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ORIGINAL ARTICLE

# Optimizing treatment of mild to moderate ulcerative colitis: CU-forum Delphi consensus

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**KEYWORDS**
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**Abstract**
*Background and objective:* Ulcerative colitis (UC) clinical guidelines include the best available evidence, although not all clinical situations are answered, so their management can be controversial. The aim of this study is to identify the situations of mild to moderate UC susceptible to controversy and to evaluate the degree of agreement or disagreement with specific proposals.
*Methods:* Inflammatory bowel disease (IBD) expert discussion meetings were used to identify criteria, attitudes and opinions regarding the management of UC. A Delphi questionnaire was then developed with 60 items regarding antibiotics, salicylates and probiotics; local, systemic and topical corticosteroids; and immunosuppressants.
*Results:* Consensus was reached in 44 statements (73.3%); 32 in agreement (53.3%) and 12 in disagreement (20.0%). Some of them were: it is not necessary the systematic use of antibiotics despite the severity of the outbreak, being reserved when there is suspicion of infection or systemic toxicity; when faced with a mild-moderate outbreak of UC and in patients who do not respond to aminosalicylates, it is appropriate to use a dose of beclomethasone of 10 mg/day for one month and 5 mg/day for another month; it is advised that the dose of azathioprine be administered in a single dose.
*Conclusions:* IBD experts agree on most of the proposals identified for managing mild to moderate UC and there is a need for scientific evidence in some specific situations where expert opinion may be helpful.


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**PALABRAS CLAVE**
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Delphi;
Inmunosupresores

**Optimización del tratamiento de la colitis ulcerosa leve a moderada: consenso Delphi CU-Forum**

**Resumen**
*Antecedentes y objetivo:* Las guías clínicas de colitis ulcerosa (CU) recogen la mejor evidencia disponible, aunque no todas las situaciones clínicas quedan respondidas, por lo que su manejo puede ser motivo de controversia. El objetivo de este estudio es identificar las situaciones de la CU leve a moderada susceptibles de controversia y evaluar el grado de acuerdo o desacuerdo a propuestas concretas.
*Métodos:* Mediante reuniones de debate de expertos en enfermedad inflamatoria intestinal (EII) se identificaron criterios, actitudes y opiniones respecto al manejo de la CU. A continuación se elaboró un cuestionario Delphi con 60 aseveraciones relativas a antibióticos, salicilatos y probióticos; corticoides locales, sistémicos y tópicos; e inmunosupresores.
*Resultados:* Se alcanzó consenso en 44 aseveraciones (73,3%); 32 en el acuerdo (53,3%) y 12 en el desacuerdo (20,0%). Algunos de ellos fueron: no es necesario el uso sistemático de antibióticos a pesar de la gravedad del brote, quedando reservados ante la sospecha de infección o toxicidad sistémica; ante un brote leve-moderado de CU y en pacientes que no responden a aminosalicilatos, es adecuado utilizar una dosis de beclometasona de 10 mg/día durante un mes y 5 mg/día durante otro mes; se aconseja que la dosis de azatioprina se administre en una única dosis.
*Conclusiones:* Los expertos en EII coinciden en la mayoría de las propuestas identificadas para manejar la CU leve a moderada y se constata la necesidad de evidencia científica en algunas situaciones concretas en las que conocer la opinión de expertos puede resultar de ayuda.


## Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) whose multifactorial aetiology is only partially understood. As there is no single criterion for the definition of UC, the diagnosis is made by a combination of clinical, endoscopic and histological criteria, ruling out infectious diseases which show similar signs.[1] The extent and severity of UC can vary from one individual to another and even over time, making different treatment strategies necessary, according to disease activity and previous history. A variety of active substances are used for treatment, including aminosalicylates, corticosteroids, immunosuppressants and biological drugs.[2–4]

There are a number of different clinical guidelines providing recommendations for the treatment of UC,[5–12] all well defined and supported by scientific evidence. However, there are situations in which, for different reasons, the recommendations are not implemented in clinical practice, or where common clinical practices are not among the recommendations, due to a lack of scientific evidence as they have not been evaluated. In some cases, results from new clinical studies after guidelines are published can make the guidelines obsolete. In others, clinical practice itself shows that there are alternatives which have not been considered or that are not suitable for certain patients.

