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TOPIC HIGHLIGHT

Giovanni Latella, MD, *Series Editor*

Role of surgery in severe ulcerative colitis in the era of medical rescue therapy

Bosmat Dayan, Dan Turner

Bosmat Dayan, Dan Turner, The Pediatric Gastroenterology Unit, Shaare Zedek Medical Center, The Hebrew University of Jerusalem, Jerusalem 91031, Israel
Author contributions: Dayan B reviewed the literature and wrote the first draft; Turner D reviewed the literature and revised the manuscript.
Correspondence to: Dan Turner, MD, PhD, The Pediatric Gastroenterology Unit, Shaare Zedek Medical Center, POB 3235, Jerusalem 91031, Israel. turnerd@szmc.org.il
Telephone: +972-2-6666482 Fax: +972-2-6555756
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Abstract

Despite the growing use of medical salvage therapy, colectomy has remained a cornerstone in managing acute severe ulcerative colitis (ASC) both in children and in adults. Colectomy should be regarded as a life saving procedure in ASC, and must be seriously considered in any steroid-refractory patient. However, colectomy is not a cure for the disease but rather the substitution of a large problem with smaller problems, including fecal incontinence, pouchitis, irritable pouch syndrome, cuffitis, anastomotic ulcer and stenosis, missed or de-novo Crohn's disease and, in young females, reduced fecundity. This notion has led to the widespread practice of offering medical salvage therapy before colectomy in most patients without surgical abdomen or toxic megacolon. Medical salvage therapies which have proved effective in the clinical trial setting include cyclosporine, tacrolimus and infliximab, which seem equally effective in the short term. Validated predictive rules can identify a subset of patients who will eventually fail corticosteroid therapy after only 3-5 d of steroid therapy with an accuracy of 85%-95%. This accuracy is sufficiently high for initiating medical therapy, but usually not colectomy, early in the admission without delaying colectomy if required. This approach has reduced the colectomy rate in ASC from 30%-70% in the past to 10%-20% nowadays, and the mortality rate from over 70% in the 1930s to about 1%. In general, restorative proctocolectomy (ileoanal pouch or ileal pouch-anal anastomosis), especially the J-pouch, is preferred over straight pull-through (ileo-anal) or ileo-rectal anastomosis, which may still be considered in young females concerned about infertility. Colectomy in the acute severe colitis setting, is usually performed in three steps due to the severity of the inflammation, concurrent steroid treatment and the generally reduced clinical condition. The first surgical step involves colectomy and constructing an ileal stoma, the second - constructing the pouch and the third - closing the stoma. This review focuses on the role of surgical treatment in ulcerative colitis in the era of medical rescue therapy.

Key words: Acute severe ulcerative colitis; Colectomy; Corticosteroids; Cyclosporine; Infliximab; Tacrolimus

Peer reviewers: Julio Mayol, MD, PhD, Department of Digestive Surgery, Hospital Clinico San Carlos, MARTIN-LAGOS S/n, 28040 Madrid, Spain; Michael Leitman, MD, FACS, Chief of General Surgery, Beth Israel Medical Center, 10 Union Square East, Suite 2M, New York, NY 10003, United States; Keiji Hirata, MD, Surgery 1, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan

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INTRODUCTION

Acute severe colitis (ASC) is one of the few emergencies in gastroenterology. The mortality rate from ASC dropped from over 70% in 1933 to 20%-25% in the 1950s when the importance of timely urgent colectomy was first recognized[1,2]. Subsequently, the mortality rate was further reduced to 7% with the introduction of corticosteroids, and eventually to about 1% nowadays[3-5].

Truelove *et al*[3], in their landmark clinical trial in 1955, defined severe disease as the passage of at least six daily bloody stools, erythrocyte sedimentation rate > 30, temperature > 37.8 ℃, pulse rate > 90/min and hemoglobin < 10.5 g/dL. These criteria remain the most common classification of ASC in adults. In a systematic review of cohort studies on ASC, 20 of 29 studies used the Truelove and Witts classification[5]. However, of these 20 studies, 12 required the fulfillment of all of the five items, and 8 applied various more liberal modifications. More recently, the European Crohn's and Colitis Organization (ECCO) issued guidelines on managing ASC defining severe attack as ≥ 6 bloody diarrhea per day with at least *one* of the other four bullets[6]. In children, severe disease has been robustly defined using the Pediatric Ulcerative Colitis Activity Index (PUCAI) with a score of at least 65 points yielding high sensitivity and specificity[7,8]. Pediatric onset ulcerative colitis (UC) is often more extensive than in adults[9], and since disease severity has been consistently associated with disease extent, children are especially susceptible to refractory severe attacks. Nearly one third of children with ulcerative colitis will experience at least one severe exacerbation before turning into adult care[10].

