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PROACTIVE MONITORING OF BIOLOGICAL DRUG CONCENTRATIONS AS AN EFFECTIVE STRATEGY TO PERSONALIZE TREATMENTS

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PERSPECTIVES ON PEDIATRIC TDM

ISSUE 3

INTRODUCTION

In this issue of Perspectives on Pediatric TDM, Dr Víctor Manuel Navas López from the Pediatric Gastroenterology and Nutrition Unit at Hospital Regional Universitario de Málaga shares his experience in real-life clinical practice on the benefits of therapeutic monitoring of biological drugs (TDM) in pediatric patients with inflammatory bowel disease (IBD) treated with anti-TNF biological therapies, and discusses the clinical evidence published to date.

Dr Navas highlights the effects of IBD on these patients' growth and delayed puberty, which affects their psychological and emotional development. He stresses the importance of adapting the treatment strategy to well-defined goals and continuously and systematically evaluating to improve long-term outcomes for patients with the disease (STRIDE-II Study, Turner D, et al, 2021).

Dr Navas goes on to present the concept of TDM (determination of drug and anti-drug-antibody levels) as an additional tool for clinical decision-making, providing the available evidence on possible TDM strategies shown to be effective in certain clinical situations (reactive, proactive, postinduction predictive, and predictive models).

He then gives his conclusions and recommendations on the utility of TDM in pediatric patients with IBD treated with anti-TNF biological drugs in terms of enhancing personalized medicine; helping improve clinical outcomes; the maximization and optimization of the use of the drug, and an aid for planning the therapeutic strategy according to clinical situations that may occur during therapy.

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GRIFOLS

Articles

PROACTIVE MONITORING OF BIOLOGICAL DRUG CONCENTRATIONS AS AN EFFECTIVE STRATEGY TO PERSONALIZE TREATMENTS

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INTRODUCTION

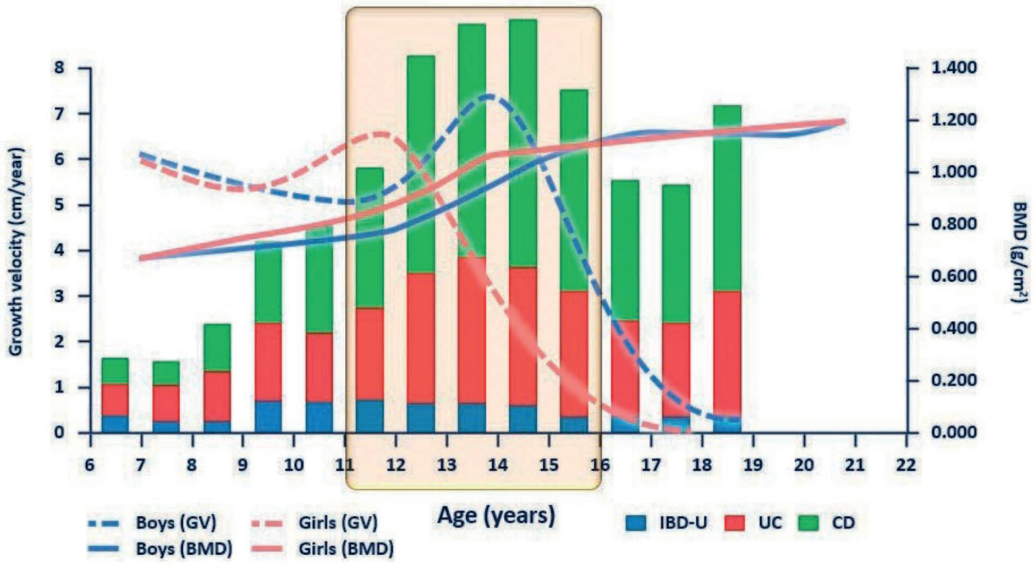
Inflammatory bowel disease (IBD) is a chronic autoimmune disease of unknown etiology that includes both Crohn's disease (CD) and ulcerative colitis (UC). Three factors condition an imbalance with the result of the appearance of a chronic inflammatory process: genetic predisposition, microbial dysbiosis, and environmental factors.

