

# NASPGHAN Clinical Report on Postoperative Recurrence in Pediatric Crohn Disease

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## ABSTRACT

Pediatric Crohn disease is characterized by clinical and endoscopic relapses. The inflammatory process is considered to be progressive and may lead to strictures, fistulas, and penetrating disease that may require surgery. In addition, medically refractory disease may be treated by surgical resection of inflamed bowel in an effort to reverse growth failure. The need for surgery in childhood suggests severe disease and these patients have an increased risk for recurrent disease and potentially more surgery. Data show that up to 55% of patients had clinical recurrence in the first 2 years after initial surgery. The current clinical report on postoperative recurrence in pediatric Crohn disease reviews the risk factors for early surgery and postoperative recurrence, operative risk factors for recurrence, and prevention and monitoring strategies for postoperative recurrence. We also propose an algorithm for postoperative management in pediatric Crohn disease.

**Key Words:** antitumor necrosis factor, Crohn disease, pediatric, postoperative recurrence, risk factors, surgery

(*JPGN* 2017;65: 475–486)

**C**rohn disease (CD) is a chronic disease with clinical and endoscopic relapses. Compared to adult-onset disease, pediatric CD is more likely to have extensive anatomic involvement. Initially, 50% of pediatric patients have ileocolonic disease, 20%

Received May 19, 2016; accepted March 14, 2017.

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The authors report no conflicts of interest.

This article has been developed as a Journal CME Activity by NASPGHAN. Visit <http://www.naspgan.org/content/59/en/Continuing-Medical-Education-CME> to view instructions, documentation, and the complete necessary steps to receive CME credit for reading this article.

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DOI: 10.1097/MPG.0000000000001606

## What Is Known

- Crohn's disease may result in complications that require surgery in children.
- Disease recurrence is common after surgery and can lead to subsequent surgical intervention.

## What Is New

- Children with complicated disease are at higher risk for postoperative recurrence.
- Endoscopic recurrence precedes clinical recurrence, and is a better predictor of the risk for future surgery.
- Anti-TNF agents appear to be the most effective treatment in preventing postoperative recurrence.
- Prophylactic treatment to prevent recurrence rather than treating after the disease recurs, appears to be more effective in preventing further surgery.
- Early Postoperative surveillance for disease recurrence allows for a change in management to prevent complications that may lead to further surgery.

have exclusively colonic disease, and at least 30% have upper gastrointestinal (esophagus, stomach, duodenum) involvement (1). The area of bowel involved often increases with time, and rapid progression typically occurs early in pediatric CD. The inflammatory process is progressive and leads to complications, which may include bowel strictures, fistulas, perianal disease, and intra-abdominal or retroperitoneal abscess (1). Hence, a large number of patients may require surgery over time. The interval between the onset of symptoms and the need for surgery appears to be shorter in children than in adults (1). CD and surgery have a major impact on growth and development providing unique challenges to pediatric gastrointestinal practitioners.

Postsurgical recurrence can be defined as endoscopic recurrence or clinical recurrence. Endoscopic changes can be seen much sooner than the recurrence of clinical symptoms (2,3). There is a paucity of data in children with regards to defining and assessing endoscopic recurrence rates and the impact of endoscopic recurrence on future disease course and surgery. Most of the existing reports stem from retrospective chart reviews and recently established registry reports. Some of the confounders in these studies include variable follow-up period, variable indications for surgery (eg, poor growth and treatment failure, and variable pre-and postoperative treatment regimens. These confounders make generalized population assessment and data analysis difficult.

TABLE 1. Incidence of initial surgery in pediatric Crohn disease

Study	Study years	Numbers	Design	1 Year	3 Years	5 Years	10 Years	Treatment
Patel et al (4)	1968–1994	204	SC		28.8	47.2		
Vernier-Massouille et al (5)	1988–2002	404	PC	7.0	20	34		77% IM 24% Anti-TNF
Van Limbergen et al (6)	2002–2015	276	PC			20	34.5	46% IM
Gupta et al (7)	2000–2003	989	MC	5.7		17	28	65% IM 19% Anti-TNF
Jakobsen et al (8)	2001–2006	105	PC	7–7.9		15.9–23		IM and anti-TNF
Schaefer et al (9)	2002–2008	854	MC pro obs	3.4		13.8		83% IM 18% Anti-TNF

MC = multicenter and MC Prospective Observational study; PC = population cohort; SC = single center.

## FIRST SURGERY IN PEDIATRIC CROHN DISEASE

A review of first surgery in pediatric CD may be helpful in understanding the risk of postoperative recurrence (POR). Table 1 reviews the incidence of first surgery in pediatric inflammatory bowel disease (IBD) (4–9). Approximately 3.4% to 7.9% of patients required surgery in the first year after diagnosis. By 5 years, 13.8% to 47.2% of patients required surgery and by 10 years 28% to 34.5% required surgery. Penetrating and stricturing disease results in defined complications requiring surgery such as abscess, fistula, and obstruction. Indications for surgery in 1 study included ileocecal disease (63%), TI stricture (7.1%), diffuse disease (7.4%), abscess/peritonitis (11%), hemorrhage (7%), and perforated cecum/ileum (3.7%) (10). A summary of several studies suggests that penetrating indications such as abscess or fistula occurred in 9% to 19%, and stricturing in 7.4% to 25% (4,7,11). Inflammatory behavior (B1) was noted in 37% to 45%, stricturing (B2) pattern in 45% to 56% and penetrating (B3) in 7% to 10% of patients in 2 population-based studies (12,13). This suggests that the majority of patients underwent surgery for indications of treatment failure and/or poor growth. Medical failure was cited as an indication in 56% of patients in 1 study (11). Surgery resulted in improved postoperative growth (10,13–15). The most common surgery was resection of the ileum with partial or total colectomy with a range of 44% to 71%, colectomy 10% to 18%, small intestinal resection 4% to 17% (4,7,12,13). The number of patients who had colectomies varied widely in the various studies and some of the patients were subsequently reclassified as ulcerative colitis. All studies showed an increase in the cumulative numbers of patients who required surgery with increasing years of disease. The highest surgical rate

was noted in the study that predated the general use of immunomodulators (IMs) (4). Treatment with IM ranged from 46% to 83% in the more current studies that reported it (5–7,9). The study with the highest IM usage had the lowest rate of surgery at 5 years (9). The percentage of patients on antitumor necrosis factor (anti-TNF) biologicals ranged from 18% to 24% in the studies that noted the use of these medications (5,7,9). Anti-TNF was usually started as a result of treatment failure.

