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Management of acute severe ulcerative colitis

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Abstract

The management strategy of acute severe ulcerative colitis has evolved over the past decade from being entirely restricted to twin choices of intravenous steroids or colectomy to include colon rescue therapies like cyclosporin as well as infliximab. However it still remains a medical emergency requiring hospitalization and requires care from a multidisciplinary team comprising of a gastroenterologist and a colorectal surgeon. The frame shift in management has been the emphasis on time bound decision making with an attempt to curtail the mortality rate to below 1%. Intravenous corticosteroids are the mainstay of therapy. Response to steroids should be assessed at day 3 of admission and partial/non-responders should be considered for alternative medical therapy/surgery. Medical rescue therapies include intravenous cyclosporin and infliximab. Cyclosporin is administered in a dose of 2 mg/kg per day and infliximab is administered as a single dose intravenous infusion of 5 mg/kg. Approximately 75% patients have short term and 50% patients have long term response to cyclosporin. Long term response to cyclosporin is improved in patients who are thiopurine naïve and are started on thiopurines on day 7. Infliximab also has a response rate of approximately 70% in short term and 50% in long term. Both cyclosporin and infliximab are equally efficacious medical rescue therapies as demonstrated in a recent randomized control trial. Patients not responding to infliximab or cyclosporin should be considered for colectomy.

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Key words: Ulcerative colitis; Acute severe colitis; Intravenous steroids; Cyclosporin; Infliximab

Core tip: The mortality of severe ulcerative colitis has drastically reduced from 30%-60% in pre steroid era to 1%-2.9% at present. However these figures are for specialist centers and at peripheral centers the mortality figures may be higher. The objective of this review is to provide in depth information for what can be categorized as a gastrointestinal medical emergency with the hope that informed clinical practices may translate to superior patient care at tertiary as well as peripheral centers treating ulcerative colitis. This review provides time bound framework, which looks at stepwise management of acute severe ulcerative colitis and explores the recent concepts of choice between biologics and cyclosporin colon rescue therapies in case of steroid refractory disease.

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INTRODUCTION

Acute severe ulcerative colitis (UC) is a medical emergency characterized by[1] (Table 1) presence of more than 6 bloody stools/d along with any one of the following: tachycardia > 90 bpm, fever > 37.8 ℃, Hb < 10.5 gm/dL, and/or ESR > 30 mm/h (Truelove and Witt's criteria). Other indices for defining severity include modified Mayo's classification[2], which is a combination of clinical and endoscopic findings, and Montreal classification[3], which is primarily based on Truelove and Witt's criteria.

Table 1 Modified Truelove and Witt's criteria for classification of severity of ulcerative colitis

	Mild	Moderate	Severe
Bloody stools per day	< 4	4-6	> 6
Pulse	< 90 bpm	≤ 90 bpm	> 90 bpm
Temperature	< 37.5 ℃	≤ 37.8 ℃	> 37.8 ℃
Hemoglobin	> 11.5 gm/dL	≥ 10.5 gm/dL	< 10.5 gm/dL
ESR	< 20 mm/h	≤ 30 mm/h	> 30 mm/h
CRP	Normal	≤ 30 mg/dL	> 30 mg/dL

However, Truelove and Witt's criteria is the most widely accepted disease severity index in clinical practice. The term acute severe colitis is preferred over fulminant colitis because the term fulminant is not well defined. It was coined in 1950 when it meant that single attack of UC could lead to mortality within 1 year[4], which is no longer relevant today. Approximately 20% UC patients with initial disease flares have severe UC[4], and about 15% patients have a severe attack at some stage of their disease[5]. Megacolon refers to presence of dilated colon (> 5.5 cm) on a plain abdominal X-ray film. Toxic megacolon is presence of megacolon with signs of systemic toxicity (fever, tachycardia, hypotension, leukocytosis). The overall lifetime incidence of toxic megacolon in patients with UC is 1%-2.5%[6]. Prior to introduction of corticosteroid therapy, mortality with acute severe UC was reported to be upto 22%-75% within first year of diagnosis[7]. First clinical trial of steroids for severe UC was performed in the 1950s and this trial reported a mortality of 7% in patients treated with steroids compared with 24% in the placebo group[8]. The mortality with severe UC has reduced to < 1% in specialist centers.

APPROACH TO MANAGEMENT

Investigations required at admission

In addition to monitoring patient's clinical feature and vital signs, all patients should have their full blood counts, liver and kidney function tests, electrolytes including serum magnesium and inflammatory markers [C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)]. At least 3 stool samples for *Clostridium difficile* (*C. difficile*) toxin should be obtained to rule out superimposed pseudo-membranous colitis[9]. A plain abdominal X-ray should be done to exclude megacolon. Plain radiograph can also provide information about the extent of disease and can also predict response to treatment. The distal distribution of fecal residue can provide a rough estimate of disease extent as it correlates with the proximal extent of disease[10]. The predictors of poor response to treatment on a plain abdominal radiograph are presence of mucosal islands which are small, circular opacities that represent residual mucosa isolated by surrounding ulceration, or presence of more than two gas-filled loops of small bowel[11]. Flexible unprepared sigmoidoscopy with minimal air insufflation should be performed to confirm the diagnosis and exclude superimposed infection, especially cytomegalovirus (CMV) colitis[12]. Endoscopic markers of severe disease activity include hemorrhagic mucosa with deep ulceration, mucosal detachment on the edge of these ulcerations, and well like ulcerations[13].

Treatment

General management: In addition to specific therapy these supportive measures are very important in the management of patients with acute severe UC. These include: (1) Monitoring and replacement of intravenous fluid and electrolytes to correct and prevent dehydration or electrolyte imbalance as hypokalaemia/hypomagnesaemia can precipitate toxic dilatation[6]; (2) Anticholinergic, antidiarrheal, non-steroidal anti-inflammatory drugs and opioid drugs should be promptly withdrawn as these may precipitate colonic dilatation; (3) Malnourished patients should receive adequate nutritional support. Enteral nutrition is most appropriate and is preferred over parenteral nutrition as it is associated with significantly fewer complications than parenteral nutrition in acute colitis[14]. There is no evidence that bowel rest with parenteral nutrition alters the outcome[15]; (4) Flexible unprepared sigmoidoscopy and biopsy should be done to confirm the diagnosis of acute severe UC and exclude infections[16] such as CMV. Presence of active CMV infection is indicated by presence of cytomegalovirus inclusion bodies on colonic biopsies. However inclusion bodies are not very frequent even in patients with active disease with a sensitivity as low as 37.5%[17]. Special immunohistochemical staining against immediate early antigens of CMV increases the diagnostic sensitivity of histologic examination for CMV. In addition positive plasma real time PCR assays for CMV DNA at levels > 20 copies/100 μL is also an indicator of active CMV disease[18]. Presence of active CMV disease requires treatment with ganciclovir, especially if the patient is slow to respond to conventional therapy; (5) Stool analysis (in atleast 3 stool samples) to exclude co-existing *C. difficile* toxin is required especially in patients with history of prolonged hospitalization[19]. *C. difficile* infection co-existing with acute severe UC has been associated with increased morbidity and mortality, and requires appropriate antibiotic therapy (oral vancomycin or metronidazole)[20]; (6) There is increased risk of thromboembolic phenomena, in patients with active IBD compared to controls, especially during disease flares[21]. Therefore prophylaxis with subcutaneous low molecular weight heparin is indicated to reduce the risk of thromboembolism; (7) Topical corticosteroids or mesalazine may be administered if patient can tolerate and is able to retain them, although there have been no systematic studies in acute severe colitis; (8) Antibiotics are indicated only if infection is suspected or immediately prior to surgery. Controlled trials of antibiotics such as oral or intravenous metronidazole or ciprofloxacin in acute colitis have not shown any significant benefit in addition to conventional therapy[22,23]; and (9) Blood transfusion is indicated in patients with hemoglobin < 10 gm/dL[24].

