Consensus Statements on the Management of Acute Severe Ulcerative Colitis (ASUC)

November 2017

Extract from "Review article: acute severe ulcerative colitis - evidence-based consensus statements.", JH Chen et al, Wiley AP&T, 2016 (full article available on www.gesa.org.au)

Acute severe ulcerative colitis (ASUC) is a potentially life-threatening complication of ulcerative colitis (UC). 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. 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 harmonize management. Few guidelines have focused specifically on ASUC. The Toronto Consensus Statements cover hospitalised management without discussing maintenance therapy, pregnancy-related issues, opportunistic infections or multidisciplinary management. The evidence based consensus statements on optimal ASUC management that follow were developed by a multi-disciplinary group of clinicians using the Delphi process. They provide up-to-date best practice recommendations that improve and harmonise management as well as provide auditable quality assessments. The Australian National Health and Medical Research Council (NHMRC) grades of recommendation and levels of evidence were applied.

Summary Table of Statements

Statement 1: Definition
The diagnosis of ASUC is defined by the modified Truelove and Witts criteria as ≥6 bloody stools per day plus at least one of the following:
i) Temperature >37.8 degree Celsius;
ii) Pulse rate >90 beats per minute
iii) Haemoglobin <105g/L
iv) Erythrocyte sedimentation rate >30mm/h
Hospital admission under a gastroenterologist is strongly recommended. Confirmation of the diagnosis requires exclusion of infective colitis.
EL: III-2 **RG:** B **LA:** **A: 47% B: 53%** C: 0% D: 0% E: 0%

Statement 2: Aim
The immediate treatment aim in ASUC is to achieve clinical remission. The long term goal is to achieve clinical, endoscopic, and histological remission.
EL: III-3 **RG:** B **LA:** **A: 63% B: 37%** C: 0% D: 0% E: 0%

Statement 3: First presentation investigations - laboratory
On presentation with ASUC, tests required include FBC, EUC, CRP, ESR, LFT, Mg^{2+}, lipid profile, abdominal x-ray, stool microscopy/culture/ sensitivities and Clostridium difficile testing.
In addition, assessment for TB risk, hepatitis B serology (HBsAg, HBsAb, and HBcAb), TPMT testing, CMV IgG and IgM, EBV IgG and IgM, serology for HIV and VZV, and Streptococcus pneumonia and influenza vaccination status should be considered.
EL: III-2 **RG:** B **LA:** **A: 32% B: 68%** C: 0% D: 0% E: 0%

Statement 4: First presentation investigations – endoscopy
A flexible sigmoidoscopy without any preparation should be performed, preferably within 24 hours of admission. Biopsies collected should be tested for CMV colitis.
EL: III-2 **RG:** B **LA:** **A: 74% B: 26%** C: 0% D: 0% E: 0%

Statement 5: Clinical pathway
The management of patients with ASUC, where available, should be guided by a clinical pathway to aid treatment, identify variance, and to audit outcomes. **EL:** IV **RG:** C **LA:** **A: 68% B: 21%** C: **11%** D: 0% E: 0%

Statement 6: Ongoing review
Ongoing assessment should include at least once daily review of haemodynamic status and abdominal examination by a medical officer, stool charts (frequency, consistency, presence of blood and estimated stool volume), FBC, EUC, CRP, albumin, and serial abdominal x-ray.
EL: III-2 **RG:** B **LA:** **A: 63% B: 37%** C: 0% D: 0% E: 0%

Statement 7: Management team
Patients with ASUC are best managed by a multidisciplinary team comprising a gastroenterologist, colorectal surgeon, gastrointestinal nursing staff, dietitian, pharmacist, and stomal therapist on a specialised gastrointestinal ward. If the above are not available, discussion with a specialist centre should be considered.
EL: IV **RG:** C **LA:** **A: 55% B: 45%** C: 0% D: 0% E: 0%

Statement 8: Nutrition
The nutritional status of the patient should be assessed by a dietitian. 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.
EL: II **RG:** B **LA:** **A: 80% B: 20%** C: 0% D: 0% E: 0%

Statement 9: Venous thromboembolism – inpatient
Venous thromboembolism prophylaxis should be administered to all hospitalised patients with ASUC, using subcutaneous heparin or low molecular weight heparin and graduated compression stockings, unless contraindicated. **EL:** III-2 **RG:** A **LA:** **A: 84% B: 16%** C: 0% D: 0% E: 0%

Statement 10: Venous thromboembolism – outpatient
Continuation of VTE prophylaxis for several days following discharge from hospital should be considered.
EL: Nil **RG:** **Not recommended** **LA:** A: 0% B: 5% C: 5% **D: 58% E: 32%**

Statement 11: Corticosteroids
Intravenous hydrocortisone 100mg 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.
EL: III-2 **RG:** A **LA:** **A: 58% B: 37%** C: 5% D: 0% E: 0%

