(^{147}\) The rate of induction of remission is up to 69% and the response rate is up to 84%.\(^{148-150}\) Maintenance of remission is higher than placebo with efficacy extending for at least 2 years.\(^{151,152}\) Azathioprine was not statistically superior to placebo based on a meta-analysis of 5 studies.\(^{153}\) However, after selecting the two highest quality studies, including one from India, AZA had a pooled relative risk for ‘treatment success’ of 2.05 (95% confidence interval [CI] 1.30–3.23).\(^{153,154}\) Another meta-analysis based on four trials found AZA to be superior for the maintenance of remission as compared to placebo (failure to maintain remission: odds ratio [OR] 0.41; 95% CI 0.24–0.70).\(^{145}\) A controlled study showed AZA to be more efficacious than using 3.2 g/day of 5-ASA in steroid-dependent UC.\(^{144}\)

Thiopurines are metabolized by genetically-determined polymorphic enzyme pathways. Azathioprine and 6-MP are considered equivalent in efficacy at the equivalent doses. A survey of the efficacy and safety of AZA/6-MP in a Japanese pediatric population with UC found that 40% developed adverse drug effects including aplastic anemia, leukopenia and hepatotoxicity.\(^{155}\) Lower starting doses in Asian compared to Caucasian populations to thiopurines, such as biologic agents, in many parts of Asia.

Biologic therapy. Tumor necrosis factor (TNF) alpha inhibitors, in particular, IFX, have been evaluated in the maintenance of remission in UC. Current guidelines recommend that biologic agents are used only in patients failing conventional therapies or who are steroid dependent.

Infliximab in moderate-to-severe ulcerative colitis. IFX is a TNF-alpha inhibitor with steroid-sparing effect in UC and may be given every 8 weeks for scheduled maintenance after the initial loading dose. Two large randomized placebo-controlled trials of IFX (ACT 1 and ACT 2) enrolled moderate to severe UC patients unresponsive to standard therapy.\(^{158}\) The studies showed that the clinical response rates in patients treated with IFX given at weeks 0, 2, and 6 and then every 8 weeks through week 46, was significantly higher (46%) than for placebo at week 54 (20%) (P = 0.001). Similarly, the 54-week remission rate was significantly higher for the groups treated with IFX at 35% compared to placebo remission rate of 17% (P = 0.001). Further analysis of the ACT 1 & 2 trial data indicates that there was an associated reduction in colectomy (hazard ratio 0.57, 95% CI 0.37–0.89) during the trial. However, even at 5 mg/kg IFX every 8 weeks, only 21% (at 7 months) and 26% (at 12 months) achieved steroid-free remission.\(^{30}\)

Adverse effects to anti-TNF-alpha agents. Adverse events reported with IFX therapy include increased susceptibility to infections that might be primary, opportunistic or reactivation, infusion-related reactions, serum sickness-like reaction, neurological, immunological and other reactions. IFX is contraindicated in people with moderate or severe heart failure, active infections, and demyelinating conditions. Anti-TNF drugs increase the risk of reactivation of latent TB and can result in overwhelming disseminated and extra-pulmonary disease by 4–20 fold.\(^{159}\)

Other biologic agents. Adalimumab may be an option in the maintenance of clinical remission of UC patients intolerant to, or with lost efficacy to, IFX.\(^{160}\) Large scale studies are currently underway in the evaluation of this and other biologic agents in UC.

Methotrexate. Data on methotrexate (MTX) in the treatment of UC remain limited and inconsistent. A randomized placebo-controlled study using MTX at the dose of 12.5 mg/week orally showed no benefit.\(^{161}\) Higher dosage and parenteral administration, however, may be beneficial. Open labeled studies have achieved remission rates of 42–60% including in patients who had failed AZA/6-MP.\(^{162,163}\) Adequately-powered prospective randomized controlled studies of MTX in UC are required. Methotrexate remains a therapeutic option in refractory UC patients who failed AZA/6-MP treatment given the limited availability of alternatives to thiopurines, such as biologic agents, in many parts of Asia.

