

## Indian Society of Gastroenterology consensus on ulcerative colitis

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Indian Society of Gastroenterology Task Force on Inflammatory Bowel Diseases**

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**Abstract** In 2010, the Indian Society of Gastroenterology's Task Force on Inflammatory Bowel Diseases undertook an exercise to produce consensus statements on ulcerative colitis. This consensus, produced through a modified Delphi process,

reflects our current understanding of the definition, diagnostic work up, treatment and complications of ulcerative colitis. The consensus statements are intended to serve as a reference point for teaching, clinical practice, and research in India.

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## Introduction

Inflammatory bowel disease, once thought to be uncommon in India, is now increasingly diagnosed in clinical practice. The Indian Society of Gastroenterology (ISG), in 2003, established a Task Force on Inflammatory Bowel Diseases (IBD). This Task Force collected data on IBD in the country, which is presented as an accompanying paper [1]. The Task Force also evolved a series of consensus statements on ulcerative colitis (UC), the predominant form of IBD seen in India. These statements reflect the current status of evidence and practice with respect to UC in India.

## Methods

A group of gastroenterologists working in tertiary-care institutions, secondary-care institutions and in private practice, and representing different geographic areas of the country, were invited by the ISG to become members of the Task

Force. An invitation was also put up on the website of the Society and of its publication, the Indian Journal of Gastroenterology, to member-gastroenterologists to contribute data to the Task Force. Those who contributed such data were made members of the Task Force.

A modified Delphi process [2] was adopted to develop the consensus statements on UC. For this purpose, four areas were defined, namely, epidemiology, diagnosis, management, and follow up. In each of the sections, the issues were determined according to perceived clinical importance. BSR and GKM generated a list of statements, which were then taken up for discussion, revision, voting, and final consensus.

The initial statements were circulated to the Task Force members. The first vote was conducted by email, without explanation or justification for the statements; feedback regarding the statements was collated and modifications made where appropriate. The relevant literature was then made available to all those who voted in the first round, and they were advised that they could change their vote on the statements after reviewing the literature. The results of the second vote were collated. Finally, the group met and discussed the statements developed based on feedback from the two rounds of votes by email.

At this meeting, in addition to the members of the Task Force, Indian experts in IBD as demonstrated by publication, research or participation in national or regional guidelines development groups, and specialty experts in histopathology and surgery, were invited as advisors. The group discussed the evidence to support specific statements; the evidence was presented in four parts by VJ, UCG, BSR and GKM. All relevant literature available for each statement was reviewed with emphasis on Indian data when available.

A third vote was held at the end of the talks, using electronic vote pads to capture the vote anonymously. The options given for each statement were (A) accept completely, (B) accept with some reservation, (C) accept with major reservation, (D) reject with reservation, and (E) reject completely. Consensus on a statement was considered to be achieved when 80 % or more of the voting members chose to “accept completely” or “accept with some reservation” the statement. A statement was considered to be refuted when 80 % or more of the voting members indicated “reject completely” or “reject with some reservation”. When no consensus was reached on a particular statement, it was modified and a second vote sought. If the second vote also remained inconclusive, the statement was deleted.

The participants were then asked to grade the level of evidence available and the strength of recommendation for the accepted statements, using a modification of the scheme suggested by the Canadian Task Force on the Periodic Health Examination (Table 1) [3].

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**Table 1** Quality of evidence, classification of recommendation and voting for recommendation [from Ref. 3]

Quality of evidence	
I	Evidence obtained from at least 1 RCT
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 recommendations	
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 recommendation	
A	Accept completely
B	Accept with some reservation
C	Accept with major reservation
D	Reject with reservation
E	Reject completely

RCT randomized controlled trial

## Consensus statements on ulcerative colitis of the ISG-IBD Task Force

### Epidemiology and clinical manifestations

#### 1. Ulcerative colitis is not uncommon in India

Voting: A16, B1, C1

Level of evidence: II-2

Grade of recommendation: B

The incidence and prevalence of ulcerative colitis in Western countries is determined through data in population-based registries. The incidence rates are 6–15.6 and 10–20.3 per 100,000 in North America and North Europe, respectively [4]; the corresponding prevalence rates are 37.5–229 and 21.4–243 per 100,000 population [4]. There are only two studies from India, both from northern states, reporting the population prevalence of UC. A study of 21,971 persons in Haryana in 1984 recorded a prevalence rate of 42.8 per 100,000 [5]. The second study was conducted in Ludhiana, Punjab, where a population of 51,910 was screened through a cluster random sampling method, and 23 patients were diagnosed with definite UC. The prevalence of UC was 44.3 per 100,000, and the crude incidence rate calculated after a second visit 1 year later was 6.02 per 100,000 [6]. Both these studies suggest that UC is not uncommon, at least in northern India.

#### 2. The prevalence of ulcerative colitis appears to be higher in India than in the rest of Asia

Voting: A6, B11, C1

Level of evidence: II-2

Grade of recommendation: B

The incidence of UC in Asian countries ranges from 0.4 to 2.1 per 100,000 population [7–10], which is lower than the incidence rate of 6.02 per 100,000 recorded in India [6]. The prevalence rates also appear to be lower in Asia, ranging from 6 to 30 per 100,000 population [7–10]. Studies from Singapore and Malaysia comparing populations of Indian, Chinese and Malay ethnic origin have shown that residents of Indian origin had a higher prevalence of UC than those of Chinese or Malay origin [11–13]. Indians in these studies had odds ratios of 2.9–4.8 compared to Chinese or Malays of having UC.

#### 3. There are insufficient data to show regional differences in the prevalence of ulcerative colitis in India

Voting: A16, B2

Level of evidence: III

Grade of recommendation: C

UC has been reported from all parts of India [14–17]; however, there are no population-based studies from southern India. There are no data to show any regional differences in incidence or prevalence, and the voting group did not think there was any difference in frequency of UC in their practice in different parts of India.

#### 4. In India ulcerative colitis is more common than Crohn's disease (CD)

Voting: A16, B2, C1

Level of evidence: II-3

Grade of recommendation: B

This statement was based on the personal experience of the voting members of the Task Force, since there are no population-based studies on CD incidence or prevalence in

India. In the accompanying article on the data collected by the Task Force [1], there were 741 patients with UC and 406 patients with CD.

5. Family history of ulcerative colitis is uncommon in India

Voting: A12, B6, C1

Level of evidence: II-3

Grade of recommendation: B

A history of UC in another member of the family has been noted in 14.6 % to 29.4 % of Western patients with UC [18]. In Asia, a positive family history appears to be much less common, varying from 0.6 % to 8 % [19–21]. A study of South Asian migrants in the United Kingdom revealed that positive family history for UC was much less common in South Asian (3.5 times increased risk) compared to Caucasian (14.6–19.2 times increased risk) patients with UC [22]. The ISG-IBD Task Force data collection found a positive family history in only 2.3 % of UC patients [1].

