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STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD

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BACKGROUND: The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative of the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) has proposed treatment targets in 2015 for adult patients with inflammatory bowel disease (IBD). We aimed to update the original STRIDE statements for incorporating treatment targets in both adult and pediatric IBD. **METHODS:** Based on a systematic review of the literature and iterative surveys of 89 IOIBD members, recommendations were drafted and modified in 2 surveys and 2 voting rounds. Consensus was reached if ≥75% of participants scored the recommendation as 7 to 10 on a 10-point rating scale. **RESULTS:** In the systematic review, 11,278 manuscripts were screened, of which 435 were included. The first IOIBD survey identified the following targets as most important: clinical response and remission, endoscopic healing, and normalization of C-reactive protein/erythrocyte sedimentation rate and calprotectin. Fifteen recommendations were identified, of which 13 were endorsed. STRIDE-II confirmed STRIDE-I long-term targets of clinical remission and endoscopic healing and added absence of disability, restoration of quality of life, and normal growth in children. Symptomatic relief and normalization of serum and fecal markers have been determined as short-term targets. Transmural healing in Crohn's disease and histological healing in ulcerative colitis are not formal targets but should be assessed as measures of the remission depth. **CONCLUSIONS:** STRIDE-II encompasses evidence- and consensus-based recommendations for treat-to-target strategies in adults and children with IBD. This frameworkshould be adapted to individual patients and local resources to improve outcomes.

Keywords: Treat-to-Target; Endoscopic Healing; Biologics; Patient-Reported Outcomes; Biomarkers.

Knowledge of clinically relevant targets of individual treatments is important for improving management of patients with inflammatory bowel diseases (IBD). The Selecting Therapeutic Targets in IBD (STRIDE) program was initiated by the International Organization for the Study of IBD (IOIBD) in 2013 using an evidence-based expert consensus process. It subsequently led to a

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Abbreviations used in this paper: **AUC, area under the curve; CD, Crohn's disease; CDAI, Crohn's disease activity index; CRP, C-reactive protein; EH, endoscopic healing; ESR, erythrocyte sedimentation rate; FC, fecal calprotectin; IBD, inflammatory bowel diseases; IOIBD, International Organization for the Study of Inflammatory Bowel Disease; MES, Mayo endoscopic subscore; PRO, patient-reported outcome; QoL, quality of life; SF, stool frequency; STRIDE, Selecting Therapeutic Targets in IBD; TNF, tumor necrosis factor; UC, ulcerative colitis.**

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Timely introduction and adjustment of appropriate medications according to well-defined treatment goals is the fundamental basis of managing Crohn's disease and ulcerative colitis.

NEW FINDINGS

The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE-II) group, has updated the 2015 STRIDE recommendations and has developed 13 updated and new recommendations for treating to target in Crohn's disease and ulcerative colitis, in both adults and pediatrics.

LIMITATIONS

These consensus recommendations are based on a systematic review of the literature in a rapidly evolving medical field, but often the available evidence was insufficient to make firm conclusions.

IMPACT

STRIDE-II presents the accumulating data on available treatment targets in an intuitive and time-dependent clinically-useful algorithm in order to facilitate treatment of IBD and improving long term disease outcomes.

position statement determining therapeutic targets for IBD to be used for a "treat-to-target" clinical management strategy.[1] Since then, the rapid advent of novel biologics and small molecules has increased our ability and aspirations in reaching beyond the conventional treatment goals of STRIDE-I. In parallel, advanced diagnostic tools are becoming widely available, such as bedside bowel ultrasound and home-based measurement of fecal inflammatory biomarkers, introducing new opportunities to improve disease outcomes. Nonetheless, these have also introduced further complexity into management algorithms, such as which drugs should be used in which particular sequence, when to start, when to dose-modify, when to stop, and when to consider surgery. This complexity is inevitably associated with discussions on new treatment goals and targets, such as histological healing, transmural healing, and molecular-based measures.

The overall goal of this position statement is to update the previous STRIDE guidance on treatment outcomes by providing contemporary consensus recommendations for using the different targets over the treatment course. Specifically, we aimed to review and discuss existing and potential endpoints on the basis of recently published new evidence data and to extend the previous recommendations also to pediatric IBD. Finally, we aimed to tabulate the reviewed endpoints in an escalating algorithm along the timeline of specific treatments. Importantly, the STRIDE recommendations are focused on clinical practice rather than the clinical trial setting.

Methods

This project has been developed as part of the IOIBD endpoints cluster initiative and followed several stages to reach consensus among international IBD experts after careful review of existing evidence. A flow diagram of the various consensus procedures including the Delphi-like process and the systematic literature review is depicted in Figure 1. A steering committee of 10 IOIBD members formulated the search questions and scope. A systematic review of the literature was performed in July 2019 by the informatician of Shaare Zedek Medical Center in Jerusalem using an identical search strategy as in STRIDE-I[1] and starting from the end date of the previous search, which reviewed the literature until the end of 2013. Similar to STRIDE-I, the following potential targets were explored separately in ulcerative colitis (UC) and in Crohn's disease (CD): clinical, endoscopic, histologic, imaging, biomarkers, and patient-reported outcomes (PROs). Four bibliographic fellows (2 for CD and 2 for UC) reviewed all identified abstracts and potentially eligible studies were retrieved in full text. The fellows drafted summary reports of the evidence of each potential target addressing both accuracy and time to achieving the target following initiation of treatment. These reports were circulated to all IOIBD members before voting.