In addition to these measures daily assessment

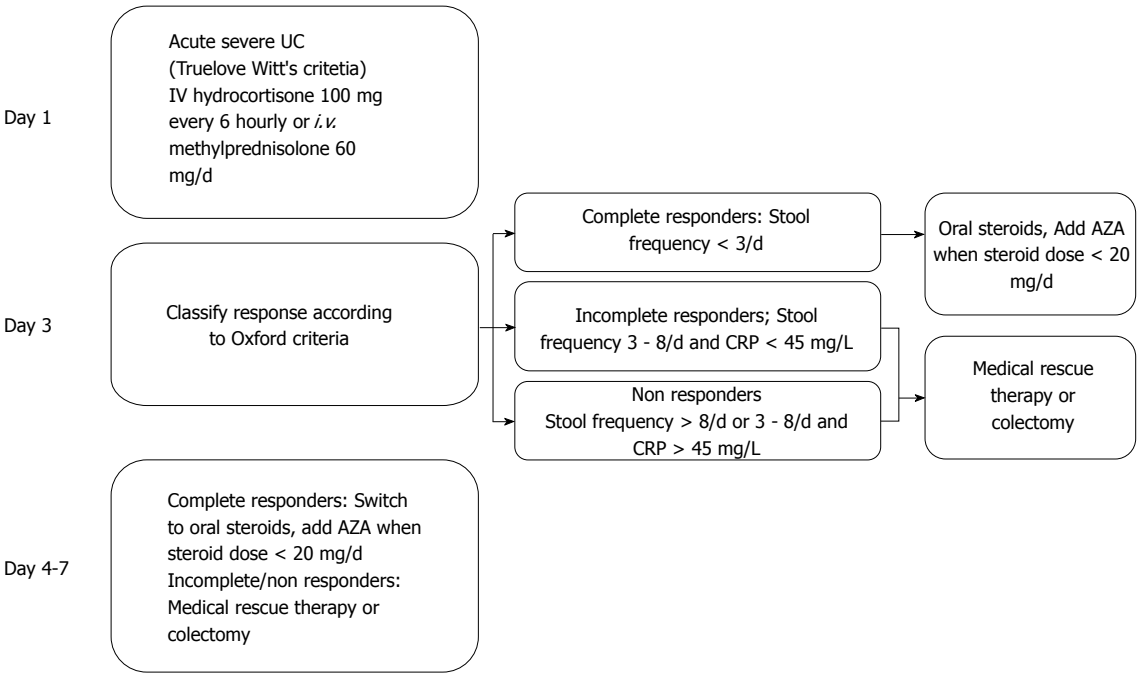

Figure 1 Algorithm for treatment decisions for patients with acute severe ulcerative colitis on intensive steroid therapy. AZA: Azathioprine.

of patients' clinical status should be done in following manner: (1) Physical examination is required daily to evaluate abdominal and rebound tenderness. Joint collaboration between medical and surgical team is required for appropriate management of such patients; (2) Vital signs should be recorded four times daily and more often if deterioration is noted; (3) A stool chart which records the number and character of bowel movements, including the presence or absence of blood and liquid versus solid stool should be properly maintained; (4) Measurement of blood count, CRP, serum electrolytes, serum albumin, liver function tests, and glucose should be done every 24 h; and (5) Abdominal radiographs should be done daily, especially in patients in whom there are signs of colonic distension and/or there is significant deterioration in clinical condition or laboratory parameters.

CORTICOSTEROIDS

Corticosteroids are the mainstay of therapy for acute severe UC. Steroids are given intravenously with methylprednisolone given in a dose of 60 mg/d or hydrocortisone 100 mg every 6 h. Treatment duration is usually limited to 7 to 10 d; continuing corticosteroid treatment beyond that period carries no additional benefit[25]. Truelove and Jewell published the first clinical trial of intravenous corticosteroids for acute severe UC in 1974[26]. Of 49 patients treated with intravenous steroids, 36 (73%) achieved complete remission by day 5. In a recently published systematic review of 1991 patients from 1974 to 2006[25], overall response to steroids was 67%. The overall short-term colectomy rate was 29% (565/1991) and mortality was 1%.

Predictors of response to steroids

Response to steroids is indicated by improvement in patients' symptoms (decreased stool frequency, urgency and rectal bleeding, improved stool consistency, reduction in abdominal pain, and improvement in general well being) and improved laboratory parameters (reduced CRP and ESR and improvement in hemoglobin and albumin).

At day 3 of admission, response to steroids should be measured by assessing stool frequency and CRP levels (Figure 1). In the landmark study by Travis *et al*[10], which included patients with 51 episodes of severe UC, presence of more than 8 stools/d or 3-8 stools/d plus a CRP > 45 mg/L at day 3 predicted a colectomy rate of 85%. In another prospective study by Lindgren *et al*[27] which included 97 episodes of severe UC, the following mathematical model was devised to predict colectomy: number of stools/d + 0.14 × CRP (mg/L) ≥ 8 predicted a colectomy rate of 72%.

Therefore regular assessment of response to steroids is of paramount importance in treating patients with acute severe UC. In a group of 80 patients who underwent emergency colectomy for severe UC between 1994 and 2000 in Oxford[28], patients with significantly longer duration of preoperative medical therapy (> 8 d) were more likely to have major post-operative complications.

Therefore at day 3 of admission, in cases of non response to steroids according to above mentioned criteria (stool frequency > 8/d or stool frequency 3-8/d and CRP > 45 mg/L) other treatment options or surgery should be considered. In cases of partial response, therapy should be continued till day 5-7, and if the patient still does not respond, other therapies/surgery should be considered (Table 2). In patients who respond to steroids, oral steroids should be started after 5-7 d of

Table 2 Ten year follow up of patients of Oxford cohort categorized at day 7 of intensive therapy

Parameter	Complete responders	Incomplete responders
Colectomy rate at 1 yr	5%	54%
Number requiring colectomy	6/19 (32%)	10/13 (76.9%)
Maximum steroid free remission	3.5 yr	< 1 yr

intensive therapy.

