



HAL
open science

Review Article: Acute Severe Ulcerative Colitis, An Update on Optimal Medical Management

Ailsa Hart, Siew C Ng

► **To cite this version:**

Ailsa Hart, Siew C Ng. Review Article: Acute Severe Ulcerative Colitis, An Update on Optimal Medical Management. *Alimentary Pharmacology and Therapeutics*, 2010, 10.1111/j.1365-2036.2010.04392.x . hal-00552585

HAL Id: hal-00552585

<https://hal.science/hal-00552585>

Submitted on 6 Jan 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

**Review Article: Acute Severe Ulcerative Colitis,
An Update on Optimal Medical Management**

Journal:	<i>Alimentary Pharmacology & Therapeutics</i>
Manuscript ID:	APT-0264-2010.R3
Wiley - Manuscript type:	Review Article
Date Submitted by the Author:	08-Jun-2010
Complete List of Authors:	Hart, Ailsa; St Mark's Hospital, IBD Unit Ng, Siew; Institute of Digestive Diseases, Chinese University of Hong Kong
Keywords:	Ulcerative colitis < Disease-based, Inflammation < Topics, Inflammatory bowel disease < Disease-based, Biologics (IBD) < Topics

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Review Article: Acute Severe Ulcerative Colitis, An Update on Optimal Medical Management

Ailsa L Hart¹ and Siew C Ng²

¹St Mark's Hospital, London, United Kingdom.

²Institute of Digestive Disease, Chinese University of Hong Kong, Hong Kong

Correspondence

Ailsa L Hart, PhD

Consultant Gastroenterologist

St Mark's Hospital

Watford Road, Middlesex

HA1 3UJ

Tel: 02088695805

Fax: 02082354001

E-mail: ailsa.hart@nwlh.nhs.uk

Keywords: Acute severe ulcerative colitis, ciclosporin, infliximab,

corticosteroids

Abbreviations: UC: ulcerative colitis; 6-MP: 6-mercaptopurine; CRP: C-

reactive protein; CyA: ciclosporin; ESR: erythrocyte sedimentation ratio

Short running title: Medical management of acute ulcerative colitis

Conflict of interest: nil

For Peer Review

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

SUMMARY

Background: Management of acute severe ulcerative colitis (UC) is a clinical challenge, with an associated mortality rate of approximately 2-3% reported early post-colectomy. Traditional management with intravenous corticosteroids has been modified by introduction of ciclosporin and more recently infliximab.

Aim: To provide a detailed and comprehensive review of the medical management of acute severe UC

Methods: PubMed and recent conference abstracts were searched for articles relating to treatment of acute severe UC.

Results: Two thirds of patients respond to intravenous steroids in the short term. In those who fail steroids, low-dose intravenous ciclosporin at 2mg/kg/day is effective. Approximately 75% and 50% of patients treated with ciclosporin avoid colectomy in the short and long term, respectively. Long term outcome of ciclosporin therapy is improved by introduction of azathioprine on discharge from hospital, together with oral ciclosporin as a bridging therapy. Controlled data show that infliximab is effective as rescue therapy for acute severe UC and the effect appears to be durable although longer term follow up data are needed.

Conclusions: Both ciclosporin and infliximab have demonstrated efficacy as rescue medical therapies in patients with acute severe UC, but surgery needs to be considered if there is failure to improve or clinical deterioration.

INTRODUCTION

Acute severe ulcerative colitis (UC) will affect 15% of UC patients at some point in their disease course (1). Twenty percent of first attacks of UC are “acute severe” in nature (1). Acute severe UC has been defined by the Truelove and Witt’s criteria: the patient passing more than six bloody stools per day plus one or more of the following: temperature $>37.8^{\circ}\text{C}$; pulse greater than 90bpm; Hb $<10.5\text{g/dL}$ or ESR $>30\text{mm/hr}$ (2). In this review, we will focus on the management of patients classified as having acute severe UC by the Truelove and Witt’s criteria and who are hospitalised.

The goal of medical therapy is to avoid colectomy while preventing complications of disease, side effects of medications and mortality. Corticosteroids, ciclosporin and infliximab have been used in the setting of acute UC. In addition to these medical therapies, optimisation of the overall supportive care of patients with acute severe UC is essential. This includes intravenous fluid replacement with potassium supplementation, careful exclusion of enteric infection by stool cultures and *Clostridium difficile* toxin testing, and an unprepared flexible sigmoidoscopy (and biopsy) with minimal air insufflation in patients not responding or those slow to respond to medical therapy to assess mucosal severity of inflammation and to exclude cytomegalovirus infection. Patients presenting with acute UC with co-existing *Clostridium difficile* infection have an increased colectomy rate and worse long-term clinical outcome (3), and should be treated with metronidazole or vancomycin (4). The presence of cytomegalovirus inclusion bodies on

1
2
3 colonic biopsies should prompt treatment with ganciclovir, in particularly in
4 patients slow to respond to conventional therapy. Malnourished patients
5 should be considered for calorie supplementation and should be weighed and
6 reviewed by a dietician. Additionally, prophylactic subcutaneous heparin to
7 reduce the risk of thromboembolism, and blood transfusions to maintain the
8 Hb >10g/dL are crucial (5;6). Any medications which may precipitate toxic
9 dilatation in the colon including opioids, non-steroidal anti-inflammatory drugs
10 and anti-cholinergics should be stopped. Topical therapy (mesalazine or
11 corticosteroids) is effective if tolerated although there are no systematic
12 studies in acute severe UC (7). Careful daily monitoring of the patient with
13 clinical assessment (bowel frequency and presence of blood, abdominal pain,
14 temperature, pulse, abdominal tenderness), biochemical assessment (blood
15 count, inflammatory markers, biochemistry) and radiological monitoring
16 (abdominal radiography with the frequency determined by the clinical status
17 and response of the patient) with integration of input from the physician and
18 surgeon is imperative for optimal outcome.

1. Corticosteroids

19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48 The mainstay of therapy for acute severe UC is corticosteroids. In 1955
49 Truelove & Witt published a 'final report on a therapeutic trial' of cortisone in
50 UC. 213 patients were randomised to receive cortisone 100mgs each day or
51 placebo for six weeks. The cortisone-treated patients did better than the
52 corresponding control patients with cortisone being particularly beneficial in
53 those with a first attack of disease. Furthermore, in 120 patients who had a
54
55
56
57
58
59
60

1
2
3 sigmoidoscopic examination at the end of treatment in addition to pre-
4 treatment, normal or improved sigmoidoscopic appearances were more
5 frequent in the cortisone group than the control group (8). Subsequently, in
6 1974, Truelove & Jewell published the results of a trial using an intensive
7 intravenous regimen for severe attacks of UC. Forty-nine patients were
8 treated with intensive intravenous corticosteroids and 36 out of 49 (73%) were
9 in complete remission at day five (7). A recent systematic review of 32 trials
10 consisting of over 2,000 patients treated with steroids for acute severe UC
11 between 1974 and 2006 showed that the overall response rate to steroids
12 was 67%. Approximately one third of patients came to a colectomy in the
13 short term (9). The introduction of steroids to the management of acute
14 severe UC has dramatically reduced mortality figures from more than 50% to
15 1-2 % (8). Mortality from acute severe UC in the first year from a study in
16 Birmingham in 1933 and a study from Oxford in 1950 was 75% and 22%,
17 respectively. However, after the introduction of steroids in 1955, the mortality
18 rate from acute severe UC had fallen to 7%. The current overall mortality in
19 specialist centres is less than 1% (10).