The incidence of pediatric IBD in Spain was evaluated in a multicenter retrospective study led by Dr Javier Martín de Carpi, published in IBD (Martín-de-Carpi J, et al, 2013) in 2013. In that study, a peak incidence of IBD was found around 12 to 13 years of age, a time that coincides with the peak growth velocity of pediatric patients, the time of the pubertal growth spurt and when the greatest amount of bone tissue is being produced (Figure 1).

In many patients, the onset of IBD coincides with the development of secondary sexual characteristics; in other words, with puberty, and one of the consequences is that puberty is delayed. This situation can lead to feelings of isolation and abandonment in these patients, weakening peer relationships, poor body image, and depression or anxiety.

The onset of IBD coincides with one of the most critical stages of Erikson's psychosocial development theory, identity vs role confusion. It, therefore, goes without saying how significant developing a disease of this type is at such a crucial point in a person's life.

In pediatrics, the first case of treatment with anti-TNF, a 14-year-old Dutch girl, was in 1995. Since then, thousands of IBD patients have been treated with anti-TNF. Although new molecules have been developed in recent years, this article will focus on the use of intravenous or subcutaneous anti-TNF.



Adapted from: Martin de Carpi J, et al. IBD. 2013;19:73–80; del Rio L, et al. Pediatr Res. 1994;35:362–6; Carrascosa A, et al. Horm Res Paediatr. 2011;75:106–14.

Figure 1. Growth velocity, bone health, and onset of pediatric IBD.

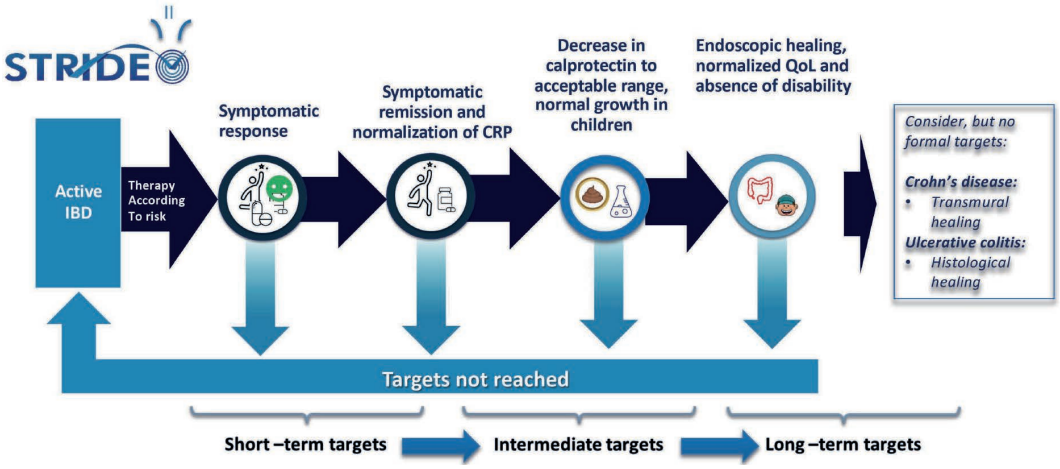
TREATMENT STRATEGIES

The therapeutic strategy for IBD should be established after a systematic, exhaustive diagnosis and evaluation of the risk of poor disease progression (STRIDE-II Study, Turner D, et al, 2021). The goals are progressive and time-dependent (short-, medium-, and long-term). We have to systematically re-assess patients to check whether or not the particular goal has been achieved, and if not, we need to re-evaluate the therapeutic strategy. If the target has been achieved, we move on to the next goals (Figure 2).

The first goal is the symptomatic response. Eliminating the symptoms is paramount. Not having bloody stools, not having pain, and not having to get up at night to go to the toilet are targets with a very positive impact on patients' quality of life.

The next goal is clinical remission, meaning the complete absence of symptoms and normalization of inflammatory laboratory parameters such as C-reactive protein (CRP). The next medium-term goal is the normalization of fecal calprotectin values and a normal growth rate.

The ultimate goals are mucosal healing, histological healing in UC, transmural healing in CD, normalization of quality of life, and absence of disability.