There are several other studies which have predicted response to steroids in acute severe UC. Ho *et al*[29], in a retrospective study found that, number of stools/day (score 1-4); hypoalbuminaemia < 3 mg/dL (score 1) and colonic dilatation > 5.5 cm (score 4) were useful in predicting colectomy as 85% of patients with a score ≥ 4 required colectomy. In another study by Ananthakrishnan *et al*[30], anemia, malnutrition, need for blood transfusion and total parenteral nutrition would independently predict colectomy. Radiological markers which can predict colectomy include the presence of mucosal islands on a plain abdominal radiograph which is associated with a 75% colectomy rate[31], and presence of an ileus (indicated by 3 or more small bowel loops of gas) which is associated with 73% colectomy rate[11]. In a study, presence of deep ulcers on endoscopy after gentle air insufflation identified 42/49 patients who required colectomy[32].

CYCLOSPORIN

Two controlled clinical trials established the efficacy of intravenous cyclosporin (fungal calcineurin inhibitor) as medical rescue therapy for acute severe UC not responding to intravenous corticosteroids. In the first landmark trial by Lichtiger *et al*[33] 9 out 11 patients in the cyclosporin (4 mg/kg per day) group had a response *vs* none of 9 placebo treated patients. The trial was terminated early for ethical reasons because of marked response to cyclosporin. Of nine placebo treated patients 5 patients were crossed over to cyclosporin and all five responded. In another study 73 patients were randomized to 4 mg/kg *vs* 2 mg/kg of intravenous cyclosporin[34]. Response rates at 8 d were similar in both groups (83% and 82% respectively), with 9% and 13% colectomy rate in 2 and 4 mg/kg group respectively. Therefore, cyclosporin dose of 2 mg/kg per day has become the standard in clinical practice. Another European study compared intravenous cyclosporin (4 mg/kg) with intravenous steroids and found similar response rates between the two groups (64% *vs* 53%)[35]. Therefore cyclosporin monotherapy may be preferred over steroids in patients who have high chances of side-effects with steroids including patients with osteoporosis, poorly controlled diabetes and those who are susceptible to steroid-psychosis. Overall, pooled results from controlled and non-controlled trials show response rates with intravenous cyclosporin to vary from 76% to 85%, with median time to response being 4 d[35].

Table 3 Long term response rates to cyclosporin[38]

Initial response	74%
1 yr	65% relapsed
3 yr	90% relapsed
7 yr	58% colectomy rates

However, one of the major limitations associated with cyclosporin use is its side effect profile. The short-term side effects are a cause of concern because cyclosporin is generally used as bridge to immunomodulators. These include minor side effects, which occur in 31%-51% patients, including tremors, paresthesias, malaise, headache, abnormal liver function tests, gingival hyperplasia and hirsutism. Major complications are reported in 0%-17%; including hypertension, renal impairment, infections and neurotoxicity[36]. Cyclosporin therapy in UC is associated with a mortality rate of approximately 1.8%-3.5%[36]. Therefore, following points should be considered before starting cyclosporin therapy.

Cyclosporin should not be used if cholesterol < 115 mg/dL or magnesium < 1.4 mEq/L. It should also be avoided in presence of hypertension, renal impairment, epilepsy, sepsis, age > 80 years. Magnesium, cholesterol, and creatinine should be measured at baseline and within 48 h of starting cyclosporin.

Cyclosporin should be administered in a dose of 2 mg/kg per day intravenously aiming for levels 150-250 ng/mL[37].

Oral microemulsion 4 mg/kg twice daily can be alternatively considered.

Blood Pressure and renal function should be monitored and cyclosporin should be stopped if serum creatinine rises > 25%.

Cyclosporin should be stopped if there is no improvement in 7 d.

In responders intravenous cyclosporin (Figure 2) should be switched to oral cyclosporin 4 mg/kg per day twice daily. Monitoring of trough levels (150-250 ng/mL) should be regularly done. Azathioprine should be started along with oral cyclosporin. Cyclosporin should be stopped after 3 mo.

Infective complications with cyclosporin can be avoided by minimizing concomitant immunosuppressants and by using prophylactic antibiotics when indicated.

Regarding long term efficacy of cyclosporin (Table 3) several cohorts have been evaluated long term colectomy in patients treated with cyclosporin. In the retrospective cohort from Oxford, 42% patients could avoid colectomy after 7 years[38]. Overall, approximately 50% patients will avoid colectomy over a period of 2-3 years[39,40]. Immunomodulators when used with cyclosporin can decrease the colectomy rate, thus improving the long term efficacy of cyclosporin. In a study by Cohen *et al*[41] probability of avoiding colectomy at long-term follow-up (5.5 years) was 66% in patients receiving cyclosporin and azathioprine/mercaptopurine compared with 40% in those who received cyclosporin alone. Further studies in this regard

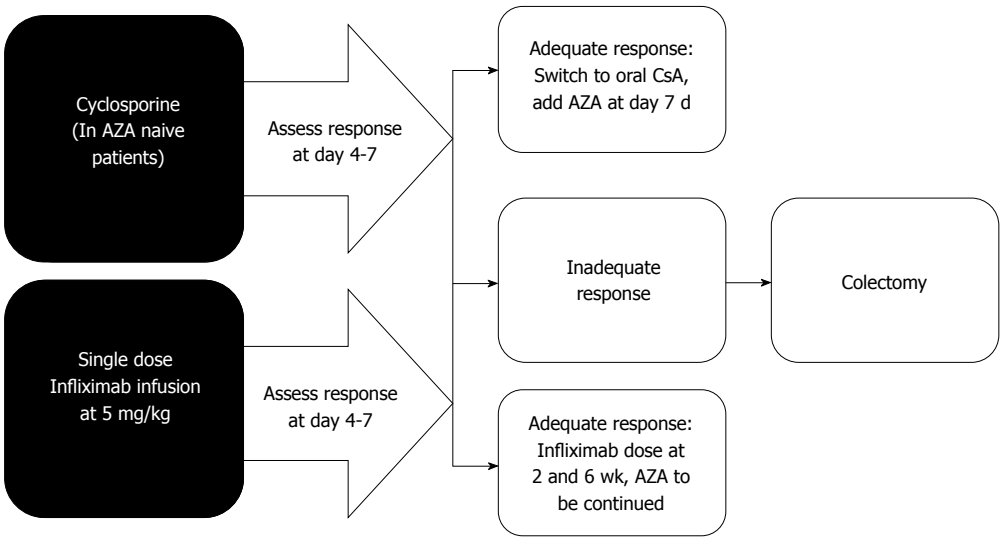

Figure 2 Algorithm for medical rescue therapy after failure of response to intravenous steroids.

have shown that in patients already on immunomodulators at the time of admission with acute severe UC, the likelihood of needing a colectomy following treatment with cyclosporin is higher than among those in whom immunomodulators are started after admission[40].

