European Society of COLOPROCTOLOGY

ESCP

2019 ESCP audit

STUDY PROTOCOL

Management of Acute Severe Ulcerative Colitis (MASC)

Study period: 1st February 2019 – 31st March 2020

Protocol version 4.0 (10th May 2019)

Key dates:	
3rd January 2019	**Protocol V2.0 published**
1st February 2019- **1st July 2019**	**Patients inclusion window starts** ***Sites should start including at least 6 months of consecutive data for patients hospitalized for acute severe ulcerative colitis within this study window.*** ***Sites should follow up each patient for 90 days.***
1st January 2020	**Last day to include new patients hospitalized for ASUC**
31st March 2020	**Last day of patient follow up (90 days for patients hospitalized on 1st January 2020).**
1st May 2020	**REDCap database locked** ***This is the deadline for data submission***

MASC Study Steering and Management Committee

COLORECTAL SURGEONS

Matteo Frasson [Coordinator](Spain) (dr.frasson.matteo@gmail.com, Twitter: @frasson_matt)
Oded Zmora (Israel), Thomas Pinkney (UK), Gaetano Gallo (Italy), Francesco Pata (Italy), Gianluca Pellino (Spain), Christianne Buskens (Netherlands)

GASTROENTEROLOGISTS

Javier Gisbert (Spain), Krisztina Gecse (Netherlands), Matthew Brookes (UK), Pilar Nos (Spain), Gionata Fiorino (Italy), Iago Rodríguez-Lago (Spain)

PATIENT REPRESENTATIVES

Azmina Verjee (UK), Salvatore Leone (Italy)

ESCP Cohort Studies Committee

Matteo Frasson [MASC Coordinator] (Spain), Thomas Pinkney [Chair] (UK), Aneel Bhangu (UK), Nick Battersby (UK), Nicolas Buchs (Switzerland), Christianne Buskens (Netherlands), Sanjay Chaudhri (UK), Stefan Clermonts (Netherlands), Alaa El-Hussuna (Denmark), Gaetano Gallo (Italy), James Glasbey (UK), Michael Kelly (Ireland), Laura Magill (UK), Ana Maria Minaya Bravo (Spain), Dion Morton (UK), Dmitri Nepogodiev (UK), Peter Neary (Ireland), Ionut Negoi (Romania), Francesco Pata (Italy), Tomas Poskus (Lithuania), Luis Sanchez-Guillen (Spain), Baljit Singh (UK), Emre Sivrikov (Turkey), Oded Zmora (Israel)

Rita Perry, ESCP Cohort Study Data Manager **(Email: escp@contacts.bham.ac.uk)**

ESCP Research Committee

Charles Knowles (UK) [Chair], Tom Pinkney (UK) [Assistant Chair], Erman Aytac (Turkey), Willem Bemelman (Netherlands), Steven Brown (UK), Christianne Buskens (Netherlands), Quentin Denost (France), Audrius Dulskas (Lithuania), Matteo Frasson (Spain), Nikoloas Gouvas (Greece), Søren Laurberg (Denmark), Jérémie H. Lefèvre (France), Dion Morton (UK), Gabriela Möeslein (Germany), Antonio Sampaio Soares (Portugal), Peirpaulo Sileri (Italy), Carolynne Vaizey (UK), Oded Zmora (Israel)

Abstract

Background: Acute severe ulcerative colitis (ASUC), can be a life-threatening condition. Corticosteroids remain the cornerstone of initial medical therapy for ASUC both for inducing clinical remission as well as reducing mortality. However, up to 30-40% of patients show no or only partial response to steroids and will need rescue therapy with cyclosporine or infliximab. When rescue therapy also fails, surgery is necessary in the form of a colectomy. Co-ordinated and patient-specific decision-making is paramount in ASUC because prolonged but ultimately unsuccessful medical treatment could increase the risks of morbidity and mortality in those subsequently undergoing surgery.

