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Clinical guidelines for the management of inflammatory bowel disease: update of a French national consensus

Aurélien Amiot¹, Guillaume Bouguen², Guillaume BONNAUD³, Yoram BOUHNİK⁴, Hervé HAGEGE⁵, Laurent PEYRIN-BIROULET⁶ on behalf of **the French National Consensus Clinical guidelines for the management of IBD study group**.*

1- Department of Gastroenterology, Henri Mondor University Hospital, APHP, EC2M3-EA7375, Paris Est-Creteil University, Creteil, France;

2- CHU and University of Rennes, INSERM, CIC1414, Institut NUMECAN (Nutrition Metabolism and Cancer), F-35000 Rennes, France;

3- Ambroise Paré Clinic, Toulouse, France ;

4- CHU Paris Nord-Val de Seine, Beaujon Hospital, Department of Gastroenterology, IBD and nutritive support, Clichy;

5- Intercommunal Hospital of Créteil, Department of Gastroenterology, Créteil, France;

6- Department of Gastroenterology, Nancy University Hospital, Vandoeuvre-lès-Nancy, France; Inserm U1256 NGERE, Lorraine University, Vandoeuvre-lès-Nancy, France

*Aurelien Amiot and Guillaume Bouguen equally contributed to this work.

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Please address correspondence and reprint requests to:

Professeur Aurelien AMIOT

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* The Members of the “French National Consensus Clinical guidelines for the management of IBD study group” are listed **APPENDIX A.**

Henri Mondor University Hospital – Universite Paris Est Creteil

51, Avenue du Marechal de Lattre de Tassigny CRETEIL F-94010 – FRANCE

-Tel: +33-1 49 81 23 62

Fax: +33-1 49 81 23 52

E-mail: aurelien.amiot@aphp.fr

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Keywords: Crohn's disease; ulcerative colitis; inflammatory bowel disease; algorithm; consensus; clinical guidelines.

Abbreviations: Crohn's Disease: CD; Ulcerative Colitis: UC; inflammatory Bowel Disease: IBD; TDM: therapeutic drug monitoring; ADA: antibodies to anti-TNF.

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Abstract

Background: New treatments and therapeutic approaches repeatedly emerged in the field of inflammatory bowel disease.

Aim: to update the French treatment algorithms for Crohn's disease (CD) and ulcerative colitis (UC).

Methods: A formal consensus method was used to determine changes to the treatment algorithms for various situations of CD and UC. Thirty-seven experts voted on questions that had been drafted by the steering committee ahead of time. Consensus was defined as at least 66% of experts agreeing on a response.

Results: Anti-TNF were reinforced as a first-line therapy rather than the use of immunosuppressant alone. Vedolizumab for UC, ustekinumab for CD took place as second-line maintenance therapy and potentially as a first-line therapy in the setting of unrestricted reimbursement for vedolizumab. Tofacitinib was recommended by the experts in case of vedolizumab failure for UC. Algorithms for complicated CD with abscess, intestinal and complex anal fistula were updated according to recent prospective cohort studies.

Conclusion: The changes incorporated to the algorithms provide up-to-date and easy-to-use guidelines to treat patients with IBD.

Introduction

1
2 The advent of immunosuppressant and biologic treatments significantly improved outcomes of
3
4 inflammatory bowel disease (IBD) patients[1,2]. The burden of disease, however, remains high;
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6 and common complications remain difficult to manage[3,4]. Patients with perianal Crohn's
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8 disease, for instance, suffer from persistent pain, impaired quality of life, and a high rate of
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10 recurrence of perianal sepsis[5].
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14 New treatments and treatment strategies are continually emerging, being approved, and being
15
16 integrated into clinical practice. Vedolizumab was the first non-anti-TNF agent to be approved
17
18 in Europe for refractory Crohn's disease (CD) and ulcerative colitis (UC) in 2014, promptly
19
20 followed by ustekinumab for CD in 2016[6–9]. Tofacitinib was approved in 2019 for the
21
22 treatment of moderate to severe active UC in patients who have failed treatment with
23
24 conventional treatment and anti-tumor necrosis factor alpha (anti-TNF α), but not for patients
25
26 with CD[10]. This rapidly evolving environment creates a need to update guidelines regularly
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28 and to provide practicing physicians with recommendations about how and when to integrate
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30 new therapies into treatment strategies.
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36 The last French consensus treatment recommendations were published in 2016 for UC and in
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38 2017 for CD[11,12]. After several years of experience with new molecules, such as
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40 ustekinumab or tofacitinib, experts are now in a position to discuss their use and how to
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42 integrate them into clinical practice guidelines.
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Methods

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2 Current French treatment guidelines for CD and UC were updated using a consensus based
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4 approach and following methods that were similar to those described in STRIDE and were in
5
6 compliance with the recommendations of the French Health Authority[11–14]. Thirty-one
7
8 gastroenterologists practicing in France who were members of gastroenterology associations,
9
10 namely ANGH (Association Nationale des hepato-Gastroenterologues des Hopitaux generaux),
11
12 CREGG (Club de REflexion des cabinets et Groupes d'hepatoGastroenterologie) and GETAID
13
14 (Groupe d'Etude Therapeutique des Affections Inflammatoires Digestives), were invited to
15
16 participate in a one-day meeting by a steering committee of 6 gastroenterologists. All the
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18 algorithms were previously designed assuming that patients experienced a first flare of IBD and
19
20 are naïve of any treatment.
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26 The consensus meeting took place on December 3, 2019 in Paris, France. In the first plenary
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28 session, a first vote on 16 general treatment questions took place. Though all 16 questions were
29
30 phrased as CD questions, questions 1-4 and 10-13 applied to both CD and UC. Participants
31
32 were then divided into two groups for the breakout sessions to discuss specific changes to the
33
34 CD algorithms. For each question, a first vote took place. Questions for which consensus was
35
36 not reached were discussed, reworded when needed, and voted on a second time. In the second
37
38 plenary session, all experts voted on the finalized versions of the questions from the breakout
39
40 sessions. Questions, for which consensus had been reached in the breakout session, were put to
41
42 a confirmation vote. Questions for which consensus had not been reached in the breakout
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44 sessions were voted on, discussed and reworded if needed, and voted on again. Based on
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46 discussions, new questions could be added to the plenary session. A third plenary session took
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48 place to discuss and vote on questions pertaining to the algorithms for UC. The same voting
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50 method was used.
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Consensus was defined as at least 66% agreement of the experts for each statement. The group voted on 72 CD questions and 27 UC questions. Consensus results were used to update algorithms.

Definitions used for the purposes of algorithm are those agreed on by the European Crohn's and Colitis Organisation and listed as supplementary materials (APPENDIX 2)[15,16].

Results

Results of the breakout sessions and the plenary sessions for CD and UC are presented in Table S1.

General considerations

For both CD and UC, experts considered that the immunosuppressant of choice in the absence of contraindications (question number [Q]1; 90%) should be a thiopurine (either azathioprine or mercaptopurine). In patients over the age of 65 (Q3; 81%), experts considered that methotrexate would be most appropriate, whereas for patients with a history of cancer or of a hematologic disease in the previous 5 years, no consensus was reached (Q4; 65% for methotrexate; 34% no opinion). Experts did not reach consensus on how to treat patients who are seronegative for the Epstein-Barr virus (Q2).

Considering therapeutic drug monitoring (TDM), an adequate infliximab and adalimumab trough level threshold of 10 µg/mL (12 µg/mL in case of fistulizing perianal lesions) was recommended to identify patients that may not benefit of anti-TNF optimization (Q10-Q13).

In case of contraindication to anti-TNF for the first line biological therapy or loss of response to the first anti-TNF agent despite adequate trough level, vedolizumab and ustekinumab were recommended for patients with UC and CD, respectively. A combination therapy with a different anti-TNF α was recommended in case of low trough level with drug antibodies (Q15; 73%).

At the beginning of the meeting, the experts unanimously agreed with ECCO statements on the use of biosimilars including biosimilarity, extrapolation as well as interchangeability and switching[39].

Management of patients failing to first-line anti-TNF therapy

In patients failing first-line anti-TNF therapy, the experts reviewed the rescue strategy that will be applied to all clinical situations with the exception of the mildly active Crohn's disease in

1 which the use of anti-TNF is off-label in the French healthcare system. Experts agreed that if
2 anti-TNF α therapy fails, TDM which involves measurement of anti-TNF α trough level and
3
4 antibodies to anti-TNF α (ADA) should guide treatment decisions (Q5; 87% and Q73; 88%).
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7 In case of adequate anti-TNF trough level, experts recommended using ustekinumab
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9 monotherapy or combination therapy (Q14; 61% and 13%, respectively) in patients with CD
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11 and vedolizumab monotherapy (Q82; 67%) in patients with UC. In case of low anti-TNF trough
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13 level and absence of ADA, experts recommended optimizing the existing anti-TNF therapy in
14
15 patients with CD (Q16; 75%) and UC (Q84; 68%). In case of low anti-TNF trough level and
16
17 presence of ADA, experts recommended combination therapy with a second anti-TNF α in
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19 patients with CD (Q15; 73%) and UC (Q83; 74%).
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24 If TDM is not available for decision-making, experts recommended a switch to ustekinumab in
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26 patients with CD, in case of primary failure or side effects of anti-TNF α treatment (Q6; 73%)
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28 (Q8; 79%) (Q9; 88%). No consensus was reached for patients who had a secondary loss of
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30 response to anti-TNF α therapy (Q7). Regarding UC, experts recommended vedolizumab after
31
32 primary failure to either subcutaneous and intravenous anti-TNF α therapy (Q74, 75%; Q75,
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34 69%; Q76, 88%), after secondary loss of response to infliximab (Q78; 77%), after
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36 discontinuation of anti-TNF therapy due to an adverse event that is not paradoxical
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38 manifestation (Q79; 85% and Q80; 83%) and after discontinuation of infliximab due to
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40 paradoxical manifestation (Q). No consensus was reached in patients with UC, after secondary
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42 failure to subcutaneous anti-TNF α therapy (Q77) and after discontinuation of anti-TNF α
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44 therapy due to paradoxical manifestation (Q81).
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51 ***Management of Crohn's disease***

52 **1. Mildly active uncomplicated Crohn's disease**

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54 A number of changes were made to this treatment algorithm (Figure S1). For patients with
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56 mildly active and colonic CD, physicians agreed that the first line of therapy should be with
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1 corticosteroids (Q18; 66%). Experts also reiterated their position that off-label treatment with
2 an anti-TNF α (adalimumab monotherapy) is appropriate for patients with mildly active CD who
3 are intolerant to oral corticosteroids (Q19; 85%) and for patients who exhibit steroid-
4 dependence despite the use of an immunosuppressant (Q22; 88%).
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9 **2. Uncomplicated moderately active Crohn's disease without poor prognostic**
10 **factor**

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12 A single additional modification was made to this algorithm (Figure S2). For patients with a
13 steroid-dependence, anti-TNF therapy is now the preferred treatment rather than
14 immunosuppressant (Q25; 71%).
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21 **3. Uncomplicated moderately active Crohn's disease with poor prognostic**
22 **factors**

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24 Experts recommended anti-TNF α combination therapy for patients with steroid-dependence
25 (Q27; 97%) or steroid-resistance (Q28; 97%) and anti-TNF α monotherapy or combination
26 therapy for patients with steroid-intolerance (Q31; 61% and 36%, respectively) (Figure 1). In
27 the clinical scenario where patients previously failed to an immunosuppressant, experts
28 recommended treatment with anti-TNF α combination therapy (Q30; 88% and Q33; 100%,
29 respectively). When specific anti-TNF α treatments, adalimumab was preferred over infliximab
30 but it only reach consensus agreement in patients with steroid-intolerance who previously failed
31 to an immunosuppressant (Q34; 68%).
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46 **4. Perianal Crohn's disease with a simple fistula, without proctitis or abscess**

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48 Experts agreed that the algorithm (Figure S3) should be modified to include a proctologic
49 evaluation, with drainage by seton when needed, as a necessary first step (Q36; 100%).
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51 Antibiotic therapy, however, was not considered necessary in all cases (Q35; 84%). Experts
52 also considered that anti-TNF α combination therapy should be the treatment of choice after
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1 antibiotic therapy (and drainage, when necessary) in patients who are naïve to
2 immunosuppressant therapy and biologics (Q37; 91%).
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4 **5. Perianal Crohn's disease with a complex fistula**

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7 In this algorithm (Figure 2), sepsis should be addressed by treating patients with an antibiotic
8 (Q39; 87%), performing an evaluative magnetic resonance imaging (MRI) (Q40; 97%),
9 performing a proctologic exam and suggesting drainage of the fistula/abscess when appropriate
10 (Q41; 100%). This algorithm was also updated to include systematic treatment with
11 infliximab/azathioprine combination (Q42; 97%).
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19 Experts agreed that treatment success should be evaluated after 3 months and that evaluation
20 should include an MRI to identify T2 hyperintensity on the fistula tracks (Q43; 94%). As there
21 are no standardized outcomes that define treatment success in fistulizing perianal CD, experts
22 agreed that the presence of discharge/oozing, an abscess, and/or a T2 hyperintensity on the
23 fistula track on an MRI would constitute treatment failure (Q44; 90%).
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31 The algorithm was also updated for patients in whom the initial multimodal approach fails.
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34 Experts agreed that either a different anti-TNF α or ustekinumab should be prescribed (Q45).
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37 Patients with controlled luminal disease, stem cells should be used if CD is active (Q46; 94%),
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39 whereas in patients with inactive CD, only seton drain removal is necessary (Q47; 87%).
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41 **6. Uncomplicated severely active Crohn's disease**

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44 In this algorithm (Figure S4), experts only broadened maintenance therapy after successful
45 corticosteroid therapy from azathioprine to immunosuppressants (Q49; 72%).
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48 **7. Complicated Crohn's disease with an intra-abdominal abscess**

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51 This algorithm was expanded substantially (Figure 3) according to the results of the GETAID-
52 MICA prospective study[17]. Regardless of the therapeutic strategy employed, experts agreed
53 that in cases of CD complicated by an intra-abdominal abscess, enteral nutrition, preventative
54 low molecular weight heparin (if high risk) (Q50; 86%), and parenteral antibiotics are
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recommended (Q51; 100%). Radiologic drainage and adjustment of antibiotics based on microbial culture results were only recommended first-line if the intra-abdominal abscess is >3 cm (Q52; 100%). Experts recommended that morphological reevaluation by magnetic resonance enterography (MRE) (Q55; 100%) take place after 3 to 4 weeks of treatment (Q53; 92%) and that antibiotics be maintained until the results of this reevaluation (Q54; 100%). Anti-TNF α combination therapy was recommended for patients in whom the abscess disappeared (Q56; 79%). However, in cases where the abscess occurred while on anti-TNF α therapy, a surgical resection was recommended after the disappearance of the abscess if there is less than <50 cm of ileal disease (Q57; 86%). For a patient with >50 cm of ileal disease, second-line drug treatment was recommended instead of surgery (Q58; 96%).

8. Complicated Crohn's disease with an intestinal stricture

This algorithm (Figure 4) was reorganized based on whether a patient is symptomatic and likely to respond to anti-TNF α therapy. For an asymptomatic ileal stricture, monitoring alone was recommended (Q65; 73%). For patients with a symptomatic intestinal stricture, experts agreed that the criteria described in the prospective GETAID-CREOLE study (Table 1) should be used to stratify patients according to their likelihood of response to anti-TNF α (Q59; 93%)[18]. For patients with high probability of response to anti-TNF (CREOLE score ≥ 3), experts chose to recommend anti-TNF α combination therapy and endoscopic dilatation if the stenosis is <5 cm (Q60; 96%). In case of failure of anti-TNF combination therapy, there was no consensus on second-line management (Q97). In patients with low probability of response to anti-TNF (CREOLE score <3), endoscopic dilatation was recommended if the stricture is <5 cm (Q61; 82%), planned surgery if the stricture is >5 cm (Q62; 93%). However, the experts recommended to stratify patients according to the expected length of resected small bowel: if the expected length of resected small bowel is <50 cm (Q63; 100%) and anti-TNF combination therapy if the expected length of resected small bowel is >50 cm (Q64; 100%).