In parallel, a survey was sent to all IOIBD members asking them to state the most important targets in UC and separately in CD. The derived list was re-sent to the group to rank by order of importance on a 5-grade scale (1 as most important, 5 as least important) until no new inputs were obtained following a Delphi-like process. At each round, responses were tabulated and summarized before re-sending to the group. The participants were also asked to comment on anticipated time to achieving the different potential targets after starting specific treatments. Finally, the group was asked to comment on which specific index or measure should be used for each potential target and to recommend optimal cutoff to define achieving the target (eg, cutoff of fecal calprotectin). Two face-to-face meetings were held to discuss the concepts: one at the initiation of the project (in Rio de Janeiro, Brazil) and another after the completion of the first draft (in Havana, Cuba).

Based on the preceding, consensus statements were drafted by the steering committee, and then sent to all IOIBD members for voting along with the literature review. Identical to the methodology used in STRIDE-I, agreement was achieved if at least 75% of participants scored the statement as 7 to 10 on a 10-point rating scale (1, do not agree at all; 10, agree completely). For those statements, where no consensus was achieved, the statements were revised based on the voters' comments, followed by a second round of voting. If no agreement was reached after 2 rounds of voting, then the statement was excluded.

Results

In total, 11,278 abstracts were screened in duplicate (6223 in CD and 5055 in UC), 1005 were reviewed as full text (413 in CD and 592 in UC) and 435 manuscripts (297 in CD and 138 in UC) were eventually included in the summary of evidence (Appendices under Supplementary Material). The following reasons for exclusion included among others: inappropriate follow-up period, reviews, irrelevant targets, small case series, and language other than English.

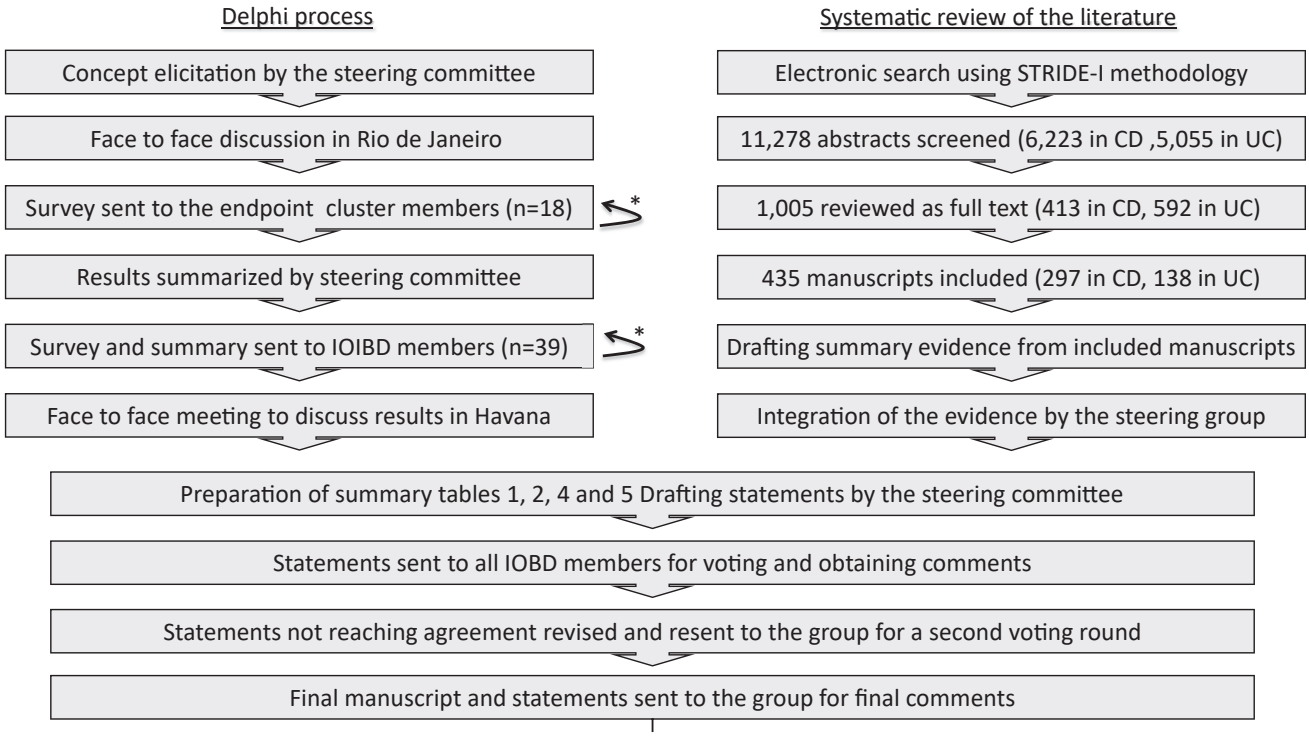

Figure 1. Flow diagram of the various consensus steps including Delphi-like process and systemic literature review.