Adapted from: Turner D, et al. Gastroenterology. 2021;160:1570-83.

Figure 2. STRIDE-II: An update on the Selecting Therapeutic Targets Initiative for treat-to-target strategies in IBD.

TDM IS A COMPLEMENTARY TOOL FOR CLINICAL DECISION-MAKING

How does knowing the drug levels help us?

- To check whether or not we have reached optimal levels for particular clinical situations. We know that the levels needed to achieve mucosal healing in luminal CD are lower than those required for the closure of a perianal fistula.
- To prevent the secondary loss of response due to the development of anti-TNF antibodies, the most common cause of therapeutic failure.

Although the determination of drug levels is cost-effective, decision-making can never be made solely and exclusively based on drug levels. The medical history and physical examination are always essential, as are the activity scores (Pediatric Ulcerative Colitis Activity Index [PUCAI] in UC or the weighted Pediatric Crohn's Disease Activity Index [wPCDAI] in CD). The investigations or biomarkers we use include the determination of CRP, albumin, ESR, and FC.

WHEN TO MEASURE LEVELS?

Levels can be measured at different points of the anti-TNF treatment:

- After induction, in the postinduction period, as we know that levels below a certain cut-off point predict the development of anti-drug antibodies in the short term
- During the maintenance phase to optimize the dose
- When a switch from combination to monotherapy is indicated
- Reactively when we identify a loss of response
- After a therapeutic intervention (for example, re-induction, surgical resection)
- When it is decided to give patients a holiday period from anti-TNF therapy

TDM may may be used reactively if we aim to respond to what has happened; it also can be performed proactively to keep the therapy optimized, or predictive if we are trying to identify what may happen in the future.

HOW TO MEASURE LEVELS? REACTIVE APPROACH TDM

Figure 3 shows a TDM algorithm from a reactive point of view; the rows are the anti-TNF drug levels, and the columns are the anti-drug antibody levels (Adapted from: Bendtzen K, 2015; Yarur A, et al, 2016; Steenholdt C, et al, 2013; Ungar B, et al 2015).

First scenario

In a first scenario, we can have a patient with symptoms suggestive of IBD, for example, diarrhea, abdominal pain, and rectal bleeding. If drug levels are subtherapeutic and the antibodies are undetectable, it is considered a pharmacokinetic failure. The first problem is knowing the optimal plasma levels of anti-TNF, as there is a lot of variability between patients. This is illustrated in the 2016 article published by Ungar B, et al, 2016, where some patients had mucosal healing with levels of 4 µg/mL while others needed 16 µg/mL to achieve healing. We know that fistula closure requires higher levels of infliximab, approximately 20-25-30 µg/mL (Yarur A, et al, 2017). In this scenario, the strategy is escalation, which can be done in two ways: shortening the interval or increasing the dose. It has been shown that the most efficient strategy is to shorten the interval (Dotan I, et al, 2014).

Through drug level	Through anti-drug antibodies (ADA) level	
	NO	YES
Subtherapeutic (full compliance)	**Scenario 1: Problem** Insufficient bioavailability of the drug and/or increased non-ADA-mediated clearance. Technical problems (Double negative) **Treatment** Intensify therapy	**Scenario 3: Problem** Insufficient bioavailability caused by ADA, including pre-existing anti-murine (Fab) IgG against IFX# **Treatment** Shift to another TNF-antagonist Re-gain response. Add IMM Note: Test ADA for cross-reactivity if shifting to biosimilar
Therapeutic or supratherapeutic	**Scenario 2: Problem** Inflammation No inflammation **Treatment** Confirm inflammatory activity - Inflammation: Anti-TNF drugs are ineffective, shift to non-TNF targeting therapy / surgery - No inflammation: treat the underlying cause	**Scenario 4: Problem** Pharmacodynamic: Non-functional ADA Methodological: False positive test **Treatment** Consider testing for functionally active, drug-neutralizing ADA Treat as in scenario 2

Adapted from: Bendtzen K. Front Immunol. 2015;6:152; Yarur A, et al, Gut. 2016;65(2):249-55; Steenholdt C, et al. Aliment Pharmacol Ther. 2013;37(12):1172-83; Ungar B, et al. World J Gastroenterol. 2015;21(6):1907-14.