20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46 Acute severe UC is associated with both early post-colectomy in-patient
47 mortality and long-term mortality post colectomy. The United Kingdom (UK)
48 Inflammatory bowel disease (IBD) audit of more than 6000 adult patients
49 admitted to UK hospitals between 2007 to 2008 with IBD (863 patients had
50 acute severe UC), and a national study from Canada reported early post
51 colectomy mortalities of 2.9 and 2.3% respectively (11;12). In the UK IBD
52 audit, the reported inpatient mortality of 1.2% was strongly associated with
53
54
55
56
57
58
59
60

1
2
3 increased age, male gender and the presence of clostridium difficile infection
4 (13). Kaplan *et al.* showed that short term mortality after surgery for UC was
5
6 higher in those who had emergency than those who underwent elective
7
8 surgery (14). Both advanced age and low volume of surgery at a given centre
9
10 contributed towards increased mortality (15;16).
11
12
13
14
15
16

17
18 In a record linkage study from England which included more than 20,000
19
20 patients admitted to hospital for more than three days for IBD, mortality rates
21
22 for patients admitted with UC three years after elective colectomy (3.7%)
23
24 appeared to be significantly lower than those who had an emergency
25
26 colectomy (13.2%) or no colectomy (13.6%) (17). Mortality was highest in the
27
28 first twelve months after admission. It was suggested that the threshold for
29
30 elective colectomy for UC in England may be too high. Using a national record
31
32 linkage database from 1998 to 2000, Nicholls *et al.* recently demonstrated that
33
34 in patients with UC requiring hospital admission, the overall three year
35
36 mortality rate is lowest in patients who had an elective colectomy (5.6%) and
37
38 highest in those who did not have surgery (9.8%) (18). Age greater than 50
39
40 years old at admission, male gender, co-morbidity, hospital stay beyond two
41
42 weeks, and prior hospital admission for IBD were independently associated
43
44 with mortality (18).
45
46
47
48
49
50
51
52

53 The timing of surgery is critical and should not be delayed for more than five
54
55 days if the patient is not responding to medical therapy. Kaplan *et al.* showed
56
57 that in patients admitted urgently for a UC flare, those whose surgery is
58
59 performed more than six days after admission had an odds ratio of in-hospital
60

1
2
3 mortality of two compared with those who had earlier surgery (14). A
4 multidisciplinary approach involving the gastroenterologist, surgeon, dietician,
5 stomatherapist to educate patients on the options of rescue therapy and
6 surgery is of paramount importance.
7
8
9
10
11

12 13 14 15 ***Predictors of response to steroids*** 16

17 In clinical practice, clinical response is assessed by improvement in
18 symptoms (reduced bowel frequency, reduced urgency, improved stool
19 constituency, reduced abdominal pain, reduced rectal bleeding, improved
20 general well being, increased energy, reduced lethargy) and improvement in
21 blood test parameters (reduced C- reactive protein (CRP), erythrocyte
22 sedimentation ratio (ESR) and platelet count, improved albumin and
23 haemoglobin).
24
25
26
27
28
29
30
31
32
33

34
35
36 Clinical response to steroids can be assessed on day three. In a prospective
37 study by Travis *et al.* on 51 episodes of severe UC, more than 8 stools per
38 day or 3 to 8 stools per day plus a C-reactive protein (CRP) >45mg/L
39 predicted a colectomy rate of 85% (19). In 1998, Lindgren *et al.* performed a
40 prospective study on 97 episodes of severe UC and devised the following
41 mathematical model to predict colectomy; number of stools per day + 0.14 x
42 CRP (mgs/L) \geq 8 predicted a colectomy rate of 72% (20). In a retrospective
43 study by Ho *et al.* in 2004 on 167 episodes of severe UC, the number of
44 stools per day (score 1-4); hypoalbuminaemia <30g/L (score 1) and colonic
45 dilatation >5.5cm (score 4) were useful in predicting a colectomy or the need
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 for second line intervention. Eight-five percent of patients with a score greater
4
5 or equal to four required a colectomy or second line intervention (21).
6
7

8
9
10 These studies highlight the importance of a time-bound approach in the
11
12 management of patients with acute severe UC. Indeed in a group of 80
13
14 patients undergoing emergency colectomy for severe UC treated between
15
16 1994 and 2000 in Oxford, patients who had a significantly longer duration of
17
18 preoperative medical therapy were more likely to have major post-operative
19
20 complications. If medical therapy was continued for 8 days or more, a higher
21
22 complication rate was noted if surgery ensued (22).
23
24
25
26
27

28
29 We suggest that at day 3, careful assessment is made of the response of the
30
31 patient in terms of stool frequency, inflammatory markers and radiological
32
33 assessment. In cases of clear non-response, the decision should be made to
34
35 consider other medical or surgical options. If there is a degree of response in
36
37 the parameters mentioned then a balanced judgement needs to be taken
38
39 regarding continuing with current therapy for a further time-bound period. We
40
41 suggest that if a patient's clinical condition does not improve after 5–7 days of
42
43 IV steroid treatment then consideration should be made for other medical
44
45 options or surgery. Recently, Ananthkrishnan *et al.* showed that anaemia,
46
47 the requirement for blood transfusion, malnutrition and total parenteral
48
49 nutrition were independent predictors of colectomy and a simple risk score
50
51 has been proposed to stratify the severity of UC hospitalizations which helped
52
53 to predict colectomy (23). Preliminary data suggested that faecal calprotectin
54
55 may be a potential non-invasive biomarker to predict response to
56
57
58
59
60

1
2
3 corticosteroids and colectomy. In 90 patients with acute severe UC treated
4 with corticosteroids, faecal calprotectin was significantly higher in patients
5 requiring colectomy with a trend toward significance when comparing
6 corticosteroid responders and non-responders (24). In daily clinical practice,
7 we propose using simple clinical and biochemical parameters including stool
8 frequency, CRP, serum albumin levels and abdominal radiograph as
9 predictive factors in assessing for response to medical therapy. The use of a
10 simple index in clinical practice may help to quantify the risk of colectomy and
11 aid decision making.
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26

27 **2. Ciclosporin**

31 ***Short term efficacy***

32
33
34
35
36 Approximately one third of patients with acute severe UC will fail to respond to
37 corticosteroids. Several medical options exist for these patients. One option
38 is ciclosporin, the fungal metabolite originally derived from a Norwegian soil
39 sample. Two controlled trials have assessed the efficacy of ciclosporin in the
40 setting of severe UC. In 1994, Lichtiger et al. performed a randomised
41 placebo-controlled trial of intravenous ciclosporin at a dose of 4mg/kg per day
42 administered over a mean of seven days. The study was stopped early for
43 ethical reasons because of the marked favourable response to ciclosporin.
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
60 Nine out of 11 and 0 out of 9 patients treated with ciclosporin and placebo,
61 respectively, had a response. When five patients who had placebo were
62 crossed over to ciclosporin, all five patients responded (25). A subsequent

1
2
3 European controlled trial compared intravenous ciclosporin (4mg/kg) with
4 intravenous steroids. Nine of 14 (64%) ciclosporin-treated patients and eight
5 of 15 (53%) corticosteroid-treated patients responded (22). Ciclosporin was
6 used as monotherapy and not as an adjunct to corticosteroid therapy. This
7 trial highlights the efficacy of ciclosporin monotherapy in severe attacks of UC
8 and it can be considered as an option for patients who wish/need to avoid
9 steroids or who have failed oral steroid therapy. The largest ciclosporin trial to
10 date of 73 patients by Van Assche *et al.* in 2003 was a head to head
11 comparison study of ciclosporin 4mg/kg versus 2mg/kg. Response rate at day
12 eight was not different in the "high dose" group (84%) versus the "low dose"
13 group (86%) (26). Several other uncontrolled trials have also assessed the
14 initial response of UC to intravenous ciclosporin (27-33) and these are
15 detailed in Table 1. Overall the short term response to ciclosporin is in the
16 range 64-86%.

37 38 **Side effect profile**

39
40
41
42 One of the major issues pertaining to the use of ciclosporin relates to its side
43 effect profile. As ciclosporin is generally used as a bridge to azathioprine in
44 the setting of acute severe UC, the short term side effects represent the main
45 issue and include hypertension, tremor, nausea/vomiting, renal insufficiency,
46 headaches, anaphylaxis, infection, paraesthesia and seizures (34). There is a
47 mortality rate associated with ciclosporin in IBD (approximately 1.8%) (34),
48 although some centres have reported higher mortality rates of up to 3.5%.
49 Side effects of ciclosporin can be limited in a number of ways. One such way
50
51
52
53
54
55
56
57
58
59
60

1
2
3 is by using a reduced dose. Actis *et al.* in 1993 treated eight patients with
4 severe steroid resistant UC with 2mg/kg a day of intravenous ciclosporin.
5
6 Seven patients responded, and two patients had reversible renal insufficiency
7
8 (35). In a separate cohort of patients treated at St Mark's Hospital, 31 patients
9
10 with acute severe steroid resistant UC were given 2mg/kg a day of
11 intravenous ciclosporin followed by the early introduction of azathioprine.
12
13 77% of patients responded and no deaths, major infective episodes or
14
15 seizures were reported (28). In the trial by Van Assche *et al.* comparing
16
17 2mg/kg with 4 mg/kg ciclosporin, although no seizures, infections or deaths
18
19 were reported, there was a trend towards increased hypertension in the
20
21 4mg/kg dose group.
22
23
24
25
26
27
28
29
30
31