The Delphi group suggested and ranked the potential targets (Table 1) and identified the preferred tools for capturing the identified targets with its recommended cutoff values. Supplementary Table 1 summarizes the most frequent cutoff scores suggested by the Delphi group and in the systematic review, as judged by the steering group that reviewed the evidence summaries.

Of the 89 IOIBD members, 39 (44%) participated in this concept elicitation stage. Based on the systematic review of the evidence and the Delphi-like process, recommendations were tabulated, along with the agreement rate obtained during 2 voting rounds returned by 70 (79%) of 89 IOIBD members (Table 2). Table 3 highlights the main new items in STRIDE-II compared with STRIDE-I. Those not responding were most often members who felt they do not have enough clinical experience to vote (including pathologists, a statistician, and surgeons). In addition, 3 members who participated in the voting procedures did not vote on the pediatric statements.

Abbreviated Supportive Text

Comprehensive review of the evidence may be found in the Supplementary Material. Tables of evidence according to outcomes along with risk of bias and quality of individual included studies are included as supplementary material both in CD (Supplementary Table 2) and in UC

Table 1. Ranking of Importance of Short-Term Treatment Goals in IBD (1, Most Important; 5, Least Important) (Mean Values)

Crohn's disease (n = 39)		Ulcerative colitis (n = 36)	
Goals (order of importance)	Score	Goals (order of importance)	Score
Clinical remission	1.8	Clinical remission	2.3
Endoscopic response	2.1	Clinical response	2.4
Clinical response	2.2	Endoscopic response	2.4
Normalization of CRP/ESR	2.2	Normalization of CRP/ESR	2.7
Normalization of calprotectin	2.6	Normalization of calprotectin	2.7
Transmural healing	3.1	Histological healing	2.7
Histological healing	3.4	Transmural healing	4.2

Table 2. Recommendations for Treating to Target in CD and UC by the IOIBD (70 Participated of 89 Invited)

Recommendations	Voting results	
	Strength of recommendation[c]	% votes 7–10
Clinical		
1. **Clinical response is an immediate treatment target.** Consider changing treatment if this target has not been achieved.[a]	9.0	94
2. Clinical response should be defined as: a) CD: decrease of at least 50% in PRO2 (abdominal pain and stool frequency), and in children decrease in PCDAI of at least 12.5 points and in wPCDAI at least 17.5 points b) UC: decrease of at least 50% in PRO2 (rectal bleeding and stool frequency), and in children decrease in PUCAI of at least 20 points	8.3	84
3. **Clinical remission is an intermediate (ie, medium-term) treatment target.** Consider changing treatment if this target has not been achieved.[a]	8.7	94
4. Clinical remission should be defined as: a) CD: PRO2 (abdominal pain ≤1 and stool frequency ≤3) or HBI <5; in children by PCDAI (<10 points or <7.5 excluding the height item) or wPCDAI (<12.5 points) b) UC: PRO2 (rectal bleeding=0 and stool frequency=0) or partial Mayo (<3 and no score >1), and in children PUCAI <10 points	8.5	81
5. Clinical response or remission are insufficient to be used as long term treatment targets	8.3	80
6. **In children, restoration of normal growth is a long-term treatment** target. Consider changing treatment if this target has not been achieved.	9.3	98
Endoscopic and transmural assessment		
7. **Endoscopic healing is a long-term target.** Consider changing treatment if this target has not been achieved.	8.7	87
8. Assessment of endoscopic healing can be achieved by sigmoidoscopy or colonoscopy. When not feasible, alternatives in CD can be capsule endoscopy or balloon enteroscopy.	8.3	86
9. Endoscopic healing should be measured by: **a**) CD: SES-CD <3 points or absence of ulcerations (e.g. SES-CD ulceration subscores = 0) b) UC: Mayo endoscopic subscore = 0 points, or UCEIS ≤1 points	8.5	85
10. Histologic remission is not a treatment-target in either CD or UC. Nonetheless, in UC it could be used as an adjunct to endoscopic remission to represent a deeper level of healing.	7.7	80
11. Transmural healing (assessed by CTE, MRE, or bowel ultrasound) is not a treatment-target in either CD or UC. Nonetheless, in CD it should be used as an adjunct to endoscopic remission to represent a deeper level of healing.	7.5	77
Biomarkers		
12. **Normalization of CRP (to values under the upper limit of normal) and fecal calprotectin (to 100–250 μg/g)[b] is an intermediate treatment target in UC and CD.** Consider changing treatment if this target has not been achieved.	8.2	80

(Supplementary Table 3). The following represents a succinct summary.