Aim: (1) To explore variability in the medical and surgical management of ASUC and the apparent impact on patient-level outcomes. (2) To determine parameters that predict which patients may benefit from medical salvage therapy and who are likely to need colectomy, thereby avoiding unnecessary delay to surgery.

Primary research question: Is it possible to identify early parameters that predict the failure of medical treatment in ASUC?

Outcome measures: mortality (primary), organ salvage, surgical morbidity, length of hospital stay, readmission (secondary)

Methods: The "Management of Acute Severe Ulcerative Colitis (MASC)" study is a multidisciplinary, pan-European, prospective audit of current practices in the management of ASUC, from the European Society of Coloproctology (ESCP) and collaborating organisations. Sites will be asked to pre-register for the audit and obtain appropriate regional or national approvals. Data collection will be undertaken for six consecutive months in each site, starting between 1st February 2019 to 1st July 2019. During the study period all consecutive patients with ASUC will be included and followed-up through 90 days from the date of admission. The audit will be performed using a standardised pre-determined protocol and a secure, anonymised, online database (REDCap). A modular data collection strategy will be used, collecting patients' demographics and clinical data, diagnostic procedures, medical treatment, progress details, operative details (in those progressing to surgery) and endpoint variables.

The protocol for this study has been prepared in accordance with the SPIRIT statement for protocols and the report will be prepared in accordance with guidelines set by the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for observational studies.

Discussion: This multicentre, pan-European audit will be delivered by a collaboration between colorectal surgery and gastroenterology teams (consultants, trainees, students and specialist nurses) following a pre-registered protocol. The data obtained about areas of variability in provision or practice, and how this may impact upon outcomes, will allow international benchmarking to improve the standard of care provided to this patient group, as well as generating hypotheses and inform future randomised research. In the previous three audits promoted by ESCP, performed between 2015 and 2017, 11.368 patients were prospectively recruited, demonstrating the success of such methodology.

1 - Introduction

Acute Severe Ulcerative Colitis

Acute Severe Ulcerative Colitis (ASUC) is a serious, potentially life-threatening condition requiring immediate hospitalization. It is normally diagnosed using the Truelove and Witt's severity index which is a composite measure of stool frequency, rectal bleeding, signs of systemic toxicity (tachycardia, fever, anaemia) and biochemical markers of inflammation[1]. Intravenous corticosteroids remain the first-line treatment for ASUC [2,3]. However other measures, such as fluid and electrolyte replacement, blood transfusion, thromboprophylaxis, nutritional support and exclusion of infections (*Cytomegalovirus, Clostridium difficile* etc), should be considered .Combined clinical, biochemical, radiological and endoscopic criteria are often useful to identify poor responders to first-line treatment and start salvage therapy in a timely fashion. Patients that do not respond to steroids usually need a second-line medical treatment with cyclosporine or biological anti-TNF agents [4, 5].

In case of failure of medical therapy the standard approach is currently to undertake a total or sub-total colectomy with formation of an end-ileostomy and preservation of the rectum/recto-sigmoid colon. Total proctocolectomy with ileal pouch-anal anastomosis (IPAA) is usually deferred until the patient has recovered a better performance and nutritional status and is weaned off medications that may potentially influence post-operative morbidity.

Delayed colectomy surgery is probably associated with an increased risk of post-operative complications and a multidisciplinary management between gastroenterologists and colorectal surgeons is critical to correctly choose the optimal timing of surgery [6]. In order to early identify patients in whom medical treatment will fail, three different clinical scores have been previously proposed (Oxford, Edinburgh and Lindgren), all of them based on small series before the anti-TNF era [7-9].

Despite the frequency of ASUC, there remains uncertainty about many topics regarding optimal medical treatment, use of cyclosporine and biological drugs, parameters to indicate surgery and the best surgical technique, which results in a range of different medical and surgical strategy of treatment between different groups and countries. In addition, patient demographics and disease characteristics may vary between units and countries, making it more difficult to determine which is the best strategy of treatment.

