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Ulcerative colitis

What is ulcerative colitis?

Ulcerative colitis is an idiopathic chronic inflammatory disease of the colon that follows a course of relapse and remission. In a small number of cases, ulcerative colitis is associated with extra-intestinal features. Disease extent can be divided into:

- Distal disease (left-sided colitis): colitis confined to the rectum (proctitis) or rectum and sigmoid colon (proctosigmoiditis).
- More extensive disease includes: left-sided colitis (up to the splenic flexure, 40% of patients), extensive colitis (up to the hepatic flexure) and pancolitis (affecting the whole colon, 20% of patients).
- Some patients with pancolitis may have involvement of the terminal ileum due to an incompetent ileocaecal valve.

It is sometimes difficult to distinguish between ulcerative colitis and isolated colonic Crohn's disease. These patients can be described as having indeterminate colitis.

How common is ulcerative colitis? (Epidemiology) [1]

- Ulcerative colitis is the most common form of inflammatory bowel disease, and the incidence and prevalence is increasing worldwide. The prevalence is estimated at 5-500 per 100,000 worldwide.
- Incidence estimates range from 0.9 to 24.3 per 100,000 person-years, and prevalence estimates range from 2.4-294 cases per 100,000 people in Europe.
- Within Europe, the highest incidence and prevalence rates are in Scandinavia and the UK.

- The incidence of childhood-onset ulcerative colitis, which represents about 15-20% of all ulcerative colitis cases, ranges from 1-4 per 100,000 per year in most North American and European regions.
- The peak incidence occurs in late adolescence and early adulthood in the second to fourth decades of life, with a small second peak in the fifth decade. Ulcerative colitis affects males and females at approximately equal rates.

Causes of ulcerative colitis (aetiology) [1]

- The aetiology is unknown. Ulcerative colitis is probably an autoimmune condition triggered by colonic bacteria causing inflammation in the gastrointestinal tract.
- The risk of ulcerative colitis is greatest in first-degree relatives but is also raised in second-degree and third-degree relatives of people with ulcerative colitis.
- There is concern that non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of relapse or exacerbation of inflammatory bowel disease (IBD) - ulcerative colitis and Crohn's disease.
- Appendicectomy before adulthood is thought to be protective against the development of ulcerative colitis.
- The risk of ulcerative colitis is decreased in smokers.

Signs and symptoms of ulcerative colitis

Symptoms

- The cardinal symptom is bloody diarrhoea.
- Associated symptoms include colicky abdominal pain, urgency, or tenesmus (a feeling of incomplete defecation with an inability or difficulty to empty the bowel at defecation).
- Disease limited to the rectum (proctitis) may present with constipation and rectal bleeding.

- There may be symptoms of systemic upset, including malaise, fever, weight loss and symptoms of extra-intestinal (joint, cutaneous and eye) manifestations.
- The presentation may mimic gastrointestinal infection and the history should include recent foreign travel in considering the possibility of an infective cause.
- Recent medication history is also important in considering other possible causes of the presenting gastrointestinal upset.

Signs

- Depending on disease severity, the patient may be clearly unwell, pale, febrile and dehydrated. He or she may have a tachycardia and hypotension.
- Abdominal examination may reveal tenderness, distension or palpable masses.
- If abdominal tenderness is associated with abdominal distension then acute admission to hospital is required, as the patient could have toxic megacolon, which is potentially fatal. Other warning signs of potentially severe disease include tachycardia, fever and anaemia.

Extra-intestinal disease[1]

Approximately 4% of patients will have extra-intestinal disease which may include:

- Related to the activity of colitis:
    - Erythema nodosum.
    - Aphthous ulcers.
    - Episcleritis.
    - Acute arthropathy affecting the large joints (eg, the wrists, the hips and the knees).

- Usually related to activity of colitis:
    - Pyoderma gangrenosum.
    - Anterior uveitis.
- Not related to activity of colitis:
    - Sacroiliitis.
    - Ankylosing spondylitis.
    - Primary sclerosing cholangitis.

Differential diagnosis

- The main differential is Crohn's disease which has very similar clinical features. The diagnosis is usually made from the biopsy result following a sigmoidoscopy or colonoscopy.
- Prolonged use of laxatives.
- Infective colitis (chronic schistosomiasis, amoebiasis, tuberculosis).
- Mild colitis may mimic irritable bowel syndrome.
- Other conditions which occasionally cause diagnostic difficulty include:
    - Ischaemic colitis
    - Radiation colitis
    - Bowel trauma
    - Colorectal cancer
    - Diverticulitis
    - Polyposis syndromes
    - Colonic polyps

Diagnosing ulcerative colitis (investigations)

The diagnosis should be made on the basis of clinical suspicion supported by appropriate macroscopic findings on sigmoidoscopy or colonoscopy, typical histological findings on biopsy and negative stool examinations for infectious agents.

