See "Consensus recommendations for patient-centered therapy in mild-to-moderate ulcerative colitis: the i Support Therapy–Access to Rapid Treatment (iSTART) approach" on page 522-528.

CONSENSUS STATEMENTS

1. Epidemiology

Statement 1: The global incidence and prevalence of UC is rising (grade B)
(strongly agreed 90.0%; agreed 10.0%; disagreed 0.0%: CONSENSUS REACHED)

The incidence and prevalence of UC has been documented in a number of systematic reviews,[1-3] with numerous primary epidemiological studies providing supporting evidence. There has been a rapid increase in the incidence and prevalence of UC since the mid-20th century across many countries.[1,2] The EpiCom study reported incidence rates in Europe of 4 to 19 per 100,000 in 2010,[4] with similar rates found in Canada,[1,5,6] and Australia;[1,7] whereas Asia and Latin America have lower rates of around 1 to 5 per 100,000.[1,7,8] The prevalence of UC in Europe, Canada and Australia has been estimated at 100 to 290 per 100,000.[1,5,6,9,10] Prevalence is lower across Asia and Latin America at 10 to 60 per 100,000.[1,11,12]

Statement 2: Mild-to-moderate disease is most prevalent at diagnosis (grade B)
(strongly agreed 100%; statement revised and CONSENSUS REACHED via discussion)

Despite differences classification scales, the proportion classified with mild-to-moderate UC was 70% to 95% at diagnosis and therefore is the predominant form of the disease.[13-18]

Statement 3: An intermittent-relapsing course is most common (grade B)
(strongly agreed 60.0%; agreed 40.0%; disagreed 0.0%: CONSENSUS REACHED)

Four disease courses have been described in UC: single relapse followed by sustained remission; intermittent relapses separated by remission periods; chronic active; and fulminant. The most common form of UC is an intermittent-relapsing course, affecting 40% to 60% of patients.[19-22]

Statement 4: Episodes of disease activity (in contrast to remission periods) are associated with a significantly decreased patient quality of life, a significant impact on daily life, and increased healthcare costs and burden (grade C)
(strongly agreed 100%; statement revised and CONSENSUS REACHED via discussion)

A key consequence of active disease is an increased number and frequency of symptoms.[23] Symptoms that are more common in active UC compared to remission include fatigue,[24,25] pain,[26] extraintestinal manifestations (EIMs),[27] and fecal incontinence.[28] Active disease has also been associated with depression,[29-31] anxiety,[30,31] and sleep disruption.[32,33] Symptoms disrupt daily life for 94% of patients during a flare,[34] leading to a reduced quality of life during active disease.[35-38] Quality of life has been found to correlate the frequency of symptoms,[39] and the number of relapses experienced.[40,41] Studies from many countries have shown that EQ-5D is significantly reduced during active compared to inactive disease.[42-44] Relapses in UC are associated with higher rates of physician, emergency and outpatient visits,[45-47] which leads to increased healthcare costs.[43,45,48] Furthermore, active UC also leads to increased absences from work,[49] and a higher likelihood of claiming a disability pension.[49,50]

Statement 5: At any time, ~25% of patients have active disease with symptoms that may require additional therapeutic intervention (grade B)
(strongly agreed 100%; statement revised and CONSENSUS REACHED via discussion)

The largest available, recent dataset (EpiCom study) shows that 70% to 74% of patient were in remission at any time, with the remainder showing symptomatic disease.[51] These figures are supported by a Canadian systematic review that found 75% to 90% of patients were in remission at any time.[52]

Statement 6: Patients within 1 year of diagnosis have the highest rate of relapse, with ~50% having symptomatically active disease that may require additional therapeutic intervention (grade B)
(strongly agreed 100%; statement revised and CONSENSUS REACHED via discussion)

Longitudinal epidemiological studies have shown a gradual decrease in the rate of relapse over time after diagnosis.[53,54] Similar data are seen for 5-ASA treated patients,[55-58] and a longitudinal investigation of 5-ASA treatment clearly demonstrated the highest risk of relapse during the first 2 to 3 years after diagnosis.[56,57] Around 50% of newly diagnosed patients have active disease at any time.[51,59-61] The EpiCom study found that 89% of patients had active disease at diagnosis, which dropped to 59% after 3 months and 28% after 1 year.[51]

Statement 7: Rate of spontaneous remission is low; <10% when using a strict definition of clinical and endoscopic remission (grade B)
(strongly agreed 30.0%; agreed 70.0%; disagreed 0.0%: CONSENSUS REACHED)

The placebo arms in clinical trials give the best available estimate as to the effects of delayed treatment on disease activity. The rate of remission varies depending on the definition used, but overall these trials have shown a low rate of spontaneous remission in UC of around 17%.[62] However, the rate of remission in placebo-treated patients is lower (<10%) when a stricter definition of remission is used that incorporates clinical and endoscopic definitions.[63,64]

