Predicting outcome in acute severe colitis – controversies in clinical practice in 2021

Vipin Gupta*[1,4], Waled Mohsen* [1,2], Thomas P Chapman*[1,3], Jack Satsangi[1].

*Co-first authors

[1] Translational Gastroenterology Unit, Nuffield Department of Experimental Medicine, University of Oxford, Oxford, UK

[2] Digestive Diseases Unit, Gold Coast University Hospital, Queensland, Australia

[3] Department of Gastroenterology, Western Sussex Hospitals NHS Foundation Trust, Worthing, UK

[4] Department Of Gastroenterology, University Hospital of Wales, Cardiff and Vale University Health Board, Cardiff, UK

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Authors Contributions

VG: Contributed to the review and synthesis articles. Wrote up the pediatrics, scoring systems, endoscopic assessment, and prediction to response to second line therapy sections. Involved in revision and writing of final manuscript.

WM: Contributed to review and synthesis of articles. Wrote up biomarkers, radiological parameters, scoring systems, novel biomarkers, multi-omic and machine learning sections. Completed tables and figures. Involved in revision and writing of final manuscript.

TC: Contributed to the review and synthesis of articles. Wrote up COVID-19 and ASUC section. Participated in critical revision of final manuscript.

JS: Came up with the concept, design, structure and ideas for the manuscript. Involved in the revision and writing of the final manuscript.

Abstract

Acute severe ulcerative colitis (ASUC) remains a common medical emergency, with 25% of patients with ulcerative colitis experiencing at least one event in their disease course. Despite advances in medical therapy, ASUC continues to be associated with considerable morbidity and mortality, with up to 30% of patients requiring colectomy during initial admission. Our aim was to review the current controversies and recent progress in risk stratification, prediction of outcome, and personalisation of care in ASUC. We re-assess the use of Truelove and Witts' criteria, serum biomarkers and the use of composite clinical indices in current clinical practice. We explore the potential for endoscopic prediction using defined validated indices for accurate and early prognostication, and the need to define outcome. We also consider the impact of the current COVID-19 pandemic. Finally, we discuss the current research agenda including the application of new and emerging biomarkers coupled with multi-omics and the implications in management and optimisation of outcome.

Research priorities for the prediction of outcome in Acute Severe Colitis

Development of an accurate admission score to guide early medical rescue therapy or colectomy

Utility of point-of-care faecal calprotectin, with determination of optimal cut-off values

Role of serum and faecal infliximab levels to both predict outcome and guide accelerated infliximab dosing

Role of novel biomarkers, including serum calprotectin in predicting response to corticosteroids or rescue therapy

Specific predictors of response to ciclosporin and infliximab to allow rationalisation of drug use.

Utility of validated endoscopic scores

Utility of radiological assessment beyond use of plain abdominal X-ray

Introduction

Acute severe ulcerative colitis (ASUC) remains a common medical emergency, with up to 25% of patients with ulcerative colitis experiencing at least one severe attack in their life-time.[1, 2] The condition requires early recognition, accurate risk assessment, and informed, appropriate, and intensive management in order to minimise the risk of complications and ensure the best outcome. Notably, morbidity and mortality remain appreciable in the 21st century, with estimated mortality around 1%, and colectomy rates of up to 30% in the initial admission[3, 4, 5]. The elderly and those with significant co-morbidity are at greatest risk of mortality, and complications [4, 6]. ASUC is also an important marker for subsequent challenging disease course, and overall up to 40% of patients will come to colectomy.[1]

There is, therefore, a clear need to innovate and improve the management of ASUC in key areas, most notably the introduction of second-line therapies in patients unresponsive to corticosteroids. A key issue critical in management is the early identification of patients with severe ulcerative colitis, with delay in decision-making consistently identified as a determinant of morbidity [7]. Truelove and Witts first proposed a classification of ulcerative colitis based on available markers of severity more than 60 years ago. In their landmark publication, they put forward simple bedside criteria to define episodes of acute severe colitis which still remain widely used, but following significant advances in medical therapy their utility in the modern era must be carefully reassessed[3, 8, 9] Indeed the emergence of multiple other prognostic scores, and the potential value of endoscopic assessment, has led to considerable uncertainty over how to most accurately predict outcome in ASUC.

The purpose of this article is to review a number of key areas - the evidence that the Truelove and Witts criteria remain of value in prognostication and identification of patients with ASUC, the utility of individual biomarkers, and of composite clinical indices in clinical practice; and   progress in predicting response to second-line agents used as rescue therapy. We discuss the potential of endoscopic prediction using defined validated indices on admission; and we address the issues inherent in prognostication in paediatric-onset ulcerative colitis. We also consider the unprecedented challenges in ASUC that COVID-19 now presents. Finally, we discuss the current

exciting research agenda including the application of new and emerging biomarkers and imaging modalities, and the implications for management and optimisation of outcome.

Methods:

An electronic search of Pubmed was conducted to identify relevant manuscripts from their inception until August 2020. The search combined the MeSH terms "Acute Severe Colitis", "Ulcerative Colitis" with the sub-headings "biomarkers", "Truelove and Witts", "endoscopy", "radiology", "X-Ray", "computed tomography", "MRI" "paediatric", "Covid-19", "score", "rescue therapy", "multi-omics" and "machine learning". We also reviewed bibliographies of the included studies to identify additional important data. Recent guidelines and topical reviews were also assessed. Only papers published in English were reviewed.

Controversy 1: Are the Truelove and Witts criteria of value when predicting outcome?