6. The incidence of ulcerative colitis in Indians migrating to countries with a higher prevalence is higher as compared to Indians residing in India

Voting: A12, B6, C1

Level of evidence: II-3

Grade of recommendation: B

The evidence for this statement comes from studies performed on immigrants from South Asia (largely from India and Bangladesh) to the United Kingdom. The age-standardized incidence of UC among South Asians in the UK was about twice as high as that in Europeans [23, 24], and was one of the highest in the world. There were marked differences in the incidence rates of UC, excluding proctitis, among different South Asian ethnic groups – the incidence was 10.8/100,000/y in Hindus, 16.5/100,000/y in Sikhs, and 6.2/100,000/y in Muslims, while that of Europeans was 5.3/100,000/y. The incidence in Bangladeshi Muslims (1.8/100,000/y) was marginally lower than in Europeans (6.2/100,000/y) in another study from Tower Hamlets, England [25]. Taken together, the incidence of UC in Hindus was about twice as high as that in Muslims; the higher frequency of smoking among Muslims was used to explain the observed difference. The incidence of UC was lower among Indian migrants in Fiji [26] and Durban, South Africa [27], both relatively low-incidence areas for UC, than among Indians in England.

7. Extraintestinal manifestations are observed in up to a third of Indian patients with ulcerative colitis

Voting: A16, B3

Level of evidence: II-2

Grade of recommendation: A

There are at least 19 studies from India that have reported the prevalence of extraintestinal manifestations in patients

with UC, but most of these are as Abstracts. The overall reported prevalence ranged from 6 % to 39 % [28–31]. Kochhar reported extraintestinal manifestations in 34.7 % of UC patients attending a tertiary-care center; these included sacroiliitis in 14 %, peripheral arthritis in 10.7 %, ocular manifestations in 8 %, mucocutaneous lesions in 2.7 %, vascular complications in 2 %, and hepatobiliary complications in 1.3 %. Habeeb et al. reported extraintestinal manifestations in 39 %, including arthralgia in 21 %, ocular involvement in 7 %, and sacroiliitis in 5 %. Extraintestinal manifestations were less common (6 %) in another study of 46 patients with UC; one patient had peripheral arthritis and 2 had ocular involvement (anterior uveitis). In the data collected by the ISG-IBD Task Force [1] 50.6 % of patients with UC had extraintestinal symptoms, principally arthralgias, backache, ocular lesions and skin lesions.

Diagnosis

8. Criteria for diagnosis of ulcerative colitis include compatible clinical history, confluent colonic involvement proximally from the rectum to a variable extent on endoscopy, consistent histology, and exclusion of infection as the primary cause

Voting: A12, B4, C1, D1

Level of evidence: III

Grade of recommendation: A

The criteria for diagnosis of UC are similar to those recommended by various other groups of experts [32–35]. These include combination of consistent clinical presentation (large-bowel diarrhea with blood-mixed stool), colonoscopic findings consistent with UC (loss of vascular pattern, confluent ulceration, granularity, disease starting from rectum and extending to variable extent proximally into colon, lack of skip areas), consistent histology (cryptitis, crypt abscesses, crypt distortion, branching and loss, chronic inflammation, muscularis mucosae hypertrophy), and exclusion of an infective cause. In India, particular attention must be given to exclude infective causes such as bacillary and amebic dysentery, which may mimic UC [36–40] or may precipitate relapse in patients with existing disease [41].

9. Infections should be excluded in ulcerative colitis patients with steroid-non-responsive disease

Voting: A15, B3

Level of evidence: III

Grade of recommendation: C

Several colonic infections, which are common in India, may be close mimickers of first attack of IBD including UC or may cause exacerbation of existing disease in remission. These include amebiasis, shigellosis, colonic tuberculosis and rarely Cytomegalovirus (CMV) colitis [36–45]. In a

study on 25 patients with acute colitis caused by *Shigella dysenteriae* I, various abnormalities recorded on colonoscopy included mucosal edema, ulcers, friability, punctate spots, erythematous areas and luminal exudate (involvement was subtotal in 20 patients and total in 5). The mucosal disease lasted for 39 (SD 12; range 10–65) days and then normalized. This study suggested that some changes in the colon in patients with bacillary dysentery may mimic UC [42].

Infections should be particularly excluded in patients with first attack of UC, during exacerbations of disease previously in remission, and steroid-non-responsive disease. In a study on 50 patients with UC, evidence of infection with protozoal and bacterial agents was more common in patients with acute exacerbation than those in remission (32 % with acute exacerbation vs. 4 % in remission) [43]. In another study including 61 patients with UC, 10 (15.8 %) were infected with CMV (DNA alone in four, IgM antibody alone in two, and both in four, inclusion body in one) [44]. Patients with CMV infection were more often female, had pancolitis, histological activity, and used azathioprine. On multivariate analysis, female gender, pancolitis and histological activity were the independent factors associated with infection. This study suggested that patients with active disease in spite of immunosuppressive treatment including corticosteroids are more likely to have CMV infection.

In a study on 49 consecutive patients with UC (84 % of whom had moderate to severe disease), 12 % had parasitic infestation (*Strongyloides stercoralis* in 4 %, *Ankylostoma duodenale* in 4 %, *Cryptosporidium* in 2 % and *Entameba histolytica* in 2 %) [45]. The prevalence of CMV and herpes simplex virus in rectal biopsies using qualitative PCR was 8 % and 10 %, respectively. A study suggested that CMV DNA load determined in inflamed intestinal tissue predicted resistance to steroid treatment in UC. The authors suggested that early initiation of antiviral treatment in these patients might delay the occurrence of resistance to treatment [46]. In a study on 94 patients with UC, 12/94 (12.8 %) fecal samples were *Clostridium difficile* toxin-positive, which was significantly associated with fecal lactoferrin positivity, suggesting that colonic inflammation in these patients may be exacerbated by this infection [47].

10. The optimal screening for infections should include three stool examinations for parasites, stool culture (including *Campylobacter*), stool for *Clostridium difficile* toxins A and B and testing for CMV. The latter may include IgM antibody, tissue histology and PCR, and blood PCR

Voting: A10, B8

Level of evidence: II-2

Grade of recommendation: A

Work up for infection would depend partly on facilities available. However, examination of three consecutive stool specimens is generally recommended. Conventional wet mount and iodine-stained smear are recommended to look for most parasites except the opportunistic pathogens such as coccidia; modified acid-fast staining is needed for the latter [48]. It is important to note that stool microscopy may miss parasites such as *Strongyloides stercoralis* as the sensitivity of single stool examination is only 30 % to 50 % and multiple examinations increases sensitivity marginally [49]. Eosinophilia is a common finding in patients with chronic *Strongyloides stercoralis* infection, but the eosinophil count is unreliable in hyperinfection and in patients receiving immunosuppressant therapy. Stool culture should be done to look for enteropathogens [50].