Therefore, cyclosporin is more beneficial in patients with acute severe UC who are thiopurine naïve at the time of admission. In patients who are already on thiopurine at the time of admission, the outcome with cyclosporin would be less favourable and other medical options or surgery needs to be considered.

INFLIXIMAB

Infliximab the chimeric monoclonal antibody against tumor necrosis factor (TNF) alpha has been found to have a favorable response in patients with steroid refractory acute severe UC. In an open label study of 6 steroid refractory severe UC patients[42], single infusion of infliximab in a dose of 5 mg/kg showed marked clinical improvement at day 7 in all patients. Four out of these 6 patients were in long term remission at median follow up of 5.5 mo. Later a randomized placebo controlled trial of 45 patients (24 infliximab and 21 placebo) showed that a colectomy rate at 3 mo was significantly lower in infliximab group as compared to placebo group (29% *vs* 67%, $P = 0.017$)[43]. The maximum benefit of infliximab was seen in patients with moderately severe disease than in those with most severe disease. Prior exposure to thiopurines does not seem to affect the outcome of patients treated with infliximab[43]. Other factors which may adversely affect outcome with infliximab include increased baseline CRP (> 20 mg/L), concomitant steroid use, disease duration ⩽ 3 years and baseline Mayo score ⩾ 10[44]. Screening for infections and immunization history should be obtained prior to initiating infliximab therapy. Screening tests which need to be done include hepatitis B serology, HIV serology, chest radiograph and tuberculin skin test or Interferon gamma release assays for latent tuberculosis.

Long term follow up data up to 3 years in infliximab treated severe UC patients are available. Two studies with follow up data of 1 year show colectomy rates of approximately 25% at 1 year in infliximab treated patients[45,46]. In another Swedish study, colectomy rate at 3 years in infliximab treated patients was 50% as compared to placebo (76%)[47].

There are no exclusive trials of other anti TNF agents for acute severe UC. However, there are few trials of adalimumab in moderate to severe active UC which showed efficacy of adalimumab over placebo. Reinisch *et al*[48] showed that adalimumab induced remission in 18.5% patients as compared to 9.2% patients in placebo group ($P = 0.031$). In another study Sandborn *et al*[49], in a similar group of patients showed efficacy of adalimumab over placebo (16.5% *vs* 9.3%, $P = 0.019$) in inducing remission.

CYCLOSPORIN *VS* INFLIXIMAB

Before the landmark randomized trial CYSIF (Cyclosporin With Infliximab in Steroid-refractory Severe Attacks of Ulcerative Colitis) between cyclosporin and infliximab there was limited evidence to suggest any difference in efficacy of cyclosporin and infliximab. In a retrospective review of two cohorts (43 treated with cyclosporin and 49 treated with infliximab) there was lower short term colectomy rate in the cyclosporin group[50]. The CYSIF trial[51] randomized 111 thiopurine naïve patients with severe UC after 5 d of IV steroids to cyclosporin (2 mg/kg per day for 8 d followed by 4 mg/kg per day orally) and infliximab (5 mg/kg *iv* infusion at 0, 2 and 6 wk). Patients who responded at day 7 received oral azathioprine and tapered steroids from day 8. The response to treatment at day 7 was seen in approximately 85% patients in both groups. Colectomy rates at day 98 were also similar be-

Table 4 Mortality according to day of surgery after intensive steroid therapy

Timing of surgery Total emergency surgeries = 72	Number of patients	Mortality
Overall	51	8
≤ 5 d	17	0/17
> 5 d	34	8/34

tween cyclosporin and infliximab (18% *vs* 21%, $P = 0.66$). Treatment failure at day 98 was also similar, seen in 60% patients in the cyclosporin group *vs* 54% in the infliximab group. There was no clear evidence of superiority of any one therapy over other.

Therefore choosing between cyclosporin and infliximab depends upon physician and patient preferences as both appear to be equally efficacious in the setting of acute severe colitis.

SWITCHING BETWEEN INFLIXIMAB AND CYCLOSPORIN

In cases of non-response to infliximab or cyclosporin, switching to either therapy is associated with significant morbidity and mortality and is not recommended. In the largest study of 86 patients on this aspect, 65 patients were administered infliximab after cyclosporin and 21 patients had cyclosporin after infliximab. Thirty three percent patients underwent colectomy within 3 mo and 1/3rd of the patients had adverse effects in form of infections[52].

TACROLIMUS

Tacrolimus is also a calcineurin inhibitor with mechanism of action similar to that of cyclosporin. A randomized trial of tacrolimus included 27/60 patients with severe UC[53]. In this trial partial response was seen in 67% patients, although complete remission was not seen on any patient. However, further case series have shown results similar to that of cyclosporin[54,55].

TOXIC MEGACOLON AND OTHER COMPLICATIONS OF SEVERE UC

Toxic megacolon may be defined as colonic dilatation of more than 5.5 cm along with signs of systemic toxicity. Lifetime incidence of toxic megacolon in patients with UC varies from 1%-2.5% and approximately 5% severe UC patients who are hospitalized may develop toxic megacolon[6]. Risk factors include dyselectrolytemia, full bowel preparation and medications (antidiarrheal, anticholinergic, and opiods)[6]. Earlier identification of this condition, prompt institution of medical therapy (nil per oral, intravenous broad spectrum antibiotics, fluid and electrolyte management, and intensive therapy) and low threshold of surgery in cases of non-response to medical therapy within 48 h will decrease the morbidity and mortality of this condition.

Other complications include perforation which is the most serious complication of severe UC. Risk factors include inappropriate total colonoscopy and delaying treatment of toxic megacolon. Diagnosis of perforation can often be delayed as abdominal signs can be masked when patient is on steroids. Therefore, patients with severe UC should be monitored closely for abdominal signs and on the slightest suspicion abdominal radiographs should be obtained. Other complication includes severe hemorrhage.

SURGERY

Surgery is the final option for patients with severe UC not responding to medical therapy. Other indications for surgery include toxic megacolon, perforation and severe haemorrhage. The decision for surgery should not be delayed as this increases the morbidity and mortality of surgery. In a study performed at our center, the mortality of emergency surgery was very high if the intervention was delayed beyond 5 d following non-response to intravenous steroid therapy (Table 4)[56]. In another study from Oxford, higher surgical complication was noted if surgery was delayed beyond 8 d of medical therapy[28]. Therefore management of severe UC requires close collaboration between surgeon and gastroenterologist so that appropriate decisions can be taken without delay.

