

## Review article: acute severe ulcerative colitis – evidence-based consensus statements

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## SUMMARY

### Background

Acute severe ulcerative colitis (ASUC) is a potentially life-threatening complication of ulcerative colitis.

### Aim

To develop consensus statements based on a systematic review of the literature of the management of ASUC to improve patient outcome.

### Methods

Following a literature review, the Delphi method was used to develop the consensus statements. A steering committee, based in Australia, generated the statements of interest. Three rounds of anonymous voting were carried out to achieve the final results. Acceptance of statements was pre-determined by  $\geq 80\%$  votes in 'complete agreement' or 'agreement with minor reservation'.

### Results

Key recommendations include that patients with ASUC should be: hospitalised, undergo unprepared flexible sigmoidoscopy to assess severity and to exclude cytomegalovirus colitis, and be provided with venous thromboembolism prophylaxis and intravenous hydrocortisone 100 mg three or four times daily with close monitoring by a multidisciplinary team. Rescue therapy such as infliximab or ciclosporin should be started if insufficient response by day 3, and colectomy considered if no response to 7 days of rescue therapy or earlier if deterioration. With such an approach, it is expected that colectomy rate during admission will be below 30% and mortality less than 1% in specialist centres.

### Conclusion

These evidenced-based consensus statements on acute severe ulcerative colitis, developed by a multidisciplinary group, provide up-to-date best practice recommendations that improve and harmonise management as well as provide auditable quality assessments.

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## INTRODUCTION

Acute severe ulcerative colitis (ASUC) is a potentially life-threatening complication of ulcerative colitis (UC).<sup>1</sup> The established principles of ASUC management combine a multi-disciplinary approach, high dose parenteral corticosteroids, venous thromboembolism (VTE) prophylaxis, surgical co-management and close observation. Rescue medical therapy includes infliximab or ciclosporin, which may obviate the need for urgent colectomy. Improved management paradigms have decreased mortality. However, short-term colectomy rates of approximately 30% have remained stable.<sup>2, 3</sup> Given this and the uncommon but serious nature of ASUC, consensus statements based on a systematic review of the literature, may assist clinicians in improving patient outcomes and harmonise management. Few guidelines have focused specifically on ASUC. The Toronto Consensus Statements<sup>4</sup> cover hospitalised management without discussing maintenance therapy, pregnancy-related issues, opportunistic infections or multidisciplinary management. The consensus statements on optimal ASUC management that follow were developed by a multi-disciplinary group of clinicians using the Delphi process. The Australian National Health and Medical Research Council (NHMRC) grades of recommendation and levels of evidence<sup>5</sup> were applied. (Data S1, Tables S1 and S2).

## METHODS

The guidelines were developed through a modified Delphi process.<sup>6</sup> Statements were generated by the steering committee (RL, JC, CC, VK, PG, NM), all members of inflammatory bowel disease (IBD) Sydney Organisation, an association of members with specific interest in IBD. The statements were then circulated via an online survey to Consensus Group members. Feedback from the initial survey was incorporated into a revised set of statements. A systematic literature review was conducted using PubMed and MEDLINE by the literature review team using search terms based on the statements and a password-secured website was populated with the relevant literature. National and international guidelines and their references were specifically referenced. Consensus group voting members completed a second round of voting after review of the collected evidence. Each statement was assigned to a member of the consensus group according to their expertise and interest. A face-to-face meeting was conducted and the consensus group members presented their statements, discussed the relevant literature and edited the wording of statements prior to a final round of anonymously

conducted voting. Five levels of agreement were used: A: agree completely; B: agree with minor reservation; C: agree with major reservation; D: reject with some reservation, E: reject completely. A statement was considered to be accepted when 80% or more of the voting members indicated 'agree completely' or 'agree with minor reservation'. The statement was rejected if 80% or more of the members indicated 'reject completely' or 'reject with some reservation'. If consensus was not achieved then further discussion was carried out and voting may be repeated only once. The level of evidence and grade of recommendation for each statement were agreed upon by the voting members according to the Australian NHMRC recommendations for the development of guidelines.<sup>5</sup> The grade of recommendation for every statement is based on the strength of evidence, consistency, clinical impact, generalisability and applicability. The grades range from A: indicating that the body of evidence can be trusted to guide practice, to D: indicating weak body of evidence and recommendation must be applied with caution.

The manuscript was written and revised by the manuscript writing committee comprising members of the steering committee and IBD experts from around Australia. The statements have been, so far, endorsed by the Agency of Clinical Innovation of New South Wales Department of Health, New South Wales Therapeutic Advisory Group and the Australian Inflammatory Bowel Disease Association of the Gastroenterological Society of Australia. All consensus group members and authors approved the manuscript.

### Membership of the consensus group

Voting members were experts selected after an open call for participants using the following criteria:

- (i) Demonstration of knowledge and expertise in IBD through publication, research and leadership and/or prior participation in national or regional guideline development.
- (ii) Geographical representation across Australia and representation of the Australian Inflammatory Bowel Disease Association of the Gastroenterological Society of Australia and the medical director of Crohn's and Colitis Australia representing the consumer group.
- (iii) Multidisciplinary representation by adult gastroenterologists across major Australian metropolitan cities, gastroenterologists from rural settings, a colorectal surgeon, a paediatric gastroenterologist, an IBD nurse and a dietitian.

(iv) A Professor of Pharmacology representing the regulatory Therapeutic Goods Administration of the Australian Government Department of Health.

Non-voting members of the consensus group included a patient-representative and interstate gastroenterologists with expertise on IBD (IL, GRS).

