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Review article: Practical management of acute severe ulcerative colitis

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ABSTRACT

BACKGROUND: Acute Severe Ulcerative Colitis (ASUC) is a life-threatening condition for which optimal management strategies remain ill-defined.

AIM: To review the evidence regarding the natural history, diagnosis, monitoring and treatment of ASUC to inform an evidence-based approach to management.

METHODS: Relevant articles addressing the management of ASUC were identified from a search of MEDLINE, the Cochrane Library and conference proceedings.

RESULTS: 31-35% of ASUC is steroid-refractory. Infliximab and ciclosporin salvage therapies have improved patient outcomes in randomised-controlled trials. Short-term response rates (within 3 months) have ranged from 40-54% for ciclosporin and 46-83% for infliximab. Long-term clinical response rates (≥1 year) have ranged from 42-50% for ciclosporin and 50-65% for infliximab. Short-term and long-term colectomy rates have been respectively: 26-47% and 36-58% for ciclosporin, and 0-50% and 35-50% for infliximab. Mortality rates for ciclosporin and infliximab-treated patients have been: 0-5% and 0-2% respectively. At present, management challenges include the selection, timing and assessment of response to salvage therapy, utilisation of therapeutic drug monitoring and long-term maintenance of remission.

CONCLUSIONS: Optimal management of ASUC should be guided by risk stratification using predictive indices of corticosteroid response. Timely commencement and assessment of response to salvage therapy is critical to reducing morbidity and mortality. Emerging pharmacokinetic models and therapeutic drug monitoring may assist clinical decision-making and facilitate a shift toward individualised ASUC therapies.

KEY WORDS: Ulcerative Colitis; Acute Severe Colitis; Steroid; Infliximab; anti-TNF; Ciclosporin

INTRODUCTION

Acute Severe Ulcerative Colitis (ASUC) is a potentially life-threatening condition. The lifetime risk of a severe exacerbation requiring hospitalisation is between 15 and 25%(1, 2). Severe flares of UC are associated with considerable morbidity and a mortality rate of approximately 1% (3). Following one or more episodes of severe flares, there is a 40% colectomy rate and one in five patients are predicted to undergo colectomy during their first hospital admission(1, 4). Long-term colectomy rates remain high, despite salvage therapies, and are thought to range from 50-62% at 3 years(5, 6). ASUC is diagnosed according to Truelove and Witts' criteria, which consists of bloody stool frequency≥6 per day and at least one of the following: pulse rate >90 beats per minute, temperature >37.8^{O}C, haemoglobin <10.5g/dL, and ESR >30mm/hr *(Table 1)*(7). ASUC may occur in the context of varying baseline disease extent or activity. Three modes of presentation are recognised in clinical practice: (1) new-onset colitis – representing roughly one third of the ASUC population; (2) acute-on-chronic colitis, and; (3) relapsing and remitting patterns of disease(1). Sixty-five to 69% of ASUC will respond adequately to intravenous corticosteroid therapy alone(8). Salvage or rescue medical therapy may be initiated for steroid-refractory ASUC as defined by recognised clinical indices such as the Oxford criteria(7, 9) *(Table 2)*. Up to 56% of patients who fail steroid therapy require second-line salvage therapy with either infliximab or ciclosporin(3). Although a recent multicentre randomised controlled trial showed no significant differences in the relative effectiveness of ciclosporin compared with infliximab there is no clear consensus at this stage as to the most appropriate strategy for treating steroid-refractory ASUC(10).

This review summarises the current evidence regarding: 1) the natural history of ASUC; 2) diagnosis and monitoring in the ASUC setting; 3) published studies evaluating available salvage therapy agents; 4) predictors of non-response to salvage therapy; and 5) management of common precipitants and complications of ASUC. Our aim was to synthesise and integrate these data to develop a comprehensive and practical approach to ASUC management.

REVIEW CRITERIA AND METHODOLOGY

The following sources were searched and relevant material was included: 1) PubMed and MEDLINE were searched for all original research studies and systematic reviews published in English-language journals, with a last cut-off publication date of October 1955, using the following key words alone or in combination: “acute severe colitis”, “ulcerative colitis”, “drug therapy”, “salvage therapy”, “rescue therapy”, “infliximab”, “ciclosporin”, “cyclosporin”, “treatment outcomes”, “*Clostridium difficile*”, “cytomegalovirus”, “thrombosis”, “toxic megacolon”; 2) The Cochrane Database of Systematic Reviews was searched for systematic reviews using the medical subject heading (MeSH): “ulcerative colitis”; 3) The reference lists from all identified full publications; 4) Abstracts presented at the United States Digestive Disease Week 2014/2015. The search strategy is outlined in Figure 1. All databases were last accessed in August 2015.

Both authors assessed study eligibility independently. To be eligible for inclusion, studies needed to include patients diagnosed with ASUC, fulfilling the Truelove and Witts criteria, as well as patients hospitalised with severe UC, classified according to the Mayo scoring system or Lichtiger clinical activity index. Studies were excluded if patients had a subsequent diagnosis of Crohn’s disease or indeterminate colitis.

PREDICTING DISEASE COURSE AND REQUIREMENT FOR SALVAGE THERAPY

Optimal management of ASUC relies on timely and repeated evaluation of disease response to therapy, in order to improve clinical outcomes. One of the major challenges faced by clinicians is the absence of a widely accepted management and monitoring protocol(11, 12). In particular, 3 key stages of assessment in the acute setting have been investigated in the literature: 1) on admission; 2) after initiation of steroid therapy, and; 3) after initiation of salvage therapy. More recently, studies have also focussed on long-term outcomes; however, further prospective studies in this area are required.

Steroid Therapy

Preliminary risk stratification is generally performed according to Truelove and Witts criteria (Table 1), with intravenous corticosteroids remaining the first-line therapy for severe flares. Management of severe flares is time-limited. Current guidelines recommend the use of hydrocortisone 100mg intravenously QID or methylprednisolone 60mg/day, administered via multiple intravenous injections or a continuous 24 hour infusion(13). There are few trials that have focussed on assessing steroid response at varying doses in ASUC. Oral prednisolone dosing has been evaluated in ambulatory patients with mild disease, with results suggesting that 60mg/day was as effective as 40mg/day; however, comparative studies have not been performed in the ASUC setting(14). While studies have not yet established an optimal corticosteroid dosage, higher doses have not been shown to improve outcomes(8, 15). The use of intravenous corticosteroids has reduced mortality in ASUC from almost 30% to <1%(16). Systemic steroid therapy was first established as a treatment for UC in a landmark trial by Truelove & Witts(7). Outcomes following intravenous hydrocortisone were evaluated in a total of 210 patients with acute flares of varying severity. After 6 weeks of therapy, higher rates of clinical remission were seen in steroid-treated patients when compared with placebo controls [41% (45/109) and16% (16/101)], and a greater proportion of patients in the cortisone group experienced endoscopic improvement. Longer-term data indicated that rates of clinical remission remained higher in the cortisone group in those admitted with a first attack of UC; however, after 9 months, any clinical benefit associated with steroid therapy was lost in those who initially presented with a relapse of their disease. A subsequent study of 49 patients with severe exacerbations of UC reported a clinical remission rate of 73%, 5 days after receiving intravenous methylprednisolone(17). There have been no head-to-head trials of intravenous cortisone compared to methylprednisolone, and the optimal steroid dose for induction of remission in ASUC is unknown. Nonetheless, steroid efficacy in ASUC has been the focus of a large number of studies. A 2007 systematic review compiled the results of 26 studies between 1974 and 2006, assessing corticosteroid response in 1,948 adult patients with moderate to severe UC flares. These data indicate that intravenous corticosteroids play a significant role in reduction morbidity and mortality associated with ASUC(8).

Adjunctive Therapy

Discontinuation of nonsteroidal anti-inflammatory drugs, narcotics and anticholinergic agents is recommended to minimise the risk of further disease exacerbation. In addition, careful symptom monitoring is needed in patients started on an aminosalicylate agent during an acute flare, with prompt discontinuation of therapy if there is an association with worsening symptoms. The use of antibiotics has not been shown to improve patient outcomes in ASUC. Clinical trials have evaluated numerous antibiotics, including metronidazole, tobramycin and ciprofloxacin as potential adjuncts to corticosteroid therapy; however, there is currently no evidence to support their use(18-20). Similarly, despite early evidence suggesting otherwise, studies have not found parenteral nutrition to provide any clinical benefit in ASUC, when compared to a regular oral diet(21-27). Instead, enteral feeding has yielded better outcomes in a head-to-head comparison with parenteral nutrition in this population(24). In a randomised trial of 42 patients with moderate to severe flares of UC, enteral nutrition increased median serum albumin by 16.7% [-0.5% to 30.4%], whereas parenteral nutrition was associated with only a 4.6% gain [-12.0% to 13.7%] (p=0.019). Enteral feeds were also associated with fewer complications (9% and 35%, p=0.046); however, greater evidence is required before supplemental nutrition with enteral feeding (above and beyond oral nutrition supplements) can be routinely recommended.

Risk Stratification

Given that 31-35% of severe attacks of UC in the adult population are steroid-refractory, methods to predict disease course and the requirement for salvage therapy have become a priority(8). The reason for this is two-fold. In the context of minimal response to intravenous steroids, early steroid cessation firstly, prevents unnecessary immunosuppression, and secondly, facilitates earlier induction of salvage therapy – potentially improving outcomes(28). Protracted steroid therapy beyond 7-10 days is not recommended and studies have proposed that 3-5 days is sufficient to determine likelihood of remission(29, 30).

According to ECCO guidelines, published in 2008, steroid-refractory colitis is defined as active disease that remains present despite up to 0.75mg/kg/day prednisolone over the course of 4 weeks(31). However, as acknowledged by the authors, greater usage of newer biologic therapies may necessitate reworking of this definition. Steroid-refractoriness can be predicted with an evaluation of clinical, biochemical, endoscopic and radiologic markers(32-35). The monitoring of clinical signs – predominantly, the number of bowel motions per day and presence of rectal bleeding, and acute phase reactants (CRP, ESR) has been advocated in multiple studies.

Prognostic stratification should begin on admission. Greater biological severity on admission, based on Truelove and Witts criteria (Table 1), and more extensive underlying disease have been shown to correlate with increased rates of progression to surgery(1, 36). In particular, UC extending proximal to the splenic flexure has been associated with poorer prognosis and is predictive of steroid-refractory disease(36). Retrospective data published by Dinesen *et al.* demonstrated that colectomy rates in ASUC increase in proportion to the number of Truelove and Witts criteria satisfied. Patients admitted with one criterion in addition to ≥6 bloody stools per day had a colectomy rate of 8.5% (11/129), whilst patients with two additional criteria underwent colectomy at a rate of 31% (29/94). The highest colectomy rate – 48% (34/71), was observed in patients with three or more additional criteria on admission(1).

An Italian prospective cohort study determined that, on admission, elevation in ESR above 75mm/hr and body temperature >38^{0}C were associated with a 4.6 and 8.8-fold increased risk of colectomy, respectively(33). Persistence of diarrhoeal symptoms despite intravenous corticosteroids has also been associated with poorer outcomes. A less than 40% reduction in bowel motions after 5 days of steroids has been shown to predictive of eventual treatment failure, whereas cessation of rectal bleeding was predictive of steroid responsiveness(28, 33).

Following three days of intravenous steroids, established prognostic models should guide further management. In a study by Travis *et al*., 51 cases of ASUC were treated with intensively scheduled 6-hourly 100mg doses of intravenous hydrocortisone and rectal steroid enemas(9). Low stool frequency and CRP on day 3 following steroid initiation were predictive of treatment response – with clinical remission defined as ≤ 3 stools/day with the absence of visible blood after 7 days. In contrast, patients with >8 stools/day, or 3-8 stools/day with CRP>45mg/L had an 85% risk of steroid failure and progression to colectomy (PPV 85%) *(Table 2)*.

The Ho risk index *(Table 3)* was derived from findings of a Scottish cohort study(37), which identified key predictors of steroid failure in 167 patients with ASUC. A scoring system was established with regression analysis based on statistically significant variables – including day 3 stool frequency, serum albumin and the presence of colonic dilatation. The study showed that 6-9 daily bowel motions in conjunction with hypoalbuminaemia (<30g/L) had a 45% positive predictive value for colectomy. The presence of colonic dilatation or >9 daily stools was predictive of non-response in 85% of patients. Hypoalbuminaemia also correlated with poorer outcomes in a Scottish retrospective study involving 39 patients with steroid-refractory ASUC(38). Serum albumin levels of <34g/L on day 3 of steroid therapy (seen in 31/39 patients) were found to be predictive of colectomy – 9/18 patients (50%) with albumin <34g/L underwent colectomy compared to 1/13 patients (8%) with >34g/L; (p=0.02, OR 12.0 95% CI: 1.28-112.7). In this study, hypoalbuminaemia had a sensitivity of 57.1% (95% CI: 34.0-78.2%) and specificity of 90.0% (95% CI: 55.5-99.8) for colectomy.

Studies have also advocated the measurement of faecal markers, in particular faecal calprotectin (FC) and lactoferrin, and more recently S100A12 and M2-pyruvate kinase(39, 40). However, the utility of faecal markers in comparison to clinical monitoring is yet to be determined as the former are generic measures of colonic inflammation, lack specificity for the disease process and are limited by large inter-individual variation. While FC levels appear to be reliable markers of treatment response during steroid therapy, levels measured early in the disease course (days 0 and 4 post-steroid administration) have not been found to correlate with disease prognosis beyond 12 months(41). In the paediatric setting, clinical monitoring with the Paediatric Ulcerative Colitis Activity Index (PUCAI) has been shown to predict short-term colectomy more accurately than any faecal marker(39).