9. Post-operative Crohn's disease

In this algorithm (Figure 5), the experts recommended systematic post-operative treatment in patients with at least one risk factor for post-operative recurrence, that include active smoking, history of bowel resection for CD, fistulizing phenotype (B3 according the Montreal Classification) and length of resected bowel > 50 cm. However no consensus was reached on the type of treatment (Q66: 65% for thiopurine and 27% for anti-TNF). At the 6-month ileocolonoscopy, experts agreed that anti-TNF α treatment should be prescribed for patients, who received no treatment, and showed endoscopic recurrence defined by a Rutgeerts score >i2 (Q67: 66%). For patients with a Rutgeerts score >i2, who had received anti-TNF α monotherapy, experts recommended optimizing the monotherapy or switching to combination therapy (Q68; 94%). Experts distinguished Rutgeerts i2a and i2b (Q70; 92%). No consensus was reached about whether treatment should be modified after 6 months of anti-TNF α therapy in a patient with an i2a classification (Q71). However, all experts agreed that in a patient with an i2b classification already under anti-TNF α treatment, the therapeutic approach needs to be changed (Q72; 100%). Experts did not reach consensus on whether to use therapeutic drug monitoring to guide decisions (Q69).

Management of Ulcerative colitis

1. Moderately-to-severely active ulcerative colitis not requiring hospitalization

Experts considered that one algorithm would be sufficient for patients with moderate or severe UC experiencing a flare-up. Previous algorithms were merged accordingly with the only remaining difference would be first-line treatment with oral 5-ASA \geq 4g per day plus topical 5-ASA for patients with moderate UC and oral corticosteroids for patients with moderate UC that did not respond to 5-ASA and those with severe UC. After induction of remission, maintenance

1 therapy is indication using 5-ASA in case of moderate UC with no more than one flare-up every
2 2 years and azathioprine in the other cases of moderate UC and severe UC.
3

4 Although discussion is ongoing with French healthcare insurance, vedolizumab is currently
5 reimbursed only after failure, intolerance and/or contraindication to at least one anti-TNF. The
6 experts considered two situations for patients with moderate to severe UC: current
7 reimbursement policy and the setting of unrestricted reimbursement of first-line biologics.
8

9 In the current reimbursement situation (figure 6), the experts recommended anti-TNF
10 combination therapy in patients with steroid-refractory (Q90: 84%), anti-TNF in patients with
11 steroid-intolerance (Q86: 100%) and consensus was no reached in patients with steroid-
12 dependency (Q88: 63% for immunosuppressant and 37% for anti-TNF).
13

14 In the setting of unrestricted reimbursement of first-line biologics (figure S5), the consensus
15 was not reached in patients with steroid-refractory (Q91: 57% for IV anti-TNF in combination
16 therapy and 34% for tofacitinib), vedolizumab in patients with steroid-intolerance (Q87: 67%)
17 and consensus was no reached in patients with steroid-dependency (Q89: 50% for
18 immunosuppressant and 34% for vedolizumab). Tofacitinib was recommended by the experts
19 in case of vedolizumab failure for UC (Q99: 86%).
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22 **2. Severely active, ulcerative colitis requiring hospitalization**

23 The algorithm (figure S6) was modified to reflect a lack of consensus on how to proceed after
24 patients responded to intravenous corticosteroids and/or cyclosporin. In this setting, the experts
25 recommended maintenance therapy (Q92) but did not reach agreement on a specific treatment
26 (Q92-94).
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29 **3. Refractory proctitis**

30 The treatment algorithm for refractory proctitis was removed after experts voted for a similar
31 management than for a more extensive UC (Q95: 84%).
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4. Refractory pouchitis

Experts voted that for patients with refractory pouchitis (figure S7), anti-TNF α should be the first line of treatment in patients who are naïve to anti-TNF α (Q96: 93%). No consensus was reached on a treatment strategy for patients who did not respond to optimized anti-TNF α treatment (Q97).

Accepted manuscript

Discussion (see APPENDIX 3)

Conclusions

For inflammatory bowel disease, treatment options have changed substantially over the last few years. These updates to the treatment guidelines for CD and UC should provide practicing physicians with recommendations about how and when to integrate new treatments and treatment strategies.

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Figure legends

Figure 1. Treatment algorithm for uncomplicated moderately active Crohn's disease with poor prognostic factors (upper gastrointestinal damage, small intestine damage, severe ileal involvement, severe rectal involvement, perianal damage, severe lesions on endoscopy (large and/or deep ulcer), and young age at diagnosis).

Treatment algorithm for a first flare-up in a patient who is naive to treatment and shows right ileocolonic involvement. †In the absence of PK testing, ustekinumab is the alternative treatment in case of primary failure or when adverse event led to anti-TNF α discontinuation while no consensus was reached on the other scenarios.

Figure 2. Treatment algorithm for perianal Crohn's disease with a complex fistula with or without abscess

*Treatment failure was defined as discharge/oozing from fistulae, and/or presence of an abscess, and/or T2 hyperintensity on the fistula track.

Figure 3. Treatment algorithm for complicated Crohn's disease by an intra-abdominal abscess

Figure 4. Treatment algorithm for complicated Crohn's disease with an intestinal stricture

†In the absence of PK testing, ustekinumab is the alternative treatment in case of primary failure or when adverse event led to anti-TNF α discontinuation while no consensus was reached on the other scenarios.

Figure 5. Post-operative Crohn's disease

* Recurrence was defined as a lesion with a Rutgeerts score ≥ 2 . †Risk factors for post-operative recurrence: active smoking, history of intestinal resection for Crohn's disease, concomitant perianal disease (B3 on the Montreal classification), length of intestinal resection (>50 cm).

Figure 6. Treatment algorithm for moderately or severely active ulcerative colitis

Treatment algorithm for a flare-up in adherent patients taking 1.6-2.0 g of 5-ASA and with a total Mayo score ≤ 9 . *Vedolizumab if intolerance or contraindication †In the absence of PK testing, vedolizumab is the alternative treatment in case of primary failure, secondary loss of response to infliximab or when non-paradoxical adverse events led to anti-TNF α discontinuation while no consensus was reach in the other scenarios.

APPENDIX A: the French National Consensus Clinical guidelines for the management of

IBD study group

APPENDIX B: Definitions

APPENDIX C: Discussion

APPENDIX D: List of supplementary materials

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APPENDIX A: The members of the French National Consensus Clinical guidelines for the management of IBD study group are as follows:

Vered Abitbol and Georgia Malamut. Department of Gastroenterology, Cochin University Hospital, Paris, France

Aurelien Amiot. Department of Gastroenterology, Henri Mondor Hospital, APHP, EC2M3-EA7375, Paris Est-Créteil Val de Marne University, Creteil, France.

Arnaud BORUCHOWICZ. Service de gastroentérologie, centre hospitalier de Valenciennes, avenue Desandrouin, 59300 Valenciennes, France

Guillaume Bouguen, Laurent Siproudhis, Marie DeWitte. Department of Gastroenterology, CHU Rennes and University of Rennes, INSERM, CIC1414, NUMECAN institute, F-35000 Rennes, France

Yoram BOUHNIK and Carmen STEFANESCU. Department of Gastroenterology, IBD and Nutrition Support, Beaujon Hospital, University Paris 7 Denis Diderot, Clichy, France

Anthony Buisson. Department of Hepato-Gastroenterology, University Hospital Estaing of Clermont-Ferrand, Université d'Auvergne, Clermont-Ferrand, France

Ludovic Caillo. Department of Gastroenterology, Nimes University Hospital, Nimes, France.

Maryan CAVICCHI. Department of Gastroenterology, Clinique de Bercy, Creteil, France

Nina Dib. Department of HepatoGastroenterology, Angers University Hospital, Angers, France

Isabelle ETIENNEY. Department of Coloproctology, Groupe Hospitalier Diaconesses Croix Saint-Simon, Paris, France.

Jerome Filippi. Department of Gastroenterology and Clinical Nutrition, CHU of Nice, University Côte d'Azur, Nice, France

Mathurin Fumery. Department of Gastroenterology, Amiens University Hospital, Amiens, France.

1 Felix Goutorbe. Department of HepatoGastroenterology, Cote Basque Hospital, Bayonne,
2 France.

3
4 Hervé HAGEGE, Laurent COSTES and Mathias VIDON. Intercommunal Hospital.
5 Department of Gastroenterology, Creteil, France.
6

7
8
9 Frédéric HELUWAERT. Centre Hospitalier Annecy Genevois, Pringy, France

10
11 Christophe LOCHER. Department of Gastroenterology, Est-Francilien Great Hospital, 6-8 Rue
12 Saint-Fiacre, 77100 Meaux, France
13

14
15 Mehdi Kaassis. Department of HepatoGastroenterology, Cholet Hospital, Cholet, France.
16

17
18 Patrick MAMOU. Department of Gastroenterology, Clinique du Landy, Saint-Denis, France.
19

20
21 Chloe MARTINEAU. Department of Gastroenterology, AP-HP, Hôpital Saint-Antoine, F-
22 75012, ERL 1057 INSERM/UMRS 7203, UPMC Université Paris 6, Paris, France
23

24
25 Nicolas Mathieu. Department of Hepato-Gastroenterology and Digestive Oncology, Grenoble
26 Alpes University Hospital, Grenoble, France.
27

28
29 Benjamin PARIENTE and Pauline WILS. Department of Gastroenterology, Huriez Hospital,
30 Université of Lille, Lille, France.
31

32
33
34 Stephane Nancey. Department of Gastroenterology, Hospices Civils de Lyon and INSERM
35 U1111, University Claude Bernard Lyon 1, Lyon, France.
36

37
38
39 Magalie PICON-COSTE. Intercommunal Hospital. Department of Gastroenterology, Aix-en-
40 Provence, France.
41

42
43
44 Laurent Peyrin-Biroulet, Camille Zallot. INSERM U954 and Department of Gastroenterology,
45 Université de Lorraine, Nancy, France
46

47
48
49 Marie-Pierre PINGANNAUD. 23 Cours Gouffé, Marseille, France
50

51
52
53 Xavier Roblin. Department of Gastroenterology, Saint-Etienne University Hospital, Saint-
54 Etienne, France.
55
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1 Julia ROUX. Intercommunal Hospital. Department of Gastroenterology, Villeneuve-Saint-
2 Georges, France.
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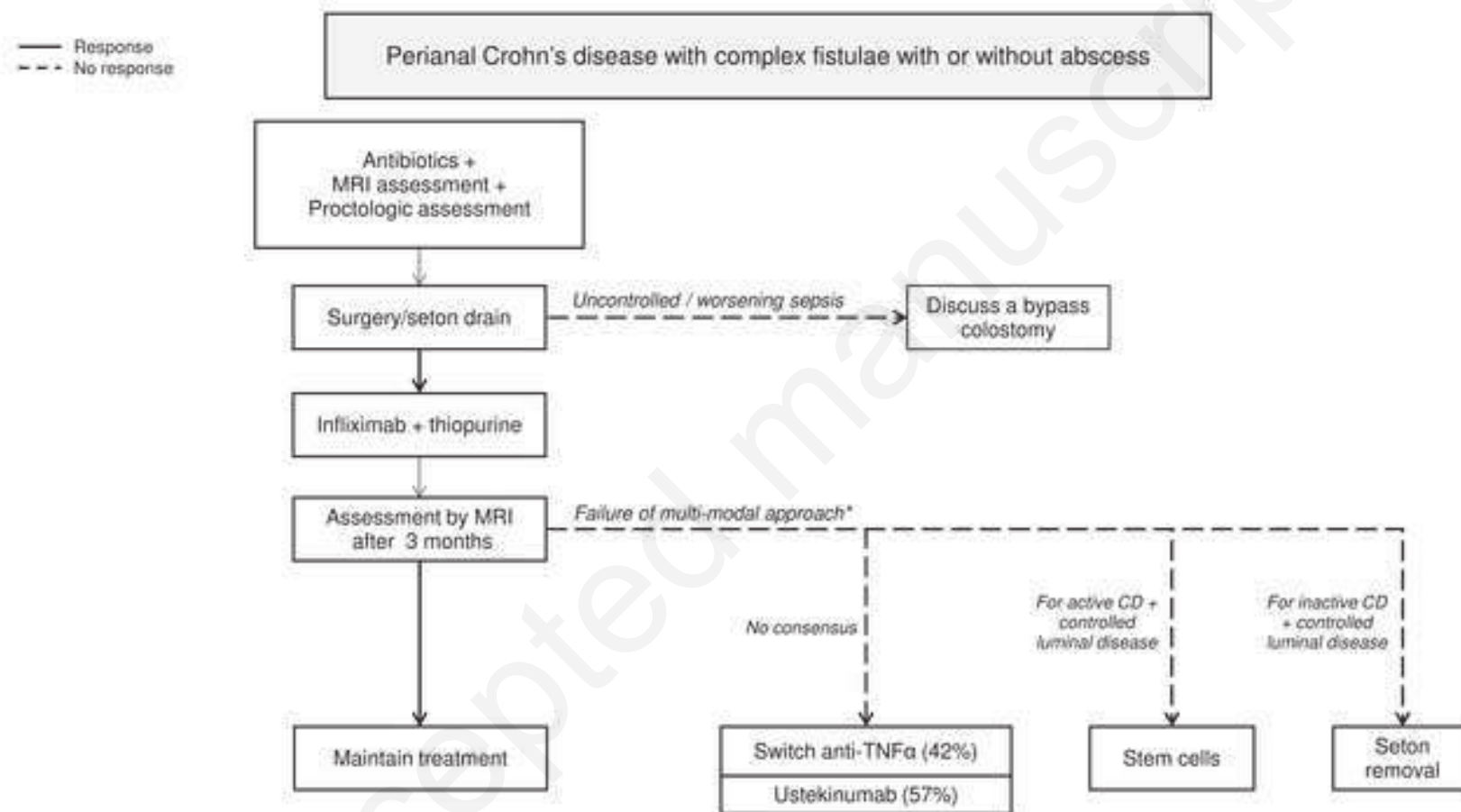
4 Melanie Serrero. Hôpital Nord, Centre d'investigation clinique Marseille Nord, Université
5 Méditerranée, Marseille, France
6