Truelove and Witts defined severe colitis as the presence of bloody diarrhoea, with a stool frequency of at least six motions/24 hours together with systemic compromise, evidenced by at least one of four additional criteria: 1) Tachycardia (>90bpm), 2) Temperature >37.8^{o}C, 3) Anaemia (haemoglobin <10.5g/dL), or 4) Elevated ESR (>30mm/hr). In routine modern practice, CRP >30mg/l is substituted for ESR.[8] First proposed in 1955, and of clear utility in identifying patients with severe disease requiring hospital admission and treatment with intravenous corticosteroids, it should be noted that the Truelove and Witts' criteria were not devised to predict outcome. However, it has since been demonstrated that the number of additional criteria met on admission are associated with failure to respond to corticosteroids and risk of colectomy.[1] In a retrospective study of 294 admissions in 196 patients in Oxford, United Kingdom from 1950-2007, the colectomy rate was 8.5% (11/129) if one additional criterion was met, 31% (29/94) if two additional criteria, 48% (29/60) if three additional criteria and 45% (5/11) if four additional criteria. This important finding may be considered intuitive, as the additional Truelove and Witts criteria assess systemic

inflammatory response, and it follows that the biological severity of an episode of acute severe colitis predicts risk of colectomy.[5] Numbers receiving second-line rescue therapy in this study were however relatively small, potentially limiting interpretation for current practice.

Further studies have now addressed the performance of Truelove and Witts criteria in the biologics era. A very recent retrospective study from Oxford of 131 consecutive admissions of 117 patients from 2015-2019, found that the number of additional criteria on admission were strongly associated with both need for second-line rescue therapy, and for colectomy either during the index admission (p=0.037) or in the subsequent 12 months (p=0.033).[10] When compared with a Truelove and Witts score of 1, a score of at least 3 was associated with a relative risk (RR) of rescue therapy of 1.65, RR of 3.86 for colectomy during index admission and RR of 2.98 for colectomy in the subsequent 12 months. In this dataset, the Truelove and Witts criteria outperformed any single biomarker, or endoscopic score. An earlier retrospective study of 89 patients from 2010-2012, also from Oxford, found that the number of additional Truelove and Witts criteria on admission was significantly greater in patients who met any adverse endpoint, defined as need for second-line rescue therapy, colectomy or readmission (number of additional criteria 2 [1–4] versus 1 [1–3]; p = 0.02).[11]

It has however been suggested that the strict application of the Truelove and Witts criteria may risk the undertreatment of a cohort of patients who have active UC without the markers of systemic disturbance that the criteria assess.[12] Indeed data from the UK IBD audit, that analysed UK hospital admissions with active colitis in 2008 and 2010, found that patients who did not meet Truelove and Witts criteria for ASUC still had corticosteroid non-response rates of 21% and colectomy rates of 6.6%. A recent retrospective multi-centre study from Scotland has reported similar findings. The authors performed a subanalysis of 187 patients hospitalized with active ulcerative colitis where Truelove and Witts score could be calculated, with 68 patients identified by Truelove and Witts as non-severe, although all received intravenous corticosteroids. Of these 68 classed as non-severe, only 12 (17.7%) did not respond to intravenous corticosteroids.[12]

In summary, the Truelove and Witts criteria remain predictive of outcome in acute severe colitis in the modern era. However, they should not be used as the sole means of assessing requirement for hospitalisation and corticosteroids, as this risks undertreating an important subset of patients.

Controversy 2: What is the accuracy of individual biomarkers in predicting outcome?

A key issue in the field remains the extent to which the use of biomarkers improves prognostic or predictive accuracy. The most validated individual biochemical parameters when predicting response in acute severe colitis are albumin and CRP. Many other biochemical parameters have been assessed in studies to predict response in acute severe colitis and are listed in Table 1.

ESR/CRP

While ESR is one of the original Truelove and Witts criteria, the test is not widely used as this has been superseded by CRP (C-reactive protein) in most centres [3]. The evidence for the role of ESR in predicting outcome in ASUC is mixed. In a prospective study of 67 patients from Italy, and a prospective study by Myers et al, an elevated ESR at day 1 of steroid treatment was predictive for colectomy [13, 14]. However, two prospective studies, one in a paediatric cohort, demonstrated that elevated ESR is not predictive for colectomy [15, 16]

C-reactive protein (CRP) is an acute phase reactant, synthesised in the liver in acute inflammation and largely stimulated by pro-inflammatory cytokines, notably IL-6 [17]. There have been several prospective studies which demonstrate that CRP elevation at day 3 of IV steroid treatment is an independent predictor of colectomy and/or medical rescue treatment in patients with ASUC. In all but two studies, there is a trend towards a higher risk of colectomy in those with a higher CRP [18, 19] (Table 1). Further, CRP has been shown to be the key biochemical marker in two studies. [20, 21]. In a prospective study of 49 patients from Oxford, the combination of 3-8 bowel motions per day and CRP >45 mg/dl at day 3 of intravenous corticosteroid treatment was predictive of colectomy in 85% of patients (p<0.00625 corrected for multiple comparisons) [20]. The second study, also from the 1990s, was a retrospective analysis from Sweden of 97 patients. This found that CRP $\geq$25 mg/dl on day three of intravenous corticosteroid treatment was an independent predictor of steroid failure [21]. There is additional supportive evidence in the paediatric cohort. In the prospective Outcome of Steroid Therapy in Colitis Individuals (OSCI) study, which evaluated short-term corticosteroid response rates in 128 children hospitalised with acute severe colitis, one of the

significant predictors of colectomy at day 3 of steroid treatment was CRP (OR 1.3, 95% CI 1.1 to 1.6) [22].

The specific utility of CRP in predicting outcome at initiation of rescue therapy remains to be determined. In a recent multicentre retrospective Australian study of 54 patients with ASUC, CRP value at start of rescue treatment with infliximab was not predictive of colectomy [23].

In conclusion, CRP is now clearly superior to ESR, and has been demonstrated to be a robust biomarker for predicting non-response to corticosteroids. However, the role of CRP in predicting response to rescue therapy requires clarification.