Crohn's Disease

Endoscopic healing. It is widely accepted that treating to the target of endoscopic healing (EH) is associated with improved long-term outcomes and may reduce the risk of bowel damage.[2] Mucosal inflammation, even in the presence of clinical remission, is associated with long-term disease-related complications, flares, and surgeries.[3] Indeed, EH was selected as the primary treatment target in the original STRIDE initiative and was also scored highest in our Delphi-like process as a

Table 2. Continued

Recommendations	Voting results: Strength of recommendation[c]	Voting results: % votes 7–10
Quality of life and disability		
13. **Absence of disability and normalized health-related quality of life are long-term treatment targets.** Consider changing treatment if this target has not been achieved.	7.7	75

[a]Time to achieving the target vary based on therapy and mechanism of action (Table 3).
[b]The cutoff value of fecal calprotectin is dependent on the desired outcome. Lower thresholds (eg, <100 μg/g) have been proposed for reflecting deep healing (both endoscopic and transmural healing) or histological healing, whereas higher values (eg, <250 μg/g) reflect less stringent outcomes (eg, MES of 0 or 1 in UC).
[c]Calculated as the mean score of all responders (on a scale of 1–10 where "10" demotes complete agreement and "1" complete disagreement).
NOTE. The following 2 statements were removed after the second voting given low endorsement: "Absence of health-related fatigue is a long-term treatment target" (47% agreement) and "Absence of health-related anxiety and depression is a long-term treatment target" (37% agreement).
CTE, computerized tomography enterography; MRE, magnetic resonance enterography; PRO, patient reported outcome; PUCAI, pediatric UC activity index; SES-CD, simple endoscopic score in CD; UCEIS, endoscopic index of severity; wPCDAI, weight pediatric CD activity index.

long-term target (Table 1). It has been emphasized by the Delphi group that EH is suitable for the longer term, whereas in the short term, endoscopic response may suffice. There is a lack of consistency in defining thresholds for endoscopic response and remission. In the systematic review and the Delphi group, the following definitions prevailed: for endoscopic response a >50% decrease in the SES-CD (simple endoscopic score in CD) or CDEIS (endoscopic index of severity) and for endoscopic remission SES-CD ≤2 points or CDEIS <3 and lack of ulcerations (ie, any ulcerations, including aphthous ulcers) (Supplementary Table 1).

Clinical indices. Clinical symptoms are poorly correlated with degree of mucosal inflammation in CD and it is not infrequent to discover significant mucosal inflammation during complete clinical remission.[4] The CALM trial demonstrated that treatment escalation based on symptoms alone led to a lower rate of EH than guiding treatment by a composite strategy of clinical and biochemical activity assessment (fecal calprotectin [FC] and C-reactive protein [CRP]).[5] On the other hand, and not surprisingly, patients identify clinical symptoms as the most important parameters to treat. Accordingly, most experts in the Delphi group considered symptom relief (clinical response and then clinical remission) as important short-term and intermediate treatment goal in IBD (Table 1). Taken together, clinical remission should be considered as a mandatory intermediate target but in addition, objective improvement in measures of inflammation must subsequently be shown.

When considering signs and symptoms, PROs are becoming the standard of measure. Different perceptions of patients and their physicians on the condition often lead to misalignment in estimating health concerns.[6] Due to the strong correlation of PROs with patient well-being, this target should be assessed early and frequently throughout the disease course. Empirically derived PROs have been developed to satisfy regulatory requirements. The most commonly used PRO in adult CD is the PRO2, which is the sum of the weighted daily stool frequency (SF) and abdominal pain items from the CDAI.[7] PRO2 is the only currently available PRO measures that is simple enough for

Table 3. What Is New in STRIDE-II?

- The STRIDE group, under the auspices of the IOIBD, has updated the 2015 first reported STRIDE recommendations and has developed 13 updated and new recommendations for treating to target in CD and UC (STRIDE-II recommendations).
- Time to expected response, remission, and endoscopic healing with the different treatments have been introduced for incorporating the treatment targets.
- STRIDE-II added clinical response and remission as well as normalization of CRP as immediate and short-term targets.
- Reduction of FC to an acceptable range has been added as a formal intermediate treatment target.
- Pediatric targets, reflected by different measuring scales and the addition of restoration of normal growth as a formal treatment target have been added.
- Restoration of QoL and absence of disability have been added to EH as long-term targets.
- Transmural healing in CD and histological healing in UC have been newly recognized as important adjunctive measures but were not endorsed as formal new treatment targets.

clinical use and has been explored in several studies. Once more clinically oriented tools will be developed the recommendations may be adapted. Cutoff values of remission are suggested in Supplementary Table 1 based on the review of the literature and the Delphi results.

Serum and fecal inflammatory biomarkers. FC and CRP are the 2 most widely used biomarkers in IBD, with FC generally outperforming CRP. A recent meta-analysis summarized the performance of FC when using all available data, whatever the cutoff values used, showed pooled sensitivity of 82%, specificity of 72% and area under the curve (AUC) of 0.84 for FC in reflecting endoscopic disease activity in CD.[8] The evidence (detailed in the Supplementary Material) suggests that a reduction in FC, as well as a target below a certain threshold, have clear prognostic significance, justifying utilization of this biomarker as a treatment target. FC predicted long-term clinical outcomes when measured 12 weeks after initiating medical treatment.[9] A meta-analysis of 6 studies indicated that patients with elevated FC had 53% to 83% probability of relapse during the subsequent 2 to 3 months.[10] Our systematic review of the evidence and the Delphi-like process both supported using an FC cutoff value of 150 μg/g to identify EH (Supplementary Table 4). Nonetheless, given the low reliability of FC, the range of 100 to 250 μg/g is considered a gray zone, whereas even values $<$600 μg/g can still be associated with minimal inflammation. FC determined at time of anti–tumor necrosis factor (TNF) discontinuation predicted subsequent relapse at cutoff values 50 to 150 μg/g.[11–13] In a small anti-TNF study, FC $<$300 μg/g or 50% decrease at week 12 was associated with corticosteroid-free remission at 1 year.[14] A pediatric study showed that FC $<$500 or decrease $>$50% had predictive value for inactive endoscopic disease.[15] Other studies support that FC at week 12 to 14 following anti-TNF initiation is predictive of clinical remission, as well as EH, with cutoff values of 82 to 168 μg/g.[16,17]

