

## AMANDA RICCIUTO MD, PHD, FRCPC



Amanda Ricciuto is a paediatric gastroenterologist and clinician-investigator at The Hospital for Sick Children (SickKids), in Toronto. She completed her paediatric GI fellowship at SickKids, including subspecialty training in paediatric inflammatory bowel disease (IBD). She holds a PhD in Clinical Epidemiology from the University of Toronto. Her primary areas of research are IBD-associated primary sclerosing cholangitis (PSC) and precision medicine in paediatric IBD, including examining predictors of treatment response.

### Affiliations:

Division of Gastroenterology, Hepatology and Nutrition, SickKids, Toronto, Ontario

## BRINGING STRIDE2 TO LIFE IN CLINICAL PRACTICE

### STRIDE2 – A Narrative Review

STRIDE (Selecting Therapeutic Targets in Inflammatory Bowel Disease [IBD]) is an initiative by the International Organisation for the Study of IBD that aims to delineate a core set of therapeutic targets for IBD based on literature review and expert consensus. The first iteration was published in 2015,<sup>1</sup> with an update in 2021 (STRIDE2),<sup>2</sup> which qualifies targets as short-, intermediate- or long-term and adds pediatric-specific targets.

The goal of treating any disease is to allow patients to feel well and to enjoy good quality of life (QOL), while avoiding disease- and treatment-related complications. The inflammatory bowel diseases, Crohn's disease (CD) and ulcerative colitis (UC), are no exception. Given this overarching objective, it is not surprising that the traditional target in treating IBD has been symptom resolution, while avoiding corticosteroids. The challenge is that symptom control neither guarantees the absence of intestinal inflammation in a cross-sectional fashion, nor prevents progression to "damage" (including, for example, fibrosis, strictures and fistulae). This does not imply that symptom alleviation is irrelevant; it is a necessary, but insufficient treatment target. STRIDE2 includes clinical response (immediate/short-term) and clinical remission (intermediate) as treatment targets, but the method of symptom assessment has shifted from the physician (physician-administered clinical activity indices) to the patient (patient-reported outcomes [PROs]),<sup>3</sup> aligning with

the FDA's requirement for PROs as a co-primary endpoint in clinical drug trials (typically alongside an objective disease marker such as endoscopy). STRIDE2 also introduces restoration of QOL and disability avoidance as key treatment goals. This further highlights the importance of the patient experience, and acknowledges normal linear growth as a critical pediatric-specific clinical target.

### IBD Treatment Targets

If not symptom control, what constitutes a sufficient IBD treatment target? The optimal target should satisfy several criteria; it should be 1) causally linked with improved long-term outcomes; 2) rooted in disease biology (i.e., biologically relevant); 3) measurable (feasibly, reliably and accurately); and 4) attainable with currently available therapies (although an argument can be made for "aspirational" targets that are not yet attainable). It is the advent of biological therapies, starting with the tumour necrosis factor- $\alpha$  (TNF) antagonist, infliximab, that raised the therapeutic efficacy ceiling and, in so doing, brought targets beyond symptom control into the realm of possibility.

Criteria #1 above (causal link between target and improved outcomes) warrants discussion. Numerous observational studies have demonstrated an *association* between deep remission and superior outcomes; invariably, the deeper the healing (histologic remission<sup>4</sup> or even molecular remission<sup>5</sup> > endoscopic remission<sup>6</sup> > clinical remission), the better the outcome. Such studies should not be misconstrued as

evidence that treating to a given endpoint causes the better outcome. Causality can only be definitively established by randomized controlled trials in which a treat-to-target (T2T) intervention (treatment escalation based on failure to meet prespecified targets) is compared to a reference standard. The CALM trial, for example, showed that CD patients who were treatment escalated to weekly adalimumab ± azathioprine based on C-reactive protein (CRP)  $\geq 5$  and/or fecal calprotectin (FCP)  $\geq 250$   $\mu\text{g/g}$  experienced higher rates of mucosal healing at one year.<sup>7</sup>