Calcineurin inhibitors. Cyclosporin and tacrolimus are calcineurin inhibitors that reduce interleukin-2 production.

Cyclosporin. Intravenous CsA is indicated within 7 days of commencing IV steroids if clinical and laboratory parameters do not show adequate therapeutic response. (see statement 23). CsA is usually ceased after 3–6 months of overlap with AZA/6-MP or methotrexate used as monotherapy after this time. Complications of CsA include hypertension, nephrotoxicity, seizure, gingival hyperplasia and hypertension. Both CsA and IFX can be used in IV-corticosteroid refractory UC and randomized comparative study of the two agents are in progress. Rescue treatment after failure of the first agent has a 33–40% chance of inducing remission with the second agent but at the risk of developing severe septic complications.\(^{136}\)

Tacrolimus. Tacrolimus has a greater potency, more predictable pharmacokinetic profile and better adverse effect profile than CsA.\(^{164}\) Tacrolimus has steroid-sparing effects, is rapid in onset...
and colectomy can be averted in a proportion of UC patients. Ogata et al. conducted a placebo-controlled study in Japanese patients with refractory UC randomizing them to high-trough levels of 10–15 ng/mL, low-trough levels of 5–10 ng/mL versus placebo and showed that the clinical remission rates were 19%, 9% and 5%, respectively. The clinical improvement rates at 2 weeks were 62%, 36%, and 10%, respectively. Colectomy was avoided in all patients. Overall, the long-term colectomy rate in another tacrolimus study was 22–34%. Adverse drug effects tend to be mild and include tremor, hyperglycemia, hypertension and infection.

Statement 27

Toxic megacolon, non-responsiveness or drug-induced adverse effects to medical treatment, high-grade dysplasia, carcinoma, steroid dependency, massive bleeding, bowel perforation and failure to thrive in the pediatric patient are indications for surgery.

Level of agreement: a-100%, b-0%, c-0%, d-0%, e-0%

Classification of evidence: III

Indications for surgery. Surgery remains an important component in the treatment algorithm of UC and early colorectal surgery consultation is recommended especially for acute severe UC that requires hospitalization. The decision to operate is best taken by the gastroenterologist and colorectal surgeon in conjunction with the patient. The type of surgery is dependent on the acuteness of the indication and the patient’s condition. Indications for surgery include toxic megacolon, non-responsiveness or drug-induced adverse effects to medical treatment, high-grade dysplasia, carcinoma, steroid dependency, massive bleeding, and failure to thrive in the pediatric patient are indications for surgery. Toxic megacolon is defined as total or segmental non-obstructive dilatation of the colon of at least 6 cm associated with systemic toxicity. This represents severe colitis and is associated with colonic perforation. Bowel perforation is the most serious of UC complications and is associated with high morbidity and mortality.

Statement 28

Depending on the extent of disease, oral and or per-rectal 5-aminosalicylates help maintain remission. [I,A] 5-ASAs may have a role in the chemoprophylaxis of dysplasia [II-2,C] and cancer. Ursodeoxycholic acid may reduce colorectal cancer with concurrent ulcerative colitis and primary sclerosing cholangitis. [II-3,B]

Level of agreement: a-69%, b-31%, c-0%, d-0%, e-0%

Quality of evidence and Classification of recommendation: as above

5-Aminosalicylic Acid in Maintenance of Remission. 5-ASAs are effective in the maintenance of remission of mild-to-moderate UC. The OR for the failure to maintain clinical or endoscopic remission (withdrawals and relapses) for 5-ASA versus placebo was 0.47 (95% CI: 0.36–0.62). Sulphasalazine may be better than newer 5-ASA preparations in the maintenance of remission in UC but both formulations were generally safe and well tolerated. In Asia, UC tends to be milder with a lower requirement for proctocolectomy. In a review of 172 Chinese UC patients, 84% were on oral and/or topical 5-ASA. Distal UC may be adequately maintained with intermittent topical rectal 5-ASA. To improve adherence, oral 5-ASA treatments may be given once daily, which has a similar efficacy to multiple daily doses.