Table 2 summarizes the reported risk factors associated with first surgery after diagnosis (4,5,7,9,16–18). The most consistent factors that increased the risk of surgery in these studies, included complicated disease behavior, poor growth, anti-*Saccharomyces cerevisiae* antibody (ASCA) positivity and nucleotide-binding oligomerization domain-containing protein 2 (NOD2) genotype. Important factors that did not appear to affect the risk for surgery included, IM within the first 30 days of diagnosis, race, and family history of IBD. A few factors decrease risk of surgery, including upper gastrointestinal tract disease and distal colonic disease, and younger age at presentation (7,9). Clinical factors such as severity of abdominal pain, diarrhea, hematochezia, decreased activity due to disease, abdominal tenderness, perianal disease, or extraintestinal manifestations were not associated with risk for surgery. This suggests that clinical factors are inadequate for defining risk for surgery. This study also noted that certain laboratory indicators at the time of diagnosis such as leukocytosis, hypoalbuminemia, and ASCA positivity conferred an increased risk of surgery (7). Dubinsky et al (16) demonstrated that the rate of surgery increases with the number and magnitude of serological markers in a group of 796 pediatric patients. Two pediatric cohort studies show that 3 common mutations of NOD2/Caspase recruitment domain

TABLE 2. Risk factors for first surgery in pediatric Crohn disease

Increased	No effect	Decreased
Leukocytosis (7)	IM within first 30 days (9)	Age <12 years (7,9)
Hypoalbuminemia (7)	Gender (9)	Fever (7)
ASCA positivity (7,16)	Race (9)	IFX/5 ASA/AZA (5,7)
Female (7)	Family history of IBD (9)	Distal colonic disease (9)
Poor growth (5,7)	Perianal disease (5)	Upper GI disease (5)
Initial diagnosis of UC (7)		
Greater disease severity (9)		
Complicated B2/B3 disease (4,5,7,9)		
Treatment with corticosteroids (5)		
NOD2 (17,18)		

5-ASA = 5 aminosalicylates; ASCA = anti-*Saccharomyces cerevisiae* antibody; AZA = azathioprine; GI = gastrointestinal; IM = immunomodulators; INF = infliximab; NOD2 = nucleotide-binding oligomerization domain-containing protein 2.

(CARD15) are associated with the need for surgery during childhood (17,18). Treatment with infliximab (IFX) and mesalamine (aminosalicylate [5-ASA]) were associated with a decreased risk of surgery (7). Vernier-Massouille et al (5) noted that the use of azathioprine (AZA) decreased the risk of first surgery. They also demonstrated that disease phenotype progresses from B1 inflammatory (nonstricturing, nonfistulizing disease) at diagnosis to more complicated stricturing and penetrating phenotypes over time, increasing the risk of surgery (5). Schaefer et al (9) showed that severe phenotype (as measured by Physician Global Assessment) and stricturing and penetrating disease increased the risk for surgery, in agreement with the other registry-based studies. Their registry data showed the lowest cumulative surgical risk compared to the other studies. A number of factors could have accounted for this difference including, short follow-up time, increased percentage of younger patients, and increased colonic disease in the cohort. In addition, 83% of the patients were on IM and 18% were on IFX within 1 year of diagnosis, potentially affecting the natural history of the disease (9).

### POSTOPERATIVE RECURRENCE IN PEDIATRIC CROHN DISEASE

POR refers to *the de novo* development of CD after a “curative” resection in which all grossly evident diseased bowel is removed (19). *Clinical recurrence* has been broadly defined as the reappearance of symptoms associated with objective signs of active disease after intestinal resection (19). *Endoscopic recurrence* indicates subclinical endoscopic lesions, such as ulceration, identified on ileocolonoscopy (2,3). In contrast to clinical recurrence, which may take years to develop, endoscopic recurrence may occur within weeks to months of surgery. Table 3 reviews the current data on POR in pediatric CD (4,10–15,20). Clinical recurrence was frequent, occurring in up to 55% in the first 1 to 2 years postsurgery. Approximately 50% to 73% had clinical recurrence by 5 years and similar rates were noted at 10 years. Few studies are published on endoscopic recurrence early in the postoperative period. Baldassano et al (14) reported clinical recurrence of 17% and endoscopic recurrence of 50% by 1 year after surgery, suggesting that endoscopic recurrence precedes clinical recurrence. Hyams et al (21) found histologically documented recurrent disease in 42% of 79

patients with CD within 5 years after removal of all affected bowel. Piekkala et al (11) showed 94% endoscopic recurrence by 10 years. Recurrent surgical rates varied from 8% to 18.5% in the first 1 to 2 years after surgery. Rates at 10 years ranged from 29% to 55%. In Pacilli et al’s (10) study 100% of patients were treated prophylactically with AZA after the first surgery and still had a high rate of surgery at 2.5 years. Anti-TNF did not appear to affect the rate of surgery, but it was started in response to treatment failure and not prophylactically. The lower rates in Boualit et al’s (13) study most likely reflect the fact that this was a population-based study, so patients with less severe disease would be more likely to be included. The single-center and multicenter studies may reflect a referral population of children with more severe disease. These findings are similar to adult data from randomized controlled trials (RCTs) in which clinical recurrence occurred in 10% to 38% of patients after the first year (22). Endoscopic recurrence in the first year was 35% to 85% of patients. Three years after surgery, the rate of endoscopic recurrence increased to 85% to 100%, whereas symptomatic recurrence was only 34% to 86%. These studies support the conclusion that surgery is not curative for CD. Understanding the risk of recurrence is important in defining who requires treatment postoperatively, when the treatment should be initiated, and which treatment will be the most effective to ensure growth, quality of life, and avoidance of complications.

### RISK OF POSTOPERATIVE RECURRENCE IN CHILDREN

A number of studies have reviewed the risk of POR in adults (2,3). The severity of the endoscopic lesions 1 year after surgery predicts the likelihood of recurrent disease and the risk of repeat surgery (3). The recurrence is usually proximal to the ileocolonic anastomosis. The Rutgeerts et al’s scoring system has been used to evaluate the endoscopic recurrence of disease and the risk of subsequent surgery with i0, i1 representing <5 ulcers suggesting a low risk of progression and i2–i4 representing progressively deeper and more confluent lesions and a higher risk of progression to surgery. Similar data are not available for children. RCTs in adults suggest that smoking is one of the strongest risk factors for recurrent disease (22). A recent meta-analysis suggests that smoking increases the risk of a recurrent surgery in 10 years

TABLE 3. Postoperative recurrence in pediatric Crohn disease

Study	Study years	N	Mean Follow-up, y	Study population	Clinical	Endoscopic	Surgical	Treatment
Pacilli et al (10)	1998–2008	27	1	S	55%			100% IM
Pacilli et al (10)	1998–2008	27	2.5	S			18.5%	100% IM
Besnard et al (20)	1975–1994	30	2	S	50%			5-ASA
Patel et al (4)	1968–1994	94	1.8*	S	44%			
Baldassano et al (14)	1978–1996	68	1	S	17%	50%		
Boualit et al (13)	1988–2004	130	2	P	18%		8%	18% IM or Bio
Hansen et al (12)	1978–2007	115	1	P	50%			61% IM/34% Bio
Griffiths et al (15)	1970–1986	82	5*	S	50%			
Baldassano et al (14)	1978–1996	68	5	S	60%	77%		
Boualit et al (13)	1988–2004	130	5	P	34%		17%	34% IM or Bio
Hansen et al (12)	1978–2007	115	5	P	73%			61% IM/34% Bio
Piekkala et al (11)	1985–2008	36	10	MC		94%	55%	
Boualit et al (13)	1988–2004	130	10	P	47%		29%	47% IM or Bio
Hansen et al (12)	1978–2007	115	10	9	77%		34%	61% IM/34% Bio

Recurrence defined as increase in meds, PGA, radiological evidence of recurrent disease, or repeat surgery.