Albumin

As albumin synthesis is suppressed by pro-inflammatory cytokines, serum albumin typically falls with severe colitis. This has led to interest in the role of albumin as a predictive biomarker in ASUC. Several retrospective studies have suggested that low albumin is associated with a greater risk of colectomy in ASUC. Seo et al found that mean albumin was significantly reduced in patients with moderate to severe ulcerative colitis who progressed to colectomy (3.2 mg/dl ± 0.7) when compared to patients who could be managed with medical therapy (3.7 ±0.6) ($P < 0.001$)[24] Ho et al reported that hypoalbuminaemia at day 1 of steroid treatment was associated with non-response to medical therapy and colectomy during the acute admission, leading to the development of the Ho index.[25] A very recent study has again suggested the potential utility of day 1 albumin in a composite score, The ACE (Albumin, CRP and Endoscopy) Index.[12] Both of these scoring indices are discussed in more detail later.

Hypoalbuminaemia may also predict non-response to rescue therapy. Importantly, lower serum albumin levels are associated with increased infliximab clearance and reduced drug half-life in UC.[26, 27] This may in part reflect a higher inflammatory burden and target antigen load leading to enhanced degradation through the reticuloendothelial system, with higher CRP levels also associated with increased infliximab clearance.[26, 27] Hypoalbuminaemia may also result from a protein losing enteropathy with severe colonic mucosal inflammation. Indeed, there is evidence of

increased faecal shedding of infliximab in those with lower serum albumin levels.[28] In an observational study, high faecal levels of infliximab in the days following first infliximab infusion were associated with early primary non-response in moderate to severe UC, although there was no correlation between faecal and serum infliximab levels.[28] A retrospective study of just 39 patients suggested that hypoalbuminaemia on both admission and day 3 of intravenous corticosteroids predicted urgent colectomy following non-response to infliximab.[29]

A separate retrospective study suggested that albumin as part of the Ho index predicted colectomy within 3 months following non-response to ciclosporin.[30] Nevertheless, multivariate analysis in three prospective case series have not identified albumin on admission as an independent marker for colectomy [13, 16, 20](Table 1). Further, in a multicentre retrospective study of 54 patients with ASUC, albumin was not predictive of colectomy when measured on admission, at induction with infliximab, or three days after rescue infliximab was given [23].

In summary, while data suggests albumin shows promise as a biomarker for predicting colectomy and rescue therapy in ASUC, the evidence underpinning its utility is not as strong as for CRP.

Faecal Calprotectin

Calprotectin is a neutrophil derived protein, with faecal levels shed from inflamed intestinal mucosa correlating with severity of intestinal inflammation. This protein has become a focus of intense clinical as well as research interest. Recent data demonstrate that faecal calprotectin (FC) correlates with endoscopic activity in ulcerative colitis, and may predict histological healing [31]. In 109 patients with UC who presented for colonoscopy, FC correlated more closely than CRP or clinical activity index with endoscopic disease activity (Spearman's rank correlation coefficient r =0.834) [32]. Multiple studies have also suggested the utility of FC in predicting colectomy in ASUC. In a prospective cohort of 90 patients, FC was significantly higher in those requiring a colectomy (1,200.0mcg/g vs. 887.0; P=0.04) [33]. There was a trend towards significance when comparing corticosteroid non-responders/responders (1100.0mcg/g vs. 863.5; p=0.08) and infliximab non-responders/responders (1795.0 vs. 920.5; p=0.06). Receiver-operator characteristic (ROC) analysis found a cut-off of 1922.5mcg/g had a likelihood ratio of 9.23 to predict colectomy during initial

admission, with specificity of 97.4% and sensitivity of 24.0% (p=0.04). The ability of FC to predict subsequent colectomy was also tested, with 87% of patients with FC above the same cut-off of 1922.5mcg/g requiring colectomy over a median follow-up of 1.1 years.

A prospective study of 49 patients with ASUC further validated FC as a prognostic biomarker. FC levels were significantly higher on both admission and on day 3 in steroid non-responders. In this cohort, day 3 FC >1000mcg/g was an independent early predictor of failure of corticosteroid therapy.[19]. Data supporting the prognostic role of FC in children with ASUC has also been reported in a prospective study. (27)

The utility of FC for predicting colectomy following infliximab rescue therapy was assessed prospectively in an Australian cohort. Serial FC measurement, analysed using a concentration-time graph to derive area under curve calculations for FC values days 1-3 and 4-7 post infliximab infusion was a more discriminative predictor of post infliximab outcomes than similar analysis of serum CRP or serum albumin [34].

Overall, FC remains potentially a biomarker of prognostic value in the setting of ASUC, if the practical issues inherent in testing are addressed. These have been usefully addressed in recent studies [19, 35]. In the context of ASUC, delay in receiving results (up to a few weeks in some centres) will need be addressed to maintain the clinical utility of FC in the acute setting – the development of point-of-care assays has made this realistic as an issue for detailed exploration. It is also evident that the optimal cut-off level for FC in predicting outcome in ASUC requires clarification and should be a topic of further research if this test is to guide treatment decisions.

Radiological parameters as biomarkers

A plain abdominal x-ray (AXR) is widely considered to be the standard of care in admissions with ASUC and can be almost universally offered. Established prognostic criteria in ASUC include the presence of colonic dilatation greater than 5.5 cm or mucosal islands on AXR; both are associated with a 75 % risk of colectomy [36]. The presence of an ileus (indicated by three or more small bowel loops of gas) was associated with colectomy risk of 73% in a

retrospective study [37], and 50% in a prospective study [20]. Colonic dilatation is an influential component in the Ho score (25).

