A Mobile Infliximab Dosing Calculator for Therapy Optimization in Inflammatory Bowel Disease

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Background: Inadequate infliximab (IFX) drug exposure remains a clinical challenge and leads to high loss of response rates and therapy failure in inflammatory bowel disease (IBD). We aimed to determine the feasibility and pilot effectiveness of a novel, web-based, mobile IFX dosing calculator (mIDC) for therapy optimization.

Methods: We developed an mIDC leveraging the known clinical variables of C-reative protein (CRP), albumin, patient's weight, disease activity indices, calprotectin, drug trough levels, and antibodies to IFX that significantly affect pharmacokinetics and/or outcomes. A prospective observational cohort study in pediatric and young adult IBD patients receiving maintenance IFX was performed. System-wide practice adoption of mIDC was achieved through a quality improvement (QI) initiative within a hospital-based infusion unit.

Results: Forty-nine patients (median age: 16.0 years; 55% female; 65% Crohn's disease) were followed over 9 months. mIDC recommendations for dose optimization were followed by the treating physicians in 198 (89%) out of 222 infusions. Twenty-eight (13%) of 222 mIDC recommendations were to escalate IFX dosing; 15 (54%) of 28 escalation recommendations were declined, and these patients were more likely to already be receiving IFX dose intensification compared with those in whom escalation recommendations were followed ($P < 0.05$). From mIDC initiation to end of follow-up, mean albumin levels remained unchanged at 3.8 g/dL. Median CRP remained unchanged at 2 g/L. Median calprotectin levels showed a downward trend from 30 to 27 µg/g (n = 9, $P < 0.05$). The percentage of patients undergoing therapeutic drug monitoring in clinical care increased from 34% to 86% with the QI initiative. The target median IFX trough goal of >5 µg/mL was achieved with 81% probability throughout the QI initiative, an increase of 12% compared with pre-QI values.

Conclusions: The use of a novel mIDC is feasible and potentially effective, facilitating both standardization and individualization of therapy in clinical care. mIDC appears to be a practical IFX dosing tool for point-of-care use, leveraging individual pharmacokinetic considerations.

Key Words: Crohn's disease, infliximab, mobile, pharmacokinetics, point of care, therapeutic drug monitoring, ulcerative colitis

Inflammatory bowel disease (IBD) is a chronic, immune dysregulatory response resulting in inflammation of the gastrointestinal tract, and it encompasses both Crohn's disease (CD) and ulcerative colitis (UC).[1] The use of biologic therapies has effectively improved health outcomes in patients with IBD, especially in pediatric IBD care as childhood onset of disease is associated with a more relapsing and remitting course.[2]

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Infliximab (IFX), a chimeric monoclonal antibody against tumor necrosis factor alpha, has become a mainstay therapy to achieve deep remission in children and young adults affected by CD or UC.

While effective, IFX dosing is based on the original randomized controlled trials in adult patients with standard dosing determined to be 5 mg/kg at weeks 0, 2, and 6 during induction, followed by 5 mg/kg every 8 weeks during maintenance.[3, 4] However, treatment failure is common, with up to 64% of patients experiencing loss of response by 54 weeks, depending on disease type.[3–6] With the limited number of biologic drugs available in children affected by IBD, minimizing this loss of response and sustaining treatment success with the firstline biologic is of the utmost importance.

Evidence suggests that loss of response may be attributed to differences in patients' individual pharmacokinetics, leading to low drug exposure and subsequent development of antibodies to IFX (ATI).[7] Loss of response to IFX can be reduced by identifying those patients with low drug exposure and correcting this subtherapeutic exposure by optimizing the patient's dosing.[8, 9] IFX therapy optimization using dose escalation represents an opportunity to individualize treatment strategies in this vulnerable population. However, what is less clear to many

treating physicians is how to optimize therapy at the point of care and reliably identify those patients who need therapy optimization. While personalization is important for each individual patient, there is also a need to standardize the optimization process and limit practice variation to ensure patient safety and evidence-based practice. Additionally, along with personalization and standardization, an IFX dosing aid needs to be user-friendly and mobile, guiding treating physicians at the point of care.