5-ASA = 5 aminosalicylates; IM = immunomodulators; MC = multicenter.

\*Median. Mean S-single center P-population-based study.

approximately 2.5-fold (23). Exsmokers have similar rates to non-smokers. Prior intestinal resection, penetrating behavior, and extensive disease >50 cm and perianal disease are established risk factors for POR (22). Gender, a family history of CD or IBD, granulomas, and the length of resection have all been investigated for their impact on POR, but either have inconsistent data or do not appear to play a significant role in the risk for surgery or POR (2,3,24–28). Other risk factors noted to be implicated in POR in adults include microbial biomarkers and genetic polymorphisms. McGovern et al (29) showed an association between ASCA titer and endoscopic recurrence. Furthermore, Stone et al (30) demonstrated that immunoglobulin A ASCA positivity was linked with earlier surgical recurrence in a cohort of 176 adult patients. A number of adult studies have shown that mutations in NOD2/CARD15 genetic loci lead to a more aggressive disease course (including progression to a fibrostenosing phenotype) and ileocecal resection, but the effect on POR is mixed (22). No studies are reported on the effect of NOD2/CARD15 mutations on POR in pediatrics. The data for POR risk factors in children are summarized in Table 4. Notably, lack of sufficient data on smoking in children obviates our ability to address this as a risk factor. The type of first surgery may affect the risk for POR. Griffiths et al (15) noted that patients who had ileocolonic resections (26.9% of the surgical patients) had the shortest time to relapse. Two studies report that 100% of patients with strictures relapsed (10,12). Patients with a left colectomy had a high rate of relapse (12). The most common first resection is ileocectomy (47%–66%) and the relapse rate was 55% to 58.8% in 2 studies (10,12). Patel et al (4) noted that early relapse was associated with staged colonic resection and those who had a diverting ileostomy. The relapse rates after surgery for diffuse disease and abscess/peritonitis, penetrating disease were 50% and 66%, respectively (10). This supports the conclusion that diffuse disease, penetrating, and stricturing disease increase the risk for POR. Diffuse disease most likely relates to residual disease. The decreased risk with early resection (penetrating disease) may relate to adequate removal of inflamed tissue allowing for a longer period before symptoms recur. Disease that has been present for 4 years and finally results in surgery may have caused more tissue damage. It is disappointing that even when AZA was given prophylactically a high rate of

surgery persists (10). Piekkala et al (11) reported a high risk of anastomotic stenosis, but 85% were successfully dilated. Gender, age at diagnosis, granuloma, or fistula in the resected specimen did not impact the risk of early relapse (15). Nineteen percent had a permanent ostomy in Piekkala et al’s (11) study and 47% had colectomy or proctocolectomy. In summary, children have a significant risk for POR. Diffuse ileocolonic disease, severe disease, complex disease, and failure of medical management increase the risk for POR.

### OPERATION-RELATED FACTORS FOR POSTOPERATIVE RECURRENCE

Data presented in this section are from adult studies unless otherwise stated.

#### General Factors

Surgery for CD is performed primarily for the management of complications of the disease (stricture, fistula, and perforation) and medical intractability. The goals of surgery are to address the complication while sparing bowel length. The extent of resection is limited to the segment(s) of intestine that are both grossly affected by disease and also responsible for the complications to be addressed (the site of the stricture, fistula, or perforation). The width of the resection margin and the presence of microscopic disease at the margin have no effect on the rate of recurrence (31). Data on operation-related factors for POR in CD are primarily based on studies in adults and have been reviewed in detail elsewhere (28,32).

#### Laparoscopy

Laparoscopy is broadly accepted in gastrointestinal surgery for its potential advantages and should be strongly considered for most patients with CD requiring surgical management of disease-related complications. A Cochrane Collaboration review of laparoscopic versus open surgery for CD of the small intestine found no difference in the rate of recurrence requiring surgical treatment between the 2 techniques (33).

TABLE 4. Risk factors for postoperative recurrence in pediatric Crohn disease

Increased	No effect	Decreased
Severe disease (14)	Age at first surgery (13–15)	Surgery <1–3 years of diagnosis (13,15)
Colonic Crohn’s (14)	Race (14)	Surgery for a specific complication (15)
Diffuse ileocolonic disease (7,10,15)	Gender (14,15)	
Failure of medical therapy (7,10,15)	Appendectomy (14)	
Age <14 (13)	Preoperative disease duration (13,14)	
Complex disease B2/B3 (13)	Length of resection (14)	
Upper GI tract disease (13)	Post-operative complications (14)	
Duration of disease >4 years before surgery (15)	Growth failure (14)	
	Failure of medical therapy (14)	
	Perforating indication (14)	
	Stricture/abscess (14)	
	Granuloma (14,15)	
	Location at diagnosis (13)	
	Anal/perineal lesions (13)	
	EIM (13)	
	CRP at diagnosis (13)	
	IM/anti-TNF (12,13)	

anti-TNF = anti-tumor necrosis factor alpha; CRP = C-reactive protein; EIM = extraintestinal manifestations; GI = gastrointestinal; IM = immunomodulator.

## Anastomosis Type

Intestinal anastomosis type (stapled vs hand sewn) was previously thought to influence the risk of recurrent disease. A randomized multicenter trial, however, demonstrated no effect of the anastomosis type on the risk of recurrence after ileocolic resection (34), settling this issue. The risk of anastomotic leak after ileocolic resection is, however, lower with stapled side-to-side, rather than end-to end anastomosis and hand-sewn anastomosis (35).

## Strictureplasty Versus Resection

Strictureplasty is an alternative to resection and anastomosis employed in areas of noninflamed stricture to relieve intestinal obstruction. It is most commonly employed in jejunoileal disease in the setting of limited bowel length following prior resections or extensive disease, when concern arises that resection may lead to short bowel syndrome. Strictureplasty outcomes are comparable to intestinal resection with regard to recurrent disease (36–38). A meta-analysis of strictureplasty versus resection suggested that surgical recurrence after strictureplasty was more likely (37.8% vs 31%, odds ratio = 1.36,  $P = 0.09$ ), but it did not reach statistical significance (36). Patients undergoing resection had a longer recurrence-free survival compared to strictureplasty alone. In a large series of 1124 strictureplasties in 314 patients with a median follow-up period of 7.5 years, 34% developed recurrent stricture requiring surgery, although usually not in the same site as the strictureplasty (39).