Up to 70% of children and teenagers referred to a paediatric gastroenterology centre with suspected IBD do not have the disease. Using a simple clinical case definition for suspected IBD in combination with a positive faecal calprotectin result increases the specificity to detect IBD and reduces the need for referral to a paediatric gastroenterology centre, with a very low risk of missing cases.[2]

- Initial investigations should include FBC, renal function and electrolytes, LFTs, ESR, CRP, iron studies, vitamin B12 and folate.
- Faecal calprotectin testing is recommended as an option to support the differential diagnosis of IBD or irritable bowel syndrome in adults with recent-onset lower gastrointestinal symptoms for whom specialist assessment is being considered and cancer is not suspected.[3]
- Microbiological testing for *Clostridium difficile* toxin and other pathogenic organisms. *C. difficile* infection has a higher prevalence in patients with IBD, may not be confined to the colon and is associated with increased mortality. A minimum of four stool samples is required to detect 90% of cases.
- Cytomegalovirus (CMV) should be considered in severe or refractory colitis, as reactivation is common in patients with IBD on immunosuppression.
- Sigmoidoscopy and rectal biopsy: for all patients presenting with diarrhoea, rigid sigmoidoscopy should be performed unless there are immediate plans to perform flexible sigmoidoscopy.

- Imaging:
    - Abdominal radiography is essential in the initial assessment of patients with severe colitis, in order to exclude colonic dilatation; it may also help assess disease extent in ulcerative colitis or identify proximal constipation.
    - Other imaging studies that may be used for the initial evaluation of a patient with IBD include abdominal ultrasound, CT, MRI, barium fluoroscopy and isotope-labelled scans.
- Endoscopy:
    - Colonoscopy with multiple biopsies (at least two biopsies from five sites, including the distal ileum and rectum) is the first-line procedure for diagnosing colitis.
    - Full colonoscopy is rarely needed in acute severe colitis and may be contra-indicated. Upper gastrointestinal endoscopy should be considered if there is co-existing dyspepsia.
- Initial investigations include:
    - FBC, renal function and electrolytes, LFTs, ESR and CRP.
    - Low magnesium and serum albumin levels are sometimes found in ulcerative colitis.
    - Stool culture, including ova, cysts and parasites and also *C. difficile* toxin.
    - Serological markers have been developed to differentiate ulcerative colitis from Crohn's disease. p-ANCA is more commonly associated with ulcerative colitis, whilst ASCA is more commonly associated with Crohn's disease.
- Abdominal imaging: this is essential in the initial assessment of patients with suspected ulcerative colitis, to exclude toxic dilatation and perforation. It may also help to assess disease extent or identify proximal constipation. In milder forms, ultrasound, CT, MRI and radionuclide scanning may all be contributory.

- Sigmoidoscopy and rectal biopsy: for all patients presenting with diarrhoea, rigid sigmoidoscopy should be performed unless there are immediate plans to perform flexible sigmoidoscopy.
- Colonoscopy:
    - This is usually preferable to flexible sigmoidoscopy because the extent of disease can be assessed; however, in moderate-to-severe disease, there is a higher risk of bowel perforation and flexible sigmoidoscopy is safer.
    - The extent of the disease is defined as the proximal margin of macroscopic inflammation because this is most clearly related to the risk of complications, including dilatation and cancer.
    - It is advisable that patients with ulcerative colitis should have a colonoscopy after 8-10 years to re-evaluate disease extent.

Disease severity in ulcerative colitis[4]

The National Institute for Health and Care Excellence (NICE) uses the categories of disease severity of mild, moderate and severe, based on the Truelove and Witts' severity index for adults and the Paediatric Ulcerative Colitis Activity Index (PUCAI) for children and young people.

For adults:

- **Mild**: fewer than four stools daily, no more than small amounts of blood in stools, no anaemia, pulse rate not above 90, no fever and normal ESR and CRP.
- **Moderate**: four to six stools a day with more blood in stools than for mild disease. No anaemia, pulse rate not above 90, no fever and normal ESR and CRP.
- **Severe**: six or more stools per day, visible blood in stools and at least one feature of systemic upset (temperature above 37.8°C, pulse rate greater than 90, anaemia, ESR above 30).