The aim of this study was to identify situations in which IBD experts treat patients with UC in a manner not reflected in the guideline recommendations, or such options are simply not included in the guidelines. We also assessed the degree of agreement among specialists on the management of patients with mild to moderate UC in such clinical situations. To this end, we carried out two activities: discussion meetings with IBD experts; and a consensus using Delphi methodology. The aim of the discussion meetings was to determine from the experts what their usual practice was in the treatment of UC, as well as their concerns and reflections on the subject. On the basis of the conclusions from these meetings, a Delphi questionnaire was drawn up, consisting of statements on the most controversial, complex or evidence-lacking issues, in order to ascertain the experts' degree of agreement with these statements.

## Methods

### Study design

The study was designed using a modified Delphi method, a structured communication technique which enables a group of experts to explore and unify opinions on a complex or controversial topic for which there is insufficient evidence or where understanding is incomplete or uncertain.[13,14]

The study was conducted in several phases: (1) creation of a scientific committee of experts; (2) preparation of a survey on standard clinical practice in the treatment of UC; (3) review of the most recent literature on therapeutic recommendations for UC; (4) presentation of the evidence found at six virtual meetings to compare actual clinical practice with clinical guideline recommendations and discuss; (5) preparation of a Delphi questionnaire with statements regarding the controversies considered most relevant; (6) two-round

Delphi consensus to obtain the opinion of a panel of experts; and (7) compilation, analysis and discussion of the results of the Delphi consensus in order to draw up conclusions.

### Participants

The study involved IBD specialists, either as members of the scientific committee or as members of the expert panel, as well as a technical team. The scientific committee consisted of a coordinator and six experts in the treatment of UC from the speciality of gastroenterology whose role was to prepare a survey to obtain information about usual clinical practice in the treatment of UC, review the most recent literature on UC treatment, lead the various discussion meetings and draw up the Delphi questionnaire. The technical team, which directed and supervised the entire process, was responsible for the instrumental implementation of the method (literature search, distribution of the survey and the Delphi questionnaire, analysis of the responses and statistical interpretation of the consensus). The panel of experts was made up of healthcare professionals from the gastroenterology specialties with recognised clinical experience in UC. This panel consisted of 50 experts and we made every effort to ensure their geographic distribution represented all the Autonomous Regions in Spain.

### Local pre-consensus meetings

In order to understand current clinical practice in the treatment of UC, beyond the recommendations of clinical guidelines, the scientific committee prepared a survey, which was then sent to the expert panel. In order to discuss the results obtained in the survey, six meetings were held at local level and in a virtual format in which the recommendations based on the published scientific evidence were presented. These were compared with the clinical practice of the panellists. Each meeting was attended by a member of the scientific committee and about eight to ten experts.

### Delphi questionnaire

Based on the findings of the local meetings, a Delphi questionnaire of 60 statements was drawn up to capture the most relevant issues, which were grouped into the following subject areas: antibiotics, salicylates and probiotics (38 statements); local, systemic and topical corticosteroids (14 statements); and immunosuppressants (8 statements).

For the assessment of the questionnaire, a single 9-point Likert scale was proposed, according to the model developed by the UCLA-RAND Corporation for comparative assessment and prioritisation between different health options (minimum 1 - strongly disagree - and maximum 9 - strongly agree).[14] This scale was structured in three groups according to the level of agreement/disagreement with the statement: from 1 to 3, interpreted as disagreement or rejection; from 4 to 6, interpreted as no agreement or no disagreement; and from 7 to 9, interpreted as agreement or support.

### Phases of the Delphi consensus

Following the Delphi method procedure,[15] the questionnaire with the statements was sent to the panel of experts for them to respond by showing their degree of agreement with each statement. In the first round, the panellists responded to the questionnaire *online* and were given the option of adding their opinion in free text. Statements for which there was no consensus were sent back to the panellists to be assessed in a second round. The project was closed with a meeting of the scientific committee to discuss and analyse the results.

### Analysis and interpretation of the results

To analyse group opinion and the type of consensus reached on each statement, we used the median and interquartile range of the scores obtained for each statement. Consensus was considered to exist on any of these statements when 2/3 or more respondents ($\geq$66.7%) scored within the 3-point range (1–3 or 7–9) contained in the median. The type of consensus reached on each statement was determined by the value of the median score. There was consensus on agreement if the median was $\geq$7 and consensus on disagreement if the median was $\leq$3.