5-Aminosalicylic Acid in Dysplasia Chemoprevention. Colorectal cancer is one of the most devastating complications of chronic colitis in the setting of IBD. The risk of colitis-associated CRC in Asia is likely to be similar to Western countries and emerging data, such as from the Korean population-based IBD registry, confirms this. In Korea, the overall prevalence of CRC in UC patients was 0.37%. The cumulative risk of UC-associated CRC was 0.7%, 7.9% and 33.2% for the respective disease durations of 10, 20 and 30 years. The use of chemoprophylaxis was not detailed in this study. Therefore, the 30-year rate of colitis-associated CRC in Korea exceeds population-based CRC rates of 2.1–7.5% in Western population studies of the equivalent duration of disease.

From a meta-analysis that included 334 cases of CRC, 140 cases of dysplasia and a total of 1932 subjects, 5-ASA protected against the development of CRC (OR: 0.51; 95% CI: 0.37–0.69) or a combined endpoint of CRC/dysplasia (OR 0.51; 95% CI: 0.38–0.69). Other studies have not shown the chemoprotective effect of 5-ASA. The high tolerability of 5-ASA and the potential to prevent CRC supports the use 5-ASA chemoprophylaxis.

Ursodeoxycholic Acid. The presence of PSC in the setting of UC significantly increases the risk of CRC with OR 4.79 (95% CI: 3.58–6.41). A randomized controlled study of ursodeoxycholic acid in PSC-UC patients found on intention-to-treat analysis a significantly reduced rate of CRC development (RR 0.26; 95% CI: 0.06–0.92). Ursodeoxycholic acid (13–15 mg per kilogram of body weight) should therefore be included in all patients with PSC-UC.

Statement 29

Fertility, pregnancy, breast feeding, nutrition and osteoporosis are important considerations in the management of UC.

Level of agreement: a-100%, b-0%, c-13%, d-0%, e-0%

Classification of evidence: III

Fertility and pregnancy. As IBD affects young adults, fertility and pregnancy must be considered. Active UC reduces fertility through inflammation effects on the female reproductive system and previous surgery, and sulphasalazine can induce reversible decrease in sperm motility in men. Clinical remission is recommended prior to conception and maintenance of remission during pregnancy is the goal during pregnancy to reduce fetomaternal complications. Active flares during pregnancy need to be treated aggressively using drugs established to be safe in pregnancy. Corticosteroids tend to be safe in pregnancy as placental 11-hydroxygenase converts steroids to less active metabolites. Although spontaneous abortion and congenital cleft palate are
risks with corticosteroids in animals, no increase in congenital malformations in humans have been found. Fecundity and surgery is discussed in statement 30. Drugs that absolutely need to be avoided during pregnancy are methotrexate and thalidomide.

**Breastfeeding.** 5-ASA and corticosteroids are safe with breastfeeding. Recommendation is to avoid breastfeeding for 4 hours following per oral drug administration to reduce neonatal exposure to drugs. Azathioprine metabolites have not been found in babies exclusively breastfed by mother receiving thiopurines. Therefore most clinicians believe that women should not stop a thiopurine when breastfeeding. There is some evidence that breastfeeding for at least 6 months reduces an infant’s risk of developing both CD and UC therefore the decision to breast feed needs to take this into consideration. Co-management with an obstetrician experienced in managing IBD is recommended.