For *Clostridium difficile* infection, culture may not have clinical significance in the absence of toxin production; assay for *C. difficile* toxins A and B is recommended [51]. Tests for CMV should be done only in the appropriate clinical setting, for example those having active disease in spite of multiple immunosuppressive medications [44]. The tests for CMV include pp65 antigen in the blood, assessment of CMV DNA in colonic biopsy, serum IgM anti-CMV antibody, and histology for inclusion body. Although demonstration of inclusion bodies in the colonic biopsies is the most definitive evidence of active colonic CMV infection; the sensitivity of this test however is quite low [52].

In a recent survey in Asia, in which India was not included, 50 % of respondents agreed that exclusion of enteric infection, including tuberculosis, using stool examination and culture of stool and tissue biopsy was necessary [53].

11. Extent of involvement of colon should be determined for deciding the mode of treatment and prognostication

Voting: A17, B1

Level of evidence: II-2

Grade of recommendation: A

A full-length colonoscopy is the method to evaluate extent of disease [54]. Most studies suggest that patients with proctitis and left-sided colitis have less severe disease than those with pancolitis [55]. Also, limited disease may be managed by topical treatment [56] though the Indian data suggest that topical treatment is less often preferred [22].

The risk of colorectal carcinoma may be lower in patients with limited disease than in those with extensive disease particularly when duration of disease was longer than 10 years, underlining the prognostic value of evaluation of the extent. In a northern Indian retrospective study on 436 patients, 6 of 8 patients developing colorectal carcinoma had

pancolitis [57]. In a southern Indian retrospective study, 5 of 532 UC patients developed colon cancer, pancolitis and disease longer than 10 years being the main risk factors [58].

12. Extent of colonic involvement is best determined by colonoscopy and segmental biopsy

Voting: A17, B1

Level of evidence: II-1

Grade of recommendation: A

Currently, colonoscopy and segmental biopsy is the best method for evaluation of extent of the disease [59]. Generally, disease up to 18 cm is considered as ulcerative proctitis, up to the splenic flexure as left-sided colitis and up to transverse colon or beyond as extensive colitis or pancolitis [60]. In the Indian Task Force data, 18 %, 38 % and 42 % of 724 patients with UC colitis had proctitis, left-sided colitis and pancolitis, respectively [1].

13. Full-length colonoscopy should be withheld in patients with severe active disease

Voting: A15, B3

Level of evidence: II-3

Grade of recommendation: B

Most endoscopists will avoid performing a full-length colonoscopy to evaluate extent of the disease when the patient has severely active colitis as it may increase the risk of perforation. However, data to support this practice is limited. Moreover, evaluation of extent of the disease after it has been successfully treated may result in underestimation of the extent. In fact, in a study in which 80 patients with active UC underwent full-length colonoscopy, none developed perforation [61]. However, the Task Force experts remained committed to the view that it is advisable to perform only limited colonoscopic examination during active disease. It is important that limited colonoscopic examination and biopsy must be performed in all patients with clinical feature suggestive of UC.

14. Disease activity should be assessed using any of the clinical disease assessment scores in order to facilitate management. Both clinical and endoscopic indices of severity should be documented especially in a trial setting

Voting: A15, B3

Level of evidence: I

Grade of recommendation: A

In clinical trials, it is mandatory to use some scoring system, based on the protocol, for uniformity of data reporting from different centers. Several systems of assessment of severity of the disease are available. These include Truelove-Witts scoring system, clinical disease activity index, Powell-Tuck index, Sutherland and Mayo endoscopy scoring system. The Truelove-Witts scoring system and

clinical disease activity index are used in clinical practice by many Indian gastroenterologists. This helps to monitor clinical improvement of patients, to assess need for additional drugs in management, and to assess failure of medical management and need for surgery. The Mayo scoring system is also useful for reporting of colonoscopy findings [62].

## Management

The aims of treatment in UC include induction of remission, maintenance of remission, avoidance of complications, and avoidance of prolonged use of steroids.

15. The choice of treatment for many patients in India depends substantially on the cost and affordability of treatment regimens

Voting: A15, B2, C1

Level of evidence: III

Grade of recommendation: C

UC is a disease with a remitting and relapsing course, and most patients will require lifelong treatment either for control of activity of the disease or for maintenance of remission. Some of the drugs used to treat UC are very expensive. Most patients in India meet the costs of healthcare on their own, as they do not have health-insurance cover. Therefore, compliance and adherence to treatment also depends on their ability to afford it. A recent study from Mumbai found that 81 % of patients with IBD were non-adherent to treatment (defined as taking less than 80 % of the dose advised). Non-adherent patients were three times more likely to develop a relapse as compared to those who adhered to medicines (OR 3.389, 95 % CI 1.29–8.88,  $p=0.012$ ) [63].

16. Topical treatment is more effective than oral therapy for induction and maintenance of remission in patients with ulcerative proctitis and left-sided colitis

Voting: A10, B7, C1

Level of evidence: I

Grade of recommendation: A

The treatment of UC depends upon extent, activity and severity of the disease. The route of delivery of anti-inflammatory drugs (5-aminosalicylates) should be guided by the proximal extent of the disease and the preference of the patient. Topical treatment has distinct advantages over oral treatment, including shorter time to response, less frequent dosing, and less systemic absorption. Topical treatment could be in the form of suppositories, foams or enemas. Suppositories have been shown to reach approximately 10 cm from the anal verge, foam to approximately 15–20 cm, and enemas up to the splenic flexure [64].

Two meta-analyses [65, 66] considered during the consensus vote had shown that topical therapy was better than

oral therapy for inducing remission in distal colitis. However, a Cochrane review published in 2010, that was not considered during the consensus vote, concluded that topical 5-ASA was not superior to oral 5-ASA in inducing remission in UC distal to the splenic flexure [67]. Mesalamine suppositories can be used in doses of either 500 mg twice daily or 1000 mg once daily for induction of remission as well as maintenance of remission of ulcerative proctitis [68, 69]. Mesalamine enemas in a dose of 4 g were more successful than corticosteroid enemas in inducing remission [66]. Mesalamine enemas in doses of 1–4 g may be able to reach as proximal as the splenic flexure and are effective in inducing and maintaining remission in distal colitis [70, 71]. 5-ASA enemas and suppositories are preferred first-line therapies for patients with distal UC and ulcerative proctitis, respectively. Foam is often better tolerated by patients who have difficulty retaining enemas.