Most centers advocate a 3 step surgery in emergency setting. The surgical procedure of choice in acute setting is sub-total colectomy and ileostomy, with the rectum left in situ. The whole of rectum and inferior mesenteric artery should be preserved, which facilitates further surgery. The bowel can either be closed in subcutaneous fat or brought forward as mucous fistula, depending upon the surgeon's decision. Subtotal colectomy is a safe procedure even in critically ill patients[57,58] and will relieve the patient from burden of severe colitis, thus allowing the patient to normalise health and nutrition. Reconstructive surgery is best performed approximately 6 mo after primary surgery[59]. The second step consists of ileal pouch formation and defuctioning temporary ileostomy. In the final step ileal pouch anal anastomosis (IPAA) is done restoring normal continuity.

There appears to be a strong association of prolonged use of immunosuppression and poor wound healing after surgery which may manifest as wound dehiscence, infection following intestinal leak or a pelvic abscess following anastomotic leak. Long-term preoperative steroid use has been found to be a significant risk factor for anastomotic leak. Immunosuppressive agents (azathioprine and 6-mercaptopurine) have not been associated with increased postoperative complications. When used alone, cyclosporin has not been associated with increased postoperative complications. The use of infliximab (IFX) and its impact on postoperative course is debatable and is a subject of intense interest. Two studies have identified a relationship between IFX and postoperative complica-

tions in IPAA patients. The first report came from Mayo Clinic[60] which included a retrospective survey of 47 patients who received preoperative IFX and 254 who did not. In the multivariate analysis, IFX was independently associated with increased risk of pouch-related and infectious complications. The authors concluded that IFX was a surrogate for critical patients who were at a higher risk for postoperative complications. The second study by Mor *et al*[61], had a case control design. It suggested that patients who had preoperative IFX were 3.5 times more likely to experience an early postoperative complication as compared to control patients. IFX-exposed patients were nearly 14 times more likely to suffer infectious complications. Other studies, which have not been in agreement with the conclusion of above-mentioned studies, include a large retrospective review of 413 patients with UC and CD over a 14-year period[62]. This study did not find any association between IFX and postoperative complications. The study faced certain criticisms, which included a heterogeneous population with > 50% of patients having CD and only 26 patients with UC who had a preoperative exposure to IFX. Another study[63], evaluating surgical outcomes in 141 UC patients over a 10-year period, found no association of IFX exposure with postoperative complications. In the same study, steroid use was related to increased infectious complications. The limitation of this study was that only 22 patients had IFX exposure prior to surgery. A recent meta-analysis concluded that infliximab use is not associated with increased risk of post-operative complications[64]. At present, no firm conclusions can be drawn. All these studies suffer from a retrospective design. Moreover, it is possible that patients who require IFX represent a patient population, which is at a higher risk for postoperative complications. At the same time, evidence exists that IFX may have a causal role in impairing wound healing and causing anastomotic failure and pelvis sepsis. The definite conclusion which can be drawn is that in patients who have received IFX, a three-stage procedure for IPAA should be considered rather than a two-stage procedure.

Mortality rates associated with emergency colectomy are higher as compared to elective colectomy[65]. In a study from England which included more than 20000 patients with IBD, mortality rates for patients with UC 3 years after colectomy was significantly lower with elective as compared to emergency colectomy (3.7% *vs* 13.2%)[66]. Surgery is not the preferred modality of therapy in young females as ileal pouch anal anastomosis has been associated with lower fertility and fecundity rates[67,68]. In patients with severe malnutrition, surgery may have to be deferred as the risk of post operative complications is significantly increased in this setting.

CONCLUSION

Acute severe ulcerative colitis as defined by Truelove Witt's criteria is a medical emergency that requires immediate hospitalization. Fluid and electrolyte balance, withdrawl of drugs promoting colonic dilatation and adequate nutritional support are important adjuncts in the management of severe UC. Intravenous corticosteroids are the first line therapy for severe UC, and approximately two thirds of patients respond. Response to steroids should be assessed at day 3, and in non-responders/partial responders, medical rescue therapy or surgery should be considered. Efficacy of both cyclosporin and infliximab in this setting is comparable as shown in a recent randomized trial. A close coordination between gastroenterologist and surgeon is required for optimal management of severe UC. Surgery is always an option after failure of IV steroids, and all patients should be given an option of surgery. A time bound strategy is required to manage such patients and surgery should not be delayed beyond 5 d of intensive therapy, as a delay increases surgical morbidity and mortality.

REFERENCES

1 **Truelove SC**, Witts LJ. Cortisone in ulcerative colitis; preliminary report on a therapeutic trial. *Br Med J* 1954; **2**: 375-378 [PMID: 13182220 DOI: 10.1136/bmj.2.4884.375]

2 **D'Haens G**, Sandborn WJ, Feagan BG, Geboes K, Hanauer SB, Irvine EJ, Lémann M, Marteau P, Rutgeerts P, Schölmerich J, Sutherland LR. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. *Gastroenterology* 2007; **132**: 763-786 [PMID: 17258735 DOI: 10.1053/j.gastro.2006.12.038]

3 **Silverberg MS**, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, Caprilli R, Colombel JF, Gasche C, Geboes K, Jewell DP, Karban A, Loftus EV, Peña AS, Riddell RH, Sachar DB, Schreiber S, Steinhart AH, Targan SR, Vermeire S, Warren BF. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005; **19** Suppl A: 5A-36A [PMID: 16151544]

4 **Rice-Oxley JM**, Truelove SC. Ulcerative colitis course and prognosis. *Lancet* 1950; **255**: 663-666 [DOI: 10.1016/S0140-6736(50)90550-2]

5 **Edwards FC**, Truelove SC. The Course And Prognosis Of Ulcerative Colitis. *Gut* 1963; **4**: 299-315 [PMID: 14084741 DOI: 10.1136/gut.4.4.299]

6 **Gan SI**, Beck PL. A new look at toxic megacolon: an update and review of incidence, etiology, pathogenesis, and management. *Am J Gastroenterol* 2003; **98**: 2363-2371 [PMID: 14638335]

7 **Hardy TL**, Bulmer E. Ulcerative colitis: a survey of ninety-five cases. *Br Med J* 1933; **2**: 812-815 [PMID: 20777868 DOI: 10.1136/bmj.2.3800.812]

8 **Jakobovits SL**, Travis SP. Management of acute severe colitis. *Br Med Bull* 2005; **75-76**: 131-144 [PMID: 16847166 DOI: 10.1093/bmb/ldl001]

9 **García Rodríguez LA**, González-Pérez A, Johansson S, Wallander MA. Risk factors for inflammatory bowel disease in the general population. *Aliment Pharmacol Ther* 2005; **22**: 309-315 [PMID: 16097997 DOI: 10.1111/j.1365-2036.2005.02564.x]