Consensus was considered to be lacking when the scores of one third or more of the panellists ($\geq$33.3%) were in the 1–3 range and another third or more in the 7–9 range. When the median score was in the 4–6 range, the statements were considered uncertain to a representative majority of the group.

## Results

### Delphi consensus

Of the 50 experts consulted, 45 completed the two rounds of the Delphi consensus without proposing new statements. In the first round, consensus was reached on 24 of the 60 statements; 20 in agreement and four in disagreement. In the second round, 36 statements were returned for reconsideration and consensus was reached on 20 of them; 12 in agreement and eight in disagreement. After two rounds, consensus was reached on 44 statements (73.3%); 32 in agreement (53.3%) and 12 in disagreement (20.0%). For the remaining 16 statements (26.7%) there was neither agreement nor disagreement. Fig. 1 shows the results of the two rounds and Tables 1 to 3 show the overall results for all the statements analysed.

### Block 1: antibiotics, salicylates and probiotics

Of the 38 proposed statements on the use of antibiotics, salicylates and probiotics, consensus was reached on 29 after two rounds; 21 in agreement and eight in disagreement. No consensus was reached on the remaining nine statements (Table 1). Among the consensus statements, the one with the highest degree of agreement was that patients with ulcerative proctitis require a high dose of mesalazine (>3 g) for induction, particularly in oral-only treatment (statement 13;

**Table 1** Results obtained by the expert panel after two rounds of consultation for the block of antibiotics, salicylates and probiotics.

| | Median (IQR) | Agreement (%) | Disagreement (%) | Type of consensus |
|---|---|---|---|---|
| *Block 1: antibiotics, salicylates and probiotics* | | | | |
| 1. In the case of a severe flare-up of ulcerative colitis with suspected infectious colitis, the use of antibiotics is recommended | 8 (1) | 82.22 | 2.22 | Consensus in agreement |
| 2. Antibiotics are recommended for severe flare-ups of steroid-refractory ulcerative colitis | 2 (1) | 6.66 | 80.00 | Consensus in disagreement |
| 3. In the case of a severe flare-up of steroid-refractory ulcerative colitis with fever (>38°C), the use of antibiotics is recommended, due to the possibility of bacteraemia resulting from bacterial translocation | 7 (2) | 68.52 | 12.96 | Consensus in agreement |
| 4. In the case of a severe flare-up of ulcerative colitis, the use of antibiotics is recommended only if infection is suspected | 8 (2) | 81.49 | 12.96 | Consensus in agreement |
| 5. In the treatment of a severe flare-up of ulcerative colitis with hospitalisation, antibiotics are recommended as part of the initial treatment along with intravenous corticosteroids | 3 (4) | 20.36 | 70.37 | Consensus in disagreement |
| 6. In the treatment of a severe flare-up of ulcerative colitis with hospitalisation, the use of antibiotics is recommended as part of the initial treatment together with intravenous corticosteroids, if prescribed by the emergency department, if the history is unknown | 2 (2) | 8.88 | 82.23 | Consensus in disagreement |
| 7. In the treatment of a severe flare-up of ulcerative colitis with hospitalisation, the use of antibiotics is recommended as part of the initial treatment along with intravenous corticosteroids, in the case of a very sudden onset | 2 (4) | 15.56 | 66.66 | No consensus |
| 8. In the treatment of a severe flare-up of ulcerative colitis with hospitalisation, the use of antibiotics is recommended as part of the initial treatment along with intravenous corticosteroids, in the case of systemic toxicity complications | 8 (2) | 75.93 | 14.82 | Consensus in agreement |
| 9. In the treatment of a moderate to severe flare-up of ulcerative colitis, the use of antibiotics is recommended as an alternative in very selected cases of steroid-refractory colitis | 3 (1) | 8.88 | 80.00 | Consensus in disagreement |
| 10. In the treatment of ulcerative colitis, the use of antibiotics is recommended for segmental colitis associated with diverticular disease | 7 (4) | 68.51 | 14.81 | Consensus in agreement |
| 11. Rifaximin plays an important role in the treatment of IBS symptoms in ulcerative colitis in remission | 5 (3) | 37.77 | 17.78 | No consensus |
| 12. Metronidazole plays an important role in the treatment of IBS symptoms in ulcerative colitis in remission | 2 (2) | 3.70 | 75.93 | Consensus in disagreement |
| 13. In patients with ulcerative proctitis, high-dose mesalazine (>3 g) is required for induction, particularly in exclusive oral therapy | 8 (2) | 93.34 | 4.44 | Consensus in agreement |