Consistent with the evidence generated by CALM, STRIDE2 introduces CRP normalization and FCP reduction to an “acceptable” level as formal intermediate treatment targets (previously adjunct targets in STRIDE1). A thorough discussion of these biomarkers is beyond the scope of this review, but it is important to recognize their imperfect accuracy for intestinal inflammation, with FCP being more sensitive, and CRP more specific.<sup>8</sup> The concept of cut-offs is challenging, particularly for FCP as the relationship between inflammation severity/extent and FCP is not linear. Moreover, although progressively lower FCP values are generally associated with progressively deeper healing, there is significant overlap in cut-offs for each level of healing. Recognizing these limitations, STRIDE2 recommends FCP reduction to the 100–250  $\mu\text{g/g}$  range.

At its core, IBD is a disease of dysregulated intestinal immune response and intestinal inflammation. Moreover, it is this unchecked intestinal inflammation that directly leads to the disease’s complications. By extension, resolution of the macroscopic manifestations of intestinal inflammation (i.e., endoscopic healing [EH]) would appear the most intuitive and biologically relevant treatment target. It is perhaps surprising, therefore, that the STARDUST trial, a T2T RCT in which CD patients not achieving a predefined endpoint including endoscopic improvement were escalated to ustekinumab every four weeks, did not meet its primary outcome.<sup>9</sup> Whether this relates to the more refractory nature of the patient cohort (biologic/conventional treatment failures), or possibly the limited escalation options, is unclear. While we await additional high-quality data to confidently ascertain if treating to an endoscopic endpoint leads to superior outcomes, STRIDE2 has retained EH as a long-term treatment target. Acknowledging that there is no consensus definition for EH, STRIDE2 proposes an SES-CD<sup>10</sup> score  $\leq 2$  or absence of ulcers for CD, and a Mayo endoscopic score of 0 or UCEIS<sup>11</sup> score  $\leq 1$  for UC.

Arriving at a consensus definition for EH (and other targets as well) is particularly challenging due to the lack of data on the incremental gain associated with each deeper level of healing, and the counterbalancing costs/risks associated with the “extra” treatment needed to achieve it. This includes monetary terms (at a patient and societal level); adverse effects (e.g., increased immune suppression, risk of malignancy); and inconvenience (e.g., needing to take more medication). Is a UCEIS 0 a “better” target than a UCEIS 1? Without data characterizing the precise benefits

and risks of pursuing a UCEIS 0 over 1, with corresponding numbers needed to treat and numbers needed to harm, this question cannot be clearly answered.