## RESULTS

### Statement 1: Definition

The diagnosis of acute severe ulcerative colitis (ASUC) is defined by the Truelove and Witts criteria as  $\geq 6$  bloody stools per day plus at least one of the following:

- (i) Temperature greater than 37.8 °C;
- (ii) Pulse greater than 90 beats per minute
- (iii) Haemoglobin less than 105 g/L
- (iv) Erythrocyte sedimentation rate (ESR) greater than 30 mm/h

Hospital admission under a gastroenterologist is strongly recommended. A diagnosis of infective colitis must be excluded.

Acute severe ulcerative colitis is life-threatening and requires early diagnosis and initiation of treatment. The Truelove and Witts criteria are endorsed by The American College of Gastroenterology, the Association of Coloproctology of Great Britain and Ireland, and the European Crohn's and Colitis Organisation (ECCO).<sup>7–10</sup> The ECCO guidelines also include C-reactive protein (CRP) >30 mg/L as an additional criterion.<sup>10</sup> Intravenous corticosteroid and expert consultation significantly reduce mortality in ASUC,<sup>2, 11, 12</sup> and 70% of patients will respond to intravenous corticosteroids.<sup>7</sup> Stool cultures for enteric pathogens and *Clostridium difficile* testing are mandatory.

### Statement 2: Aim

Immediate treatment of ASUC aims to achieve clinical remission. Long-term goals are to achieve clinical, endoscopic, and histological remission.

Clinical remission of ASUC is defined as  $\leq 3$  stools per day without rectal bleeding.<sup>10, 13</sup> Extrapolated evidence from moderate to severe UC suggests endoscopic and histological remission are more rigorous.<sup>14</sup> Endoscopic mucosal healing at week 8 increases the likelihood of clinical remission at 30 weeks on infliximab fourfold.<sup>15</sup> Mucosal healing increases duration of clinical remission.<sup>16, 17</sup> Basal plasmacytosis<sup>18</sup> or neutrophilia, seen histologically in rectal biopsies, are associated with a

4.5-fold and two to threefold increase in risk of relapse respectively.<sup>19, 20</sup> Increased histologically graded inflammation correlates with hospitalisation and surgery.<sup>21, 22</sup> The long-term goal, therefore, is not only clinical and endoscopic remission but also histological remission.

### Statement 3: Investigations on initial presentation – laboratory

On presentation with ASUC, full blood count (FBC), electrolyte/urea/creatinine, CRP, ESR, liver function tests (LFT), magnesium, lipid profile, abdominal X-ray, stool microscopy/culture/sensitivities and *C. difficile* testing should be performed.

In addition, tuberculosis (TB) exposure, hepatitis B serology (surface antigen, surface antibody, and core antibody), thiopurine methyltransferase (TPMT), cytomegalovirus (CMV) IgG and IgM, Epstein-Barr virus (EBV) IgG and IgM, human immunodeficiency virus (HIV) and varicella zoster serologies, and *Streptococcus pneumoniae* and influenza vaccinations should be considered.

Investigations assess disease severity, exclude infections and predict for poorer outcomes and relative-contraindications of rescue therapy. Stool microscopy, culture and sensitivity exclude infective colitis. Intravenous corticosteroids should not be delayed while waiting for these results. *Clostridium difficile* is more prevalent and associated with increased morbidity and mortality in UC patients.<sup>23, 24</sup> Enzyme-linked immunosorbent assay or polymerase chain reaction (PCR) of serial stool samples can detect *C. difficile* toxin.<sup>23, 25, 26</sup>

Serum magnesium and lipid profile are relevant in those under consideration for ciclosporin. Hypomagnesaemia and low serum cholesterol decreases seizure threshold.<sup>26</sup> Toxic megacolon is diagnosed by a colonic diameter of >5.5 cm on abdominal X-ray in the presence of systemic toxicity. Routine abdominal computed tomography is not indicated.

Conduct interferon-gamma release assay such as QuantiFERON-gold (Cellestis/Qiagen, Carnegie, Australia) and chest X-ray for patients at risk of previous TB exposure. Ideally, start anti-tuberculous treatment or prophylaxis for active or latent TB, prior to commencing immunomodulators or high-dose corticosteroids. Quantify HBV DNA if hepatitis B surface antigen is positive.<sup>7</sup>

### Statement 4: Investigations on initial presentation – endoscopy

Perform a flexible sigmoidoscopy without preparation, within 24 h of admission. Take multiple colonic biopsies to assess for evidence of CMV colitis.

A full colonoscopy is not recommended in patients with ASUC due to the risk of colonic perforation.<sup>10, 11</sup> Exclude CMV colitis in patients on immunosuppression (see statement 31). A validated endoscopic scoring system with high inter- and intra-individual agreement may grade severity and aid follow-up. The Ulcerative Colitis Endoscopic Index of Severity (UCEIS) is suggested but the Mayo endoscopic sub-score remains more widely used.<sup>27–29</sup>

#### Statement 5: Clinical pathway

*The management of patients with ASUC, should follow a clinical pathway to aid treatment, identify variance, and to audit outcomes.*

A meta-analysis of 27 studies, including 19 randomised controlled trials, and involving 21 different conditions or interventions demonstrated clinical pathways can reduce in-hospital complications and improve documentation without negatively impacting on the length of stay and hospital costs.<sup>30</sup> The UK IBD audits identified areas of concern including documentation, assessment of stool frequency, *C. difficile* toxin testing and VTE prophylaxis.<sup>31–33</sup> A well-developed clinical pathway may improve such auditable activities.