Table 1 (*Continued*)

| | Median (IQR) | Agreement (%) | Disagreement (%) | Type of consensus |
|---|---|---|---|---|
| 14. In patients with ulcerative proctitis, high-dose mesalazine (>3 g) is required for maintenance, particularly in exclusive oral therapy | 7 (3) | 51.11 | 20.00 | No consensus |
| 15. In patients with ulcerative proctitis, isolated oral treatment is only recommended in the case of intolerance to topical treatments or allergy to mesalazine | 8 (2) | 71.11 | 17.77 | Consensus in agreement |
| 16. In patients with ulcerative proctitis, topical treatment alone or in combination with oral treatment is recommended, with use of oral treatment alone only in cases which do not respond to topical treatment | 8 (1) | 82.22 | 2.22 | Consensus in agreement |
| 17. In patients with moderate ulcerative colitis high doses of mesalazine are needed, as increasing the dose may increase its efficacy and speed of action | 8 (2) | 90.74 | 1.85 | Consensus in agreement |
| 18. When high doses are required in patients with moderate ulcerative colitis, the dose of mesalazine should be >4 g per day | 8 (1) | 88.88 | 1.85 | Consensus in agreement |
| 19. When high doses are required in patients with moderate ulcerative colitis, the dose of mesalazine should be >3 g per day | 7 (1) | 77.78 | 11.11 | Consensus in agreement |
| 20. In patients with moderate ulcerative colitis, high doses of mesalazine are required for induction only | 3 (0) | 6.67 | 75.56 | Consensus in disagreement |
| 21. In patients with moderate ulcerative colitis, high doses of mesalazine are required for maintenance only | 3 (3) | 1.85 | 74.08 | Consensus in disagreement |
| 22. In patients with moderate ulcerative colitis, high doses of mesalazine are required for both induction and maintenance | 7 (1) | 86.67 | 4.44 | Consensus in agreement |
| 23. In the treatment of ulcerative colitis, calprotectin measurement should be used to optimise induction | 8 (2) | 75.55 | 17.78 | Consensus in agreement |
| 24. In the treatment of ulcerative colitis, calprotectin measurement should be used to calculate the maintenance dose | 7 (3) | 68.52 | 11.1 | Consensus in agreement |
| 25. In the treatment of ulcerative colitis, mainly when the patient is asymptomatic, calprotectin measurement is useful in monitoring to establish appropriate doses of mesalazine | 8 (2) | 85.18 | 1.85 | Consensus in agreement |
| 26. To optimise the treatment of ulcerative colitis, the dose of mesalazine which has achieved remission of symptoms should be maintained indefinitely | 6 (4) | 33.33 | 42.22 | No consensus |
| 27. To optimise treatment of ulcerative colitis, maintenance mesalazine should be used, even at low doses, while monitoring calprotectin | 8 (2) | 85.19 | 1.85 | Consensus in agreement |
| 28. In the treatment of ulcerative colitis, if calprotectin is elevated, it is necessary to increase the dose of mesalazine to $\geq$4 g, even if the patient is asymptomatic | 7 (1) | 75.92 | 9.26 | Consensus in agreement |

Table 1 (*Continued*)