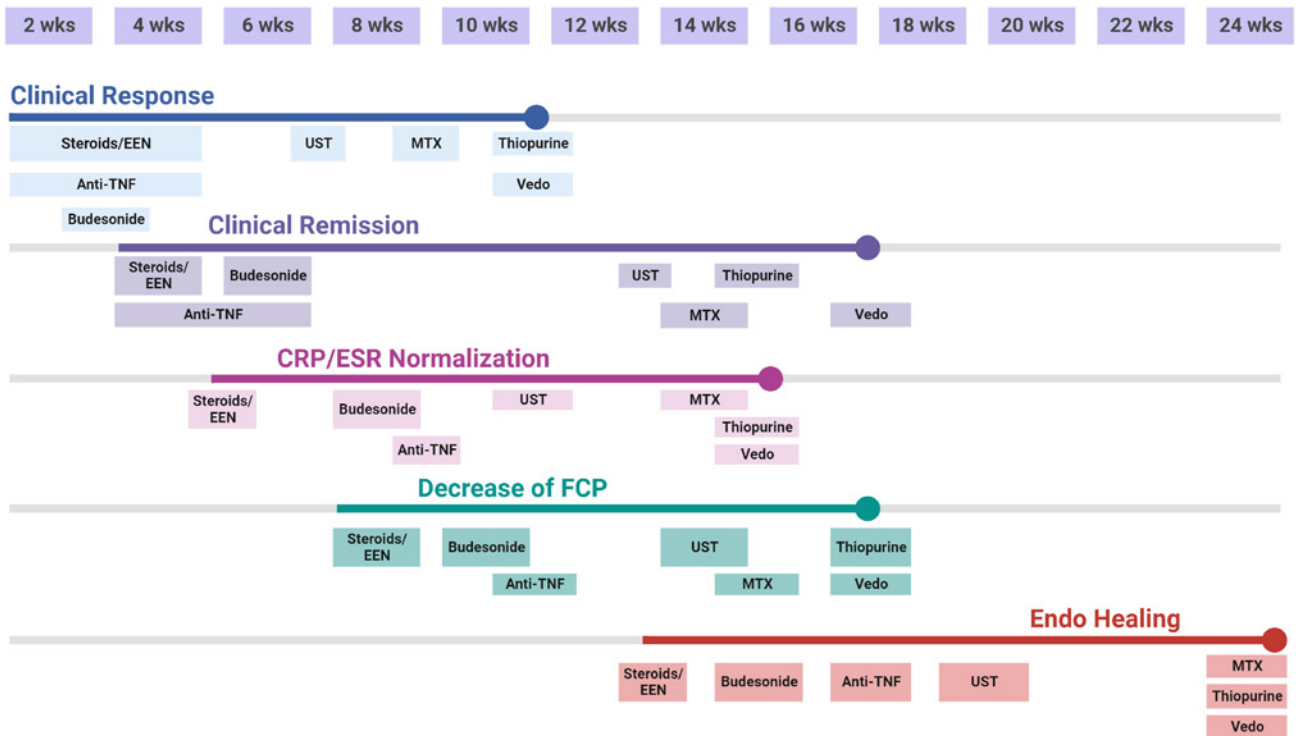
### Bringing STRIDE2 to Life

To summarize, the STRIDE2 therapeutic targets include short-term clinical response; clinical remission; CRP normalization; FCP 100–250  $\mu\text{g/g}$  (intermediate); EH; normal growth; and QOL without long-term disability. Even equipped with today’s armamentarium of biologics and small molecules, these are demanding targets, achievable in some, but certainly not all (and likely not most) patients. To modify treatment every time one of these targets is not achieved, blind to contextual factors, is ill-advised and would lead to rapid drug cycling and exhaustion of all available therapies in many patients.

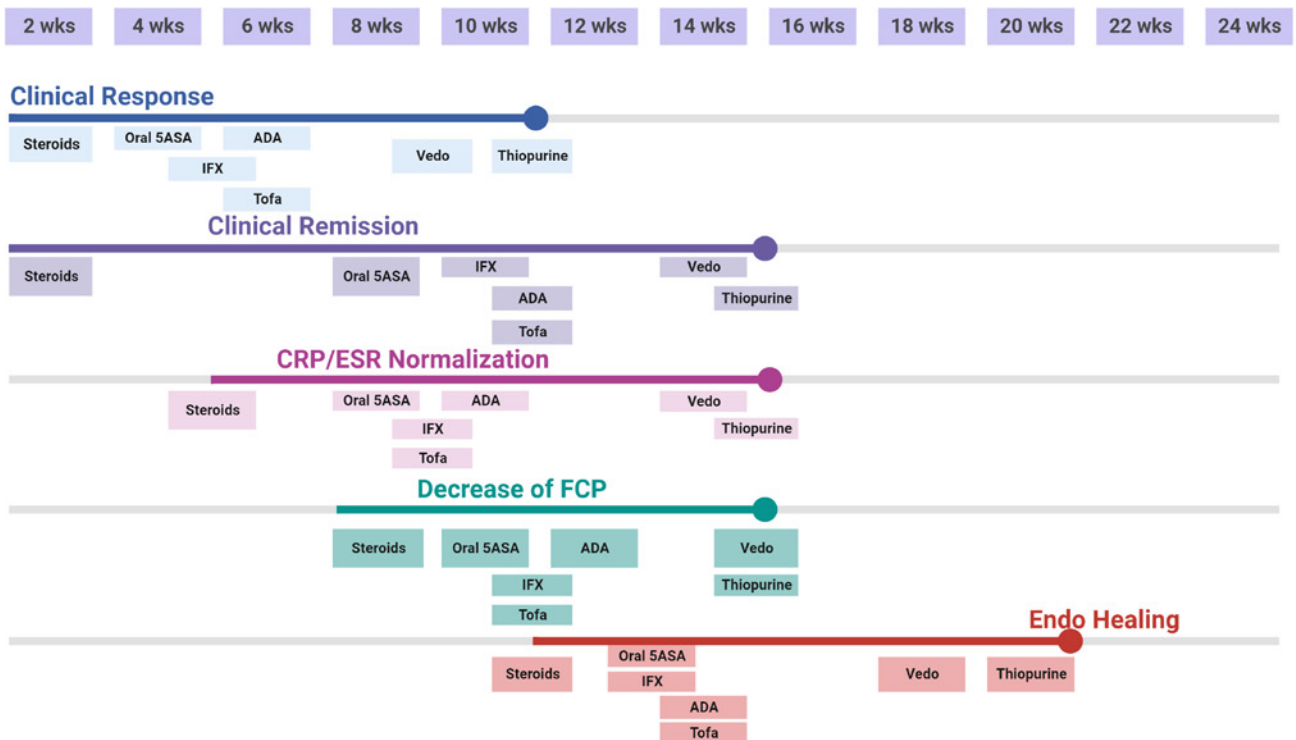
In translating STRIDE2 to clinical practice, one must first consider the element of time. It would be nonsensical, for example, to assess for EH one month after initiating azathioprine given its prolonged time to effect. In other words, the reassessments that comprise the “tight monitoring” of STRIDE’s T2T paradigm must be adapted to both the endpoint and mechanism of action of the treatment in question. To assist with this, STRIDE2 presents the average time to its various targets for several commonly used medications (summarized in **Figure 1**). This provides an approximate framework/time for disease reassessment.