**Nutrition.** Up to 85% of patients hospitalized with exacerbations of IBD have protein-calorie malnutrition.

**Osteoporosis.** Systemic inflammation secondary to active colitis and recurrent or chronic use of high dose corticosteroids are risk factors for osteoporosis, which may increase fracture risk. Osteopenia and osteoporosis are common in Asian patients with IBD. Optimal nutrition, calcium and vitamin D intake, weight bearing exercise, cessation of smoking, moderation of alcohol consumption, and minimization of the use of corticosteroids are recommended. A review of diet by a dietician is recommended. Patients with established osteoporosis should be referred to an endocrinologist or rheumatologist.

**Statement 30**

When indicated, the gold standard elective surgery for ulcerative colitis is restorative proctocolectomy with ileal pouch anal anastomosis (IPAA) and this should be performed in a specialized centre.

**Level of agreement:** a-67%, b-33%, c-0%, d-0%, e-0%

**Quality of evidence:** III

**Classification of recommendation:** C

Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) offers patients an unchanged body image with no stoma, a preserved anal route of defecation and good postoperative quality of life. Ileal pouch-anal anastomosis is best performed in the elective setting, whereas a staged procedure with subtotal colectomy with ileostomy as the initial stage is the safest surgical option for the management of acute severe colitis or when high dose prolonged corticosteroids have been utilised. Ileal pouch-anal anastomosis also requires expertise and centralization of experience to fewer treatment centers can be recommended. Acute complications of IPAA include anastomotic leak, sepsis, injury to local structures including pelvic nerves. Because fecundity can be impaired with IPAA in young female patients, ileorectal anastomosis should be considered. Also, in the elderly and females with delivery-related injury during childbirth, anal sphincter may be weakened and IPAA may be complicated by fecal incontinence. Pouchitis is a non-specific inflammation of the ileal reservoir and the most common complication of IPAA in patients with UC.

**Statement 31**

Screening tests according to local practice for hepatitis B virus infection [III,A], human immunodeficiency virus [III,C], and TB [II-3,A] need to be considered prior to commencement of corticosteroids, immunomodulators and/or biologic agents. Vaccination, prophylaxis or therapy should be performed in appropriate clinical settings. [III,C]

**Level of agreement:** a-19%, b-81%, c-0%, d-0%, e-0%

**Quality of evidence and Classification of recommendation:** as above

**Hepatitis B virus infection.** The prevalence of hepatitis B virus (HBV) infection is higher in the Asia-Pacific region than Western countries. The withdrawal of immunosuppressive therapy can result in severe HBV reactivation thus preemptive treatment with a nucleoside or nucleotide analogue may suppress viral replication on initiation of immunosuppression. Case reports of HBV reactivation are described following the use of IFX, AZA/6-MP with or without corticosteroids and rarely results in fulminant hepatic failure. In the Asia-Pacific region, HBV serology should be performed in all IBD patients as HBV-negative and HBV surface-antibody negative patients can receive vaccination, and HBV surface antigen-positive patients can be treated with anti-viral agents prior to immunosuppression. Hepatitis B virus anti-core-antibody-positive surface antigen-negative patients require close monitoring for possible HBV reactivation and hepatitis flare.

**Tuberculosis.** The prevalence of tuberculosis (TB) is high in many parts of the Asia-Pacific region. Intestinal TB is a differential diagnosis in newly diagnosed IBD. Screening for TB is mandatory in Asian countries and high-risk cases require anti-TB treatment or chemoprophylaxis with isoniazid according to acceptable local practice. Screening strategies differ according to endemic TB prevalence and BCG vaccination practice but can include chest radiograph, tuberculin skin testing, human mycobacterium-specific interferon gamma assays, and high vigilance in the development of breakthrough infection.

**Other opportunistic infections.** Opportunistic infections are increased in immunosuppressed patients. Multi-modal treatment increases this risk more than monotherapy and the recommendation is to simplify treatment to monotherapy whenever possible. Methotrexate and 5-ASA appear to be safer agents than corticosteroids, anti-TNF and AZA/6-MP. Vaccination against opportunistic infections, such as HBV, varicella-zoster, human papilloma virus, pneumococcus, and influenza virus, should be considered.