Topical corticosteroids can be used as second-line therapy for patients intolerant to, or failed, topical mesalamine. Patients who prefer, or are intolerant to, topical therapy can be treated with oral mesalamines. Patients who have failed to improve on a combination of oral mesalamine with either topical mesalamine or topical corticosteroids may be treated with oral prednisolone. Stool bulking agents or laxatives can be used with care to relieve constipation associated with ulcerative proctitis in some patients. Oral and/or topical mesalamine are effective maintenance treatments for distal colitis [72].

17. Mesalamine alone is adequate for most patients with mild disease activity  
 Voting: A12, B4, C1, D1  
 Level of evidence: I  
 Grade of recommendation: A

When the extent of the disease is beyond the descending colon, topical therapy alone is not effective. For clinically mild to moderate, but anatomically extensive, disease the first-line therapy is oral 5-ASA compounds. The response to 5-ASA is dose related and up to 80 % of patients receiving daily doses of 4–6 g sulfasalazine show complete clinical remission or significant clinical improvement within 4 weeks; of them, approximately one-half have mucosal remission [73]. The main limiting factor with high-dose sulfasalazine is the frequency of side effects such as drug intolerance, hepatitis, pancreatitis and hypospermia. The “newer” aminosalicylates – Eudragit-S-coated, pH-dependent mesalamine, ethylcellulose-coated mesalamine, balsalazide, olsalazine, and multi-matrix-release mesalamine are all superior to placebo and equivalent to sulfasalazine in the induction of remission of mild to moderately active disease [74]. As with sulfasalazine, therapeutic benefit requires a threshold dose, with daily doses less than 2 g of mesalamines being ineffective [74].

For induction of remission in mild or moderate pancolitis, the effective dose of sulfasalazine is 4 g and 6 g a day in four divided doses; for mesalamine 2.4 g and 4.8 g/day in three divided doses; for balsalazide 6.75 g/day in three divided doses; and for olsalazine 1.5–3 g/day in two divided doses. These drugs generally exert their effect within 2–4 weeks and are effective in 40 % to 80 % of patients [65]. A newer multi-matrix mesalamine formulation has similar efficacy with once-daily dosing of 2.4–4.8 g [75, 76].

18. Topical and oral mesalamine may be combined in patients with mild disease activity  
 Voting: A14, B4  
 Level of evidence: I  
 Grade of recommendation: B

Some patients with limited disease or extensive disease do not respond to either topical therapy or oral therapy alone, respectively. Combined oral and topical mesalamine is superior to oral mesalamine alone for patients with distal colitis [77]. Oral mesalamines are also effective in the treatment of active distal colitis and may be preferred for convenience and compliance [65, 66].

19. Oral steroids are indicated for patients with moderate disease activity  
 Voting: A13, B5  
 Level of evidence: II-1  
 Grade of recommendation: B

Failure of mild or moderately active disease to respond within 2 weeks to mesalamines, or development of intolerance, is an indication to consider oral prednisolone. Population-based studies suggest that almost one-third of patients with active UC require corticosteroids for induction of remission [78]. There are no randomized trials to study the efficacy of corticosteroids in active UC. The recommendation to use oral steroids in the management of active UC is based upon two open-label studies done in the 1960s [79, 80]. A combination of oral prednisolone (starting at dose of 40 mg daily) and steroid enemas induced remission in 77 % of 118 patients with mild to moderate disease within 2 weeks, compared to 48 % of patients treated with 8 g/day sulfasalazine and steroid enemas. Similar findings were reported by Lennard-Jones, who found the combination of oral and rectal steroids to be better than either alone [80]. The Omsted County data suggest that up to 86 % of patients treated with steroid show remission (complete in 58 %, partial in 26 %) at 30 days [81]. Oral prednisone shows a dose–response effect between 20 mg and 60 mg/day, with 60 mg/day modestly more effective than 40 mg/day but with more frequent side effects [82].

There are no randomized studies to guide the tapering of steroids. The general consensus is to start prednisolone or its equivalent at a dose of 40–60 mg/day, and continue at that

dose until significant clinical improvement is achieved. Tapering should be done at 5–10 mg weekly until a daily dose of 20 mg is reached and thereafter tapering should be slower at 2.5 mg per week. Shorter courses (<3 weeks) are associated with early relapse, and doses of prednisolone <15 mg/day are ineffective for active disease [83]. Oral steroids with low systemic bioavailability (budesonide) are available; however presently available budesonide preparations (designed for release in the distal ileum and right colon) are not suitable for use in patients with UC.

20. Intravenous steroids are indicated for patients requiring hospitalization with severe disease activity

Voting: A14, B4

Level of evidence: II-1

Grade of recommendation: A

Patients with moderate to severely active UC who fail to respond to oral prednisone should be hospitalized and given IV corticosteroids in the form of hydrocortisone (300–400 mg daily) or methylprednisolone (48–60 mg daily) by continuous or bolus infusion [84]. Methylprednisolone may be preferred since this has lower mineralocorticoid activities compared with hydrocortisone. Placebo-controlled studies have not been performed because of the high mortality associated with severe attacks of UC. The studies by True-love et al. in the 1960s showing the efficacy of IV hydrocortisone in severe UC have been the basis for use of IV steroids. The response to IV corticosteroids has remained around 67 % (95 % CI 65–69) according to a systematic review including 32 trials of corticosteroids for acute severe colitis involving 1,991 patients from 1974 to 2006 [85].

The patient should be monitored for number and consistency of stool, amount of blood in the stool, vital signs, and abdominal signs (fullness, abdominal tenderness, rebound tenderness, and bowel sounds). Hemogram, ESR, C-reactive protein, serum electrolytes and serum protein should be tested every 2–3 days. If on initial abdominal radiography the diameter of the transverse colon is >5.5 cm, abdominal X-ray should be repeated every day. Anticholinergic, anti-diarrheal agents and opioid drugs are best avoided as they can precipitate colonic dilatation. NSAIDs can worsen disease activity. Other measures during hospitalization include rest to the intestine, monitoring and correction of fluid and electrolyte balance, and investigation and treatment of acute infection. Bacterial, parasitic infection or even CMV infection should be investigated using appropriate tests, since infection can precipitate acute exacerbations of otherwise quiescent colitis. During the treatment of acute severe colitis with IV steroids, there is no additional benefit for mesalamine therapy, which may be withdrawn temporarily. Addition of topical mesalamines or steroids may be considered if the frequency of stool is high.