"Snapshot" Collaborative Audits

Multicentre, snapshot cohort studies or audits have the ability to gather large patient numbers in short time periods from many hospitals. They allow exploration of differences in patients, techniques and management across the cohort to identify areas of practice variability that may result in apparent differences in outcome. As such, whilst not providing true evidence of efficacy or the impact of a particular variable, they can be hypothesis-generating and can identify areas warranting further study in randomised controlled trials.

The European Society of Coloproctology has recognised the strengths of this form of observational study, as well as its power in bringing together surgeons and colorectal units across multiple regions or countries for a common research goal, thus strengthening an active network of research participation internationally.

The first snapshot audit promoted by the ESCP focused on right hemicolectomy and ileocecal resection surgery and succeeded in recruiting 3208 patients from 38 countries, five of them were outside Europe. This success continued with the second audit on stoma closure, which recruited 2527 patients from 312 centres in 48 countries. The third snapshot audit, about left, sigmoid and rectal resections, 5641 patients from 49 countries were recruited and a truly global network of contributing clinicians.

Objective

The primary objective of MASC is to explore differences in patients, diagnostic procedures, medical treatment, surgical techniques and outcomes across non-operated and operated patients with ASUC to identify areas of practice variability resulting in apparent differences in outcome warranting further study.

2 - Methods

A) Period of Study

International, prospective audit of consecutive patients hospitalized for ASUC. The audit shall include patients hospitalized (1st day) during the study period (from 1st February 2019 to 1st January 2020). The sites must include patients for at least 6 consecutive months. In order to meet this minimum 6 months criterion, sites must start running the audit by 1st July 2019 (i.e. screening for eligible patients for entry).

Final date for inclusion: The sites can include patients with the first day of hospitalization that occur up to, and including, 1st January 2020.

All patients will be followed for a minimum of 90 days after the first day of hospitalization. Data collection should therefore be completed by 31st March 2020.

As this is an audit, no change to normal patient management is allowed.

B) Audit Questions

Primary

Is it possible to identify early parameters that predict the failure of medical treatment and the necessity of colectomy?

Secondary

-Does the duration of medical therapy relate to post operative morbidity in those who progress to surgery?

- What is the variability in terms of diagnostic procedures, medical treatment, surgical techniques and outcomes across the entire cohort?

- Are existing scores (Oxford, Edinburgh, Lindgren, Mayo) reliable to predict the failure of medical treatment or can they be improved?

C) KEY OUTCOME MEASURES

(1) All patients: mortality, rate of progression to surgery, readmission, rescue therapy success rate, overall length of stay.
(2) Operated patients only - postoperative complications (Clavien-Dindo grade), comprehensive complication index (CCI)

D) Inclusion Criteria

- Adult patients hospitalized for acute ulcerative colitis classified as “severe” according to the Truelove & Witt’s (see appendix 1). The severity of the colitis could be classified as “severe” either at admission or during hospitalization as result of the worsening of a flare previously classified as “mild” or “moderate”.
- UC could have been previously diagnosed or, in the case of first presentation, other causes (infectious, ischemic) should be excluded.
- All management strategies (medical or surgical, including any operative approach) are eligible for inclusion.
- Both patients admitted under the acute medical service or acute surgical service are eligible for inclusion.