Statement 12: Indicators for rescue therapy
A. Failure to achieve an adequate response to IV corticosteroids is defined by:
i) on day 3, >8 stools per day or 3-8 stools per day with a CRP>45mg/L;
ii) on day 7, >3 stools per day or visible blood; or
iii) a PUCAI >65 (in patients <18 years old) on day 5
An emphasis should be placed on formal assessment of severity at day 3 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.
EL: III-2 (A); III-3(B) **RG:** B **LA:** **A: 42% B: 58%** C: 0% D: 0% E: 0%

Statement 13: Optios of rescue therapy
Rescue therapies include infliximab, ciclosporin, or surgery, with the choice depending on the judgment of the treatment team, drug availability, and patient factors such as preference and prior thiopurine failure.
EL: II **RG:** A **LA:** **A: 53% B: 47%** C: 0% D: 0% E: 0%

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 TGN for >3 months) should preferably not receive ciclosporin. An alternative rescue therapy such as infliximab is recommended.
EL: III-3 **RG:** B **LA:** **A: 37% B: 63%** C: 0% D: 0% E: 0%

Statement 15: Rescue therapy – other biologics
There are currently no data on the efficacy and safety of adalimumab, vedolizumab, and golimumab in ASUC.
EL: Nil **RG:** B **LA:** **A: 90% B: 5%** C: 5% D: 0% E: 0%

Statement 16: Surgical rescue therapy
Following failure of one rescue medical treatment, surgery is recommended. Sequential rescue medical therapy risks sepsis and a delay in surgery.
EL: III-3 **RG:** B **LA:** **A: 37% B: 63%** C: 0% D: 0% E: 0%

Statement 17: Efficacy of rescue therapy
The efficacy of the rescue therapy should be assessed daily. In the event of deterioration or failure to improve patients should proceed to surgery.
EL: III-3 **RG:** B **LA:** **A: 89% B: 11%** C: 0% D: 0% E: 0%

Statement 18: Failure of rescue therapy
Colectomy in ASUC should be performed by a surgeon experienced in emergency colectomy, who will discuss with the patient regarding surgical options, outcomes and possible complications. Patients should be reviewed by a stomal therapist where available.
EL: Nil **RG:** Expert Opinion **LA:** **A: 89% B: 11%** C: 0% D: 0% E: 0%

Statement 19: Rescue therapy – Infliximab dosage
The product information of infliximab recommends infusions at week 0, 2, and 6 at a dose of 5mg/kg. The value of shorter dosing intervals and/ or higher doses of infliximab remains to be determined.
EL: IV **RG:** B **LA:** **A: 68% B: 26%** C: 6% D: 0% E: 0%

Statement 20: Combination of infliximab and thiopurine
If infliximab is used for maintenance therapy, combination of thiopurine and infliximab is more efficacious than infliximab alone.
EL: III-1 **RG:** B **LA:** **A: 68% B: 32%** C: 0% D: 0% E: 0%

Statement 21: Infliximab trough level
The maintenance dose of infliximab should be guided by the trough infliximab level.
EL: III-2 **RG:** **Not Recommended** **LA:** A: 0% B: 0% C: 20% **D: 48% E: 32%**

Statement 22: Ciclosporin as rescue therapy
Ciclosporin should be administered as a continuous IV infusion at the initial dose of 2 mg/kg/day adjusted to blood levels (target 150-250ng/ ml). Thereafter dosing is converted to oral ciclosporin at a dose of 4mg/ kg/daily, and continued for approximately three months. The target trough level for oral ciclosporin is 150-250 ng/ml.
EL: II **RG:** A **LA:** **A: 52% B: 48%** C: 0% D: 0% E: 0%

Statement 23: Pharmacy
All rescue medical therapies should be readily available into hospital pharmacies that manage ASUC, and have a mechanism for prompt dispensing.
EL: Nil **RG:** Expert Opinion **LA:** **A: 100% B: 0%** C: 0% D: 0% E: 0%

Statement 24: Pharmacy
There is no evidence of occupational health and safety risks relating to occupational exposure to anti-TNF agents. Standard precautions are sufficient for drug preparation and administration.
EL: IV **RG:** B **LA:** **A: 84% B: 16%** C: 0% D: 0% E: 0%

Statement 25: Maintenance therapy - thiopurines
Patients who respond to rescue medical therapy but have not yet failed thiopurine maintenance therapy (such as thiopurine-naïve patients) should be commenced on a thiopurine as a maintenance medication.
EL: I **RG:** A **LA:** **A: 100% B: 0%** C: 0% D: 0% E: 0%

Statement 26: Maintenance therapy - thiopurines
TPMT genotype/ phenotype can guide the starting dose if available. However, thiopurine therapy can be commenced without TPMT results. FBC and LFTs should be measured weekly for 4 weeks after commencement of thiopurine, then fortnightly for next 4 weeks, and then 3-monthly.
EL: III-3 **RG:** B **LA:** **A: 48% B: 48%** C: 4% D: 0% E: 0%