32 The neurotoxicity and seizure risk associated with ciclosporin can be limited
33
34 by monitoring and ensuring normal levels of magnesium and cholesterol or
35
36 alternatively the use of oral ciclosporin. Data from the transplant literature has
37
38 shown an increased seizure risk with low total cholesterol. In liver transplant
39
40 patients treated with ciclosporin, toxicity occurred with a cholesterol
41
42 concentration below 3.1 mm (36;37). It has been suggested that lower
43
44 cholesterol levels increased ciclosporin bound to low-density lipoprotein
45
46 particles and that this may result in increased delivery of ciclosporin to
47
48 astrocytes, which have low-density lipoprotein receptors (38).
49
50 Hypomagnesaemia increases the risk of seizures in patients treated with
51
52 ciclosporin therefore correcting deficiencies can limit neurotoxicity. Oral
53
54 ciclosporin is also effective in the treatment of acute severe colitis (33), and
55
56 there is also some evidence that oral formulations of ciclosporin may limit
57
58
59
60

1
2
3 neurotoxicity (39). In a retrospective study of patients with severe UC, 54
4 patients were treated with intravenous ciclosporin and 22 patients with oral
5 ciclosporin. Oral ciclosporin (used as rescue therapy) was superior to
6 intravenous ciclosporin with regards to the time to first relapse and time to
7 surgery at a median follow up of 2.9 years (range 0.2 to 7 years) (33). Once
8 ciclosporin has been started, drug levels should be monitored on day two to
9 three and dosage should be adjusted to the levels of 150 to 300 ng/mL
10 (28;33). Random levels can be measured during intravenous infusion, and
11 trough levels for oral formulations.
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26

27 Limiting infective complications associated with intravenous ciclosporin can be
28 achieved by minimising concomitant immunosuppressant use and using
29 prophylactic antibiotics. The risk of infection is greater with triple and double
30 immunosuppressive therapy than with single therapy. In a case-control study
31 the relative risk of opportunistic infections is highest in those who are on two
32 or three immunosuppressive agents (Odds Ratio; OR 14.5) compared with
33 those on any one of steroids, azathioprine or infliximab (OR 2.9) (40). In
34 clinical practice, rapid weaning of steroids as appropriate is one means of
35 limiting the risk of infections. Prophylaxis with Cotrimoxazole for patients on
36 triple immunomodulators is advised. In patients on two immunomodulators,
37 one of which is a calcineurin inhibitor or an anti-TNF agent, the European
38 Crohn's and Colitis Organisation (ECCO) consensus could not reach a verdict
39 on the use of prophylactic Cotrimoxazole (41).
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Long term efficacy

1
2
3
4
5
6 The long term benefit of ciclosporin is an important issue. In a cohort of 42
7
8 patients with severe UC treated with intravenous ciclosporin and followed up
9
10 long term, the probability of avoiding colectomy was 67% within one year and
11
12 58% at 5.5 years. If only the patients who initially responded to ciclosporin
13
14 were included in the analysis, the probability of avoiding colectomy was 80%
15
16 at 1 year and 70% at 5.5 years (31). In a separate cohort of 31 patients with
17
18 acute UC treated with intravenous ciclosporin, 45% of patients did not require
19
20 a colectomy over a median of 17.5 months (28). In a retrospective long term
21
22 follow up study from Oxford of 76 patients with acute UC treated with
23
24 ciclosporin, 42% of patients had avoided colectomy after 7 years (33). A
25
26 recent study from the same unit in Oxford showed that incomplete responders
27
28 to ciclosporin within one week after admission with acute severe UC had a
29
30 50% chance of colectomy within a year and 70% within five years (42).
31
32
33
34
35
36
37
38

39 Investigators from Leuven showed that of all treated patients, 55% would
40
41 avoid colectomy during a period of 3 years using prediction from life table
42
43 analysis (43). When this cohort of patients was followed up long term, the
44
45 probability of avoiding colectomy after successful intravenous ciclosporin
46
47 therapy was 63% at one year, 41% at 4 years, 16% at 6 years and 12% at 7
48
49 years (44). Overall, there is a long term benefit in preventing colectomy when
50
51 ciclosporin is used in a subgroup of patients. The likelihood of avoiding
52
53 colectomy over 2 to 3 years is approximately 50%.
54
55
56
57
58
59
60

Influence of immunomodulators on long term efficacy

1
2
3
4
5
6 What is the influence of concurrent immunomodulator therapy on the long
7
8 term outcome of patients with acute severe colitis treated with intravenous
9
10 ciclosporin? Data from the trial by Cohen et al in 1999 showed that the
11
12 probability of avoiding colectomy was 66% at long term follow up (5.5 years)
13
14 in patients receiving ciclosporin and azathioprine/ 6-mercaptopurine (6-MP)
15
16 compared with 40% in those who received ciclosporin alone, suggesting that
17
18 azathioprine improves the long term efficacy of ciclosporin (31). In patients
19
20 who had an initial response to ciclosporin, this rate increased to 71% in those
21
22 who were treated with azathioprine/6MP, versus 55% in those who received
23
24 ciclosporin alone. The timing of azathioprine/6MP in the ciclosporin
25
26 responders was such that 28% had started azathioprine /6MP a mean of 15
27
28 months before starting ciclosporin; 32% started azathioprine/6MP “during”
29
30 ciclosporin therapy; 8% started azathioprine/6MP simultaneously with
31
32 stopping ciclosporin and the remaining started azathioprine/6MP a mean of 8
33
34 months after stopping ciclosporin.
35
36
37
38
39
40
41
42

43
44 Further studies have suggested that in patients who were already on
45
46 immunomodulators at the time of admission with acute severe UC, the
47
48 likelihood of needing a colectomy following treatment with ciclosporin is high.
49
50 Moskowitz *et al.* showed that 77% of patients who were taking azathioprine at
51
52 the time of admission with acute severe colitis required a colectomy compared
53
54 with 35% of patients who were started on azathioprine during the same
55
56 admission as their intravenous ciclosporin. 88% of patients already on
57
58
59
60

1
2
3 azathioprine and requiring colectomy underwent surgery within the first year
4
5 of receiving ciclosporin (44).
6
7
8
9

10 Overall, it is beneficial in patients with acute severe UC naive to thiopurine to
11 be started on thiopurine during the acute admission when treated with
12 intravenous ciclosporin to optimise long term outcome and avoid colectomy. If
13 a patient presenting with acute severe UC is already taking a thiopurine at the
14 time of admission, the outcome with ciclosporin is less favourable and other
15 medical options or early surgery need to be considered (45).
16
17
18
19
20
21
22
23
24
25
26

Predictive factors of response to ciclosporin

27
28
29
30
31
32

33 In addition to determining predictive factors for response or non-response to
34 corticosteroids, several studies have assessed predictive factors for response
35 to ciclosporin. In one study, two clinical parameters (body temperature >37.5
36 and pulse rate >90 bpm) and one biochemical marker (CRP level >45)
37 predicted colectomy. Rates of colectomy at 6 months were 0.22, 0.47, 0.55,
38 and 0.90 when 0, 1, 2, and 3 of these factors were present, respectively (46).
39
40 Cautious sigmoidoscopy within a few days of starting ciclosporin can be
41 helpful. Severe endoscopic lesions (deep ulceration or large mucosal
42 abrasion or weld-like ulceration or mucosal detachment) were independent
43 predictors of colectomy. The rate of colectomy at 6 months in patients with
44 severe endoscopic lesions was 73% versus 42% in patients without them.
45
46 Colonoscopy was particularly helpful in patients with intermediate clinical and
47 biological severity of their disease such that colonoscopy changed the
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 therapeutic decision in patients with one or two of the criteria mentioned
4
5 above: 71% of the patients with severe endoscopic lesions had a colectomy
6
7 versus 17% of the patients without severe endoscopic lesions (46). Rowe *et*
8
9 *al.* showed that low serum albumin, tachycardia and neutrophils were
10
11 predictors of poor response to ciclosporin (47). Taken together, the monitoring
12
13 of ciclosporin using clinical, biological and endoscopic criteria is crucial to help
14
15 to predict response to the drug. This is necessary to help a timely move to
16
17 the next therapy and minimise procrastination.
18
19
20
21
22
23
24
25

26 In summary, ciclosporin is effective in the treatment of acute severe UC in the
27
28 short term. In the longer term ciclosporin can prevent colectomy in a subgroup
29
30 of patients. Careful patient selection is critical to identify those most likely to
31
32 benefit in the short and long term; patients who are naïve to thiopurines and
33
34 those who show good early response with clinical, biological and endoscopic
35
36 parameters are most likely to do well. The side effect profile of ciclosporin
37
38 needs to be taken into consideration in each individual patient and its safety
39
40 optimised by careful monitoring.
41
42
43
44
45
46

47 **3. Infliximab**

48
49
50

51
52 Infliximab is a chimeric monoclonal antibody to human tumour necrosis factor
53
54 (TNF)- α which is known to play an important role in the inflammation process
55
56 of UC. Increased levels of TNF- α have been found in faeces from patients
57
58 with active UC (48).
59
60