Radiologic predictors of disease course include abdominal plain films to screen for colonic dilatation (>5.5cm). Typically, the presence of colonic dilatation is indicative of the need for high acuity care and confers a 75% positive predictive value for progression to colectomy(42). The presence of mucosal islands and small bowel ileus, evidenced by 3 or more small bowel loops of gas on X-ray, has also been shown to predict medical therapy failure, with the latter associated with colectomy in 73% of patients(43). A potential role for colonic MRI has been explored in the literature. The total colonic inflammation score (TCIS) was devised to enable standardised MRI assessment of severity and prognosis in ASUC(44). The score, ranging from 6-95, was derived from radiologist assessment of T2-weighted images, on the basis of segmental haustral loss, mural thickness, oedema and colonic dilatation. TCIS on admission was shown to correlate with levels of CRP (Kendall's tau=0.45, 95% CI: 0.11-0.79, p=0.006), and stool frequency (Kendall's tau=0.39, 95% CI: 0.14-0.64, p=0.02). Accordingly, the TCIS fell after therapy indicating a decrease in levels of inflammation. Unlike CRP and stool frequency, radiological scoring correlated with length of hospital stay (Kendall's tau 0.40, 95% CI 0.11-0.69, p = 0.02). Amongst patients discharged within 1 week of admission, 14% (1/7) had an admission TCIS >20; whereas amongst patients who required more extensive admission for 1 week or longer, 64% (7/11) had an admission TCIS >20 [(PPV 0.9, NPV 0.5, sensitivity 65% (95% CI: 36-86) and specificity 86% (95% CI: 42-99)]. Overall, these data suggest that the MRI-based TCIS may represent a radiological counterpart to established laboratory markers in UC. However, effective implementation of this approach is contingent on accessibility and availability of appropriate imaging modalities.

There is an emerging role for endoscopic risk stratification in identifying patients likely to require salvage therapy. A recent retrospective study of 89 patients with ASUC correlated greater endoscopic severity on admission with poorer disease outcomes(45). Endoscopic severity was classified according to the Ulcerative Colitis Endoscopic Index of Severity (UCEIS), accounting for a range of endoscopic findings, including vascular pattern, active bleeding and the presence and depth of colonic erosions and ulcers(46). Study outcomes were defined as colectomy, readmission, death and the requirement for rescue therapy, with a median follow-up duration of 13 months. In total, 36 patients (40%) required either infliximab or ciclosporin rescue therapy. Of patients with an UCEIS score ≥7/8, 11 out of 14 (79%) required salvage therapy. Similarly, 27 out of 54 (50%) patients with UCEIS score ≥5/8 needed salvage therapy; in contrast to only 9 out of 33 (27%) patients with UCEIS score <5/8 (p=0.037).

European Crohn's and Colitis Organisation (ECCO) guidelines define an adequate steroid response as a decrease in activity index of >30% with a reduction in rectal bleeding and endoscopic subscore(31). At present there is no standardised activity index for ulcerative colitis and multiple activity indices are utilised in clinical practice(47). While numerous studies have established the importance of monitoring clinical and laboratory variables alongside radiological and endoscopic parameters, the criteria for steroid non-response and predictors of non-response in ASUC remain relatively heterogeneous.

SALVAGE THERAPIES

Historically, failure to induce clinical remission with intravenous corticosteroids invariably led to colectomy. The introduction of medical rescue, or salvage, therapies has provided an alternative option to patients previously facing only surgical management. Salvage therapy appears to have improved clinical outcomes in patients with ASUC and in particular, its use has been associated with a reduction in overall colectomy rate. Kaplan *et al.* identified patients within the Canadian Calgary database, admitted with ASUC between 1997 and 2009, demonstrating a significant reduction in elective colectomy rate(48). Applying linear regression models, investigators found that the average annual percent change (AAPC) in elective colectomy rate was -7.4% (95% CI: -10.8%, +3.9%). Correlating with this, thiopurine use increased across this time period (OR 1.15, 95% CI: 1.09-1.22) alongside infliximab use, which had increased since 2005 (OR 1.68, 95% CI: 1.25-2.26). Emergent colectomy rates, which are associated with significant morbidity and mortality in this population, were relatively unchanged (AAPC: -1.4%, 95% CI: -4.8%, +2.0%). Overall, these data suggest that patients with chronic active colitis are more likely to respond to infliximab than patients with an acute severe flare. The current infliximab dosing schedule (weeks 0,2,6) does not appear to be adequately effective in preventing progression to emergent colectomy. Clinicians may need to reconsider optimal infliximab dosing and adopt a more aggressive dosing strategy in order to minimise colectomy rates in the acute setting.

There are a number of options available when considering salvage therapy. Ciclosporin and infliximab have been the focus of most active research and currently represent the mainstays of salvage therapy; however, a number of emerging therapies are also under investigation.

Salvage therapies are predominantly used in the context of steroid failure; however, their use as a first-line treatment option in selected cases of inflammatory bowel disease has been proposed in order to minimise immunosuppression-associated morbidity(49). The latter ‘top-down’ management approach has been suggested for patients at high risk of steroid failure; however, it carries the risks of overtreatment as well as the potential adverse effects associated with the potent salvage therapies themselves.

CICLOSPORIN

Short-term Efficacy

Lichtiger *et al.* first demonstrated the efficacy of the calcineurin inhibitor ciclosporin in ASUC, in a randomised controlled trial of 20 steroid-resistant patients, who had failed to respond to ≥7 days intravenous hydrocortisone together with nightly hydrocortisone enemas(50). Steroid therapy was maintained in the enrolled patient sample while in addition, 11 patients received 4mg/kg/day intravenous ciclosporin and 9 received placebo. Of the 11 patients treated with ciclosporin, 9 (82%) showed significant improvement after 7 days – measured as a decrease in clinical activity score from 13 to 6 on a modified Truelove and Witts severity index (*Supplementary Table 2)*(7). In contrast, the placebo group demonstrated minimal improvement ($p<0.001$) – with a mean score decrease from 14 to 13. The relative risk of failing to induce remission with ciclosporin was 0.18 (95% CI 0.05-0.64). At 2-week follow-up, 3 of 11 patients (27%) had undergone colectomy in the intervention group, in contrast with 4 of 9 placebo group patients (44%) – with the relative risk of colectomy calculated as 0.6 (95% CI 0.18-2.06)(51). After failure to achieve the primary endpoint of a reduction in Lichtiger score below 10, five of the placebo treated patients subsequently responded to open-label ciclosporin. Taken together these findings successfully helped establish the role of ciclosporin in steroid-refractory ASUC.

A randomised double-blinded Belgian study of 30 patients with ASUC directly compared ciclosporin and steroid therapy. Nine of 14 subjects (64%), who received ciclosporin, entered remission, as compared to 8 of 15 (53%) who received methylprednisolone(52). At 1-year follow-up, 7 of 9 patients (78%) initially controlled with ciclosporin had maintained remission, compared to 3 of 8 (37%) initially controlled with methylprednisolone. A 2005 Cochrane review suggested that the short-term efficacy of ciclosporin monotherapy is similar to that of conventional steroid treatment; however, this analysis was limited by the inclusion of only 2 prospective studies(51).

Randomised controlled trials evaluating ciclosporin use, have reported rates of immediate response, at 1-2 weeks, between 64% and 82%(50, 52). Results from the latest round of the UK IBD audit (2014), found that 26% of patients (68/261) treated with ciclosporin following steroid failure progressed to colectomy prior to discharge(53). In clinical trials, colectomy rates at 3 months have ranged from 26-47%(10, 50, 52, 54, 55). Rates of short-term clinical response, 3 months following ciclosporin have been between 40-54%(10, 54, 55). These data are described in *Table 6*.

Long-term Efficacy

Despite proven efficacy for induction of remission, ciclosporin has failed to maintain remission at longer-term follow-up. Campbell *et al.* demonstrated a 65% relapse rate at 1-year follow-up post-ciclosporin administration and a 58% colectomy rate at 7-year follow-up, while Actis *et al.* demonstrated a 1-year relapse rate of 56% and a 100% relapse rate after 7 years(5, 56). Patients in both studies were treated with intravenous ciclosporin infusion or oral ciclosporin, with initial dosing set at 2mg/kg/day or 4mg/kg/day intravenously or 5mg/kg/day orally. The heterogeneity of interventions both between the studies and within each study itself may account for the differences in reported treatment effects. Numerous studies advocate the use of purine analogues (azathioprine, mercaptopurine) for maintenance therapy, following induction of remission with intravenous ciclosporin(5, 57, 58). In the Actis study, 10% of ciclosporin responders, who were not given azathioprine, had avoided relapse at 3-year follow-up; in contrast, of those maintained on azathioprine, 26% remained relapse-free ($p=0.0635$). Differences in route of administration, dosage and maintenance therapy likely contribute to the variability in results. Nevertheless, the literature demonstrates that the long-term relapse rate following initial induction of remission with ciclosporin is high and colectomy is often merely delayed by ciclosporin treatment(56, 59). Overall, ciclosporin response rates in randomised controlled trials, at 1-year follow-up and beyond were in the range of 42-50%, while long-term colectomy rates were between 36-58%(10, 52, 54, 55). Long-term ciclosporin data are described in further detail in *Table 6*.

There has been recent suggestion that more extended durations of therapy may enhance greater durability of remission and improve rates of colectomy-free survival(60). Whilst the duration of optimal therapy is yet to be established, in a retrospective study, Molnar *et al.* found that treatment for 1 year correlated with a 66% probability of avoiding colectomy at 4-year follow-up and beyond(31, 60). Further prospective studies are needed to confirm this association.

Safety Profile

Ciclosporin should be avoided in patients who have relapsed with optimal thiopurine maintenance therapy, those with hypocholesterolaemia and poor renal function, and those affected by active infection or recent immunosuppression secondary to recent infliximab infusion. Treatment with ciclosporin may be associated with potentially serious side effects including renal failure, neurotoxicity (seizures), anaphylaxis and infectious complications, thereby limiting it use as long-term therapy(60, 61). Randomised controlled trials have reported mortality rates between 0-5%(10, 50, 52, 54, 55).

Dosing Schedule

In a study by Van Assche *et al*. no significant difference in short-term colectomy rates, median time response and side effects was found between patients receiving 2mg/kg/day and 4mg/kg/day(62). Current guidelines suggest administration of the lower 2mg/kg/day dose to offset the risk of long-term ciclosporin toxicity.

INFLIXIMAB

Short-term and Long-term Efficacy

Although early randomised controlled trials failed to establish the role of infliximab in the management of ASUC, more recent studies have demonstrated its efficacy and it has become the salvage therapy used most widely in clinical practice, principally due to its ease of administration(10, 55, 63).

An initial study by Sands *et al*. in 2001 suggested a superior clinical response to infliximab compared to placebo in steroid-refractory ASUC, but was underpowered (n=11) – preventing a definitive conclusion(63). In a subsequent randomised controlled trial, Jarnerot *et* *al*. established a lower 3-month colectomy rate in patients with moderate to severe attacks of betamethasone-refractory UC, given single infusion 5mg/kg infliximab (7/24 patients – 29%) compared with those receiving placebo (14/21 patients – 67%). At 3-month follow-up, of the patients who avoided colectomy, clinical and endoscopic remission was confirmed in 6/15 infliximab-treated patients (40%) and 2/6 placebo patients (33%)(64). Three-year follow-up of these patients demonstrated sustained benefits, with a total of 12/24 infliximab-treated patients (50%) undergoing colectomy in comparison to 16/21 patients (76%) given placebo (p=0.012)(6). Overall colectomy rates remained in favour of infliximab. However, selection of maintenance therapy following induction of remission was not standardised and the higher rate of azathioprine use in the infliximab group (75% and 57%) may have biased findings at follow-up(65, 66).

Multiple retrospective analyses support these prospective data(38, 67-70). In general, retrospective studies have suggested that infliximab treatment in ASUC induces higher rates of remission than placebo and reduces progression to colectomy.

The Scottish Society of Gastroenterology Infliximab Group found that 26/39 (67%) ASUC patients given infliximab avoided early colectomy during hospitalisation and remained colectomy-free at 3-month follow-up(38). A Canadian cohort study similarly found that 16/21 patients (76%) with severe UC avoided early colectomy following infliximab, with 13/21 (62%) remaining colectomy-free at 3-month follow-up(70). Comparable findings were described in a Danish multicentre analysis, with infliximab administration to glucocorticoid non-responders with ASUC resulting in a 61% (34/56) colectomy-free survival when followed up after a median of 1.5 years(69).

In randomised controlled trials, clinical response rates following infliximab salvage therapy were similar within the acute admission period, extending to 3 months post-infliximab. Immediate response rates ranged from 50-83%, while short-term response rates ranged from 46-83%(10, 54, 63, 64, 71). Longer-term response was marginally lower and was in the range of 50-65%(54, 64). In the latest (2014) round of the UK IBD audit, 15% of patients (79/512) treated with anti-TNF salvage therapy, for steroid-refractory disease, underwent colectomy prior to discharge from hospital(53). Rates of colectomy in infliximab-treated ASUC were 0-50% and 35-50%, at short-term and long-term follow-up, respectively(10, 54, 63, 64, 71). Prospective and retrospective studies evaluating clinical outcomes in ASUC following infliximab therapy are outlined in *Table 7*.

Multiple Dosing Strategy

Although a single dose of infliximab does confer some benefit in ASUC, the outcomes appear better in those who receive a more than one dose. In a multicentre Italian trial, a total of 70/83 (84%) patients avoid colectomy within 2 months, with an overall colectomy rate of 30% (25/83) at two-year follow-up(68). In the latter study, a combination of retrospective (n=46) and prospective analyses (n=37) was undertaken. Results from this trial demonstrated that patients treated with two or more infliximab infusions had lower rates of early colectomy (3/57 – 5%) in comparison to those given a single infusion (9/26 – 35%) (OR: 9.53; 95% CI: 2.31 – 39.26, p = 0.001). Unlike in previous studies, maintenance therapy used did not influence relapse rates. This was mirrored in a study by Mortensen *et al.*, who noted a lower colectomy rate in patients given three or more infusions (6/24 – 25% colectomy rate after a median of 9 months) when compared to patients given a single infusion only (13/26 – 50% colectomy rate after a median of 7 days)(69).