First, we aimed to develop a mobile IFX dosing calculator (mIDC) and determine its feasibility and pilot effectiveness. Second, we aimed to assess the impact of mIDC on physician dosing practices by integrating a system-wide quality improvement (QI) initiative including therapeutic drug monitoring (TDM) within a hospital-based infusion unit.

METHODS

We performed a prospective observational cohort study in children and young adults receiving IFX for CD or UC. In this study, we made dosing recommendations to the treating physician using a novel mIDC as part of standard clinical practice leveraging QI methods. The Stanford University Institutional Review Board approved the study.

Development of the Mobile Infliximab Dosing Calculator

The final mIDC is available for use on a mobile-friendly, web-based platform at http://med.stanford.edu/gastroenterology/infliximab-calc/.

The initial development of mIDC required a comprehensive literature review to identify evidence-based determinants of individual dose needs based on underlying patient-specific pharmacokinetics and disease activity. The major predictors of IFX clearance in children and adults with IBD include serum albumin, current weight, concomitant immunomodulatory therapy, and presence of ATI.[10–12] C-reactive protein (CRP), fecal calprotectin, and IFX trough level were identified as objective markers of treatment response and general outcome.[7, 13–25] Patient symptoms, a marker of disease activity, were accounted for by a validated activity index such as the Pediatric Ulcerative Colitis Activity Index (PUCAI) or the Pediatric Crohn's Disease Activity Index (PCDAI).[26–28]

After identifying these determinants of patients' individual dose needs, a categorical scoring system was developed for each variable to be used in mIDC, with scores associated with change in disease outcome or change in endoscopic or mucosal disease. Table 1 shows the individual components of mIDC stratified by subscores. Higher scores were assigned for values that indicate the patient may have increased IFX clearance, decreased disease response to treatment, or worsened disease severity. The subscore was determined using cutoffs established in the literature. In the case of CRP, levels <5 mg/L in maintenance treatment and a decrease from baseline CRP have been shown to be associated with improved outcomes.[13–16] In the case of calprotectin, more conservative estimates were used based on work that showed values associated with endoscopic and mucosal healing.[17, 18] Albumin cutoffs were determined by normal values and categorized based on severity of hypoalbuminemia. Pharmacokinetic consideration for a patient's weight was determined by Dotan et al., showing that a weight of 40 kg corresponded to ~80% of the reference IFX exposure.[12] The mIDC used validated activity indices to account for patient symptoms. For patients with UC or CD, the PUCAI or PCDAI was used, respectively. When full activity indices could not be obtained, abbreviated or more age-specific versions were used, including the Short PCDAI, Abbreviated PCDAI, and Adult-specific Crohn's Disease Activity Index (CDAI), or Mayo subscore for UC.[29, 30]

TABLE 1. mIDC Components and Scoring System

	Scoring System	
Variable (Maintenance)	Level	Score
Prior CRP	0–5 mg/L OR ≥50% reduction from previous CRP	0
	>5 mg/L AND <50% reduction from previous CRP	1
Prior albumin, g/dL	≥3.5	0
	2.8–3.4	1
	<2.8	2
Current weight	≥40 kg	0
	<40 g	1
Current Disease Activity Index (ie, PUCAI/PCDAI)	Mild/remission	0
	Moderate	1
	Severe	2
Calprotectin within the last 8 wk, µg/g	< 200	0
	200–499	1
	≥500	2
Prior IFX trough, µg/mL	<5	Escalate
Antibodies to IFX	Detected	Escalate

Drug Optimization Using mIDC

The maximum composite score possible using mIDC is 8 if calprotectin is available and 6 when calprotectin is not available. The minimum score possible is 0 in all cases. A composite score ≥50% of the total possible points generated a recommendation to dose-escalate. For example, if calprotectin was available, a score ≥4 generated a recommendation to escalate. If calprotectin was not available, a score ≥3 generated a recommendation to escalate.

The calculator also accounted for IFX trough and presence of ATI. IFX trough and presence of ATI have a well-characterized relationship with treatment success or failure.[7, 19–24] IFX trough <5 µg/mL or presence of ATI also

generated a recommendation to dose-escalate, regardless of the composite score.