1
2
3 In an open label study, six patients with severe steroid refractory UC were
4 treated with a single infusion of Infliximab 5mg/kg. All patients experienced
5 marked clinical improvement at the end of seven days and colonoscopy
6 confirmed significant healing of endoscopic lesions. Four of the six patients
7 experienced long term remission at median follow up of 5.5 months (49).
8
9 Sands *et al.* reported the results of a placebo-controlled trial of Infliximab in
10 patients with severe steroid refractory UC, which was terminated early due to
11 slow enrolment. Of the patients treated with Infliximab four out of eight (50%)
12 were treatment successes at 2 weeks compared with zero out of three
13 patients treated with placebo (50). A further randomised controlled trial was
14 performed in 13 hospitalised patients with acute UC randomised to three
15 infusions of 5mg/kg of Infliximab or high dose corticosteroids. Five out of 6
16 patients on Infliximab and six out of seven patients on high dose
17 corticosteroids were better (51).
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38

39 The largest randomised placebo controlled trial to date of Infliximab in acute
40 severe UC was reported in 2004 by Jarnerot *et al.* Forty-five patients with
41 moderately severe UC were given a single infusion of 5mg/kg Infliximab four
42 days after initiation of steroids. Significantly more patients who had placebo
43 (67%) required surgery than those who had infliximab (29%) within 90 days of
44 randomisation (52). The greatest benefit of infliximab was seen in patients
45 who had severe or moderately severe but not fulminant UC. Lees *et al.*
46 reported experience of 39 patients hospitalised for acute severe UC treated
47 with Infliximab. They found that 66% responded and avoided colectomy
48 during the acute admission (53) and higher early responses were reported by
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Kohn *et al.* with 85% of hospitalised patients with acute severe UC avoiding
4 colectomy initially (54). Table 2 summarised clinical studies of infliximab in
5
6 acute UC.
7
8
9

10 11 12 ***Influence of immunosuppression*** 13

14
15
16
17 Does treatment with Azathioprine influence the outcome of patients with acute
18 severe UC treated with Infliximab? Some studies suggest that whether the
19 patient was on existing azathioprine or not at the time of admission with acute
20 severe UC did not affect the outcome (52). If patients were on azathioprine at
21 the initiation of infliximab, 80% avoided a colectomy at 90 days. This is in
22 contrast with the data using ciclosporin where the chance of a colectomy in
23 patients who were already on azathioprine and needed ciclosporin was high.
24 However, other studies suggest that Infliximab is less efficacious as rescue
25 therapy if patients are on immunosuppression at the time of admission. In a
26 Scottish cohort of 39 patients with acute severe colitis treated with Infliximab,
27 although previous treatment with azathioprine/6MP did not affect urgent
28 colectomy rates, two additional colectomies were performed at longer follow
29 up in patients who had had prior exposure to azathioprine (53).
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

50 51 ***Screening for opportunistic infections*** 52

53
54
55 A complete history of risk factors for infection and an immunisation history
56 needs to be obtained prior to infliximab (and immunomodulators).
57
58 Recommended screening tests include a full blood count, hepatitis B virus
59
60

1
2
3 serology, varizella zoster virus serology (in the absence of a history of
4 chickenpox), HIV serology, a chest radiograph and tuberculin skin test or
5 interferon γ release assay according to local or national practice guidelines
6 (41;55;56).
7
8
9
10
11

12 13 14 15 16 17 18 19 20 **Side effect profile** 21

22
23
24 The periodic safety update report (2008) showed that the benefit risk profile of
25 Infliximab is well defined and positive. There are over 15 years of clinical trial
26 experience and over ten years of post marketing experience in which
27 1,700,682 infliximab-treated patients have been assessed. There are two
28 registries in Crohn's Disease, The Crohn's Disease Therapy, Resource,
29 Evaluation and Assessment Tool (TREAT) and European National Crohn's
30 Observational Registry (ENCORE) with a total of approximately 10,000
31 patients monitored for five years. Although data in such registries may be
32 incomplete and/or biased, they do serve to provide information on drug safety.
33 Data from the US TREAT registry consists of more than more than 6000
34 patients treated with infliximab with a mean follow-up of 3.4 year has not
35 shown a significant increase of malignancy, mortality, incidence of lymphoma
36 in IBD patients treated with infliximab compared with other therapies (57). A
37 recent meta-analysis assessing the safety of anti-TNF therapy showed that
38 there was no increased risk of death, serious infection, or malignancy in
39 overall, subgroup and sensitivity analyses (58). The TREAT registry and the
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 European ENCORE CD registry have identified steroid use as an independent
4 risk factor for serious infections. In a recent longer term study of the TREAT
5 registry with a follow-up of 4.8 years, infliximab-treated patients showed
6 similar rates of mortality and malignancy (including lymphoma), but an
7 increased risk of serious infections compared with non-infliximab treated
8 patients (59). A very rare form of non Hodgkin's lymphoma, hepatosplenic T
9 cell lymphoma has been reported in patients with inflammatory bowel disease,
10 predominantly Crohn's disease, usually treated with combination anti-
11 TNFalpha agents and azathioprine. This malignancy was first described in
12 1990 as distinct subtype of lymphoma. There are only about 150 cases
13 documented in the literature. It predominantly affects paediatric and young
14 adult patients (predominantly male) and tends to have a very aggressive
15 disease course with a usually fatal outcome. This form of lymphoma has been
16 described in 14 Crohn's Disease patients, one patient with indeterminate
17 colitis and one with UC (age 12-40 years) (60;61).

40 ***Long term efficacy***

41
42
43
44
45
46 As with ciclosporin, it is important to determine the duration of response with
47 Infliximab. There have been data up to one year in 110 patients with severe
48 steroid refractory UC from ten Italian centres treated with Infliximab 5mg/kg at
49 0, 2 and 6 weeks and subsequently maintained on Infliximab, azathioprine or
50 both. The colectomy rate at one year was 24.5% (61). These data are
51 consistent with a separate study of 20 patients hospitalised for acute severe
52 UC demonstrating that colectomy was prevented in 75% of patients one year

1
2
3 following initiation of infliximab (62). Additionally data up to three years from a
4 Swedish/Danish trial showed a 50% colectomy rate in Infliximab-treated
5 patients compared with a 76% colectomy rate in placebo-treated patients.
6
7
8
9
10 However in this study the use of subsequent immunomodulators in the two
11 groups were not equal, and this may influence the long term outcome (63;64).
12
13
14

15
16 Several other uncontrolled studies have also examined the long term effects
17 of infliximab treatment for acute severe UC. A study from Edinburgh reported
18 that approximately two thirds of patients treated with infliximab avoided
19 colectomy during the acute admission and when patients were followed up to
20 a median of 203 days there were 2 additional colectomies (53). A study from
21 Oxford showed that about half of their patients with refractory UC treated with
22 infliximab came to a colectomy at a median of 140 days after the first infusion
23 (65). In a large Italian study of 83 patients with severe steroid-refractory UC
24 treated with infliximab, 15% of patients underwent colectomy within two
25 months, and more than 50% of the patients avoided colectomy up to a median
26 of 23 months. Two or more infliximab infusions appeared to be more effective
27 than a single infusion in the short term (54).
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44

45
46 Overall infliximab is effective in preventing colectomy in acute severe UC in
47 the short term and the response may be durable. A recent systematic review
48 of 34 studies including 896 patients with moderate to severe UC showed that
49 infliximab was more effective than placebo for inpatients and outpatients with
50 severe UC. 40 percent of patients were in remission at approximately nine
51 months follow-up (66).
52
53
54
55
56
57
58
59
60

Predictors of Response to Infliximab

Investigators from Leuven identified predictors of early clinical response to infliximab in their first 100 patients with severe UC treated with infliximab. The majority of patients received a single dose 5mg/kg infliximab whereas one third of patients received a three-dose infliximab induction at week 0, 2 and 6. More than half of the patients were on concomitant immunomodulators. Younger patients and those without a pANCA+/ASCA-ve serotype tended to have an early clinical response (67) .

Independent predictors of failure to infliximab as rescue therapy for severe intravenous steroid-refractory UC have been assessed in another retrospective study and these factors include a disease duration of \leq three years, bowel frequency of greater than six times per day on admission and prior hospitalisation in the past three months for UC (68).

Lees et al. showed that serum albumin at admission and day 3 of intravenous steroids predicted response to infliximab. A serum albumin of $<34\text{g/L}$ at day 3 showed a sensitivity of 57% and specificity of 90% for colectomy (53).