7 Marion Simon. Department of Gastroenterology, Institut Mutualiste Montsouris, Paris, France.
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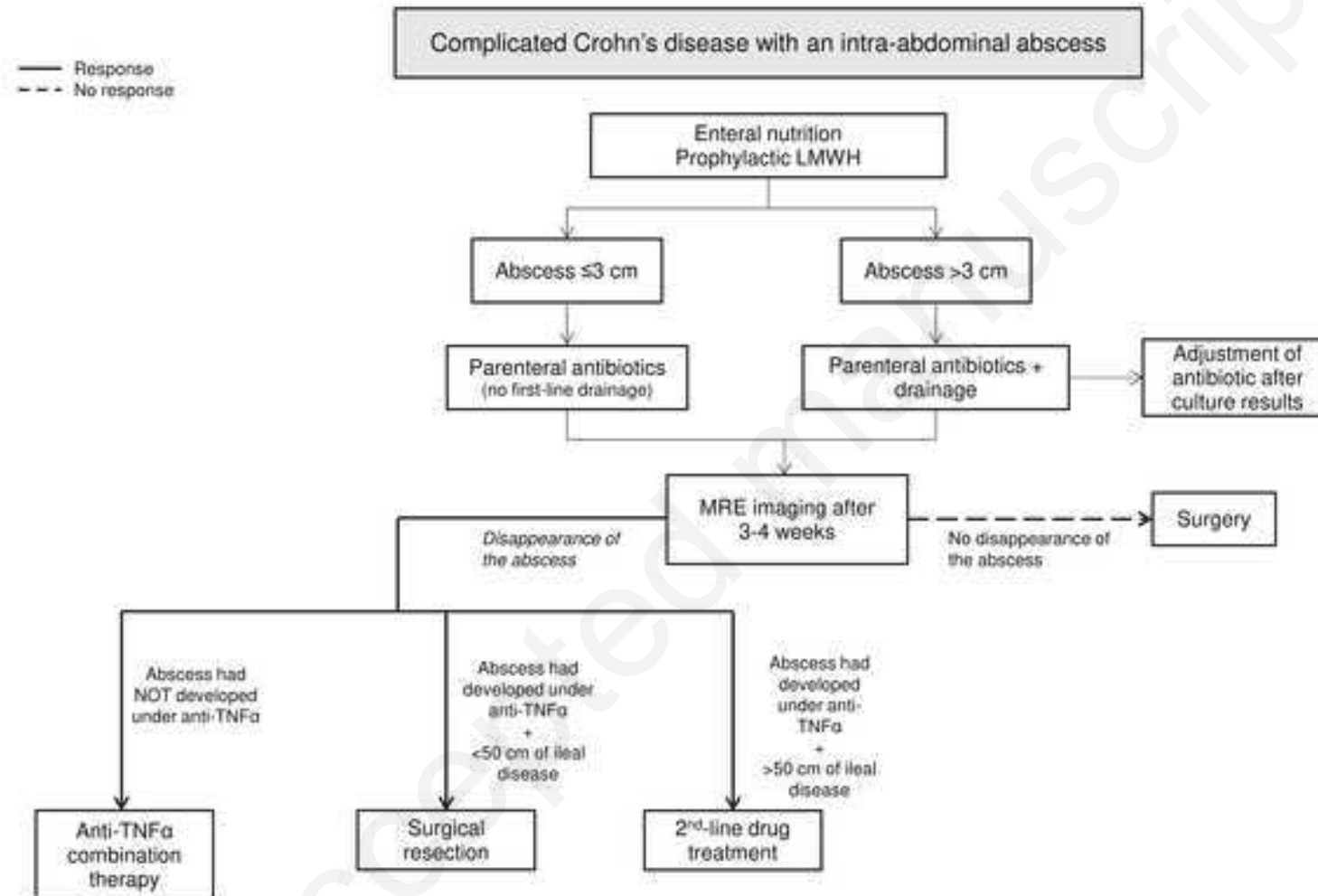
9 Florence SKINAZI. Saint-Denis Hospital. Department of Gastroenterology, Saint-Denis,
10 France.
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12 Lucas SPINDLER. Department of Coloproctology. Saint-Joseph Hospital. Paris, France.
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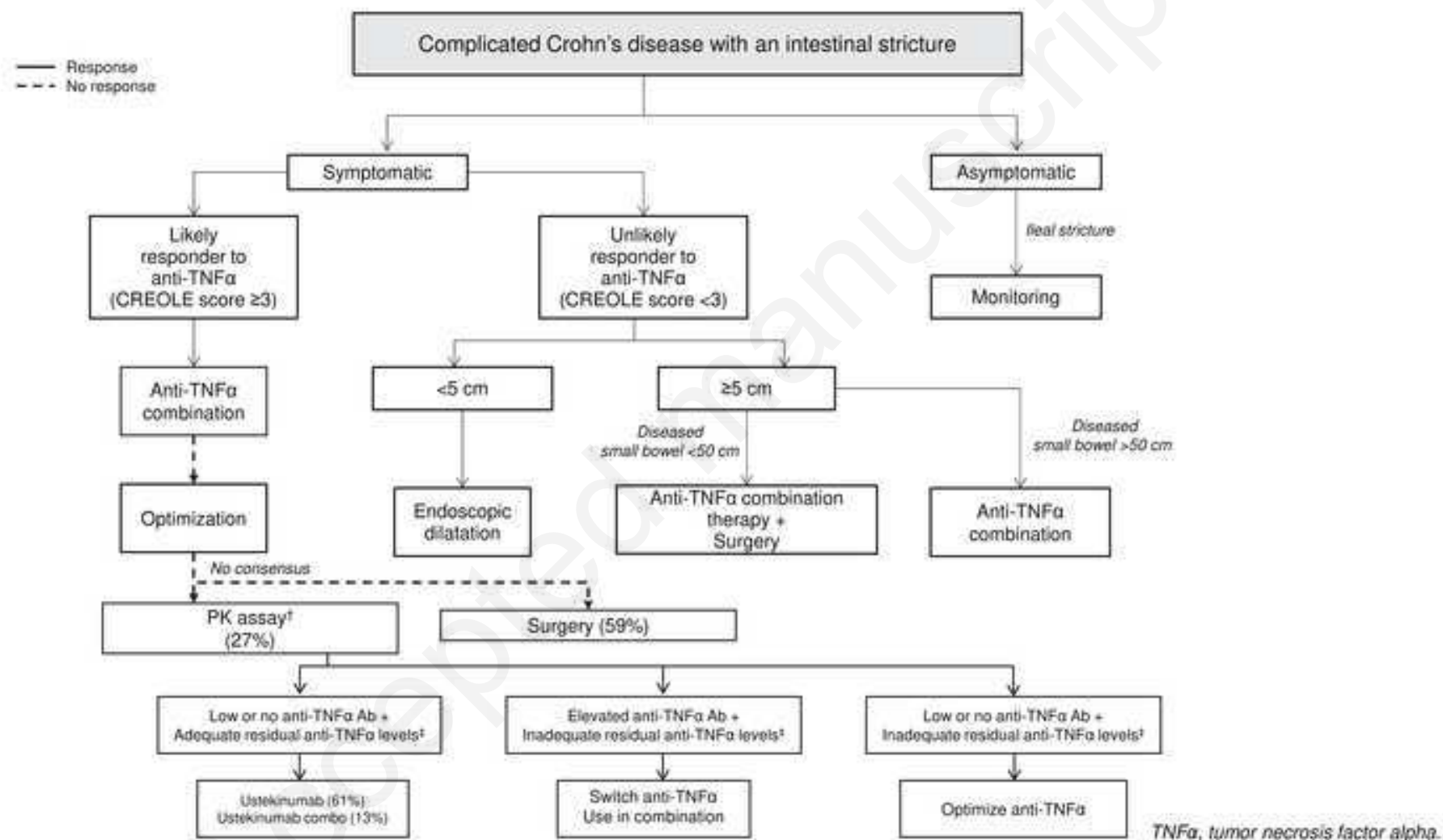
14 Stephanie Viennot. Department of Gastroenterology, Caen University Hospital, Caen, France
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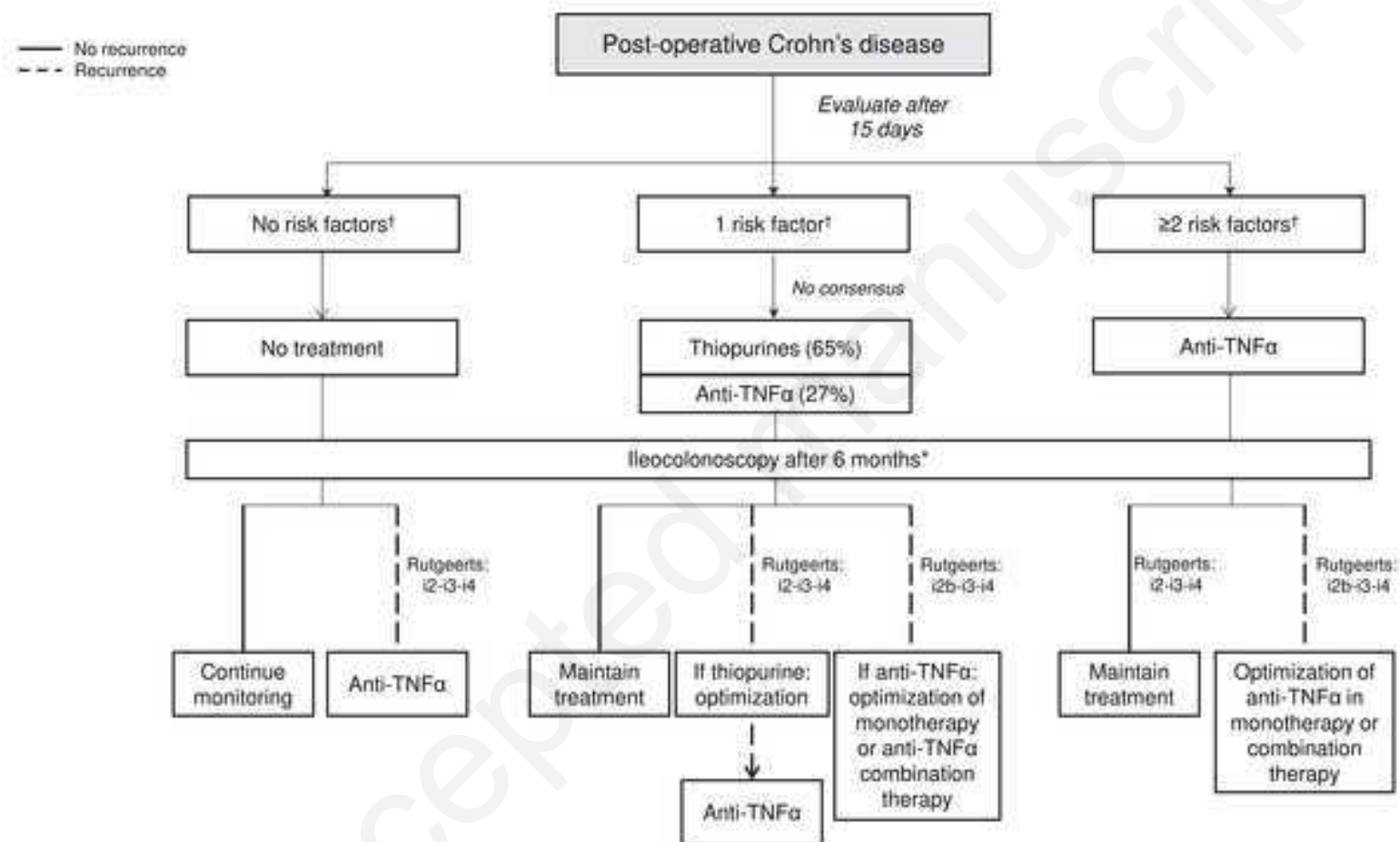


CD, Crohn's disease; MRI, magnetic resonance imaging; TNF α , tumor necrosis factor alpha.

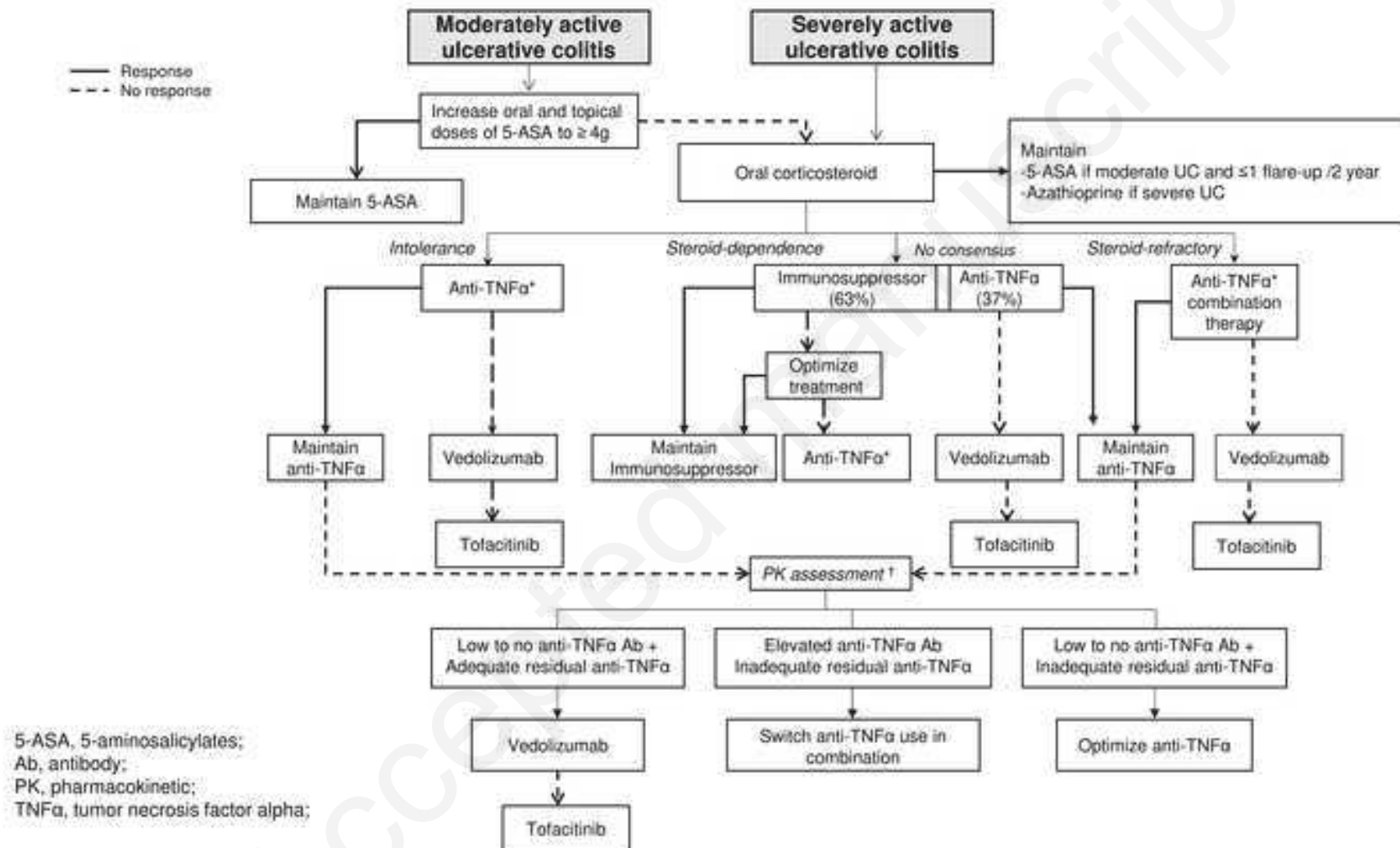


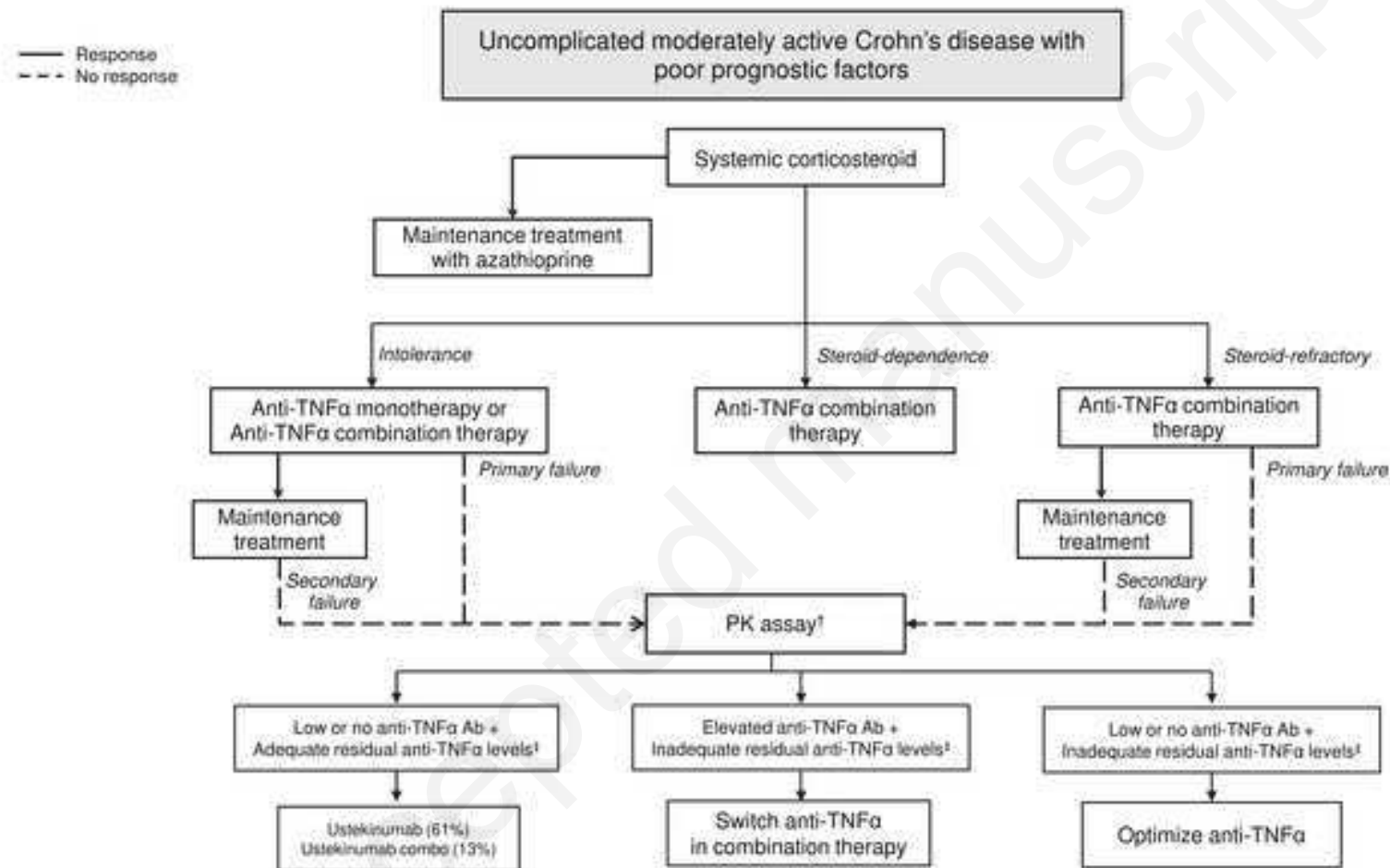
LMWH, low-molecular-weight heparin; MRE, magnetic resonance enterography; TNF α , tumor necrosis factor alpha.