21. Corticosteroid use on a daily basis beyond 3 months is not desirable. Azathioprine/6-mercaptopurines should be used in patients with steroid-dependent disease

Voting: A17, B1

Level of evidence: II-2 & I

Grade of recommendation: A & A

In some patients with UC the disease becomes active after stopping or tapering corticosteroids used for induction of remission of active disease. These are patients with steroid-dependent UC, which 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. Corticosteroids have no role in maintenance of remission and even low-dose long-term use of steroids should be avoided.

The frequency and severity of steroid toxicity is substantial. Long-term use of corticosteroids is associated with somatic (cushingoid features, skin striae, impaired wound healing), metabolic (hyperglycemia, sodium and fluid retention, hypokalemia, metabolic alkalosis, hyperlipidemia, and metabolic bone disease), and infective complications. Such patients are also predisposed to cataracts and glaucoma [83]. All patients with steroid-dependent disease should be treated with thiopurine analogs such as azathioprine (AZA) and 6-mercaptopurine (6-MP) that effectively maintain remission in patients with UC [86, 87].

In UC, thiopurines are commonly used as steroid-sparing agents and are increasingly considered early in the course of treatment [88, 89]. 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-dependent and frequently relapsing UC. Response can take weeks to months from onset of therapy [88]. The rate of induction of remission is up to 69 % and the response rate is up to 84 %. Maintenance of remission is higher than with placebo, with efficacy extending for at least 2 years. Azathioprine was not statistically superior to placebo in a meta-analysis of 5 studies [90]. However, after selecting the two highest quality studies, including one from India [91], AZA had a pooled relative risk for ‘treatment success’ of 2.05 (95 % CI 1.30–3.23). 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 0.41; 95 % CI 0.24–0.70) [87].

22. Patients on azathioprine need close monitoring. Some patients may be unduly sensitive and develop pancytopenia even with smaller doses. The dose should therefore be tailored to the individual

Voting: A11, B4, C3

Level of evidence: III

Grade of recommendation: B



A dose lower than the typical 2 mg/Kg azathioprine used in Caucasians has been advised in Asian populations because of fears of myelotoxicity [92]. The Indian literature on azathioprine for maintenance of remission in UC suggests that lower doses combined with sulfasalazine are useful [91, 93, 94]. Eighteen of 156 UC patients treated for up to 4 years developed side effects, including pancreatitis, marrow suppression, hepatitis, gastrointestinal intolerance, and alopecia [94]. Allergic reactions (fever, arthralgia and rash) characteristically occur after 2–3 weeks and cease rapidly when the drug is withdrawn.

Profound leukopenia can develop suddenly and unpredictably. It is recommended that all patients on azathioprine should be monitored. Full blood count and liver function tests should be done every 2–4 weeks initially for 2 months and then every 4–8 weeks. Azathioprine should be started at a lower dose and the dose should be built up while complete blood count and liver functions are monitored.

23. If available, biochemical or molecular testing for TPMT can be done prior to initiation of therapy

Voting: A15, B3

Level of evidence: II-3

Grade of recommendation: B

Azathioprine is metabolized to 6-mercaptopurine (6-MP). 6-MP is metabolized to 6-thioisonine 5-monophosphate by the enzyme hypoxanthine phosphoribosyl transferase (HPRT). 6-thioisonine-5-monophosphate is eventually metabolized to 6-thioguanine, the active metabolite causing inhibition of DNA and RNA synthesis. 6-MP is also metabolized to 6-methylmercaptopurine (6-MMP) by the enzyme thiopurine methyltransferase (TPMT) and 6-thiouric acid by the enzyme xanthine oxidase. Both 6-thiouric acid and 6-MMP are inactive metabolites of 6-MP. The three enzymes metabolizing 6-MP—HPRT, TPMT and xanthine oxidase—are in constant competition for substrate, and the concentration of the metabolites of 6-MP is based on the concentrations of these enzymes. Eighty-four percent of 6-MP is quickly metabolized by xanthine oxidase found in high concentrations in enterocytes and hepatocytes, leaving only 16 % to be catabolized by TPMT and HPRT [95].

The gene regulating TPMT activity in human tissues is susceptible to a common polymorphism; 90 % of the Caucasian population have above normal or high enzyme activity and are homozygous for the wild-type allele, 10 % have intermediate activity due to heterozygosity of the TPMT, and 1 in 300 inherit TPMT deficiency as a homozygote without functional TPMT activity.

Where available, TPMT and thiopurine metabolite testing for 6-thioguanine and 6-methylmercaptopurine may assist dose optimization of AZA/6-MP to avoid drug-induced toxicity [95]. Molecular testing for polymorphisms that may affect TPMT activity in Indian patients (albeit not ulcerative

colitis patients) has not proved sufficiently reliable at predicting marrow toxicity to warrant use in routine practice [96–98].

24. There is evidence for the use of cyclosporine or infliximab in the treatment of patients with refractory severe UC and as rescue therapy for fulminant ulcerative colitis

Voting: A15, B2, D1

Level of evidence: I

Grade of recommendation: A

Patients not responding within 5–7 days of intensive therapy are unlikely to respond to continuation of the therapy, and alternative therapy should be considered. Acute severe colitis refractory to standard conventional therapy occurs in two clinical settings. The more severe category is of patients who remain non-responsive to 5–7 days of intensive in-hospital treatment including IV corticosteroids. The other type of steroid-refractory UC includes patients who otherwise have moderate to severe colitis and are non-responsive to outpatient treatment with oral steroids for 3 weeks.

The options for the first group are IV cyclosporine (CsA) [99] or anti-tumor necrosis factor (TNF) therapy, or surgery. The options for the second group include infliximab and surgery. There is no literature to support the use of CsA in patients who have been treated with corticosteroids in outpatient setting. The choice between surgery and alternative medical therapy depends on the local expertise in surgery in the acute condition, affordability, and the patient's choice. There is no head-to-head comparison of the efficacy of CsA and anti-TNF therapy in the management of steroid-refractory UC. Patients who do not respond to CsA should go directly to surgery rather than another rescue therapy including anti-TNF therapy.

Cyclosporine is an immunosuppressive macrolide that inhibits the production of interleukin-2 by activated T lymphocytes through a calcineurin-dependent pathway. A placebo-controlled trial showed that 82 % of patients with steroid-refractory severe UC treated with IV CsA in a dose of 4 mg/Kg/day experienced improvement and were able to avoid colectomy in the acute stage [99]. These results in the acute phase are consistent with evidence from multiple open-label series. Additional randomized controlled trials showed similar efficacy with intravenous CsA in a dose of 2 mg/Kg/day [100]. Sood et al. in an open-label study including 24 patients with steroid-refractory severe UC who were treated with CsA 4 mg/Kg, reported that surgery could be avoided in all but four patients, and on a mean follow up of 38 months (range 12–62), 79 % of patients did not require surgery [101]. After induction of remission with IV CsA, the drug may be administered orally for the next 2–3 months. All these patients should be put on thiopurine analogs for the long-term for maintenance of remission.