There is perhaps surprisingly limited data on the role of computed tomography (CT) in UC. A sensitivity of 79% and specificity of 82% for predicting moderate to severe UC has been reported for CT enterography in a trial of 46 patients, when compared to colonoscopy.[38] However, no studies have assessed the role of CT in predicting outcome in ASUC, and at present it is typically used in the acute setting to exclude complications such as perforation, or if there is diagnostic uncertainty.[39]

Magnetic resonance imaging (MRI) has emerged as an alternative imaging modality in UC. Sensitivities of up to 88%, and specificity of 100% have been reported for active colonic inflammation, with water enema preparation improving accuracy, when compared with colonoscopy as the reference standard.[39, 40] T2 Weighted MRI total colonic inflammation score (TCIS) was trialed in 21 patients with ASUC in a UK center. Patients underwent MRI at admission and after 5 days of treatment. In this cohort, TCIS correlated with CRP and stool frequency. Admission TCIS but not stool frequency or CRP correlated with length of patient stay [41]. While admission TCIS was higher in the three patients requiring colectomy, this did not reach statistical significance. Although MRI therefore shows promise, it is a highly technical examination which requires a standardized technique and waiting times are typically significantly longer, which currently precludes more extensive use.

Figure 1: Plain abdominal radiograph showing abnormal colonic dilation (double headed white arrow), loss of normal haustration, and thumbprinting in ASUC (left image) and MRI abdomen showing oedematous wall thickening loss of haustration in sigmoid and descending colon (right image)

There is accumulating evidence validating intestinal ultrasound (US) as a cost effective, radiation sparing, point of care radiological tool for small bowel and colonic assessment.[42] A skilled operator can provide adequate visualisation of the majority of the colon, although the transverse colon is often challenging due to variable anatomy and position, and rectal views may be limited. Although the majority of research relates to Crohn's disease, in UC a sensitivity of 90% and specificity of 96% for the diagnosis of colonic inflammation has been reported on a per-patient analysis, although sensitivity is significantly lower on a per-segment analysis.[42] However, to date there are no

predictive studies which correlate intestinal ultrasound findings with risk of colectomy and rescue therapy in patients with ASUC.

In summary, plain abdominal X-ray remains the only modality shown to have predictive value in ASUC. Although research is ongoing to determine the potential utility of other imaging techniques, AXR holds significant advantages including low cost and ready availability, with no requirement for technical expertise or bowel preparation.

Table 1: Different parameters used in studies when predicting colectomy in acute severe ulcerative colitis

Controversy 3: Which simple scoring system is the most accurate in predicting outcome in severe colitis?

Combining clinical and laboratory data has proven to be useful when developing a predictive index for complex clinical cases. The combination of CRP greater than 45 mg/l and a stool frequency of three to eight per day, or a stool frequency greater than eight per day on day 3 ('Oxford index') is the simplest formula. In the index paper from 1996, a retrospective study of 51 consecutive episodes of ASUC in 49 patients, eighty-five per cent of those who met the Oxford criteria came to colectomy on that admission [20].

The Swedish ('fulminant colitis') index or Lindgren score was derived from retrospective data on 97 patients: the index is calculated on day 3 (stool frequency/day + 0.143*CRP mg/l) and has been prospectively evaluated in a clinical trial. The positive predictive value of a score of 8 or greater for colectomy within 90 days was 69% [21, 43].

In the Ho or Edinburgh predictive index, a retrospective analysis of 167 admissions used stool frequency, hypoalbuminaemia (<30 g/l) and colonic dilatation, to create a simple score. 85% of those who scored 4 or more came to colectomy. It is not entirely clear whether the score is best applied on day 1 (an advantage) or day 3 [25].

To date, two key studies have retrospectively compared predictive scores in adult patients with ASUC. The largest study used the IBD UK IBD audit. This retrospective analysis of 980 ASUC patients of whom 420 had enough data, compared the Oxford (Travis) and Edinburgh (Ho) scores. Patients in the high-risk categories had a 30% chance of colectomy during their admission (34.0% for Travis and 33.1% for Ho; $P < 0.0001$), indicating that both scores are adequate for identifying patients at risk of IV steroid failure. Both Travis and Ho scores identified patients at higher risk of colectomy, although their accuracy was lower than reported in the original papers. In this dataset. Travis's score was more accurate in predicting patients failing second line medical therapy, when compared to the Ho score (44.6% vs. 20.0%) (P = 0.01) [44].

In a retrospective study of 124 ASUC patients admitted over a 5-year period, a CRP/albumin ratio of 0.85 on day 3 of IV steroids predicts colectomy with a specificity of 76% a sensitivity of 76% [45]. Most recently Grant et al proposed the ACE (Albumin, CRP and Endoscopy) Index.[12] Derived from a retrospective analysis of 235 admissions with acute ulcerative colitis, although not all met Truelove and Witts criteria for ASUC. In this study, 25/32 (78,1%) patients with CRP $\geq$50mg/l, albumin $\leq$30g/l and increased endoscopic severity (severe on physician's global assessment) did not respond to intravenous steroids. The study was performed before the widespread use of anti-TNF therapy in induction, and maintenance of remission.

Table 2: Main scoring systems which predict outcome in Acute Severe Colitis

The British Society of Gastroenterology (BSG) guidelines recommend that rescue therapy should be given at day three for any patient who meets clinical and biochemical criteria as judged by a suitable scoring system [46]. These scoring systems include: Ho [47], Travis [20], Lindgren [21] or Gibson [45] (see figure 2). One concern in all recent studies assessing and validating these scoring systems retrospectively is that systems were wholly or partially used in decision-making by the clinicians involved and the circularity of argument that this introduces.

