Management of acute severe colitis

Simon L. Jakobovits* and S. P. L. Travis
Gastroenterology Unit, John Radcliffe Hospital, Oxford OX3 9DU, UK

The management of acute severe ulcerative colitis depends on early recognition of the unwell patient with colitis, the prompt initiation of treatment and objective assessment of the likelihood of medical failure. This deters ‘hopeful expectation’ in an attempt to avoid surgery. Intravenous corticosteroids remain first-line therapy but are completely effective in only 40%, partially effective in 30% and around 30% come to colectomy. The decision to use ciclosporin or infliximab for those with a poor response to steroids should be made at an early stage, often 3 or 4 days after starting intensive therapy. Decision-making is becoming more difficult with agents such as visilizumab, tacrolimus and the technique of leucocytapheresis as further options. Nevertheless, intravenous corticosteroids and timely colectomy have reduced mortality from nearly 30% to <1% in specialist centres. Ciclosporin has delayed the need for urgent colectomy in many patients, but long-term follow-up suggests the majority come to colectomy within 7 years. Long-term outcome with newer agents, including infliximab, is not yet known.

Keywords: ulcerative colitis, colitis, colectomy, infliximab, corticosteroids, visilizumab, ciclosporin, tacrolimus, leucocytapheresis

Introduction

Severe acute ulcerative colitis is usually defined by the original classification put forward by Truelove and Witts (Table 1) [1]. They suggested six or more bowel motions per day associated with one or more of the following: temperature >37.8°C, large amounts of rectal bleeding, heart rate >90 beats per minute, haemoglobin of <10.5 g/dl or an erythrocyte sedimentation rate (ESR) >30 mm/h were indicative of severe colitis. These criteria have been validated over half a century and allow simple, rapid stratification of outpatients with ulcerative colitis.

The natural history of untreated severe ulcerative colitis shows a mortality of 24%. This was reduced to 7% with the introduction of intravenous corticosteroids and subsequently to <1% with timely and expert surgical input [1, 2]. The importance of a combined medical and surgical team approach from the time of patient presentation to hospital...
cannot be overstated. In 2001, an audit from a District General Hospital in the UK revealed a mortality rate of 24% for patients admitted with severe ulcerative colitis [3]. Half of the deaths occurred in the perioperative period, suggesting that the cause may have been delays in deciding to operate, perhaps due to an unwarranted belief in the ability of medicine to treat this condition. A simple objective predictor of the need for colectomy was proposed in 1996 and has subsequently been validated [4]. A stool frequency of ≥8 or a C-reactive protein (CRP) of >45 on day 3 of admission predicts an 85% likelihood of requiring a colectomy during that admission. This allows early, meaningful discussions involving the patient, surgeon and stoma therapist, maximizing the time allowed for the patient to come to terms with the prognosis. It should also alert the physician to the likelihood of pharmacological failure and prevent delayed decision-making which may lead to increased peri-operative morbidity and mortality.

**Initial assessment**

Immediate admission to hospital is warranted for all patients fulfilling the Truelove and Witts’ criteria for severe colitis. For about 10% of patients, their first presentation with ulcerative colitis will fulfil the criteria of a severe attack [5]. For these patients, especially, it is important to consider a differential diagnosis which includes infective, ischaemic, drug-induced and other inflammatory causes of colitis.

Sigmoidoscopy is often very helpful in evaluating the severity of an attack of ulcerative colitis. Endoscopic scoring systems have been devised for ulcerative colitis. The most frequently used in clinical trials is the modified Baron score [6] (Table 2).