Ascertaining failure to meet a therapeutic target is easy enough; the decisions that ensue, however, are often highly complex and must consider several factors according to a shared decision-making process between physician and patient. The factors at play are summarized in **Figure 2** and include: 1) current disease severity (i.e., how far off target the patient is, clinically, biochemically and endoscopically), 2) the likelihood and severity of complications if no steps are taken (for example, the potential consequences of stricturing ileal CD are quite different from those of stricturing rectal CD); 3) the patient’s disease history, including treatments tried and response (proof of refractoriness); 4) therapies that remain to be tried and the likelihood that one or more of these will be more effective than previous therapies; and 5) patient values and preferences. The patient scenarios in **Figure 3** illustrate the process of working through these factors. In scenario A, the decision to treatment-escalate is obvious, with all factors weighing heavily in that direction. In scenario B, at first glance, the markedly elevated FCP and ongoing endoscopic disease would appear to mandate a treatment change; however, when one considers the other factors listed, the decision becomes less clear. In this scenario, the patient currently feels better than at any point previously in her disease course. She has previously proven to be refractory to several therapies and there is no compelling reason to believe a different biologic or small molecule will be more effective than her current combination adalimumab plus immunomodulator. The practical reality is that the more refractory the patient, the higher the bar (the sicker he/she needs to be) in considering abandonment of the current treatment.

## Time to Target After Treatment Start Crohn's Disease (A)



## Time to Target After Treatment Start Ulcerative Colitis (B)



**Figure 1.** Mean number of weeks to achieve various treatment targets with commonly utilized therapies, based on Table 4 from STRIDE<sup>2</sup> – CD (A), UC (B); Created with BioRender.com  
5ASA – 5-aminosalicylic acid; EEN – exclusive enteral nutrition; MTX – methotrexate; TNF – tumour necrosis factor; UST – ustekinumab

## Factors Informing Decision to Change IBD Treatment Approach when Therapeutic Target Not Met

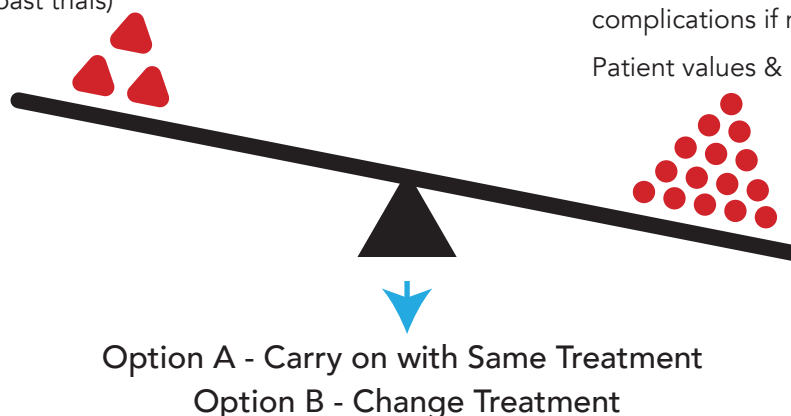
Therapies tried/failed  
(refractoriness)