Intensified Dosing Strategy

The efficacy of an intensified dosing strategy utilising 10mg/kg of infliximab has not been prospectively evaluated in ASUC, with the exception of a study by Sands *et al.,* which was limited by insufficient statistical power(63). Nonetheless, doses of 10mg/kg have been investigated in chronic active colitis. Two double-blinded placebo-controlled studies, the Active Colitis Trials 1 and 2 (ACT1/2), evaluated the use of infliximab for induction and subsequent maintenance of remission in chronic active colitis(72). Both trials involved 728 patients, who were randomised to receive 5 or 10mg doses of infliximab or a placebo, administered at weeks 0, 2 and 6, then given every 8 weeks. After 8 weeks, ACT2 reported clinical response rates of 64.5% (78/121) and 69.2% (83/120) with 5mg and 10mg infliximab respectively. There was a significantly higher rates of clinical response, remission and mucosal healing at week 8 in those who received 10mg/kg compared to placebo at both week 8 and 54, suggesting that a higher dose of infliximab is clinically efficacious(73). Further evaluation of a more intensive dosing regimen in the ASUC setting is warranted.

Accelerated Dosing Strategy

Recent evidence has also indicated that an accelerated infliximab dosing regimen may reduce early colectomy rates in patients with highly active disease. A single-centre retrospective study analysed outcomes in 50 patients with ASUC, admitted for infliximab induction therapy(74). Thirty-five patients were treated with standard induction therapy, with infliximab infusions at weeks 0,2,6. Fifteen patients alternatively received an accelerated dosing regimen, with 3 induction doses of infliximab administered within 3-4 weeks. Responders were given 8-weekly maintenance infliximab doses. The early colectomy rate during infliximab induction was shown to be significantly lower in the group that had received an accelerated induction regimen compared to those on the standard regimen – 7% (1/15) and 37% (13/35), p = 0.039. Furthermore, the standard infliximab regimen was associated with a reduced time to colectomy. However, 2-year follow-up revealed equivalent colectomy rates in both groups. Further prospective studies are needed to establish any potential role for accelerated induction regimens.

Anti-TNF Pharmacokinetics

The pharmacokinetics of anti-TNF therapy may be utilised to optimise infliximab dosing in patients with ASUC. Therapeutic drug monitoring is becoming increasingly relevant in the clinical setting; however, a significant proportion of patients progress to early colectomy within 1 month of initial salvage therapy – 29% in a study by Jarnerot *et al.*(64). For these patients, there is a narrow window of opportunity for dose optimisation, during which serum infliximab levels are still unavailable. Introduction of alternative treatment strategies based on known pharmacokinetic behaviours has been suggested. In a recent review, Rosen *et al.* proposed a three-pronged model, explaining accelerated clearance of anti-TNF drugs in ASUC due to: high TNF burden; anti-TNF neutralisation; and reduced tissue penetration(75).

Elevated levels of both serum and mucosal TNF have been associated with greater disease severity(76). Olsen *et al.* found that higher levels of pre-treatment TNF-alpha gene expression, within the colorectal mucosa, were predictive of clinical non-remission (odds ratio 2.5, p=0.01) and endoscopic non-remission (odds ratio 4.8, p=0.003) following standard week 0,2,6 infliximab induction therapy(77). High mucosal TNF, in conjunction with low mucosal anti-TNF levels, has been shown to correlate with endoscopically active UC(78). Higher serum and lower mucosal levels of anti-TNF also appear to predict for mucosal disease activity(78).

Systemic inflammation associated with severe flares of UC is thought to be responsible for reduced drug efficacy. This is postulated to be due to mononuclear phagocyte upregulation and subsequent ligation and destruction of exogenous anti-TNF monoclonal antibodies(79). Proteolytic degradation by cells of the reticuloendothelial system is thought to be a major contributor to primary non-response to infliximab therapy. This is corroborated by findings that higher CRP levels are associated with faster infliximab clearance(80).

In addition, highly permeable colonic mucosa in ASUC can result in reduced tissue penetration of therapeutic infliximab. Infliximab clearance is suggested to be faster in IBD patients with higher body weight and hypoalbuminaemia(81). Faecal drug loss may occur rapidly after infliximab administration, resulting in the delivery of effectively *episodic* doses. The consequence of this is the promotion of immune sensitisation and the formation of antibodies against infliximab, detectable within the blood. The detection of these antibodies may have implications for future management. In their retrospective study, Afif *et al.* demonstrated that in the presence of antibodies against infliximab, rates of clinical response following dose escalation were significantly lower than response rates after changing to another anti-TNF agent (1/6 (17%) and 11/12 (92%), p<0.004)(82). Studies exploring the potential clinical effects of antibodies against infliximab have been performed in the broader IBD population and there are currently no studies that specifically investigate the impact of antibody formation in ASUC. Although, as in Crohn's disease, it is likely that combination therapy with a thiopurine may reduce immunogenicity compared with infliximab monotherapy this is yet to be proven in ASUC. Moreover it remains to be demonstrated as to which dosing strategy is most likely to reduce the development of antibodies in the acute setting.

In patients who have been previously non-responsive to infliximab therapy, the adoption of a high dose induction regimen may enable greater treatment success. It has been postulated that intensive dosing (10mg/kg) may overcome faecal infliximab losses and successfully establish a therapeutic serum infliximab level. Bridging to infliximab with non-protein based therapy may represent an alternative strategy in these patients. These management approaches are yet to be evaluated in the clinical setting. It is increasingly clear that patients with ASUC do not respond to infliximab equally and methods to assess pharmacokinetic suitability for anti-TNF therapy are needed to guide selection of medical salvage.

Overall, taking into account pharmacokinetic considerations, there is growing evidence that the standard week 0,2,6 infliximab induction regimen may be inadequate in the context of ASUC. Accelerated or intensified dosing regimens may offer better clinical and endoscopic outcomes. Moreover, integration of pharmacokinetic models and dose optimisation strategies into the current management paradigm will enable clinicians to offer individualised administration protocols to ASUC patients. Further research into this area is required to facilitate improvements in anti-TNF therapy dosing schedules.

Safety Profile

Infliximab is considered safe overall in the setting of ASUC; however, contraindications to infliximab therapy include untreated latent tuberculosis infection, congestive cardiac failure (New York Heart Association Class III or IV), demyelinating disease and active infection(35). The significant immunosuppression caused by infliximab necessitates a number of screening tests before initiation of therapy, including tuberculosis and hepatitis screening. Infliximab carries risks of reactivation of latent tuberculosis, opportunistic upper respiratory tract and urinary tract infections, as well as cellulitis and sepsis(63, 64, 83, 84). Mortality following infliximab use is comparable to mortality risk associated with ciclosporin and randomised controlled trials report rates to be between 0-2%(10, 54, 55, 63, 64, 71).

COMPARING INFLIXIMAB AND CICLOSPORIN

Current international guidelines recommend both ciclosporin and infliximab as rescue therapy(31). In the last five years, head-to-head research comparing infliximab and ciclosporin has been undertaken and suggest that they are equally effective.

An Italian randomised trial of 21 patients with steroid-refractory ASUC demonstrated no statistically significant difference in 1-month outcomes between patients treated with infliximab (infusions at weeks 0,2,6) and those given oral ciclosporin (5mg/kg, adjusted on plasma levels)(85). Remission rates (infliximab 57%; ciclosporin 43%) and colectomy rates (43% in both groups) were very similar. Infliximab was associated with infective complications in two patients (systemic cytomegalovirus infection and one fatal case of *Pneumocystis jiroveci* pneumonitis) whereas patients given ciclosporin avoided any adverse effects.

In the seminal randomised controlled trial CySIF (Cyclosporin With Infliximab in Steroid-refractory Severe Attacks of Ulcerative Colitis), 116 patients were enrolled into either the ciclosporin group (2mg/kg daily IV ciclosporin for 1 week followed by 4mg/kg daily oral ciclosporin until day 98) or infliximab group (5mg/kg infusions at weeks 0,2,6)(10). The two groups demonstrated no differences in immediate outcomes (day 7) or short-term outcomes (day 98). Rates of clinical response at day 7 were comparable – 86% (50/58) of patients treated with ciclosporin demonstrated improvement in Lichtiger score, compared to 84% (48/57) of the infliximab group (p=0.76). At 3-month follow-up, treatment failure was observed in 35/58 patients (60%) receiving ciclosporin compared to 31/57 patients (54%) receiving infliximab. Similar rates of mucosal healing at 3-month endoscopic assessment were achieved in the two treatment streams – 47% (26/55) of ciclosporin-treated patients and 45% (25/55) of infliximab-treated patients (p=0.85). Colectomy rates did not differ either – colectomy was performed in 17% (10/58) of the ciclosporin group and 21% (12/57) of the infliximab group. Safety profiles were also similar (adverse events – ciclosporin 16%; infliximab 25%).

Preliminary results from the recently completed CONSTRUCT study (Comparison Of INfliximab And Ciclosporin In STeroid Resistant Ulcerative Colitis Trial) demonstrated no significant differences between infliximab & ciclosporin in steroid-refractory ASUC(55). CONSTRUCT was a UK-based, multicentre randomised controlled trial with 3.5 year follow-up, involving 270 participants – evenly randomised into infliximab and ciclosporin treatment groups. Quality of life questionnaires were completed by participants on enrolment, at 3 and 6 months and then at 6-monthly intervals. No significant difference in quality-adjusted survival was found between infliximab and ciclosporin groups (infliximab: mean 614.6 days, standard deviation 229.8 days; ciclosporin: mean 626.0 days, standard deviation 226.8 days). Investigators also reported no significant differences in rates of colectomy (infliximab: 41% colectomy, ciclosporin: 48% colectomy), mortality or adverse effects.

A number of retrospective analyses have similarly found no differences in rates of clinical remission and short-term colectomy between patients treated with either agent(86, 87). Nevertheless, some studies have advocated for the use of infliximab over ciclosporin. In their open-label study, Croft *et al.* evaluated 83 cases of steroid-refractory ASUC(54). Primary outcomes were defined as colectomy-free survival at different time points – on discharge from hospital, and 3 and 12 months following admission. Twenty-four of forty-three patients (56%) avoided colectomy at discharge after receiving≥72 hours c iclosporin 2-4mg/kg; whereas 32/38 (84%) patients were discharged without colectomy after receiving a single infliximab 5mg/kg infusion (p = 0.006). Infliximab remained more efficacious at maintaining colectomy-free survival at 3 months (28/37 – 76% and 23/43 – 53%, p=0.04) and 12 months (24/37 – 65% and 18/43 – 42%, p=0.04). Two serious adverse events were reported – both in the ciclosporin group. The authors concluded that infliximab produces a lower rate of colectomy and adverse effects in the short and medium-term. However, it is important to note that patients who were on immunosuppressant therapy at the time of salvage therapy initiation had lower colectomy rates, with the authors acknowledging that further investigation into the effect of prior immunosuppression is required(88). Results from a Dutch respective review, presented as an abstract at ECCO 2015, showed that rates of colectomy-free survival in a single IBD centre were significantly higher following infliximab use compared to ciclosporin, at 1 month [98% (136/139) and 74% (32/43), p<0.0005], 6 months [84% (117/139) and 56% (24/43), p<0.0005], 12 months [80% (108/135) and 49% (21/43), p<0.0005] and 36 months [67% (67/100) and 45%

(19/42), p=0.015](89). These findings were amongst patients with moderate to severe UC, they suggest that infliximab may be associated with better long-term treatment response.

Existing literature supporting efficacy of ciclosporin over infliximab has been largely derived from retrospective studies. A cohort study of 49 patients found that rates of colectomy-free survival at 2 weeks, 3 months and 12 months were higher following intravenous ciclosporin, compared to infliximab(90). However, patients included this study were only given a single infliximab infusion in place of three doses, as is now commonly used for standard induction therapy.

When choosing the optimal rescue therapy for a patient, clinicians must also consider factors beyond clinical efficacy and safety profile. Lowenberg *et al.* (2014) established that when comparing ciclosporin with infliximab, use of the anti-TNF agent is associated with a shorter length of hospital stay – median length of stay was 4.0 days (IQR 4.0-5.75) in the infliximab group and 11.0 (IQR 7.75-13.25) in the ciclosporin group (p<0.01). However, total costs of infliximab administration and treatment at 3 months post-initiation of salvage therapy were significantly higher than costs associated with ciclosporin use(91). In comparison to this, recent findings from the multicentre CONSTRUCT study demonstrated no significant difference in length of stay between the two treatments and while infliximab was found to be more expensive than ciclosporin, other associated costs were similar. Patients enrolled in the CONSTRUCT trial reported greater treatment satisfaction with infliximab, with the treating teams also preferring infliximab to ciclosporin. Finalised data may provide added insights into this ongoing debate(55).

Differences in drug half-life must also be taken into consideration. Ciclosporin has a relatively short half-life of a few hours, whereas infliximab can persist in the blood for weeks. While the head-to-head effects of these agents on post-operative recovery are still being researched, if emergent colectomy is required following initiation of salvage therapy, any potential risks associated with immunosuppression, such as post-operative sepsis, is likely to be more pronounced with infliximab treatment.

The CySIF and Croft trials prospectively compared infliximab and ciclosporin but have yielded conflicting results. From the outset, Croft *et al.* aimed to illustrate salvage therapy use in a real-life clinical cohort typically encountered in clinical practice. In contrast, the CySIF study was a multicentre randomised controlled trial. When comparing these two studies – both have reasonably large sample sizes (CySIF: n=116; Croft: n=83); however, due to uncertainty about the relative efficacy of the two agents, power calculations were not performed in the Croft study. Patient inclusion criteria in CySIF were based on the Lichtiger CAI score (>10), whilst the Croft trial enrolled patients who satisfied the stricter Truelove and Witts criteria for ASUC. Within the literature, European IBD centres adopt more inclusive criteria for hospitalisation for ASUC, when compared to centres in other regions. Relevant raw clinical data is required to properly compare baseline disease severity in these two studies, in order to interpret their findings with respect to each other and existing literature. Both trials were open-label and in addition, interventions were not randomised in the Croft cohort. Perhaps most importantly, treatment failure was defined according to composite criteria in the CySIF trial – based on Lichtiger CAI, Mayo score, colectomy and death. Colectomy at discharge, 3 and 12 months constituted treatment failure in the Croft study – providing a significantly narrower scope for failure.