TNFα, tumor necrosis factor alpha.





Ab, antibody; PK, pharmacokinetic; TNF α , tumor necrosis factor alpha. Anti-TNF refers either to intravenous or subcutaneous anti-TNF.

Table S1. Results of breakout and plenary votes.

Questions		Responses				
		A thiopurine (azathioprine or mercaptopurine)	Methotrexate	No op		
Q1	During the course of Crohn's disease, what immunomodulator treatment do you recommend when no specific contraindications are present? (P)	/	90%	3%	6%	
Q2	During the course of Crohn's disease, in a patient who has a <u>negative EBV</u> serology, what immunomodulator treatment do you recommend when no specific contraindications are present? (P)	V 1	21%	50%	28%	
	During the course of Crohn's disease, in a patient who has a <u>negative EBV</u> serology, what immunomodulator treatment do you recommend as a <u>monotherapy</u> when no specific contraindications are present? (P)	V 2 R	9%	37%	53%	
			A thiopurine (azathioprine or mercaptopurine)	Methotrexate	No op	
Q3	During the course of CD, in a patient over <u>65 years</u> of age, what immunomodulator treatment do you recommend when no specific contraindications are present? (P)	V 1 V 2	9% 3%	65% 81%	25% 15%	
Q4	During the course of CD, in a patient with a history of <u>cancer or of a hematologic disease</u> in the previous 5 years, what immunomodulator treatment do you recommend when no specific contraindications are present? (P)	V 1 V 2	0% 0%	59% 65%	40% 34%	
			PK dosing* of anti-TNF	Decision without PK dosing	No op	
Q5	In all the algorithms, during the course of CD, when the first course of anti-TNF therapy has failed, what approach do you recommend? (P)	/	87%	9%	3%	
			Switch anti-TNF	Vedo	Ustek	No op
Q6	In all the algorithms, during the course of CD, when the first course of anti-TNF therapy has failed, in the	V 1	18%	3%	57%	21%

	<u>absence of PK dosing</u> , what do you recommend for a patient presenting with a <u>primary failure</u> of the first anti-TNF treatment? (P)	V 2	8%	0%	73%	17%		
Q7	In all the algorithms, during the course of CD, when the first course of anti-TNF therapy has failed, in the <u>absence of PK dosing</u> , what do you recommend for a patient presenting with a <u>secondary loss</u> of response to the first anti-TNF? (P)	V 1	51%	5%	25%	17%		
		V 2	60%	0%	14%	25%		
Q8	In all the algorithms, during the course of CD, when the first course of anti-TNF has therapy has failed, and in the <u>absence of PK dosing</u> , what do you recommend for a patient presenting with a side effect that is <u>not a paradoxical effect</u> to the first anti-TNF treatment that justifies its discontinuation? (P)	V 1	5%	8%	62%	22%		
		V 2	0%	5%	79%	14%		
Q9	In all the algorithms, during the course of CD, when the first course of anti-TNF has therapy has failed, and in the <u>absence of PK dosing</u> , what do you recommend for a patient presenting with a <u>paradoxical effect</u> to the first anti-TNF treatment that justifies its discontinuation? (P)	/	5%	2%	88%	2%		
Q10	In all the algorithms, during the course of CD, with respect to the <u>PK dosing</u> of anti-TNFs, above which concentration of residual <u>infliximab</u> do you choose <u>not</u> to optimize treatment? (P)		1 µg/ml	3 µg/ml	5 µg/ml	7 µg/ml	10 µg/ml	No op
		V 1	0%	0%	3%	36%	60%	0%
		V 2	0%	0%	2%	22%	74%	0%
Q11	In all the algorithms, during the course of CD, with respect to the <u>PK dosing</u> of anti-TNFs, above which concentration of residual <u>infliximab</u> do you choose <u>not</u> to optimize treatment when <u>perianal</u> lesions are present? (P)	V 1	2 µg/ml	3 µg/ml	7 µg/ml	10 µg/ml	15 µg/ml	No op
			0%	0%	2%	37%	57%	2%
		V 2	2 µg/ml	3 µg/ml	7 µg/ml	10 µg/ml	12 µg/ml	No op
		R	0%	0%	0%	20%	76%	2%
Q12	In all the algorithms, during the course of CD, with		5 µg/ml	7.5 µg/ml	10 µg/ml	No op		
		V 1	2%	48%	42%	5%		

respect to the PK dosing of anti-TNFs, above which concentration of residual adalimumab do you choose not to optimize treatment? (P)

V 2

2%

20%

73%

2%

		5 µg/ml	7.5 µg/ml	10 µg/ml	12 µg/ml	No op				
Q13	In all the algorithms, during the course of CD, with respect to the <u>PK dosing</u> of anti-TNFs, above which concentration of residual <u>adalimumab</u> do you choose not to optimize treatment, when <u>perianal</u> lesions are present? (P)	0%	2%	13%	75%	8%				
		Opt anti-TNF	Opt anti-TNF in comb	Switch anti-TNF	Switch anti-TNF in comb	Vedo	Vedo in comb	Ustek	Ustek in comb	No op
Q14	In all the algorithms, during the course of CD, when the first course of therapy with anti-TNF has failed and <u>PK dosing</u> has been performed, what do you recommend in cases where <u>residual concentrations of the first anti-TNF are adequate</u> ? (P)	2%	5%	0%	11%	0%	0%	61%	13%	5%
Q15	In all the algorithms, during the course of CD, when the first course of therapy with anti-TNF has failed and <u>PK dosing</u> has been performed, what do you recommend in cases where residual concentrations are <u>low</u> and anti-TNF Ab are <u>present</u> ? (P)	V 1 0%	6%	6%	58%	2%	0%	18%	8%	0%
		V 2 0%	2%	0%	73%	0%	0%	23%	0%	0%
Q16	In all the algorithms, during the course of CD, when the first course of therapy with anti-TNF has failed and <u>PK dosing</u> has been performed, what do you recommend in cases where residual concentrations are <u>low</u> AND anti-TNF Ab are <u>not</u> present? (P)	/	75%	19%	0%	0%	0%	5%	0%	0%

MILD, ACTIVE CROHN'S DISEASE

		Yes	No	No op
Q17	With the exception of the parts of the algorithm that need to be voted on again by the nominal group, do you agree with the algorithm: mild, active Crohn's disease? (B)	/ 100%	0%	0%

	Do you confirm the breakout session consensus? (P) /		90%		0%	9%	
Q18	In a patient presenting with mildly active colonic Crohn's disease (Harvey-Bradshaw index <8), what treatment do you recommend? (B)		5-ASA 33%		Corticosteroids 66%	No op 0%	
Q19	In a patient presenting with mildly active Crohn's disease (Harvey-Bradshaw index <8), assuming treatment with an oral corticosteroid, what treatment seems to you to be most suitable in cases of <u>intolerance</u> to oral corticosteroids? (B)		IS 16%	Anti-TNF 77%	Vedo 5%	Ustek 0%	No op 0%
	Do you confirm the breakout session consensus? (P) /		Yes 85%		No 14%	No op 0%	
Q20	In a patient presenting with mildly active Crohn's disease, what anti-TNF treatment strategy in cases of <u>intolerance</u> to corticosteroids? (B)		Adalimumab mono 88%	Adalimumab comb 5%	Infliximab mono 0%	Infliximab comb 5%	No op 0%
	Do you confirm the breakout session consensus? (P) /		Yes 93%		No 6%	No op 0%	
Q21	In a patient presenting with mildly active Crohn's disease (Harvey-Bradshaw index <8), assuming treatment with an oral corticosteroid, what treatment seems to you to be most suitable in cases of <u>steroid dependency</u> ? (B)	V 1	IS 58%	Anti-TNF 41%	Vedo 0%	Ustek 0%	No op 0%
		V 2	66%	33%	0%	0%	0%
	Do you confirm the breakout session consensus? (P) /		Yes 66%		No 33%	No op 0%	
Q22	In a patient presenting with mildly active Crohn's disease, what anti-TNF treatment strategy in cases of <u>steroid dependency</u> ? (B)		Adalimumab mono 83%	Adalimumab comb 11%	Infliximab mono 0%	Infliximab comb 5%	No op 0%
	Do you confirm the breakout session consensus? (P) /		Yes 88%		No 11%	No op 0%	

			IS	Anti-TNF in mono	Anti-TNF in comb	Vedo	Ustek	No op
Q23	In a patient presenting with mildly active Crohn's disease (Harvey-Bradshaw index <8), assuming treatment with an oral corticosteroid, what treatment seems to you to be most suitable in cases of steroid- <u>resistance</u> (at least 4 weeks of corticosteroid >0.75 mg/kg/d)? (B) New vote on Q23 during the plenary session (P)	V 1	5%	47%	47%	0%	5%	0%
		V 2	5%	55%	38%	0%	0%	0%
			0%	57%	34%	2%	5%	0%

MODERATELY ACTIVE UNCOMPLICATED CROHN'S DISEASE WITHOUT POOR PROGNOSTIC FACTORS

			Yes		No		No op
Q24	We are not proposing modifications to the treatment algorithm for uncomplicated moderately active Crohn's disease without poor prognostic factors with the exception of the modifications concerning failure of first line anti-TNF. Do you agree with this algorithm? (B)	/	33%		66%		0%
	Do you confirm the breakout session consensus? (P)	/	33%		66%		0%

			IS	Anti-TNF	Vedo	Ustek	No op
Q25	In a patient with moderately active Crohn's disease without poor prognostic factors, assuming treatment with an oral corticosteroid, what treatment seems to you to be most suitable in cases of steroid <u>dependency</u> ?	/	22%	77%	0%	0%	0%
	Do you confirm the breakout session consensus? (P)	/		Yes		No	No op
				71%		28%	0%

UNCOMPLICATED MODERATELY ACTIVE CROHN'S DISEASE WITH POOR PROGNOSTIC FACTORS

			Yes		No		No op
Q26	With the exception of the parts of the algorithm that need to be voted on again by the nominal group, do you agree with the algorithm "uncomplicated moderately active Crohn's disease with poor prognostic factors"? (B)		72%		27%		0%
	Do you confirm the breakout session consensus? (P)	/	97%		2%		0%

			5-ASA	IS	Anti-TNF mono	Anti-TNF comb	Vedo	Ustek	No op
Q27	In a patient treated with an oral corticosteroid and presenting with a steroid <u>dependency</u> (inability to decrease treatment to less than 10 mg/d over a three month period without a relapse within 3 months of discontinuation), what therapeutic option to you recommend? (B)	/	0%	0%	33%	66%	0%	0%	0%
				Yes			No		No op

	Do you confirm the breakout session consensus? (P)	/			97%		2%		0%
			5-ASA	IS	Anti-TNF mono	Anti-TNF comb	Vedo	Ustek	No op
Q28	In a patient treated with an oral corticosteroid and presenting with a steroid- <u>resistance</u> (3 weeks of prednisone/prednisolone at 0.75 mg/kg/d), what treatment option do you recommend? (B)	V 1	0%	0%	38%	61%	0%	0%	0%
		V 2	0%	0%	22%	77%	0%	0%	0%
				Yes			No		No op
	Do you confirm the breakout session consensus? (P)	/			97%		0%		2%
			Adalimumab mono	Adalimumab comb	Infliximab mono	Infliximab comb			No op
Q29	In a patient presenting with moderately active Crohn's disease, <u>risk factors</u> and a steroid- <u>resistance</u> , what anti-TNF strategy? (B)	V 1	33%		38%	0%	11%		16%
		V 2	33%		44%	0%	5%		16%
	New vote on Q29 in the plenary session (P)		14%		57%	0%	11%		17%
			2nd IS	Subcu anti-TNF in mono	Anti-TNF in mono	Anti-TNF in comb	Vedo	Ustek	No op
Q30	In a patient treated with an oral corticosteroid and presenting with a steroid- <u>resistance</u> (3 weeks of prednisone/prednisolone at 0.75 mg/kg/d) and after failure of an immunomodulator, what treatment option do you recommend? (B)	/	0%	27%	0%	72%	0%	0%	0%
				Yes			No		No op
	Do you confirm the breakout session consensus? (P)	/			88%		11%		0%
			5-ASA	IS	Anti-TNF in mono	Anti-TNF in comb	Vedo	Ustek	No op
Q31	In a patient treated with an oral corticosteroid and presenting with an <u>intolerance</u> to steroids, what treatment option do you recommend? (B)	V 1	0%	0%	44%	50%	0%	5%	0%
		V 2	0%	0%	38%	61%	0%	0%	0%
	New vote on Q31 during the plenary session (P)		0%	0%	36%	61%	0%	2%	0%
			Adalimumab mono	Adalimumab comb	Infliximab mono	Infliximab comb			No op
Q32	In a patient presenting with moderately active Crohn's disease, <u>risk factors</u> , and an <u>intolerance</u> to steroids, what anti-TNF strategy? (B)	V 1	38%		33%	0%	22%		5%
		V 2	50%		27%	0%	16%		5%
	New vote on Q32 during the plenary session (P)		25%		48%	0%	11%		14%