**Table 1** Truelove and Witts’ classification of severity of ulcerative colitis [1]

<table>
<thead>
<tr>
<th>Activity</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of bloody stools per day (n)</td>
<td>&lt;4</td>
<td>4–6</td>
<td>&gt;6</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>Afebrile</td>
<td>Intermediate</td>
<td>&gt;37.8</td>
</tr>
<tr>
<td>Heart rate (beats per minute)</td>
<td>Normal</td>
<td>Intermediate</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>&gt;11</td>
<td>10.5–11</td>
<td>&lt;10.5</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/h)</td>
<td>&lt;20</td>
<td>20–30</td>
<td>&gt;30</td>
</tr>
</tbody>
</table>

**Table 2** Modified Baron score [6]

<table>
<thead>
<tr>
<th>Normal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal mucosa</td>
<td>Erythema</td>
<td>Marked erythema</td>
<td>Spontaneous bleeding</td>
</tr>
<tr>
<td>Inactive disease</td>
<td>Decreased vascular pattern</td>
<td>Loss of vascular pattern</td>
<td>Ulceration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mucosal friability</td>
<td></td>
</tr>
</tbody>
</table>
This simple, four-stage classification is readily translated into clinical practice, but interobserver variability has never been validated. Some patients may have severe ulcerative colitis at endoscopy, despite not fulfilling the clinical criteria of severity (Table 1).

In these patients, the disparity should be recognized, but there is no validated management approach. If the mucosa on a plain abdominal radiograph is unremarkable, a sensible approach is to treat decisively with corticosteroids, review the patient within a few days and admit for intensive treatment if there is no improvement, although this aspect of ulcerative colitis has never been studied.

In those with clinical criteria for severe ulcerative colitis, sigmoidoscopy and biopsy should be performed as part of the initial assessment of the patient. Rectal sparing in a patient who has not been treated with topical agents should make one question the diagnosis of ulcerative colitis. Biopsies confirm the severity of the inflammation and allow other diagnoses such as cytomegalovirus (CMV), indicated by viral inclusion bodies, to be excluded. CMV colitis can mimic ulcerative colitis and is thought to be responsible for treatment failure in up to 10% of patients labelled as steroid-refractory [7]. Treatment of CMV may obviate colectomy.

The question is often raised about the need for, and safety of, colonoscopy in the assessment of severe colitis. Despite a report that careful colonoscopy appears safe [8], it is unnecessary and should be avoided. Bowel preparation is distressing and potentially dangerous since it can provoke megacolon. The extent of disease activity can be determined with acceptable accuracy by the distal extent of faecal residue visible on a plain abdominal radiograph [4]. In the setting of acute severe ulcerative colitis, flexible sigmoidoscopy confirms the diagnosis and all the necessary information. If the distal colon is normal, the diagnosis is not ulcerative colitis and the management is beyond the scope of this article.

Stool microscopy and culture should be performed as part of the initial assessment. A test for Clostridium difficile toxin should be performed, because pseudomembranous colitis can complicate or mimic severe ulcerative colitis. Other conditions are suspected from the history. Recent overseas travel, contact with other people with diarrhoea or immunosuppression suggest a potential infective cause for colitis. Infections which may mimic ulcerative colitis include Campylobacter, Shigella, Salmonella, Yersinia, Entamoeba histolytica and Escherichia coli. Often, these infections will show rectal sparing at sigmoidoscopy. Medications including non-steroidal anti-inflammatory drugs (NSAIDs), chemotherapeutic agents, cocaine or amphetamines can cause or exacerbate colitis [9]. Ischaemic colitis should be suspected in patients with vascular disease, and vasculitides, including Behçet’s, can cause colitis. It may be impossible to distinguish diffuse Crohn’s colitis from ulcerative colitis in the early stages, but the initial treatment is similar.
Plain abdominal radiographs are essential. They allow the diagnosis of perforation, assessment of disease extent and prediction of outcome after medical therapy. Disease extent has been found to be estimated accurately in 80% of 97 patients in a study that compared radiographs with colonoscopic findings, histology and surgical specimens [10]. Abdominal radiographs contribute to the prediction of colectomy. Lennard-Jones found that 75% of those with visible mucosal islands (areas of oedematous mucosa surrounded by deep ulceration) or a colonic diameter of >5.5 cm would fail treatment with steroids and require surgery [11]. A retrospective report that ileus (three or more isolated loops of small bowel) was associated with severe colitis needing colectomy in 73% could not be confirmed in a prospective study [4].