In summary, while multiple earlier studies favoured either infliximab use in ASUC over ciclosporin or vice-versa, emerging prospective data have demonstrated no difference in efficacy between the two salvage therapy agents. More recent studies have featured larger sample sizes and utilised an infliximab induction dosing at weeks 0,2,6, which yields comparable clinical outcomes to those achieved with intravenous ciclosporin. However, it remains to be proven as to whether a more intensive infliximab induction schedule will make any difference to outcome when compared to ciclosporin.

PREDICTORS OF RESPONSE TO SALVAGE THERAPY:

Despite significant advances in medical therapy for ASUC, surgery remains a safe and viable option when medical alternatives have been exhausted. The decision to forego or abandon salvage therapy should be made as soon as an inadequate response to treatment has been identified, as delaying surgery can often worsen outcomes(92-94). Timely cessation of medical therapy relies on recognition of patients likely to require colectomy and close monitoring for markers of treatment failure. Application of the Ho index for use in predicting response to ciclosporin has been proposed; however, novel prognostic tools have yet to be devised(95). Currently, there is no established predictive index for response to infliximab. A number of methods to predict non-response to salvage therapy have been proposed and are explored below and outlined in *Table 4*.

AGE

Multivariate analysis of the CySIF trial identified age greater than 40 years as an independent predictor of treatment failure following salvage therapy (hazard ratio: 2.7; 95% CI: 1.2-6.1; p=0.018)(10).

PREVIOUS THIOPURINE EXPERIENCE

Ongoing active disease despite treatment with an immunomodulator is predictive of non-response to salvage therapy with ciclosporin. In a retrospective single centre study, non-responsiveness to thiopurines was found to be predictive for non-responsiveness to ciclosporin and colectomy (96). A total of 19 patients with ASUC underwent colectomy following ciclosporin salvage therapy during the study, with 68% (13/19) having previously failed to respond to at least 3 months of azathioprine or mercaptopurine; in contrast, a significantly lower colectomy rate was reported amongst patients who were thiopurine-naïve – 31% (6/19) (p=0.006). Prospective evaluation is warranted.

CLINICAL PARAMETERS

Several clinical parameters have been shown to be predictive for salvage therapy failure. A retrospective review of 135 ASUC patients reported clinical outcomes during hospital admission, following treatment with intravenous ciclosporin(97). Sixty-seven percent (90/135) of patients responded to ciclosporin; however, 33% (45/135) underwent colectomy. Clinical factors that were predictive of non-response to ciclosporin included body temperature >37.5^{O}C (hazard ratio: 1.94; 95% CI: 1.51-2.49) and heart rate >90bpm (hazard ratio: 1.86; 95% CI: 1.45-2.38).

LABORATORY VARIABLES

High levels of CRP on admission and at the time of infliximab therapy initiation have been associated with colectomy(68, 69, 98). A Danish retrospective study reviewed the records of 56 patients with acute steroid-refractory UC, who received infliximab as rescue therapy(69). Patients were followed up for a median of 18 months. Patients who progressed to colectomy had significantly higher levels of CRP on admission (p=0.0036) and at infliximab initiation (p=0.012), when compared to non-surgical patients. At first infusion, a CRP>29mg/L was predictive of colectomy, whereas CRP<29mg/L had a significantly reduced risk of colectomy (p=0.035).

The recent Monterubbianesi study supported the association between high baseline CRP and progression to early colectomy, following infliximab salvage therapy (RR 2.15; 95% CI:

1.05-4.36; p=0.003)(98). Kohn *et al.* followed 86 patients with acute ulcerative colitis, non-responsive to steroids, who received infliximab, reporting similar findings. CRP levels on day 3 and 7 following the first infliximab infusion were predictive of colectomy within 2 months (p=0.006 and p=0.001, respectively)(68).

In their retrospective review of 50 ASUC patients treated with infliximab, Gibson et al. reported found that serum albumin >22g/L at infliximab initiation was associated with a reduced colectomy rate (RR: 0.84, 95% CI: 0.75-0.95, p=0.003)(74). On univariate analysis, investigators found that a CRP:albumin ratio≤1.7 approached significance (p=0.06) and was also predictive of colectomy-free survival.

Levels of CRP may also have a role in predicting responsiveness to ciclosporin rescue therapy. In addition to identifying clinical predictors of ciclosporin failure, Cacheux *et al.* found that CRP>45mg/L, at the time of ciclosporin initiation, were predictive for colectomy within 6 months (hazard ratio: 1.70; 95% CI: 1.34-2.16)(97). Prospective evaluation of elevation in CRP as a predictor of non-response to salvage therapy is needed.

A retrospective trial of 50 hospitalised patients with ASUC, evaluated clinical, laboratory and endoscopic variables associated with colectomy following infliximab induction therapy(74). Predictors of colectomy on univariate analysis included serum albumin >22g/L at time of infliximab induction (p<0.001), while CRP:albumin ratio >1.7 trended toward statistical significance (p=0.06) on log rank test.

Raised faecal calprotectin (FC) levels have also demonstrated predictive value when assessing non-response to infliximab. This was investigated in a prospective observational study(40). Analysis of 90 patients with ASUC was performed with outcomes defined as colectomy, corticosteroid response and infliximab response. Elevated calprotectin levels on admission were seen in cases that exhibited steroid and infliximab non-response as well as those that eventually progressed to colectomy within 1–8 days following infliximab initiation. Of 21 patients, who received infliximab, 11 (52%) did not respond and underwent emergency colectomy. Infliximab non-responders had higher levels of FC than infliximab responders (1795.0 and 920.5 ug/g; p=0.06); however, this result was not statistically significant. Prospective evaluation of FC monitoring in ASUC is awaited.

ENDOSCOPIC SEVERITY

There is conflicting evidence regarding the relevance of endoscopic severity as a means to evaluate risk of salvage therapy failure. In their retrospective study, Cacheux *et al.* identified the presence of at least one severe endoscopic lesion at the time of ciclosporin initiation as an independent predictor of colectomy following intravenous ciclosporin salvage therapy (hazard ratio: 2.38; 95% CI: 1.80-3.14); however, Jarnerot *et al.* concluded that endoscopic severity did not predict for response to infliximab(64, 97). More recently, a randomised prospective study of 113 infliximab-treated patients with steroid-refractory UC, reported that the presence of severe endoscopic lesions at baseline, such as deep ulcerations or spontaneous bleeding on colonoscopy, was independently associated with colectomy following infliximab salvage therapy. On multivariate analysis, severe endoscopic lesions were associated with an increased risk of both early colectomy (RR=5.13, 95% CI: 1.55-16.96; p=0.007) and long-term risk of colectomy in the context of early colectomy avoidance (RR=7.0; 95% CI 1.09-44.7; p=0.03)(98).

There is suggestion that 3-month endoscopic outcomes are predictive of longer-term progression to colectomy. Three-year follow-up of the Jarnerot trial found that no patients (0/8) in endoscopic remission at 3 months had progressed to colectomy, whereas 50% (7/14) of those who were not in endoscopic remission had required surgery for a new attack of ASUC or steroid-dependent disease (p=0.02) (6). However, the lack of standardization of maintenance therapy in this trial, may have influenced colectomy rates(65).

THERAPEUTIC DRUG MONITORING

Therapeutic drug monitoring may play an important role in predicting response to infliximab rescue therapy.

In a prospective cohort study of 115 UC patients given infliximab induction and maintenance therapy, a detectable trough serum infliximab concentration predicted for clinical remission (OR 12.5, 95% CI: 4.6-33.9, p<0.001) and endoscopic improvement (OR 7.3, 95% CI 2.9-18.4; p<0.001)(99). Conversely, undetectable trough infliximab levels were associated with higher rates of colectomy (OR 9.3; 95% CI 2.9-29.9; p<0.001). The presence of antibodies against infliximab did not impact on patient outcomes. Similar data was reported in a multicentre prospective study by Brandse *et al.*, currently available only as an abstract. In this study, serum infliximab ≤7ug/mL at day 42, following week 0,2,6 infliximab, was predictive of endoscopic non-response (OR 36; 95% CI: 1.9-719; p=0.03) (100). Furthermore, a recent prospective cohort study found that faecal infliximab concentrations were significantly higher in patients who experienced primary non-response to infliximab induction therapy, compared to patients who experienced clinical response at 2 weeks(101). These findings support the theory that mucosal changes in severe UC lead to faecal loss of infliximab, which may dampen clinical efficacy. Evidence suggests that ASUC engenders accelerated infliximab clearance from the body – with accelerated clearance linked to hypoalbuminaemia, which has been associated with infliximab treatment failure(102).

A retrospective analysis of the ACT1/2 studies has corroborated these prospective results(103). Higher median infliximab concentrations, measured at weeks 8, 30 and 54 following three-dose induction, were associated with higher rates of clinical response, remission and mucosal healing. Multivariate regression analysis correlated low serum infliximab with reduced efficacy, regardless of antibody titre. Although these results have not been replicated in an ASUC setting, they represent a potential area of further research, with the aim of improving the use of biological therapies.

GENETIC VARIABILITY

Genetic predictors of response in anti-TNF therapy have been identified within the paediatric IBD population. Six susceptibility loci were common amongst paediatric patients who exhibited primary non-response to infliximab ($p<0.05$) – including the pANCA locus(104). The presence of 2 or more loci was associated with a 15-fold relative risk of non-response. pANCA seropositivity has also been shown to be associated with early infliximab non-response(105). Homozygous expression of the IL23R genotype was predictive of infliximab response at 16-month follow-up. Further investigation of genetic predictors of response to salvage therapy is required.

POST-SALVAGE THERAPY MONITORING

Patients who exhibit primary non-response to salvage therapy require a colectomy. If a clinical response is not achieved and symptoms fail to improve or deteriorate - represented by an increase in severity score (Truelove and Witts, Lichtiger, partial Mayo score), prompt liaison with a colorectal surgeon and stomal therapist is advisable to expedite surgery. Early involvement of a surgeon and stomal therapist will allow a patient and their family to make a considered decision about surgery. Sequential salvage therapy is an option only for a subgroup of patients with ASUC and its risks and benefits must be assessed for each patient individually, in consultation with a multidisciplinary team.

In patients who achieve clinical remission with salvage therapy, management may be continued in an outpatient setting. While patients may no longer require high acuity care, they continue to be at high risk of disease relapse. Following discharge from hospital, ASUC patients who have received salvage therapy must remain closely monitored with respect to clinical, biochemical and endoscopic disease activity. Current guidelines do not recommend any particular monitoring protocol, and current practice is largely at the discretion of the individual physician. A disease surveillance strategy that mirrors time points selected in published randomised controlled trials may allow comparison to published data on a case-by-case basis. Frequent re-evaluation of clinical and biochemical parameters, with emphasis on results at 1-month, 3-month and 12-month follow-up; as well as an endoscopic assessment at 3 months, may help guide decisions on maintenance therapy. If predictors of non-response to salvage therapy *(Supplementary Table 1)* are present, an intensive maintenance strategy, including combination therapy with azathioprine and infliximab, may be warranted. Conversely, in the absence of these predictors, thiopurine monotherapy in thiopurine-naïve patients may be a sufficient maintenance strategy. Methotrexate may be an alternative bridging strategy amongst patients who are thiopurine-intolerant(106).

SEQUENTIAL THERAPY

Second-line rescue therapy, following non-response to initial infliximab or ciclosporin remains controversial. While so-called sequential therapy for refractory flares appears to halt progression to colectomy, such intensive immunosuppression raises safety concerns(107-109).

A retrospective analysis compared outcomes in patients given infliximab therapy following ciclosporin failure, to those given ciclosporin after infliximab non-response(109). A total of 86 patients received sequential therapy, 65 (76%) were given ciclosporin then infliximab and 21 (24%) were given infliximab then ciclosporin. At 3 and 6-month follow-up, the colectomy-free survival rates of ciclosporin non-responders, who received infliximab were 60% and 55%, respectively. Colectomy-free survival in infliximab non-responders who received ciclosporin was 66% and 45% at 3 and 6 months, respectively. Nineteen patients (22%) suffered from adverse events following second-line salvage therapy, including one death (pulmonary embolus). Chaparro *et al.* (2012) likewise noted that the rate of colectomy-free survival was 30% following infliximab treatment after ciclosporin non-response, but the rate of adverse events was 23% (11/47 patients), once again including one death, due to nosocomial pneumonia(108).

Profound immunosuppression appears to be the limiting factor in sequential therapy and any therapeutic response must be carefully weighed against the risk of potentially fatal infectious complications.

MAINTENANCE THERAPY

Clinical and endoscopic steroid-free remission is the goal of therapy in UC. It is important to note that following salvage therapy there are no controlled trials to demonstrate the effectiveness of drug therapy as a strategy to maintain remission. Aminosalicylates have been established as first-line maintenance therapy with proven efficacy in reducing relapse risk; however, in cases of persistent symptom flares, a second-line maintenance drug is required. This role traditionally has been fulfilled by thiopurines; however, infliximab has now become a viable option for maintenance therapy (72, 110). In addition, patients who receive intravenous ciclosporin salvage therapy are typically transitioned onto oral ciclosporin maintenance. However, the risk of nephrotoxicity limits the use of ciclosporin as a long-term maintenance agent, hence its use is usually limited to a 3 month duration.

Scheduled Infliximab

Although scheduled maintenance therapy with infliximab has not been evaluated following infliximab salvage therapy, it has been demonstrated to be an effective strategy in patients with chronic active moderate to severe UC despite conventional therapy (5-aminosalicylates, corticosteroids and immunosuppressants)(72). Whilst the data on a maintenance strategy for ASUC cannot be directly extrapolated from these data, given the high rates of relapse following induction of remission with infliximab, a maintenance strategy with infliximab may be considered in some patients, particularly those who are thiopurine-experienced; however, such an approach remains to be proven.

A retrospective audit conducted across six centres in the UK found that of 38 steroid-refractory patients who received induction with infliximab, 28 (73.6%) exhibited a sustained response with 8-weekly infusions (5mg/kg) for a mean duration of 16.8 months (range: 4-59), with 21 (55.3%) maintaining remission. Secondary loss of response after a mean duration of 10 months was seen in 3 patients (7.9%), while 7/38 (18.4%) patients did not respond to infliximab. Seven cases progressed to colectomy (7/38 – 18.4%) – five non-responders and two who experienced secondary loss of response(110). While these results are encouraging, their relevance in the ASUC setting may be limited, as only 19/38 (50%) patients satisfied Truelove and Witts criteria for severe disease.