Anti-TNF therapy is another option in patients with steroid-refractory severe UC. A Cochrane systematic review of 7 studies showed that in patients with moderate to severe UC refractory to conventional treatment using corticosteroids and/or immunosuppressive agents, infliximab (three intravenous infusions at 0, 2 and 6 weeks) was more effective than placebo in inducing clinical remission (RR 3.22, 95 % CI 2.18 to 4.76), endoscopic remission (RR 1.88, 95 % CI 1.54 to 2.28) and clinical response (RR 1.99, 95 % CI 1.65 to 2.41) at 8 weeks [102].

Two large randomized controlled trials (ACT 1 and ACT 2) enrolling moderate to severely active UC patients unresponsive to standard therapy including oral steroids and treated on outpatient basis showed that clinical response rates on treatment with infliximab at weeks 0, 2, and 6 and then every 8 weeks through week 46 was significantly higher (46 %) than with placebo (20 %;  $p=0.001$ ) at week 54 [103]. Similarly, the 54-week remission rate was significantly higher for the groups treated with infliximab (35 %) as compared to placebo (17 %;  $p=0.001$ ). Further analysis of the ACT 1 and 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.

25. Before starting infliximab or potent immunosuppression, patients should be screened for hepatitis B (HBV) and C (HCV) viruses, HIV, and tuberculosis

Voting: A16, B2

Level of evidence: II-3

Grade of recommendation: A

All patients with IBD who require immunosuppressive medications should ideally be screened for HBV, HCV, HIV and tuberculosis. Societal guidelines in other countries would also include other viral infections that are common in those countries [104, 105]. Reactivation of HBV is an important concern in patients on immunosuppressive therapy for IBD, but the frequency with which it occurs is unknown. There are several case reports of HBV reactivation after use of infliximab in combination with prednisone and/or azathioprine for control of activity of IBD [106–108].

All patients with IBD, either UC or CD, should be immunized for HBV. HBV vaccine is a recombinant DNA vaccine and is administered in three doses at 0, 1 and 2 (or 6) months. The efficacy of this vaccine is close to 95 %. Patients with HBV infection should be considered for prophylactic treatment for prevention of HBV reactivation prior to instituting treatment with any immunosuppressive medication such as steroids, immunomodulators or biological. Patients with IBD with evidence of chronic hepatitis B (elevated ALT/AST and HBV DNA levels) should receive treatment for HBV as per standard guidelines. A meta-analysis including 21 studies on use of lamivudine for prophylaxis of HBV reactivation in immunosuppressed

patients showed a mortality benefit (OR 0.36; 95 % CI 0.23–0.56) [108].

Lamivudine, the only medication used in randomized trials for HBV reactivation prophylaxis, is associated with a high rate of drug resistance caused by a single genetic mutation in the tyrosine-methionine-aspartate-aspartate motif (YMDD) of the HBV DNA polymerase. YMDD mutation rates have been reported to be 14 % to 32 % by 1 year and 60 % to 70 % by 5 years of treatment with lamivudine [108]. Lamivudine may be appropriate for short-duration prophylaxis during chemotherapy; immunosuppressive medications for IBD may be required indefinitely.

Alternative antiviral medications for HBV, such as tenofovir, adefovir, telbivudine and entecavir, have not been evaluated in the prophylaxis of HBV reactivation in patients receiving immunosuppressive treatment. Because of lower rates of resistance and excellent safety profiles, tenofovir or entecavir are preferable antiviral agents for prophylaxis of HBV reactivation in IBD patients. If lamivudine, adefovir or telbivudine are to be used, serum aminotransferase levels and HBV DNA levels need to be monitored regularly for appearance of drug resistance. Tenofovir and entecavir are also the preferred agents for treatment of chronic HBV infection.

Tuberculosis is endemic in India and it can be reactivated on use of immunosuppressive therapy. Furthermore, intestinal tuberculosis is a differential diagnosis in newly diagnosed IBD, mostly CD. All patients planned for prolonged use of immune-suppression or biologics should be evaluated for tuberculosis by Mantoux test and chest X-ray. Interferon-gamma release assays are more specific to the presence of latent tuberculosis than the Mantoux test, which can react to previous BCG administration. The reliability of these screening methods has not been established in India. Immunosuppression can result in reactivation of latent TB and therefore exclusion of tuberculosis, treatment of tuberculosis, or institution of TB chemoprophylaxis is required prior to immunosuppressive therapy. Screening strategies should also include high vigilance in the development of breakthrough infection. In view of the cost, and concern over infective complications, of biologic agents in India, surgery may be favored over prolonged use of biological in the treatment of severe steroid-refractory UC.

Opportunistic infections occur more frequently in patients on immunosuppressive treatments [109, 110]. Multi-modal treatment increases this risk more than monotherapy and the recommendation is to simplify treatment to monotherapy whenever possible. Vaccination against opportunistic infections, such as HBV, varicella-zoster, human papilloma virus, pneumococcus, and influenza virus, should be considered [111].

26. Surgery is indicated in the management of patients with fulminant ulcerative colitis refractory to medical therapy, and its complications

Voting: A16, B2

Level of evidence: II-2

Grade of recommendation: A

Surgery is an important treatment option for patients with UC especially those suffering from severe acute/fulminant colitis who are refractory to medical therapy and those who have complications of UC such as toxic megacolon, perforation, massive bleeding or large-bowel obstruction [112–114]. A surgeon should be involved in the management of patients with acute severe UC right at the beginning of the hospital admission. The decision to operate is best taken jointly by the medical and surgical team in consultation with the patient, and should not be unduly delayed even if rescue medical therapy with CsA or infliximab is chosen [115–117]. This ensures better surgical outcomes in the acute setting.

In particular, following a failed medical ‘rescue’ therapy (with infliximab or CsA) after the initial failure of intensive steroid therapy, colectomy should be promptly undertaken as there is evidence that surgery following another attempt at medical salvage in this setting leads to disastrous results [118]. Prompt emergency colectomy is indicated in toxic megacolon, perforation and massive bleeding as otherwise the mortality can be prohibitive. Toxic megacolon developing during the course of intensive medical therapy should be considered as failure of medical therapy. In the emergency setting, subtotal colectomy with Hartmann’s rectal pouch and end-ileostomy is generally considered the surgical procedure of choice [119].