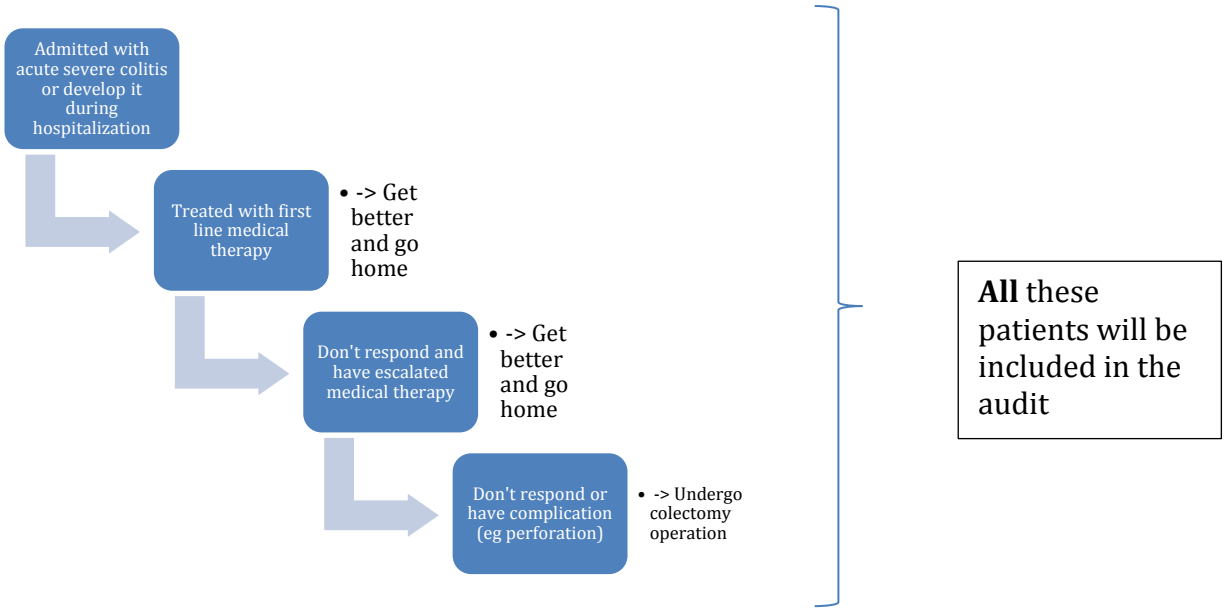
E) Exclusion Criteria

- Patients younger than 16 years old
- Infectious or ischemic colitis in patients without previous diagnosis of UC.

F) Methods for identifying patients

Multidisciplinary involvement and collaboration between gastroenterologist and colorectal surgeons will be fundamental. Multiple methods may be used according to local circumstances/staffing:

1. At the emergency assessment before hospitalization
2. Daily review of patients hospitalized in the gastroenterology and colorectal surgery ward
3. Daily review of emergency theatre lists
4. Review of theatre logbooks



G) Centre eligibility

All hospitals/units treating medically or surgically patients with ASUC are eligible to join this audit. No unit size or case throughput stipulations are made. Countries anywhere in the world can participate in this audit.

All participating centres will be required to register their details with the ESCP cohort study office and will be responsible for their own local approvals process prior to the start of the data collection period.

Centres should ensure before starting that they have appropriate pathways and manpower to include all consecutive eligible patients during the study period and provide >95% completeness of data entry before locking of REDCap database on the 1st May 2020.

H) Patient follow-up

The audit is designed so normal patient follow-up pathways can be utilised to obtain outcomes data. No additional visits or changes to normal follow-up should be made. A minimum 90-day follow-up will be required, considering as day 1 the first day of hospitalization (in patients that develop ASUC when already hospitalized, day 1 will be the day of diagnosis of ASUC).

Local investigators should be proactive in identifying complications and post-operative events (or lack thereof), within the limits of normal follow-up. These may include reviewing the patient notes (paper and electronic) during admission and before discharge to note in-hospital complications, reviewing hospital systems to check for re-attendances or re-admissions, and reviewing post-operative radiology reports, as well as the notes from the in-person outpatient review.

I) Data completion and organisation

This research takes the form of an audit study. Therefore, this is an observational study and no changes to the normal patient pathway should be made. Case report forms (CRFs) have been designed to reflect the normal practice and be completed with minimal extra work from the clinical team. We envisage that hospitals opening for the study will identify a team of 8 members, including one Consultant-level surgeon, one Consultant-level gastroenterologist, plus 6 more local team members including trainee surgeons or gastroenterologists, junior doctors or data administrators who will undertake the organisational and logistical roles as well as co-ordinate data entry. One of the consultant-level investigators will be the official local 'lead' of the study.