| | Median (IQR) | Agreement (%) | Disagreement (%) | Type of consensus |
|---|---|---|---|---|
| 29. In the treatment of ulcerative colitis, in the case of persistently elevated calprotectin despite increasing the dose of mesalazine to ≥4 g, it is necessary to perform a colonoscopy | 8 (1) | 81.49 | 3.7 | Consensus in agreement |
| 30. For a mild-to-moderate flare-up of ulcerative colitis, it is recommended to start combined therapy (oral and rectal) always using doses >3 g orally | 7 (1) | 75.93 | 5.56 | Consensus in agreement |
| 31. In a mild-to-moderate flare-up of ulcerative colitis, it is recommended to start combined therapy (oral and rectal) if rectal symptoms are very severe | 8 (2) | 83.33 | 5.55 | Consensus in agreement |
| 32. When treatment of ulcerative colitis is escalated to immunosuppressive or biological drugs, it is necessary to continue mesalazine therapy | 6 (4) | 48.89 | 24.44 | No consensus |
| 33. The mesalazine should be continued as part of the ulcerative colitis treatment when escalating to immunosuppressive or biological drugs because the patient has been taking it for a long time and it has few side effects | 3 (2) | 13.34 | 64.45 | No consensus |
| 34. When treatment of ulcerative colitis is escalated to biological agents, discontinuation of mesalazine treatment is recommended | 5 (5) | 44.44 | 33.33 | No consensus |
| 35. When treatment of ulcerative colitis is escalated to immunosuppressants, discontinuation of mesalazine treatment is recommended | 4 (4) | 22.22 | 44.44 | No consensus |
| 36. When treatment of ulcerative colitis is escalated to immunosuppressants or biological agents, it is necessary to continue with mesalazine for the duration of the induction with the biologic or until the immunosuppressant becomes effective | 8 (2) | 75.55 | 4.44 | Consensus in agreement |
| 37. In patients with a mild-to-moderate flare-up of ulcerative colitis, additional probiotics are recommended | 2 (3) | 5.55 | 74.08 | Consensus in disagreement |
| 38. In mesalazine-allergic patients with a mild-to-moderate flare-up of ulcerative colitis, the use of additional probiotics is recommended | 2 (5) | 24.45 | 64.45 | No consensus |

IQR: interquartile range.

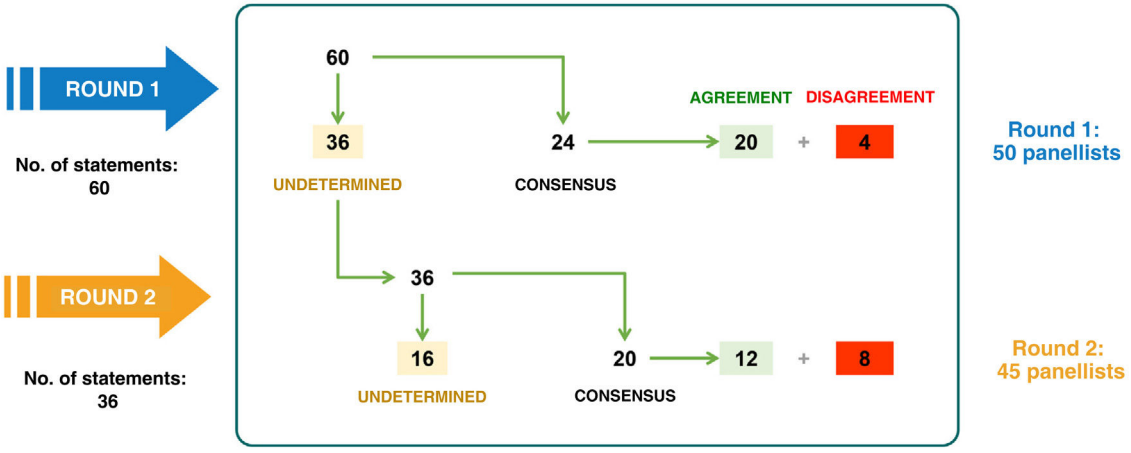


**Figure 1** Main results of the Delphi consensus.

93.3% agreement). In contrast, the statement with the highest degree of disagreement said that in severe UC flare-ups with hospitalisation, the use of antibiotics is recommended as part of the initial treatment along with intravenous corticosteroids if prescribed by the emergency department, if the history is unknown (statement 6; 82.23% disagreement).

Among the statements with no consensus, we should highlight one on the borderline of consensus in disagreement. This statement said that in the treatment of a severe UC flare-up with hospitalisation, in the case of a very sudden onset, the use of antibiotics as part of the initial treatment along with intravenous corticosteroids is recommended (statement 7; 15.16% in agreement and 66.66% in disagreement).