PREDICTING THE NEED FOR SALVAGE THERAPY

The only factor associated with a major surgical complication among 80 adults who underwent urgent colectomy in Oxford for ASC, was longer duration of medical therapy before colectomy[11]. It is of great importance to recognize those who are likely to fail intravenous corticosteroid early during the admission and to introduce timely rescue therapy. This approach may reduce morbidity and mortality and avoid futile toxic medical therapy.

Several clinical predictive indices have been proven to perform well in identifying those who require salvage therapy after only 3-5 d of admission. In a prospective study, Travis *et al*[12] from Oxford suggested that a stool frequency of > 8/d or 3-8/d and C-reactive protein (CRP) > 45 mg/dL on the third day of corticosteroid therapy should be sufficient for initiating rescue therapy. Lindgren *et al*[13] developed the fulminant colitis index (n = 97) based on the same variables as the Oxford index - stool frequency/d + 0.14 × CRP mg/L. Ho *et al*[14] based the Scottish index on stool frequency, presence of colonic dilatation, and hypoalbuminemia. Others have also shown some predictive ability of their indices[15,16]. In children, a predictive rule based on the PUCAI score at days three and five of steroid therapy has been validated[10,17] and incorporated in the combined ECCO and European Society for Paediatric Gastroenterology Hepatology and Nutrition recent guidelines on pediatric ASC[8]. A PUCAI score of > 45 points on day 3 should dictate planning of second-line therapy and > 65-70 points on day 5 should prompt execution of the planned therapy. All aforementioned indices are based on the consistently reproduced fact that the likelihood for responding to medical corticosteroids is inversely associated with the degree of disease severity even before treatment has been initiated.

Despite the significant improvement in patient care with the implementation of indices-based management schemes, their accuracy is still imperfect. The positive predictive value (PPV) of the Oxford index in predicting steroid failure is 85% for colectomy and the sensitivity and specificity of the Scottish index is 85% and 75%, respectively. The PPV of the fulminant colitis index at a cutoff score of > 8 at day 3 is 69%-72%[13,18]. The PUCAI successfully identifies those for whom the likelihood of failing corticosteroids is 92%. These indices should be perceived as accurate enough for initiating salvage medical therapy (i.e., infliximab or calcineurin inhibitors) but probably not for early irreversible colectomy (Table 1).

SALVAGE MEDICAL THERAPY

Medical rescue therapy should be utilized as the first-line treatment in ASC before colectomy in most corticosteroid-failed patients who do not present with surgical abdomen or toxic megacolon. During the last 20 years, cyclosporine has been widely used[19] and more recently also infliximab[18], and tacrolimus[20] . These medications reduced the short-term colectomy rate from 30%-70%[3,5,21,22] to approximately 10%-20% nowadays[17,23]. The increasing use of second-line medical therapy before colectomy has been based on the high effectiveness of these drugs and the notion that colectomy is not a cure for the disease, but rather the substitution of one large problem with several smaller problems.

Experience with cyclosporine showed that, although the short-term response rate reaches 70%-80%[5,9], approximately 50% of responders will eventually require colectomy when the drug is discontinued, typically after 4 mo[5,21,24-26]. The likelihood of colectomy is reduced if cyclosporine is used as a bridging medication to thiopurines[27]. The other calcineurin inhibitor, tacrolimus (FK-506), has recently been proved effective as a second-line regimen in the clinical trial setting, while aiming at high trough levels of 10-15 ng/mL[20]. It seems that tacrolimus is as effective as cyclosporine for salvage therapy in ASC, both in adults and children[21,28,29]. Tacrolimus, a more expensive medication, has a better bioavailability than cyclosporine, allowing for oral treatment. The toxicity profile is more appealing but there are fewer published studies to support its use.

Table 1 Prediction rules for corticosteroid failure in patients with acute severe ulcerative colitis