Available therapies  
(and "confidence" they will be more  
successful than past trials)

Disease severity, including objective  
markers, symptoms, QOL  
(How far "off target" is the patient?  
How intolerable is the current state?)

Likelihood and seriousness of  
complications if no changes made

Patient values & preferences



**Figure 2.** Factors informing decision to modify treatment when therapeutic target not met; Created with BioRender.com  
QOL – quality of life

### Scenario A

40 yo M, pancolitis UC

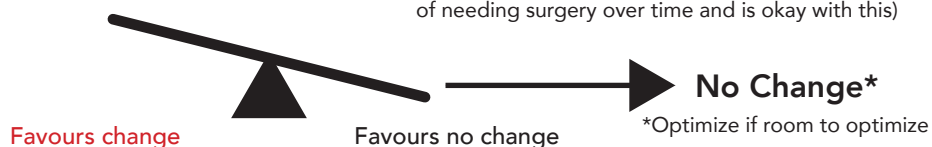
- Current: severely clinically active, Mayo 3 on flex sig, 6 months on optimized oral + PR 5ASA
- Past Rx history: successful oral corticosteroid induction prior to %ASA; nil else tried
- Current state is unacceptable to patient and MD
- Risk of "doing nothing" is serious and high (perforation, emergent, colectomy)
- Patient has tried few therapies, there are several other options that are statistically more likely to be more effective (e.g., anti-TNF, vedolizumab)



### Scenario B

17 yo F, ileal CD x 20 cm

- Current: 2 y on ADA 40 mg weekly (drug level 30 + concomitant MTX, sustained clinical remission, great QOL, normal CRP, growing well)
- BUT FCP persistently up (1500 ug/u), SES-CD 6 (9 at Dx), early stenotic changes on MRE (unchanged over 2 y)
- Past Rx history: previous corticosteroid dependence, failed thiopurine and UST
- Patient is off target (FCP, endo)
- Risk of "doing nothing" is progression to frank structuring and/or penetrating disease requiring surgery
- There are other agents to try
- Several targets achieved (clinical, CRP)
- Risk of "doing nothing" is likely manageable with limited ileal resectional targets achieved (clinical, CRP)
- Patient has proven herself refractory, no compelling evidence next treatment will be better, it may be less effective
- Patient is moving out soon for college, does not want to "rock the boat" and risk what she feels is her current state of "good health" (she understands there is a risk of needing surgery over time and is okay with this)



**Figure 3.** Patient scenarios illustrating factors to consider in deciding whether or not to modify IBD treatment when therapeutic targets are not met, in a shared decision-making process between physician and patient; Created with BioRender.com  
5ASA – 5-aminosalicylic acid; ADA – adalimumab; CD – Crohn's disease; CRP – C-reactive protein; Dx – diagnosis; FCP – fecal calprotectin; MTX – methotrexate; QOL – quality of life; Rx – treatment; SES-CD – simple endoscopic score for CD; TDM – therapeutic drug monitoring; TNF – tumour necrosis factor; UC – ulcerative colitis; UST – ustekinumab

