ACUTE ULCERATIVE COLITIS & CROHN'S DISEASE
Supporting information

This guideline has been prepared with reference to the following:

NICE. Ozanimod for treating moderately to severely active ulcerative colitis. 2022. NICE. London

https://www.nice.org.uk/guidance/ta828

NICE. Colorectal cancer prevention: colonoscopic surveillance in adults with ulcerative colitis, Crohn's disease or adenomas. 2022. NICE. London

https://www.nice.org.uk/guidance/cg118

NICE. Ulcerative colitis: management : guidance. 2019. London. NICE

https://www.nice.org.uk/guidance/ng130

NICE. Crohn's disease: management. 2019. NICE. London

https://www.nice.org.uk/guidance/ng129

European Crohn's and Colitis Organisation. ECCO guidelines on therapeutics in crohn's disease : medical treatment. 2019. ECCO

https://academic.oup.com/ecco-jcc/article/14/1/4/5620479

European Crohn's and Colitis Organisation. ECCO guidelines on therapeutics in crohn's disease : surgical treatment. 2019. ECCO

https://academic.oup.com/ecco-jcc/article/14/2/155/5631809

European Crohn's and Colitis Organisation. 3rd European evidence-based consensus on the diagnosis and management of crohn's disease 2016. ECCO

https://academic.oup.com/ecco-jcc/article/11/1/3/2456546/

NICE. Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy. 2015. NICE. London

https://www.nice.org.uk/guidance/ta329

NICE. Vedolizumab for treating moderately to severely active ulcerative colitis. 2015. NICE. London

https://www.nice.org.uk/guidance/ta342

NICE. Tofacitinib for moderately to severely active ulcerative colitis. 2015. NICE. London

https://www.nice.org.uk/guidance/ta329

Mowatt, C, Cole, A, Windsor, A, et al. Guidelines for the management of inflammatory bowel disease in adults. Gut 2011:60: 571-607

http://gut.bmj.com/content/60/5/571.full.pdf+html

Immediate treatment

In patients with a haemoglobin concentration <8 g/dl, a blood transfusion of 4 units plus an extra unit for each g/dl below 8 is the optimal treatment?

A 2017 evidence review stated that, “Although there are different levels of evidence and variable degrees of recommendations, almost all scientific societies recommend the implementation of a restrictive transfusion policy (haemoglobin levels ranging between 6 and 8 g/dL) in surgical, haemodynamically stable patients. However, the appropriateness of RBC transfusion at higher haemoglobin levels should be evaluated case by case, considering acute ongoing blood losses, comorbidities, signs of organ ischaemia and symptoms indicative of hypoxia. In any case, published guidelines … generally agree that RBC transfusion is not beneficial when the haemoglobin concentration is greater than 10 g/dL” (Franchini, 2017).
A 2014 systematic review focused on the question as to whether the lower 7 g/dL threshold is superior to the higher threshold of 8 g/dL (Salpeter, 2014). Pooled data from three RCT of critically ill or bleeding patients (n=2,364) showed that a haemoglobin threshold <7 g/dL significantly reduces negative outcomes, as well as in-hospital and total mortality, when compared to a haemoglobin threshold <8 g/dL.
No evidence was identified which recommended a specific number of units required.

Franchini M, Marano G, Mengoli C et al. Red blood cell transfusion policy: a critical literature review. Blood Transfus. 2017;15:307-17
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5490725/

Salpeter SR, Buckley JS, Chatterjee S. Impact of more restrictive blood transfusion strategies on clinical outcomes: a metaanalysis and systematic review. Am J Med. 2014;127:124–31