## Postoperative Complications

A small number of studies report a relationship between postoperative complications and recurrence of CD with conflicting findings. Expert reviews conclude that postoperative complications do not affect the risk of recurrent CD (28,32).

### PREVENTION OF POSTOPERATIVE RECURRENCE IN CROHN DISEASE

Data presented in this section are from adults studies unless otherwise specified.

Two potential treatment strategies in postoperative CD include treatment to prevent recurrence of disease (prophylactic) and treatment of disease after it has reoccurred. Data from adult studies suggest that prevention of recurrence provides superior outcomes compared with intervention after the documentation of endoscopic inflammatory changes (40,41). Prevention of recurrence, especially among patients with high risk of recurrence, seems to be the more preferred treatment strategy. The target of treatment in earlier studies was clinical remission. Recent data favor assessment of endoscopic and histologic remission which appear to be better predictors of long-term outcome and surgical recurrence (42–44).

## Aminosalicylates

Sulfasalazine has been evaluated in 3 placebo-controlled trials and only 1 trial was able to demonstrate a statistically significant reduction in postoperative CD recurrence (45–47). Data from 4 placebo-controlled mesalamine studies show more favorable yet heterogeneous results (48–51). The heterogeneous results for the mesalamine studies are, despite large sample sizes, likely to be due to differences in: 5-ASA release mechanisms, dosages, duration of follow-up, and definition of recurrence with only limited studies showing endoscopic or radiologic evidence of reduced recurrence (48,49,52). Doherty et al (53) also performed a meta-analysis,

which found that mesalamine decreased clinical, but not endoscopic recurrence and was inferior to AZA or mercaptopurine for all outcomes with the number needed to treat to prevent clinical recurrence being 12 and to prevent severe endoscopic recurrence being 8. A more recent meta-analysis of 5 trials comparing mesalamine with placebo did not show an overall difference in POR (54). The evidence therefore suggests that 5-ASA's has minimal benefit in preventing POR with potentially greater efficacy at higher doses, and if used at all, should be restricted to those at low risk of POR.

## Antibiotics

The Cochrane Review by Doherty et al assessed the role of antibiotics (nitroimidazole class) in preventing POR, and noted that available evidence favors usage of postoperative antibiotics to prevent clinical and endoscopic recurrence with numbers needed to treat being 4. Higher numbers of side effects were noted in the treatment groups compared with placebo groups, leading to larger numbers of withdrawals from the treatment groups compared to the placebo groups, minimizing the effectiveness of this strategy for preventing POR (53).

## Probiotics

The Cochrane Review failed to demonstrate any benefits of probiotics in preventing POR (53).

## Immunomodulators

A recent Cochrane analysis of RCT (7 in number with 584 patients) of thiopurines (TPs) in maintaining surgically induced remission showed mixed results with 2 studies ( $n = 255$ ) showing less clinical relapse (48% with TP vs 63% for placebo) and fewer endoscopic relapses (17% for TP vs 42% for placebo) (55). When TPs were compared to 5-ASA medications, no major differences in clinical relapse rates were seen between the 2 groups at 1 or 2 years (63% in TP group vs 54% in the 5-ASA group) with a trend favoring TP versus 5-ASA for preventing endoscopic relapse at 24 months (17% vs 48%). At the end of 12 months the numbers needed to treat to decrease clinical recurrence were 7 and for endoscopic recurrence was 4 (55).

D'Haens et al (56) demonstrated in a trial of 81 postoperative patients with CD, that the combination of metronidazole for 3 months and AZA for 12 months was superior to metronidazole monotherapy in preventing endoscopic POR at 12 months (55% vs 78%,  $P = 0.035$ ). Manosa et al (57) found that the combination of metronidazole and AZA was no better than AZA alone for the prevention of postoperative endoscopic recurrence in an RCT. VanLoo et al conducted a large retrospective cohort study of 567 patients who underwent surgery for CD in a mixed academic and regional setting with a median follow-up of 11 years reported a significant effect of TP in preventing POR (43). Kariyawasam et al reported results from a specialist referred cohort in Australia (1035 pts) comparing postoperative IM either TP or methotrexate (MTX). They used metabolite levels to maintain adequate therapeutic levels of TP and used MTX for those who failed TP and demonstrated a significant reduction in initial surgery within 5 years of diagnosis, and a reduction in recurrent abdominal surgery and perianal surgery with introduction of IM within 3 years of diagnosis (58). Two small studies demonstrated that AZA could result in mucosal improvement in patients with CD who had severe endoscopic recurrence after ileocecal resection (59,60). These studies suggest that TP are effective at decreasing endoscopic recurrence. Hansen et al's (12) observational pediatric study on POR did not demonstrate a

reduction in recurrence with postoperative AZA. Utilizing optimal dosing and monitoring levels may be the key to obtaining the best results with TP. The role of MTX in preventing POR in adult or pediatric CD has not been adequately studied.

## Enteral Nutrition

Enteral nutrition can be effective in both induction and maintenance remission in pediatric CD (61,62). Some studies suggest that supplementation with enteral nutrition may also be beneficial for maintaining clinical remission (62–64). The application of enteral nutrition for the prevention of POR has not been well studied. Yamamoto et al (65) evaluated the effect of nocturnal enteral nutrition administered by nasogastric tube postoperatively for a year in a prospective, nonrandomized parallel controlled study. Forty consecutive patients were studied and 20 were assigned to enteral formula at night with low-fat foods during the day and 20 controls had no nutritional therapy or food restriction. Groups were determined by compliance with enteral feeds before surgery. One patient (5%) in the enteral group and 7 (35%) in the nonenteral group developed clinical recurrence at 1 year ( $P = 0.048$ ). At 1 year, endoscopic recurrence was seen in 6 (30%) in the enteral group and 14 (70%) in the nonenteral group ( $P = 0.028$ ) (65). Esaki et al (66) showed that risk factors for failure of enteral nutrition were penetrating disease, colonic disease, and a previous history of surgery suggesting that more studies are needed before enteral feeding can be recommended as therapy to prevent POR. No comparable pediatric studies are reported in the literature.