27. Steroid-dependent disease, cancer or high-grade dysplasia are other indications for surgery

Voting: A15, B3

Level of evidence: II-2

Grade of recommendation: A

Surgery continues to have a role in the elective management of patients with chronic UC with steroid-dependent disease and in patients with dysplasia or colorectal cancer. Epidemiologic studies from the West have shown that the cumulative life-time risk of surgery in patients with UC is 25 % to 30 % especially in those with pancolitis [113, 119].

28. Inability to afford medical treatment is a relative indication for surgery

Voting: A15, B3

Level of evidence: III

Grade of recommendation: C

Compliance with maintenance medical treatment may be an issue in some Indian patients [63]. Two- or three-staged

surgery is usually recommended for patients on long-term steroids/immunosuppressants or following prior colectomy. Surgical options include restorative proctocolectomy with ileal pouch-anal anastomosis or total proctocolectomy with permanent end-ileostomy. Though elective surgery has a low mortality in experienced hands, it is not bereft of complications such as intestinal obstruction, pelvic sepsis, pouchitis and pouch failure. Indian patients requiring elective surgery for ulcerative colitis have good long-term functional outcome and improved quality of life following restorative proctocolectomy with ileal pouch-anal anastomosis [120, 121]. Surgery should be viewed as an alternative therapeutic modality, and not only for failure of medical therapy, to achieve optimal outcome over the lifetime of the individuals suffering from UC.

29. Surgery should be offered to patients with dysplasia-associated lesion or mass (DALM)

Voting: A16, B2

Level of evidence: II-3

Grade of recommendation: B

UC is associated with increased risk of malignancy that develops through a dysplasia-carcinoma sequence. Dysplasia, defined as unequivocal neoplastic epithelium, is currently the most important and best-defined marker of increased risk of malignancy [122, 123]. Dysplasia is present in 70 % of UC patients with carcinoma. From an endoscopic viewpoint, dysplasia is characterized as flat (endoscopically invisible but detected in mucosal biopsy specimens), or raised (“dysplasia-associated lesion or mass” - DALM). Microscopically, dysplasia is classified as low- (LGD) or high-grade (HGD).

Findings of carcinoma, DALM, or HGD in flat mucosa, as well as repeated, confirmed findings of multifocal LGD are generally considered as indications for proctocolectomy, although there are significant variations in practice [124]. Proctocolectomy, if done for precancerous dysplasia or early cancer, differs from non-colorectal cancer (CRC) indications of proctectomy in UC in that the oncological principles of total mesorectal excision have to be followed.

Although Western guidelines recommend colonoscopic surveillance after 8–10 years of extensive pancolitis and 12–15 years of left-sided colitis [125], surveillance approaches in the Indian context may need to be modified based on the fact that there is a lower incidence of CRC in Indian patients. Data from a cross-sectional study of UC patients from Vellore showed the CRC risk was 0 % at 10 years, 2.3 % at 20 years and 5.8 % for disease duration greater than 20 years [58].

30. Osteoporosis is a matter of concern in patients with ulcerative colitis. Those at high risk should receive

calcium and vitamin D

Voting: A16, B2

Level of evidence: II-3

Grade of recommendation: B

Data regarding osteoporosis, osteopenia and osteomalacia in UC are available mostly for Western populations. In these studies, the consensus was that UC had only a modest effect on bone mineral density (BMD) [126]. Osteomalacia and vitamin D deficiency in Western patients with UC are unlikely to be secondary to the disease per se. The overall incidence of fractures in UC patients was not greater than in age- and gender-matched healthy controls in two large Western studies [127, 128].

Osteoporosis was more common in subjects over age 60 years. Males and females were equally susceptible. Osteoporosis, defined as a T score <2.5 using dual-energy X-ray absorptiometry (DEXA) occurs in approximately 15 %, but is strongly influenced by age, being higher in older subjects. DEXA can predict fracture risk, but should be used in conjunction with other clinical variables. Corticosteroid use is the variable most strongly associated with osteoporosis but cannot be easily distinguished from disease activity (and resultant cytokine output) in terms of their relative impact on bone density [128]. Biochemical bone markers do not correlate well with BMD and should not be routinely used to assess fracture risk. The ileo-anal pouch procedure after curative colectomy in UC was associated with improvement in BMD [129]. Risk factors for osteopenia included advancing age, low body mass index, and non-use of daily calcium supplements [126, 130, 131].

In an Indian study, 22 UC patients were compared with 46 healthy controls and were found to have significantly lower BMD at both spine and hip [132]. Ninety percent of patients had daily calcium intakes <200 mg. BMD did not correlate with age, duration of disease or cumulative steroid dose. The recommendation to increase calcium intake is based on the very low intake recorded in these patients. Other recommendations suggested by the Task Force members included the need to identify those at greatest risk, i.e. steroid-dependent, elderly, and post-menopausal patients, and advice on optimal nutrition, weight-bearing exercise, cessation of smoking, moderation of alcohol consumption, and minimization of the use of corticosteroids.

31. There is no evidence to support recommending curtailment of milk or milk products in the majority of patients with ulcerative colitis

Voting: A17, B1

Level of evidence: III

Grade of recommendation: C

Many patients with UC restrict milk intake either on their own or following their physician's advice [133, 134]. There

is no evidence to suggest that milk intolerance is more common in UC than in the general population [133, 134]. Milk is a source of high-quality protein and of calcium and restriction of intake affects the patient's nutrition [133, 134]. The treating physician must bear in mind, however, that adult hypolactasia is common in India and lactose intolerance may aggravate diarrhea in hypolactasic UC patients. Such patients may potentially be advised an increased intake of curd, which has anti-inflammatory effects in animal models of UC [135].

32. Specific probiotics are useful in the management of pouchitis occurring in patients after ileal-anal pouch anastomosis surgery

Voting: A13, B4, C1

Level of evidence: I

Grade of recommendation: A

Nearly 10 % of Indian patients undergoing restorative proctocolectomy with ileal pouch-anal anastomosis develop pouchitis in the intermediate term [120, 121]. Treatment of this condition includes antibiotics as well as probiotics. A meta-analysis evaluated 5 trials in which probiotics were used to maintain remission of pouchitis [136]. All trials showed highly significant beneficial effect of the probiotics in preventing relapses of pouchitis. The two preparations used in these trials were *Lactobacillus rhamnosus* GG and VSL#3, a combination of lactobacilli and bifidobacteria. There are no Indian data available on this aspect of UC management. Probiotic effects are strain-specific and it is therefore important to take into consideration both the strain and numbers of bacteria actually delivered in order to produce a therapeutic effect.