Colonic wall thickening is the most common finding in severe ulcerative colitis. Abdominal films should be taken daily whilst the patient fulfills the criteria for severe colitis and at any sign of deterioration indicated by an increase in pulse rate, niggle of temperature or increase in stool frequency. Typical clinical signs of perforation may be minimal, because patients are being treated with steroids.

The full blood count, electrolyte and liver function tests and inflammatory markers should be checked on admission and then on day 3 to determine the likelihood of needing a colectomy during that admission (see above). Care should be taken to monitor and correct electrolytes on a daily basis. Almost every patient with severe colitis becomes hypokalaemic during intensive treatment unless receiving >60 mmol potassium daily. This is not due just to loss of potassium-rich faecal fluid but also due to corticosteroids. Unfractionated heparin should be administered for prophylaxis against venous thrombosis, and the haemoglobin is best kept above 10 g/dl [12].

There is no value in continuing 5-aminosalicylic acid (5-ASA) drugs during severe attacks of colitis. All opioids and anticholinergic medication should be avoided to prevent development of megacolon, and NSAIDs should also be ceased. Conversely, bowel rest has not been shown to alter the outcome but is advised if complications are likely to necessitate early surgery (perforation, impending megacolon or obstruction) [13].

The role of antibiotics in acute severe colitis appears clear but continues to be debated. Randomized controlled trials have shown no benefit of metronidazole or ciprofloxacin in addition to standard therapy for severe ulcerative colitis [14, 15]. Although the non-absorbable rifamycin antibiotic, rifaximin, decreased the frequency and amount of blood in stools, compared with placebo in steroid-refractory ulcerative colitis, the primary endpoint of clinical outcome was not significant [16]. Antibiotics cannot be recommended routinely. In special situations, including toxic megacolon and perforation, or where the possibility of infection is
high on the list of differential diagnoses, such as a first presentation of colitis or recent overseas travel, however, antibiotic cover seems a reasonable precaution.

A colorectal surgeon is best notified at the time of admission of any patient with severe ulcerative colitis [12] and should be involved in decision-making throughout the hospital stay. At the very least, when any patient is started on ciclosporin or infliximab for severe colitis not responding to steroids, a colorectal surgeon should review the patient daily. Such a change in treatment is an opportunity for contingency planning, preparing the patient for possible colectomy and introducing them to a stoma therapist, while continuing to hope that medical therapy will be effective. The practice of waiting to call surgeons until medical therapy has failed is unfair on the patient and the surgeon and akin to an ostrich burying its head in the sand in the hope of not being seen.

**Treatment**

**Corticosteroids**

Intravenous corticosteroids remain the mainstay of therapy in severe ulcerative colitis. The landmark article of Truelove in 1955 showed a reduction in mortality from 24% in the placebo group to 7% in the steroid-treated group [1]. Treatment with corticosteroids should not be delayed whilst awaiting microbiological results for possible infective causes. Corticosteroids are generally given as hydrocortisone 100 mg four times daily or methylprednisolone 60 mg daily. Higher doses (including 500 mg–1 g of methylprednisolone) are not more effective, but lower doses are less effective [17]. Treatment is best given for about 5 days, since extending therapy beyond 7–10 days is of no benefit. If the patient objectively responds to treatment, oral prednisolone is instituted at 40 mg daily and tapered. It is important to attain a full remission before beginning tapering of steroids or rapid recurrence of symptoms may ensue.

Around 60% of people will not respond completely to corticosteroids, and this figure has stayed remarkably constant for 50 years [2, 4, 18–20]. It has been suggested that steroid resistance may be a property of the T lymphocyte, with resistant cells showing an increase in interleukin-2 (IL-2) concentrations *in vitro* [21]. This has led to attempts to sensitize the T lymphocytes to steroids using basiliximab, an antibody that binds to the IL-2 receptor preventing ligand binding. This technique has shown promise in a small trial [22].