Statement 27: Maintenance therapy – thiopurines metabolites
Metabolite levels may be used to determine the management in patients with failure of response, toxicity or to assess medication adherence.
EL: III-2 **RG:** B **LA:** **A: 84% B: 16%** C: 0% D: 0% E: 0%

Statement 28: Maintenance therapy – thiopurines with allopurinol
Thiopurine shunters (those with inadequate TGN levels and 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 third/ quarter of original dose in conjunction with close monitoring of FBC and LFT, as outlined in Statement 14b, and thiopurine metabolites.
EL: III-3 **RG:** B **LA:** **A: 74% B: 21%** C: 5% D: 0% E: 0%

Statement 29: Pregnancy
The management of ASUC in pregnant patients should be no different from the management of the non-pregnant patients. Corticosteroids, ciclosporin, thiopurines, infliximab, and colectomy should be used as needed in all stages of pregnant and during breast feeding.
EL: III-2 to IV **RG:** B **LA:** **A: 89% B: 11%** C: 0% D: 0% E: 0%

Statement 30: Opportunistic infections – pneumocystis jiroveci pneumonia (PJP)
Patients on corticosteroids, thiopurine, and either a calcineurin inhibitor or infliximab require prophylaxis against PJP using cotrimoxazole 800mg/160mg three times per week. Dapsone 100mg daily or atovaquone 1500mg daily are options for patients with sulphur allergy.
EL: III-2 **RG:** A **LA:** **A: 89% B: 11%** C: 0% D: 0% E: 0%

Statement 31: Opportunistic infections – Cytomegalovirus (CMV) diagnosis
CMV colitis should be considered in all patients with ASUC . The diagnosis of CMV colitis should be made on the basis of colonic biopsy, histology, and immunohistochemistry. Additional supportive information is provided by colonic biopsy PCR and plasma PCR.
EL: III-2 **RG:** B **LA:** **A: 100% B: 0%** C: 0% D: 0% E: 0%

Statement 32: Opportunistic infections – CMV treatment
Treatment of CMV colitis is intravenous ganciclovir 5mg/kg twice daily for 3-5 days followed by oral valganciclovir 900mg PO twice daily for 2-3 weeks. Early infectious disease physician consultation is recommended. Temporary withdrawal of immunosuppressive therapy should be considered on a case-by-case basis.
EL: III-3 **RG:** B **LA:** **A: 28% B: 72%** C: 0% D: 0% E: 0%

Statement 33: Opportunistic infections – EBV
Seronegative-status adolescents and young adults should avoid thiopurines and use alternative immunomodulators.
EL: Nil **RG:** **Not Recommended** **LA:** A: 0% B: 0% C: 39% **D: 44% E: 17%**

Abbreviations:

ASUC	Acute severe ulcerative colitis	EUC	Electrolyte / urea / creatinine	LA	Level of agreement	RG	Grade of recommendation
CMV	Cytomegalovirus	FBC	Full blood count	LFT	Liver function test	TB	Tuberculosis
CRP	C-reactive protein	HBcAb	Hepatitis B core antibody	MMP	Methylmercaptopurine	TGN	Thioguanine nucleotide
EBV	Epstein-Barr virus	HBsAb	Hepatitis B surface antibody	PCR	Polymerase chain reaction	TMPT	Thiopurine methyltransferase
EL	Level of evidence	HBsAg	Hepatitis B surface antigen	PUCAI	Paediatric ulcerative colitis activity index	VTE	Venous thromboembolism
ESR	Erythrocyte sedimentation rate	HIV	Human immunodeficiency virus			VZV	Varicella zoster virus

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Wall Chart Supplement

Table 1: Evidence hierarchy: designations of 'levels of evidence' according to type of research question

Level	Intervention[1]	Diagnosis accuracy[2]	Prognosis	Aetiology[3]	Screening intervention
I[4]	A systematic review of level II studies	A systematic review of level II studies	Systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with an independent, blinded comparison with a valid reference standard,[5] among consecutive persons with a defined clinical presentation[6]	A prospective cohort study[7]	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternative allocation or some other method)	A study of test accuracy with an independent, blinded comparison with a valid reference standard,[5] among non-consecutive persons with a defined clinical presentation[6]	All or none[8]	All or none[8]	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: • Non-randomised experimental trial[9] • Cohort study • Case-control study • Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: • Non-randomised experimental trial • Cohort study • Case-control study
III-3	A comparative study without concurrent controls: • Historical control study • Two or more single arm study 10 • Interrupted time series without a parallel control group	Diagnostic case-control study[5]	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: • Historical control study • Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study or diagnostic yield (no reference standard)[11]	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

Table 2: Definition of NHMRC grades of recommendations

Grades of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provide some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Reference: NHMRC additional levels of evidence and grades for recommendations for developers of guidelines
https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf

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