Figure 3. Reactive TDM: Decision algorithm for patients on treatment with anti-TNF biological drugs and loss of response. We have to demonstrate that there is active IBD.

Second scenario

In our second scenario (Figure 3), a patient with symptoms suggestive of IBD does not have anti-drug antibodies and their drug levels are therapeutic or supratherapeutic.

This scenario may be due to two clinical situations: there is active IBD or another inflammatory condition (for example, infection, ischaemic colitis, vasculitis); or the symptoms are secondary to an underlying cause other than IBD (for example, irritable bowel syndrome, stenosis, cancer, lactose intolerance, celiac disease, bacterial overgrowth syndrome). The strategy consists of confirming the underlying cause. If there is inflammation and it is related to

active IBD, it may be due to a "shift" in the cytokines, which are at that point regulating IBD traffic, with TNF no longer being the cytokine regulating the inflammation (Ben-Horin S, et al, 2014). Another reason could be tissue damage that makes it impossible for anti-TNF to reach the site of inflammation. In both cases, the problem is referred to as pharmacodynamic failure. In this scenario, when the cause is uncontrolled inflammation due to IBD, the most efficient strategy is a change of target or surgery of the inflamed segment.

Third scenario

In the third scenario (Figure 3), a patient has symptoms suggestive of IBD and decreased drug availability due to the development of anti-drug antibodies. In this scenario of immunogenic failure, there are two possible strategies:

- Switch to another anti-TNF (Ordas I, et al, 2012) or, if it is the second anti-TNF because infliximab or adalimumab failed, start treatment with ustekinumab, vedolizumab, tofacitinib, etc, according to the underlying disease
- Re-gain the response by adding an immunomodulator (IMM) if the patient's clinical condition so allows (Ben-Horin S, et al, 2014)

In this scenario, switching to a biosimilar is not indicated due to its cross-reactivity (Ruiz-Argüello B, et al, 2016).

Fourth scenario

The fourth scenario (Figure 3) is more theoretical, and is treated as in scenario 2.

In summary:

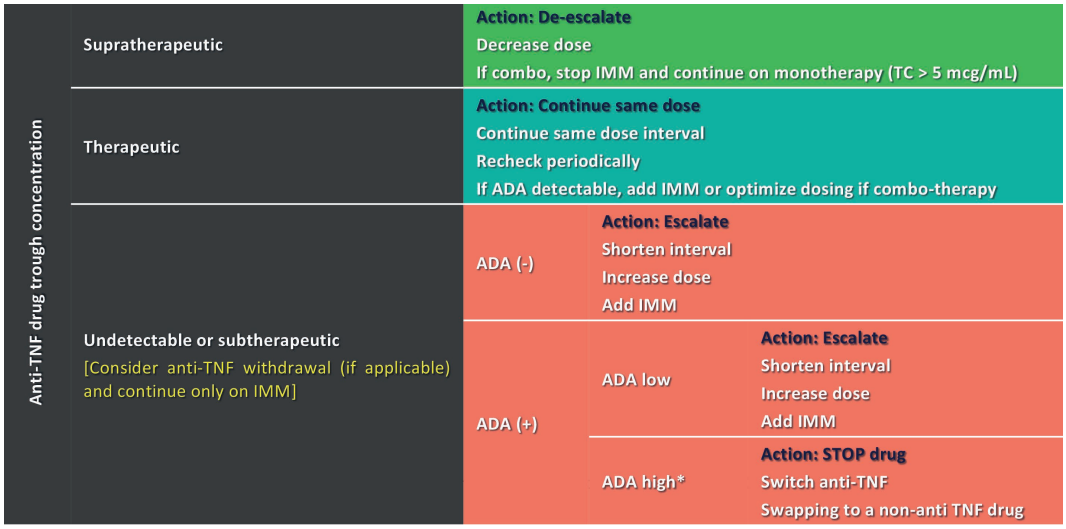
- Scenario 1: Pharmacokinetic failure: decrease interval, increase dose, or both
- Scenarios 2 and 4: Pharmacodynamic failure: surgery of resectable segment, out-of-class switch, or in-class switch
- Scenario 3: Immunogenic failure: change within class or add IMM