			2nd IS	Subcu anti-TNF in mono	Anti-TNF in mono	Anti-TNF in comb	Vedo	Ustek	No op
Q33	In a patient treated with an oral corticosteroid and presenting with an <u>intolerance</u> to steroids, after <u>failure of an immunomodulator</u> , what treatment do you recommend? (B)	/	0%	22%	5%	72%	0%	0%	0%
	Do you confirm the breakout session consensus? (P)	/		Yes 100%			No 0%		No op 0%
			Adalimumab mono	Adalimumab comb	Infliximab mono	Infliximab comb	No op		
Q34	In a patient presenting with moderately active Crohn's disease, <u>risk factors</u> , and an <u>intolerance</u> to steroids, after <u>failure of an immunomodulator</u> , what anti-TNF strategy? (B)	V 1	11%	55%	0%	27%	5%		
		V 2	11%	66%	0%	22%	0%		
	Do you confirm the breakout session consensus? (P)	/		Yes 68%			No 18%		No op 12%
PERIANAL CROHN'S DISEASE WITH A SIMPLE FISTULA									
			Yes			No			No op
Q35	In cases of perianal Crohn's disease, with a simple fistula, independently of future drug treatment and surgical interventions, does prescription of an <u>antibiotic</u> without postponing surgery seem absolutely necessary to limit the progression of sepsis? (B)	V 1	50%			50%			0%
	New vote on Q35 during the plenary session (P)	V 2	38%			61%			0%
			15%			84%			0%
Q36	In cases of perianal Crohn's disease, with a simple fistula, independently of future drug treatment, does it seem absolutely necessary to plan a proctology evaluation and to suggest drainage using a seton when necessary? (B)	/	100%			0%			0%
	Do you confirm the breakout session consensus? (P)	/	100%			0%			0%

		None	Thiopurine	Anti-TNF mono	Anti-TNF comb	Ustek	Vedo	No op	
Q37	In cases of perianal Crohn's disease, with a simple fistula, after antibiotics and potentially drainage of the fistula, what treatment do you recommend in a patient who is <u>naive</u> to immunomodulator therapy and/or biologics? (B)	V 1	0%	0%	38%	50%	0%	0%	11%
		V 2	0%	0%	33%	66%	0%	0%	0%
	Do you confirm the breakout session consensus? (P)	/		Yes 91%		No 8%		No op 0%	
		Adalimumab mono	Adalimumab comb	Infliximab mono	Infliximab comb	No op			
Q38	In cases of perianal Crohn's disease, with a simple fistula, after antibiotics and potentially drainage of the fistula, what treatment do you recommend in a patient who is <u>naive</u> to immunomodulator therapy and/or biologics? (B)	V 1	11%	55%	0%	27%	5%		
		V 2	16%	55%	0%	22%	5%		
	New vote on Q38 during the plenary session (P)		11%	42%	0%	40%	5%		
PERIANAL CROHN'S DISEASE WITH A COMPLEX FISTULA									
				Yes		No		No op	
Q39	In cases of complex perianal Crohn's disease, independently of future drug treatment and surgical intervention, does <u>prescription of an antibiotic</u> without postponing surgery seem a legitimate way to limit the progression of sepsis? (B)	/		77%		22%		0%	
	Do you confirm the breakout session consensus? (P)	/		87%		12%		0%	
Q40	In cases of complex perianal Crohn's disease, independently of future drug treatment, does it seem <u>absolutely necessary</u> to perform an assessment <u>MRI</u> before considering surgical intervention? (B)	/		100%		0%		0%	
	Do you confirm the breakout session consensus? (P)	/		97%		2%		0%	
Q41	In cases of complex perianal Crohn's disease, independently of future drug treatment, does it seem absolutely necessary to plan a proctology evaluation and to suggest drainage using a seton drain? (B)	/		100%		0%		0%	
	Do you confirm the breakout session consensus? (P)	/		100%		0%		0%	

			Infliximab	Adalimumab	No op			
Q42	When considering an anti-TNF + thiopurine combination therapy for the treatment of complex perianal Crohn's disease, which anti-TNF do you recommend first-line? (B)	/	66%	16%	16%			
	Do you confirm the breakout session consensus? (P)	/	Yes 97%	No 2%	No op 0%			
Q43	In cases of complex perianal Crohn's disease, after surgical intervention and introduction of an anti-TNF and thiopurine combination therapy, is it absolutely necessary to reevaluate after 3 months the perianal disease by MRI specifically to look for T2 hyperintensity on the fistula tracks? (B)	/	72%	11%	16%			
	Do you confirm the breakout session consensus? (P)	/	94%	5%	0%			
Q44	In cases of complex perianal Crohn's disease, treatment failure after 3 months is defined as the persistence of discharge/oozing from the fistula, the presence of an abscess, and/or T2 hyperintensity on the fistula tracks on an MRI? (B)	/	100%	0%	0%			
	Do you confirm the breakout session consensus? (P)	/	90%	9%	0%			
			Switch Anti-TNF	Vedo	Ustek	No op		
Q45	In cases of active, complex perianal Crohn's disease, what treatment do you suggest when treatment with infliximab/azathioprine combined with drainage fails? (B)	V 1	50%	0%	38%	11%		
		V 2	50%	0%	38%	11%		
	New vote on Q45 during the plenary session (P)		42%	0%	57%	0%		
			Stem cells	Fistula plug	Glue	Adv flap	Fistulotomy	No op
Q46	In cases of <u>active</u> perianal Crohn's disease with controlled luminal disease, what local treatment do you suggest when treatment with infliximab/azathioprine combined with drainage fails? (B)	/	83%	0%	5%	0%	0%	11%
	Do you confirm the breakout session consensus? (P)	/	Yes 94%	No 2%	No op 2%			

			Stem cells	Ligation of IT	Fistula plug	Glue	Adv flap	Fistulotomy	Seton removal	No op	
Q47	In cases of <u>inactive</u> perianal Crohn's disease with controlled luminal disease, under treatment with infliximab/azathioprine combined with a seton drain, what local treatment do you suggest? (B)	V 1	41%	17%	0%	52%	47%	0%	64%	11%	
		V 2	35%	17%	0%	41%	47%	0%	70%	11%	
	Do you confirm the breakout session consensus? (P)	/		Yes 87%				No 12%		No op 0%	
ACTIVE, UNCOMPLICATED SEVERE CROHN'S DISEASE											
Q48	We are not proposing modifications to the treatment algorithm for uncomplicated with the exception of the modifications concerning failure of first line anti-TNF. Do you agree with this algorithm? (B)	/		Yes 44%				No 55%		No op 0%	
Q49	In the case of a patient with active, uncomplicated severe Crohn's disease who responds to steroids and tolerates them, keeping in mind the prescribing information, what treatment do you recommend? (B)	V 1	None 0%	IS 64%		Anti-TNF 11%		Ustek 23%		Vedo 0%	
		V 2	0%	72%		5%		22%		0%	
	Do you confirm the breakout session consensus? (P)	/		Yes 58%				No 37%		No op 3%	
	New vote on Q48 during the plenary session (P)		None 3%	IS 72%		Anti-TNF 3%		Ustek 20%		Vedo 0%	
CROHN'S DISEASE COMPLICATED BY AN INTRA-ABDOMINAL ABSCESS											
			Ent nutri	Parent nutri	Syst parent nutri	Prev LMWH	NG feeding	Comp bowel rest	Elimin diet	Nutrient supp	No op
Q50	Independently of drug therapy, in cases of Crohn's disease complicated by an intra-abdominal abscess, what therapeutic measures do you recommend? (B)	/	83%	44%	0%	100%	0%	0%	38%	27%	0%
	Do you confirm the breakout session consensus? (P)	/		Yes 86%				No 13%		No op 0%	

		Parent antibiotic	Oral antibiotic	No first-line radiologic draining	Radiologic drainage and adjustment of antibiotics‡	Surgical drainage† and adjustment of antibiotics‡	No op
Q51	In cases of Crohn's disease complicated by an intra-abdominal abscess, if the abscess measures ≤3 cm, what strategy do you recommend? (several answers possible) (B)	88%	16%	72%	22%	0%	0%
Do you confirm the breakout session consensus? (P) /			Yes 100%		No 0%		No op 0%
		Parent antibiotics	Oral antibiotics	No first-line radiologic draining	Radiologic drainage and adjustment of antibiotics‡	Surgical drainage† and adjustment of antibiotics‡	No op
Q52	In cases of complicated Crohn's disease with an intra-abdominal abscess, if the abscess measures more than 3 cm, what strategy do you recommend? (B)	100%	0%	0%	100%	27%	0%
Do you confirm the breakout session consensus? (P) /			Yes 100%		No 0%		No op 0%
		2 weeks	4 weeks	6 weeks	8 weeks	Until morph eval results	No op
Q53	In cases of Crohn's disease complicated by an intra-abdominal abscess, for how long do you recommend following antibiotic treatment? (B)	0%	44%	5%	5%	44%	0%
In cases of improvement under antibiotics ± radiologic drainage for Crohn's disease complicated by an intra-abdominal abscess, after how long do you recommend a morphological reevaluation with the intent of initiating a medical treatment? (B)		2 weeks 0%	3-4 weeks 88%	6 weeks 11%	8 weeks 0%		No op 0%
Do you confirm the breakout session consensus? (P) /			Yes 92%		No 7%		No op 0%

		2 weeks 0%	Until the next morph eval 94%	Beyond the next morph eval 5%	No op 0%		
Q54	In cases of Crohn's disease complicated by an intra-abdominal abscess, for how long do you recommend following the antibiotic treatment when a test is planned after 3-4 weeks?						
	Do you confirm the breakout session consensus? (P) /		Yes 100%	No 0%	No op 0%		
		MRE	Abdominopelvic CT with contrast	Ileocolonoscopy	Capsule endoscopy	US	
Q55	In cases of favorable progression under antibiotics ± radiologic drainage for Crohn's disease complicated by an intra-abdominal abscess, what tests do you recommend for a morphologic reevaluation with the goal of starting a drug treatment?	/ 100%	38%	11%	5%	16%	
	Do you confirm the breakout session consensus? (P) /		Yes 100%	No 0%	No op 0%		
		Planned surgical resection	Anti-TNF mono	Anti-TNF comb	Thiopurine	Methotrexate	
Q56	In cases of favorable progression under antibiotics ± radiologic drainage for Crohn's disease complicated by an intra-abdominal abscess and after morphologic reevaluation that shows the <u>disappearance of the abscess</u> , what treatment do you recommend?	/ 0%	27%	72%	0%	0%	
	Do you confirm the breakout session consensus? (P) /		Yes 79%	No 20%	No op 0%		
		Planned surgical resection	Anti-TNF mono	Anti-TNF comb	Ustek	Vedo	No op
Q57	In cases of favorable progression under antibiotics ± radiologic drainage for Crohn's disease complicated by an intra-abdominal abscess that <u>developed under anti-TNF</u> and after morphologic reevaluation that shows the <u>disappearance of the abscess</u> , what treatment do you recommend?	/ 66%	0%	0%	22%	0%	11%
	Do you confirm the breakout session consensus? (P) /		Yes 86%	No 13%	No op 0%		

		Planned surgical resection	Anti-TNF mono	Anti-TNF comb	Ustek	Vedo	No op
Q58	In cases of favorable progression under antibiotics ± radiologic drainage of Crohn's disease complicated by an intra-abdominal abscess that <u>developed under anti-TNF</u> and after morphologic reevaluation that shows the <u>disappearance of the abscess</u> in a patient with more than <u>50 cm of ileal disease</u> . What treatment do you recommend? (P)	V 1 7%	0%	35%	57%	0%	0%
		Planned surgical resection	2nd line drug treatment based on algorithm				No op
		V 2 R 3%			96%		0%

CROHN'S DISEASE WITH AN INTESTINAL STRICTURE

Q59	With regards to the management of Crohn's disease with a <u>symptomatic</u> intestinal stricture, do you agree to use the criteria described in the study CREOLE to stratify patients according to the probability of response to anti-TNF? (B)	/	Yes 100%			No 0%	No op 0%	
	Do you confirm the breakout session consensus? (P)	/	93%			3%	3%	
Q60	With regards to the management Crohn's disease with a <u>symptomatic</u> intestinal stricture, in a patient with a <u>high probability of responding</u> to anti-TNF, what treatment do you recommend? (B)	/	Anti-TNF mono 22%	Anti-TNF comb 88%	Surgery if stenosis >5 cm 5%	Endo dilatation if stenosis <5 cm 94%	No op 0%	
	Do you confirm the breakout session consensus? (P)	/		Yes 96%		No 3%	No op 0%	
Q61	With regards to the management of Crohn's disease with a <u>symptomatic</u> intestinal stricture, in a patient with a <u>low probability of responding</u> to anti-TNF, what treatment do you recommend if the <u>stricture is <5 cm</u> ? (B)	/	Anti-TNF mono 0%	Anti-TNF comb 38%	Surgery 44%	Endo dilatation 88%	Endo prosthesis 16%	No op 0%
	Do you confirm the breakout session consensus? (P)	/		Yes 82%		No 13%	No op 3%	

			Anti-TNF mono	Anti-TNF comb	Surgery	Endo dilatation	Endo prosthesis	No op
Q62	With regards to the management of <u>symptomatic</u> Crohn's disease with intestinal stricture, in a patient presenting with a <u>low probability of responding</u> to anti-TNF, what treatment do you recommend if the <u>stricture is >5 cm</u> ? (B)	/	0%	5%	94%	0%	0%	0%
	Do you confirm the breakout session consensus? (P)	/		Yes 93%		No 6%		No op 0%
			Anti-TNF mono	Anti-TNF comb	Surgery	Endo dilatation	Endo prosthesis	No op
Q63	With regards to the management of <u>symptomatic</u> Crohn's disease with intestinal stricture, in a patient presenting with a <u>low probability of responding</u> to anti-TNF, what treatment do you recommend if the <u>stricture is >5 cm</u> and there is <u>less than 50 cm</u> of small bowel disease? (B)	/	0%	66%	100%	0%	0%	0%
Q64	With regards to the management of <u>symptomatic</u> Crohn's disease with intestinal stricture, in a patient presenting with a <u>low probability of responding</u> to anti-TNF, what treatment do you recommend if the <u>stricture is >5 cm</u> and there is <u>more than 50 cm</u> of small bowel disease? (P)	/	0%	100%	46%	3%	3%	0%
			Biotherapy	Dilatation if <5 cm	Surgery if >5 cm	Monitoring	No op	
Q65	With regards to the management of asymptomatic Crohn's disease with an ileal stricture, what do you do? (B)	/	33%	22%	5%	77%	11%	
	Do you confirm the breakout session consensus? (P)	/		Yes 73%		No 26%	No op 0%	
POST-OPERATIVE TREATMENT OF CROHN'S DISEASE								
			None	Thiopurine	Anti-TNF	Ustek	Vedo	
Q66	Immediately postoperatively, in a patient presenting only one risk factor for recurrence, what treatment do you recommend? (P)	V 1 V 2	7% 6%	50% 65%	42% 27%	0% 0%	0% 0%	

		IS	Anti-TNF mono		Anti-TNF comb			
Q67	When lesions Rutgeerts >i2 are identified after a reevaluation by ileocolonoscopy at 6 months in a patient who has received <u>no treatment</u> , what treatment options do you suggest? (B only – no P vote)	V 1	33%		38%		27%	
		V 2 R		IS 33%		Anti-TNF 66%		
			Add IS to anti-TNF	Opt anti-TNF in mono	Opt anti-TNF in comb	Ustek in mono or comb	Vedo in mono or comb	Another anti-TNF in mono or comb
Q68	When lesions Rutgeerts >i2 are identified during a reevaluation by ileocolonoscopy at 6 months in a patient who has <u>received anti-TNF monotherapy</u> , what treatment options do you suggest? (B only – no P vote)	V 1	5%	35%	47%	11%	0%	0%
		V 2 R		Add IS to anti-TNF	Opt anti-TNF in mono or comb	Ustek in mono or comb	Vedo in mono or comb	Another anti-TNF in mono or comb
			0%		94%	5%	0%	0%
Q69	When lesions Rutgeerts >i2 are identified during an reevaluation by ileocolonoscopy at 6 months in a patient who has received anti-TNF monotherapy, do you recommend basing your decision on therapeutic drug monitoring? (P)	V 1		Yes 50%			No 50%	
		V 2		44%			56%	
Q70	In the Rutgeerts classification, do you think there is a difference between i2a (anastomotic only) and i2b? (B)	/		66%		16%		16%
	Do you confirm the breakout session consensus? (P)	/		92%		8%		0%
Q71	In an i2a patient under anti-TNF, do you modify you therapeutic approach? (B only – no P vote)	V 1		18%		37%		43%
		V 2		17%		29%		52%