### Block 2: local, systemic and topical corticosteroids

Of the 14 proposed statements on the use of local, systemic and topical corticosteroids, consensus was reached on nine after two rounds; six in agreement and three in disagreement. No consensus was reached on the remaining five statements (Table 2). The statement with the highest degree of agreement said that the dose of systemic corticosteroids should be adjusted by weight in patients with moderate UC, with a maximum of 60 mg/kg (statement 46; 100% agreement). The statement with the highest degree of disagreement was that in a patient who does not respond to aminosalicylates in the induction treatment for a mild-to-moderate UC flare-up, beclomethasone 5 mg is needed for one month, reducing to 5 mg every other day for one to two weeks, then discontinuing (statement 41; 88.88% disagreement).

### Block 3: immunosuppressants

Of the eight statements on the use of immunosuppressants, there was consensus on six; five in agreement and one in disagreement. No consensus was reached on the remaining two (Table 3). The statement with the highest degree of agreement said that a single dose regimen is recommended for patients with UC on azathioprine treatment in order to promote adherence to therapy (statement 57; 98.14% agreement). The statement with the highest degree of disagreement was that patients on azathioprine treatment should be prescribed several divided doses (statement 58; 75.56% disagreement).

## Discussion

Despite numerous clinical guidelines on the treatment of UC, there are questions which remain unresolved by the published studies on the practical use of antibiotics and some aspects concerning aminosalicylates, and on the use of corticosteroids and immunosuppressants. Although the experts consulted showed a high degree of agreement with the proposed statements (53.3%), they disagreed with a not insignificant number of them (20.0%). For 26.7% of the statements, there was no clear position at all, and no consensus could be reached. This shows that in certain specific cases of UC management, there is a broad gap between expert opinion and judgement on the same issues.

### Block 1: antibiotics, salicylates and probiotics

Regarding the use of antibiotics in severe UC, it was concluded that routine use was not necessary despite the severity of the flare-up, the need for hospital admission or the suddenness with which the flare-up occurred, being reserved for cases with strong suspicion of associated infection or systemic toxicity. This consensus is in line with the clinical guidelines on the use of antibiotics.[5,8] Another scenario in which agreement was reached on the use of antibiotics in UC was in segmental colitis associated with diverticular disease (rifaximin), but not in UC-associated irritable bowel syndrome; in this case, in contrast with the clinical guidelines, which include these situations.[5,16,17]

On salicylates in UC, no agreement was reached on the use of high doses in ulcerative proctitis for maintenance, particularly in purely oral treatment, but they did agree for some patients with moderate UC (3—4 g). The available evidence on salicylate dosing includes studies conducted at different doses in different settings.[5,8,18] Another consensus issue was the use of faecal calprotectin measurement to optimise salicylate dosage in UC. Available data indicate

**Table 2** Results obtained by the expert panel after two rounds of consultation for the block of local, systemic and topical corticosteroids.