Implementation of mIDC Using QI Methods

All IBD patients ≥6 years old receiving IFX at a hospital-based infusion unit were included as part of a QI initiative. The QI initiative occurred from November 1, 2015, to August 1, 2016. Figure 1 shows the QI swimlane describing the workflow to execute universal adoption of mIDC for all IFX encounters. mIDC's recommendation was communicated to the treating physician—"escalate" or "do not escalate." The treating physician could escalate by increasing the dose at the current infusion and/or increase frequency by making the following infusion sooner. This was not dictated explicitly by mIDC, but the recommended escalation schedule was progressive from 5 mg/kg every 8 weeks to 7.5 mg/kg every 6 weeks initially, followed by the schedule outlined in Fig. 2A. mIDC did not recommend escalating beyond 12.5 mg/kg every 6 weeks or 10 mg/kg every 4 weeks.

The process of patient evaluation started as part of QI previsit planning, as shown in Fig. 2B. A member of the QI team (T.L.P.) reviewed the most recent clinical variables for each patient. Most of the clinical data were from a previous infusion or an interval clinic visit. Laboratory values from the previous infusion used in mIDC inputs were serum albumin, CRP, fecal calprotectin, IFX trough level, and ATI status. Patient activity index scoring and weight were obtained on the day of the infusion. Using these data, the QI lead inputted the data into mIDC. mIDC's recommendation to "escalate" or "do not escalate" was communicated directly to the treating physician as part of clinical practice. The final dosing decision was deferred to the treating physician. The dosing decisions were recorded and tracked by the QI team. The QI initiative also included recommendation to the treating physician to standardize therapeutic drug monitoring by following IFX troughs every 6 months to assure adequate drug exposure. The final decision to collect trough data was also deferred to the treating physician.

Patient data and the treatment decisions were collected on a HIPAA-secure Box account as part of the QI initiative.

Describing the Population and Determining Feasibility and Effectiveness

Baseline characteristics were collected at the first maintenance infusion under the QI initiative. Patient treatment regimen and baseline disease status were characterized. The feasibility of mIDC was evaluated by determining the ability of the QI lead to uniformly implement mIDC on the entire patient population throughout the 9-month period. Additionally, to assess pilot effectiveness of mIDC, we compared the patient's baseline data with the patient's last evaluated infusion data. Effectiveness was also assessed by the mIDC's ability to sustain treatment response across our patient population.

Drivers of mIDC Recommendation and Physician Response

Using the collected data, we performed post hoc analysis to determine the drivers of mIDC's recommendations as well as

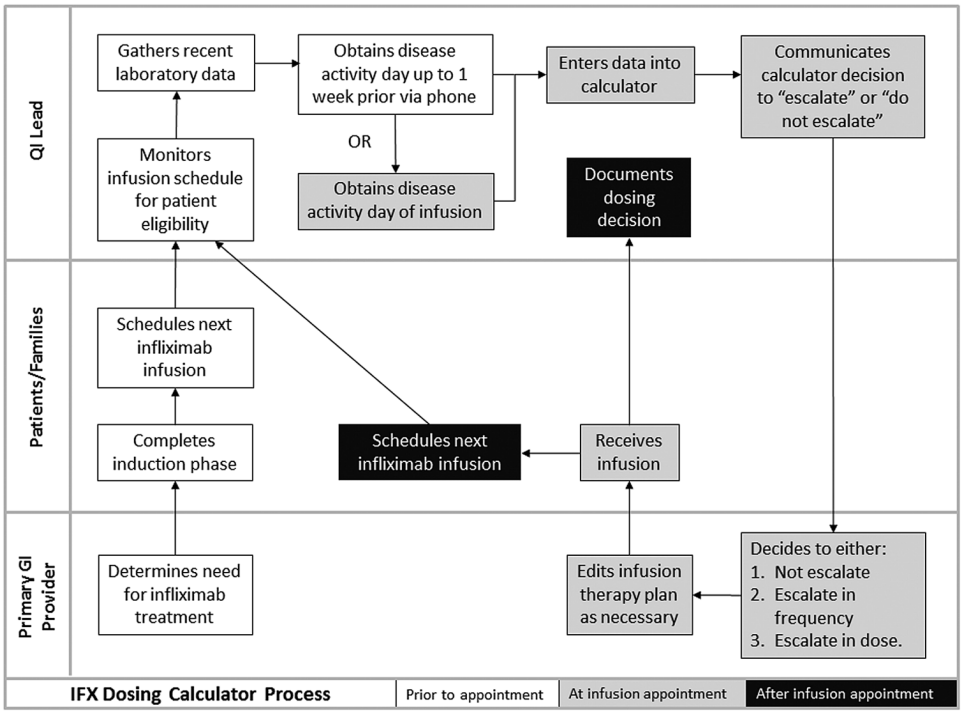

FIGURE 1. Quality improvement swimlane work flow diagram.