The UC SUCCESS outpatient trial conducted in patients with steroid-refractory UC demonstrated improved efficacy with concomitant use of infliximab and azathioprine compared to either drug in isolation(111). Steroid-free remission rates achieved by patients who had received combination therapy at 4-month follow-up were approximately 2-fold greater than either monotherapy [combination, 40% (31/78), infliximab, 22% (17/77) (p=0.017), AZA, 24% (18/76) (p=0.032)]. Combination therapy with these two agents may be considered once patients have moved beyond the acute setting. Prospective studies evaluating the efficacy of combination therapy in ASUC is required before any definitive conclusions can be made.

Methotrexate

The success of methotrexate in induction and maintenance of remission in Crohn's disease has sparked interest in its potential use in ulcerative colitis(112-115). A recent Cochrane review concluded that induction of remission with methotrexate is not supported by currently published literature, predominantly owing to insufficient data(116). Retrospective data evaluating methotrexate maintenance therapy has yielded conflicting results(117, 118). More prospective trials are required to further evaluate the utility of methotrexate in maintenance of remission. Results from the METEOR trial, currently available only as an abstract, have supported the use of methotrexate as a bridge to oral therapies in steroid-dependent UC(106). This approach awaits further evaluation.

Maintenance therapy for thiopurine-naïve patients should consist of a thiopurine, however methotrexate may be considered in those who are thiopurine-intolerant. If there is evidence of ongoing disease activity at 3-month follow-up after salvage therapy, maintenance infliximab should be considered. Other options at this juncture include novel biological therapies, including vedolizumab and anti-MAdCAM1(119, 120). Early escalation to an intensive maintenance strategy for thiopurine-experienced patients may be necessary and scheduled infliximab may be required to maintain remission in these patients.

SURGICAL MANAGEMENT

Patients who do not respond to medical therapy must be rapidly made ready for surgery. Operative management of ASUC should ideally occur in a semi-elective rather than emergency setting and a staged approach has been widely adopted. To underpin this point, a recent systematic review and meta-analysis demonstrated a significantly higher post-operative mortality in patients with UC, following emergent but not elective colectomy (5.3% and

0.7%)(121). Patients generally undergo a laparoscopic proctocolectomy and ileostomy, followed by an ileal pouch-anal anastomosis (IPAA). The close timing of medical salvage therapy and surgical intervention has raised safety concerns. The majority of data investigating the preoperative use of infliximab and ciclosporin has been retrospective in nature. When compared to matched controls, the number of complications was not significantly different at 1-month follow-up after pre-operative salvage therapy in patients with surgically managed ASUC(122, 123). The impact of perioperative salvage therapy on post-operative outcomes is yet to be fully explored.

COMPLICATIONS ASSOCIATED WITH ACUTE SEVERE ULCERATIVE COLITIS

The management of ASUC encompasses the appropriate diagnosis and treatment of common complications, encountered in clinical practice. Management of these complications is discussed in further detail below.

OPPORTUNISTIC INFECTIONS

Clostridium difficile

Infectious precipitants of a flare of colitis must be screened for and excluded in patients presenting with ASUC. Inflammatory bowel disease is associated with an increased risk of *C. difficile* infection (CDI), particularly amongst those with colonic disease – even in the absence of recent antibiotic exposure(124). CDI is formally defined as the presence of diarrhoea with the biochemical detection of *C. difficile* or *C. difficile* toxins, or colonoscopic evidence of pseudomembranous colitis(125). Twenty-five percent of IBD patients, who develop CDI, have no other risk factors predisposing them to the condition. The incidence of CDI has been found to be 2.9 times higher in IBD patients compared to non-IBD patients, and 4 times higher in patients with UC(126). Corticosteroid initiation in IBD has also been shown to triple the risk of developing CDI compared to any other immunosuppressant – including thiopurines and methotrexate (RR: 3.4; 95% CI: 1.9-6.1)(127). IBD admissions complicated by CDI(128) have been associated with a higher mortality rate (adjusted OR 4.7; 95% CI: 2.9-7.9) than non-CDI IBD admissions, with higher rates of bowel surgery and mortality seen in UC compared to their Crohn's disease counterparts.

In particular, CDI must be suspected in patients, who present with signs and symptoms, inconsistent with their regular exacerbations. Clinical suspicion necessitates early diagnosis and appropriate management. Diagnosis is generally made on the basis of stool analysis(129). Specific investigations include enzyme-linked polymerase chain reaction (PCR) analysis of stool samples or a glutamate dehydrogenase assay; either of these tests can be used in combination with enzyme-linked immunosorbent assays for *C. difficile* toxins(130). On meta-analysis, the glutamate dehydrogenase assay exhibited >90% sensitivity and ≥98% specificity when compared with stool culture. Endoscopic and histologic findings of CDI in IBD patients are either less obvious or absent compared with non-IBD patients and therefore cannot be relied upon in isolation for a diagnosis(124).

Given the morbidity and mortality associated with CDI in the setting of ASUC, first-line therapies should include metronidazole and vancomycin(131). Fidaxomicin may be an alternative to the latter strategy but has not been formally evaluated in the IBD setting. The initial use of vancomycin, in lieu of metronidazole, has been retrospectively shown to have reduced colectomy rates from 45% to 3% over a 2-year interval(132). CDI can be classified into severe and non-severe based on the presence of endoscopic evidence of pseudomembranous colitis, treatment in the ICU or 2 or more of the following: age >60 years, temperature >38.3^{O}C, hypoalbuminaemia, or white cell count >15,000 cells/mm^3(133). When compared to metronidazole, vancomycin use in non-severe CDI was associated with lower 30-day (0% compared to 31%; p=0.04) and results were suggestive of lower rates of 12-week (15% compared to 31%; p=0.45) readmission and colectomy during the index admission (15% compared to 24%; p=0.70), although the latter two associations did not reach statistical significance(134). Although faecal microbiota transplantation appears to have a role in recurrent CDI, it has not been fully evaluated in patients with ASUC(135). A concern is the increased risk of bacterial translocation, given the ulcerated and denuded mucosa, which may increase the risk of systemic toxicity.

Management of CDI should occur simultaneously with conventional therapy for ASUC; however, the use of immunomodulatory agents in the context of CDI remains controversial. A small case series in the non-IBD setting, demonstrated steroid efficacy in six patients with pseudomembranous colitis(136). Based on the latter small study, ECCO guidelines continue to support the use of corticosteroid therapy when treating CDI(137). A 12% rate of adverse outcome, indicated in a multicentre retrospective study amongst those who were treated with immunomodulators in addition to antibiotics, has suggested that immunomodulators should be withdrawn in the setting of *C. difficile* in IBD(131). Adverse outcomes were defined as death or colectomy within 3 months of admission, in-hospital megacolon, bowel perforation, haemodynamic shock or respiratory failure. Prospective data supporting these findings are required before immunomodulator cessation can be routinely recommended. Recent guidelines suggest that ongoing immunosuppression should be considered on a case-by-case basis and perhaps maintained in severe colitis, whilst warning against dose escalation in untreated CDI(138). Infliximab has not been shown to be associated with any increased incidence of serious bacterial infection, including CDI. However, the safety and efficacy of treatment with infliximab in comparison to ciclosporin in patients with ASUC, complicated by CDI requires further investigation.

Cytomegalovirus

In patients with UC, cytomegalovirus (CMV) infection (or reactivation) must be carefully distinguished from active CMV colitis – a term used to describe CMV infection leading to colonic inflammation. In most cases, uncomplicated CMV infection in patients with IBD remains subclinical and self-limiting and latent CMV reactivation, while detectable in the blood, does not influence disease activity during a flare(139, 140). A prospective study of 69 patients with moderate to severe UC demonstrated no significant differences in outcome between patients who were seropositive and those who were seronegative for CMV infection(140). Furthermore, a retrospective case-control study of CMV-infected patients, diagnosed on blood PCR, compared with CMV negative controls, revealed no difference in colectomy rate and admission length between the two groups(139).

In contrast to this, CMV infection that causes colonic inflammation, termed CMV colitis, has been associated with higher rates of emergency colectomy and poorer patient outcomes(141). The diagnosis of CMV colitis is generally made on the basis of tissue analysis of colonic biopsy specimens, taken during an acute flare of colitis. The mechanism by which CMV infection precipitates acute colitis is thought to be related to ischaemic, thrombotic and autoimmune changes(142-145).

Immunosuppressive therapies are a major risk factor for the development of CMV disease in IBD. In particular, prospective data has demonstrated that concomitant treatment with azathioprine and corticosteroids is associated with CMV infection(146). Diagnostic criteria for CMV infection in this study consisted of a positive result in one or more of the following tests:

IgM antibody, CMV PCR of colonic biopsy and inclusion bodies on haematoxylin & eosin stain of colonic biopsy specimen. Standard induction therapy (week 0,2,6) with salvage therapy agent, infliximab, does not appear to increase the risk of developing CMV in patients with IBD(147). Current ECCO guidelines recommend screening for CMV infection only in the context of acute steroid-resistant colitis(137). Over a third of patients with steroid-refractory colitis have biochemically active CMV; as such, exclusion of clinically significant infection is of high priority in this patient group. Sigmoidoscopy and colonic biopsy to detect CMV should be performed within 48 hours of admission for ASUC and tissue samples are analysed on the basis of histopathology (CMV inclusions denoted by an 'owl's eye appearance), immunohistochemistry and/or PCR results(137). Timely administration of antiviral therapy, with 2-3 weeks of ganciclovir, is the current standard of care in patients with confirmed infection(148). CMV infection should be excluded prior to escalation of immunomodulator therapy to minimise the risk of precipitating opportunistic CMV colitis(137). Careful consideration should also be given to the option of discontinuing immunomodulators until colonic inflammation subsides. In practice, whilst delaying immunosuppressant therapy may be appropriate in a subset of patients with ASUC, it may not be feasible in the setting of 3-5 days of steroid non-response. In these cases, rapid sequential or concurrent antiviral therapy may need to be administered alongside a salvage therapy agent. Prompt withdrawal of immunomodulator therapy is required in systemic CMV disease.

VENOUS THROMBOEMBOLISM

Venous thromboembolism (VTE) is a potentially fatal complication of IBD that is closely linked with active disease. The risk of VTE in IBD is three times higher than that seen in the general population and the likelihood of developing VTE is even higher during a flare (HR 8.4; 95% CI: 5.5-12.8; $p<0.0001$)(149). The mechanism by which IBD increases thrombotic risk is unclear. Low molecular weight heparin and fondaparinux have been shown to significantly reduce VTE risk in hospitalised patients(150). Despite the latter evidence, surveys indicate that up to 65% of gastroenterologists fail to administer VTE prophylaxis to patients admitted for ASUC(151-153). Thromboprophylaxis does not appear to precipitate excessive bleeding during flares of IBD, even in patients experiencing bloody diarrhoea, and is recommended in all patients with ASUC(154, 155). The VTE risk in IBD patients appears to be highest in ambulant outpatients following discharge from hospital (HR 15.8; 95% CI: 9.8-25.5, $p<0.0001$), suggesting that there may be a role for maintaining prophylaxis in the outpatient setting. However, there are no published data to support this recommendation. Prospective studies to evaluate the efficacy and safety of VTE prophylaxis in IBD are needed.

TOXIC MEGACOLON

Toxic megacolon (TM) is a life-threatening condition, which complicates approximately 5% of presentations with ASUC(156). It is classically defined according to the Jalan clinical criteria *(Table 5)* and describes segmental or entire colonic distension accompanied by a systemic inflammatory response(157-159). A high index of clinical suspicion is required – especially in the setting of severe, refractory or worsening symptoms as patients with toxic megacolon are often profoundly unwell and carry a heightened risk of poor outcomes. Complications of TM include colonic perforation, peritonitis, massive haemorrhage and, in rare cases, even death – seen in 0-2% of ulcerative colitis(158, 160).

Clinical signs cannot be relied upon for the diagnosis of TM as corticosteroid therapy is known to attenuate examination findings(161, 162). Daily abdominal plain films should be performed for all patients with ASUC, looking for gas distension of the transverse colon >6cm in diameter and the disappearance of normal haustral patterns(159, 163); Distension of the ascending colon and/or presence of colonic air fluid levels together with exclusion of a pneumoperitoneum(158). Although computed tomography (CT) imaging is the optimal imaging modality for patients with TM, it carries with it a risk of unnecessary radiation exposure and therefore should not be used as a serial imaging modality(164-167).

Management of TM involves close collaboration between physicians and surgeons. While some patients may respond to medical therapy with high-dose corticosteroids, broad-spectrum antibiotics and salvage therapies, although not an absolute indication for surgery, there should be a low threshold for surgical intervention (15, 157, 158, 168-170). Emergent colectomy is associated with a significantly higher mortality rate compared to elective colectomy (30% and 5%)(171). Medications that reduce colonic motility should be withdrawn - antidiarrhoeals, anticholinergics and narcotic drugs. Total parenteral nutrition in order to facilitate bowel rest may be considered as an adjunct to surgery; however, it has not been shown to exert any primary therapeutic effect(172). Although positional gas redistribution through rolling and adopting the knee-elbow position has had some success, as has endoscopic decompression, these techniques are not a substitute for definitive surgical management in all patients(173-176).

CONCLUSIONS & OPTIMAL MANAGEMENT STRATEGY

The availability of salvage therapies has changed dramatically the outlook for patients with ASUC who may previously have been destined to undergo colectomy. On the basis of the available evidence, we have proposed a strategy for the optimal management of steroid-refractory ASUC *(Figure 2)*. The general approach advocated by current guidelines and literature comprises intensive medical therapy and close monitoring, with early surgical intervention in cases of inadequate response.

Methods for assessing responsiveness to salvage therapy are not yet clearly defined. Management decisions must account for clinical severity, with temperature and heart rate elevation as poor prognostic markers. Endoscopic evaluation for mucosal healing is valuable in predicting responsiveness to rescue therapy. Indirect markers of luminal disease activity include CRP, platelets, white cell count and haemoglobin. Therapeutic drug monitoring for infliximab appears to be predictive of outcomes in ASUC; however, further studies are needed to confirm its utility. Risk stratification based on previous response to thiopurines has been shown to be useful in determining choice of both salvage and maintenance therapies.