It is also noteworthy that these scoring systems were all designed in the era when biological agents were not widely available for induction, and maintenance of remission in ulcerative colitis. The

validation and development of scoring systems relevant to clinical practice in 2020 and beyond will need to involve a demonstration of their relevance in patients admitted with severe colitis, already on maintenance therapy with one of the available licensed biological therapies – anti-TNF, vedolizumab, or ustekinumab – or indeed on tofacitinib.

Controversy 4: What predictors are relevant in daily use in the paediatric population?

Paediatric Ulcerative Colitis Activity index (PUCAI) is the most widely used index to assess disease severity and outcome in the paediatric population. Developed by Turner et al, this score has been validated in prospective studies [16, 48]. Abdominal pain, rectal bleeding, stool consistency, stool frequency over 24 hours, nocturnal stool and activity level are the six parameters on which PUCAI is calculated. It stratifies patients with score < 10: remission; 10-34: mild; 35-64: moderate and 65-85: severe disease.

In a comparative study of scores in ASUC in 128 children, 29% (37/128) children failed intravenous steroid therapy requiring Infliximab (89%, Cyclosporine (3%) and Colectomy (8%). On day 3, a PUCAI greater than 45 screened for patients likely to fail intravenous corticosteroids (negative predictive value, 94%; positive predictive value, 43%; P .001). On day 5, a PUCAI score greater than 70 predicted need of salvage therapy (positive predictive value, 100%; negative predictive value, 79%; P .001) [16]. When compared to other scores including Seo, Lindgren and when compared to biomarkers including CRP and faecal calprotectin, the PUCAI performed best, followed closely by Travis score. Day 3 PUCAI score also predicted response up to 1 year post discharge [16].

The PUCAI score was validated in a recent multicentre study of 141 patients aged < 18 years with acute severe colitis (defined as PUCAI ≥ 65). The colectomy free rates were 71.3%, 66.4% and 63.6% at 1, 3 and 5 years respectively post-initial ASUC admission [49]

Controversy 5: Can we use endoscopy in early prognostication?

While just one of the scoring systems discussed above has incorporated endoscopic findings, this is clearly a parameter worthy of careful consideration as a prognostic tool. Indeed, flexible sigmoidoscopy is already considered appropriate in all admissions with ASUC, both to confirm the diagnosis in index presentations, and exclude cytomegalovirus infection (CMV) which is associated with a steroid-refractory disease course and requires specific anti-viral treatment.[50] A panel of 16 international IBD experts from the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) has recently proposed that the presence of endoscopic inflammation is the most important clinical factor for determining severity of UC, followed by impact of symptoms on daily living, use and effectiveness of biologics and recent hospitalization [51].

Although endoscopic severity was first shown to predict outcome in ASUC in 1994, with a retrospective study of 85 patients suggesting that deep colonic ulceration was predictive of colectomy, subsequent progress was hindered by the lack of validated, reproducible and accepted indices of endoscopic severity [52]. The emergence of the Mayo endoscopy score (MES) and more recently the Ulcerative Colitis Endoscopic Index of Severity (UCEIS), therefore represents a major development.

In a recent analysis of 92 patients with ASUC, UCEIS performed better than MES in predicting colectomy during admission and follow up. Receiver-operator characteristic (ROC) area of UCEIS was 0.85, with a sensitity of 60.3% and specificity of 85.5% using cut-off value of 7. This outperformed MES, which had an ROC area of 0.65 [53]. Importantly, UCEIS accounts for 86–88% of the variance between observers in the overall assessment of endoscopic severity, reducing the risk of interobserver bias in assessment. [54, 55].

In a retrospective analysis of 89 ASUC patients, median UCEIS was higher in patients requiring rescue therapy or colectomy. When UCEIS was ≥5, 18/54 (33%) came to colectomy during follow-up, compared with 3/33 (9%) with UCEIS ≤4[11] . A prospective study of 49 patients identified UCEIS>6 at admission as an independent predictor for colectomy[19].

The emergence of validated tools for endoscopic scoring provide real grounds for future research – whether the predictive value in determining outcome is better than that of conventional scoring systems; or whether a composite clinical/endoscopic score will outperform either modality individually needs to be formally assessed. An inherent issue in interpreting these data in retrospective datasets is the concern that there will be an inevitable element of circularity in decision-making - with clinicians using the known indices, and endoscopic scores in deciding as to whether escalate therapy, or not.

Controversy 6: How accurately can we predict response to second-line medical therapy in steroid-refractory patients?

There are two established second line agents for steroid refractory ASUC, infiximab and ciclosporin. The CONSTRUCT and GETAID studies have demonstrated that both agents are equally as efficacious for the treatment of ASUC. In the CONSTRUCT study 270 patients were randomly allocated (1:1) to receive either infliximab or ciclosporin. There was no significant difference in colectomy rates (55 (41%) of 135 patients in the infliximab group vs 65 [48%] of 135 patients in the ciclosporin group; p=0·223 [56]. Similarly, in the GETAID study of 115 patients; 58 patients were allocated to receive ciclosporin and 57 to receive infliximab. Treatment failure occurred in 35 (60%) patients given ciclosporin and 31 (54%) given infliximab (absolute risk difference 6%; 95% CI −7 to 19; p=0·52). Following a median follow-up of 5.4 years, colectomy-free survival rates at 1 and 5 years were 70.9% and 61.5% in patients who received ciclosporin and 69.1% and 65.1% in those who received infliximab (p=0.97)[57].

To date, there is a paucity of data examining the role of serum and faecal biomarkers when predicting response to second line rescue therapy. In a recent multicenter Australian study of 54 patients, CRP/albumin ratio cut-off of 0.37 post-commencement of infliximab and before discharge was a significant predictor of colectomy in one year with an area under receiver operating curve (AUROC) of 0.73 [23].