| | Median (IQR) | Agreement (%) | Disagreement (%) | Type of consensus |
|---|---|---|---|---|
| *Block 2: local, systemic and topical corticosteroids* | | | | |
| 39. In a patient who does not respond to aminosalicylates in induction treatment for a mild-to-moderate flare-up of ulcerative colitis, beclomethasone 5 mg, one tablet with breakfast, is required for one month then discontinue | 3 (4) | 17.77 | 68.89 | Consensus in disagreement |
| 40. In a patient who does not respond to aminosalicylates in induction treatment for a mild-to-moderate flare-up of ulcerative colitis, beclomethasone 10 mg is required for one month (in combined or divided doses), 5 mg for another month (at breakfast) then discontinue | 8 (2) | 83.33 | 1.85 | Consensus in agreement |
| 41. In a patient who does not respond to aminosalicylates in induction treatment for a mild-to-moderate flare-up of ulcerative colitis, beclomethasone 5 mg is required for one month (at breakfast), reducing to 5 mg every 2—3 days for 1—2 weeks, then discontinue | 2 (2) | 0 | 88.88 | Consensus in disagreement |
| 42. In treatment to induce remission of a mild-to-moderate flare-up of ulcerative colitis, corticosteroid dependence is considered when early relapse occurs after a course of beclomethasone (<3 months) | 7 (4) | 71.1 | 22.22 | Consensus in agreement |
| 43. In treatment to induce remission of a mild-to-moderate flare-up of ulcerative colitis, corticosteroid dependence is considered when beclomethasone (5 mg) is discontinued and symptoms recur | 7 (4) | 60.00 | 20.00 | No consensus |
| 44. Corticosteroid dependence when using beclamethasone (topical) is defined by the same criteria as corticosteroid dependence with classic (systemic) corticosteroids | 6 (3) | 44.45 | 22.22 | No consensus |
| 45. In the case of corticosteroid dependence with beclomethasone (topical), alternative immunosuppressive drugs or biological agents should be sought | 7 (2) | 75.56 | 8.89 | Consensus in agreement |
| 46. In patients with moderate ulcerative colitis, it is recommended that the dose of systemic corticosteroids be adjusted by weight (for example, 0.75—1 mg/kg) with a maximum of 60 mg/day | 9 (1) | 100 | 0 | Consensus in agreement |
| 47. In the case of moderate steroid-refractory ulcerative colitis, it is necessary to admit the patient to assess the response to intravenous corticosteroids for 48—72 hours and if there is no response, an alternative drug should be used | 9 (2) | 77.78 | 11.1 | Consensus in agreement |
| 48. In the case of moderate steroid-refractory ulcerative colitis, it is necessary to admit the patient to assess the response to intravenous corticosteroids for 3–5–7 days using the steroid-refractory indices for a severe flare-up | 7 (3) | 72.22 | 12.96 | Consensus in agreement |
| 49. For a mild-to-moderate flare-up of left-sided ulcerative colitis, it is recommended to alternate every 24 h topical salicylates (in the evening) with topical corticosteroids (the following evening) | 3 (4) | 22.22 | 55.55 | No consensus |
| 50. For a mild-to-moderate flare-up of left-sided ulcerative colitis, it is recommended to prescribe topical salicylates and topical corticosteroids on the same day (morning and evening for example) | 6 (5) | 48.89 | 31.11 | No consensus |
| 51. For a mild-to-moderate flare-up of left-sided ulcerative colitis it is recommended to prescribe topical salicylates for 3—4 days followed by topical corticosteroids for 2—3 days | 2 (2) | 2.22 | 77.77 | Consensus in disagreement |
| 52. With a mild-to-moderate flare-up of left-sided ulcerative colitis, it is recommended to intensify treatment with salicylates morning and night, and to consider the use of tacrolimus if there is no response | 3 (3) | 17.78 | 60.00 | No consensus |

IQR: interquartile range.

**Table 3** Results obtained by the expert panel after two rounds of consultations for the immunosuppressant block.

| | Median (IQR) | Agreement (%) | Disagreement (%) | Type of consensus |
|---|---|---|---|---|
| *Block 3: immunosuppressants* | | | | |
| 53. In patients with ulcerative colitis, thiopurine methyltransferase levels (if available) should be requested when starting treatment with azathioprine | 8 (4) | 68.89 | 6.66 | Consensus in agreement |
| 54. In patients with ulcerative colitis, when starting treatment with azathioprine, a single daily dose is recommended in order to encourage adherence to therapy | 8 (2) | 77.78 | 7.4 | Consensus in agreement |
| 55. In patients with ulcerative colitis, when starting treatment with azathioprine, it is recommended that it be administered in several divided doses | 5 (5) | 22.22 | 44.45 | No consensus |
| 56. In patients with ulcerative colitis, when starting treatment with azathioprine, if the patient has gastrointestinal symptoms with a single daily dose, the regimen should be changed to several divided doses | 8 (2) | 96.29 | 1.85 | Consensus in agreement |
| 57. In patients with ulcerative colitis on azathioprine treatment, a single dose regimen is recommended in order to encourage adherence to therapy | 8 (1) | 98.14 | 1.85 | Consensus in agreement |
| 58. In patients with ulcerative colitis on azathioprine treatment, a regimen of several divided doses is recommended | 2 (2) | 2.22 | 75.56 | Consensus in disagreement |
| 59. In patients with ulcerative colitis on azathioprine treatment, if the patient has gastrointestinal symptoms with a single daily dose, the regimen should be changed to several divided doses | 8 (2) | 94.44 | 1.85 | Consensus in agreement |
| 60. In patients with ulcerative colitis with good gastrointestinal tolerance, the use of oral rather than IV ciclosporin is recommended from the start | 5 (4) | 26.67 | 31.12 | No consensus |

IQR: interquartile range.