10 **Travis SP**, Farrant JM, Ricketts C, Nolan DJ, Mortensen NM, Kettlewell MG, Jewell DP. Predicting outcome in severe ulcerative colitis. *Gut* 1996; **38**: 905-910 [PMID: 8984031 DOI: 10.1136/gut.38.6.905]

11 **Chew CN**, Nolan DJ, Jewell DP. Small bowel gas in severe ulcerative colitis. *Gut* 1991; **32**: 1535-1537 [PMID: 1773962 DOI: 10.1136/gut.32.12.1535]

12 **Criscuoli V**, Casà A, Orlando A, Pecoraro G, Oliva L, Traina

M, Rizzo A, Cottone M. Severe acute colitis associated with CMV: a prevalence study. *Dig Liver Dis* 2004; **36**: 818-820 [PMID: 15646428 DOI: 10.1016/j.dld.2004.05.013]
13 **Carbonnel F**, Lavergne A, Lémann M, Bitoun A, Valleur P, Hautefeuille P, Galian A, Modigliani R, Rambaud JC. Colonoscopy of acute colitis. A safe and reliable tool for assessment of severity. *Dig Dis Sci* 1994; **39**: 1550-1557 [PMID: 8026269 DOI: 10.1007/BF02088063]
14 **González-Huix F**, Fernández-Bañares F, Esteve-Comas M, Abad-Lacruz A, Cabré E, Acero D, Figa M, Guilera M, Humbert P, de León R. Enteral versus parenteral nutrition as adjunct therapy in acute ulcerative colitis. *Am J Gastroenterol* 1993; **88**: 227-232 [PMID: 8424426]
15 **McIntyre PB**, Powell-Tuck J, Wood SR, Lennard-Jones JE, Lerebours E, Hecketsweiler P, Galmiche JP, Colin R. Controlled trial of bowel rest in the treatment of severe acute colitis. *Gut* 1986; **27**: 481-485 [PMID: 3084344 DOI: 10.1136/gut.27.5.481]
16 **Papadakis KA**, Tung JK, Binder SW, Kam LY, Abreu MT, Targan SR, Vasiliauskas EA. Outcome of cytomegalovirus infections in patients with inflammatory bowel disease. *Am J Gastroenterol* 2001; **96**: 2137-2142 [PMID: 11467645 DOI: 10.1111/j.1572-0241.2001.03949.x]
17 **Kandiel A**, Lashner B. Cytomegalovirus colitis complicating inflammatory bowel disease. *Am J Gastroenterol* 2006; **101**: 2857-2865 [PMID: 17026558 DOI: 10.1111/j.1572-0241.2006.00869.x]
18 **Matsuoka K**, Iwao Y, Mori T, Sakuraba A, Yajima T, Hisamatsu T, Okamoto S, Morohoshi Y, Izumiya M, Ichikawa H, Sato T, Inoue N, Ogata H, Hibi T. Cytomegalovirus is frequently reactivated and disappears without antiviral agents in ulcerative colitis patients. *Am J Gastroenterol* 2007; **102**: 331-337 [PMID: 17156136 DOI: 10.1111/j.1572-0241.2006.00989.x]
19 **Issa M**, Ananthakrishnan AN, Binion DG. Clostridium difficile and inflammatory bowel disease. *Inflamm Bowel Dis* 2008; **14**: 1432-1442 [PMID: 18484669 DOI: 10.1002/ibd.20500]
20 **Jen MH**, Saxena S, Bottle A, Aylin P, Pollok RC. Increased health burden associated with Clostridium difficile diarrhoea in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2011; **33**: 1322-1331 [PMID: 21517920 DOI: 10.1111/j.1365-2036.2011.04661.x]
21 **Grainge MJ**, West J, Card TR. Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study. *Lancet* 2010; **375**: 657-663 [PMID: 20149425 DOI: 10.1016/S0140-6736(09)61963-2]
22 **Mantzaris GJ**, Hatzis A, Kontogiannis P, Triadaphyllou G. Intravenous tobramycin and metronidazole as an adjunct to corticosteroids in acute, severe ulcerative colitis. *Am J Gastroenterol* 1994; **89**: 43-46 [PMID: 8273796]
23 **Mantzaris GJ**, Petraki K, Archavlis E, Amberiadis P, Kourtessas D, Christidou A, Triantafyllou G. A prospective randomized controlled trial of intravenous ciprofloxacin as an adjunct to corticosteroids in acute, severe ulcerative colitis. *Scand J Gastroenterol* 2001; **36**: 971-974 [PMID: 11521989 DOI: 10.1080/00365520120413]
24 **Gasche C**, Berstad A, Befrits R, Beglinger C, Dignass A, Erichsen K, Gomollon F, Hjortswang H, Koutroubakis I, Kulnigg S, Oldenburg B, Rampton D, Schroeder O, Stein J, Travis S, Van Assche G. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases. *Inflamm Bowel Dis* 2007; **13**: 1545-1553 [PMID: 17985376 DOI: 10.1002/ibd.20285]
25 **Turner D**, Walsh CM, Steinhart AH, Griffiths AM. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. *Clin Gastroenterol Hepatol* 2007; **5**: 103-110 [PMID: 17142106]