Failure to respond to corticosteroids can be predicted through objective measures (Table 3). At presentation, low albumin, high CRP, short
duration of illness and prior steroid use all portend an increased risk of medical failure [23]. Lennard-Jones et al. reviewed 189 patients with acute severe ulcerative colitis in an attempt to stratify outcomes [11]. After 24 h of corticosteroids, a stool frequency $>9$ in the first 24 h, an albumin $<30$ g/l or a pulse rate $>90$ beats per minute was predictive of a 62% failure rate to respond to steroids. Of patients who had a fever after 24 h of corticosteroids, 80% failed to respond to medical therapy. In a prospective study, a stool frequency $>8$/day and a CRP $>45$ mg/l on day 3 of intensive therapy were predictive of the need for colectomy in 85% during that admission [4]. There are other predictive indices, but it matters less which is used than that one is used to facilitate decision-making [24]. It makes sense, but has never been validated in a prospective study, to use a predictive index for deciding whether to institute ‘rescue’ therapy with ciclosporin or infliximab. It is notable that in a study of the impact of ciclosporin on the outcome of severe colitis including colectomy, it was those patients treated late or longest with ciclosporin, before colectomy, who had the most complications and highest cost [25].

The best ‘rescue’ therapy should be based on a joint decision by the patient, physician and surgeon. It is important to help the patient understand that by failing corticosteroids, their likelihood of requiring a colectomy in the next 10 years is 80%, regardless of the treatment [26]. Armed with this information, patients may choose to avoid potentially toxic medications, but these are always difficult decisions and frequently depend on the pattern or extent of disease prior to the severe episode.

### Ciclosporin

Ciclosporin is a calcineurin inhibitor derived from the fungus *Tolympocladium inflatum*. By binding to calcineurin, ciclosporin prevents a cascade of downstream events that are necessary for T-cell activation and proliferation.

Ciclosporin is used in an attempt to prevent surgery when intravenous corticosteroids have failed to induce a response. Lichtiger’s article in
1994 demonstrated that intravenous ciclosporin at 4 mg/kg was capable of preventing urgent colectomy [27]. Nine of 11 patients failing steroids improved on ciclosporin, whilst all the nine on placebo failed to improve. The study was criticized for its small numbers, but the recruitment was cut short when a clear benefit in favour of ciclosporin was detected by the safety committee. Subsequent studies have put the response rate to intravenous ciclosporin at 70–80% [28]. Van Assche et al. found that similar results were achievable with 2 mg/kg intravenously, with a median time to response of 4 days with potentially less toxicity than 4 mg/kg of ciclosporin[29].

Ciclosporin has also been used as intravenous monotherapy (4 mg/kg) in patients with severe ulcerative colitis, with similar efficacy to methylprednisolone 40 mg intravenously (10 of 15 patients responded to ciclosporin compared with a response of 8 of 15 in the steroid group) [30]. Ciclosporin may be a useful option in those with contraindications to steroids, including steroid-induced psychoses, severe osteoporosis, uncontrolled diabetes or patient preference.

Although ciclosporin was the first drug shown to work after steroid failure, there has been appreciable resistance to using it in many centres [31]. The rapid response and low toxicity of the intravenous 2-mg/kg/day dose should increase its role, despite the advent of infliximab (see below). It is best started on day 3 when steroids are failing, with conversion to oral ciclosporin 5 mg/kg once a response has occurred. Oral ciclosporin is then generally continued for about 3 months, and azathioprine or mercaptopurine (6-MP) introduced to maintain remission once the steroid dose tapers below 20 mg/day. This limits the duration of combined immunosuppression and potential toxicity. In patients with a serum cholesterol <3 mmol/l or a serum magnesium <0.5 mmol/l, the oral micro-emulsion of ciclosporin (5 mg/kg) is a safe alternative, because it is not associated with the seizures provoked by a chromophore in the intravenous preparation. The oral micro-emulsion formula appears to be at least as good and may even be superior to intravenous therapy [28, 32]. Ciclosporin does not increase the risk of peri-operative complications in those who do not respond and progress to colectomy [33]. Long-term data on response to ciclosporin report that at 7 years, 58% of those treated with ciclosporin had come to colectomy [28].