In scenario B, the treatment regimen was purposefully presented as “optimized” (adequate anti-TNF level, combination immunomodulator) to make it more challenging. However, this underlines the concepts of optimization and “add-ons,” and that not all treatment changes need to involve completely abandoning the current therapy in place of a new therapy. This is particularly the case for the patient who has shown some response to a treatment but has not ticked all the STRIDE2 checkboxes. There are numerous options for optimization/add-ons, including but not limited to: ensuring compliance; ensuring adequate drug exposure (through proper dosing, therapeutic drug monitoring if available) with dose escalation if indicated; adding rectal 5ASA to the oral route in the UC patient; adding oral 5ASA to the UC patient who has not previously had a 5ASA trial (as in the corticosteroid refractory acute severe UC patient who receives infliximab upfront); adding an immunomodulator to a biologic (for its inherent efficacy and/or role in decreasing immunogenicity); and the addition of dietary interventions (e.g., CD exclusion diet), as well as combination biologics. The latter may become increasingly more commonplace as it is generally thought that combination therapy may be required to break through the therapeutic efficacy ceiling that has emerged in IBD. Finally, surgery should not be conceptualized as the end result of having failed all medical options, but rather as a treatment option in its own right for both CD and UC, at various timepoints, potentially even early in the disease course.

### Conclusions and Future Directions

STRIDE is founded on the educated guess that actively treating toward its suggested targets will enhance a patient’s likelihood of experiencing a favourable disease course, and uses as its starting point the idealized notion that achieving these targets is feasible. These targets are based on the “best” currently available data and, as such, provide important guidance to the practicing IBD specialist. However, there are practical realities that need to be considered in translating STRIDE2 to real life and important knowledge gaps that remain to be addressed. One of the most critical of these is the lack of biomarkers to aid with predicting individual patient response to specific therapies in order to enable a personalized approach to positioning therapies. It remains likely that there is a finite window of time within which effective therapy has the potential to alter the natural history of IBD and it is therefore imperative to initiate treatment with the agent(s) most likely to be effective, while representing a sensible balance between benefits and risks for the disease severity in question. The advent of such biomarkers will power a shift from our current trial-and-error approach to a precision medicine approach, which will allow the T2T paradigm endorsed by STRIDE to achieve its full potential.

### Correspondence:

Dr. Amanda Ricciuto

Email: amanda.ricciuto@sickkids.ca

### Financial Disclosures:

None declared

### References

1. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting therapeutic targets in inflammatory bowel disease: (STRIDE): determining therapeutic goals for treat-to-target. *Am J Gastroenterol.* 2015;110:1324-1338.
2. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: An update on the selecting therapeutics 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. *Gastroenterology.* 2021;160:1570-1583.
3. Marcovitch L, Focht G, Carmon N, et al. Development and validation of the TUMMY-UC: a patient-reported outcome for pediatric ulcerative colitis. *Gastroenterology.* 2023;164:610-618.e4.
4. Yoon H, Jangi S, Dulai PS, et al. Incremental benefit of achieving endoscopic and histologic remission in patients with ulcerative colitis: a systematic review and meta-analysis. *Gastroenterology.* 2020;159:1262-1275.e7.
5. Argmann C, Hou R, Ungaro RC, et al. Biopsy and blood-based molecular biomarker of inflammation in IBD. *Gut.* 2023;72:1271-1287.
6. Arai M, Naganuma M, Sugimoto S, et al. The ulcerative colitis endoscopic index of severity is useful to predict medium-to-long-term prognosis in ulcerative colitis patients with clinical remission. *J Crohns Colitis* 2016;10:1303-1309.
7. Colombel JF, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn’s disease (CALM): a multicentre, randomised, controlled phase 3 trial. *Lancet.* 2017;390:2779-2789.
8. Mosli MH, Zou G, Garg SK, et al. C-reactive protein, fecal calprotectin, and stool lactoferrin for detection of endoscopic activity in symptomatic inflammatory bowel disease patients: a systematic review and meta-analysis. *Am J Gastroenterol.* 2015;110:802-19; quiz 820.
9. Danese S, Vermeire S, D’Haens G, et al. Treat to target versus standard of care for patients with Crohn’s disease treated with ustekinumab (STARDUST): an open-label, multicentre, randomised phase 3b trial. *Lancet Gastroenterol Hepatol.* 2022;7:294-306.
10. Daperno M, D’Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn’s disease: the SES-CD. *Gastrointest Endosc.* 2004;60:505-512.
11. Travis SP, Schnell D, Krzeski P, et al. Reliability and initial validation of the ulcerative colitis endoscopic index of severity. *Gastroenterology.* 2013;145:987-995.