Whereas FC has high sensitivity and lower specificity in identifying mucosal inflammation, CRP has the opposite characteristics: it has higher specificity but low sensitivity.[18] Thus, normal CRP after initiating treatment should be considered as a minimal obligatory short- to medium-term target but insufficient for the longer term. Low CRP values are associated with reduced risk of clinical relapse, with AUC of 0.70 to 0.72.[19–22] On the other side, high CRP values determined at time of anti-TNF discontinuation are associated with higher risk of relapse.[23,24] CRP normalization at 8 to 14 weeks after treatment predicts remission at 1 year,[14,25,26] as well as anti-TNF success at 2 years.[27] In a post hoc analysis of the ACCENT trial, week 14 CRP decrease by $\geq$60% predicted durable sustained response to infliximab with AUC 0.75.[28] Similarly, CRP $>$5 mg/dL at week 22 has been shown to predict secondary loss of response to anti-TNF.[29]

Transmural healing. Ileocolonoscopy has a limited role in tight monitoring strategies because it cannot be performed repeatedly. In addition, mucosal assessments may not be feasible in certain scenarios, such as in proximal small bowel disease and, as shown in the prospective ImageKids study of 240 children with CD, mismatch between endoscopic healing and transmural healing is not uncommon.[30] Given the complementary nature of both modalities, cross-sectional imaging, using ultrasound, contrast-enhanced computed tomography, and magnetic resonance enterography, has been increasingly used in addition to endoscopic assessments. The use of bedside bowel ultrasound has revolutionized our ability to assess the degree of inflammation in IBD.[31] It allows frequent assessments and has the advantage of assessing the entire gastrointestinal tract, including transmural healing. Numerous studies have confirmed the usefulness of cross-sectional imaging modalities in detecting therapy-related changes, a feature mandatory for any treatment target (see Supplementary Material). However, given the limited ability of the currently available treatments to achieve transmural healing, the IOIBD Delphi group agreed that the use of imaging should be considered as an adjuvant assessment rather than a formal treatment target.

Histology. Histologic remission has been increasingly studied in recent years with the assumption that the deeper the remission, the better the outcomes. However, the Delphi-like survey rated histology low, indicating that it should not be included as a formal treatment target in CD. Some of the reasons mentioned are lack of well-validated, reliable, and accepted measuring tool (a notion that became evident in our systematic review), and insufficient data to justify intensified immunosuppressant medications to reach this expanded goal. Another reason is that currently available treatments have limited effectiveness in inducing histologic remission, especially in CD. Indeed, in one study, only 13% of patients with CD treated with long-term anti-TNF regimens had achieved histologic remission.[32]

Well-being (relevant to both CD and UC section later in this article). Health-related well-being concepts correlate only modestly with markers of disease activity, such as fecal calprotectin,[33] as they tap a separate aspect of the disease. Supporting the notion that "the patient is at the center," well-being domains must thus be frequently assessed during the disease course, independently of objective markers of inflammation, even when not considered formal targets. The recent LIR!C trial, which compared surgical resection with anti-TNF in CD used quality of life (QoL) as its primary outcome, highlighting the increasing importance attributed to this endpoint.[34] Unexpressed illness perceptions of IBD are strongly associated with the patients' QoL.[6] Higher QoL was found in patients undergoing laparoscopic surgery compared with open surgery, and patients with a stoma have worse health-related QoL.[35,36] Sustained poor QoL is associated with increased risk of opiate use in UC.[37] Restoration of QoL at week 14 after initiation of therapy was associated with sustained remission at 1 year.[38]

Patients with CD showed overall reduced disability compared with patients with UC.[39] Mood disorders are of major concern in IBD, as they appear to be associated with disability. In a cross-sectional study of 200 patients with IBD, 105 of whom had UC, 27% had anxiety or depression, which was associated with worse scores on the IBD