Close monitoring following administration of salvage therapy is necessary. The ability to predict clinical outcomes from salvage therapy is currently limited and relies on clinical gestalt to draw together several clinical parameters in order to make an informed decision. There are substantive data demonstrating the efficacy of infliximab and ciclosporin as salvage therapy agents; however, the frequency of the dosing schedule, optimal dosing, duration of therapy and long-term outcomes of these therapies require further evaluation – especially with regards to an accelerated and/or intensive dosing regimens. Irrespective of the medical treatment options available, proctocolectomy may be the best available management for some patients and should not be deferred unnecessarily. Further investigation into predictors of response to salvage therapy is therefore required to expedite surgical treatment among those who are unlikely to respond and facilitate refinement of the current management strategy.

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TABLES & FIGURES

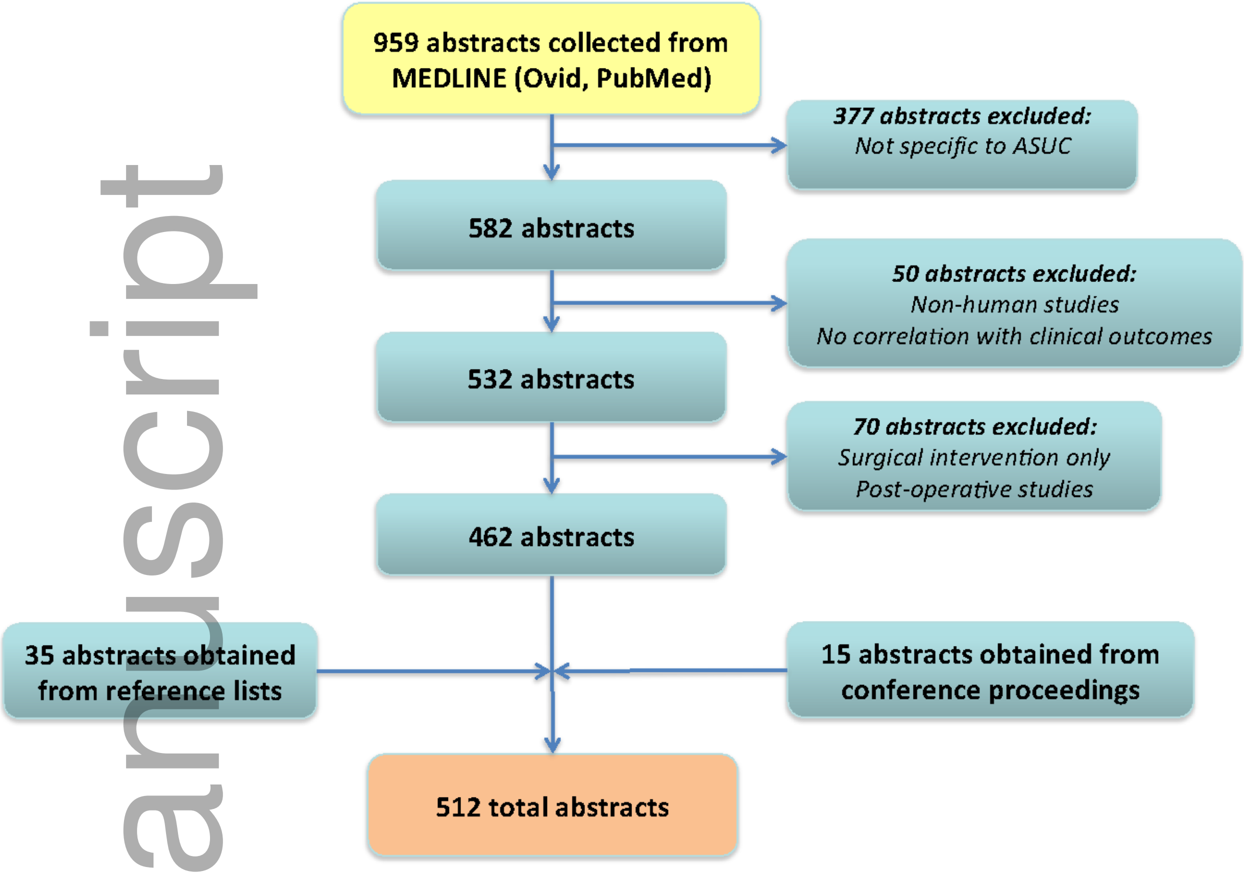

Figure 1: Literature search strategy

Modified Truelove and Witts Criteria for Acute Severe Ulcerative Colitis			
Criterion	**Mild**	**Moderate**	**Severe**
Stools per day	≤4	5 – 6	>6
	PLUS at least one of the following:		
Blood in stool	Small / intermittent	Moderately frequent	Frequent
Temperature	Normal	>37.5^{O}C	>37.5^{O}C
Pulse rate	Normal	>90bpm	>90bpm
Haemoglobin	>75% of normal	≤75% of normal	≤75% of normal
Erythrocyte sedimentation rate (ESR)	≤30mm/hr	>30mm/hr	>30mm/hr

Table 1: Truelove and Witts criteria for acute exacerbations of UC.

Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. British medical journal. 1955;2(4947):1041-8.

Travis Risk Score (i.e. Oxford Index)		
Day 3–5 Assessment		**Risk**
Daily stool frequency	> 8	85% positive predictive value for requiring colectomy
Daily stool frequency	> 2	85% positive predictive value for requiring colectomy
PLUS		
C-reactive protein (CRP)	> 45mg/L	

Table 2: The Travis risk score for estimating risk of steroid failure and requirement for colectomy.

Travis SP, Farrant JM, Ricketts C, Nolan DJ, Mortensen NM, Kettlewell MG, et al. Predicting outcome in severe ulcerative colitis. Gut. 1996;38(6):905-10.

Ho Index		
Day 3–5 Assessment		**Score**
Mean stool frequency	< 4	0
	4 ≤ 6	1
	6 ≤ 10	2
	> 9	4
Colonic dilatation	Present	4
Hypoalbuminaemia	< 30g/L	1
Total score 0–1: Low risk of steroid failure (11%) *Total score 2–3: Intermediate risk of steroid failure (45%)* *Total score ≥4: High risk of steroid failure (85%)*		

Table 3: The Ho index for predicting risk of steroid failure in ASUC.

Ho GT, Mowat C, Goddard CJ, Fennell JM, Shah NB, Prescott RJ, 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. Alimentary pharmacology & therapeutics. 2004;19(10):1079-87.

Predictors of Salvage Therapy Non-Response						
Variables	**Ciclosporin**	**Hazard ratio**	**p-value**	**Infliximab (IFX)**	**Hazard ratio**	**p-value**
Demographics	Age > 40 years(10)	2.7	0.018	Age > 40 years(10)	2.7	0.018
	Previous non-response to thiopurines(96)	–	<0.001	–		
Clinical	Temperature > 37.5^{O}C(97)	1.94	<0.001			
	Heart rate > 90bpm(97)	1.86	<0.001			
Biochemical	CRP > 45mg/L at ciclosporin initiation(97)	1.69	0.002	CRP		
				≥30mg/L on admission(98)	2.15	0.003
				> 29mg/L at IFX initiation(69)	–	0.035
				Higher^ on day 3 post-IFX(68)	–	0.006
				Higher^ on day 7 post-IFX(68)	–	0.001
	–			Albumin		
				CRP:albumin ratio > 1.7(74)	–	0.06#
				Albumin < 34g/L at day 3 of intravenous steroids	12.0	0.02
				Albumin > 22g/L at time of IFX induction(74)	0.84	0.003
				High^ FC on admission(40)	–	0.06*

Therapeutic drug monitoring	–			Serum IFX		
				Undetectable trough IFX level (threshold not defined)(99)	9.3	<0.001
				Serum IFX≤7ug/mL at week 6(100)	36 (endoscopic non-response)	0.03
				Higher^ faecal IFX level at time of IFX induction(101)	–	0.0047 (week 2 clinical response)
Endoscopic	Severe endoscopic lesion(s) at time of ciclosporin initiation(97)	2.38	<0.01	Severe endoscopic lesion(s)		
				At baseline(98)	5.13 (colectomy at 3 months)	0.007
					7.0 (colectomy at 2 years)	0.03
				At 3 months(6)	–	0.02 (colectomy at 3 years)

Table 4: Predictors of non-response to salvage therapy agents – including ciclosporin and infliximab.

*Figure legend: infliximab (IFX), C-reactive protein (CRP), faecal calprotectin (FC), * not statistically significant, but suggesting a trend toward significance; # on univariate analysis only (therefore not an independent predictor)*

*NB: A p-value included without a hazard ratio denotes whether there was a significant difference between responders and non-responders (i.e. those who experienced relapse or came to colectomy)^*

Jalan Clinical Criteria for Toxic Megacolon	
	At least three of the following criteria:
Evidence of toxicity	• **Temperature > 38.6^{O}C** • **Heart rate > 120 beats per minute** • **White cell count > 10.5 x 10^9/L** • **Hb < 60g/dL**
	PLUS at least one of the following:

	• **Dehydration** • **Altered mental state** • **Electrolyte disturbance** • **Hypotension**
PLUS	
Evidence of colonic dilatation	• **Visible abdominal distension** • **± Peritonism**
PLUS	
Physician's impression of UC flare severity at time that complication occurred	

Table 5: Clinical criteria for toxic megacolon.

Study (ref)	Study design (e.g. RCT)	Disease severity	Sample size	Dose (mg/kg)	Ciclosporin response rate (%)			Colectomy rate (%)			Mortality rate (%)	Follow-up duration	Comments
					Immediate	Short-term	Long-term	Immediate	Short-term	Long-term			
Lichtiger *et al.* 1994 (50)*	Randomised Placebo-controlled	Severe	11 Total 20	4	9/11 (82)	–	–	2/11 (2)	–	–	0/11 (0)	Immediate: 2 weeks	Treatment response defined as reduction in Lichtiger score to <10 on two consecutive days Following the trial period, 5 patients from the placebo group subsequently responded to open-label ciclosporin
Travis *et al.* 1996 (9)	Controlled Cohort study	Severe	14 Total 51 (ASUC episod	4	7/14 (50)	4/14 (29)	–	7/14 (50)	10/14 (71)	–	1 (unclear as to whether from ciclosp	Immediate: time of discharge	

			es)								orin or steroid group)	Short-term: 3 months	
Cohen *et al.* 1999 (177)	Retrospective	Severe	42	4	–	36/42 (86)	26/36 (72)	–	6/36 (14)	16/36 (38)	0/42 (0)	Short-term: NS Long-term: 2 years (mean)	
D'Haens *et al.* 2001 (52)*	Randomised Placebo-controlled	Severe	14 Total 30	4	9/14 (64)	–	7/14 (50)	0/14 (0) (2 colectomies shortly after day 8)	–	5/14 (36)	0/14 (0)	Immediate: 8 days Long-term: 1 year	One patient was withdrawn from the trial following detection of *C. difficile* toxin on stool testing Demonstrated efficacy of ciclosporin monotherapy
Van Assche *et al.* 2003 (62)	Randomised	Severe	73 (2mg/kg: 35; 4mg/kg: 38)	2, 4	2mg/kg: 30/35 (86) 4mg/kg: 32/38 (84)	–	–	2mg/kg: 3/35 (9) 4mg/kg: 5/38 (13)	–	–	0/73 (0)	Immediate: 8 day response; 2 week colectomy rate	Dose comparison (2mg/kg compared to 4mg/kg) Severity

													classified according to Lichtiger score ≥10
Rayner *et al.* 2003 (178)	Retrospective	Severe	31	2	24/31 (77)	14/31 (45)	–	7/31 (23)	17/31 (55)	–	0/31 (0)	Immediate: 1 week Short-term: 3 months	4 patients presented with toxic megacolon but were not excluded from the study
Benazzato *et al.* 2004 (33)	Uncontrolled Cohort study	Severe	25 Total 67	2-4	19/25 (76)	–	NS	6/25 (24)	–	NS	0/25 (0)	Immediate: 5 days	Severity classified according to Lichtiger score >12 Response defined as ≥6 point reduction in Lichtiger score
Arts *et al.* 2004 (179)	Retrospective	Severe	Overall 86 2mg/kg: 15 4mg/kg: 71	2, 4	–	72/86 (84)	39/86 (45)	–	14/86 (16)	32/86 (37)	3/86 (3)	Short-term: 1 week post-discharge Long-term: 773 days [~2 years]	

Campbell *et al.* 2005 (56)	Retrospective	Severe	Overall 76 Oral (5mg/kg): 22 IV (4mg/kg): 54	4, 5	Overall 56/76 (74) IV: 36/54 (67) Oral: 20/22 (90)	–	(58)	20/76 (26)	–	(42)	1/76 (1)	Immediate: NS Long-term: 7 years	A proportion of patients received oral ciclosporin due to low cholesterol or magnesium. Death deemed to be unrelated to ciclosporin use
Moskovitz *et al.* 2006 (59)	Retrospective	Severe	142	2, 4	–	118/142 (83)	77/142 (54)	–	24/142 (17)	65/142 (46)	NS	NS	Dose comparison
Actis *et al.* 2007 (5)	Retrospective	Severe	61 IV: 38 Oral: 23	2 (IV), 5 (oral)	39/61 (64)	–	1 year: (44) 3 years: NS 7 years: (0)	22/61 (36)	–	1 year: (39) 3 years: (62) 7 years: (65)	1/61 (2)	Immediate: 1 week Long-term: 1, 3, 7 years	Severity classified according to Rachmilewitz clinical activity score Treatment failure defined as relapse with or without

													colectomy Death due to pulmonary embolism proven on autopsy, deemed unrelated to ciclosporin
Cacheux *et al.* 2008(97)	Retrospective	Severe	135	2 (81%), 4 (19%)	90/135 (67)	(55)	(44)	45/135 (33)	(45)	(56)	1/135 (1)	Immediate: time of discharge Short-term: 6 months Long-term: 3 years	
Bossa *et al.* 2009 (abstract) (85)	Randomised	Severe	7 Total 21	5 (oral)	–	3/7 (43)	NS	–	NS	3/7 (43)	0.7 (0)	Short-term: 1 month Long-term: NS	Results demonstrated that infliximab trended toward higher clinical remission rates
Holme *et al.* 2009	Uncontrolled Cohort	Severe	18	5	15/18 (83)	–	8/18 (44)	3/18 (17)	–	10/18 (56)	1/18 (5)	Immediate: time of	