**Statement 32**

Colonoscopy surveillance for colorectal cancer is recommended in patients with long-standing ulcerative colitis with the exception of proctitis.

**Level of agreement:** a-60%, b-40%, c-0%, d-0%, e-0%

**Quality of evidence:** II-3

**Classification of recommendation:** C

Current strategies in the reduction or management of colitis-associated CRC include chemoprophylaxis, colonoscopy
surveillance of at-risk individuals and proctocolectomy, which is a potentially curative treatment for those with precancerous dysplasia or early cancer. Colonoscopy surveillance is recommended after 8–10 years of extensive colitis and 12–15 years of left-sided colitis.\(^\text{189}\) The detection of colorectal dysplasia is considered a strong predictor of CRC in IBD.\(^\text{190}\) Data not supportive of the benefit of surveillance colonoscopy may be due to missed lesions during the procedure. Newer endoscopy technologies may further improve the sensitivity of dysplasia detection. The incorporation of high resolution video with methylene blue or indigo-carmine chromoendoscopy is superior to traditional random colonic biopsies in the detection rate of neoplastic lesions. The Korean data showing a high prevalence of CRC in longstanding UC of 30 years may be reduced through greater awareness of colitis-associated CRC and regular screening.\(^\text{106}\)

**Conclusions**

These are the first Asia-Pacific consensus statements on UC developed through a rigorous process of voting using the Delphi process and taking into account evidence from the current literature, regional data and input from a multi-disciplinary panel of experts belonging to the APAGE Working Group on IBD. Included in these statements for the first time are recommendations specific to the Asia-Pacific region with regards to testing of HBV and TB for patients considered for steroids, immunomodulators and biologic therapies. These were designed to harmonize definitions and provide recommendations in the diagnosis and management of an increasingly recognized disease in the Asia-Pacific. Differentiation of UC infectious colitis remains vital. Although available now for some time, biologic agents have not been used widely given their cost and risks in developing opportunistic infections such as TB. There is a need therefore to research this field further and develop guidelines on the use of chemoprophylactic treatments relevant to specific countries.

While these statements were designed for the region, it is acknowledged that modification may be required for the individual needs of specific countries within the Asia-Pacific. The need for uniform definitions to enable data collection from Asia-Pacific was recognized. We also attempted to highlight important areas where more studies will be required including the environmental exposure risk factors that have led to the rise of IBD in the past three decades, the long-term data on colorectal dysplasia and cancer and the safety and efficacy of biologic therapies in the Asia-Pacific region. The recent increase in IBD in Asia provides an opportunity to explore the evolving epidemiology of IBD and may support the inverse correlation of infectious and complex immunological diseases otherwise known as the ‘hygiene hypothesis’.

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Appendix I

**List of participants (voting/face to face meeting)**

Australia—Peter R Gibson, Rupert WL Leong
China—Qin Ouyang
Hong Kong—Wai Keung Leung
India—Vineet Ahuja, Govind K Makharia, B Ramakrishna
Malaysia—Khean Lee Goh, Ida Hilmi
New Zealand—Richard Gearry
Philippines—Jose Sollano
Singapore—Cora Chau, Kwong Ming Fock, Wee Chian Lim, Khoon Lin Ling, Doris Ng, Boon Swee Ooi, Choon Jin Ooi—Kelvin Thia
South Korea—Seung Jae Myung
Sri Lanka—H Janaka de Silva
Taiwan—Shu-Chen Wei
Thailand—Sathapor Manatsathit, Rungsun Rerknimitr (Representatives from Japan and Indonesia were invited but did not participate)

**List of speciality resource individuals who attended face to face meeting**

Pathologist—Cora Chau, Kiat Hon Lim
Colorectal Surgeon—Boon Swee Ooi
Pharmacist—Teong Guan Lim
Nurse Clinician/Patient Support Group representative—Kia Lan Loy