Prediction rule	Study	Measure	Prediction accuracy
Oxford index	Travis *et al*[12], prospective; Turner *et al*[10], retrospective	Stool frequency of > 8/d or 3-8/d and CRP > 45 mg/L (on day 3 of IVCS)	Adults: PPV = 85% Children: Sens = 38%, Spec = 100%, PPV = 88%, NPV = 75%
Swedish index (the fulminant colitis index)	Lindgren *et al*[13], retrospective; Järnerot *et al*[18], prospective; Turner *et al*[10], retrospective	CRP mg/L × 0.14 + daily stool frequency (cutoff > 8 on day 3 of IVCS)	Adults: Sens = 78%, Spec = 81%, PPV = 69%-72% Children: Sens = 64%, Spec = 92%, PPV = 88%, NPV = 75%
Seo index	Seo *et al*[15], retrospective; Turner *et al*[10], retrospective	60 × bloody stool + 13 × bowel movements + 0.5 × ESR - 4 × Hb - 15 × albumin + 200	Adults (cutoff > 180 on day 7 of IVCS): PPV = 52%, NPV = 97% Children: (cutoff > 240 on day 5 of IVCS): Sens = 27%, Spec = 93%, PPV = 80%, NPV = 56%
Scottish index	Ho *et al*[14], prospective	The score (0-9) includes: stool frequency, presence of colonic dilatation, and albumin level (cutoff > 4 on day 3 of IVCS)	Adults: Sens = 85%, Spec = 75%
PUCAI	Turner *et al*[10], retrospective; Turner *et al*[17], prospective	The score (0-85) includes: stool frequency and consistency, presence of blood, nocturnal stools, activity level, and abdominal pain	Children: PUCAI > 45 on day 3 of IVCS: Sens = 92%-93%, NPV = 88%-94% PUCAI > 70 on day 5: Sens = 35%-44%, Spec = 93%-100%, PPV = 87%-100%, NPV = 63%-79%

NPV: Negative predictive value; PPV: Positive predictive value; Hb: Hemoglobin; ESR: Erythrocyte sedimentation rate; IVCS: Intravenous corticosteroids; Spec: Specificity; Sens: Sensitivity; CRP: C-reactive protein; PUCAI: Pediatric Ulcerative Colitis Activity Index.

Infliximab has been established as an effective regimen for moderate to severe ulcerative colitis, including ASC. The ACT-1 and ACT-2 randomized controlled trials assessed the ability of infliximab to induce and maintain remission in moderate to severe ulcerative colitis[30,31]. A total of 728 adult patients received placebo or infliximab (5 or 10 mg/kg) through week 46 (ACT-1) or 22 (ACT-2). In the ACT-1 and 2 trials respectively, 61% and 69% of infliximab-treated subjects had a short-term clinical response compared with 29% and 37% of those who received placebo. In steroid-refractory ASC, infliximab is effective as salvage medical therapy in approximately 70%-80% of children and adults, reducing short- and long-term colectomy rate[17,18,32]. In the Jarnerot trial, the colectomy-free rate was 12/24 (50%) after 3 years[33]. Combining the data of both ACT trials has shown that the 1-year colectomy rate in the infliximab-treated arm was 10% *vs* 17% in the placebo arm[34]. It should be emphasized that the ACT trials did not include patients who were refractory to intravenous steroid in the setting of ASC.

In the recent steroid-refractory severe attacks of ulcerative colitis trial, 116 adults with ASC who did not respond to a 5-d course of intravenous steroids were randomized to receive intravenous cyclosporine or infliximab using standard doses and protocols, both combined with azathioprine[35]. Both the 7-d response rate (85.4% *vs* 85.7%) and treatment failure rate through day 98 (60% *vs* 54%) were similar between the cyclosporine and the infliximab arms, suggesting that the two regimens are equally viable alternatives to colectomy in steroid-refractory ASC. Similar effectiveness has also been suggested in a systematic review of non-randomized studies in children[21]. In contrast, a nonrandomized study showed that 52% of patients receiving cyclosporine proceeded to colectomy by discharge, *vs* 18% of those administered infliximab[36].

SURGERY

Although, in general, medical rescue therapy should be regarded as the first-line treatment in steroid-refractory ASC, colectomy is still a cornerstone of the management scheme. Colectomy is indicated in ASC not responding to medical therapy, toxic megacolon, perforation, and uncontrolled colorectal bleeding (rare)[37,38]. Colectomy in steroid-refractory ASC cases may be considered before medical salvage therapy in chronic active UC previously resistant to thiopurines and infliximab, since no maintenance therapy would be available after discontinuing the calcineurin inhibitor. Surgery is usually the preferred therapeutic option in patients with toxic megacolon, a life threatening event. However, a 24-48 h trial of conservative treatment (i.e., bowel rest, broad spectrum antibiotics and rectal tube) may be cautiously attempted in the non-severe cases in specialized centers only while under intense monitoring. Sequential therapy of calcineurin inhibitors followed by infliximab or vice versa may be successful in approximately 25%-40% of adult patients, but is associated with significant morbidity and even mortality[39-42]. Therefore, most recommend timely referral for colectomy after failing one medical salvage therapy, rather than attempting another regimen[6,8]. Expected response to calcineurin inhibitors and infliximab is roughly 1-2 wk and colectomy should not be withheld in non-responders.