Evidence Level: V

Intravenous hydrocortisone influences the clinical outcome in patients with acute ulcerative colitis?
A study of intravenous corticosteroid treatment in inflammatory bowel disease (Faubion, 2001) included 63 with ulcerative colitis. Immediate outcomes were complete remission in 34 (54%), partial remission in 19 (30%) and no response in 10 (16%). One-year outcomes were prolonged response in 31 (49%), corticosteroid dependence in 14 (22%) and operation in 14 (22%).
There is evidence from clinical trials and meta-analysis (Sandborn, 2003) that budesonide is as effective as hydrocortisone or prednisolone, but with far fewer adverse effects.
A Cochrane review of 4 RCTs (Steinhart, 2003) concluded that corticosteroids did not appear to reduce the risk of relapse over a 24 month period of follow-up in patients with Crohn’s disease.
A 2016 review concluded that Intravenous hydrocortisone 100 mg three to four times daily or equivalent is the standard initial treatment of acute “severe” ulcerative colitis (Chen, 2016). The overall response rate is 67%. Treatment beyond 7-10 days was not beneficial.

Chen JH, Andrews JM, Kariyawasam V et al. Review article: acute severe ulcerative colitis - evidence-based consensus statements. Aliment Pharmacol Ther. 2016;44:127-44
http://onlinelibrary.wiley.com/wol1/doi/10.1111/apt.13670/full

Faubion WA, Loftus EV, Harmsen WS, et al. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. Gastroenterology 2001;121:255-60

Sandborn WJ, Feagan BG. Review article: mild to moderate Crohn’s disease: defining the basis for a new treatment algorithm. Aliment Pharmacol Ther 2003;18:263-77
http://onlinelibrary.wiley.com/doi/10.1046/j.1365-2036.2003.01661.x/full

Steinhart AH, Ewe K, Griffiths AM, et al. Corticosteroids for maintenance of remission in Crohn's disease. The Cochrane Database of Systematic Reviews 2003
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000301/full

Evidence Level: II

Metronidazole influences the clinical outcome in acute ulcerative colitis?
A 2021 RCT found that a combination of intravenous ceftriaxone and metronidazole did not improve outcomes in acute ulcerative colitis (Mishra, 2021). Fifty patients with were randomized to either infusions of placebo or intravenous ceftriaxone and metronidazole in addition to standard care. There was no significant difference in change in CRP, Partial Mayo score, and fecal calprotectin between the two groups on day three.

Antibiotics have not been shown to be superior to placebo in patients with ulcerative colitis (Jani, 2002; Podolsky, 2002), except as a component of an intensive, empirical regimen in severe transmural colitis (Stein, 1999).

Mishra S, Mandavdhare HS, Singh H et al. Adjuvant use of combination of antibiotics in acute severe ulcerative colitis: A placebo controlled randomized trial. Expert Rev Anti Infect Ther. 2021;19:949-55

Jani N, Regueiro MD. Medical therapy for ulcerative colitis. Gastroenterol Clin N Am 2002;31:147-66

Podolsky DK. Inflammatory bowel disease. N Engl J Med 2002;347:417-29

Stein RB, Hanauer SB. Medical therapy for inflammatory bowel disease. Gastroenterol Clin N Am 1999;28:297-321

Evidence Level: II

Giving anti-diarrhoeal drugs in the acute phase of inflammatory bowel disease can increase the risk of toxic dilatation?

In a review of 12 cases of toxic dilatation of the colon in Crohn's disease (Whorwell, 1981), all but one of whom had been admitted as emergencies without a previous diagnosis having been made, anti-diarrhoeal drugs had previously been prescribed in 83%.
In an earlier series of 18 patients (Binder, 1974), anti-diarrhoeal drugs or opiates had been given to 13 (72%).
Further evidence is provided by a review (Hanauer, 1991).

Binder SC, Patterson JF, Glotzer DJ. Toxic megacolon in ulcerative colitis. Gastroenterology 1974;66:909-15

Hanauer SB, Stathopoulos G. Risk-benefit assessment of drugs used in the treatment of inflammatory bowel disease. Drug Safety 1991;6:192-219

Whorwell PJ, Isaacson P. Toxic dilatation of colon in Crohn's disease. Lancet 1981;ii:1334-7

Evidence Level: IV

Barium enema or colonoscopy in the acute phase of inflammatory bowel disease carries a high risk of perforation of the colon?