## Anti-Tumor Necrosis Factor

A number of adult studies have shown efficacy of anti-TNF- $\alpha$  therapy in preventing POR. Sorrentino et al (41) reported the results of a prospective, parallel, nonrandomized study in which 7 patients were treated with a conventional dosing of IFX plus low-dose oral MTX and compared to 16 patients treated with 2.4 g/day of mesalamine, to prevent POR. None of the IFX-treated patients had evidence of disease recurrence by endoscopy and either magnetic resonance imaging or small bowel enteroclysis 2 years after surgery compared with endoscopic recurrence rate of 75% and clinical recurrence rate of 25% of the patients in the mesalamine group. Sorrentino et al (67) also reported 12 consecutive patients treated immediately after surgery with IFX 5 mg/kg without endoscopic or clinical recurrence for 24 months. IFX was discontinued after 36 months, resulting in endoscopic recurrence in 10 out of 12 patients. Patients were placed on low-dose IFX 1 mg/kg with dose escalation in patients who had abnormal endoscopic scores. All patients had Rutgeerts scores below  $i2$  after restarting IFX with the dose being escalated to a maximum of 3 mg/kg of IFX. Yamamoto et al (68) investigated IFX and its use in treating early endoscopic recurrence. Twenty-six patients, placed on 3 g of mesalamine per day maintained clinical remission, but were noted to have endoscopic recurrence at a 5-month colonoscopy. They were then randomized to 3 groups: ongoing mesalamine, AZA 50 mg/day, or IFX q 8 weeks (without induction dosing). After 6 months, 0 of 8 IFX patients, 3 of 8 AZA patients, and 7 of 10 mesalamine-treated patients had clinical recurrence. At 6 months healing of endoscopic recurrence was documented in 75% of IFX-treated patients, 38% of AZA-treated patients, and none of the mesalamine-treated patients.

Regueiro et al (69) conducted an RCT in 24 patients who were randomly assigned to either IFX (5 mg/kg) or placebo within 4 weeks of surgery and continued on IFX or placebo every 8 weeks for 1 year. At 1 year, 9.1% of actively treated patients had

endoscopic recurrence compared to 84.6% of those receiving placebo ( $P = 0.0006$ ). Clinical relapse occurred in none of the 11 IFX-treated patients and 5 of the 13 placebo-treated patients. Among those experiencing recurrence, placebo-treated patients more commonly experienced more severe endoscopic recurrence (grade 2, 30.8%; grade 3, 23.1%; grade 4, 30.8%). In the present study, adverse event rates did not significantly differ between treatment arms. Following the primary endpoint at 12 months postsurgery, patients were offered open-label IFX and followed for another year. Of the 7 patients that opted for open-label IFX, 5 (71%) were in remission at the 2-year time period. Three of the patients who had previously been in remission while on IFX stopped this therapy after the initial year and all 3 developed endoscopic recurrence at the 2-year follow-up time period. Patients in the placebo group that started IFX at 1 year after having evidence of endoscopic recurrence ( $i2$ – $i4$ ) had an attenuated response to IFX (ie, their endoscopic scores improved, but over half still had scores of at least  $i2$ ). Subsequently these patients have been followed 5 years, with the major conclusions being that IFX started within 4 weeks postoperatively and continued for a year prevents postoperative endoscopic and surgical recurrence (70). Initiating IFX on the basis of postoperative endoscopic recurrence at a year did promote mucosal healing and prevented recurrent surgery in those with less advanced disease, but not those with severe disease. Stopping IFX results in disease recurrence and recurrent surgery in 50% of the patients by 5 years. This suggests that IFX can induce postoperative endoscopic remission after mild recurrence, but it also shows that the maximal benefit occurs with early/prophylactic treatment. In a recent randomized placebo controlled multicenter study (PREVENT) involving 297 patients the efficacy of IFX in preventing postoperative endoscopic recurrence was convincingly demonstrated (71). The endoscopic recurrence rate at 76 weeks based on a Rutgeert's score of  $>i2$  was demonstrated in 51% of the placebo group and 22.4% of the IFX-treated group ( $P < 0.001$ ). No difference was found in the clinical recurrence rate defined by the Crohn's Disease Activity Index (CDAI) at 76 or 104 weeks; however, as shown in previous studies the CDAI does not correlate with endoscopic recurrence and clinical recurrence lags behind endoscopic recurrence (72). The severity of endoscopic recurrence is also a better predictor of the risk for future resection than clinical recurrence (3,70). The differences in endoscopic recurrence may have been even greater if the study had allowed for optimization of the IM and IFX levels to prevent the induction of antibodies to IFX (ATI). At week 72 median IFX levels were 4.89  $\mu\text{g/mL}$  in patients on IM versus 2.18  $\mu\text{g/mL}$  in patients not on IM. ATI were present in 16% of the patients not on IM. Endoscopic recurrence was seen in 64% of patients with ATI and 46% of patients with negative ATI and 30% of patients with inconclusive ATI.

Savarino et al conducted an RCT to determine the effectiveness of adalimumab (ADA) compared with TP and mesalamine to prevent POR after ileocolonic resection in CD. This study reports on 51 adult patients followed for 2 years postoperation. The rate of endoscopic recurrence (Rutgeert's score of  $i2$  or greater) was 6.3% in the ADA group and 64.7% in the conventional treatment group (73). Tursi et al (74) compared IFX and ADA in an RCT and found them to be equivalent in preventing histological, endoscopic, and clinical recurrence after a surgical resection. In addition, a recent meta-analysis of adult studies comparing anti-TNF to conventional therapy in POR of CD at 1 year postoperatively demonstrated endoscopic remission in 80.8% of the anti-TNF group compared to only 19.6% in the conventionally treated group (75). A recent Cochrane Review has evaluated different interventions for prevention of POR of CD in adults with most studies favoring anti-TNF as the most effective therapy for preventing POR (53).

These studies suggest superior effectiveness of anti-TNF in preventing postoperative endoscopic recurrence in CD. It appears to work better at preventing POR if started prophylactically. New American Gastroenterological Association (AGA) guidelines recommend prophylaxis post resection over waiting for recurrence of disease before initiating therapy (76). The guidelines also recommend anti-TNF and TP over other agents. The data for these recommendations are presented in the accompanying article (77). Stopping anti-TNF results in disease recurrence and the risk for further surgery. No equivalent studies have assessed the role of anti-TNF in preventing POR in children.

## MONITORING FOR POSTOPERATIVE RECURRENCE IN CROHN DISEASE

An optimal monitoring regimen for POR of CD in children has yet to be established and pediatric data on the subject is scarce. Endoscopic recurrence occurs in 73% to 93% of adults 1 year after surgery and 85% to 100% of adults 3 years after surgery without postoperative treatment (3,78). No current pediatric data support a different natural history or improved outcomes in children with CD after resection compared to adults. Symptom recurrence rates in adults are 20% to 37% at 1 year and 34% to 86% at 3 years after surgery with similar recurrence rates found in children as previously noted (3,14,78). These results demonstrate that many patients with endoscopic recurrence may remain asymptomatic for some time. This underscores the importance of a postoperative monitoring approach that can identify patients with subclinical, early recurrence to allow prompt treatment that may prevent symptom onset, ameliorate symptoms if they already exist, and prevent the development of disease complications and progression and the need for further surgical management.