Statement 8: During the average year, ~70% of patients with UC will experience at least 1 relapse (grade C)
(strongly agreed 100%; statement revised and CONSENSUS REACHED via discussion)

Around 30% of patients experience no relapses in a year and therefore around 70% experience at least 1 relapse.[43,45,65,66]

Statement 9: The rate of relapse is reduced by ~25% in the year following no flare compared to a year following a flare (grade C)
(strongly agreed 100%; statement revised and CONSENSUS REACHED via discussion)

Only a small number of studies have attempted to quantify the difference in risk between patients who have had a flare and those who have not in the previous year. In a study from Norway, 30% of patients relapsed after a period of remission compared to 63% after a period of active disease, a 52% reduction ($P<0.001$).[60] An Iranian study reported a 20% reduction in relapse rate for all patients compared to those with a previous relapse.[65] A Korean cohort study showed a 46.3% reduction in the relapse rate for patients who showed mucosal healing compared to those who did not (36.3% vs. 19.5%, $P=0.006$).[67] These limited data were combined with the panel's expert opinion to estimate risk reduction at 25%.

Statement 10: Clinicians are not fully aware of the number of relapses patients experience (grade C)
(strongly agreed 70.0%; agreed 30.0%; disagreed 0.0%: CONSENSUS REACHED)

A survey of patients and clinicians found that physicians and nurses had a lower estimate of the number of relapses for each patient compared to the numbers self-reported; patients reported a mean of 5.5 flares over a year, versus estimates of 3.4 by doctors

and 3.8 by nurses.[68] Patients reported discussing only an average of 4.2 flares with their primary healthcare professional (HCP), which implies the majority of this perception gap occurs due to non-disclosure of flares by patients to HCPs.[68]

2. First-Line Treatment and Treatment Failure

Statement 11: Optimized 5-ASA is the accepted first-line treatment for mild-to-moderate UC across all treatment guidelines (grade A)
(strongly agreed 90.0%; agreed 10.0%; disagreed 0.0%: CONSENSUS REACHED)

The treatment guidelines reviewed were those of the European Crohn's and Colitis Organisation (ECCO),[69,70] the Canadian Association of Gastroenterology (CAG),[71] the World Gastroenterology Organisation,[72] the American Gastroenterology Association,[73] the American College of Gastroenterology,[74] and the Pan American Crohn's and Colitis Organization.[75]

Statement 12: Optimized 5-ASA treatment is sufficient to achieve remission in ~50% to 70% of patients (grade B)
(strongly agreed 100%; statement revised and CONSENSUS REACHED via discussion)

Optimized 5-ASA therapy is a high dose oral regimen combined with a topical 5-ASA regimen designed to induce remission quickly and effectively. A recent Cochrane Review reported that high dose regimens of 5-ASA are able to induce remission in between 50% and 70% of UC patients.[62]

Statement 13: 5-ASA treatment failure can be defined as the inability to achieve steroid-free remission with an optimized regimen of high dose oral and/or rectal 5-ASA (grade B)
(strongly agreed 81.8%; agreed 0.0%; disagreed 18.2%: CONSENSUS REACHED)

Statement 14: Optimized 5-ASA treatment (high dose oral and/or rectal) can be considered insufficient and additional treatment is required when 5-ASA is unable to maintain steroid-free remission (grade B)
(strongly agreed 45.5%; agreed 45.5%; disagreed 9.0%: CONSENSUS REACHED)

Treatment failure is often not explicitly defined. Guidelines define UC treatment goals to be the induction and maintenance of remission;[70,72,74] this infers that treatment failure is an inability to meet these goals. The CAG guidelines define 5-ASA treatment failure to be the "inability of the patient to achieve and maintain complete corticosteroid-free remission despite optimal treatment with oral, rectal, or combination 5-ASA therapy."[71] The opinion of the panel was that the ability to achieve and maintain remission are distinct occurrences and so they are presented as separate statements.

Statement 15: An increased bowel frequency above normal (for that individual) and the presence of rectal bleeding on consecutive days should be considered to be suggestive of a flare (grade B)
(strongly agreed 54.6% agreed 36.4%; disagreed 9.0%: CONSENSUS REACHED)

Where defined, guidelines define remission as a normal stool frequency (≤3/day) with no blood in stool and potential confirmation of mucosal healing.[69,71] The guidelines define relapse/flare as the opposite of being in remission.[69,71] The consensus was that remission is defined as a normal bowel frequency (≤3/day), absence of rectal bleeding and normal mucosal appearance on endoscopy, with relapse/flare defined as the opposite. There is little guidance available on the timescale over which symptoms need to be present for a flare to be determined. It was the opinion of the expert panel that these changes need to be present on consecutive days in order for a UC flare to be the most likely cause.