**Infliximab**

Infliximab is a monoclonal antibody that binds to free and membrane-bound tumour necrosis factor-α (TNFα) to induce apoptosis of activated lymphocytes. Its use in Crohn’s disease is well established, and elevated concentrations of TNFα in the mucosa and stool of patients with ulcerative
colitis made it a putative treatment agent in this disease. Three small uncontrolled trials supported a role for infliximab for the treatment of severe ulcerative colitis [34–36]. In one of those trials, 8 of 11 patients avoided urgent colectomy. The study by Järnerot randomized 45 patients with steroid-refractory ulcerative colitis to ongoing steroids and a single dose of infliximab at 5 mg/kg or to steroids and placebo [37]. After 90 days, 14 of 21 (66%) in the placebo group had undergone colectomy, whilst only 7 of 24 (29%) in the infliximab group required surgery ($P = 0.017$). In subgroup analysis, there was no statistical significance between rates of colectomy in patients with severe colitis, as defined by the fulminant colitis index (69% in placebo and 47% in infliximab). However, in those with less-severe colitis as determined by the Seo index, the benefit of infliximab was significant. This data in conjunction with the recently published Active Ulcerative Colitis Trials (ACTs) 1 and 2 suggest moderate ulcerative colitis in outpatients refractory to aminosalicylates, steroids or thiopurines responds to infliximab, but there is as yet insufficient evidence to establish its effectiveness in severe, steroid-refractory ulcerative colitis [38]. Nevertheless, it seems very probable that infliximab will establish itself as a treatment option for these circumstances. The familiarity of infliximab to gastroenterologists will play a part, but more evidence of benefit and safety is needed from controlled clinical trials. Inpatients with severe colitis in the Swedish study [37] represent a very different patient population to the outpatients in the ACT 1 and 2 studies [38].

The current clinical conundrum is whether to use infliximab or ciclosporin for rescue therapy if intravenous steroids show signs of failing or indeed to try the other if one fails. Both have a rapid onset of action. Although it is possible that ciclosporin works more rapidly, the median times to response of ciclosporin and infliximab have not been published in a form that can be compared. The short-term safety profile may favour infliximab, since it does not provoke seizures or hypertension, while the jury is out on the longer-term safety profile of both drugs. It comes down to the half-life [39]. The real advantage of ciclosporin is that it has a short half-life compared with infliximab. This means that if ciclosporin is not working, it is only a matter of hours ($t_{1/2} = 8$ h) before it disappears from the circulation, while infliximab ($t_{1/2} = 9$ days) will circulate for weeks. This may matter if colectomy is performed, since septic complications are the major cause of postoperative morbidity and mortality. Although the TREAT registry (database of infliximab use and complications in Crohn’s) has not shown an increase in peri-operative infections, this cohort is significantly different to the sick, severe ulcerative colitic that one should keep an open mind to this possibility. There are no data on the efficacy of infliximab for ciclosporin-resistant colitis, but great caution should be exercised before using both
agents in a patient with severe colitis. The combination of TNF blockade and T-cell suppression is powerful immunomodulation that must increase the chances of sepsis. If one agent fails, then this is reason enough to proceed to colectomy.

**Visilizumab**

Visilizumab (Nuvion®) is an immunoglobulin G2 (IgG2) humanized monoclonal antibody that binds to the CD3 epsilon chains on human T cells. This leads to a rapid disappearance of T cells from the circulation, with recovery over 3–5 days. Only activated T cells are affected, with no apoptosis of resting T cells. It is given as two separate boluses, 24 h apart, and has been trialled in two separate dose-ranging studies. It was found to induce a response (as measured by a Modified Truelove and Witts’ score) to intravenous, steroid-refractory ulcerative colitis in nearly 80% of patients, with around 30% going into remission [40]. A predictable cytokine-release syndrome occurs, with fevers, chills, myalgias and headaches predominating, which is dose related. The minimum effective dose has not been established, but a dose of 5 μg/kg is as effective as 10 μg/kg. Doses of 15 μg/kg produced intolerable side effects and exceed the maximum tolerated dose. Despite the T-cell depletion, no increase in opportunistic infections or lymphoproliferative disorders has been documented. More than half the patients treated had a sustained response beyond 6 months (180 days). The duration of response was prolonged in those treated with 6-MP or azathioprine after visilizumab therapy.