#### Statement 6: Ongoing review

*Ongoing assessment should include daily review of haemodynamic status and abdominal examination by a medical officer, stool charts (frequency, consistency, presence of blood and estimated stool volume), FBC, electrolyte/urea/creatinine, CRP, albumin and serial abdominal X-ray.*

Assessing these parameters, at least daily, identifies complications, failure to respond to intravenous corticosteroids and required rescue therapy. Validated indices can guide assessment.<sup>34–38</sup> Avoid opioids and anti-diarrhoeal agents as they may precipitate colonic dilatation. Review drug allergies, drug interactions and prior adverse effects, with the ward pharmacist, as part of routine care.

#### Statement 7: Management Team

*Patients with ASUC are best managed by a multidisciplinary team (MDT) comprising a gastroenterologist, colorectal surgeon, gastroenterology nurse, dietitian, pharmacist, and stomal therapist on a specialised gastrointestinal ward. If such care is unavailable, discuss the case at an early stage with an IBD-focused gastroenterology centre.*

ECCO, the National Institute for Health and Clinical Excellence, UK IBD Standards and British Society of

Gastroenterology guidelines advocate the multidisciplinary management of patients with ASUC in a specialised gastroenterology ward.<sup>7, 39–41</sup> Timely and expert surgical input have reduced the mortality rate in ASUC from 24% prior to the advent of corticosteroid use to <1%.<sup>2, 11, 12</sup> Joint gastroenterologist and surgical management is recommended with dietitian, pharmacist, stomal therapist and IBD nurse consultation.<sup>42</sup> In areas where IBD expertise and resources are unavailable, discussion with a specialist centre to establish the management plan and the threshold for patient transfer is strongly recommended.

#### Statement 8: Nutrition

*A trained dietitian should assess the nutritional status of the patient. Enteral supplements should be introduced as required. There is no proven role for routine parenteral nutrition in ASUC. There is also no role for routine fasting.*

Nutritional status assessment is based on a dietary history, physical examination, objective clinical and laboratory parameters.<sup>43, 44</sup> Bowel rest with total parenteral nutrition is not superior to enteral feeding and is associated with increased complications such as sepsis.<sup>44, 45</sup> Rehydration, enteral feeding and management of nutritional deficiencies are recommended.

#### Statement 9: Venous thromboembolism prophylaxis – in-patient

*Venous thromboembolism prophylaxis should be administered to all hospitalised patients with ASUC, using subcutaneous or low molecular weight heparin and graduated compression stockings, unless contraindicated.*

Venous thromboembolism (VTE) risk in IBD and relapsing IBD increases three and eightfold respectively.<sup>46, 47</sup> Hospitalisation and need for steroids further increases VTE-risk by 1.5 to twofold.<sup>46, 48–50</sup> Pharmacological and mechanical VTE prophylaxis is necessary in hospitalised ASUC patients unless contraindicated.<sup>51</sup> Rectal bleeding is not a contraindication.

#### Statement 11: Corticosteroids

*Intravenous hydrocortisone 100 mg three to four times daily or equivalent is the standard initial treatment of ASUC and should not be delayed pending screening tests for infectious colitis.*

Intravenous corticosteroid is highly effective in the initial treatment of ASUC. A systematic review showed the overall corticosteroid response rate is 67%.<sup>12, 52</sup> There is no additional benefit of high-dose

methylprednisolone above 60 mg per day, but lower doses were less effective.<sup>2, 7</sup> Intravenous corticosteroid was not beneficial beyond 7–10 days of treatment, signifying the need for earlier rescue therapy.<sup>2</sup>

#### Statement 12: Indicators for rescue therapy

*A. Failure to achieve an adequate response to intravenous corticosteroid is defined by:*

*(i) on day 3, >8 stools per day or three to eight stools per day with a CRP >45 mg/L;*

*(ii) on day 7, >3 stools per day or visible blood; or*

*(iii) a Paediatric Ulcerative Colitis Activity Index (PUCAI) >65 (in-patients <18 years old) on day 5. Formal assessment of severity at day 3 is required to identify these patients.*

*B. Additional indicators of severity include mucosal islands and colonic dilatation on abdominal X-ray and deep ulceration on flexible sigmoidoscopy.*

Risk stratification identifies prognostic variables for failure of medical therapy and commencing rescue therapy. Assessment on day 3 of intravenous corticosteroid therapy can predict need for colectomy and allow for timely treatment escalation.<sup>34–36</sup> The Oxford criteria, defined by >8 stools per day or three to eight stools per day with a CRP >45 mg/L on day 3 of intravenous corticosteroid therapy, corresponded to 85% rate of colectomy. On day 7, >3 stools per day or visible blood had a 40% rate of colectomy in ensuing months.<sup>34</sup> These criteria remain the simplest to apply in clinical practice. For paediatric patients, a PUCAI score of >45 points on day 3 is a strong indicator for planning rescue therapy, and >65 points on day 5 should prompt use of planned rescue therapy.<sup>37</sup>

The Swedish index, also known as the fulminant colitis index [stool frequency/day + 0.14 × CRP (mg/L)], has a positive predictive value (PPV) of 72% for colectomy at a cut-off score of >8 on the third day of corticosteroid therapy.<sup>35</sup> The Edinburgh risk score assesses the mean stool frequency over the first 3 days of admission, presence of colonic dilatation (>5.5 cm) and hypoalbuminaemia on admission (<30 g/L). A score of >4 on day 3 of intravenous corticosteroid therapy predicts intravenous corticosteroid failure (sensitivity 85%, specificity 75%).<sup>36</sup> The index of Seo *et al.* calculated after 1 week of intravenous corticosteroid therapy, has a PPV of 52% and negative predictive value of 97% for colectomy at a cut-off of 180 points.<sup>38</sup>

In addition, colonic dilatation of >5.5 cm measured at the transverse colon and the presence of mucosal islands

on a plain abdominal X-ray, as well as deep ulcers on flexible sigmoidoscopy predict for increased colectomy rate.<sup>34, 53</sup> The presence of any of these prognostic factors increases the need for rescue therapy.