PUCAI for children and young people includes scoring of the presence and severity of abdominal pain, rectal bleeding, stool consistency of most stools, number of stools per 24 hours, stools causing wakening at night and level of activity. Details can be found in the NICE guideline.

Subacute ulcerative colitis is defined as moderately to severely active ulcerative colitis that would normally be managed in an outpatient setting and does not require hospitalisation or the consideration of urgent surgical intervention.

Indications for urgent hospital referral[5]

- Patients with severe colitis should be admitted to hospital for assessment and treatment.
- Patients with moderate disease, who fail to respond to steroids within two weeks, should be admitted to hospital.
- Patients who respond partially to treatment should be seen urgently in the outpatient department and treated for refractory colitis.

Management of ulcerative colitis [6] [7]

- Topical management is appropriate for some patients with active disease. This is usually the case for those with proctitis and often the case if the disease extends into the sigmoid.
- For those with more extensive disease, oral or parenteral therapy is the mainstay of treatment, although some of these patients may get additional benefit from topical therapy.
- Leukophoresis (extracorporeal removal of leukocytes from the blood) may be beneficial in carefully selected patients with ulcerative colitis. It is available in specialised centres as part of research trials.[8] [9] A recent meta-analysis found that leukophoresis was more efficacious than conventional pharmacotherapy in improving response and remission rate.[10]
- Beware antimotility drugs (eg, codeine, loperamide) and antispasmodic drugs, which may precipitate paralytic ileus and megacolon in active ulcerative colitis.

Drug treatments

Stool bulking agents[4]

- In left-sided disease, distal transit is rapid but proximal transit is slowed, which can result in proximal constipation.

- Relief of proximal constipation by stool bulking agents or laxatives may help to induce remission in proctitis.

Aminosalicylates

- Mesalazine - 5-aminosalicylic acid (5-ASA) - is now the treatment of choice for induction and maintenance of remission of mild-to-moderate ulcerative colitis.[11] Oral mesalazine is less effective than oral corticosteroids and so should be used as sole treatment only in mild attacks. Topical mesalazine is probably slightly more effective than topical corticosteroids.
- Oral mesalazine is mostly used to maintain remission. Mesalazine also seems to help reduce the risk of colorectal cancer.
- Modified once-daily mesalazine preparations and a multi-matrix oral formulation are now available for patients who have compliance problems.[12] [13]
- The newer 5-ASA preparations olsalazine and balsalazide are inferior to sulfasalazine in maintenance therapy but have fewer adverse effects. Sulfasalazine has a higher incidence of side-effects compared with newer 5-ASA drugs but selected patients (eg, those with a reactive arthropathy) may benefit.
- Olsalazine has a higher incidence of diarrhoea in pancolitis and is best for patients with left-sided disease, or intolerance of other 5-ASAs.

Corticosteroids

- Corticosteroids are used to induce remission in relapses of ulcerative colitis. They have no role in maintenance therapy.
- Corticosteroids may be applied topically (suppositories, liquid or foam enemas), orally or intravenously.

Thiopurines

- Azathioprine and its active metabolite 6-mercaptopurine may be used when:
    - Patients are intolerant to corticosteroids.
    - Patients need two or more corticosteroid courses in a calendar year.
    - Disease relapses when the dose of prednisolone is less than 15 mg a day.
    - Disease relapses within six weeks of stopping steroids.
- Azathioprine seems to be effective for at least five years and increasing the duration of treatment will keep patients in remission for longer.

Ciclosporin

- This is an effective salvage therapy for patients with severe refractory colitis and it has a rapid onset of action.
- It reduces the colectomy rate by 50% in the short term but its use is controversial because of toxicity (drug-associated mortality is about 3%) and the long-term failure rate.

NICE guidance[4]

Inducing remission in people with ulcerative colitis

Treating mild-to-moderate ulcerative colitis:

Proctitis:

- To induce remission in mild-to-moderate first presentation or inflammatory exacerbation of proctitis, offer a topical aminosalicylate as first-line treatment.
- If remission is not achieved within four weeks, consider adding an oral aminosalicylate.
- If further treatment is needed, consider adding a time-limited course of a topical or an oral corticosteroid.

- For people who decline a topical aminosalicylate, consider an oral aminosalicylate as first-line treatment, and explain that this is not as effective as a topical aminosalicylate
- If remission is not achieved within 4 weeks, consider adding a time-limited course of a topical or an oral corticosteroid.
- For people who cannot tolerate aminosalicylates, consider a time-limited course of a topical or an oral corticosteroid.