Lower doses of visilizumab are being trialled to determine whether clinical efficacy can be maintained whilst reducing the cytokine-related side effects. Whether visilizumab will change the pattern of disease and reduce long-term colectomy rates is not known.

**Tacrolimus**

Tacrolimus is a calcineurin inhibitor acting through a mechanism similar to ciclosporin. No randomized trials have been performed in ulcerative colitis. Case series have shown broadly similar results to ciclosporin after both intravenous (0.01–0.02 mg/kg) and oral (0.1–0.2 mg/kg) administration. In the initial series, 18 of 32 patients had a response, with 34% requiring colectomy over 16 months [41]. Unfortunately, it carries many of the risks and side effects (including nephrotoxicity) of ciclosporin, so it is hard to see a therapeutic advantage (Table 4).
Leucocytapheresis

This is a technique in which white blood cells are selectively removed from the circulation via an extracorporeal circuit. Selected white blood cells are adsorbed onto acetate beads in a column via CD-binding ligands. There are currently two different systems being trialled, and each removes a different subset of the white blood cell population.

Pioneering work has been done in Japan. A single randomized study was presented this year comparing leucocytapheresis with intravenous steroids for severe colitis. The definitions of severe colitis and remission overlapped with what are more commonly recognized as moderate and mildly active disease, respectively. The trial randomized 66 patients with ‘severe’ colitis [colitis activity index (CAI) 10–18; \( n = 33 \)] to leucocytapheresis with Adacolumn® twice weekly for 3 weeks, then weekly up to 10 weeks, or to intravenous prednisolone (40–60 mg/day for 5–10 days; \( n = 33 \) [44]). ‘Remission’ rates (CAI < 4) at 2 weeks were 9 and 21%, respectively, but at 12 weeks were 76 and 39%. Remission was not steroid-free. Unfortunately, trials up to date have been of a poor standard with variable numbers, inconsistent definitions, unblinded and very rarely randomized. Better designed trials are underway to address these issues, but at present, the only role for this therapy in acute severe ulcerative colitis is as part of a trial.

Surgery

Surgery is still the definitive procedure for the treatment of ulcerative colitis, and its timing is of paramount importance. The decision is ultimately a triangular decision between patient, surgeon and physician. Daily review of the patient by an experienced colorectal surgical team with the gastroenterologist facilitates decision-making. The patient must be fully informed about the likelihood and site of a stoma, and despite a natural resistance on the part of patient and physician, introduction to a stoma therapist is best done at an early stage. In this way, the patient is prepared, misconceptions can be addressed and if not ultimately needed

Table 4 Case series of tacrolimus for steroid-refractory ulcerative colitis compared with a case series of ciclosporin therapy in similar patients

<table>
<thead>
<tr>
<th>Series</th>
<th>n</th>
<th>Response</th>
<th>Colectomy at</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1–3 months</td>
</tr>
<tr>
<td>Ciclosporin (Oxford) [28]</td>
<td>76</td>
<td>56/76</td>
<td>10/76</td>
</tr>
<tr>
<td>Tacrolimus intravenous 0.01 mg/kg or oral 0.2 mg/kg [42]</td>
<td>38</td>
<td>18/38</td>
<td>3/38</td>
</tr>
<tr>
<td>Tacrolimus intravenous 0.01 mg/kg [41]</td>
<td>23</td>
<td>22/23</td>
<td>2/23</td>
</tr>
<tr>
<td>Tacrolimus oral 0.15 mg/kg [43]</td>
<td>9</td>
<td>9/9</td>
<td>1/9</td>
</tr>
</tbody>
</table>
then at the very least knowledge is gained. Far better to make contingency plans than for a patient to wake with an unexpected stoma. Close liaison with a stoma therapist is necessary for continued education, support and postoperative follow-up.