#### Statement 13: Options of rescue therapy

*Rescue therapies include infliximab, ciclosporin, or surgery, depending on the judgment of the treating physicians, drug availability, prior thiopurine failure, and patient preference.*

Commence rescue therapy when intravenous corticosteroid fails to induce a clinical response by day 3. Infliximab is effective in severe refractory UC assessed according to the fulminant colitis index with seven patients requiring colectomy within 3 months after infusion, vs. 14 treated with placebo ( $P = 0.017$ ).<sup>54</sup> A retrospective study of ASUC showed two-thirds of patients avoided colectomy in the short term.<sup>55</sup> Other case series demonstrated variable colectomy rates after infliximab rescue therapy.<sup>56–58</sup> Intravenous ciclosporin at 4 mg/kg body weight/day significantly reduced the short-term colectomy rate compared to placebo in severe refractory UC.<sup>59</sup> Subsequently, an intravenous dose of 2 mg/kg was found to be equivalent to 4 mg/kg with fewer adverse events.<sup>60</sup>

A prospective trial of infliximab with ciclosporin as rescue therapy in 115 patients with ASUC demonstrated equivalent efficacy and adverse events. However, retrospective cohorts subsequently showed lower colectomy rates with infliximab compared to ciclosporin.<sup>3, 61, 62</sup> The CONSTRUCT trial of ciclosporin vs. infliximab will provide additional data on the outcomes of ASUC.<sup>63</sup> Surgery should be performed when indicated, such as in the event of toxic megacolon, when medical rescue therapy is contraindicated, or failure of medical rescue therapy.

#### Statement 14: Rescue therapy in thiopurine-experienced patients

*Patients who have previously had an inadequate response to thiopurine maintenance therapy (i.e. appropriately dosed, with treatment adherence or have therapeutic levels of thioguanine nucleotide (TGN) for >3 months) should not receive ciclosporin. An alternative rescue therapy such as infliximab is recommended.*

In thiopurine-naïve patients, ciclosporin may induce clinical remission. Responders to ciclosporin may be bridged to thiopurine maintenance treatment. Following previous failure of thiopurine, however, the colectomy rate is 59% compared to thiopurine-naïve patients at

31%.<sup>64</sup> Infliximab is therefore the preferred rescue treatment in corticosteroid-refractory ASUC patients who have previously failed thiopurine maintenance therapy.

#### Statement 15: Rescue therapy – other biologics

*There are currently no data on the efficacy and safety of adalimumab, vedolizumab, and golimumab in ASUC.*

Adalimumab, vedolizumab and golimumab are efficacious in chronic active moderate to severe UC. However, there are insufficient data for the use of biologics in ASUC. Although adalimumab was statistically better in inducing clinical remission than placebo (18.5% vs. 9.2%,  $P = 0.031$ ) in moderate to severe UC, the absolute benefit was low.<sup>65</sup> Vedolizumab was more effective in inducing remission than placebo in active disease (47.1% vs. 25.5%;  $P < 0.001$ ), but there is currently no data in the ASUC cohort.<sup>66</sup> Golimumab was more efficacious at achieving clinical remission than placebo (17.8% vs. 6.4%;  $P < 0.001$ ) in moderate-to-severe UC<sup>67</sup> but there are no trials in ASUC patients. There is, at present, insufficient data to recommend the use of these biologics for ASUC.

Tacrolimus showed promising results (clinical response: 50% vs. 13.3%,  $P = 0.003$ <sup>68</sup>; clinical improvement: 68.4% vs. 10%,  $P < 0.001$ ) in the treatment of corticosteroid-refractory moderate to severe UC.<sup>68–73</sup> However, there are insufficient data in ASUC.

#### Statement 16: Surgical rescue therapy

*Following failure of one rescue medical treatment, surgery is recommended. Sequential rescue medical therapy risks sepsis and delays surgery.*

Following failure of ciclosporin or infliximab rescue therapy, surgery is preferred. Sequential rescue immunomodulator therapy delays surgery, and cumulative immunosuppression increases the risk of sepsis.<sup>74</sup> Sequential therapy with a calcineurin inhibitor followed by infliximab or vice versa has reported success rates of 25–40%. Infliximab followed by ciclosporin is associated with 16% risk of severe adverse events including sepsis, pancreatitis and herpetic oesophagitis.<sup>75–77</sup> Sequential therapy may be considered on a case-by-case basis only in highly specialised centres.<sup>7</sup>

#### Statement 17: Assessing efficacy of rescue therapy

*The efficacy of rescue therapy should be assessed daily. In the event of deterioration or failure to improve, patients should proceed to surgery.*

The Ho-based score predicts success of ciclosporin rescue therapy<sup>78</sup> while the Lichtiger score is used to

monitor the progress of ciclosporin therapy.<sup>59</sup> Increasing age, thrombocytosis and previous use of ciclosporin can predict for poor response to ciclosporin rescue therapy.<sup>79</sup> Colectomy predictors in patients who received infliximab as rescue therapy include no clinical response after infliximab induction, CRP >10 mg/L at infliximab initiation, ASUC and previous treatment with ciclosporin.<sup>80</sup> Patients with fulminant disease have a decreased response to infliximab than patients with milder corticosteroid-refractory UC.<sup>54</sup> No studies have formally evaluated timing for rescue therapy failure but commonly response at 7 days is used to declare failure, unless indications for immediate colectomy arise.