26 **Truelove SC**, Jewell DP. Intensive intravenous regimen for severe attacks of ulcerative colitis. *Lancet* 1974; **1**: 1067-1070 [PMID: 4135487 DOI: 10.1016/S0140-6736(74)90552-2]
27 **Lindgren SC**, Flood LM, Kilander AF, Löfberg R, Persson TB, Sjödahl RI. Early predictors of glucocorticosteroid treatment failure in severe and moderately severe attacks of ulcerative colitis. *Eur J Gastroenterol Hepatol* 1998; **10**: 831-835 [PMID: 9831403 DOI: 10.1097/00042737-199810000-00003]
28 **Randall J**, Singh B, Warren BF, Travis SP, Mortensen NJ, George BD. Delayed surgery for acute severe colitis is associated with increased risk of postoperative complications. *Br J Surg* 2010; **97**: 404-409 [PMID: 20101648 DOI: 10.1002/bjs.6874]
29 **Ho GT**, Mowat C, Goddard CJ, Fennell JM, Shah NB, Prescott RJ, Satsangi J. Predicting the outcome of severe ulcerative colitis: development of a novel risk score to aid early selection of patients for second-line medical therapy or surgery. *Aliment Pharmacol Ther* 2004; **19**: 1079-1087 [PMID: 15142197 DOI: 10.1111/j.1365-2036.2004.01945.x]
30 **Ananthakrishnan AN**, McGinley EL, Binion DG, Saeian K. Simple score to identify colectomy risk in ulcerative colitis hospitalizations. *Inflamm Bowel Dis* 2010; **16**: 1532-1540 [PMID: 20091926 DOI: 10.1002/ibd.21225]
31 **Lennard-Jones JE**, Ritchie JK, Hilder W, Spicer CC. Assessment of severity in colitis: a preliminary study. *Gut* 1975; **16**: 579-584 [PMID: 1183857 DOI: 10.1136/gut.16.8.579]
32 **Almer S**, Bodemar G, Franzén L, Lindström E, Nyström P, Ström M. Use of air enema radiography to assess depth of ulceration during acute attacks of ulcerative colitis. *Lancet* 1996; **347**: 1731-1735 [PMID: 8656906 DOI: 10.1016/S0140-6736(96)90808-9]
33 **Lichtiger S**, Present DH, Kornbluth A, Gelernt I, Bauer J, Galler G, Michelassi F, Hanauer S. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* 1994; **330**: 1841-1845 [PMID: 8196726 DOI: 10.1056/NEJM199406303302601]
34 **Van Assche G**, D'Haens G, Noman M, Vermeire S, Hiele M, Asnong K, Arts J, D'Hoore A, Penninckx F, Rutgeerts P. Randomized, double-blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. *Gastroenterology* 2003; **125**: 1025-1031 [PMID: 14517785 DOI: 10.1016/S0016-5085(03)01214-9]
35 **D'Haens G**, Lemmens L, Geboes K, Vandeputte L, Van Acker F, Mortelmans L, Peeters M, Vermeire S, Penninckx F, Nevens F, Hiele M, Rutgeerts P. Intravenous cyclosporine versus intravenous corticosteroids as single therapy for severe attacks of ulcerative colitis. *Gastroenterology* 2001; **120**: 1323-1329 [PMID: 11313301 DOI: 10.1053/gast.2001.23983]
36 **Sternthal MB**, Murphy SJ, George J, Kornbluth A, Lichtiger S, Present DH. Adverse events associated with the use of cyclosporine in patients with inflammatory bowel disease. *Am J Gastroenterol* 2008; **103**: 937-943 [PMID: 18177449 DOI: 10.1111/j.1572-0241.2007.01718.x]
37 **Rayner CK**, McCormack G, Emmanuel AV, Kamm MA. Long-term results of low-dose intravenous ciclosporin for acute severe ulcerative colitis. *Aliment Pharmacol Ther* 2003; **18**: 303-308 [PMID: 12895214 DOI: 10.1046/j.1365-2036.2003.01618.x]
38 **Campbell S**, Travis S, Jewell D. Ciclosporin use in acute ulcerative colitis: a long-term experience. *Eur J Gastroenterol Hepatol* 2005; **17**: 79-84 [PMID: 15647646 DOI: 10.1097/00042737-200501000-00016]
39 **Bojic D**, Radojicic Z, Nedeljkovic-Protic M, Al-Ali M, Jewell DP, Travis SP. Long-term outcome after admission for acute severe ulcerative colitis in Oxford: the 1992-1993 cohort. *Inflamm Bowel Dis* 2009; **15**: 823-828 [PMID: 19145641 DOI: 10.1002/ibd.20843]
40 **Moskovitz DN**, Van Assche G, Maenhout B, Arts J, Ferrante M, Vermeire S, Rutgeerts P. Incidence of colectomy during long-term follow-up after cyclosporine-induced remission of severe ulcerative colitis. *Clin Gastroenterol Hepatol* 2006; **4**: 760-765 [PMID: 16716758 DOI: 10.1016/j.cgh.2006.04.001]
41 **Cohen RD**, Stein R, Hanauer SB. Intravenous cyclosporin in ulcerative colitis: a five-year experience. *Am J Gastroen-*