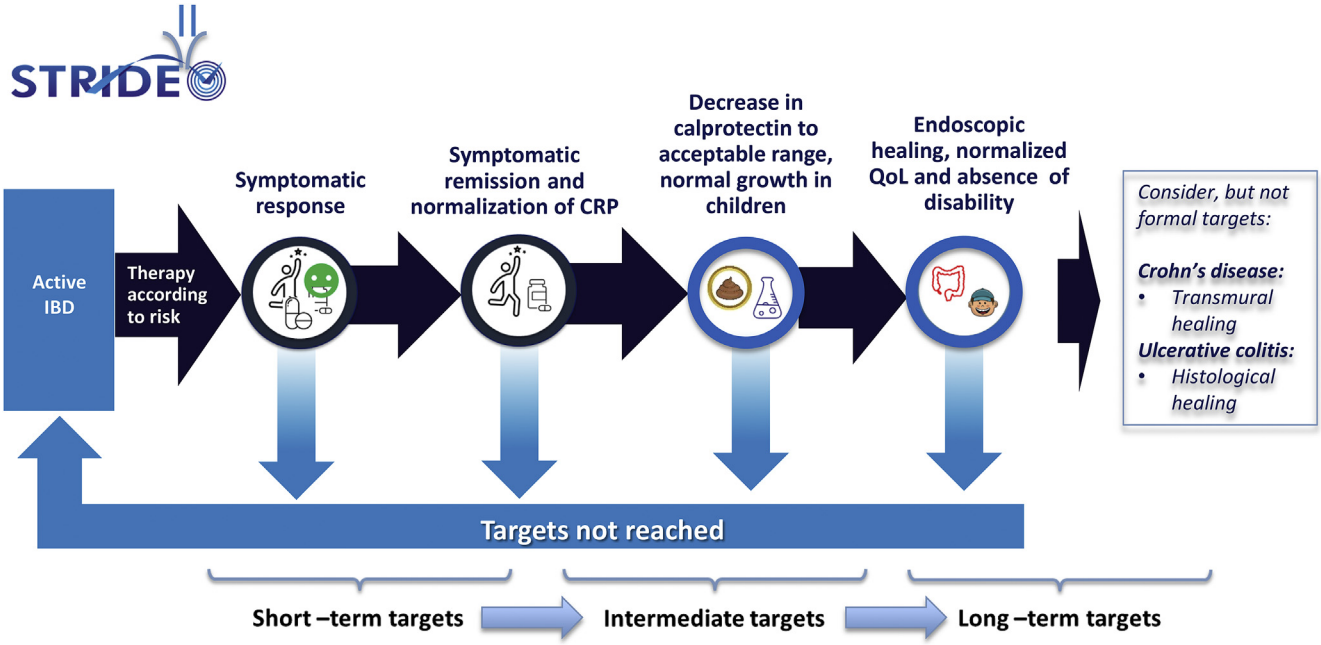

Figure 2. Treatment targets in CD and UC.

disability index (IBD-DI).[40] In the PRO Measurement Information System (PROMIS) study of Internet-based collection of PROs, 6689 patients with CD and 3945 with UC reported more depression, anxiety, fatigue, sleep disturbance, and pain interference than the general population, as well as less social satisfaction.[41] A Japanese study looking at sexual function after ileal pouch anal anastomosis found relatively poor sexual activity postoperatively, whereas another study did not.[42,43] Fatigue was reported in 26% of 220 patients with IBD and associated with poor QoL, disability, and depression, even when controlling for disease activity.[44]

The IOIBD Delphi group voted to include restoration of QoL and reduction in disability as formal long-term treatment targets irrespective of other objective markers of inflammation. One possible implication of this statement is that a given treatment impairing QoL should be revisited even if deep healing has been achieved with this treatment. Because EH is also a treatment target, shared decision making with the patient is of utmost importance to balance the different targets, as not always all can be achieved. Nonetheless, QoL (including food-related QoL), disability, fatigue, depression, anxiety, sexual dysfunction, and body image must all be heavily factored in the regular assessment of patients with IBD (see Supplementary Material for details).

"The more the merrier": Combining targets as a strategy to improve patient outcomes. The individual merit of each of the aforementioned targets can be further enhanced by the development and use of composite endpoints involving several targets instead of individual ones. A post hoc analysis of the CALM trial demonstrated that the combination of CRP with FC is superior to FC alone in predicting endoscopic healing after 48 weeks of adalimumab treatment.[45] This has also been shown in the pediatric ImageKids cohort using the MINI (Mucosal-Inflammation-Non-Invasively)-index.[46] The MINI index performed better in reflecting endoscopic inflammation when it included CRP in addition to FC alone, especially in the gray FC values zone of 100 to 600 μg/g. A similar study in adults showed that adding CRP to FC to the Utrecht Activity Index had a superior performance than using FC alone.[47] Another retrospective study reported improved accuracy in diagnosing CD among 128 children with elevated FC levels by considering also erythrocyte sedimentation rate (ESR), CRP, and albumin.[48] In a small pediatric study, FC $<$500 μg/g, CRP $<$5 mg/dL, and pediatric CDAI (PCDAI) $<$10 had excellent negative likelihood ratio (0.2) for endoscopically inactive disease.[15]