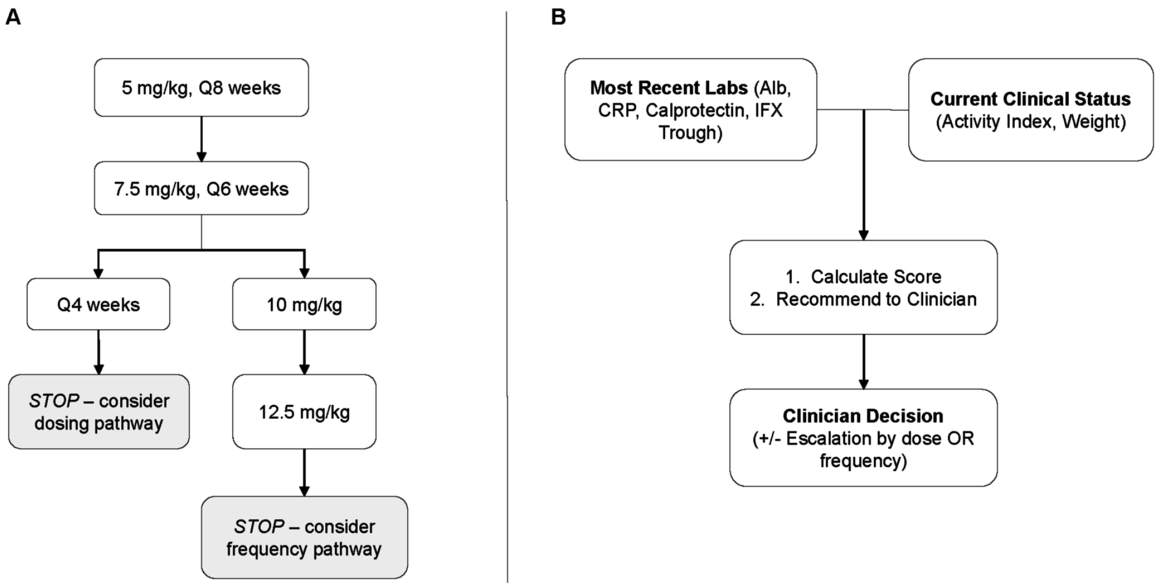

FIGURE 2. A, Recommended escalation flowchart. B, mIDC implementation flowchart.

possible drivers of the treating physician's response to these recommendations. We characterized the primary driver of mIDC recommendation to escalate by assessing if the escalation recommendation was due to symptoms/labs (clinical variables) score, IFX level, or both drivers.

To identify possible drivers of the physician's dosing decisions, we compared those events where the physician followed the mIDC recommendation to escalate with those events where the physician did not follow the recommendation to escalate. Dose escalation was defined as a 25% increase in the IFX exposure when measured by mg/kg/wk. This definition encompasses the mIDC's recommended dose escalation schedule.

Statistical Analysis

Descriptive statistics were used to describe baseline population demographics. Changes in the continuous variables (ie, albumin, CRP, calprotectin, and IFX exposure in mg/kg/wk) at the start and end of the QI initiative were compared using the paired Student *t* test. Right-skewed data were log-transformed, confirming normality of data distribution, prior to performing the *t* test.