(180)	study											discharge Long-term: 5 years	
Walch *et al.* 2010(96)	Retrospective	Severe	64	2-5	NS	NS	1.5 years: 33/64 (52) 5.5 years: 26/64 (41)	NS	NS	1.5 years: 15/64 (23) 5.5 years: 16/64 (25)	2/64 (3)	Long-term: 1.5 years, 5.5 years	Deaths due to pulmonary embolism post-colectomy; and suicide
Dean *et al.* 2012(181)	Retrospective	Severe	19 Total 38	2	–	7/19 (37)	6/19 (32)	–	12/19 (63)	13/19 (68)	0/19 (0)	Short-term: 3 months Long-term: 1 year	
Moccario *et al.* 2012(86)	Retrospective	Severe	35 Total 65	2	–	25/35 (71)	1 year: (52) 2 years: (46) 3 years: (43)	–	10/35 (29)	1 year: (48) 2 years: (54) 3 years: (57)	0/35 (0)	Short-term: 3 months Long-term: 1 year, 2 years, 3 years	Results suggested similar efficacy at 3 months but greater efficacy with infliximab at 12 months
Laharie *et al.* 2012	Randomised Head-to-	Severe	58 Total	2	50/58 (86)	23/58 (40)	NS	2/58 (3)	10/58 (17)	(39)	3/58 (5)	Immediate: 1 week	Severity classified according

(published in full) / Laharie *et al.* 2015 (abstract) (10)*	head (IFX versus ciclosporin)		115									Short-term: 3 months Long-term: 5 years	to Lichtiger clinical activity index Composite criteria for 'treatment failure'
Croft *et al.* 2013 (54)*	Randomised Head-to-head (IFX versus ciclosporin)	Severe	43 Total 83	2-4	24/43 (56)	23/43 (53)	18/43 (42)	–	20/43 (47)	25/43 (58)	0/43 (0)	Immediate: time of discharge Short-term: 3 months Long-term: 1 year	Patient-led decision to receive specific salvage agent
Lynch *et al.* 2013 (3)	Multicentre Retrospective	Severe	2008: 97 2010: 133	2	2008: 45/97 (46) 2010: 77/133 (58)	–	–	2008: 42/97 (43) 2010: 47/133 (35)	–	–	2008: 3/54 (6) 2010: 0/79 (0)	Immediate: time of discharge	
Molnar *et al.* 2014(60)	Retrospective	Severe	73	4-5	NS	53/73 (73)	39/73 (53)	NS	20/73 (27)	34/73 (47)	0/73 (0)	Short-term: 3 months Long-term: 4 years	Demonstrated that longer duration of ciclosporin therapy was associated with longer

													colectomy-free disease course
Naves *et al.* 2014(87)	Retrospective	Moderate to severe 50% severe	20 Total 50	2-4	–	13/20 (65)	14/20 (70)	–	2/20 (10)	6/20 (30)	0/20 (0)	Short-term: during hospital admission or steroid weaning period Long-term: following steroid-free clinical remission (median 3.5 ears)	Initial efficacy defined as steroid-free clinical remission Early non-responders received sequential therapy with infliximab
Seagrove *et al.* 2014 (abstract) (55)*	Uncontrolled Randomised Head-to-head (IFX versus ciclosporin)	Severe	135	2	NS	NS	NS	NS	NS	65/135 (48)	0/135 (0)	3.5 years	Full-text not yet available
Duijvis *et al.* 2015 (abstract) (89)	Retrospective	Moderate to severe	43 Total 182	NS	–	1 month: 32/43 (74)	1 year: 21/43 (49)	–	1 month: 11/43 (26)	1 year: 22/43 (51)	NS	Short-term: 1 month, 6 months	Infliximab was associated with lower colectom

						6 months: 24/43 (56)	3 years: 19/42 (45)		6 months: 19/43 (44)	3 years: 23/42 (55)		Long-term: 1 year, 3 years	y rates than ciclosporin

Table 6: Summary of published studies evaluating clinical response, colectomy and mortality in ciclosporin-treated ASUC

*, randomised controlled trial

n, number of patients who received ciclosporin

NS, not stated

IFX, infliximab

All response, colectomy and mortality rates have been expressed as a proportion of the patients who initially received salvage therapy

Definitions of immediate, short-term and long-term have been defined based on duration of follow-up within each individual study

Infliximab

Study	**Study design**	**Disease severity**	***n***	**Dose (mg/kg)**	**Number of infusions (%)**	**Infliximab response rate (%)**			**Colectomy rate (%)**			**Mortality rate (%)**	**Follow-up duration**	**Comments**
						Immediate	**Short-term**	**Long-term**	**Immediate**	**Short-term**	**Long-term**			
Sands *et al.* 2001 (63)*	Randomised Placebo-controlled	Severe	8 Total 11	5, 10, 20	1	Overall: 4/8 (50) 5mg/kg: 2/3 (66) 10mg/kg: 1/3 (33) 20mg/kg: 1/2 (5)	4/8 (50)	–	1/8 (13)	4/8 (50)	–	0/8 (0)	Immediate: 2 weeks Short-term: 3 months	Median IV steroid therapy duration 10 days (Range 5-17)
Ochsenkuhn *et al.* 2004 (71)*	Randomised Placebo-controlled	Severe	6 Total 13	5	3	5/6 (83)	5/6 (83)	–	0/6 (0)	0/6 (0)	–	0/6 (0)	Immediate: 3 weeks	Non-steroid refractory

													Short-term: 3 months	population
Jarnerot *et al.* 2005 (182) / Gustavsson *et al.* 2010 (6)*	Randomised Placebo-controlled	Moderately severe: 9/24 (38) Severe: 15/24 (63)	24 Total 45	4-5	1	–	17/24 (71)	12/24 (50)	–	7/24 (29)	12/24 (50)	0/24 (0)	Short-term: 3 months Long-term: 3 years	Seo index severity classification Follow-up study by Gustavsson
Regueiro *et al.* 2006 (183)	Retrospective	Severe	12	5	3	–	3/12 (25)	–	–	9/12 (75)	–	0/12 (0)	Short-term: 6 months	Patients who required colectomy before completion of induction
Kohn *et al.* 2007 (68)	Non-randomised Uncontrolled Cohort study	Severe	83	5	1: 26/83 (31) 2: 14/83 (17) 3:	–	Overall 70/83 (84)	Overall: 40/80 (50)	–	Overall: 12/83 (15) 1 infusion:	Overall: 25/83 (30)	1/83 (1)	Short-term: 2 months Long-term: 2	Number of infusions dependent on physician

					43/83 (52)					9/26 (35) ≥2 infusions: 3/57 (5)			years	preference
Lees *et al.* 2007 (38)	Retrospective	Severe	39	5	1, 2, 3	26/39 (67)	26/39 (67)	–	13/39 (33)	13/39 (33)	–	0/39 (0)	Immediate: time of discharge Short-term: 3 months	
Bressler *et al.* 2008 (70)	Retrospective	Severe	21	5	3	16/21 (76)	–	–	5/21 (24)	8/21 (38)	–	0/21 (0)	Immediate: time of discharge Short-term: 3 months	
Yamamoto-Furosho *et al.* 2008 (184)	Uncontrolled	Severe	10	5	1	–	2/10 (20)	–	–	8/10 (80)	–	0/10 (0)	Short-term: 6 weeks	All patients were refractory to at least 7 days

														of IV hydrocortisone 300mg/day
Bossa *et al.* 2009 (abstract) (85)	Randmoised	Severe	14 Total 21	5	3	–	8/14 (57)	NS	–	NS	6/14 (43)	1/14 (7)	Short-term: 1 month Long-term: NS	Results demonstrated that infliximab trended toward higher clinical remission rates
Ho *et al.* 2009 (40)	Uncontrolled Cohort study	Severe	21	5	1	10/21 (48)	–	–	11/21 (52)	–	–	1/21 (5)	Immediate: time of discharge	Demonstrated that higher faecal calprotectin was predictive of response to IFX
Seow	Uncontr	Mode	115	5	3	–	Overall:	Overall:	–	Over	Ove	NS	Short-	Maint

et al. 2010 (99)	olled Cohort study	rately severe: 73/115 (63) Severe: 42/115 (37)					68/115 (59) Moderately severe: (70) Severe: (17)	55/115 (48) Moderately severe: 60% Severe: 29%		all: 14/115 (12) Moderately severe: 1/73 (1) Severe: 13/42 (31)	rall: 38/115 (33) Moderately severe: 29% Severe: 60%		term: 10 weeks Long-term: 1 year	enance consisted of scheduled 8-weekly IFX with adjustment to 10mg/kg at physician discretion Associated detectable trough serum IFX with better clinical outcomes
Mortensen *et al.* 2011(69)	Retrospective	Severe	56	5	1-9	46/56 (82)	39/56 (70)	34/56 (61)	10/56 (18)	17/56 (30)	22/56(39)	0/56 (0)	Immediate: 2 weeks Short-term:	Severity classified according to a

													3 months Long-term: ~1.5 years (538 days)	simple colitis activity index (median 10) and modified Mayo score (median 8). 33/56 patients received oral steroids only prior to IFX IFX dosing varied according to physician preference
Dean *et al.* 2012(1	Retrospective	Severe	19 Tot	5	1-5	–	15/19 (79)	12/19 (63)	–	4/19 (21)	7/19 (37)	0/19 (0)	Short-term: 3	

81)			al 38										months Long-term: 1 year	
Moccario *et al.* 2012(86)	Retrospective	Severe	30 Total 65	5	3	–	25/30 (83)	1 year: (83) 2 years: (77) 3 years: (73)	–	5/30 (17)	1 year: (17) 2 years: (23) 3 years: (27)	0/30 (0)	Short-term: 3 months Long-term: 1 year, 2 years, 3 years	Results suggested similar efficacy at 3 months but greater efficacy with infliximab at 12 months
Laharie *et al.* 2012 (published in full) / Laharie *et al.* 2015 (abstract) (10)*	Randomised Head-to-head (IFX versus ciclosporin)	Severe	57 Total: 115	5	3	48/57 (84)	26/57 (46)	NS	3/57 (5)	12/57 (21)	(35)	0/57 (0)	Immediate: 1 week Short-term: 3 months Long-term: 5 years	Severity classified according to Lichtiger clinical activity index

														Composite criteria for 'treatment failure'
Croft *et al.* 2013 (54)*	Randomised Head-to-head (IFX versus ciclosporin)	Severe	38 Total 83	5	1	32/38 (84)	28/37 (76)	24/37 (65)	–	9/37 (24)	13/37 (35)	0/38 (0)	Immediate: time of discharge Short-term: 3 months Long-term: 1 year	Patient-led decision to receive specific salvage agent
Lynch *et al.* 2013 (3)	Retrospective Multicentre	Severe	2008: 51 2010: 86	5	3	2008: 39/51 (76) 2010: 69/86 (80)	NS	–	2008: 6/51 (12) 2010: 16/86 (19)	NS	–	2008: 0/45 (0) 2010: 1/79 (1)	Immediate: time of discharge	
Gibson *et al.* 2014	Retrospective	Severe	50 SD: 35/50 AD: 15/	5	3	Overall: 36/50 (72) SD: 22/35 (63) AD: 14/15 (93)	–	Overall: 28/50 (56) SD: 17/35 (49)	Overall: 14/50 (28) SD: 13/3	–	Overall: 22/50 (44) SD: 18/	NS	Immediate: during infliximab induction	Demonstrated higher response rates

			50					AD: 11/15 (73)	5 (37) AD: 1/15 (7)		35 (51) AD: 4/15 (27)		Long-term: 2 years	with accelerated infliximab dosing compared to standard induction
Naves *et al.* 2014(87)	Retrospective	Moderate to severe 20% severe	30 Total 50	5	3	–	26/30 (87)	21/30 (70)	–	1/30 (3)	9/30 (30)	0/30 (0)	Short-term: during hospital admission or steroid weaning period Long-term: following steroid-free clinical remission (median 3 years)	Initial efficacy defined as steroid-free clinical remission Early non-responders received sequential therapy with ciclosporin

Monterubbianesi *et al.* 2014 (98)	Uncontrolled Cohort study	Severe	113	5	3	–	92/113 (81)	84/113 (74)	–	21/113 (19)	29/113 (26)	0/113 (0)	Short-term: 3 months Long-term: 1 year	
Seagrove *et al.* 2014 (abstract) (55)*	Uncontrolled Randomised Head-to-head (IFX versus ciclosporin)	Severe	135	5	3	NS	NS	NS	NS	NS	55/135 (41)	3/135 (2)	Long-term: 3.5 years	Full-text not yet available
Duijvis *et al.* 2015 (abstract) (89)	Retrospective	Moderate to severe	139 Total 182	NS	NS	–	1 month: 136/139 (98) 6 months: 117/139 (84)	1 year: 108/135 (80) 3 years: 67/100 (67)	–	1 month: 3/139 (2) 6 months: 22/139 (16)	1 year: 27/135 (20) 3 years: 33/100 (33)	NS	Short-term: 1 month, 6 months Long-term: 1 year, 3 years	Infliximab was associated with lower colectomy rates than ciclosporin

Table 7: Summary of published studies evaluating clinical response, colectomy and mortality in infliximab-treated ASUC

*, randomised controlled trial

n, number of patients who received infliximab

NS, not stated

IFX, infliximab

SD, standard induction

AD, accelerated induction

All response, colectomy and mortality rates have been expressed as a proportion of the patients who initially received salvage therapy

Definitions of immediate, short-term and long-term have been defined based on duration of follow-up within each individual study