#### Statement 18: Failure of rescue therapy

*A surgeon experienced in ASUC colectomy should perform emergency colectomy, and discuss surgery, outcomes and possible complications with the patient. Where available, a stomal therapist should review patients.*

The relationship between outcome and high volume work has been established in IBD surgery, although not specifically for ASUC.<sup>81–83</sup> Technical expertise and an established multi-disciplinary approach may improve the outcome of surgery.<sup>84, 85</sup> The gastroenterologist, surgeon, patient and their family should jointly decide to proceed to surgery. Delayed surgery can increase morbidity.<sup>86</sup> The preferred procedure is subtotal colectomy with end ileostomy as part of a three stage procedure, performed open or laparoscopically depending on local expertise.<sup>9, 86</sup> Definitive pathology can be established while the patient recovers and is weaned off immunomodulators before further surgery is planned. In experienced hands, laparoscopic subtotal colectomy and end ileostomy is safe and offers improved short-term surgical outcomes over open colectomy.<sup>87</sup>

#### Statement 19: Rescue therapy – Infliximab dosage

*Administer infliximab infusions at weeks 0, 2, and 6 at a dose of 5 mg/kg. The value of shorter dosing intervals and/or higher doses of infliximab is unknown.*

Detectable serum infliximab trough concentration is associated with higher rates of clinical remission, endoscopic improvement, endoscopic remission and a lower rate of colectomy compared with undetectable trough serum infliximab.<sup>88</sup> Compared to clinical responders with moderate to severe UC, primary infliximab non-responders have lower serum infliximab concentrations and increased infliximab concentrations in the faeces, representing trans-intestinal drug loss.<sup>89, 90</sup> Shortened dosing interval or increased dose may increase serum

infliximab concentration and efficacy. Accelerated infliximab dosing (three doses in a median of 24 days) protects against early colectomy.<sup>91</sup> Further prospective studies are required to establish the benefit of this practice.

#### Statement 20: Combination of infliximab and thiopurine

*If infliximab is used for maintenance therapy, the combination of a thiopurine with infliximab is more efficacious than infliximab alone.*

Combined infliximab and azathioprine therapy, increases efficacy over either azathioprine- or infliximab-monotherapy in Crohn's disease.<sup>92–94</sup> The combination also demonstrated improved corticosteroid-free, 16-week remission and mucosal healing rates in UC.<sup>95</sup> Thiopurine-combination therapy is recommended in the absence of contraindications.

#### Statement 22: Ciclosporin as rescue therapy

*Ciclosporin should be administered as a continuous intravenous infusion at the initial dose of 2 mg/kg/day. Thereafter, dosing is converted to oral ciclosporin at a dose of 4 mg/kg/daily, and continued for approximately 3 months. The target trough concentration for oral ciclosporin is 150–250 ng/mL.*

Ciclosporin is efficacious in the treatment of ASUC refractory to corticosteroid<sup>59, 96, 97</sup> and non-inferior to intravenous corticosteroid as monotherapy.<sup>98</sup> Due to dose-related adverse effects of ciclosporin, 2 mg/kg/day is advocated instead of 4 mg/kg/day with similar therapeutic benefits.<sup>60</sup> Ciclosporin has similar efficacy to infliximab in corticosteroid-refractory acute severe flare of UC, where intravenous ciclosporin was given at a dose of 2 mg/kg/day for 7 days followed by oral ciclosporin for 3 months at a dose of 4 mg/kg/day aiming for a trough concentration of 150–250 ng/mL.<sup>99</sup> Ciclosporin interacts with drugs metabolised by CYP3A4 and P-glycoprotein, for example, azole anti-fungal medications, calcium channel blockers (diltiazem and verapamil) and statins. When the interacting drug cannot be discontinued, reduce ciclosporin dose and monitor ciclosporin trough levels.

#### Statement 23: Pharmacy

*Rescue ASUC medical therapies should be readily available in hospital pharmacies, with a mechanism for prompt dispensing.*

Intravenous ciclosporin and infliximab, should be available for dispensing within 2 h of the decision to

commence rescue therapy. Drug and Therapeutics Committee approved-protocols can facilitate rapid dispensing and administration.<sup>100</sup>

#### Statement 24: Occupational health and safety

*There is no evidence of occupational health and safety risks relating to exposure to anti-tumour necrosis factor (anti-TNF) agents. Standard precautions are sufficient for drug preparation and administration.*

Currently, no data show that occupational exposure to anti-TNF agents is harmful. Anti-TNF antibodies are not listed as a hazardous by any national or international body. Casual dermal, inhaled or mucosal contact should not result in biological effects in the exposed individual.<sup>101</sup> There is no evidence for systemic absorption of these drugs in handling or accidental spillage, or reports of subsequent adverse effects.<sup>101</sup> Use of protective gloves, gown, face-mask and eye goggles are appropriate during reconstitution of anti-TNF agents in accordance with current safety consensus guidelines.<sup>101, 102</sup>

#### Statement 25: Maintenance therapy – thiopurines

*Patients who respond to rescue medical therapy but have not yet failed thiopurine maintenance therapy should be commenced on a thiopurine as a maintenance medication.*

Thiopurine therapy is more effective than placebo for the maintenance of remission in UC (RR: 0.68, 95% CI: 0.54–0.86).<sup>103</sup> In two studies comparing thiopurine to 5-aminosalicylic acids (5-ASAs), only one study showed superiority of azathioprine.<sup>104, 105</sup> In severe UC, lower colitis relapse occurred more in the azathioprine group compared to the placebo group, with no difference in the rate of remission.<sup>106</sup> Azathioprine with sulfasalazine was superior in maintaining remission than sulfasalazine alone.<sup>107</sup> Long-term colectomy rate in corticosteroid-refractory severe UC is decreased in those who are prescribed thiopurine for maintenance after initial response to ciclosporin.<sup>108–110</sup> Responders to induction therapy should, be commenced on a thiopurine, prior to discharge from hospital. Attempt switching maintenance therapy to a 5-ASA only in mucosal-healed patients without flares for at least 12 months, and with close observation thereafter. Some patients may require rapid escalation of maintenance therapy to infliximab.