A prospective study measured faecal and serum infliximab levels in ASUC patients who received their first dose of infliximab rescue therapy. The concentrations of serum infliximab levels were lower (Days 4–7 post-first infliximab dose) in early remitters and in those avoiding future colectomy. This finding might be considered paradoxical given that higher, not lower, infliximab levels are associated with remission in inflammatory bowel disease. It also contrasts with the finding from the same study that the faecal loss of infliximab [Day 1 post-first IFX dose, ≥1.0µg/g] was strongly associated both with a reduced likelihood of achieving remission at 6 weeks and with a higher risk of colectomy rate [34, 58]. Separate work has suggested poor correlation between serum and faecal infliximab levels, underlining the continuing uncertainty over the impact of faecal infliximab loss on serum infliximab levels and disease response.[28]

As the field develops, management strategies have evolved, further complicating studies of predictive accuracy. In this context, accelerated dosing of infliximab in ASUC is postulated to influence response to second line treatment. In a retrospective multivariate analysis of 50 steroid refractory ASUC patients, accelerated dosing regimen of infliximab and serum albumin (at the time starting infliximab) were independent predictors of completion of induction therapy[59]. Colectomy rate during induction therapy was significantly lower with the accelerated regimen (6.7%, 1/15) than with the standard regimen (40%, 14/35) (p=0.039). The standard regimen was associated with shorter time to colectomy (p=0.042). Among patients who completed induction therapy, subsequent need for colectomy was similar between the groups during the follow-up period. However, a separate retrospective analysis of 213 patients found no association between accelerated dosing and risk of colectomy[60]. Conversely, a recent retrospective propensity score matched cohort study has demonstrated reduced short term, but not long term, colectomy rates in those who received accelerated infliximab dosing.[61] Recent British Society of Gastroenterology (BSG) guidelines support accelerated dosing in patients who have not responded to the standard dose (5mg/Kg) after 3-5 days [46]. However, data from a randomised controlled trial are needed to definitively support this approach, with results from the ongoing PREDICT-UC study [NCT02770040] eagerly awaited.

Controversy 7: Predicting ASUC outcome in the era of COVID-19

Following the first reports from China of a novel coronavirus in December 2019, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2, also referred to as COVID-19) has become a worldwide pandemic, leading to unprecedented challenges in the assessment and management of inflammatory bowel disease.

Of particular relevance to this review are the challenges in disease assessment and prognostication of ASUC in the COVID-19 pandemic. Fever and diarrhoea with raised inflammatory markers may be a presenting feature of COVID-19, which can therefore be difficult to differentiate from ASUC.[62, 63] Further, infection with COVID-19 in conjunction with ASUC, which has been described in at least three case series, complicates assessment of severity of colitis using established criteria such as heart rate, temperature, CRP and albumin, which COVID-19 all impacts.[64, 65, 66] There are also concerns about the safety of flexible sigmoidoscopy, which as a potential aerosol generating procedure, together with evidence of prolonged faecal shedding of SARS-CoV-2, may increase the risk of healthcare workers contracting COVID-19.[67]

Importantly, up to 45% of patients with COVID-19 are asymptomatic, and thus the diagnosis may be easily missed.[68] The false negative rate of polymerase chain reaction (PCR) based swab testing, reported to be around 30%, leads to further difficulties even when the diagnosis is sought, and thus a negative swab does not rule out infection. It is important to note that the accuracy of swab testing is critically dependent upon the timing of the swab in relation to initial COVID-19 exposure, and is markedly lower in the initial infective period.[69]

A RAND appropriateness panel has recently convened to adapt the BSG guidelines on the management of ASUC in the context of the COVID-19 pandemic, with a number of recommendations made that help to address these dilemmas [63]. It is recommended that a SARS-CoV-2 swab should be sent in all on admission, and given the risks of a false negative swab, repeated prior to rescue therapy or surgery. Chest CT scan should be performed before colectomy, regardless of COVID-19 status, to ensure the diagnosis has not been missed in those who are swab negative and assess severity of pulmonary infection including complications such as pulmonary thromboembolism. It was also considered appropriate to perform a flexible sigmoidoscopy in all patients. We propose that if a flexible sigmoidoscopy

can be safely performed, markers of endoscopic severity may be of particular utility in patients with concurrent COVID-19, given the potential challenges in interpreting other criteria of severity and response. Use of established management strategies were still considered largely appropriate for patients during the pandemic, allowing ongoing use of existing prognostic scores. However, clearly patients with concurrent COVID-19 must be assessed and managed on a case-by-case basis with involvement of clinicians with specific expertise in COVID-19.[63]

Future Perspectives: Developing a research agenda

As we move to an era of individualized medicine, perspectives have changed. An aspiration is to predict disease course. After diagnosis with UC, the goal is to adopt a more personalised approach, with early escalation of therapy for patients who are likely to have an aggressive disease course during that admission or after discharge.

While few data have addressed the issue above, and most attention has concentrated on the events after index admission with ASUC, some data are available [70]. Of note, the teams from Oxford and Cambridge analyzed patients up to three years following diagnosis of UC to develop a simple predictive three-point risk score for developing ASUC using readily available biomarkers. The score was validated against two external independent cohorts of ASUC patients. The score predicted risk of ASUC in 69% of patients. One point was applied to extent of disease (E3), CRP > 10mg/l, and haemoglobin < 14g/dl for men or < 12g/dl for women at diagnosis. The risk score from 0/3 to 3/3 achieved predictive ability and good calibration [71].