HOW TO MEASURE LEVELS? PROACTIVE APPROACH TDM

This is simplified when the strategy is proactive (Figure 4; Papamichael K and Cheifetz AS, 2016), meaning that drug measurement is scheduled and the clinical decisions are made in conjunction with other factors and parameters:

- Supratherapeutic levels: the approach is to lower the dose of the drug, de-escalate. If the patient is on combination therapy and the levels are >5 µg/mL, they can switch to monotherapy with anti-TNF.
- Therapeutic levels: no change except in a specific scenario. We have found cases in which the patient was in remission, with normal CRP and stable anti-TNF doses and intervals, but drug levels were progressively decreasing.
  In this scenario, we have to consider the beginning of an immunogenic failure undetectable with ELISA techniques. It is a good idea to repeat induction or escalate to aid the clearance of anti-drug antibodies.
- Subtherapeutic or undetectable levels (Figure 4):
  - If anti-drug antibodies are negative: we escalate by shortening the interval, increasing the dose, both, or adding an IMM
  - If anti-drug antibodies are positive:

- If anti-drug antibody titers are low: we escalate by shortening the interval, increasing the dose, both, or adding an IMM
- If anti-drug antibody titers are high: we switch within the class (from infliximab to adalimumab or vice versa) or we swap to a non-anti-TNF drug (for example, vedolizumab, ustekinumab, tofacitinib)



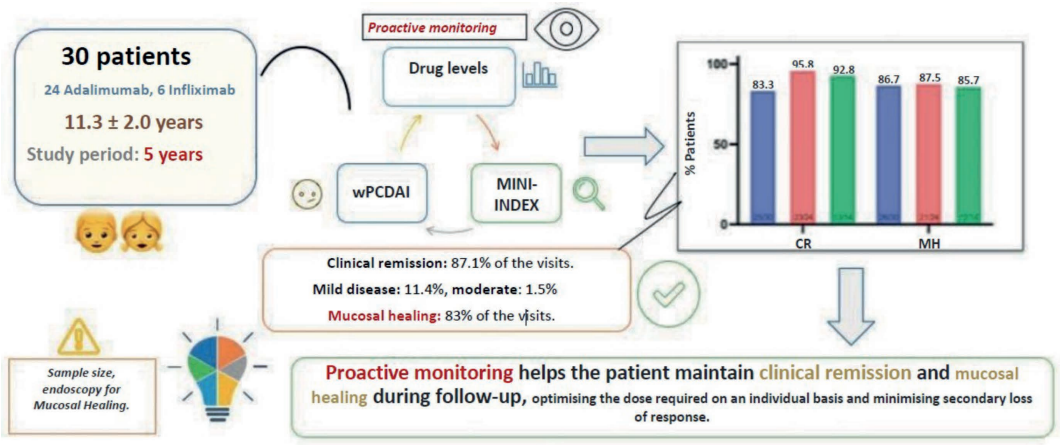
Adapted from: Papamichael K, et al, Frontline Gastroenterol. 2016;7(4):289-300.

Figure 4. Proactive TDM: Decision algorithm for patients in sustained clinical remission on treatment with anti-TNF biological drugs.

This proactive drug level measurement strategy has been shown to be cost-effective (Steenholdt C, et al, 2014; Steenholdt C, et al, 2015). The PAILOT study showed that, compared to reactive TDM, proactive TDM is better at achieving corticosteroid-free remission at weeks 8 and 72 and also improves other clinical parameters (Assa A, et al, 2019). However, this study pilots on a predetermined drug level.