#### Statement 26: Maintenance therapy – thiopurine monitoring

*Thiopurine methyl-transferase (TPMT) genotype/phenotype results can guide the starting dose of thiopurine.*

However, thiopurine therapy can be commenced without TPMT results. FBD and LFTs should be measured weekly for 4 weeks after commencing thiopurine, then fortnightly for the next 4 weeks, then 3-monthly.

Thiopurine methyl-transferase genotype/phenotype results can reduce the risk of toxicity.<sup>111, 112</sup> Thiopurines can be started before TPMT results are available with myelosuppression monitored. A normal TPMT does not exclude the development of myelotoxicity.<sup>26</sup> The rate of mild leukopenia and neutropenia is 2–10.5%.<sup>113–115</sup> Myelotoxicity can occur at any time but most frequently between 2 weeks and several months after thiopurine commencement, with half occurring within 2 months and nearly two-thirds within 4 months.<sup>114, 116</sup> The myelotoxicity incidence is approximately 3% per patient per year, indicating the need for ongoing blood count monitoring.<sup>117</sup>

Thiopurine-induced hepatotoxicity includes hypersensitivity, idiosyncratic cholestasis and nodular regeneration hyperplasia (NRH).<sup>111</sup> Transient elevation of serum transaminases (>2 times upper limit of normal) occurs in 5–10% of patients. The incidence is 2.6% per patient-year<sup>118, 119</sup> developing after a median 1.5–3 months after commencing thiopurine.<sup>118, 120, 121</sup> NRH, a cause of non-cirrhotic portal hypertension develops after a median of 50 months.<sup>122, 123</sup> Investigate for features of portal hypertension with abdominal ultrasound, if platelet levels decrease.

#### Statement 27: Maintenance therapy – thiopurine metabolites

*Metabolite levels may determine management of patients who fail to respond, have toxicity or to assess adherence.*

Thiopurine efficacy depends on production of active metabolites. A 6-TGN level of  $>235 \text{ pmol}/8 \times 10^8$  red blood cells (RBC) is associated with greater therapeutic efficacy in paediatric IBD patients.<sup>124</sup> 6-TGN levels of  $235\text{--}250 \text{ pmol}/8 \times 10^8$  RBC correlate with improved clinical response.<sup>125–128</sup> A meta-analysis concluded that 6-TGN level  $>230\text{--}260 \text{ pmol}/8 \times 10^8$  RBC was associated with remission (62%) compared to below this value (36%; OR: 3.3, 95% CI: 1.71–6.27).<sup>129</sup> However, other studies found no correlation between 6-TGN level and clinical efficacy.<sup>130–132</sup> Using an alternative method of TGN assessment, improved clinical response was seen with a 6-TGN concentration of  $>100 \text{ pmol}/8 \times 10^8$  RBC.<sup>112</sup> Metabolite level measurements help to differentiate between medication non-adherence, under-dosing, shunting towards inactive metabolites and thiopurine-refractory UC.<sup>111, 112</sup>

#### Statement 28: Maintenance therapy – thiopurines and allopurinol

*Thiopurine shunters (those with inadequate TGN levels and methylmercaptopurine (MMP):TGN ratio  $>11$ ) or patients who are intolerant of an effective dose of thiopurine, can try allopurinol with dose-reduced azathioprine or mercaptopurine to a quarter/third of the original intended dose in conjunction with close monitoring of FBC, LFTs and thiopurine metabolites.*

The efficacy and safety of adding allopurinol with dose-reduced thiopurines has been established in several cohort studies.<sup>133–142</sup> Allopurinol, typically 100 mg daily, in addition to dose-reduced thiopurine (approximately, a third of the original intended dose), can reverse the preferential shunting towards inactive thiopurine metabolites.<sup>139, 140</sup> Carefully monitor metabolite levels and for myelotoxicity and hepatotoxicity.

#### Statement 29: Pregnancy

*The management of ASUC in pregnancy does not change. Use corticosteroids, ciclosporin, thiopurines, infliximab, and colectomy as needed in all stages of pregnancy.*

The management of ASUC in pregnancy is similar to non-pregnant patients. Active IBD during pregnancy is associated with adverse pregnancy outcomes, including preterm birth, small for gestational age, increased caesarean rate,<sup>143–146</sup> increased rates of stillbirth and neonatal death.<sup>144, 146</sup> A prospective study of 58 IBD patients found poor pregnancy outcomes were associated with active disease during pregnancy.<sup>147</sup>

Prednisolone and prednisone are considered safe in pregnancy. A placental enzyme inactivates maternal cortisol but as dexamethasone is not inactivated by this enzyme it should be avoided.<sup>148</sup> Older studies suggest an increased risk of orofacial cleft malformation with corticosteroid use in the first trimester of pregnancy;<sup>149–153</sup> however, more recent and larger studies have not confirmed such association,<sup>154–157</sup> suggesting corticosteroids may be prescribed during pregnancy.<sup>158</sup>