In other studies, the addition of CDAI to FC improved area under the receiver operating characteristic curve for detecting mucosal inflammation from 0.88 to 0.96,[49] and the addition of CRP to FC improved specificity from 87% to 100%.[20] Similarly, one study showed that a CDAI-based PRO plus FC and CRP (ie, PRO+) performed better than PRO alone (area under the receiver operating characteristic curve 0.81 vs 0.56 for SES-CD $\geq$7).[50] A pediatric prospective study showed that the combination of weighted PCDAI (wPCDAI) with FC was superior to either alone in predicting long-term deep healing following infliximab treatment.[51] Additional studies support the notion that the combination of multiple targets improves the overall test performance.[52–54] Indeed, in a post hoc analysis of the EXTEND trial, achieving combined endpoint of lack of ulcerations on endoscopic evaluation and clinical remission (ie, deep remission) was associated with fewer treatment adjustments, hospitalizations, surgeries, and better QoL, compared with achieving EH alone.[55] Voiosu et al[56] showed prospectively that the combination of FC $>$30 μg/g and low QoL

Table 4. Time (Mean Number of Weeks) Required for Achieving the Goal After Starting Treatment for CD (n = 39) and UC (n = 36), Based on the Delphi-like Process and the Systematic Review of the Evidence

	Clinical response	Clinical remission	Norm of CRP/ESR	Decrease of FC[a]	EH
Crohn's disease					
Oral steroids/EEN	2	4	5	8	13
Budesonide	3	6	8	10	15
Thiopurines	11	15	15	17	24
Methotrexate	9	14	14	15	24
Anti-TNF	2–4	4–6	9	11	17
Vedolizumab	11	17	15	17	24
Ustekinumab	7	13	11	14	19
Ulcerative colitis					
Oral 5-ASA	4	8	8	10	13
Oral Steroids	2	2	5	8	11
Locally active steroids[b]	3	8	8	9	13
Thiopurines	11	15	15	15	20
Adalimumab	6	11	10	12	14
Infliximab	5	10	9	11	13
Vedolizumab	9	14	14	15	18
Tofacitinib	6	11	9	11	14

NOTE. Given the paucity of high-quality scientific data, the data in this table should be considered merely as a rough estimate of experts' opinion.

5ASA, 5-aminosalicylic acid; EEN, exclusive enteral nutrition.

[a]Below a desired threshold outlined in the text and Supplementary Table 4.

[b]Beclomethasone Diproprionate (BDP), Budesonide MMX.

(Short Inflammatory Bowel Disease Questionnaire [SIBDQ] >6) had greater specificity for active endoscopic disease than FC alone in patients who were in clinical remission. This increasing body of evidence supports the multiple targets approach as adopted in the new STRIDE-II recommendations (Figure 1).

Ulcerative Colitis

Clinical indices. Unlike in CD, clinical symptoms are well correlated with endoscopic degree of inflammation. Normal SF and absence of rectal bleeding are the main clinical targets in patients with UC. The absence of diarrhea and blood is an independent predictor of relapse-free survival, colectomy-free survival, and long-term outcomes.[57] The Mayo score and the partial Mayo score are the most frequently used clinical scores in adult clinical trials,[1] but clinical remission by the Mayo scores allows streaks of blood in the stool, which cannot be considered as complete remission. Complete clinical remission with normal SF and no blood or abdominal pain is associated with EH or near EH (Mayo Endoscopic Subscore [MES] of 0 or 1) in approximately 80% to 90% of patients (see Supplementary Material). In children, the most widely used index is the pediatric UC activity index (PUCAI), a 6-item clinical index, highly correlated with endoscopic appearance and predicts clinically important outcomes.[58–61] Thus, clinical response and remission are valuable short-term targets in UC, much more than in CD. In adults, the PRO2 has become the current standard for assessing symptoms in UC. It is composed of the 2 subjective items of the Mayo score, namely SF and rectal bleeding. Although it is now widely used, its correlation with endoscopic healing is moderate to high and thus being used in conjunction with an objective measure of inflammation.[62,63] The absence of rectal bleeding is more sensitive than normalization of SF.[63]

Endoscopic healing. In STRIDE-I, EH was the preferred long-term treatment goal in UC.[1] The current Delphi-like survey and the systematic review of the literature performed since STRIDE-I did not identify new evidence to change this conclusion. Several endoscopic scores have been explored in UC but the MES and Ulcerative Colitis Endoscopic Index of Severity are the most studied.[64] EH is commonly defined as MES ≤1, but complete endoscopic

Table 5. Gaps in Knowledge and Areas for Future Research

• PROs
o Gap: PRO2 for both CD and UC have been formulated from existing measures as a temporary measure to meet the regulatory agencies' requirement in clinical trials. They were not a product of stringent psychometric development and evaluation.
o Future research: PROs should be developed aiming at use in clinical practice, with high reliability, face validity, construct validity, responsiveness, and feasibility.
• HRQOL
o Gap: Current measuring tools were developed as research tools and are too cumbersome for using in routine clinical practice.
o Future research: Development and validation of a shorter measuring tool for everyday use.
• Histology and transmural healing
o Gap: It is still unclear whether these are significant enough to justify the increased utilization of medical treatment to achieve these extended endpoints. This is the reason why they were not selected as formal treatment target for STRIDE-II.
o Future research: More prospective studies, preferably randomized-controlled, are needed to explore the number-needed-to treat to these targets for achieving superior clinical outcomes.
• Endoscopic healing
o Gap: The thresholds to define remission or response remain un-validated.
o Future research: More studies are needed to link the optimal thresholds with specific outcomes

HRQOL, health related quality of life.

healing (ie, MES 0) is associated with superior disease outcomes (see Supplementary Material for details).