CRF A (patient demographics), CRF B (medical management) and CRF D (follow-up information) can be completed by any suitably qualified member of the local team.

We do stipulate the CRF C (surgical data) must be completed by, or in direct conjunction with, a surgeon who was present during the operation itself. It should ideally be completed immediately after surgery, at the same time as the operation notes are written, to ensure data accuracy and completeness.

J) Missing data and retrospective patient entry

The online database has been designed to allow sites to securely access an individual patient's data for all CRFs throughout the study period. This means that any missing or erroneous data can be altered by the local investigators whilst the data collection period is ongoing. In order to maximise data completion and emphasise its importance to collaborators, participating centres with >5% missing data in **mandatory fields** (i.e. less than 95% data completeness) will be excluded from the study.

The study design means that sites may retrospectively identify eligible patients that were missed primarily and for whom contemporaneous patient and operation data was not entered. We are happy for these patients to be entered during the study period providing that CRF C (operative details) is completed by, or in direct conjunction with, a surgeon who was present during the operation itself.

K) Data collection system and information governance

Data will be collected using REDCap electronic data capture tools on the Birmingham Surgical Trials Consortium (BiSTC) REDCap system hosted at the University of Birmingham. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources [10].

Patient name and address will not be recorded on REDCap.

Registered local investigators will have individual password-protected access to their unit's data entered on to REDCap. During the running of the audit, only local data will be visible to investigators; other sites' data will not be accessible.

In order to facilitate entry of follow-up data, investigators will need a way to link REDCap records to patient records. This can be achieved by keeping a password protected spreadsheet containing a look-up table. This should cross-reference the automatically generated REDCap ID number for each patient against their local identifier number. This spreadsheet should never be printed. It is the Local Lead's responsibility to be the custodian of this spreadsheet. A copy of the spreadsheet should be kept maximum for 2 years after data collection is complete.

The Birmingham Surgical Trials Consortium (BiSTC) will provide administrative support for the project and the REDCap system. REDCap was used in the 2016 and 2017 ESCP audits. Many hospitals already use these data collection tools to measure clinical practice and drive improvements in healthcare in multiple disease settings.

Data will be stored securely on encrypted and certified servers for a minimum of five years under the governorship of the European Society of Coloproctology (ESCP). The data may be used for future research although it should be noted that the anonymised nature of the database means individual patients will not be reverse-identifiable in the future.

L) Local approvals

All data collected will measure current practice, with no changes made to normal treatment. As such, this study should be registered as an audit of current practice at each participating centre. It is the responsibility of the local team at each site to ensure that local audit approval (or equivalent national/regional/local approval) is completed for their centre. Participating centres will be asked to confirm that they have gained formal approval at their site. REDCap accounts will not be issued until centres have successfully registered the audit with the appropriate body.

M) Authorship

A maximum of 8 investigators from each individual site will be included as formal co-investigators in this research, and will be PubMed searchable and citable. The output from this research will be published under a single corporate authorship – e.g "ESCP 2019 Audit Collaborating Group" or similar.

An identical process of multicentre audit and publication/authorship has been used in the publication of main study from the 2015 audit: "**The relationship between method of anastomosis and anastomotic failure: an international snapshot audit**" Colorectal Disease 2017 Mar 6. doi: 10.1111/codi.13646

N) Pilot

A two-week pilot across at least five international hospitals will be performed to test the data collection tool and case report form. Adjustments based on these experiences may be made before rolling out the main audit. Data from the pilot will be not be included in the main analysis.

O) Publication of data

Data will be published as a pool from all participating units. Subgroup analyses by disease, technique or outcome variables may be presented, but no hospital-level or surgeon/gastroenterologist-level data will be published whereby an individual unit or clinician could be identified. A breakdown of their own unit's data for benchmarking purposes and local presentation/discussion will be available after the end of the study.