Q72	In an i2b patient under anti-TNF, do you modify your therapeutic approach? (B)	/	84%	11%	3%
	Do you confirm the breakout session consensus? (P)	/	100%	0%	0%

ULCERATIVE COLITIS^s

			PK dosing of anti-TNF	Decision without PK dosing	No op		
Q73	In all the algorithms, during the course of UC, when the first course of anti-TNF has therapy has failed, what approach do you recommend? (P)	/	88%	8%	2%		
Q74	In all the algorithms, during the course of UC, when the first course of anti-TNF has therapy has failed: in the <u>absence of PK dosing</u> , in a patient presenting with a <u>primary failure</u> of the first anti-TNF, what approach do you recommend? (P)		Switch anti-TNF 6%	Vedo 75%	Ustek 0%	Tofa 10%	No op 6%
Q75	In all the algorithms, during the course of UC, when the first course of <u>subcutaneous anti-TNF</u> has therapy has failed: in the <u>absence of PK dosing</u> , in a patient presenting with a <u>primary failure</u> of the first anti-TNF, what approach do you recommend? (P)	c	Infliximab in comb 27%	Vedo 69%	Ustek 0%	Tofa 3%	No op 0%
Q76	In all the algorithms, during the course of UC, when the first course of <u>infliximab</u> has therapy has failed: in the <u>absence of PK dosing</u> , in a patient presenting with a <u>secondary failure</u> of the first anti-TNF, what approach do you recommend? (P)		Switch anti-TNF 2%	Vedo 88%	Ustek 0%	Tofa 8%	No op 0%
Q77	In all the algorithms, during the course of UC, when the first course of <u>subcutaneous anti-TNF</u> has therapy has failed: in the <u>absence of PK dosing</u> , in a patient presenting with a <u>secondary failure</u> of the first anti-TNF, what approach do you recommend? (P)	V 1 V 2	Infliximab 61%	Vedo 30%	Ustek 2%	Tofa 5%	No op 0%
			Infliximab 61%	Vedo 27%	Ustek 2%	Tofa 5%	No op 2%

			Switch anti-TNF	Vedo	Ustek	Tofa	No op
Q78	In all the algorithms, during the course of UC, when the first course of <u>infliximab</u> therapy has failed: in the <u>absence of PK dosing</u> , in a patient presenting with a <u>secondary</u> loss of response to the first anti-TNF, what approach do you recommend? (P)		5%	77%	8%	8%	0%
			Infliximab in comb	Vedo	Ustek	Tofa	No op
Q79	In all the algorithms, during the course of UC, when the first course of <u>subcutaneous</u> anti-TNF therapy has failed: in the <u>absence of PK dosing</u> , in a patient presenting with a unwanted <u>side effect, other than a paradoxical manifestation</u> , leading to its discontinuation, what approach do you recommend? (P)		8%	85%	2%	2%	0%
			Switch anti-TNF	Vedo	Ustek	Tofa	No op
Q80	In all the algorithms, during the course of UC, when the first course of <u>infliximab</u> has failed: in the <u>absence of PK dosing</u> , in a patient presenting with a unwanted <u>side effect, other than a paradoxical manifestation</u> , leading to its discontinuation, what approach do you recommend? (P)		11%	83%	5%	0%	0%
			Infliximab in comb	Vedo	Ustek	Tofa	No op
Q81	In all the algorithms, during the course of UC, when the first course of <u>subcutaneous</u> anti-TNF therapy has failed: in the <u>absence of PK dosing</u> , in a patient presenting with a <u>paradoxical manifestation</u> to the first anti-TNF and, leading to its discontinuation, what approach do you recommend? (P)	V 1	5%	47%	47%	0%	0%
		V 2	2%	40%	57%	0%	0%

		Opt of anti-TNF	Opt of anti-TNF in comb	Another anti-TNF	Another anti-TNF in comb	Vedo	Vedo in comb	Tofa	Ustek	No op	
Q82	In all the algorithms, during the course of UC, when the first course of anti-TNF therapy has failed and <u>PK dosing</u> has been performed: in cases where the <u>residual concentrations of the first anti-TNF are adequate</u> , what approach do you recommend? (P)	5%	5%	0%	0%	67%	8%	5%	5%	0%	
Q83	In all the algorithms, during the course of UC, when the first course of anti-TNF therapy has failed and <u>PK dosing</u> has been performed: in cases where the <u>residual concentrations of the first anti-TNF are low</u> and <u>anti-TNF Ab are present</u> , what approach do you recommend? (P)	V 1	2%	11%	2%	55%	19%	2%	2%	2%	0%
		V 2	0%	8%	0%	74%	11%	2%	2%	0%	0%
Q84	In all the algorithms, during the course of UC, when the first course of anti-TNF therapy has failed and <u>PK dosing</u> has been performed: in cases where the <u>residual concentrations are low</u> and anti-TNF <u>Ab are not present</u> , what approach do you recommend? (P)	/	68%	28%	0%	3%	0%	0%	0%	0%	

MODERATE TO SEVERE ACTIVE UC

		Yes	No	No op
Q85	With the exception of the parts of the algorithm that need to be voted on again by the nominal group and previously voted on, do you agree with the algorithm "moderate active UC"? (P)	66%	34%	0%

			Subcu anti-TNF in mono	Subcu anti-TNF in comb	IV anti-TNF in mono	IV anti-TNF in comb	No op			
Q86	For <u>moderate</u> active UC, in cases where treatment with <u>aminosalicylates has failed</u> and of systemic steroid <u>intolerance</u> , what treatment do you recommend? (P)	V 1	47%	26%	0%	26%	0%			
	For <u>moderate to severe</u> active UC, in cases where treatment with <u>aminosalicylates has failed</u> and of systemic steroid <u>intolerance</u> , what treatment do you recommend? (P)	V 2 R	38%	26%	0%	35%	0%			
			Subcu anti-TNF in mono	Subcu anti-TNF in comb	IV anti-TNF in mono	IV anti-TNF in com	Ustek	Tofa	Vedo	No op
Q87	For <u>moderate to severe</u> active UC, in cases where treatment with <u>aminosalicylates has failed</u> and of systemic steroid <u>intolerance</u> , what treatment would you recommend <u>if drug costs were covered by health insurance</u> ? (P)	V 1	12%	6%	0%	18%	9%	9%	45%	0%
		V 2	0%	2%	0%	8%	14%	5%	67%	0%
			IS	Subcu anti-TNF in mono	Subcu anti-TNF in comb	IV anti-TNF in mono	IV anti-TNF in comb	No op		
Q88	For moderate active UC, in cases where treatment with <u>aminosalicylates has failed</u> and of <u>steroid dependency</u> (inability to decrease treatment to less than 10 mg/d over a three month period without a relapse within 3 months of discontinuation), what treatment do you recommend when you consider <u>current drug cost reimbursement</u> ? (P)	V 1	41%	23%	17%	5%	11%	0%		
		V 2	63%	21%	6%	0%	9%	0%		

			IS	Subcu anti-TNF in mono	Subcu anti-TNF in comb	IV anti-TNF in mono	IV anti-TNF in comb	Ustek	Tofa	Vedo	No op
Q89	For moderate active UC, in cases where treatment with <u>aminosalicylates has failed</u> and of <u>steroid dependency</u> (inability to decrease treatment to less than 10 mg/d over a three month period without a relapse within 3 months of discontinuation), what treatment would you recommend if <u>drug costs were covered by health insurance?</u> (P)	V 1	45%	6%	0%	0%	0%	9%	6%	33%	0%
		V 2	50%	0%	0%	0%	3%	6%	6%	34%	0%

			IS	Subcu anti-TNF in mono	Subcu anti-TNF in comb	IV anti-TNF in mono	IV anti-TNF in comb	No op
Q90	For moderate active UC, in cases where treatment with <u>aminosalicylates has failed</u> and of <u>steroid resistance</u> , what treatment do you recommend when you consider <u>current drug cost reimbursement?</u> (P)	V 1	0%	23%	26%	8%	41%	0%
		V 2	0%	12%	24%	3%	60%	0%

			IS	Subcu anti-TNF in mono	Subcu anti-TNF in comb	IV anti-TNF in mono	IV anti-TNF in comb	Ustek	Tofa	Vedo	No op
Q91	For moderate active UC, in cases where treatment with <u>aminosalicylates has failed</u> and of <u>steroid resistance</u> , what treatment would you recommend if <u>drug costs were reimbursed?</u> (P)	V 1	0%	2%	8%	0%	42%	0%	28%	17%	0%
		V 2	0%	2%	0%	0%	57%	0%	34%	5%	0%

ACUTE SEVERE ULCERATIVE COLITIS REQUIRING HOSPITALIZATION

			5-ASA	Vedo	IS	Infliximab	Subcu anti-TNF	No op
Q92	In cases of a first flare-up of acute, severe, <u>steroid sensitive</u> colitis, what maintenance treatment do you recommend? (P)	V 1	21%	3%	37%	12%	25%	0%
		V 2	20%	0%	44%	5%	29%	0%
Q93	In cases of a first flare-up of acute, severe, <u>steroid sensitive</u> colitis, after <u>failure of aminosalicylates</u> , what maintenance treatment do you recommend? (P)	V 1	0%	3%	56%	12%	28%	0%
		V 2	0%	5%	50%	14%	29%	0%

			Vedo	IS	5-ASA	No op
Q94	In cases of acute severe <u>steroid resistant</u> colitis that went into <u>remission under cyclosporine</u> and for which <u>anti-TNF are contraindicated</u> , what do you recommend? (P)	V 1	60%	37%	0%	2%
		V 2	63%	33%	0%	3%

REFRACTORY PROCTITIS

			Yes	No	No op
Q95	Would you recommend a different approach for refractory proctitis and for a more extensive involvement? (P)	/	15%	84%	0%

POUCHITIS

			Anti-TNF	Vedo	Tofa	Ustek	No op
Q96	In cases of refractory pouchitis, what is the first line treatment for patients who are <u>anti-TNF naïve</u> ? (P)	/	93%	3%	0%	0%	3%
Q97	In cases of refractory pouchitis, before colectomy, what treatment do you recommend if previous treatment with anti-TNF? (P)	V 1	34%	43%	3%	15%	3%
		V 2	29%	52%	2%	11%	2%

			Drug treatment according to PK dosing	Surgery	No op
Q98 ^f	In the case of a patient with CD with intestinal stenosis, symptomatic and unsuccessful after treatment with anti-TNF α in optimized combination therapy, what approach do you recommend? (T)	/	27%	59%	14%
Q99 ^g	With regard to UC: if vedolizumab fails, would you recommend using tofacitinib today? (T)	/	86%	9%	6%

^aResidual levels and anti-TNF antibodies. ^bIf radiologic drainage is not possible. ^cBased on culture results. ^dThe first 4 questions were not voted on and are not reported here because they were deemed to be the same as the first 4 questions for Crohn's disease. ^e22 experts responded. ^f35 experts responded. 5-ASA, aminosalicylates; Ab, antibodies; Adv, advancement flap; B, breakout session; comb, combination therapy; CD, Crohn's disease; CT, computed tomography; EBV, Epstein Barr virus; Elim, elimination; Ent nutri, enteral nutrition such as MODULEN; Endo, endoscopic;

IS, immunosuppressant; IT, intersphincteric track; IV, intravenous; mono, monotherapy; MRE, magnetic resonance enterography; morph eval, morphologic evaluation; NG, nasogastric; No op, no opinion; Opt, optimization; P, plenary; Parent, parenteral; Parent nutri, parenteral nutrition when enteral/oral feeding is not possible; PK, pharmacokinetic; Prev LMWH, preventative low molecular weight heparin for high risk; Q, question; R, rewording; Subcu, subcutaneous; Supp, supplementation; Syst parent nutri, systematic parenteral nutrition; T, telephone; TNF, tumor necrosis factor α ; Tofa, tofacitinib; UC, ulcerative colitis; US, ultrasound; Ustek, ustekinumab; Vedo, vedolizumab; V, vote.

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Table S2. Scoring algorithm to predict response to treatment with anti-tumor necrosis factors

Prognostic clinical and radiological factors	High likelihood of treatment response if total score ≥ 3
Immunosuppressive treatment	1 point if yes
Crohn's disease obstructive score	1 point if >4
Duration obstructive symptoms	1 point if <5 weeks
Length of stricture	1 point if <12 cm
Maximal small bowel diameter proximal to stricture(s)	1 point if between 18 and 29 mm
Enhancement on delayed T1-weighted sequence	1 point if marked
Fistula	1 point if no

The latter prognostic factors are derived from the prospective CREOLE study cohort [18].

Crohn's disease obstructive score has not been validated. A Crohn's disease obstructive score > 4 corresponds to either hospitalization for intestinal obstruction and/or daily obstructive pain without benefit of dietary restriction and nausea and/or vomiting at least 3 out of 56 days. The experts agreed that evidence considering this cut-off of the Crohn's disease obstructive score was poor.

APPENDIX 2: Definitions

The definitions briefly outlined below were used for the purposes of algorithm development and are those agreed on by the ECCO evidence-based consensus on the diagnosis and management of ulcerative colitis and Crohn's disease [15-16].

- Immunomodulators were defined as a thiopurine (azathioprine, mercaptopurine) or methotrexate.
- For CD, poor prognostic factors were defined as upper gastrointestinal damage, small intestine damage, severe ileal involvement, severe rectal involvement, perianal damage, severe lesions on endoscopy (large and/or deep ulcer), and young age at diagnosis.
- Disease activity is classified as mild, moderate or severe according to Mayo Clinic score for patient with ulcerative colitis and Crohn's Disease Activity Index (CDAI) and/or Harvey-Bradshaw index (HBI) for patients with Crohn's disease. For patients with ulcerative colitis, mild disease corresponds to a Mayo Clinic score between 2 to 5 points whereas moderate to severe disease corresponds to a score > 6 . For patients with Crohn's disease, mild disease corresponds to a CDAI between 150 and 220 and/or a HBI < 8 whereas moderate disease corresponds to a CDAI between 220 and 450 and/or a HBI between 8 and 12 and severe disease corresponds to a CDAI > 450 and/or a HBI > 12 and Crohn's disease.
- Pouchitis is an inflammation of the ileal pouch created to maintain the intestine-anus continuity after a total colectomy in UC patients. It is the most common long-term complication following a total colectomy and is a chronic disease in many patients.
- Proctitis describes UC in which colonic inflammation is confined to the rectum (the upper limit of the inflammation does not go beyond the recto-sigmoid junction).

- For patients with ulcerative colitis, remission is defined as the complete resolution of symptoms and endoscopic mucosal healing (Mayo score 0 or 1, Table 1). In clinical practice, the ECCO considers that there is remission when the stool frequency is ≤ 3 bowel movements a day without bleeding or urgency. For patients with Crohn's disease, remission is defined as a CDAI < 150 and/or an HBI < 4 .
- For patients with ulcerative colitis, response is defined as clinical and endoscopic improvement, depending (for the purpose of clinical trials) on the activity index used. In general, response corresponds to $>30\%$ decrease in the Mayo activity index plus a decrease in the rectal bleeding and endoscopy subscores. For patients with Crohn's disease, response is defined as a CDAI decrease ≥ 100 points and/or a HBI decrease of n HBI ≥ 3 points.
- For patients with ulcerative colitis, relapse is defined as a flare of symptoms, either spontaneously or after medical treatment, in a patient with established ulcerative colitis or Crohn's disease who is in clinical remission. For patients with ulcerative colitis, a relapse is characterized by rectal bleeding and urgency which may be associated with an increase in stool frequency and mucosal abnormalities at sigmoidoscopy and for patients with Crohn's disease as a CDAI > 150 with an increase > 70 points and/or an HBI > 4 with an increase of > 3 points.
- Steroid-refractory colitis describes patients with active disease despite receiving up to 0.75 mg/kg/day of prednisolone over a period of four weeks.
- Steroid-dependent colitis describes patients who are either (i) unable to reduce steroids below the equivalent of 10 mg/day prednisolone within three months of starting steroid treatment, without recurrent active disease or (ii) who relapse within three months of stopping steroids.