RESULTS

Patients

The mIDC made dosing recommendations in 49 children with IBD over 9 months. Table 2 shows the patient characteristics at entry into the QI initiative. The population was a relatively established group, with a median IFX exposure time of 50.4 weeks at the start of the QI initiative. The population was well treated, with 90% having a dosing regimen greater than the standard 5 mg/kg every 8 weeks. This aggressive treatment resulted in a population that was adequately treated, with 21/23 (91%) of baseline troughs being >3 μg/mL and 18/23 (78%) of baseline troughs being >5 μg/mL. Baseline labs also showed that the patients had well-controlled disease, with a mean serum albumin of 3.7 g/dL, CRP of 2 mg/L, and median fecal calprotectin of 100.5 μg/g. With respect to time spent in the QI initiative, the median time was 36.8 weeks, with an average of 5 maintenance infusions.

Feasibility and Pilot Effectiveness

We found the QI initiative to be successful in implementing mIDC on our entire population through the 9-month study period with point-of-care coordination from the QI lead. This encompassed 50 patients, with 1 patient excluded due to stopping IFX without escalation attempt, as determined by the treating physician. mIDC was used an average of 5 times per patient, for a total of 222 maintenance IFX infusions. Potential effectiveness of mIDC was observed by the sustainability of the well-controlled disease profile from initiation to the end of follow-up. Table 3 shows the comparison of outcome measures and IFX trough levels at baseline and completion of the study. The great majority of patients at QI initiation had normal serum albumin and CRP. These remained stable throughout the QI initiative (Table 3). When evaluating calprotectin, there were 9 patients with data at both QI initiation and QI end. Among these patients, we found a statistically significant decrease of quantitative fecal calprotectin, with the median improving from 30 to 27 μg/g (n = 9, $P < 0.05$).

With regard to IFX trough levels, the percentage of patients monitored with TDM in clinical care increased from 34% during the prior year to 86% during the QI initiative.

TABLE 2. Patient Demographics (n = 49)

	Median or No.	Interquartile Range	Min, Max
Age, y	16.0	13.2–18.3	6.9, 23.3
Weight, kg	54.5	44.1–65.7	22.7, 93.8
Female, No. (%)	27 (55)	***	***
Disease type, No. (%)			
Crohn's disease	32 (65)	***	***
Inflammatory, nonpenetrating/structuring penetrating/stricturing	21		
Without perianal disease	2		
With perianal disease	9		
Ulcerative colitis	17 (35)		
Pancolitis	15		
Not pancolitis	2		
Duration on IFX at enrollment			
Duration, wk	50.4	20.4–113.1	7.7, 369.7
Baseline labs			
Alb, g/dL	3.8	3.5–4	2.7, 4.4
CRP, mg/L	2	2–7	2, 46
Calprotectin, µ/g	100.5	28–793	16, 2500
Baseline treatment regimen		5.7–9.7	4.3, 12.5
Dose, mg/kg	7.2	6–8	3.3, 12
Frequency, wk	6.9	0.8–1.3	0.4, 2.9
Dose, mg/kg/wk	1.0	***	***
Dosage > 5 mg/kg dosing, No. (%)	46 (94)		
Frequency > every 8 wk dosing, No. (%)	32 (65)		
Dosage > 5 mg/kg every 8 wk, No. (%)	44 (90)		
Frequency > 7 wk dosing, No. (%)	25 (51)		
Concomitant immunomodulation, No. (%)	43 (88)	***	***
Infliximab trough at enrollment, No. (%)	23 (47)	6–18.4	2.3, 34
Infliximab trough, µg/mL	9.8		
> 3 µg/mL	21/23 (91)		
> 5 µg/mL	18/23 (78)		
Antibody to infliximab, >3.1 U/mL	0/23 (0)		

mIDC achieved adequate target drug exposure throughout the QI initiative, as evidenced by 81% of troughs being >5 µg/mL. When comparing mIDC with pre-QI values, achievement of IFX trough >5 µg/mL increased by 12%. Additionally, our data show low probability of forming ATI while implementing mIDC (Table 3).

Drivers of mIDC Recommendation and Clinician Dosing

mIDC recommended escalation of the dose at 28/222 (13%) infusion events and to "not escalate" the dose at 194/222 (87%) infusion events. When mIDC recommended escalation of the dose, the treating physician followed the recommendation on 13/28 (46%) events and did not follow the recommendation on 15/28 (54%) events.