Barium enema may be contraindicated in the acute phase of IBD as the pressure built up during the procedure may be in excess of that required to burst the colon (Gelfand, 1980). This complication is rare: approximately 2 in 10,000 examinations (Salvo, 1976).
A review on endoscopy in inflammatory bowel disease (Quinn, 1994) states that "Prior suggestion that endoscopy in acute colitis was unsafe and carried a high risk of perforation is unsubstantiated, and diagnostic endoscopy during acute disease has become routine at many centers". Several other reviews confirm this view (Froelich, 1999; Mantzaris, 1995). Much relies, however, upon the skill of the individual operator, and endoscopy is perhaps best avoided in the acute phase unless performed by senior, experienced personnel.

Froelich F, Larequi-Lauber T, Gonvers JJ, et al. Appropriateness of colonoscopy: inflammatory bowel disease. Endoscopy 1999;31:647-53

Gelfand DW. Complications of gastrointestinal radiologic procedures: I. Complications of routine fluoroscopic studies. Gastrointest Radiol 1980;5:293-315

Mantzaris GJ, Hatzis A, Archavlis E, et al. The role of colonoscopy in the differential diagnosis of acute, severe hemorrhagic colitis. Endoscopy 1995;27:645-53

Quinn PG, Binion DG, Connors PJ. The role of endoscopy in inflammatory bowel disease. Med Clin N Am 1994;78:1331-52

Salvo AF, Capron CW, Leigh KE, et al. Barium intravasation into portal venous system during barium enema examination. JAMA 1976;235:749-51

Evidence Level: V

Subsequent management

Oral metronidazole and the substitution of prednisolone for hydrocortisone is appropriate after the first 24-48 hours, if the patient's condition is improving?

Metronidazole is efficacious in the treatment of Crohn's disease (see above) and the oral preparation is equal in effect to the intravenous one (Freeman, 1997).

Oral prednisolone in a dose of 1 mg/kg/day for 3-7 weeks achieves clinical remission in 60-92% of Crohn's disease patients (Belaiche, 1998; Campieri, 1997). Oral administration of prednisolone produces similar results to corticosteroids via the intravenous route (Kjeldsen, 1993).

Belaiche J, Louis E. Corticosteroid treatment in active Crohn's disease. Acta Gastro-Enterol Belg 1998;61:153-7

Campieri M, Ferguson A, Doe W, et al. Oral budesonide is as effective as oral prednisolone in active Crohn's disease. Gut 1997;41:209-14
http://gut.bmj.com/content/41/2/209.long

Freeman CD, Klutman NE, Lamp KC. Metronidazole: a therapeutic review and update. Drugs 1997;54:679-708

Kjeldsen J. Treatment of ulcerative colitis with high doses of oral prednisolone: the rate remission, the need for surgery, and the effect of prolonging the treatment. Scand J Gastroenterol 1993;28:821-6

Evidence Level: II

Once clinical improvement has begun, mesalazine improves clinical outcome?

A 2020 systematic review of RCTs concluded that there is high-certainty evidence that mesalazine is superior to placebo for maintenance therapy in ulcerative colitis, but that there is also high-certainty evidence that mesalazine is inferior compared to sulfasalazine (Murray, 2020). About 37% (335/907) of mesalazine participants relapsed at six to 12 months compared to 55% (355/648) of placebo participants (RR 0.68, 95% CI 0.61 to 0.76; 8 studies, 1555 participants). Sulfasalazine is more effective than mesalazine for maintenance of remission. About 48% (416/871) of mesalazine participants relapsed at six to 18 months compared to 43% (336/784) of sulfasalazine participants (RR 1.14, 95% CI 1.03 to 1.27; 12 studies, 1655 participants).

A Cochrane review of 53 RCTs in a total of 8548 patients (Feagan, 2016) concluded that 5-aminosalicylic acid was superior to placebo (RR 0.86, 95% CI 0.82 to 0.89) and no more effective than sulfasalazine (RR 0.90, 95% CI 0.77 to 1.04) in inducing the remission of ulcerative colitis. However, patients on 5-aminosalicylic acid (5-ASA) suffered less adverse effects (flatulence, abdominal pain, nausea, diarrhea, headache and worsening ulcerative colitis) than those on sulfasalazine (RR 0.48, 95% CI 0.37 to 0.63).