Most expert opinions and guidelines for adults recommend endoscopic evaluation within the first year after surgery for CD as the criterion standard to monitor for disease recurrence (2,79,80). No similar guidelines exist for children with CD. Noninvasive disease monitoring techniques are increasingly used to monitor disease status. These biomarkers are of particular interest for monitoring disease activity in children and may provide useful screening tools in selecting pediatric patients who should undergo more invasive evaluation with ileocolonoscopy.

## Endoscopic Surveillance

Endoscopy remains the criterion standard for evaluation of POR and early endoscopic assessment (within 1 year of surgical resection) is almost universally recommended (2,79,80). Recurrence typically occurs first in the neoterminal ileum, proximal to the surgical anastomosis (3). Endoscopic recurrence often precedes the onset of clinical symptoms and more importantly, endoscopic disease severity is predictive of clinical recurrence, disease course, and complications postoperatively (3). Rutgeerts et al (3) developed a postoperative endoscopic scoring system that has been validated as a predictor of clinical recurrence in adults. Patients with no endoscopic disease or fewer than 5 aphthous lesions (scores of i0–i1) on ileocolonoscopy in the first year after resection had clinical recurrence rates of <5% at 3 years, whereas patients with more severe ulcerations or diffuse ileal inflammation (scores of i3–i4) had clinical recurrence rates between 40% and 90% (3). These data support early endoscopic surveillance to identify asymptomatic patients at risk for clinical recurrence and disease complications. It is important to note that the Rutgeerts' score has not been validated in children and that no similar pediatric scoring system currently exists. More recently the results of the POCER trial showed that earlier endoscopic surveillance (at 6 months), with escalation of therapy if disease recurrence was discovered, led to

lower rates of endoscopic recurrence at 18 months compared to patients who were not routinely re-evaluated with ileocolonoscopy at 6 months (44). This adult study is the first large, randomized trial to show that early postoperative surveillance may have a clinical benefit for patients. Initiating IFX treatment after the development of severe endoscopic disease recurrence, may not be totally effective in eradicating the disease, lending more support for earlier endoscopic assessment of recurrence (70,81). These results also support prophylactic treatment rather than treatment post recurrence.

## Clinical Disease Activity Scores and Routine Laboratory Studies

Although the CDAI is a commonly used, noninvasive composite scoring system used to follow disease activity in adults with CD, it is less effective at predicting disease recurrence in the postoperative setting (82). The largest study to date evaluating the CDAI in the postoperative setting found that it discriminated patients with or without endoscopic recurrence only 65% of the time when the standard cut-off score of 150 was used, yielding a specificity of 89%, but sensitivity of only 30% (83). A second smaller study found little to no agreement between CDAI and endoscopic findings 1 year after resection. The erythrocyte sedimentation rate and C-reactive protein (CRP) also correlated poorly with endoscopic findings (72). In contrast, a recent study by Walters et al supports the CDAI to be somewhat more effective at predicting endoscopic recurrence with a CDAI  $\geq 148$  as the best predictor (sensitivity 70%, specificity 81%) (84). The low sensitivity of the CDAI in the postoperative setting underscores the important concept that many asymptomatic patients have active disease that would be missed without more extensive evaluation. Thus, although the CDAI is attractive as a noninvasive measure of disease activity, it is not a sufficient tool for monitoring for POR in CD when used alone. Of note, the Pediatric Crohn's Disease Activity Index has not been evaluated or validated in the postoperative setting in children with CD.

## Fecal Markers

Fecal calprotectin (FC) and fecal lactoferrin (FL) are markers of neutrophil activity in the gastrointestinal tract that help discriminate between IBD and non-IBD causes of diarrhea and correlate well with mucosal healing. They have the potential to serve as noninvasive markers of disease activity in established IBD (85,86). FC has been evaluated as a predictor of disease recurrence in adults with CD after surgery and generally correlates with endoscopic recurrence more accurately than CRP and CDAI (87–90). Lamb et al (87) collected serial FC and FL samples from 13 adults with CD after resection. Patients with an uncomplicated postoperative course had normalization of FC and FL by 2 months. Both FC and FL correlated with clinical disease activity as measured by the Harvey-Bradshaw Index. In a cross-sectional analysis of 104 patients at a median of 24 months after ileocecal resection, patients with severe clinical recurrence had mean FC and FL levels of 661.1 and 116.6  $\mu\text{g/g}$ , respectively, compared to 70.2 and 5.9  $\mu\text{g/g}$  in patients with inactive disease. FC and FL levels correlated with clinical disease symptom scoring (Harvey-Bradshaw Index) than CRP and platelet count. Lobaton et al (90) recently evaluated FC levels with a new rapid point of care FC test in 29 adults after ileocolonic resection and showed that FC levels correlated well with endoscopic recurrence. The median FC value in patients with Rutgeerts' scores of i0 or i1 was 98  $\mu\text{g/g}$  compared to 235  $\mu\text{g/g}$  in patients with scores of i2–i4 ( $P = 0.012$ ). A cut-off FC value of 283  $\mu\text{g/g}$  had sensitivity of 67% and specificity of 72% and FC was

more accurate than the CDAI, CRP, or platelet count at predicting endoscopic recurrence. Papamichael's study demonstrated similar superiority of FC over CRP and CDAI in predicting endoscopic recurrence (88). Two large prospective adult studies both showed a positive correlation of FC and endoscopic recurrence. The optimal FC level cutoff of 100  $\mu\text{g/g}$  distinguished between endoscopic recurrence and remission with sensitivity and specificity ranging from 89% to 95% and 54% to 58%, respectively (91,92). A study by Lasson et al found no difference in the median FC levels between those patients with endoscopic remission and those with endoscopic recurrence at a year, however, they noted that most patients with low FC levels were in remission and all patients with high levels (>600) had recurrent disease (93). They noted variability in the results which could be dependent on sampling and stool consistency. Lamb et al did a cross-sectional study at a median of 24 months after surgery and did not demonstrate a correlation of FC with endoscopic appearance and speculated differences in distribution and extent of disease as possible variables (87). A recent meta-analysis of prospective studies also supports the usefulness of FC in this setting, but confirmation of disease severity and extent will be important in making therapeutic decisions (94). FC has been shown to correlate with endoscopic disease in pediatric inflammatory bowel disease but has not yet been systematically evaluated in the postoperative setting in children with CD (95). Although pediatric studies are still needed, the growing evidence from the adult trials supports that strong consideration can be given to the use of FC to help monitor for POR in children.

## Radiographic Imaging Studies

The utility of various imaging modalities including ultrasound (US), computerized tomography (CT), and magnetic resonance imaging are being increasingly evaluated in the postoperative setting in CD. Standard transabdominal US (TUS) has sensitivity and specificity rates for disease recurrence nearing 80% and 90%, when compared to ileocolonoscopy (96,97). Cammarota et al prospectively studied 196 adults with US and, identified bowel thickness of >3 mm at the anastomosis as a risk factor for surgical recurrence and reoperation (relative risk 2.1) (98).