4. Infliximab versus ciclosporin

No head to head trials comparing ciclosporin and infliximab in acute severe UC have been published but controlled trials comparing these two drugs for this indication are in progress. In a retrospective study presented in abstract form of an Austrian cohort of UC patients treated with ciclosporin (n=49) and a Swedish cohort of UC patients treated with infliximab (n=46), a lower

1
2
3 colectomy rate was observed at three and 12 months after rescue therapy
4 with ciclosporin (12%, 33%) than with a single infusion of infliximab 5mg/kg
5
6 (33%, 45%) in patients presenting with acute severe steroid-refractory UC.
7
8 Both groups received subsequent maintenance therapy with azathioprine.
9
10 However severity and extent of disease were not comparable in the two
11
12 cohorts (69). In a separate Italian study of severe steroid-resistant UC, 19
13
14 infliximab-treated patients were compared with a historical cohort of
15
16 ciclosporin-treated patients (33 patients). Rehospitalisation rates in the two
17
18 groups up to 20 months were similar (70). Both ciclosporin and infliximab are
19
20 effective in the treatment of acute severe UC and the therapeutic decision
21
22 should be individualised. In patients naïve to thiopurine therapy presenting
23
24 with their first episode of acute severe UC, intravenous ciclosporin followed by
25
26 the introduction of azathioprine while still in hospital after having
27
28 demonstrated a response, together with three months of bridging oral
29
30 ciclosporin, is an effective strategy. In these patients, ciclosporin is being used
31
32 as a bridge to azathioprine which is used as a maintenance therapy. In
33
34 contrast, in patients who have been maintained on optimal dose azathioprine
35
36 and present with a severe episode of UC, ciclosporin and probably infliximab
37
38 are less likely to be successful (44) and there is the issue of what further
39
40 maintenance therapy can be used. In this setting, the use of infliximab can be
41
42 considered as this can be used as a maintenance therapy. However
43
44 consideration for early surgery may be more appropriate.
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

5. Switching between ciclosporin and infliximab

1
2
3
4
5
6 Some patients with acute severe UC will fail ciclosporin or infliximab. There
7
8 have been reports of switching from ciclosporin to infliximab and vice versa.
9
10 However the strategy of switching between ciclosporin and infliximab or vice
11
12 versa has significant risks which are outlined below and needs to be
13
14 considered very carefully weighing up the risks and benefits of surgery with
15
16 the risks and benefits of continuing medical therapy. We would not advocate
17
18 switching as a “standard” treatment strategy. It is theoretically safer to use
19
20 infliximab after ciclosporin than to use these drugs in the reverse order in view
21
22 of the shorter half life of ciclosporin. In a Spanish study, 16 patients with acute
23
24 UC were treated with infliximab after failing ciclosporin, 37.5% of patients
25
26 required a colectomy at a median follow-up of 195 days from the first
27
28 infliximab infusion (71). In a study from Mount Sinai, 19 patients with fulminant
29
30 UC failed to respond to either ciclosporin or infliximab and crossed over to the
31
32 other medication. Ten patients received infliximab after failing ciclosporin and
33
34 9 patients received ciclosporin after failing infliximab. Four (40%) and three
35
36 (33%) patients in the infliximab- and ciclosporin salvage group achieved
37
38 remission, respectively. Remission lasted a mean of 10.4 months and 28.5
39
40 months, respectively. One patient treated with infliximab salvage died from
41
42 sepsis. Two patients who had Ciclosporin salvage developed herpetic
43
44 oesophagitis and pancreatitis (72). In the largest study to date by the GETAID
45
46 group of 86 patients, 65 patients had ciclosporin first followed by infliximab
47
48 after a median time of two days after ciclosporin withdrawal, and 21 patients
49
50 had infliximab first followed by ciclosporin after a median of 17 days since last
51
52 infliximab infusion. Corticosteroids or immunosuppressants were continued in
53
54
55
56
57
58
59
60

1
2
3 about three quarter of patients. Thirty-three patients had a colectomy within
4
5 three months. About one third of patients had adverse effects consisting
6
7 mostly of infections. One patient died after surgery from pulmonary embolism
8
9 (73).
10
11

12 13 14 15 **6. Drug-related mortality**

16
17 A single centre study from Leuven showed that ciclosporin was associated
18
19 with deaths (3.5%) from opportunistic infections (2 aspergillus and 1
20
21 pneumocystis carinii) in 3 out of 86 patients with UC (40). Other trials have
22
23 reported a mortality rate associated with ciclosporin in IBD of approximately
24
25 1.8% (34). The Scottish study showed that the major complication and
26
27 mortality rate was 5.2% and 2.6% respectively in patients with acute UC
28
29 treated with infliximab. An older man died from pseudomonas pneumonia
30
31 following successful response to infliximab for severe UC, and a young patient
32
33 had severe fungaemia post-colectomy after failing infliximab (53). Switching
34
35 between infliximab and ciclosporin is associated with serious adverse effects
36
37 and death as discussed above, and is not recommended as “standard”
38
39 approach (72;73) . Infliximab and ciclosporin appear to be efficacious as
40
41 rescue therapy for patients with acute severe UC, but serious adverse events
42
43 do occur. A risk/benefit analysis of medical therapy needs to be compared
44
45 with “curative” surgery which carries a mortality of about 2-3% in the early
46
47 post-operative period. Both short term and long-term post colectomy mortality
48
49 is substantially reduced when an elective, and not an emergency colectomy is
50
51 performed.
52
53
54
55
56
57
58
59
60

7. Other Experimental Therapies

There are no published studies reporting the efficacy of the humanised anti-TNF agent, adalimumab, in the setting of acute severe UC defined by the Truelove and Witt's criteria, although two small studies have investigated the use of Adalimumab in patients with moderately severe UC who had failed infliximab (74;75). A recent larger study of 186 patients assessing the use of Adalimumab in moderately to severely active UC showed disappointing results at eight weeks with 19.2% of patients in the adalimumab group (160mg/80mg) in clinical remission compared with 9.2% in the placebo group (76). Other agents such as tacrolimus and leukocytapheresis have been studied and recently biological agents such as basiliximab and visilizumab have been assessed. Intravenous and oral tacrolimus showed results similar to ciclosporin (77). A dose-ranging study of Visilizumab, an anti-CD3 monoclonal antibody, in acute severe UC based on the Modified Truelove and Witt's score, showed a 30-day remission and response rate of 30 and 60%, respectively (78).

8. Surgery

Surgery may be unavoidable in some patients with acute severe UC, therefore optimal management requires close collaboration between the gastroenterologist and the surgeon and the surgeon and stoma nurse should be involved early in the management. Indications for surgery include toxic megacolon, perforation, severe haemorrhage, or clinical deterioration during

1
2
3 medical therapy. Delayed surgery for patients who do not respond to medical
4
5 therapy is associated with an increased risk of postoperative complications. In
6
7 a group of 80 patients undergoing emergency colectomy for severe UC
8
9 treated between 1994 and 2000 in Oxford, patients who had a significantly
10
11 longer duration of preoperative medical therapy were more likely to have
12
13 major post-operative complications. If medical therapy was continued for 8
14
15 days or more, a higher complication rate was noted if surgery ensued (22).
16
17
18 This emphasises the importance of having a time-bound approach with both
19
20 medical and surgical teams monitoring patients closely and making the
21
22 decision to operate at the appropriate time. It has to be a part of the medical
23
24 management plan to optimise the condition of the patient for potential surgery
25
26 with regards to maximising nutrition and tapering steroids where possible.
27
28
29
30
31
32

33
34 Ferrante *et al* compared post-operative infectious complications between
35
36 patients who had infliximab 3 months prior to surgery and those who did not.
37
38 Corticosteroids and a restorative proctocolectomy without defunctioning
39
40 ileostomy, but not infliximab, were associated with an increased risk of short-
41
42 term postoperative infectious complications in UC (79). However a recent
43
44 meta-analysis showed that pre-operative infliximab use increased the risk of
45
46 total short-term post-operative complications (OR 1.8) which included wound
47
48 infection, sepsis and abscess (80).
49
50
51
52
53

54
55 The recommended operation in the acute setting is total colectomy and
56
57 ileostomy, with the rectum left in situ. Reconstructive surgery is best
58
59 performed approximately six months after primary surgery (81). Although ileal
60

1
2
3 pouch anal anastomosis offers the prospect of a life without a permanent
4
5 stoma, surgery does not always restore all aspects of quality of life to normal
6
7 and a substantial number of patients still have problems with leakage,
8
9 urgency, nocturnal soiling, sexual dysfunction, and pouchitis, and some
10
11 patients may require conversion to a permanent ileostomy after ileal J-pouch-
12
13 anal anastomosis failure (82).
14
15
16
17
18
19