33. Current evidence for probiotic efficacy in other situations remains insufficient to provide definitive recommendations

Voting: A16, B2

Level of evidence: II-2

Grade of recommendation: C

Probiotics have been tested for efficacy in maintenance of remission as well as in induction of remission in patients with UC. *E. coli* Nissle 1917 was as effective as sulfasalazine in maintaining remission [137]. Studies that examined induction of remission in UC were combined in a Cochrane review in 2007 that concluded that probiotics when added to standard therapy modestly increased the remission rate in patients with mild to moderately severe UC [138]. This and other reviews [139, 140] concluded that there were significant differences in trial design, the composition of the probiotic preparation (different strains, variable numbers), and specific patient populations that did not allow firm conclusions about the place of probiotics in the therapy of UC.

Whether probiotics are effective in patients with severe UC and whether they can replace existing therapies remains in question. The only Indian evidence comes from a study

by Sood et al. in which 77 patients with mild-to-moderate UC received VSL#3 ( $3.6 \times 10^{12}$  bacteria) twice daily for 12 weeks compared to 70 who received placebo [141]. At the end of 12 weeks, 33 patients in the probiotic group were in remission as compared to 11 patients in the control group.

34. Patients with ulcerative colitis can safely conceive, and should be counseled to conceive only when disease is in remission

Voting: A17, B1

Level of evidence: III

Grade of recommendation: C

Women with UC do conceive safely. A meta-analysis of the influence of UC on pregnancy examined 12 studies with 1,446 UC patients and 320,531 controls [142]. The incidence of low birth weight, small-for-gestational age, stillbirths and Cesarean section was not increased in patients with UC. However, there was a marginally increased risk of premature delivery (OR 1.34, 95 % CI 1.09–1.64). The incidence of congenital abnormalities was mildly increased (OR 3.88, 95 % CI 1.41–10.67) in babies born to mothers with UC. Knowledge of these risks will be useful in counseling prospective mothers with UC.

35. Mesalamine, prednisolone and azathioprine are safe in pregnancy, while methotrexate is contraindicated in pregnancy

Voting: A11, B6, C1

Level of evidence: II-2

Grade of recommendation: B

Patients with UC who are pregnant should continue to take mesalamine for maintaining remission. If azathioprine had been instituted well prior to pregnancy, it should be continued. Corticosteroids are useful in inducing remission in women who experience flare-up of illness during pregnancy. A meta-analysis of 19 studies including 1,626 women did not reveal any increase in still births, ectopic pregnancies, spontaneous abortions or low-for-birth weight babies [142]. However, there was an increase in congenital anomalies in women taking 5-ASA preparations, and those on azathioprine or monoclonal antibody to tumor necrosis factor-alpha.

The use of azathioprine induces congenital malformations in pregnant mice and it is listed as a Category D drug in pregnancy [143]. In pregnant women with IBD (both UC and CD) its use is associated with an increased risk (OR 3.4) of congenital malformations [143]. On the other hand, when used in pregnant women with autoimmune hepatitis, it did not increase the risk for congenital malformations. There are no serious consequences associated with its use during breast-feeding.

Prednisolone use in the first trimester has been associated with nonsyndromic orofacial clefts with an increased risk

(OR 4–5) for cleft lip and/or palate [144]. Prednisolone is not significantly excreted in breast milk. The Task Force members were divided on this issue, with a view expressed that steroids have effects on both mother and baby and the safety of these drugs in pregnancy has not been established beyond doubt. An informed discussion with the parents should precede any decision on use of these drugs for the first time during pregnancy, especially in the first trimester of pregnancy.

36. Treatment of ulcerative colitis is indefinite and most patients should receive maintenance treatment

Voting: A15, B2, C1

Level of evidence: II-2

Grade of recommendation: B

The natural history of UC suggests that 10 % of patients may have only a single attack of colitis and remain well thereafter. The cumulative probability of having reactivation of disease in UC patients in remission exceeds 90 % if patients are followed up for 20 years [145]. Mucosal healing in Crohn's disease has been associated with long duration of remission. Mucosal healing has not been defined for UC [146]. Most gastroenterologists however follow the practice of treating UC indefinitely [147]. Molecular studies and early evidence indicated that mesalamine use in the long term could prevent colorectal cancer in patients with UC [148, 149]. Recent evidence from clinical studies in UC patients suggests that mesalamine does not have a chemopreventive effect for colorectal cancer in patients with UC [150, 151].

37. Mesalamines, with or without azathioprine, should be used for the maintenance of remission

Voting: A18

Level of evidence: II-2

Grade of recommendation: A

UC patients who have not experienced a relapse for several years appear to be at decreased risk than those who have had a relapse during the previous 12 months [152]. It has therefore been opined that patients who experience flares of disease only every few years probably do not require maintenance medication, unless the flares are severe and difficult to control [153]. In a Cochrane review of studies evaluating mesalamine use, the OR for relapse for mesalamine vs. placebo was 0.47 (95 % CI, 0.36 to 0.62). When sulfasalazine and 5-aminosalicylates were compared, odds ratios of 1.29 (95 % CI, 1.05 to 1.57) suggest a higher degree of therapeutic effectiveness for sulfasalazine [153]. Sulfasalazine and 5-ASA had similar adverse event profiles, with OR of 1.16 (0.62 to 2.16), and 1.31 (0.86 to 1.99), respectively [154].

Another Cochrane review based on four trials concluded that azathioprine was superior to placebo for the maintenance

of remission in patients with UC [87]. The OR for relapse of UC while on azathioprine therapy was 0.41 (95 % CI 0.24 to 0.70) compared to placebo [87]. It is considered to be effective maintenance therapy for patients who have failed or cannot tolerate mesalazine or sulfasalazine, as well as for patients who require repeated courses of steroids.

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## Authors' participation

Members who participated in the all three phases of voting including face to face meeting held in Mumbai from October 8–9, 2010

Balakrishnan S Ramakrishna, Govind K Makharia, Philip Abraham, Uday C Ghoshal, Venkataraman Jayanthi, Shobna J Bhatia, Sunil Dadhich, Devendra C Desai, Bhaba Dev Goswami, Sanjeev K Issar, Ajay Jain, Goundappa Loganathan, Sri Prakash Misra, C Ganesh Pai, Sujoy Pal, Anna Pulimood, Amarender S Puri, Gautam Ray, Shivaram P Singh

Members who participated only in voting 1 and voting 2

Brij Kishore Agarwal, Vineet Ahuja, Deepak K Bhasin, Gourdas Choudhuri, Gopal Krishna Dhali, Rakesh Kochhar, Ajay Kumar, GN Ramesh, Ajit Sood, Manu Tandan