The differentiation between a UC flare and *Clostridium difficile* infection can be challenging as symptoms can be identical.[76,77] UC patients are at an increased risk for *C. difficile* infection,[76-78] both inside and outside the hospital setting.[78] However, the rate of *C. difficile* in patients with UC flares is still quite low; around 5% of UC patients with a flare test positive for *C. difficile*.[79,80] *C. difficile*

infection risk is greatest in patients with recent hospitalization, recent antibiotic use or immunosuppression.[76,78] The use of iSTART (i Support Therapy–Access to Rapid Treatment) should be at the treating physician's discretion, and only in patients at a low risk of *C. difficile* infection.

Statement 16: Factors that predict 5-ASA treatment failure include: disease extent greater than proctitis (grade C), lack of normalization of fecal calprotectin (grade B), lack of mucosal healing (grade B) and EIMs (grade C)
(strongly agreed 55.6%; agreed 33.3%: disagreed 11.1%: CONSENSUS REACHED)

The evidence regarding disease extent as a risk factor for treatment failure is mixed. However, a majority of studies showed a higher risk of relapse with a greater disease extent; particularly when considering proctitis versus a greater extent.[55,58,81] Fecal calprotectin (FC) levels have been identified as a potential predictor of relapse, and a meta-analysis found that FC had an overall sensitivity of 77% and a specificity of 71% as a predictive factor for relapse.[82] A variety of cutoff values have been used to define increased risk, varying from 50 mg/L to 200 μg/g.[83,84] The expert panel was of the opinion that a lack of normalization of FC levels is the best measure to use as a risk factor for 5-ASA treatment failure. There is strong evidence that absence of mucosal healing is linked to 5-ASA treatment failure and an increased risk/rate of relapse.[17,85-87] The presence of EIMs has been found to be associated with a higher rate of 5-ASA failure.[55,81,88] The ECCO guidelines describe the presence of EIMs as a possible risk factor for relapse in patients with quiescent disease.[70]

Statement 17: Low educational attainment (grade D), formerly smoking (grade D), unmarried status (grade D), stress (grade D) and a low-fiber diet (grade D) may predict increased rate of 5-ASA treatment failure
(strongly agreed 27.4%; agreed 63.6%; disagreed 9.0%: CONSENSUS REACHED)

A range of other potential risk factors for 5-ASA treatment failure have been identified, but all have a lack of supporting evidence. Possible risk factors include a lack education above high school level,[89] former smokers,[90] and being unmarried.[91,92] ECCO guidelines describe multiple possible risk factors for relapse in patients with quiescent disease including stress and low-fiber diet.[70] Nonadherence is a well-established risk factor for 5-ASA failure,[70] but is hard to predict and has links to many of the other risk factors described here.

3. Second-Line Treatment and Self-Led Patient Assessment

Statement 18: Corticosteroids are the recommended first-line treatment for patients with mild-to-moderate UC who show a lack of response to optimized 5-ASA therapy (grade A-C, depending on disease extent)
(strongly agreed 54.5%; agreed 45.5%; disagreed 0.0%: CONSENSUS REACHED)

Guidelines for patients with mild-to-moderate UC that do not respond sufficiently to optimized 5-ASA therapy are generally consistent, recommending corticosteroids as oral or rectal therapies (dependent on disease extent).[70,71,74,75]

Statement 19: Oral budesonide MMX® is an effective treatment option for patients failing to respond to optimized 5-ASA therapy and an alternative for patients intolerant to 5-ASA (grade A)
(strongly agreed 70.0%; agreed 30.0%; disagreed 0.0%: CONSENSUS REACHED)

A Cochrane analysis of budesonide MMX® has shown that it can induce remission in 15% of patients versus 9% for placebo (RR, 2.25; 95% CI, 1.50–3.39),[93] with no difference in adverse events (RR, 0.85; 95% CI, 0.53–1.38).[93] Remission rates were low compared to other UC therapies due to the CORE I and CORE II studies using a strict definition of "combined clinical and endoscopic remission," defined as a normal bowel frequency with no rectal bleeding and endoscopic remission based on a full colonoscopy.[94]

Statement 20: Validated patient-reported outcome measures are required for patient self-assessment of flares (grade C); the PRUCSI, PRO2 and mHI-UC are such measures that have strong discriminatory power for flares (grade C)
(strongly agreed 80.0%; agreed 20.0%; disagreed 0.0%: CONSENSUS REACHED)

Statement 21: Patient-initiated treatment allows for a rapid response to flares that can reduce flare length and healthcare utilization (grade C)
(strongly agreed 63.6%; agreed 36.4%; disagreed 0.0%: CONSENSUS REACHED)

The evidence supporting these statements is included with the main manuscript.

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