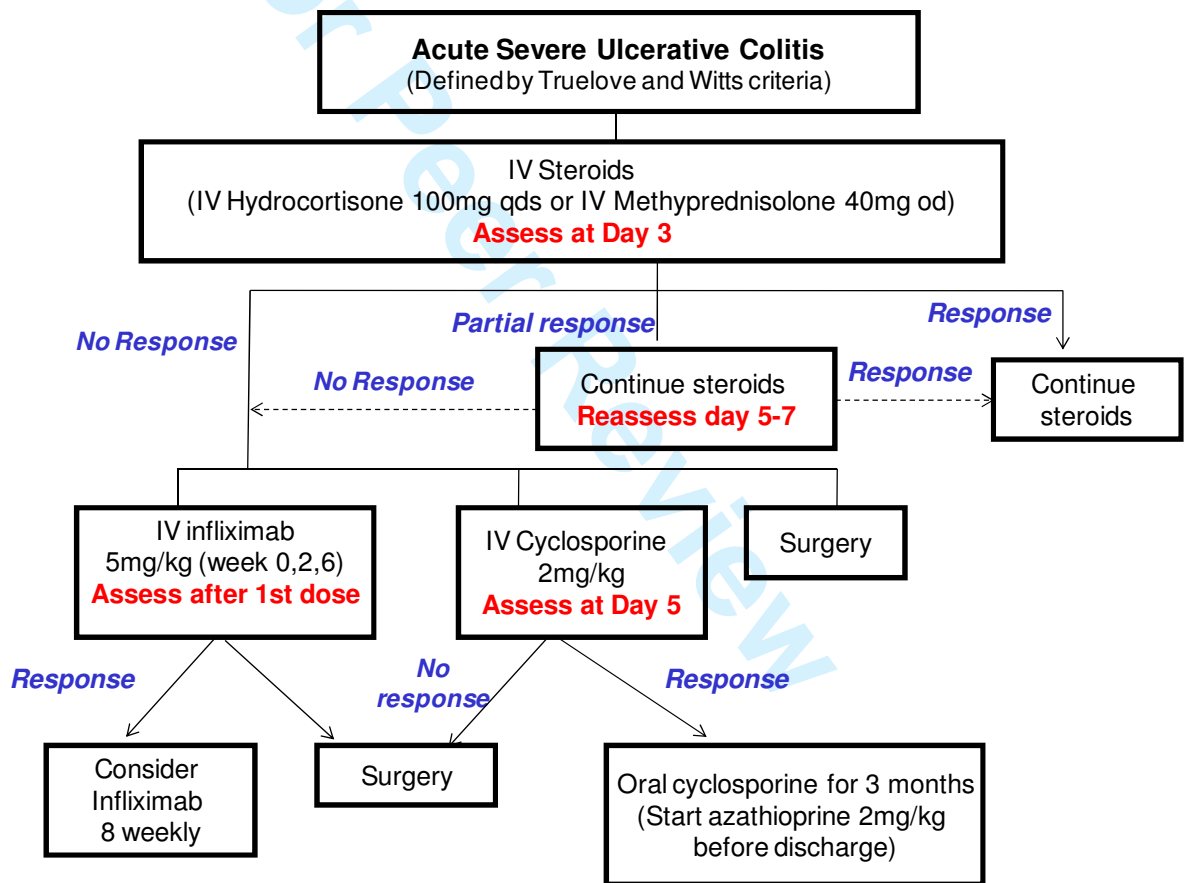
20 9. Conclusions

21
22
23
24 Approximately 15% of patients with UC will have a severe acute attack that
25
26 requires admission to hospital. Standard intensive treatment with intravenous
27
28 steroids is still the first line approach. Patients who do not respond within
29
30 three days to first line medical therapy should be considered for second line
31
32 rescue medical therapy or surgery. This decision should take into account the
33
34 patient's previous immunosuppressant history, age, and co-morbidity.
35
36 Delaying surgery, especially in older patients, those who had prior IBD
37
38 admissions and prolonged hospital stays, carries risk and is associated with
39
40 increased mortality up to three years. Surgeons and stoma nurses should be
41
42 involved early in the management of patients with acute severe UC. **A time-
43
44 limited approach with assessment of predictors of response to therapies and
45
46 close collaboration between physicians and surgeons are needed to ensure
47
48 optimised management of patients with acute severe UC.**
49
50
51
52
53
54
55
56

57
58 As we gain more information regarding the genetics of inflammatory bowel
59
60 disease there may well be genotypic predictors of disease course, likelihood

of colectomy and response to drugs, including but not limited to infliximab and ciclosporin, for the treatment of acute severe UC (83). Ultimately, additional data are required to better define the efficacy and safety of current treatment in the short and long term, and the optimal timing of colectomy if unavoidable, in an individual patient.

Figure 1: Proposed algorithm for the treatment of patients with acute severe UC



No response: defined as >8 stools daily or 3-8 stools with a CRP>45mg/L

Table 1: Ciclosporin in Acute Severe UC

	No. of patients	Dose (mg)	Short term response		Long term colectomy free-remission	Follow-up (years)	Trial type
			CyA	Placebo			
Lichtiger et al. 1994 (22)	20	4	82%	0%	-	-	Placebo-controlled
D' Haens et al. 2001 (78)	20	4	64%	-	-	-	Compared with steroids
Van Assche et al. 2006. (23)	73	2 vs. 4	82% vs 83%	-	-	-	Two dose comparison
Moskovitz et al. 2006 (41)	142	2 or 4	83%	-	12% 48% 63%	7 3 1	U
Holme et al. 2009	18	5	83%	-	56%	2	U
Campbell et al. 2005 (30)	76	4	74%	-	42%	7	U
Message et al. 2005 (29)	26	3.7	77%	-	52%	6.5	U
Arts et al. 2004 (40)	86	2 or 4	84%	-	55%	3	U
Rayner et al. 2003 (25)	31	2	77%	-	45%	1.5	U
Cohen et al. 1999 (28)	42	4	86%	-	62%	1.5	U

U = uncontrolled

Table 2: Infliximab in Acute Severe UC

	Number of patients	Short term response		Long term colectomy-free remission	Mean follow-up (months)
		Infliximab	Placebo	Infliximab	
Sands et al. 2001 (50)	11	50%	0%	-	-
Ochsenkuhn et al. 2004 (51)	13	83%	-	-	3.5
Jarnerot et al. 2005 (52)	45	71%	33%	62%	>6
Lees et al. 2007 (53)	39	66%	-	-	6.7
Kohn et al. 2007 (54)	83	85%	-	70%	23
Bressler et al. 2008 (84)	21	76%	-	-	-