terol 1999; **94**: 1587-1592 [PMID: 10364029 DOI: 10.1111/j.1572-0241.1999.01149.x]
42 **Kaser A**, Mairinger T, Vogel W, Tilg H. Infliximab in severe steroid-refractory ulcerative colitis: a pilot study. *Wien Klin Wochenschr* 2001; **113**: 930-933 [PMID: 11802508]
43 **Järnerot G**, Hertervig E, Friis-Liby I, Blomquist L, Karlén P, Grännö C, Vilien M, Ström M, Danielsson A, Verbaan H, Hellström PM, Magnuson A, Curman B. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. *Gastroenterology* 2005; **128**: 1805-1811 [PMID: 15940615 DOI: 10.1053/j.gastro.2005.03.003]
44 **Sandborn WJ**, Rutgeerts P, Feagan BG, Reinisch W, Olson A, Johanns J, Lu J, Horgan K, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab. *Gastroenterology* 2009; **137**: 1250-1260; quiz 1520 [PMID: 19596014 DOI: 10.1053/j.gastro.2009.06.061]
45 **Monterubbianesi R**, Armuzzi A, Papi C, Daperno M, Marrollo M, Biancone L, Cappello M, Lavagna A, Annese V, Orlando A, Viscido A, Riegler G, Meucci G, Sostegni R, Guidi L, Petruzziello C, Peralta S, Prantera C, Kohn A. Infliximab for severe ulcerative colitis: short-term and one year outcome of three dose regimen. An Italian multicentre open-label study. *Gastroenterology* 2009; **138** (Suppl 1): S685
46 **Venu M**, Naik AS, Ananthakrishnan AN. Early infliximab infusion in hospitalised severe UC patients: one year outcome. *Gastroenterology* 2009; **136** (Suppl1): A201 [DOI: 10.1016/S0016-5085(09)60901-X]
47 **Gustavsson A**, Jarnerot G, Hertevig E. A 2-year follow up study of the Swedish-Danish infliximab trial in steroid resistant acute ulcerative colitis. *Gastroenterology* 2007; **132**: 983-984
48 **Reinisch W**, Sandborn WJ, Hommes DW, D'Haens G, Hanauer S, Schreiber S, Panaccione R, Fedorak RN, Tighe MB, Huang B, Kampman W, Lazar A, Thakkar R. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. *Gut* 2011; **60**: 780-787 [PMID: 21209123 DOI: 10.1136/gut.2010.221127]
49 **Sandborn WJ**, van Assche G, Reinisch W, Colombel JF, D'Haens G, Wolf DC, Kron M, Tighe MB, Lazar A, Thakkar RB. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2012; **142**: 257-265.e1-3 [PMID: 22062358 DOI: 10.1053/j.gastro.2011.10.032]
50 **Sjöberg M**, Walch A, Meshkat M, Gustavsson A, Järnerot G, Vogelsang H, Hertervig E, Novacek G, Friis-Liby I, Blomquist L, Angelberger S, Karlen P, Grännö C, Vilien M, Ström M, Verbaan H, Hellström PM, Dejaco C, Magnuson A, Halfvarson J, Reinisch W, Tysk C. Infliximab or cyclosporine as rescue therapy in hospitalized patients with steroid-refractory ulcerative colitis: a retrospective observational study. *Inflamm Bowel Dis* 2012; **18**: 212-218 [PMID: 21438096 DOI: 10.1002/ibd.21680]
51 **Laharie D**, Bourreille A, Branche J, Allez M, Bouhnik Y, Filippi J, Zerbib F, Savoye G, Nachury M, Moreau J, Delchier JC, Cosnes J, Ricart E, Dewit O, Lopez-Sanroman A, Dupas JL, Carbonnel F, Bommelaer G, Coffin B, Roblin X, Van Assche G, Esteve M, Färkkilä M, Gisbert JP, Marteau P, Nahon S, de Vos M, Franchimont D, Mary JY, Colombel JF, Lémann M. Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. *Lancet* 2012; **380**: 1909-1915 [PMID: 23063316 DOI: 10.1016/S0140-6736(12)61084-8]
52 **Leblanc S**, Allez M, Seksik P, Flourie B, Peeters H, Dupas JL, Bouguen G, Biroulet LP, Bourreille A, Dewit O, Bouhnik Y, Michetti PF, Chaussade S, de Saussure P, Colombel JF, Lemann M. Successive treatment with cyclosporin and infliximab in severe ulcerative colitis. *Gastroenterology* 2009; **136** (Suppl 1): A88 [DOI: 10.1016/S0016-5085(09)60396-6]
53 **Ogata H**, Matsui T, Nakamura M, Iida M, Takazoe M, Suzuki Y, Hibi T. A randomised dose finding study of oral tacrolimus (FK506) therapy in refractory ulcerative colitis. *Gut* 2006; **55**: 1255-1262 [PMID: 16484504 DOI: 10.1136/gut.2005.081794]
54 **Baumgart DC**, Wiedenmann B, Dignass AU. Rescue therapy with tacrolimus is effective in patients with severe and refractory inflammatory bowel disease. *Aliment Pharmacol Ther* 2003; **17**: 1273-1281 [PMID: 12755840 DOI: 10.1046/j.1365-2036.2003.01534.x]
55 **Baumgart DC**, Pintoffl JP, Sturm A, Wiedenmann B, Dignass AU. Tacrolimus is safe and effective in patients with severe steroid-refractory or steroid-dependent inflammatory bowel disease--a long-term follow-up. *Am J Gastroenterol* 2006; **101**: 1048-1056 [PMID: 16573777 DOI: 10.1111/j.1572-0241.2006.00524.x]
56 **Pal S**, Sahni P, Pande GK, Acharya SK, Chattopadhyay TK. Outcome following emergency surgery for refractory severe ulcerative colitis in a tertiary care centre in India. *BMC Gastroenterol* 2005; **5**: 39 [PMID: 16316474 DOI: 10.1186/1471-230X-5-39]
57 **Alves A**, Panis Y, Bouhnik Y, Maylin V, Lavergne-Slove A, Valleur P. Subtotal colectomy for severe acute colitis: a 20-year experience of a tertiary care center with an aggressive and early surgical policy. *J Am Coll Surg* 2003; **197**: 379-385 [PMID: 12946792 DOI: 10.1016/S1072-7515(03)00434-4]
58 **Hyman NH**, Cataldo P, Osler T. Urgent subtotal colectomy for severe inflammatory bowel disease. *Dis Colon Rectum* 2005; **48**: 70-73 [PMID: 15690660 DOI: 10.1007/s10350-004-0750-5]
59 **Andersson P**, Söderholm JD. Surgery in ulcerative colitis: indication and timing. *Dig Dis* 2009; **27**: 335-340 [PMID: 19786761 DOI: 10.1159/000228570]
60 **Selvasekar CR**, Cima RR, Larson DW, Dozois EJ, Harrington JR, Harmsen WS, Loftus EV, Sandborn WJ, Wolff BG, Pemberton JH. Effect of infliximab on short-term complications in patients undergoing operation for chronic ulcerative colitis. *J Am Coll Surg* 2007; **204**: 956-962; discussion 962-963 [PMID: 17481518 DOI: 10.1016/j.jamcollsurg.2006.12.044]
61 **Mor IJ**, Vogel JD, da Luz Moreira A, Shen B, Hammel J, Remzi FH. Infliximab in ulcerative colitis is associated with an increased risk of postoperative complications after restorative proctocolectomy. *Dis Colon Rectum* 2008; **51**: 1202-1207; discussion 1207-1210 [PMID: 18536964 DOI: 10.1007/s10350-008-9364-7]
62 **Kunitake H**, Hodin R, Shellito PC, Sands BE, Korzenik J, Bordeianou L. Perioperative treatment with infliximab in patients with Crohn's disease and ulcerative colitis is not associated with an increased rate of postoperative complications. *J Gastrointest Surg* 2008; **12**: 1730-1736; discussion 1736-1737 [PMID: 18709514 DOI: 10.1007/s11605-008-0630-8]
63 **Ferrante M**, D'Hoore A, Vermeire S, Declerck S, Noman M, Van Assche G, Hoffman I, Rutgeerts P, Penninckx F. Corticosteroids but not infliximab increase short-term postoperative infectious complications in patients with ulcerative colitis. *Inflamm Bowel Dis* 2009; **15**: 1062-1070 [PMID: 19161179 DOI: 10.1002/ibd.20863]
64 **Yang Z**, Wu Q, Wang F, Wu K, Fan D. Meta-analysis: effect of preoperative infliximab use on early postoperative complications in patients with ulcerative colitis undergoing abdominal surgery. *Aliment Pharmacol Ther* 2012; **36**: 922-928 [PMID: 23002804 DOI: 10.1111/apt.12060]
65 **Kaplan GG**, McCarthy EP, Ayanian JZ, Korzenik J, Hodin R, Sands BE. Impact of hospital volume on postoperative morbidity and mortality following a colectomy for ulcerative colitis. *Gastroenterology* 2008; **134**: 680-687 [PMID: 18242604 DOI: 10.1053/j.gastro.2008.01.004]
66 **Roberts SE**, Williams JG, Yeates D, Goldacre MJ. Mortality in patients with and without colectomy admitted to hospital

for ulcerative colitis and Crohn's disease: record linkage studies. *BMJ* 2007; **335**: 1033 [PMID: 17977817 DOI: 10.1136/bmj.39345.714039.55]

67 **Johnson P**, Richard C, Ravid A, Spencer L, Pinto E, Hanna M, Cohen Z, McLeod R. Female infertility after ileal pouch-anal anastomosis for ulcerative colitis. *Dis Colon Rectum* 2004; **47**: 1119-1126 [PMID: 15164254 DOI: 10.1007/s10350-004-0570-7]

68 **Oresland T**, Palmblad S, Ellström M, Berndtsson I, Crona N, Hultén L. Gynaecological and sexual function related to anatomical changes in the female pelvis after restorative proctocolectomy. *Int J Colorectal Dis* 1994; **9**: 77-81 [PMID: 8064194 DOI: 10.1007/BF00699417]

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