When assessing the mIDC recommendation to escalate, we characterized the drivers of the recommendation by assessing whether the escalation recommendation was due to clinical variable score, IFX level, or both drivers. We found that of the 28 recommendations to escalate, 14 (50%) of the recommendations were based on symptoms/labs (clinical variables), 10 (36%) of the recommendations were based on IFX levels being <5 µg/mL, and 4 (14%) of the recommendations were based on both symptoms/labs and IFX level (Fig. 3).

To identify possible drivers of physician dosing decisions, we compared clinical variables available at the time of dosing between those events where the treating physician followed mIDC recommendation to escalate vs those events where the treating physician did not follow the mIDC recommendation to escalate. We found that the 2 populations had different starting doses. The median dose of those that escalated was 1.1 mg/kg/wk

TABLE 3. Comparing Baseline With End Point Markers of Disease and IFX Exposure

	Prior to QI (t_0 – 1 y)	QI Start	QI Initiative	Change, %	*P*
Mean albumin (SD) (n = 48), g/dL		3.7 (0.4)	3.8 (0.2)	+0.03	0.58
Median CRP (IQR) (n = 48), gm/L		2 (2, 7)	2 (2, 5)	0	0.48
Median calprotectin (IQR) (n = 9), µg/g		30 (28, 1113)	27 (17, 307)	–10[a]	<0.05
Patients with infliximab trough obtained, No. (%)	13/38 (34)		42/49 (86)	+52	***
Mean infliximab trough (SD), µg/mL	15.9 (12.9)		14.3 (10.6)	–10	***
>3 µg/mL, No. (%)	10/13 (77)		47/53 (89)	+12	
>5 µg/mL, No. (%)	9/13 (69)		43/53 (81)	+12	
Antibodies to infliximab, No. (%)	2/13 (15)		6/53 (11)	–4[b]	***
Infliximab trough with ATI, µg/mL					
>3 µg/mL, No. (%)	1/2 (50)		2/6 (33)		
>5 µg/mL, No. (%)	0/2 (0)		1/6 (17)		

[a]There were 9 patients with paired baseline and end calprotectin data (3 had elevated calprotectin that was greatly improved; 6 had sustained normal calprotectin).
[b]ATI was observed in 6/53 (11%) measured IFX troughs, and of these, 5/6 were with troughs <5 µg/mL. Of the 6 events demonstrating ATI, they occurred in 5 patients. Three patients cleared ATI with dose escalation; 1 clinically overcame with dose escalation, and 1 patient had ATI due to noncompliance and lost response to IFX after the QI initiative ended. The final patient had profound ATI (>40 U/mL) and with escalation has had improvement in therapeutic trough levels but persistence of ATI.

vs 1.8 mg/kg/wk for those that did not escalate, corresponding to ~7.5 mg/kg every 7 weeks vs ~7.5 mg/kg every 4 weeks, respectively (Supplemental Fig. 1), reaching statistical significance at $P < 0.05$. This finding may indicate that the treating physician's dosing decisions to follow or not follow mIDC recommendation to escalate may be dependent on the patient's IFX exposure at the time of the infusion.

DISCUSSION

In this investigation, we demonstrate that the use of a novel, web-based mIDC at the point of care for IFX infusions is feasible and potentially effective. Our findings directly attempt to address the clinical practice need to standardize and individualize IFX dosing for therapy optimization, which can be highly variable between clinicians and management practices. Through a QI initiative, we deployed uniform practice adoption of mIDC and implemented a standardized approach for therapeutic drug monitoring with a goal IFX trough level of >5 µg/mL, as supported in the literature.[31] We showed that under the QI initiative, there was a significant improvement in quantitative fecal calprotectin levels and that our process achieved overall stabilization of other objective markers of clinical remission, such as albumin and CRP. Throughout the course of the follow-up period, loss of response was noted in only 1 patient (2% of the population). ATI was rare and occurred in patients with low IFX trough. After the QI initiative, the presence of ATI resulted in only 1 additional case of loss of response after treatment escalation (Table 3).