- Immunomodulator-refractory colitis describes patients who have active disease or relapse in spite of thiopurines at an appropriate dose for at least 3 months (i.e. azathioprine 2.0–2.5 mg/kg/day or mercaptopurine 0.75–1.0 mg/kg/day in the absence of leukopenia).

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APPENDIX 3 LIST OF SUPPLEMENTARY MATERIALS

Supplementary tables

Table S1: Results of breakout and plenary votes.

Table S2: Scoring algorithm to predict response to treatment with anti-tumor necrosis factors

The latter prognostic factors are derived from the prospective CREOLE study cohort [18]. Crohn's disease obstructive score has not been validated. A Crohn's disease obstructive score > 4 corresponds to either hospitalization for intestinal obstruction and/or daily obstructive pain without benefit of dietary restriction and nausea and/or vomiting at least 3 out of 56 days. The experts agreed that evidence supporting this cut-off of the Crohn's disease obstructive score was poor.

Supplementary figures

Figure S1. Treatment algorithm for uncomplicated mildly active Crohn's disease

**Anti-TNF α is off-label for mild Crohn's disease*

Figure S2. Treatment algorithm for uncomplicated moderately active Crohn's disease without poor prognostic factor

Treatment algorithm for a first flare-up in a patient who is naive to treatment and shows right ileocolonic involvement. [†]In the absence of PK testing, ustekinumab is the alternative treatment in case of primary failure or when adverse event led to anti-TNF α discontinuation while no consensus was reached on the other scenarios.

Figure S3. Treatment algorithm for perianal Crohn's disease with a simple fistula (single, active, superficial and low fistula, without proctitis or abscess)

Figure S4. Treatment algorithm for uncomplicated severely active Crohn's disease

Treatment algorithm for a first flare-up in a patient who is naive to treatment and shows right ileocolonic involvement. †In the absence of PK testing, ustekinumab is the alternative treatment in case of primary failure or when adverse event led to anti-TNF α discontinuation while no consensus was reached on the other scenarios.

Figure S5. Treatment algorithm for moderately and severely active ulcerative colitis in the setting of unrestricted reimbursement of biologics

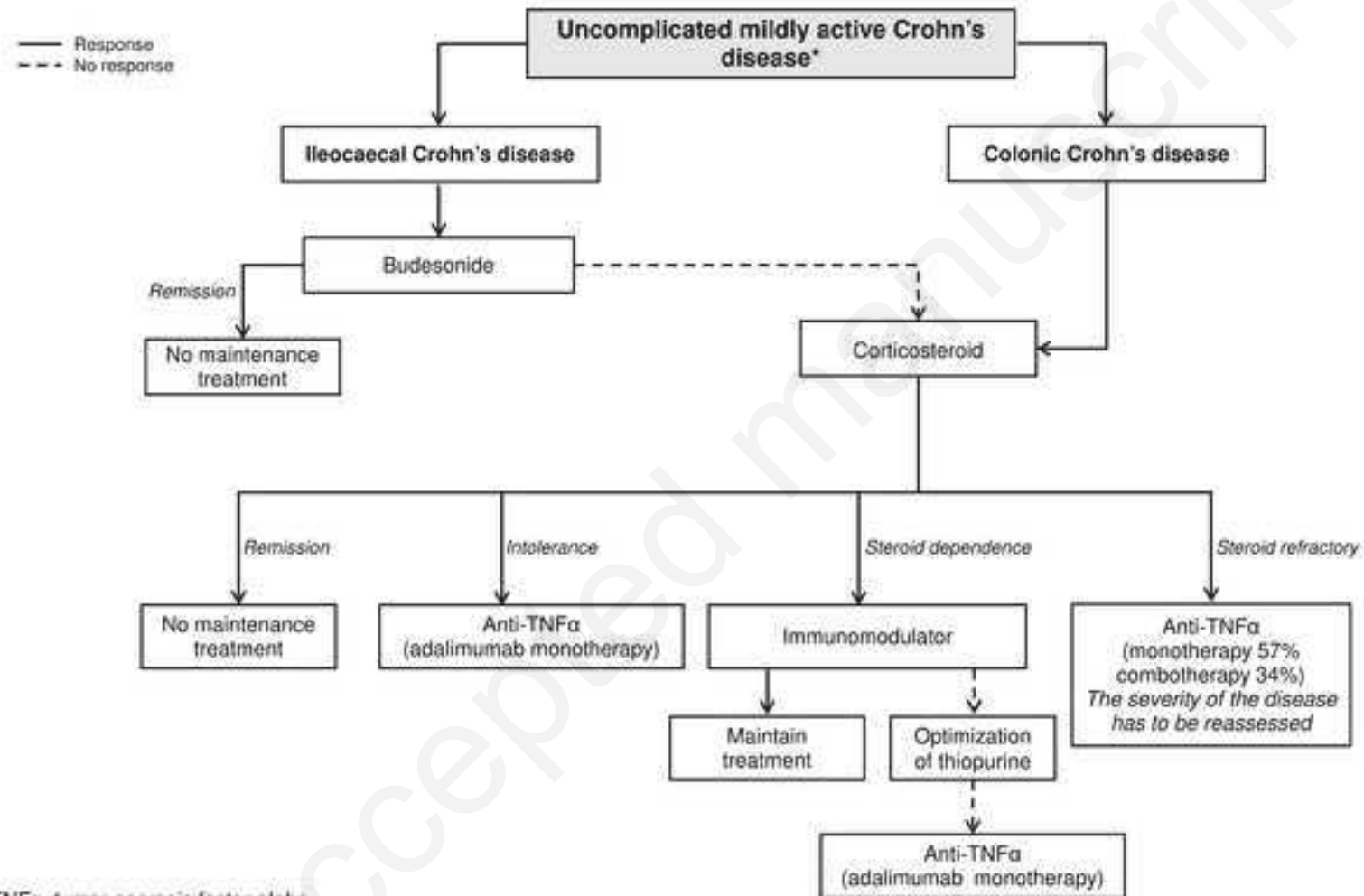
Treatment algorithm for a flare-up in adherent patients taking 1.6-2.0 g of 5-ASA and with a total Mayo score ≤ 9 . *Vedolizumab if intolerance or contraindication

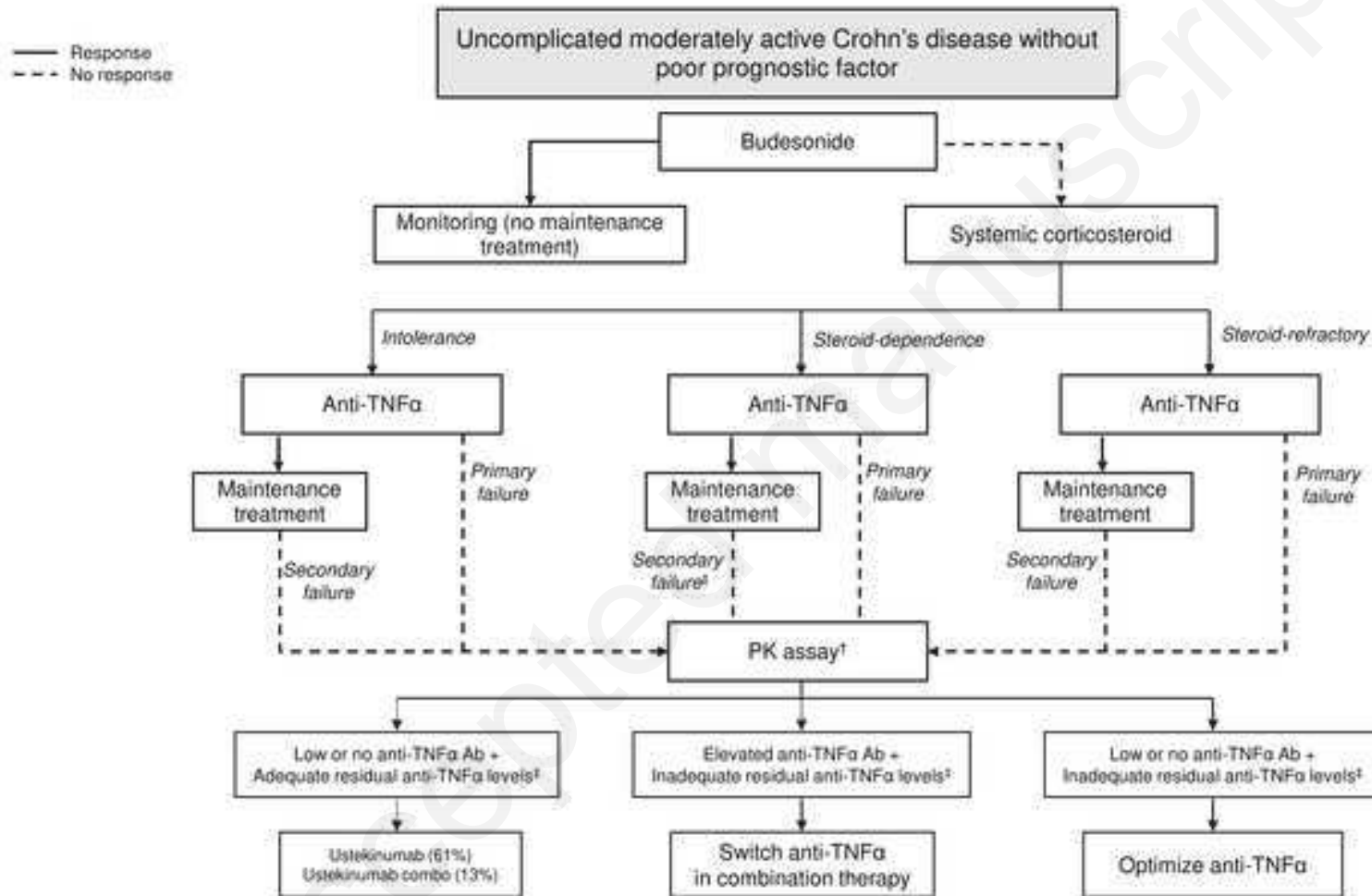
Figure S6. Treatment algorithm for acute severe ulcerative colitis requiring hospitalization

If drug treatment fails at any stage, surgery should be considered based on clinical severity.

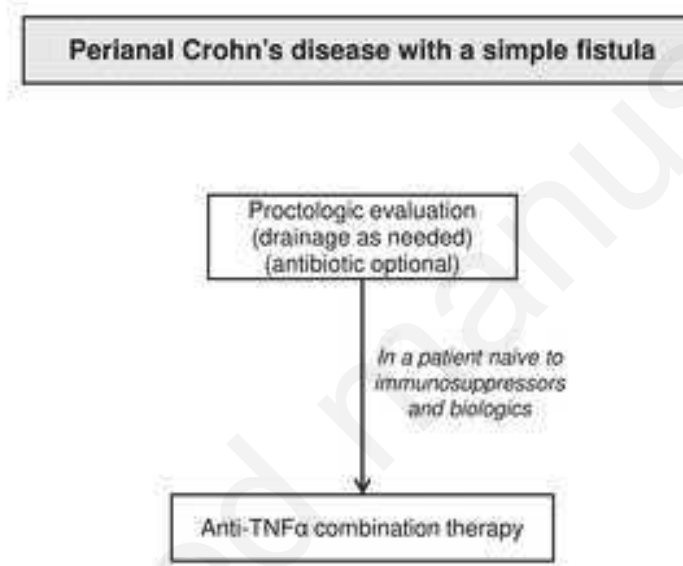
Figure S7. Treatment algorithm for refractory pouchitis

*Vedolizumab if intolerance or contraindication †Off-label

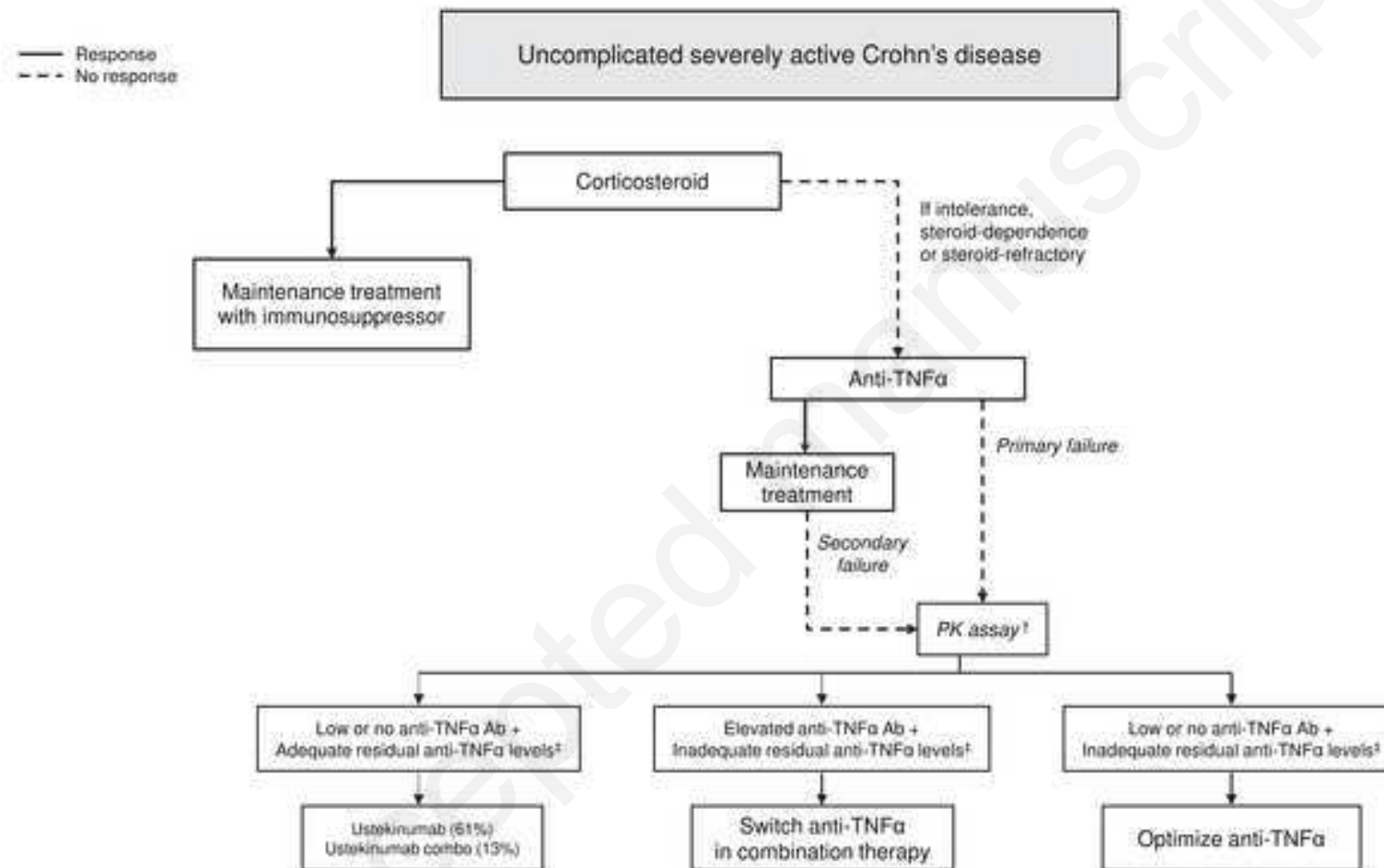




Ab, antibody; PK, pharmacokinetic; TNF α , tumor necrosis factor alpha.