Feagan BG & MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. The Cochrane Database of Systematic Reviews 2016
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000543.pub4/full

Murray A, Nguyen TM, Parker CE et al. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2020;8:CD000544
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000544.pub5/full

Evidence Level: I

For distal disease, once-daily prednisolone enema improves the clinical outcome?

Prednisolone enema was responsible for initial improvement in 88% of 100 patients in an early study (Matts, 1961). Among these 88, no relapse occurred for 3 months in 78, for 6 months in 70, and for 9 months in 66.

This treatment is particularly indicated in distal disease as the mode of action is predominantly local (Hamilton, 1984). A double blind controlled trial in 40 patients (McIntyre, 1985) concluded that this local effect had the potential of avoiding adverse systemic effects in patients needing long-term treatment.

A meta-analysis of rectal corticosteroids versus alternative treatments in ulcerative colitis in a total of 2,406 patients (Marshall, 1997) concluded that rectal 5-ASA preparations were superior to rectal corticosteroids. These conclusions were, however, challenged in a structured abstract included in the Database of Abstracts of Reviews of Effectiveness (DARE, 1997).

DARE. Rectal corticosteroids versus alternative treatment in ulcerative colitis: a meta-analysis (structured abstract). 1997
http://www.crd.york.ac.uk/crdweb/ShowRecord.asp?ID=11997000863

Hamilton I, Pinder IF, Dickinson RJ, et al. A comparison of prednisolone enemas with low-dose oral prednisolone in the treatment of acute distal ulcerative colitis. Dis Colon Rectum 1984;27:701-2

McIntyre PB, Macrae FA, Berghouse L, et al. Therapeutic benefits from a poorly absorbed prednisolone enema in distal colitis. Gut 1985;26:822-4
http://gut.bmj.com/content/26/8/822.long

Marshall JK, Irvine EJ. Rectal corticosteroids versus alternative treatment in ulcerative colitis: a meta-analysis. Gut 1997;40:775-81
http://gut.bmj.com/content/40/6/775.full.pdf

Matts SG. Intrarectal treatment of 100 cases of ulcerative colitis with prednisolone-21-phosphate enemata. BMJ 1961;i:165-8
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1952985/pdf/brmedj02877-0041.pdf

Evidence Level: II

On discharge, should the prednisolone dose be reduced daily or weekly, and to zero or to a maintenance dose?

Tapering of glucocorticoids is normally based on clinical judgement and no evidence can be found to support any particular strategy. Tapering is usually on a weekly basis in increments of 10 or 5 mg, and reduces to zero in order to avoid potential side effects of continued treatment (Kjeldsen, 1997).

Kjeldsen J, Lauritsen JK, de Muckadell OB. Serum concentrations of orosomucoid: improved decision-making for tapering prednisolone therapy in patients with active inflammatory bowel disease? Scand J Gastroenterol 1997;32:933-41

Evidence Level: V

A barium enema examination toward the end of the first week (to establish diagnosis) carries no additional hazard?

"The double-contrast barium enema is the primary radiologic tool for confirming the diagnosis of ulcerative colitis, for assessing the extent and severity of disease, and for differentiating ulcerative colitis from Crohn's disease" (Carucci, 2002). This and other reviews on the subject (Caroline, 1994) do not warn against barium enema examination in the acute phase, perhaps in view of the low incidence of complications (Salvo, 1976).

Caroline DF, Friedman AC. The radiology of inflammatory bowel disease. Med Clin N Am 1994;78:1353-85

Carucci LR, Levine MS. Radiographic imaging of inflammatory bowel disease. Gastroenterol Clin N Am 2002;31:93-117

Salvo AF, Capron CW, Leigh KE, et al. Barium intravasation into portal venous system during barium enema examination. JAMA 1976;235:749-51

Evidence Level: V

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