Reference List

1. Edwards FC, TRUELOVE SC. THE COURSE AND PROGNOSIS OF ULCERATIVE COLITIS. *Gut*. 1963;4:299-315.
2. TRUELOVE SC, WITTS LJ. Cortisone in ulcerative colitis; preliminary report on a therapeutic trial. *Br Med J*. 1954;2:375-378.
3. Jodorkovsky D, Young Y, Abreu MT. Clinical outcomes of patients with ulcerative colitis and co-existing *Clostridium difficile* infection. *Dig Dis Sci*. 2010;55:415-420.
4. Ananthakrishnan AN, Issa M, Binion DG. *Clostridium difficile* and inflammatory bowel disease. *Med Clin North Am*. 2010;94:135-153.
5. Garcia-Erce JA, Gomollon F, Munoz M. Blood transfusion for the treatment of acute anaemia in inflammatory bowel disease and other digestive diseases. *World J Gastroenterol*. 2009;15:4686-4694.
6. Gasche C, Berstad A, Befrits R, et al. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases. *Inflamm Bowel Dis*. 2007;13:1545-1553.
7. TRUELOVE SC, Jewell DP. Intensive intravenous regimen for severe attacks of ulcerative colitis. *Lancet*. 1974;1:1067-1070.
8. TRUELOVE SC, WITTS LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. *Br Med J*. 1955;2:1041-1048.
9. Turner D, Walsh CM, Steinhart AH, et al. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. *Clin Gastroenterol Hepatol*. 2007;5:103-110.
10. Jakobovits SL, Travis SP. Management of acute severe colitis. *Br Med Bull*. 2005;75-76:131-144.
11. UK IBD Audit second round. <http://www.rcplondon.ac.uk/clinical-standards/ceeu/Current-work/IBD/Pages/Overview.aspx>.
12. Arnott IDR, Leiper K, Down C, et al. Outcome of acute severe ulcerative colitis: data from the national UK IBD audit. *Gut* 2009;58;A33.
13. Arnott ID, Leiper K, Down C, et al. Outcome of acute severe ulcerative colitis: Data from the UK National IBD audit. *Gastroenterology* 2010:763.
14. Kaplan GG, McCarthy EP, Ayanian JZ, et al. Impact of hospital volume on postoperative morbidity and mortality following a colectomy for ulcerative colitis. *Gastroenterology*. 2008;134:680-687.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
15. Ananthakrishnan AN, McGinley EL, Binion DG. Inflammatory bowel disease in the elderly is associated with worse outcomes: a national study of hospitalizations. *Inflamm Bowel Dis*. 2009;15:182-189.
16. Nguyen GC, Steinhart AH. Nationwide patterns of hospitalizations to centers with high volume of admissions for inflammatory bowel disease and their impact on mortality. *Inflamm Bowel Dis*. 2008;14:1688-1694.
17. Roberts SE, Williams JG, Yeates D, et al. Mortality in patients with and without colectomy admitted to hospital for ulcerative colitis and Crohn's disease: record linkage studies. *BMJ*. 2007;335:1033.
18. Nicholls RJ, Clark DN, Kelso L, et al. Nationwide linkage analysis in Scotland implicates age as the critical overall determinant of mortality in ulcerative colitis. *Aliment Pharmacol Ther*. 2010 (epub ahead of print)
19. Travis SP, Farrant JM, Ricketts C, et al. Predicting outcome in severe ulcerative colitis. *Gut*. 1996;38:905-910.
20. Lindgren SC, Flood LM, Kilander AF, et al. Early predictors of glucocorticosteroid treatment failure in severe and moderately severe attacks of ulcerative colitis. *Eur J Gastroenterol Hepatol*. 1998;10:831-835.
21. Ho GT, Mowat C, Goddard CJ, et al. 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.
22. Randall J, Singh B, Warren BF, et al. Delayed surgery for acute severe colitis is associated with increased risk of postoperative complications. *Br J Surg*. 2010;97:404-409.
23. Ananthakrishnan AN, McGinley EL, Binion DG, et al. Simple score to identify colectomy risk in ulcerative colitis hospitalizations. *Inflamm Bowel Dis*. 2010.
24. Ho GT, Lee HM, Brydon G, et al. Fecal calprotectin predicts the clinical course of acute severe ulcerative colitis. *Am J Gastroenterol*. 2009;104:673-678.
25. Lichtiger S, Present DH, Kornbluth A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med*. 1994;330:1841-1845.
26. Van AG, D'Haens G, Noman M, et al. Randomized, double-blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. *Gastroenterology*. 2003;125:1025-1031.

- 1
 - 2
 - 3
 - 4
 - 5
 - 6
 - 7
 - 8
 - 9
 - 10
 - 11
 - 12
 - 13
 - 14
 - 15
 - 16
 - 17
 - 18
 - 19
 - 20
 - 21
 - 22
 - 23
 - 24
 - 25
 - 26
 - 27
 - 28
 - 29
 - 30
 - 31
 - 32
 - 33
 - 34
 - 35
 - 36
 - 37
 - 38
 - 39
 - 40
 - 41
 - 42
 - 43
 - 44
 - 45
 - 46
 - 47
 - 48
 - 49
 - 50
 - 51
 - 52
 - 53
 - 54
 - 55
 - 56
 - 57
 - 58
 - 59
 - 60
27. Santos J, Baudet S, Casellas F, et al. Efficacy of intravenous cyclosporine for steroid refractory attacks of ulcerative colitis. *J Clin Gastroenterol*. 1995;20:285-289.
28. Rayner CK, McCormack G, Emmanuel AV, et al. Long-term results of low-dose intravenous ciclosporin for acute severe ulcerative colitis. *Aliment Pharmacol Ther*. 2003;18:303-308.
29. Stack WA, Long RG, Hawkey CJ. Short- and long-term outcome of patients treated with cyclosporin for severe acute ulcerative colitis. *Aliment Pharmacol Ther*. 1998;12:973-978.
30. Hyde GM, Thillainayagam AV, Jewell DP. Intravenous cyclosporin as rescue therapy in severe ulcerative colitis: time for a reappraisal? *Eur J Gastroenterol Hepatol*. 1998;10:411-413.
31. Cohen RD, Stein R, Hanauer SB. Intravenous cyclosporin in ulcerative colitis: a five-year experience. *Am J Gastroenterol*. 1999;94:1587-1592.
32. Message L, Bourreille A, Laharie D, et al. Efficacy of intravenous cyclosporin in moderately severe ulcerative colitis refractory to steroids. *Gastroenterol Clin Biol*. 2005;29:231-235.
33. Campbell S, Travis S, Jewell D. Ciclosporin use in acute ulcerative colitis: a long-term experience. *Eur J Gastroenterol Hepatol*. 2005;17:79-84.
34. Sternthal MB, Murphy SJ, George J, et al. Adverse events associated with the use of cyclosporine in patients with inflammatory bowel disease. *Am J Gastroenterol*. 2008;103:937-943.
35. Actis GC, Ottobrelli A, Pera A, et al. Continuously infused cyclosporine at low dose is sufficient to avoid emergency colectomy in acute attacks of ulcerative colitis without the need for high-dose steroids. *J Clin Gastroenterol*. 1993;17:10-13.
36. de Groen PC, Aksamit AJ, Rakela J, et al. Central nervous system toxicity after liver transplantation. The role of cyclosporine and cholesterol. *N Engl J Med*. 1987;317:861-866.
37. de Groen PC, Wiesner RH, Krom RA. Cyclosporine A-induced side effects related to a low total serum cholesterol level: an indication for a free cyclosporine A assay? *Transplant Proc*. 1988;20:374-376.
38. de Groen PC. Cyclosporine, low-density lipoprotein, and cholesterol. *Mayo Clin Proc*. 1988;63:1012-1021.
39. Wijdicks EF, Dahlke LJ, Wiesner RH. Oral cyclosporine decreases severity of neurotoxicity in liver transplant recipients. *Neurology*. 1999;52:1708-1710.

- 1
 - 2
 - 3
 - 4
 - 5
 - 6
 - 7
 - 8
 - 9
 - 10
 - 11
 - 12
 - 13
 - 14
 - 15
 - 16
 - 17
 - 18
 - 19
 - 20
 - 21
 - 22
 - 23
 - 24
 - 25
 - 26
 - 27
 - 28
 - 29
 - 30
 - 31
 - 32
 - 33
 - 34
 - 35
 - 36
 - 37
 - 38
 - 39
 - 40
 - 41
 - 42
 - 43
 - 44
 - 45
 - 46
 - 47
 - 48
 - 49
 - 50
 - 51
 - 52
 - 53
 - 54
 - 55
 - 56
 - 57
 - 58
 - 59
 - 60
40. Toruner M, Loftus EV, Jr., Harmsen WS, et al. Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology*. 2008;134:929-936.
41. Rahier JF, Ben-horin S, Chowers Y, et al. European Evidence-based Consensus on the prevention, diagnosis and management of opportunistic infection in inflammatory bowel disease. *Gut* 2009;47-91.
42. Bojic D, Radojicic Z, Nedeljkovic-Protic M, et al. Long-term outcome after admission for acute severe ulcerative colitis in Oxford: the 1992-1993 cohort. *Inflamm Bowel Dis*. 2009;15:823-828.
43. Arts J, D'Haens G, Zeegers M, et al. Long-term outcome of treatment with intravenous cyclosporin in patients with severe ulcerative colitis. *Inflamm Bowel Dis*. 2004;10:73-78.
44. Moskovitz DN, Van AG, Maenhout B, et al. Incidence of colectomy during long-term follow-up after cyclosporine-induced remission of severe ulcerative colitis. *Clin Gastroenterol Hepatol*. 2006;4:760-765.
45. Stange EF, Travis SPL, Vermeire S, et al. European evidence-based Consensus on the diagnosis and management of ulcerative colitis: Definitions and diagnosis. 2008:1-23.
46. Cacheux W, Seksik P, Lemann M, et al. Predictive factors of response to cyclosporine in steroid-refractory ulcerative colitis. *Am J Gastroenterol*. 2008;103:637-642.
47. Rowe FA, Walker JH, Karp LC, et al. Factors predictive of response to cyclosporin treatment for severe, steroid-resistant ulcerative colitis. *Am J Gastroenterol*. 2000;95:2000-2008.
48. Nicholls S, Stephens S, Braegger CP, et al. Cytokines in stools of children with inflammatory bowel disease or infective diarrhoea. *J Clin Pathol*. 1993;46:757-760.
49. Kaser A, Mairinger T, Vogel W, et al. Infliximab in severe steroid-refractory ulcerative colitis: a pilot study. *Wien Klin Wochenschr*. 2001;113:930-933.
50. Sands BE, Tremaine WJ, Sandborn WJ, et al. Infliximab in the treatment of severe, steroid-refractory ulcerative colitis: a pilot study. *Inflamm Bowel Dis*. 2001;7:83-88.
51. Ochsenkuhn T, Sackmann M, Goke B. Infliximab for acute, not steroid-refractory ulcerative colitis: a randomized pilot study. *Eur J Gastroenterol Hepatol*. 2004;16:1167-1171.
52. Jarnerot G, Hertervig E, Friis-Liby I, et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. *Gastroenterology*. 2005;128:1805-1811.