Thiopurines interfere with the synthesis of adenine and guanine ribonucleosides, precursors of DNA and RNA. However, the foetus lacks the enzyme inosinate phosphorylase necessary to convert azathioprine and mercaptopurine to active metabolites.<sup>148</sup> Some studies found thiopurines are associated with pre-term birth and low birth weight,<sup>159–162</sup> and congenital abnormalities<sup>160–162</sup> but may have been confounded by greater disease severity.<sup>160, 162</sup> Several studies (389 pregnancies) found no increased adverse effects in pregnancy



with thiopurines in pregnancy.<sup>163–165</sup> A recent multicentre study found foetuses are exposed to 6-TGN, but not 6-MMP *in utero*, and that 60% were born with clinically insignificant anaemia.<sup>166</sup> Thiopurines are of low risk in breastfeeding.<sup>167, 168</sup>

Ciclosporin exposure in pregnancy has not been shown to increase foetal malformation in the solid organ transplantation and case series in IBD.<sup>169, 170</sup> Ciclosporin exposure has been associated with premature delivery and low birth weight, potentially confounded by disease severity.<sup>165</sup> Gestational hypertension, diabetes and pre-eclampsia rates are not increased.<sup>169</sup> Ciclosporin can be used during pregnancy and for ASUC when needed. There have been concerns about ciclosporin use during breastfeeding due to one reported case of therapeutic blood concentrations in a breastfed infant, without reported adverse effects.<sup>171</sup> Other studies have not reported issues associated with ciclosporin use during breast feeding.<sup>172–176</sup>

The TREAT Registry, the Infliximab Safety Database, PIANO Registry, and the Danish-Australasian study showed no significant differences in the pregnancy outcome of patients exposed to anti-TNFs compared to controls, including miscarriage rates, foetal malformation and other foetal complications.<sup>177–180</sup> There were theoretical concerns regarding the safety of infliximab during the third trimester of pregnancy with the antibodies transferring across the placenta. Data from the PIANO Registry and the Intra-uterine ExposuRe to Anti-TNF-alpha therapy (ERA) study demonstrate that continuing infliximab through pregnancy, if needed is safe.<sup>181, 182</sup> Infliximab is also compatible with breastfeeding.<sup>179, 183</sup> Following intra-uterine exposure to anti-TNF-alpha therapy, the infant should not be exposed to live vaccines until 12 months of age.<sup>182</sup>

#### Statement 30: Opportunistic infections – *Pneumocystis jiroveci* pneumonia

*Patients on corticosteroids, thiopurine, and either a calcineurin inhibitor or infliximab require *Pneumocystis jiroveci* pneumonia (PJP) prophylaxis using sulfamethoxazole–trimethoprim 800 mg/160 mg three times per week. Dapsone 100 mg daily or atovaquone 1500 mg daily are options for patients with sulfur allergy.*

*Pneumocystis jiroveci* pneumonia is an opportunistic infection that may result in respiratory failure. ECCO endorses PJP prophylaxis in patients taking corticosteroid and two immunomodulators with either one of them a calcineurin inhibitor or an anti-TNF agent.<sup>184</sup>

PJP infections have been reported in IBD patients taking ciclosporin, anti-TNFs, corticosteroid and/or thiopurines.<sup>185–189</sup> The incidence of PJP is higher in IBD patients than non-IBD controls (hazard ratio: 2.96, 95% CI: 1.75–4.29), especially those on immunomodulators (32/100 000) compared to those not (5.5/100 000).<sup>190</sup> PJP infection is associated with high mortality (39%), endotracheal intubation rate (66%) and intensive care unit admission (69%) in non-HIV immunosuppressed patients.<sup>191</sup> PJP prophylaxis, with sulfamethoxazole–trimethoprim 800 mg/160 mg three times per week is recommended first line, for patients on triple immunosuppressive therapy.<sup>192–194</sup> Use Dapsone 100 mg daily or atovaquone 1500 mg daily for patients with sulphur allergies.<sup>193, 194</sup>

#### Statement 31: Opportunistic infections – CMV diagnosis

*Cytomegalovirus colitis should be considered in all patients with ASUC. Diagnose CMV colitis based on colonic biopsy, histology, and immunohistochemistry (IHC), supported by colonic biopsy PCR and plasma PCR.*

Cytomegalovirus screening is required for corticosteroid resistant ASUC.<sup>195, 196</sup> Subclinical CMV reactivation is common in IBD with or without immunosuppression<sup>197–199</sup> and usually self-limiting.<sup>198, 200–202</sup> Acute exacerbation due to CMV colitis is associated with higher colectomy rates.<sup>196, 203–205</sup> CMV colitis is diagnosed on histology by cytomegalic cells with large eosinophilic ‘owl’s eye’ inclusions, with a sensitivity of 10–87% and specificity of 92–100%.<sup>206</sup> IHC improves the sensitivity to 78–93% and is the gold standard.<sup>206, 207</sup> Colonic tissue CMV DNA PCR can improve diagnostic sensitivity but the significance of a positive PCR in the absence of other histological features of CMV infection remains unclear. Only two of eight studies on CMV infection in IBD demonstrated concordance between histology/IHC and tissue PCR.<sup>206</sup> Whole blood leucocyte DNA PCR has diagnostic sensitivity of 65–100% and specificity of 40–92%.<sup>206, 208, 209</sup> Colonic or blood CMV DNA may confirm CMV colitis but are not a prerequisite. Further research on the role of stool PCR is required.

#### Statement 32: Opportunistic infections – CMV treatment

*Treatment of CMV colitis is intravenous ganciclovir 5 mg/kg twice daily for 3–5 days followed by oral valganciclovir 900 mg twice daily for 2–3 weeks. Consult with an infectious disease physician early. Temporary*

*withdrawal of immunosuppressive therapy should be considered.*

Ganciclovir is the therapy of choice for CMV colitis.<sup>184, 210</sup> Intravenous therapy is given for 3–5 days and switched to oral valganciclovir 900 mg twice a day for a total duration of 2–3 weeks, depending on the clinical course.<sup>184, 210</sup> Prompt anti-viral treatment and temporary discontinuation of immunomodulators is associated with clinical improvement and decreased mortality.<sup>197, 205, 211, 212</sup>

#### Statements that did not reach consensus

The following statements did not reach consensus at the final round of voting.