Small intestinal contrast ultrasonography (SICUS) uses large volume contrast to improve assessment of bowel wall thickness and limits restrictions often caused by overlying bowel gas in conventional TUS. Its accuracy in detecting POR has been evaluated but SICUS has not been directly compared to conventional TUS. The diagnostic accuracy for disease recurrence with SICUS ranges from 87.5 to 100% compared to colonoscopy (99–101). TUS and SICUS show promise as noninvasive tools to detect POR. Lack of ionizing radiation make them particularly appealing for children. Limiting factors are operator dependency and the limited availability of SICUS.

Biancone et al. studied CT colonography in 16 adults who had undergone prior surgical resection for CD, revealing a sensitivity of 73%, specificity of 100%, and accuracy of 75% (102). CT colonography was successful at detecting structural narrowing/stricture but missed milder mucosal abnormalities in the absence of structural changes in some patients. More recently, Mao et al compared, CT enterography (CTE) with ileocolonoscopy in the evaluation of POR and showed good correlation ( $r=0.782$ ,  $P<0.0001$ ) (103). In addition, CTE identified fistula, abscess, and more proximal small bowel disease not seen on ileocolonoscopy, leading to a change in therapy in 25% of patients. Interestingly, the authors found that the severity of lesions on CTE correlated with risk for reoperation, whereas the Rutgeerts' score did not. The major disadvantage of CT remains the risk of radiation exposure; however, newer scanners and protocols are decreasing the radiation exposure.

Magnetic resonance enterography (MRE) is rapidly becoming a standard for evaluation of the small bowel in children and adults with IBD. Its role in POR has been evaluated by Sailer et al (104) who compared MRE with endoscopic recurrence at ileocolonoscopy. MRE performed well with mean observer agreement of 77.8% compared with colonoscopy. The investigators created an MRE scoring system and mild findings on MRE correlated well with low-grade Rutgeerts' scores of i0-i1 with a higher mean observer agreement of 95%. The same group later reported that MRE was equally effective at predicting clinical recurrence as colonoscopy and the Rutgeerts' score (105). The biggest advantage of MRE is the lack of ionizing radiation exposure. Disadvantages include tolerance of large contrast volume, high cost, long study time, limited availability, and operator dependency. Studies in children for assessing POR with imaging modalities are lacking.

## Capsule Endoscopy

Wireless capsule endoscopy (WCE) is used to image the mucosa of the small bowel. Advantages of WCE over colonoscopy include lack of need for sedation and identification of lesions in areas of the bowel not reached by conventional upper endoscopy and ileocolonoscopy. Three small studies in adults have evaluated the usefulness of WCE in evaluating for POR in CD. Bourreille et al (106) followed 32 patients who underwent WCE and ileocolonoscopy within 6 months of resection. Although WCE was able to detect more proximal CD lesions out of the reach of standard ileocolonoscopy in up to two thirds of patients, the sensitivity of WCE to detect recurrence was inferior to colonoscopy (62%–76% vs 90%).

Pons Beltran et al (107) performed WCE and colonoscopy in 22 asymptomatic patients with CD after resection. In contrast to the previous study, WCE was found to be more effective than colonoscopy at identifying ileal disease recurrence. In addition, proximal small bowel lesions were identified by WCE in more than half of the patients. Therapy was changed in 16 patients based on WCE findings and all patients preferred WCE to colonoscopy.

Biancone et al (108) performed colonoscopy, WCE, and SICUS in 17 asymptomatic (CDAI < 150) adults 1 year after resection. Sixteen patients had endoscopic recurrence. WCE and SICUS were equally effective, identifying lesions representing endoscopic recurrence in 100% of cases and overcalling only one "true negative." WCE shows good promise as a less invasive method to monitor for POR in CD. It has not yet been evaluated for this purpose in children and its use in younger children may be limited by their inability to swallow the capsule or issues with small body habitus and capsule retention.

One concern with WCE in the postoperative setting is capsule retention at the surgical anastomosis or at other narrowed areas in the small bowel. Capsule retention did not occur in any of the 71 adult patients in the 3 studies mentioned above (106–108). It, however, should be noted that many of those studied were assessed for luminal narrowing with a patency capsule or small bowel imaging before the WCE. During this assessment, 7 subjects were found to have potential narrowing and WCE was not performed. In clinical practice, a patency capsule or contrast-enhanced small bowel imaging study should be strongly considered before WCE in this setting to avoid capsule retention at the ileocolonic anastomosis or at a more proximal location.

## Timing of Evaluation for Postoperative Recurrence

Current evidence supports evaluation for POR within 6 to 12 months after surgery for CD (76). This is driven by the finding that endoscopic recurrence often precedes the onset of clinical



symptoms and the presumption that escalation of medical therapy will benefit asymptomatic patients in whom disease has recurred. The optimal strategy for evaluation of recurrence in children is unknown. Most adult guidelines recommend endoscopic evaluation for all patients within the first year after surgery. Other less invasive markers of disease recurrence need further evaluation, particularly in children. Radiographic studies, WCE, and fecal biomarkers show the most promise as noninvasive modalities and should be considered in the postoperative setting. The efficacy of combinations of various noninvasive markers in ruling out endoscopic recurrence has yet to be evaluated in children, but may improve sensitivity. A step-wise approach, starting with noninvasive monitoring modalities, may obviate the need for invasive endoscopic surveillance in certain patients, such as those with low FC or FL levels and normal radiographic studies in whom significant endoscopic recurrence is less likely. This too has yet to be studied and for now endoscopic assessment with the first 12 months is advisable.

### DISCUSSION AND CONCLUSIONS

Over time, CD can progress from an inflammatory phenotype to fibrostenotic and or penetrating disease often requiring surgery (5). Children who have had surgery are at risk for recurrent disease and subsequent surgery. Postoperative management should reflect this risk. Available data suggest that the highest risk of surgery and recurrence exists in children with small bowel disease. The risk for initial surgery appears to be greatest in those with internal penetrating disease, hypoalbuminemia, leukocytosis, and growth issues, whereas risk of POR seems to be greatest in patients with ileocecal resections, younger age at first surgery, and in those with penetrating and stricturing disease. Hence postoperative treatment and surveillance are highly recommended especially in those patients with a high risk of recurrence. Based on the findings of this

report, the authors have suggested an algorithm (Fig. 1) as a guide for managing pediatric patients with CD postoperatively.