The procedure most commonly performed is a subtotal abdominal colectomy and ileostomy, followed about 3 months later, when the patient is off steroids with an improved nutritional state, by completion proctectomy and the formation of an ileal-pouch anal anastomosis (IPAA). Increasingly, the initial subtotal colectomy is being performed by a laparoscopic-assisted approach. This has a markedly better cosmetic result and more rapid recovery, but it depends on timely decision-making, an experienced laparoscopic colorectal surgeon and sufficient theatre time. If the patient is hypoalbuminaemic, steroid-saturated and sick when colectomy is performed, a conventional laparotomy is more appropriate. If events are anticipated appropriately by the physician, a laparoscopic-assisted approach finds much favour with patients; it remains to be seen whether it reduces adhesion formation and adhensive obstruction, which is the main complication after standard emergency colectomy.

Perforation should be exceptionally rare with a pro-active medical and surgical approach. In Oxford, which admits about 50 patients/year with severe colitis, one perforation has occurred in the past 15 years. If it occurs, the mortality is around 30%. Uncontrolled haemorrhage is also exceptionally rare. Toxic megacolon is the end of the spectrum of severe ulcerative colitis and not a separate condition. It is becoming less common with decisive medical treatment of severe colitis. It is defined as a colonic diameter of >5.5 cm on plain abdominal radiograph in a patient with features of severe colitis. In the absence of other complications, it is reasonable to allow a trial of medical therapy for 24 h, under the close supervision of the gastroenterologist and surgical team [12]. If the colonic diameter does not decrease or increases within 24 h, or if there is a persistent temperature or tachycardia after 24 h intensive treatment, then urgent surgery is indicated.

An important subgroup of patients are the young females of childbearing age. IPAA has been shown to markedly reduce fecundity in females [45]. This should prompt a discussion with the patient about delaying reversal of the ileostomy and formation of the pouch until after completing a family.

Surgery is not a ‘cure’ in the sense that the patient returns to a normal bowel pattern. It does, however, improve the quality of life, provide confidence and control in >90%, allow patients to stop immunomodulators and prevent the long-term risk of cancer. The feeling of well-being in a patient just a day after emergency colectomy for severe colitis is often astonishing. Most follow-up studies of patients undergoing IPAA
report an average of six bowel motions per day, but up to 50% experience episodes of faecal leakage at some stage [46, 47]. Complications such as small bowel obstruction, anastomotic stricture, pouch leak and pelvic abscesses may occur, as may late complications such as pouchitis in up to 50% of patients [46, 47]. However, this has to be balanced against the poor outcome of medical therapy in patients who have had an episode of severe colitis. In a 15-year follow-up of 51 episodes of severe colitis, 36% of those with a complete response and 80% of those with a partial response to intensive therapy came to colectomy within 15 years of the index admission [26]. For those who decry the outcome of surgery, the long-term morbidity and potential mortality of continuing medical therapy remain to be defined, in contrast to colectomy which has already been shown to reduce mortality.

Conclusion

No head-to-head trials of rescue therapy for severe ulcerative colitis failing to respond to steroids have ever been performed, so the optimum regimen is not clear. One difficulty in comparing drug trials is the variation in severity indices used, as illustrated by the trial of infliximab as rescue therapy [37], where the two indices yielded disparate results. Properly powered, randomized controlled trials are needed.

Current evidence supports initial treatment with intravenous steroids and objective assessment of the likely progression to colectomy on the third day. Ciclosporin 2 mg/kg intravenously or 5 mg/kg orally still has first place as salvage therapy, because of its short half-life and established short-term efficacy in about 70% who fail steroids. Infliximab may be the choice for those with indeterminate colitis or if patients have less severely active colitis and less likelihood of urgent colectomy. This is partly because it is effective in those with less severely active disease [37], but also because it has a long duration of immunomodulation that is not desirable after emergency colectomy. If infliximab is used first and fails, adding ciclosporin means that there are two active immunosuppressants on board and this sequential combination is best avoided. Intensive treatment and early and objective decision-making by an experienced multidisciplinary team with timely colectomy are the keys to keeping the mortality below 1%.

References

40 Targan SR, Salzberg BA, Mayer L *et al.* A phase I–II study: multiple dose levels of visilizumab are well tolerated and produce rapid and sustained improvement in ulcerative colitis patients refractory to treatment with intravenous steroids (IVSR-UC). *Gastroenterology* 2005;128 (Suppl. 2): A-75.