Patients in our observed cohort entered the QI initiative on robust maintenance IFX dosing regimens, often higher than the traditional 5 mg/kg every 8 weeks. While this may indicate that treating physicians were already comfortable

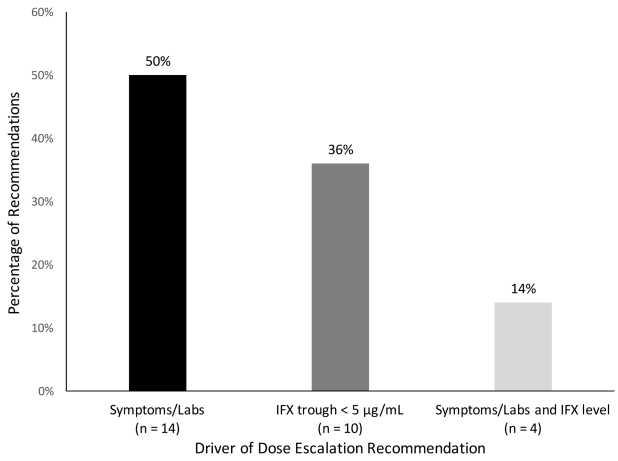

FIGURE 3. Drivers of recommendation to escalate (n = 28 recommendations).

dose-escalating within their own practice framework, a standardization for therapy optimization was made possible by uniform adoption of mIDC. Our post hoc analysis suggests that there may be a threshold for IFX dosing at ~7.5 mg/kg every 4 weeks, where escalation is not attempted, regardless of patient- and biomarker-specific indications to escalate dosing. True drivers of clinician dosing decisions in cases when they declined to escalate remain unclear and are likely unique in each case, although we can postulate that motivating reasons may be a concern for drug toxicity, overimmunosuppression with aggressive anti-TNF therapy, or the belief that the disease is not responsive to IFX at any dose. In support of this, treating physicians were more willing to dose-escalate according to the calculator's recommendation when patients were maintained

on or near the standard 5 mg/kg every 8 weeks. With regard to mIDC use after the QI initiative, our core QI team of 3 gastroenterologists, 1 IBD psychologist, and 1 QI coordinator used mIDC during weekly previsit planning meetings (see Methods and Fig. 2B). Specifically, the QI coordinator (M.C.) and physician lead (K.T.P.) reviewed IFX therapy plans in the EMR and patient-specific parameters in mIDC when necessary to generate a standardized recommendation for all treating clinicians. This process ensured the sustainability of the improvements made by the original QI initiative.

With the increasing evidence for therapeutic drug monitoring[32] and pharmacokinetic-based dosing,[33, 34] our investigation highlights the current clinical practice gap of limited access to point-of-care labs for dosing decisions. Based on our standard of care practice, the mIDC used laboratory data from the prior infusion, which may not precisely correlate with point-of-care disease burden assessed with disease activity indices (ie, PUCAI/PCDAI). When we evaluated the appropriateness of the mIDC's use of most recent laboratory data such as albumin, CRP, and calprotectin levels, we found that having point-of-care laboratory values would have led to a change in the mIDC's recommendation 15% of the time. While the majority of the mIDC's recommendations would have remained the same, we acknowledge that missed opportunity for therapy optimization is a concern and highlights the clinical need for accurate point-of-care laboratory tests to better inform clinician decision-making. This may be particularly applicable for fecal calprotectin and IFX level.

We also acknowledge—as with any QI work—that we did not have a control arm to simultaneously assess treatment effectiveness of mIDC to no intervention. As mentioned, a limitation to quantify mIDC effectiveness is that our largely pediatric patient population was oftentimes already dose-optimized at higher IFX dosing regimens than the standard 5 mg/kg every 8 weeks. The majority of patients were well-treated and in deep remission, reducing the quantifiable opportunity to assess mIDC's treatment effect. Of note, our findings of IFX therapy sustainability and low loss of response support the overall utility of mIDC. Future adoption of mIDC in a more heterogeneous patient population, including a predominantly adult cohort, may further validate its applicability.

In conclusion, our investigation addresses a common challenge across gastroenterology practices seeking to optimize IFX therapy in a standardized and individualized way. Individualized, open-access dosing platforms leveraging advanced pharmacokinetics are not yet available and currently not practical for the general clinician. The overarching goal of our QI work was to address this clinical need and accelerate a practical solution with user-friendliness, patient safety, and evidence-based support in mind. mIDC represents a novel tool that can easily and uniformly be implemented in clinical practice through a mobile, web-based platform available for open use.

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