P) Data governance

The ESCP Cohort Studies Committee welcomes the use of the data for further research that benefits patients. Requests can be submitted to the ESCP Cohort Studies Committee. Data sharing is subject to ESCP approval and the appropriate safeguarding as determined by the ESCP. Any future subprojects should also comply with our policy of a single corporate authorship e.g. "ESCP 2019 Audit collaborating group" or similar. However, authors' contributions will be highlighted in accordance with the recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals (commonly referred to as the Vancouver Convention) by the International Committee of Medical Journal Editors (ICMJE).

Q) Financial arrangements

This study is supported by the European Society of Coloproctology. Participating centres will not bear any costs. Similarly, no financial reimbursement will be made to units or investigators for their involvement in the project.

R) Parallel studies

It is permissible for the MASC study to be run alongside parallel projects or studies exploring other aspects of the management of patients with Ulcerative Colitis. Such projects would need to be separately funded and organised to comply with the MASC timelines and data points. These projects might be conducted locally, regionally, nationally or internationally and could, for example, collect more detailed patient-level data such as resource usage information or patient-reported quality of life data if appropriate ethical approvals and informed consent were in place.

In such cases, projects must agree to record all standard data points for the MASC audit to produce a homogenous dataset. Research projects exploring interventions or treatment pathways that have the potential to impact on patient-level outcomes and thus make data non-generalisable would not be possible to contribute data to the MASC study.

S) References

1. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; preliminary report on a therapeutic trial. Br Med J. 1954; 2:375-378.

2. Bewtra M, Newcomb CW, Wu Q et al. Mortality associated with medical therapy versus elective colectomy in ulcerative colitis: a cohort study. Ann Intern Med 2015; 163:262–70.

3. Turner D, Walsh CM, Steinhart AH, Griffiths AM. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. Clin Gastroenterol Hepatol 2007; 5: 103–10.

4. Gisbert JP, Chaparro M. Acute severe ulcerative colitis: state of the art treatment. Best Pract Res Clin Gastroenterol 2018: 32-33: 59-69.

5. Jarnerot G, et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. Gastroenterology 2005; 128: 1805–11.

6. Randall J, Singh B, Warren BF, et al. Delayed surgery for acute severe colitis is associated with increased risk of postoperative complications. Br J Surg. 2010;97:404-9.

7. Lindgren SC, Flood LM, Kilander AF, et al. Early predictors of glucocorticosteroid treatment failure in severe and moderately severe attacks of ulcerative colitis. Eur J Gastroenterol Hepatol. 1998;10:831-6.

8. Travis SP, Farrant JM, Ricketts C, et al. Predicting outcome in severe ulcerative colitis. Gut. 1996;38:905-910.

9. Ho GT, Mowat C, Goddard CJR, et al. Predicting the outcome of severe ulcerative colitis: development of a novel risk score to aid early selection of patients for second-line medical therapy or surgery. Aliment Pharmacol Ther. 2004;19:1079-87.

10. Harris, PA, Taylor, R, Thielke, R, Payne, J, Gonzalez, N, Conde, JG, Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support, J Biomed Inform. 2009 Apr;42(2):377-81.

Appendix 1

Disease activity in UC (Adapted from Truelove&Witts).

Acute severe ulcerative colitis is defined as bloody stool frequency ≥6 per day and at least one of the following: pulse rate >90 bpm, temperature >37.8 °C, hemoglobin <10.5 g/dL, ESR > 30 mm/h or CRP >30 mg/l)

	Mild	Moderate 'in between mild and severe'	Severe
Bloody stools/day	< 4	4 or more *if*	≥ 6 *and*
Pulse	< 90 bpm	≤ 90 bpm	> 90 bpm *or*
Temperature	< 37.5°C	≤ 37.8°C	> 37.8°C *or*
Haemoglobin	> 11.5 g/dl	≥ 10.5 g/dl	< 10.5 g/dl *or*
ESR	< 20 mm/h	≤ 30 mm/h	> 30 mm/h *or*
CRP	Normal	≤ 30 mg/l	> 30 mg/l