Although in the past ileoanal straight anastomosis has been the procedure of choice, now the ileal pouch-anal anastomosis (IPAA) (also known as "restorative proctocolectomy") is the most commonly practiced surgery, also in children. In some centers, ileo-rectal anastomosis is practiced but limited data are available to support this surgery. High early failure rates have been reported with this surgery and a life-long follow-up of the retained rectal stump is required. The ileoanal

pouch procedures are likely superior to the straight pull through (i.e., ileoanal anastomosis) as they are associated with a lower early stool frequency and better long-term continence while maintaining acceptable early complication rates. However, the IPAA procedure is associated with pouchitis in approximately 45%-60%[43-45], of whom 60% will suffer from recurrent episodes and 5%-10% will develop chronic pouchitis[45]. The probability of pouch failure has been found to be 9% at 10 years[43]. Daytime and nighttime incontinence occurred in 7%-10% and 12%-24% of patients, respectively, over a 10-15 year period[43,44]. The risk for female infertility after IPAA seems to be a major concern with an increase from approximately 10% in the average population to 25%-30%[8,46]. The role of ileo-rectal anastomosis is controversial, but may be considered in females who are primarily concerned about the reduced fecundity associated with IPAA. The apparent advantages of the IPAA procedure must be seriously balanced against the potential adverse events which should be discussed openly with the families.

IPAA can be performed in one, two or three stages. A two-stage procedure (colectomy with pouch construction and a temporary protecting loop ileostomy to be closed in the second stage) is the most frequent procedure in stable ambulatory patients. The one step procedure (restorative proctocolectomy without protecting ileostomy) may be safe in selected ambulatory patients without any risk factors (e.g., steroids treatment, malabsorption and hypoalbuminemia) in highly trained centers[8]. A three-stage approach (colectomy with temporary ileostomy in the first stage, pouch construction in the second stage and ultimately ileostomy closure) should be performed in patients with steroid-refractory acute severe colitis, those on high dose steroids and/or suffering from malnutrition, and those in whom Crohn' s disease has not been excluded[8] . With any chosen procedure, a laparoscopic-assisted procedure is feasible and safe[47,48], also in children[49,50]. The overall complication rate was higher in open surgery, compared with laparoscopic surgery (55% *vs* 39%, $P = 0.004$)[48] with longer hospital stay. Patients who had an ileal pouch created through the laparoscopic approach had fewer occurrences of pouchitis[49]. There were no significant differences between the two groups regarding daytime and night continence, or sexual function[47].

In a meta-analysis, pouch failure rate was found to be 4.3% (95% CI: 3.5-6.3) and pelvic sepsis 7.5% (95% CI: 6.1-9.1)[51]. Pouch failure was lower by 2.5% in recent studies *vs* those published prior to 2000. Functional outcome remained stable over time, with a 24-h defecation frequency of 5.9 (95% CI: 5.0-6.9), regardless of the technical aspects of the surgery[51]. Preoperative steroid therapy (> 20 mg in adults), hypoalbuminemia and malnutrition are associated with increased surgical complications[52]. Pre-operative high dose steroids and probably also infliximab[53] are associated with increased surgical complications (especially in combination with other immune suppressants), while thiopurines and calcineurin inhibitors are not.

AMBULATORY SURGERY

The most frequent indication for colectomy in ambulatory children with UC is chronic ongoing disease, at times- steroid dependent, whereas in adults- dysplasia is also a common indication[54]. The points outlined above for ASC should also be followed in the decision-making of elective colectomy. In general, thiopurines and infliximab should be strongly considered in most cases before referral to colectomy in ambulatory mild-moderate UC. While cyclosporine should be initially administered in the hospital setting only, tacrolimus may be used in selected ambulatory patients as a bridge to thiopurines. In those losing response to infliximab, adalimumab may be considered before colectomy, given the recent evidence in adults showing its moderate effectiveness in ambulatory UC[55,56]. Colectomy should be discussed as a viable alternative in children who suffer from ongoing symptoms despite multiple immunosuppressive medications, especially in steroid dependency.

CONCLUSION

Colectomy, a potentially lifesaving procedure in ASC, is associated with several long-term unwanted consequences. On the other hand, medical rescue therapy, including cyclosporine, tacrolimus and infliximab, are highly effective in steroid-refractory ASC. Therefore, medical salvage therapy should be offered before colectomy in most patients who do not present with surgical abdomen or toxic megacolon. Validated predictive rules can identify a subset of patients who will eventually fail corticosteroid therapy after only 3-5 d of steroid therapy with an accuracy of 85%-95%. This accuracy is sufficiently high for initiating medical therapy early in the admission without delaying colectomy if required. Families may elect to proceed to early colectomy before attempting medical rescue therapy, especially in chronic active disease. Therefore, whenever considering second-line medical therapy, colectomy should always be openly discussed. In patients failing one medical rescue therapy, colectomy should be regarded as the next therapeutic step.

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