In a far more modest proactive study, which included 30 patients with a mean age of 11 years, 24 were treated with adalimumab and 6 with infliximab, and during the three years of follow-up, no secondary loss of response was found due to the development of anti-drug antibodies, demonstrating this to be a successful and efficient strategy (Rodríguez-Azor B, et al, 2022). To achieve these objectives, at all visits the authors measured the drug level and other analytical parameters, calculated activity scores and applied the Mucosal Inflammation Non-invasive (MINI) index. The patients in this series were in clinical remission at 87.1% of all visits and had mucosal healing at 83% of visits. At 11% of visits they had mild disease and at 1.5%, moderate (Figure 5). In this study, the dosing regimens with infliximab were much more heterogeneous than with adalimumab. The most common regimen for adalimumab was 40 mg every two weeks, but with infliximab there was greater variety in the dosage regimens (for example, 5 mg/kg every eight weeks, 7.5 mg/kg every six weeks, 10 mg/kg every four weeks). At the three-year follow-up, 92.8% of the patients were in clinical remission and 85.7% had

mucosal healing measured with the MINI index. As in the 2016 study by Ungar B et al, we found patients who were in clinical remission or had mucosal healing with levels below 5 µg/mL or 6 µg/mL and others who needed more to achieve the same goal (Rodríguez-Azor B, et al, 2022).



Adapted from: Rodríguez-Azor B. et al, Anales de Pediatría.
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Figure 5. Proactive monitoring of anti-TNF drugs improves follow-up of pediatric patients with Crohn's disease.

HOW TO MEASURE LEVELS? POSTINDUCTION PREDICTIVE TDM

A study of 536 prospectively collected serum samples in which adalimumab drug levels were measured at the fourth week after the first two induction doses found that the risk of anti-drug antibody formation increased 25-fold if a patient had less than 5 µg/mL or more than 5 µg/mL and that combination therapy with immunomodulators reduced the formation of these antibodies (Baert F, et al, 2016).

MONITORING WITH PREDICTIVE MODELS

And, in predictive mode, using a model based on the patient's weight, albumin level and prescribed dose, we are able to predict whether or not the patient will have therapeutic levels (Frymoyer A, et al, 2016). For example, in the case of a 50 kg patient with albumin of 4 g/dL and an infliximab regimen of 10 mg/kg every four weeks, in 98% of cases the patient will achieve drug levels within the desired therapeutic ranges.

CONCLUSIONS

Treatment of IBD with biological drugs guided by measuring drug and anti-drug antibody levels is associated with better clinical outcomes.

- We have to prioritize and make a correct indication in time and form
- We have to maximize the drug, fully optimizing its use. Although very rare with proactive monitoring, a strategy can and should be planned in case of a secondary loss of response
- The future is to improve. In patients weighing less than 25 kg, the pharmacokinetics are totally different from those of adults. When it comes to pediatric patients, we must im-

prove knowledge of the pharmacokinetic profile of our anti-TNF and other biological drugs, always in combination with clinical, endoscopic, and imaging data
- Unify and validate measurement methods
- Establish predictive models and individualized strategies, what amounts to personalized medicine

ACRONYMS

IBD: inflammatory bowel disease
CD: Crohn's disease
BMD: Bone mineral density
CRP: C-reactive protein
TDM: therapeutic drug monitoring
UC: ulcerative colitis
FC: fecal calprotectin
ESR: erythrocyte sedimentation rate
MINI index: Mucosal Inflammation Noninvasive index

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TRENDING TOPICS

GUIDELINES AND RECOMMENDATIONS FOR THE MANAGEMENT OF PEDIATRIC PATIENTS WITH IBD

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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PREDICTING OUTCOMES IN PEDIATRIC CROHN'S DISEASE FOR MANAGEMENT OPTIMIZATION: SYSTEMATIC REVIEW AND CONSENSUS STATEMENTS FROM THE PEDIATRIC INFLAMMATORY BOWEL DISEASE-AHEAD PROGRAM

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PREDICTING OUTCOMES IN PEDIATRIC ULCERATIVE COLITIS FOR MANAGEMENT OPTIMIZATION: SYSTEMATIC REVIEW AND CONSENSUS STATEMENTS FROM THE PEDIATRIC INFLAMMATORY BOWEL DISEASE-AHEAD PROGRAM.

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PROACTIVE TDM IN PEDIATRIC IBD

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