**Statement 10: Venous thromboembolism prophylaxis – out-patient.** *Consider continuing VTE prophylaxis for several days following discharge from hospital.*

The relative risk of VTE is higher in IBD patients during non-hospitalised than hospitalised periods.<sup>46</sup> UC patients who undergo colectomy continue to experience VTE following hospital discharge.<sup>213</sup> A meta-analysis, however, concluded that routine post-discharge VTE prophylaxis increased major bleeding complications without significantly preventing thromboembolic complications.<sup>214</sup> Further research on the value of post-discharge VTE prophylaxis in IBD and risk stratification strategies is required.

**Statement 21: Infliximab trough level.** *The maintenance dose of infliximab should be guided by the infliximab trough level.*

The use of infliximab trough level to guide the maintenance dose regimen of infliximab has not been definitively established in the management of UC. Patients with detectable serum infliximab concentration had higher rates of clinical remission, endoscopic improvement, and endoscopic remission, and a lower rate of colectomy than those with undetectable trough serum infliximab concentration.<sup>88</sup> An increase in infliximab trough level was associated with mucosal healing in both Crohn's disease and UC.<sup>215</sup> An increase in trough level after dose optimisation was associated with restoration of response.<sup>216</sup> However, contradicting data showed clinical improvement after dose intensification is irrespective of infliximab serum concentration.<sup>217</sup> Currently, 1.4 µg/mL is the target infliximab trough concentration.<sup>75, 88, 218</sup> The use of trough infliximab level in guiding the maintenance dose and the level itself require further validation.

**Statement 33: Opportunistic infections – EBV virus.** *Avoid thiopurines in EBV seronegative-status adolescents and young adults. Use alternative immunomodulators.*

*Epstein–Barr Virus*-associated complications in the setting of immunosuppressive therapies include (i) primary EBV infection in EBV-naïve patients on immunosuppressants resulting in the very rare syndrome of haemophagocytic lymphohistiocytosis (HLH) and (ii) immunomodulator use in-patients with previous EBV infection resulting in the development of lymphoma or post-transplant lymphoproliferative disorder.<sup>219, 220</sup>

Haemophagocytic lymphohistiocytosis is a rare but commonly fatal condition with at least 25 documented cases reported in IBD patients with eight of these positive for EBV.<sup>219</sup> 80% of paediatric HLH are EBV-related with all associated with thiopurine exposure.<sup>221</sup> Apart from primary EBV infection in the setting of immunosuppression, HLH can also be secondary to other infections including CMV, *Mycobacterium tuberculosis*, and *histoplasmosis*, and following the use of a non-thiopurine immunomodulator.<sup>219</sup>

Lymphoproliferative disorders are associated with positive EBV serology and exposure to thiopurines.<sup>220, 222, 223</sup> EBV-positive lymphoma may have a propensity for the intestinal tract.<sup>184, 222</sup> However, the overall absolute risk remains small, estimated to result in one additional lymphoma for every 300–1400 years of thiopurine treatment.<sup>184</sup> On risk-benefit modelling, it has been suggested that a 10-fold risk is necessary for the overall effect of thiopurines in IBD to be detrimental.<sup>223</sup> There are conflicting data on whether older or younger age is a risk factor.<sup>220, 222–224</sup> Based on these data, there is insufficient evidence to recommend EBV seronegative adolescents and young adults to avoid thiopurines.

## CONCLUSIONS

The management of ASUC has evolved with new treatment options becoming available while retaining long established treatment paradigms. These consensus statements cover all aspects of the management of ASUC and, in contrast to the Toronto Consensus Statements,<sup>4</sup> we also include recommendations on multidisciplinary management, pharmacy-related drug dispensing issues, pregnancy, opportunistic infections, dose escalation of infliximab and use drug monitoring (TDM), rescue therapy in the setting of thiopurine failure, the management of ASUC patients after induction of remission, and use of thiopurines in EBV-naïve young patients. There was moderately strong correlation between the level of evidence and the grade of recommendation (correlation

coefficient 0.64,  $P < 0.001$ ) of these consensus statements.

We recommend that a MDT manage ASUC in a specialised centre. Hospitals without expertise should consult specialist centres at an early stage of hospitalisation to define threshold criteria for transfer. Intravenous corticosteroid should be commenced promptly and tests performed to exclude infectious colitis. All medical therapies should be available in hospital pharmacies to ensure prompt dispensing. Severity assessment on admission and again on day 3 is essential with early escalation to rescue therapy for corticosteroid-refractory cases. Infliximab is the preferred rescue therapy in patients who have failed thiopurine previously. A modified front-loaded infliximab induction regimen could be considered in ASUC with protein-losing enteropathy. Patients not requiring colectomy should be given maintenance therapy. If infliximab is required for maintenance therapy, combination with a thiopurine is recommended. *PJP* prophylaxis should be given to patients on triple immunosuppressive treatment. Finally, the management of pregnant patients is no different to non-pregnant patients. Consensus was not achieved on VTE prophylaxis following hospital discharge, use of infliximab trough levels to guide maintenance dose regimen, and thiopurine avoidance in EBV-naïve young patients.

## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

**Data S1.** Summary table of statements.

**Table S1.** NHMRC evidence hierarchy: designations of 'levels of evidence' according to type of research question.

**Table S2.** Definition of NHMRC grades of recommendations.

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