Novel biomarkers

Novel biomarkers are being tested in the ASUC cohort. In a recent observational single centre study, baseline serum procalcitonin predicted risk of IVCS failure, and short-term colectomy, and correlated significantly with UCEIS and FC in ASUC patients [72]. The novel serum calprotectin (SC), may reflect calprotectin release from activated neutrophils and other immune cells such as monocytes, macrophages, and epithelial cells [73]. The role of faecal calprotectin in predicting colectomy in acute severe colitis has been investigated (see above). More recently, SC has been

shown to predict colectomy in acute severe colitis with an AUC of 0.69 (95% CI 0.53-0.81) compared with FC (AUC 0.58; 95% CI 0.35-0.81) and CRP (AUC 0.71; 95% CI: 0.56-0.86) [74].

The future: multi-omic integration and machine learning analysis?

In the era of personalised care, there is great emerging interest in using newly developing -omic platforms that may be valuable in a variety of clinical settings in IBD. The main characteristic of multi-omics data is its high dimensionality. The aim is to deliver "personalized" or "precision medicine" by discovering molecular subtypes of IBD, new biomarkers and by matching available treatment to IBD subtypes [75, 76, 77, 78]. This concept was explored using earlier technologies, with some, albeit limited, success. The very early studies of the contribution of the HLA gene complex implicated a specific allelic variant HLA DRB1*0103 in pre-disposition to severe disease, and indeed need for colectomy; while this association has been strongly replicated in recent years and shows high statistical significance, this allele is relatively uncommon, and this discovery has not translated to clinical care [79].

More recently, genomics, transcriptomics, epigenomics and proteomics have all generated exciting data in IBD in the research setting, and the application of these complementary technologies in clinical practice and is the subject of several recent reviews . Further data generated by international research consortia based in Europe and North America are awaited in 2020. [80]

To date, 1215 patients have been enrolled as part of the prospective 1000 IBD multi-omics project in the Netherlands [78]. Meanwhile, biobank projects such as the UK-wide IBD BioResource (www.ibdbioresource.nihr.ac.uk) and Precision Medicine Initiative (PMI) cohort program continue to build large data sets for novel IBD biomarker discovery and validation [81]. The EC- funded IBD-CHARACTER and IBD-BIOM studies continue to generate new data in biomarker characterization. While there are no dedicated studies examining multi-omic data and risk of ASUC, this field is rapidly evolving.

Machine learning and artificial intelligence

Machine learning is a family of approaches used to evaluate large datasets for patterns that can predict outcomes. This tool, initially used in business is gaining momentum in medicine [82]. Machine learning is particularly useful for large data sets including genetic and microbiome data in IBD. Furthermore, this tool does not require a specific hypothesis. A lack of specific hypothesis can benefit IBD research, as potentially important (but unexpected) predictor variables will not be missed [83].

Waljee et al used machine learning for prognostication in IBD with readily available biomarkers. This prediction model incorporates longitudinal data (including use of anti TNF, CRP and albumin) readily available within the electronic medical record. The data prognostication for risk of IBD-related hospitalization or steroid use in the next 6 months, outperforming faecal calprotectin [84].

Following their previous data involving transcriptional signatures in CD8 T cells, the Cambridge group recently applied a statistical (machine) learning method to whole blood transcriptomic data for 66 patients with Crohn's Disease and 57 with Ulcerative Colitis. This method was used to identify genes that could be used to calculate the probability of an individual belonging to the validated IBD1 and IBD2 subgroups, which differ in clinical course and subsequent need for escalation of therapy. This assay is the first validated test in IBD, used as a prognostic biomarker from diagnosis. While an interventional study has not been undertaken in ulcerative colitis, a prospective biomarker-based study in Crohn's disease is underway [85]. The applicability to severe colitis remains to be explored.

Conclusion

In this review, we have provided an overview of current controversies and recent progress in risk stratification, prediction of outcome, and personalisation of care in acute severe ulcerative colitis. We reassess the use of Truelove and Witts' criteria, serum biomarkers and the use of composite clinical indices in current clinical practice. Importantly, we explore the potential for endoscopic prediction using defined validated indices for accurate and early prognostication, and the need to define outcome. Finally, we discuss the current research agenda including the application of new and emerging biomarkers coupled with multi-omics and the implications in management and optimisation of outcome.

On the basis of this data, the established clinical parameters identified by Truelove and Witts remain the best validated predictive parameters on admission with ASUC; and the accepted composite clinical/biomarker based indices from Oxford, Edinburgh and Sweden on day 3-5 provide the most reliable basis for determining need for escalation of medical therapy. Innovation over the next decade is keenly anticipated, notably the move towards biomarker-directed personalisation of therapy, and application of machine learning. These may allow early risk stratification, from the time of diagnosis, and from time of admission. We highlight the challenges and opportunities that the widespread use of biological therapies present in validating and further developing models from data generated in the pre-biologic era; and also the need for flexibility of judgement in the face of the SARS-Cov-2 pandemic.

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Figure legends

Figure 1: Plain abdominal radiograph showing abnormal colonic dilation (double headed white arrow), loss of normal haustration, and thumbprinting in ASUC (left image) and MRI abdomen showing oedematous wall thickening loss of haustration in sigmoid and descending colon (right image)

Figure 2: British Society of Gastroenterology recommended Day 3 scores used to identify patients with Acute Severe Colitis who require rescue therapy (46)

Table 1: Different parameters used in studies when predicting colectomy in acute severe ulcerative colitis