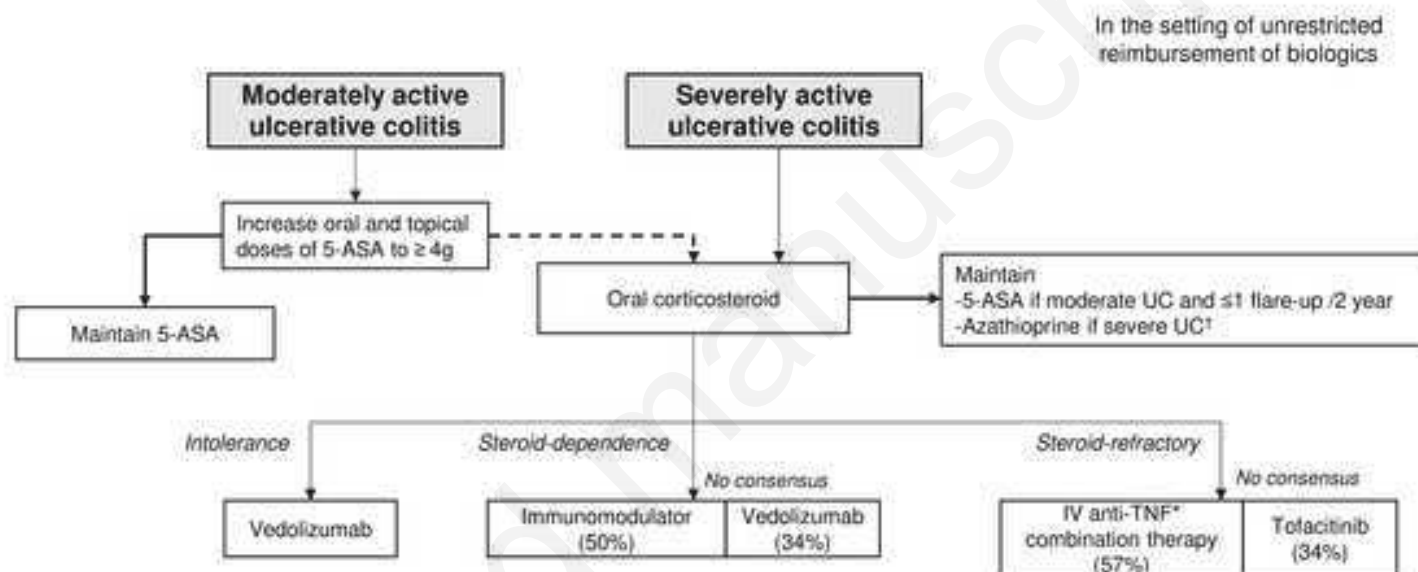


TNFα, tumor necrosis factor alpha.

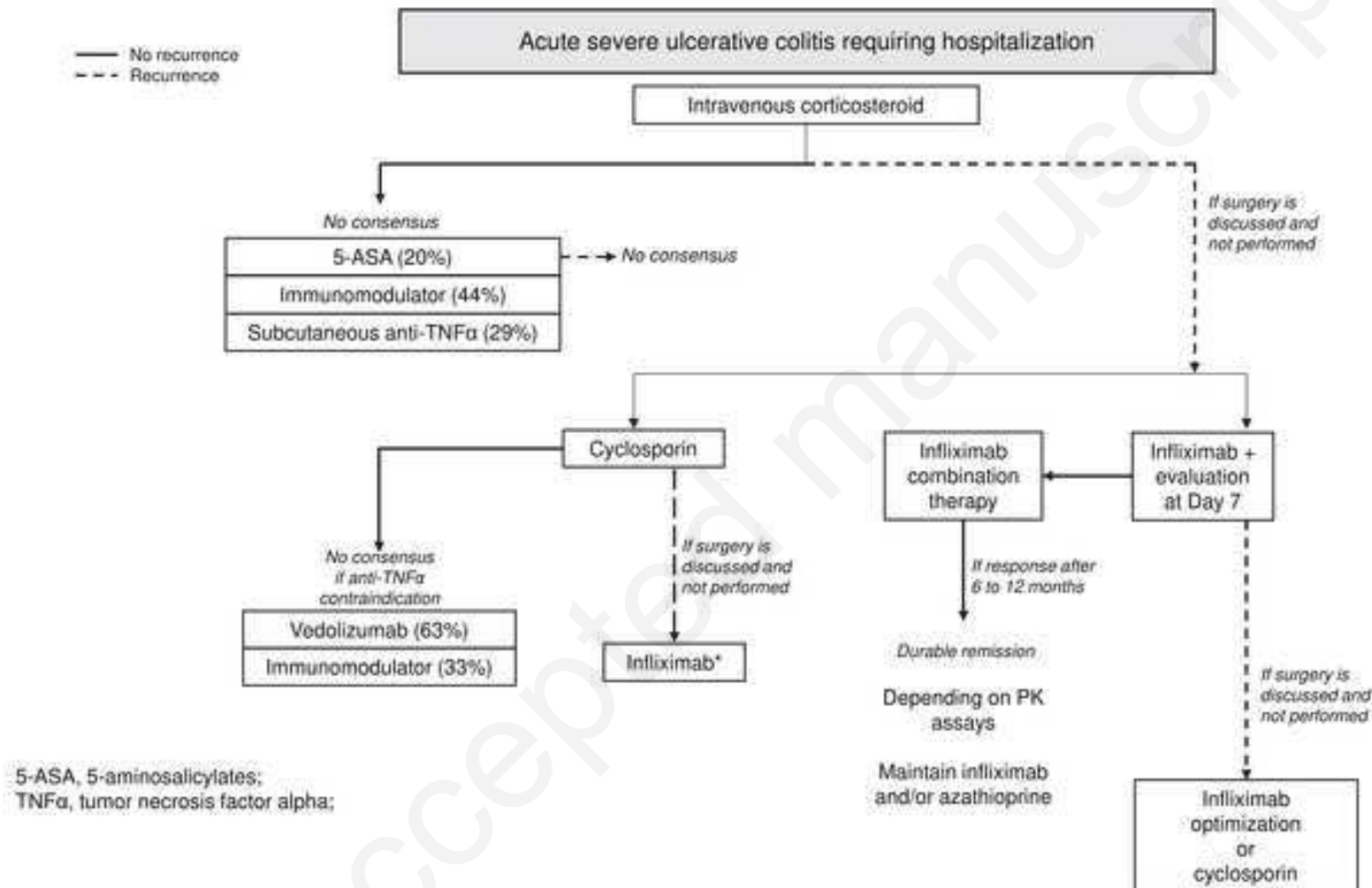


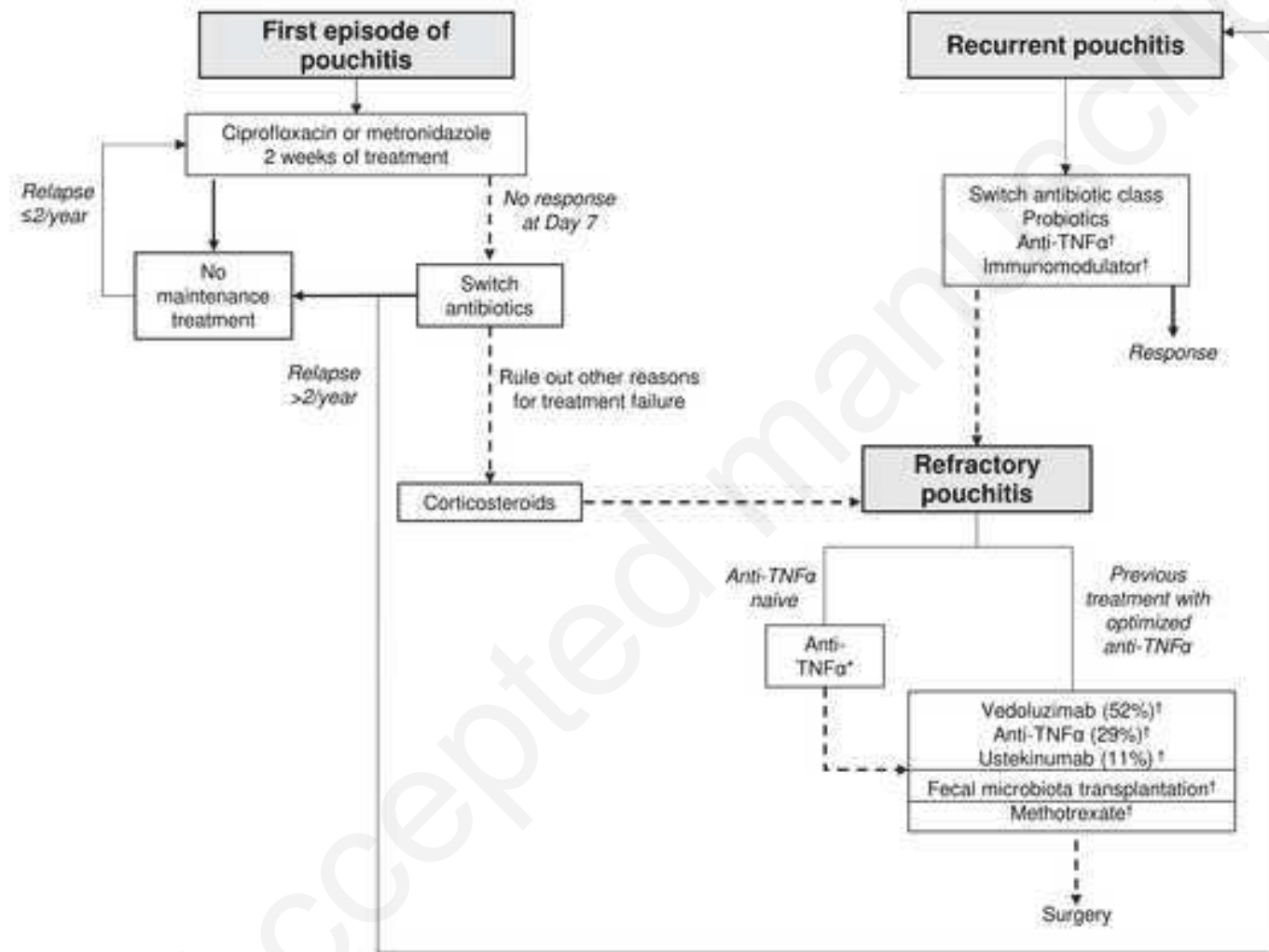
Ab, antibody; PK, pharmacokinetic; TNF α , tumor necrosis factor alpha.

— Response
 - - - No response



5-ASA, 5-aminosalicylates;
 TNF α , tumor necrosis factor alpha;





APPENDIX 4 : Discussion

The findings of this consensus meeting allowed us to update French treatment algorithms for CD and UC.

Though both ustekinumab and vedolizumab are indicated as a second-line therapy for moderate to severe CD, experts overwhelmingly chose treatment with ustekinumab over vedolizumab in instances where anti-TNF α treatment fails and PK dosing is not performed, as well as in instances when residual concentrations of anti-TNF α are adequate. This choice is supported by recent real-world studies which show good results with ustekinumab in patients who have failed anti-TNF α therapy[19–21]. It is, nonetheless, important to note that no direct comparisons between vedolizumab and ustekinumab have been made and that indirect comparisons revealed no significant differences in efficacy and safety in patients who were non-responsive or intolerant to anti-TNF α therapy[20,22]. By contrast, for UC, expert choice for vedolizumab after anti-TNF α treatment failure is likely to reflect the fact that ustekinumab is not indicated for the treatment of UC in France.

In the algorithm for CD with a complex perianal fistula, experts incorporated the need for multi-modal approaches and included strategies for patients who fail the initial strategy. In particular, experts agreed that in patients with controlled luminal disease, stem cells should be used if CD is active. Stem cell therapy is a new approach that has shown some success in randomized controlled trials[23,24]. Other approaches, such as fistulotomy, rectal advancement flap, anal fistula plug, fibrin glue, and the ligation of intersphincteric track procedure, for which there is not yet enough data in CD, were not included in the algorithm[25–27].

Experts also defined treatment failure, in patients with CD and a complex perianal fistula, as the presence of discharge/oozing, an abscess, and/or a T2 hyperintensity on the fistula track on an MRI. This definition of treatment failure/success is more limited than the one presented in a

recent publication by Sahnan et al., 2019, which included patient-reported outcomes[28]. Defining treatment outcomes is likely to be an area that will continue to develop.

In patients with CD complicated by an intra-abdominal abscess, radiologic drainage was only recommended first-line if the intra-abdominal abscess is >3 cm. Performing percutaneous drainage as a first step is meant to avoid surgery and preserve bowel length. Results of meta-analyses have shown that rescue surgery can be avoided by percutaneous drainage in up to 30% of patients[29]. However, a small study also showed that outcomes in patients who underwent drainage followed by rescue surgery were poorer than outcomes in patients who underwent immediate surgery[30].

For patients with CD complicated by an intestinal stricture, the original stratification by inflammatory/non-inflammatory characteristics was replaced by stratifications according to the presence of symptoms and to the likelihood of response to anti-TNF α treatment (Table 1). This approach, which is based on the results of the CREOLE trial, bypasses the difficulties associated with assessing inflammation and fibrosis using imaging techniques such as MRE[18]. Instead, it relies on clinical features and MRI imaging results that can be assessed reliably. The group adopted a score ≥ 3 as the cut-off for a high likelihood of response. Though this cut-off has not been tested in validation studies, it is supported by the results of the CREOLE study, which showed that 61% and 89% of patients with scores of 3 and ≥ 4 responded to treatment, respectively[18].

For patients with moderate to severe UC, the group focused on the choice of treatment when corticosteroids are not an option. The discussion was framed in the context of current drug cost reimbursement. For patients with UC, who are intolerant to corticosteroids, experts agreed that if drug reimbursement were not an issue, they would prescribe vedolizumab instead of an anti-TNF α . This choice is consistent with data from the recently published VARSITY study (N = 769), which showed that in patients with moderate to severe UC, rates of clinical remission at

52 weeks were significantly higher in the vedolizumab group than in the adalimumab group (31.3% vs 22.5%, respectively; $p = 0.006$)[31]. It is important to note, however, that rates were not significantly different in corticosteroid-free patients (12.6% vs 21.8%; $p > 0.05$). No consensus, however, was reached in cases of steroid-dependence or steroid-resistance. This is likely to reflect the fact that practices in this domain are changing rapidly and that drug reimbursement policies have limited the ability of physicians to gain experience with the prescription of tofacitinib and off-label of prescription of ustekinumab in this UC patient population.

The modifications to the refractory proctitis algorithm were largely based on clinical experience as proctitis is often an exclusion criterion in clinical trials whereas recent real-world studies support similar effectiveness of immunosuppressant and biological agents [32,33]. In a retrospective analysis of data collected from 104 patients with refractory proctitis, anti-TNF α treatment was a feasible long-term therapy[32]. After 24 months, the rates of clinical remission and mucosal healing were 50% and 60%, respectively.

For refractory pouchitis, experts considered that anti-TNF α should be the first line of treatment for patients who are naïve to anti-TNF α . This choice reflects data published in a recent systematic analysis, which showed that the pooled remission rate after treatment with biologics was 53%[34]. Opinions were, however, split when it came to treatment strategies for patients who did not respond to optimized anti-TNF α . The continued inclusion of vedolizumab as a treatment option is supported by a number of recent studies[35–38]. Ustekinumab, which was voted for by 11% of experts, has been investigated in at least one study and was shown to lead to improvement of clinical and endoscopic endpoints[38].

No specific algorithm was proposed during the consensus meeting. Regarding biosimilars, their development meets strict regulatory requirements to demonstrate that their pharmaceutical qualities, efficacy and safety are clinically equivalent to those of the reference biological agent.

In the present study, the nominal groupe technique was chosen as a formal consensus development method. This choice allowed to organize and balance group dynamics during a one-day meeting. More systematic modalities of guidelines formulation including the GRADE approach could have been useful in this setting in order to minimize the risk of letting relevant questions unanswered.

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