that statistical significance in terms of dose-response effect and endoscopic remission versus placebo is only achieved at doses higher than 3 g.[3,5,8,19] One debated scenario on which no agreement was reached due to a lack of evidence was continuing salicylate treatment in patients requiring immunosuppressants and biological agents, although the general opinion was in favour of continuing, at least during induction with immunosuppressants and/or biological agents. In this respect, it has been shown that discontinuation of salicylates in UC patients who are about to start anti-TNF therapy does not increase the risk of adverse events.[20]

Lastly, the evidence on the use of probiotics is very limited in UC, and this was reflected in the lack of agreement on their use in patients with UC allergic to salicylates.[21]

## Block 2: local, systemic and topical corticosteroids

Although the dose used in the five clinical trials validating the use of beclomethasone in the induction of mild-to-moderate UC flare-up without response to aminosalicylates was 5 mg/day for one month,[22] in clinical practice the most commonly used dose is 10 mg/day for one month followed by 5 mg/day for one month. This last regimen was the one identified with the greatest consensus by the specialists in this study, and is probably based on the case study by Papi et al. which, although not a clinical trial, reported higher remission rates with this strategy.[23]

Corticosteroid dependence was another highly debated point in the scenario of using these topically acting oral corticosteroids, but the panellists did not reach a consensus on a definition for this. This contrasts with corticosteroid dependence for systemic steroids, where the definition is clearly established.[5] In fact, in this specific scenario, there was consensus on the need to consider immunosuppressive or biological drugs.

The indication for hospital admission and the use of intravenous corticosteroids in a steroid-refractory situation, before changing treatment strategy, is another scenario not specified in the clinical guidelines. However, according to the expert panel, there is agreement in clinical practice that they should be used for at least 48—72 hours.

Lastly, the use of topical corticosteroids in patients with left-sided UC is an individual matter for each expert, with no conclusion arrived at as to how they should be prescribed; the evidence in this scenario comes from a very old clinical trial which used a magistral formula combining mesalazine and corticosteroid in the same preparation,[24] and although this cannot be done today as such, it has led to the above variability in use.

### Block 3: immunosuppressants

This analysis shows that there are uncertainties in the practical use of immunosuppressants which have not been resolved by the various published studies. Most specialists use this group of drugs in the treatment of IBD patients according to their expertise and what they have learned from experience.

There is agreement, in line with the guidelines, that thiopurine methyltransferase levels should be requested when considering starting treatment with azathioprine.[6] However, not all specialists use the full dose from the beginning, or instruct the patient to take the full daily dose as one single dose. Adverse events are feared by specialists, although in the case of gastrointestinal adverse events, there is consensus on trying azathioprine spread out in several divided doses in an attempt to continue treatment.

Methotrexate is not approved for the treatment of UC, although some specialists use it orally. Ciclosporin is indicated for the management of severe UC flare-ups, with multiple studies demonstrating its efficacy intravenously.[5,25] In our study, the question was whether, in the case of good gastrointestinal tolerance, oral rather than intravenous use could be considered. The results confirm that there is no consensus on this issue, although some centres routinely use oral ciclosporin, apparently with good results. Several studies have shown that the oral formulation is equally as or more effective than the intravenous formulation.[26–29]

### Study limitations

The limitations of this study are similar to those of others with a comparable design. The answers of the panellists are in every way subjective and should be taken with caution if they are to be extrapolated to clinical practice overall. To minimise any possible influence on the consensus, the sponsor was not involved in the conduct of the study. The main strength of the study is having the opinion of 50 experts who were able to refine their answers after the second round of the consensus, and the fact that this helps other healthcare professionals appreciate the situation faced by their colleagues in other areas and facilitates their work with patients.

## Conclusions

Of the proposals identified by the experts for the management of specific clinical situations in UC (due to their particular characteristics, complexity, peculiarities in terms of available evidence or anticipated controversy, whether or not included in the clinical guidelines), consensus was reached on most. This shows that, despite the difficulty, complexity or lack of evidence involved in some of the decisions, in most cases the experts agree. The lack of consensus on some of the proposals reflects the need for, and importance of, quality and comprehensive scientific evidence. As specialists are confronted with all the clinical situations analysed in this study, expert opinion and consensus can be helpful in optimising the management of mild to moderate UC.

## Ethical considerations

Our work did not involve the participation of patients and did not therefore require the approval of an independent ethics committee.

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## Conflicts of interest

Miquel Sans Cuffi has no conflicts of interest.

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