STUDY (YEAR OF PUBLICATION)	TYPE OF STUDY	NO OF PATIENTS	PATIENT CHARACTERISTICS	PARAMETERS	COLECTOMY RATE (%)
Truelove and Witts et al (3) (1955)	Retrospective	210	ASUC	Body temperature Pulse Stool frequency ESR	24 (includes ileostomy without colectomy)
Meyers et al (14) (1987)	Prospective	66	ASUC	ESR Haemoglobin Stool Frequency	21
Travis et al (20) (1996)	Prospective	49	ASUC	CRP Stool frequency	31
Lindgren et al (21) (1998)	Retrospective	97	ASUC	CRP	34
Benazatto et al (13) (2004)	Prospective	67	ASUC	Body temperature Pulse ESR CRP	20
Kumar et al (15) (2004)	Prospective	55	ASUC	Hypoalbuminemia CRP Fibrin degradation product Colonic diameter >5cm	8
Ho et al (25) (2004)	Retrospective	167	ASUC	Colonic dilatation Hypoalbuminemia CRP ESR Platelet count Stool frequency	40
Aceituno et al (30) (2007)	Retrospective	72	ASUC	CRP Ho index	20
Lees et al (29) (2007)	Retrospective	39	ASUC	Albumin	34
Ho et al (33) (2009)	Prospective	90	ASUC	Faecal calprotectin Albumin CRP	31
Turner et al (22) (2010)	Prospective	128	ASUC in children	Stool frequency Blood in stool CRP Faecal calprotectin	11
Turner et al (35) (2010)	Prospective	101	ASUC in children	PUCAI M2-PK Faecal Calprotectin	
Beswick et al (34) (2017)	Prospective	24	ASUC following first dose of IFX rescue therapy	Serum IFX Faecal IFX Faecal calprotectin	6
Grant et al (12) (2020)	Retrospective	235	ASUC and also those not meeting Truelove and Witts but requiring admission for intravenous steroids	CRP Albumin Endoscopic (Mayo)	18

Table 2: Main scoring systems which predict outcome in Acute Severe Colitis

SCORING SYSTEM AUTHOR (YEAR)	NUMBER OF PATIENTS	DAY THREE CRITERIA	P VALUE	SENSITIVITY SPECIFICITY	PPP[1] NPV[2]	% COLECTOMY SAME ADMISSION
Lindegren et al (1998)	97	No. of bowel movements+0.14 x CRP (mg/l)>8	P < 0.001			34% (30 day)
Travis et al (1996)	49 (51 episodes)	1.CRP>45 & 3-8 motions per day or 2. >8 bowel motions per day			PPV 85 %	31%
Ho et al (2004)	167	Colonic dilatation (4) Stool frequency[3] (0-4) Day 1 alb<30g/l (1)		Scores ≥ 4 Sensitivity 85% Sensitivity 75%		40%
Gibson et al (2018)	124	CRP/Albumin ratio > 0.85 And stool frequency > 3	P < 0.001	Sensitivity 70% Specificity 76%		18% (30 days)

Figure 1: Plain abdominal radiograph showing abnormal colonic dilation (double headed white arrow), loss of normal haustration, and thumbprinting in ASUC (left image) and MRI abdomen showing oedematous wall thickening loss of haustration in sigmoid and descending colon (right image)
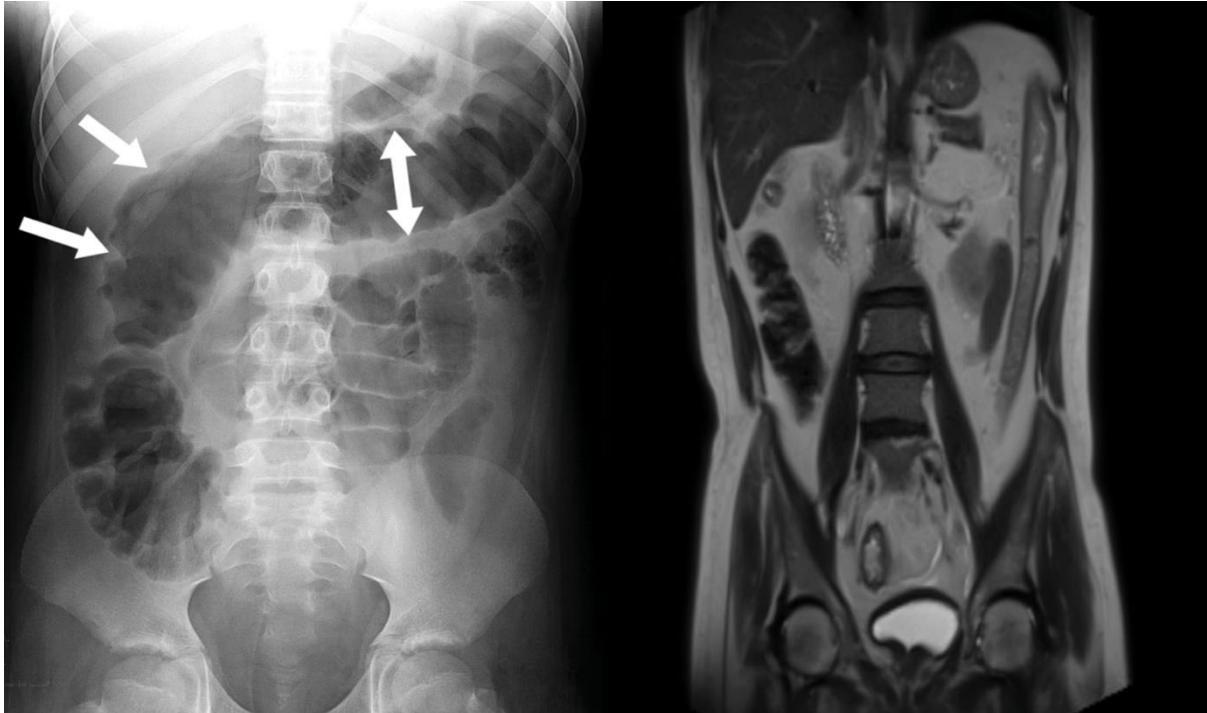

Figure courtesy of: BMJ 2013;346:f563   Courtesy of Radiopaedia.org, rID:72762

Figure 2: British Society of Gastroenterology recommended Day 3 scores used to identify patients with Acute Severe Colitis who require rescue therapy (46)