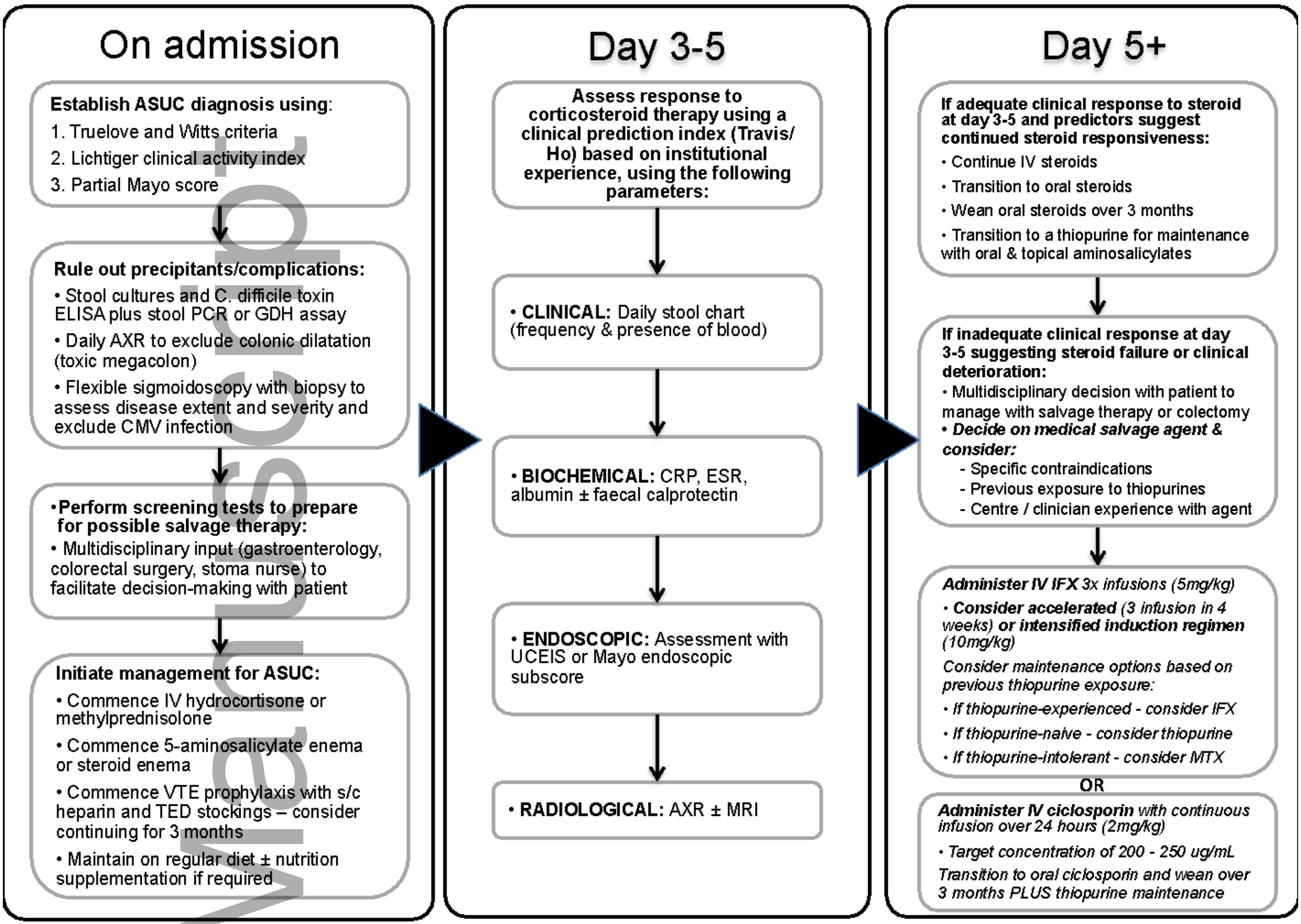

Figure 2: Algorithm outlining optimal management strategy for acute severe ulcerative colitis.

Figure legend: abdominal x-ray (AXR), C-reactive protein (CRP), cytomegalovirus (CMV), enzyme-linked immunosorbent assay (ELISA), erythrocyte sedimentation rate (ESR), glutamate dehydrogenase (GDH), infliximab (IFX), intravenous (IV), magnetic resonance imaging (MRI), methotrexate (MTX), polymerase chain reaction (PCR), subcutaneous (s/c), thromboembolic deterrent (TED), ulcerative colitis endoscopic index of severity), venous thromboembolism (VTE).

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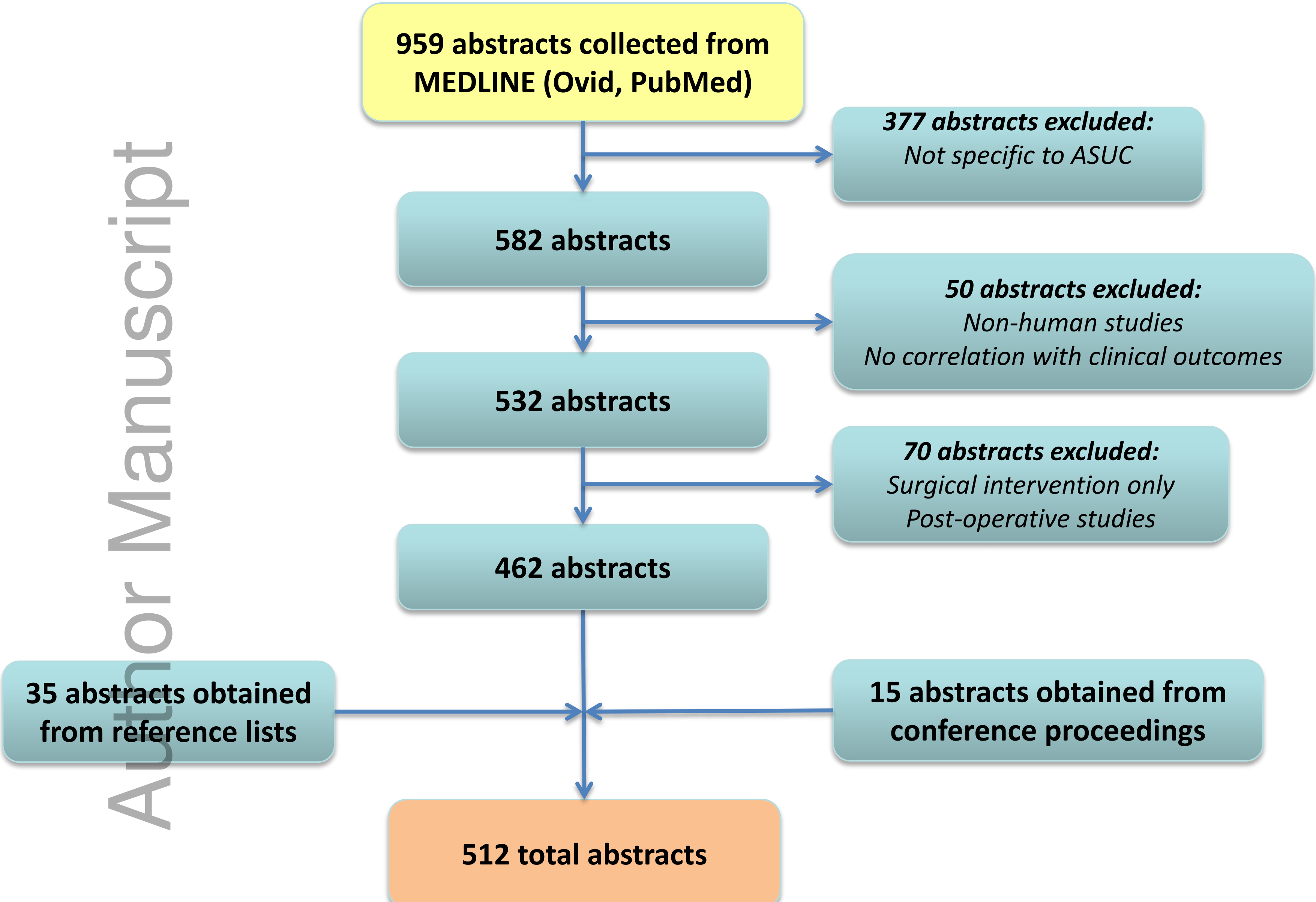

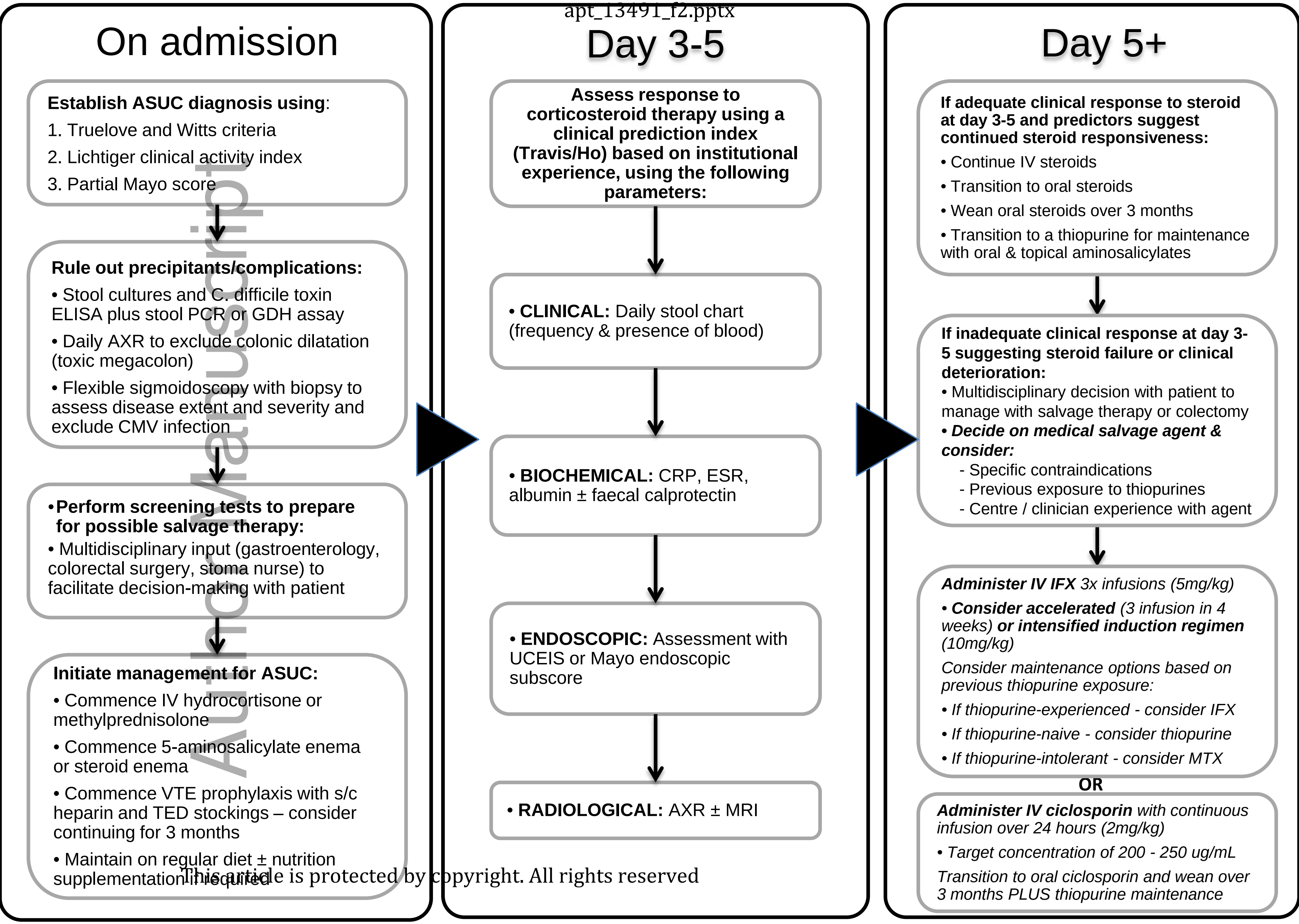
On admission
Establish ASUC diagnosis using:
1. Truelove and Witts criteria
2. Lichtiger clinical activity index
3. Partial Mayo score
Rule out precipitants/complications:
• Stool cultures and C. difficile toxin ELISA plus stool PCR or GDH assay
• Daily AXR to exclude colonic dilatation (toxic megacolon)
• Flexible sigmoidoscopy with biopsy to assess disease extent and severity and exclude CMV infection
•Perform screening tests to prepare for possible salvage therapy:
• Multidisciplinary input (gastroenterology, colorectal surgery, stoma nurse) to facilitate decision-making with patient
Initiate management for ASUC:
• Commence IV hydrocortisone or methylprednisolone
• Commence 5-aminosalicylate enema or steroid enema
• Commence VTE prophylaxis with s/c heparin and TED stockings – consider continuing for 3 months
• Maintain on regular diet ± nutrition supplementation if required
Day 3-5
Assess response to corticosteroid therapy using a clinical prediction index (Travis/Ho) based on institutional experience, using the following parameters:
• CLINICAL: Daily stool chart (frequency & presence of blood)
• BIOCHEMICAL: CRP, ESR, albumin ± faecal calprotectin
• ENDOSCOPIC: Assessment with UCEIS or Mayo endoscopic subscore
• RADIOLOGICAL: AXR ± MRI
Day 5+
If adequate clinical response to steroid at day 3-5 and predictors suggest continued steroid responsiveness:
• Continue IV steroids
• Transition to oral steroids
• Wean oral steroids over 3 months
• Transition to a thiopurine for maintenance with oral & topical aminosalicylates
If inadequate clinical response at day 3-5 suggesting steroid failure or clinical deterioration:
• Multidisciplinary decision with patient to manage with salvage therapy or colectomy
• Decide on medical salvage agent & consider:
- Specific contraindications
- Previous exposure to thiopurines
- Centre / clinician experience with agent
Administer IV IFX 3x infusions (5mg/kg)
• Consider accelerated (3 infusion in 4 weeks) or intensified induction regimen (10mg/kg)
Consider maintenance options based on previous thiopurine exposure:
• If thiopurine-experienced - consider IFX
• If thiopurine-naive - consider thiopurine
• If thiopurine-intolerant - consider MTX
OR
Administer IV ciclosporin with continuous infusion over 24 hours (2mg/kg)
• Target concentration of 200 - 250 ug/mL
Transition to oral ciclosporin and wean over 3 months PLUS thiopurine maintenance