Serum and fecal inflammatory biomarkers. The ease and low cost of noninvasive biomarkers, nicely position CRP and FC to be performed post induction and regularly throughout patients' disease course. CRP, ESR, and FC can predict endoscopic activity, although FC appears to be much more sensitive than either CRP or ESR in UC.[1,65,66] CRP and ESR levels modestly correlate with endoscopic activity in UC ($r \sim 0.5$ for CRP and ~ 0.4 for ESR); the sensitivity/specificity values are 51% to 53%/69% to 71% and 85% to 87%/63% to 66%, respectively[67]).

The high correlation of FC with clinical disease activity, endoscopic, and histological indices has been described in children and in adults.[68–73] Few studies have indicated that calprotectin can be useful in predicting relapses in UC,[70,74,75] but its added predictive value while in complete clinical remission is less clear. Two measurements of FC, 1 month apart, may best predict flares before clinical symptoms.[76] In the post induction phase of therapy, FC has been associated with 83% sensitivity and 74% specificity (cutoff $\leq$168 μg/g) for predicting a sustained clinical response at 1 year and a 79% sensitivity and a 57% specificity (cutoff $\leq$121 μg/g) for predicting endoscopic healing in UC.[17,77]

Histology. Histologic activity has emerged as an aspirational therapeutic goal in the prevention of long-term complications.[78] Indeed, the added benefit of histological remission over macroscopic EH in predicting long-term remission[78–82] and cancer prevention[83] has been well presented in UC. However, histologic remission is a high hurdle to achieve, while the number needed to treat for achieving one clinically significant outcome over EH alone or even FC is unknown and likely quite high. This must be balanced against the cost and risks of the required therapies to achieve this extended goal. Indeed, only one-third of patients with UC with EH in the ACT trials had histologic remission.[84] Furthermore, a large study showed concordance between macroscopic and microscopic degree of inflammation in UC only for the extreme groups of those in remission and those with severe disease, alluding to poor interobserver reliability.[85] It is for these reasons and for lack of standardized reporting methods, that histologic healing is still limited in its clinical utility and rated low by the Delphi group as an independent treatment target.[86]

Cross-sectional assessment. Bowel ultrasound is a noninvasive tool to assess disease activity in UC with fair interrater reliability. Colonic wall thickening, Doppler blood flow, hypoechogenic wall pattern, and the presence of lymph nodes were all associated with endoscopic activity of disease according to Mayo score.[87] Although not a formal target, the increasing use of bedside ultrasound makes this tool a valuable means to assess the bowel inflammation intuitively also in UC.

Treat-to-Target Suggested Algorithm

Based on the systematic review of the literature and the results of the IOIBD survey, we have suggested a simple algorithm for using the selected short-, medium-, and long-term targets, while endorsing also the 2 outlined in STRIDE-1: EH with clinical remission (Figure 2). For the first time, QoL and disability have been selected as formal long-term targets and inflammatory biomarkers as intermediate practical measures. The timing of reaching the goals is dependent on the specific treatment and, to that end, the Delphi group and the systematic review determined how many weeks should be allowed between the onset of

treatments and assessing these targets. The systematic review of the literature was done while a priori focusing also on this question (Supplementary Material). The steering committee tabulated estimated time to response based on judgmental estimation of the results obtained from both the IOIBD survey and the systematic review (Table 4). The table was not voted on, as it portrays cumulative evidence and expert opinion rather than practice recommendations.

Conclusion

STRIDE-II confirms that the most important long-term achievable treatment targets for patients with IBD are clinical remission, EH, restoration of QoL, and absence of disability. Symptomatic relief has been determined as an immediate goal, acknowledging that this is rated highest by patients in studies. With the accumulating clinical evidence, serum and fecal biomarkers are endorsed as intermediate medium-term feasible treatment goals, meaning that at times treatment could be revisited solely based on these tests, to facilitate care in the clinic setting (Table 3).

Although the ultimate target may be complete deep healing (ie, clinical remission + complete endoscopic and histological healing + transmural healing), more research is needed to determine the incremental gain derived from this goal, and whether this gain is worth the therapy-related risks and the costs. Moreover, this ultimate expanded target is not achievable in most patients using currently available treatments. Nonetheless, transmural healing in CD and histological healing in UC are becoming important in adjuvant assessment of the depth of treatment response. For instance, bedside bowel ultrasound performed as point of care is gradually changing the landscape of repeated assessment of treatment response, given its noninvasive character and high feasibility. It should be emphasized that the algorithm is a general scheme and the scientific evidence on which it is based has major gaps (Table 5). Clinical decisions involve a complex analysis of the patient's condition and available courses of action and thus clinical considerations may require decisions that vary from the suggested algorithm. For instance, elevated serum or fecal biomarkers at times may suffice to revise treatment and at other times require endoscopic confirmation to document the extent and severity of the disease before major treatment changes. Nonetheless, STRIDE-II has attempted to collate the accumulating data on available treatment targets in an intuitive and clinically useful algorithm to facilitate long-term outcome of IBD.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online, version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.12.031.

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Conflict of Interest
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