Postoperative treatment should be guided by the risk of disease recurrence to avoid excessive exposure to immunosuppression, medication toxicity, and cost. 5-ASAs seem to have the least impact on POR and should not be used as the sole medication in any child operated on for complicated disease. TP, on the contrary, seems to play a role in decreasing POR, but this benefit needs to be weighed against the small but real increased absolute risk of lymphoma and Hepatosplenic T cell lymphoma especially in young males (109). MTX seems to have lower risk of lymphoma but few data are available on the efficacy of MTX especially in preventing POR as a single agent. Anti-TNF agents appear to be the most effective medications in preventing POR. Despite the use of IM and IFX in the pediatric studies reviewed, there was minimal data to show an effect of IM and anti-TNF on POR. Only one of the studies, however, use IM prophylactically. Prophylactic intervention (before development of recurrent disease) appears to be the optimal approach based on adult data and should be considered in pediatric patients with moderate to high risk of recurrent disease. Prophylactic intervention is supported by a recent cohort analysis by Diederer et al (110) that looked at 122 children who had ileocecal resection (1990–2015) and found that immediate postoperative therapy decreased the risk for clinical and surgical recurrence. Only 11% of patients were on anti-TNF, but none of those patients had surgical recurrence. Anti-TNF agents can be started as early as 4 weeks after surgery. An emerging concern for anti-TNF therapies is the loss of initial response. Steenholdt et al suggest IM and maintenance of therapeutic levels minimizes the risk of antibody formation (111). If a patient does require surgical intervention while on an anti-TNF agent, efforts should be made to test for both levels and antibody as that may alter the choice of postoperative

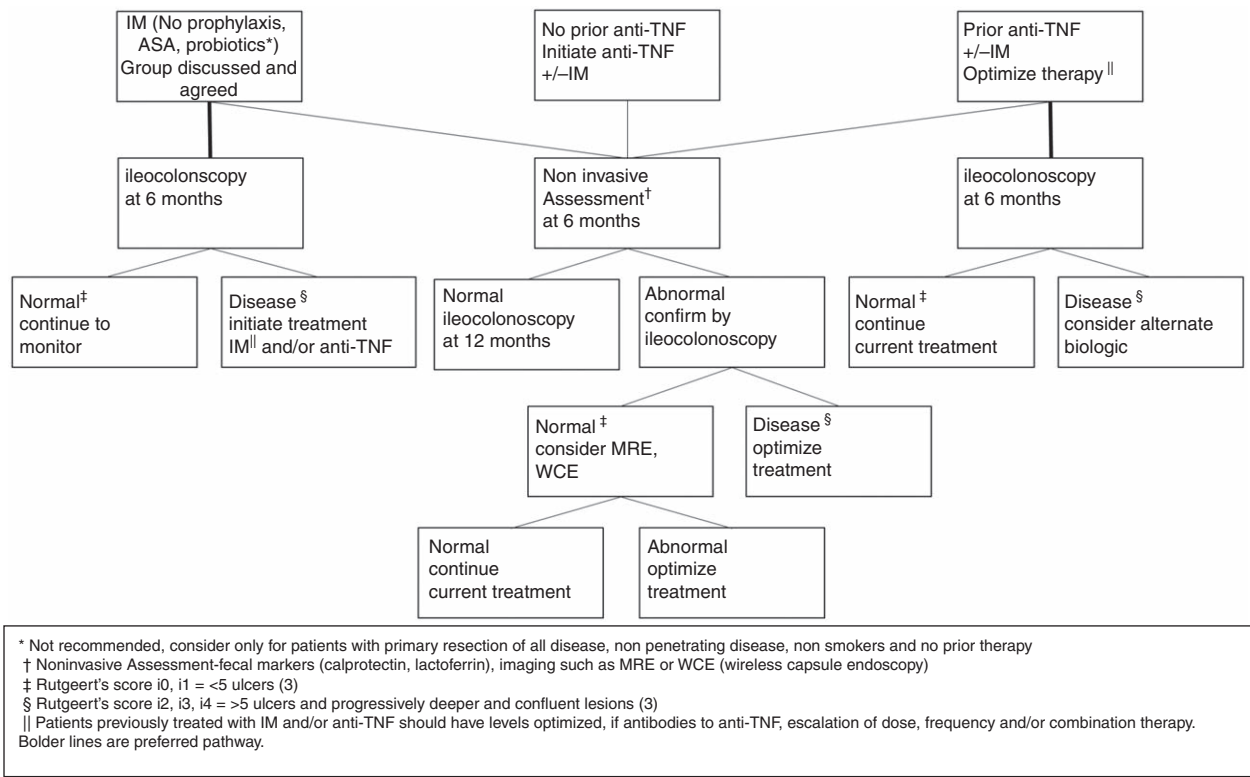


FIGURE 1. Recommendation for postoperative surveillance in pediatric Crohn disease. 5-ASA = aminosaliclate; IM = immunomodulator; MRE = magnetic resonance enterography; TNF = tumor necrosis factor; WCE = wireless capsule endoscopy.

prophylactic therapy. Dose escalation and or shortened intervals of anti-TNF can be used for those with low levels. Alternate biologics and/or addition of IM at therapeutic doses and levels can be considered in those who have developed high titer antibodies. Elective discontinuation of anti-TNF agents after surgery, even in patients with deep remission cannot be recommended at this time due to the high risk of recurrence (67,69).

Whatever treatment is chosen, early surveillance for disease recurrence is clearly needed. Clinical assessment is not sufficient, because it does not correlate with endoscopic disease (3). Noninvasive tests such as FC and FL have been shown to correlate with disease activity better than CRP (95). Studies have shown that FC and FL return to baseline levels around 2 months postsurgery, and monitoring disease activity postsurgery with these tests may help determine appropriate patient selection for more invasive testing such as endoscopy (87). Radiologic evaluation with SICUS, TUS, and MRE can evaluate wall thickness, assess for stricturing and penetrating disease without radiation exposure and are well tolerated, but may not be as sensitive for detecting mucosal recurrence. WCE is sensitive for evaluating mucosal disease and is less invasive than endoscopy, but stricturing and luminal narrowing may limit its use. The optimal timing for endoscopic evaluation of POR in children is not known. A conservative approach for patients with resection of all disease, who have never been on treatment before and who have no clinical signs of disease, may include noninvasive testing at 6 months with fecal biomarkers, capsule, or cross-sectional imaging rather than waiting for endoscopic assessment at 1 year postresection. Limited adult data suggest that waiting for 12 months may allow disease to progress to the point that treatment may not be sufficient to prevent further surgery. Therefore, in patients with a moderate or high risk of recurrent disease or in patients who are on no treatment, it seems prudent to rescope at 6 months, so that therapeutic intervention may prevent structural damage that could lead to further surgery.

A major challenge in making recommendations for pediatric postoperative patients is that nearly all the data regarding prognostic factors, medication efficacy, and monitoring techniques are extrapolated from adult data. In addition, when these patients transition to adult care we often lose track of long-term outcomes. Establishing multicenter pediatric collaborations and registries that follow patients beyond transition to adult care will provide more powerful data on long-term outcomes after surgical resection and will be essential in guiding postoperative management.

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