- 1
 - 2
 - 3
 - 4
 - 5
 - 6
 - 7
 - 8
 - 9
 - 10
 - 11
 - 12
 - 13
 - 14
 - 15
 - 16
 - 17
 - 18
 - 19
 - 20
 - 21
 - 22
 - 23
 - 24
 - 25
 - 26
 - 27
 - 28
 - 29
 - 30
 - 31
 - 32
 - 33
 - 34
 - 35
 - 36
 - 37
 - 38
 - 39
 - 40
 - 41
 - 42
 - 43
 - 44
 - 45
 - 46
 - 47
 - 48
 - 49
 - 50
 - 51
 - 52
 - 53
 - 54
 - 55
 - 56
 - 57
 - 58
 - 59
 - 60
53. Lees CW, Heys D, Ho GT, et al. A retrospective analysis of the efficacy and safety of infliximab as rescue therapy in acute severe ulcerative colitis. *Aliment Pharmacol Ther.* 2007;26:411-419.
54. Kohn A, Daperno M, Armuzzi A, et al. Infliximab in severe ulcerative colitis: short-term results of different infusion regimens and long-term follow-up. *Aliment Pharmacol Ther.* 2007;26:747-756.
55. Rahier JF, Yazdanpanah Y, Colombel JF, et al. The European (ECCO) Consensus on infection in IBD: what does it change for the clinician? *Gut.* 2009;58:1313-1315.
56. Rahier JF, Yazdanpanah Y, Viget N, et al. Review article: influenza A (H1N1) virus in patients with inflammatory bowel disease. *Aliment Pharmacol Ther.* 2010;31:5-10.
57. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. *Clin Gastroenterol Hepatol.* 2006;4:621-630.
58. Peyrin-Biroulet L, Deltenre P, de SN, et al. Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: meta-analysis of placebo-controlled trials. *Clin Gastroenterol Hepatol.* 2008;6:644-653.
59. Lichtenstein GR, Cohen RD, Feagan BG, et al. Safety of Infliximab and Other Crohn's disease Therapies: Treat Registry data with 27762 patient-year follow-up. *Gastroenterology* 2010:T1040.
60. Mackey AC, Green L, Leptak C, et al. Hepatosplenic T cell lymphoma associated with infliximab use in young patients treated for inflammatory bowel disease: update. *J Pediatr Gastroenterol Nutr.* 2009;48:386-388.
61. Monterubbianesi R, Armuzzi A, Papi C, et al. Infliximab for severe ulcerative colitis: short-term and one year outcome of three dose regimen. An Italiana Multi-centre open-label study. *Gastroenterology* 2009:A325.
62. Venu M, Naik AS, Ananthakrishnan AN. Early infliximab infusion in hospitalised severe UC patients: one year outcome. 2009:S1152.
63. Gustavsson A, Jarnerot G, Hertevig E, et al. Colectomy after rescue therapy in intravenous steroid-resistant acute ulcerative colitis: a 3-year follow-up study of the Swedish/Danish Infliximab/Placebo Trial. *Gut* 2008;57:A79.
64. 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(4):983-984.

- 1
 - 2
 - 3
 - 4
 - 5
 - 6
 - 7
 - 8
 - 9
 - 10
 - 11
 - 12
 - 13
 - 14
 - 15
 - 16
 - 17
 - 18
 - 19
 - 20
 - 21
 - 22
 - 23
 - 24
 - 25
 - 26
 - 27
 - 28
 - 29
 - 30
 - 31
 - 32
 - 33
 - 34
 - 35
 - 36
 - 37
 - 38
 - 39
 - 40
 - 41
 - 42
 - 43
 - 44
 - 45
 - 46
 - 47
 - 48
 - 49
 - 50
 - 51
 - 52
 - 53
 - 54
 - 55
 - 56
 - 57
 - 58
 - 59
 - 60
65. Jakobovits SL, Jewell DP, Travis SP. Infliximab for the treatment of ulcerative colitis: outcomes in Oxford from 2000 to 2006. *Aliment Pharmacol Ther.* 2007;25:1055-1060.
66. Gisbert JP, Gonzalez-Lama Y, Mate J. Systematic review: Infliximab therapy in ulcerative colitis. *Aliment Pharmacol Ther.* 2007;25:19-37.
67. Ferrante M, Vermeire S, Katsanos KH, et al. Predictors of early response to infliximab in patients with ulcerative colitis. *Inflamm Bowel Dis.* 2007;13:123-128.
68. Zisman TL, Lewis JR, Stein AC, et al. Predictors of avoidance of colectomy with infliximab initiation in severe, IV steroid refractory ulcerative colitis. *Gastroenterology* 2009;W1128.
69. Walch A, Sjoberg M, Meshkat M, et al. Outcome of rescue therapy in steroid-resistant ulcerative colitis: a retrospective study comparing cyclosporine and infliximab. *Gut* 2008;57:P0801.
70. Moccario F, Oliva L, Orlando A, et al. Infliximab or cyclosporine in severe steroid-refractory ulcerative colitis: short and long term results in two groups of treated patients (a historical comparison). *Gut* 2009;58:A324.
71. Manosa M, Lopez San RA, Garcia-Planella E, et al. Infliximab rescue therapy after cyclosporin failure in steroid-refractory ulcerative colitis. *Digestion* 2009;80:30-35.
72. Maser EA, Deconda D, Lichtiger S, et al. Cyclosporine and infliximab as acute salvage therapies for each other, in severe steroid-refractory ulcerative colitis. *Gut* 2007:S1132
73. Leblanc S, Allez M, Seksik P, et al. Successive treatment with cyclosporine and infliximab in severe ulcerative colitis. *Gastroenterology* 2009:561.
74. Estelles J, Fernandez-Blanco I, Mendoza JL, et al. Initial response and long-term outcome of adalimumab for ulcerative colitis previously treated with infliximab. *Gut* 2009;58:A69.
75. Peyrin-Biroulet L, Laclotte C, Roblin X, et al. Adalimumab induction therapy for ulcerative colitis with intolerance or lost response to infliximab: an open-label study. *World J Gastroenterol.* 2007;13:2328-2332.
76. Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis. 2010:7.
77. Baumgart DC, Wiedenmann B, Dignass AU. Rescue therapy with tacrolimus is effective in patients with severe and refractory

- 1
2
3
4 inflammatory bowel disease. *Aliment Pharmacol Ther.* 2003;17:1273-
5 1281.
6
7 78. Targan SR, Salzberg BA, Mayer L. A phase I-II study: multiple dose
8 levels of vedolizumab are well tolerated and produce rapid and sustained
9 improvement in ulcerative colitis patients refractory to treatment with
10 intravenous steroids. *Gastroenterology* 2005;128:A75.
11
12 79. Ferrante M, D'Hoore A, Vermeire S, et al. Corticosteroids but not
13 infliximab increase short-term postoperative infectious complications in
14 patients with ulcerative colitis. *Inflamm Bowel Dis.* 2009;15:1062-1070.
15
16 80. Yang Z, Wu Q, Wu K, et al. Meta-analysis: pre-operative infliximab
17 treatment and short-term post-operative complications in patients with
18 ulcerative colitis. *Aliment Pharmacol Ther.* 2010;31:486-492.
19
20 81. Andersson P, Soderholm JD. Surgery in ulcerative colitis: indication
21 and timing. *Dig Dis.* 2009;27:335-340.
22
23 82. Lichtenstein GR, Cohen R, Yamashita B, et al. Quality of life after
24 proctocolectomy with ileoanal anastomosis for patients with ulcerative
25 colitis. *J Clin Gastroenterol.* 2006;40:669-677.
26
27 83. Haritunians T, Taylor K, Rotter JI, et al. Genetic predictors of medically
28 refractory ulcerative colitis requiring colectomy. *Gastroenterology*
29 2009;857.
30
31 84. Bressler B, Law JK, Al Nahdi SN, et al. The use of infliximab for
32 treatment of hospitalized patients with acute severe ulcerative colitis.
33 *Can J Gastroenterol.* 2008;22:937-940.
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60