Proctosigmoiditis and left-sided ulcerative colitis:

- To induce remission in mild-to-moderate first presentation or inflammatory exacerbation of proctosigmoiditis or left-sided ulcerative colitis, offer a topical aminosalicylate as first-line treatment.
- If remission is not achieved within four weeks, consider adding a high-dose oral aminosalicylate to the topical aminosalicylate or switching to a high-dose oral aminosalicylate and a time-limited course of a topical corticosteroid.
- If further treatment is needed, stop topical treatments and offer an oral aminosalicylate and a time-limited course of an oral corticosteroid.
- For people who decline any topical treatment, consider a high-dose oral aminosalicylate alone, and explain that this is not as effective as a topical aminosalicylate.
- If remission is not achieved within four weeks, offer a time-limited course of an oral corticosteroid in addition to the high-dose aminosalicylate.
- For people who cannot tolerate aminosalicylates, consider a time-limited course of a topical or an oral corticosteroid.

Extensive disease:

- To induce remission in people with a mild-to-moderate first presentation or inflammatory exacerbation of extensive ulcerative colitis, offer a topical aminosalicylate and a high-dose oral aminosalicylate as first-line treatment.

- If remission is not achieved within four weeks, stop the topical aminosalicylate and offer a high-dose oral aminosalicylate with a time-limited course of an oral corticosteroid.
- For people who cannot tolerate aminosalicylates, consider a time-limited course of an oral corticosteroid.

Maintaining remission

Proctitis and proctosigmoiditis:

To maintain remission after a mild-to-moderate inflammatory exacerbation of proctitis or proctosigmoiditis, consider the following options:

- Topical aminosalicylate alone (daily or intermittent).
- Oral aminosalicylate plus a topical aminosalicylate.
- Oral aminosalicylate alone. This may not be as effective as combined treatment or an intermittent topical aminosalicylate alone.

Left-sided and extensive ulcerative colitis:

- To maintain remission in adults after a mild-to-moderate inflammatory exacerbation of left-sided or extensive ulcerative colitis, offer a low-maintenance dose of an oral aminosalicylate.
- To maintain remission in children and young people after a mild-to-moderate inflammatory exacerbation of left-sided or extensive ulcerative colitis, offer an oral aminosalicylate.

All extents of disease:

- Consider oral azathioprine or oral mercaptopurine to maintain remission after two or more inflammatory exacerbations in 12 months that require treatment with systemic corticosteroids or if remission is not maintained by aminosalicylates.
- To maintain remission after a single episode of acute severe ulcerative colitis, consider oral azathioprine or oral mercaptopurine. Consider oral aminosalicylates if azathioprine and/or mercaptopurine are contra-indicated or the person cannot tolerate them.

Biologics and Janus kinase inhibitors for moderately to severely active ulcerative colitis: all extents of disease

TNF-alpha inhibitors are the most used biological treatments for moderately to severely active ulcerative colitis. When TNF-alpha inhibitors have not worked, or are not tolerated, usually vedolizumab or ustekinumab are the next options considered. Mirikizumab is another biological treatment that can be used.[14]

Infliximab, adalimumab and golimumab[15]

- Infliximab, adalimumab and golimumab are tumour necrosis factor (TNF) inhibitors.
- Infliximab, adalimumab and golimumab are recommended as options for treating moderately to severely active ulcerative colitis in adults:
    - Whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or
    - Who cannot tolerate, or have medical contra-indications for conventional therapies.

Vedolizumab[16]

- Vedolizumab is a monoclonal antibody that binds specifically to the α4β7 integrin, which is expressed on gut homing T helper lymphocytes and causes a reduction in gastrointestinal inflammation.
- Vedolizumab is recommended as an option for treating moderately to severely active ulcerative colitis in adults.

Ustekinumab[17]

- Ustekinumab blocks interleukin-12 and interleukin-23 proteins.

- Ustekinumab is recommended as an option for treating moderately to severely active ulcerative colitis in adults when conventional therapy or a biological agent cannot be tolerated, or the disease has responded inadequately or lost response to treatment, only if:
    - A tumour necrosis factor-alpha inhibitor has failed (inadequate response or lost response to treatment) or
    - A tumour necrosis factor-alpha inhibitor cannot be tolerated or is not suitable.

Filgotinib [18]

- Filgotinib is a selective inhibitor of the Janus-associated tyrosine kinase JAK1. Until recently, it has mainly been used in rheumatoid arthritis.
- NICE recommends using this medication as an option in those people who are having a moderate to severe flare of ulcerative colitis.
- It can only be given in adults and under certain conditions. These are if the more conventional treatments used in a flare:
    - Are not tolerated by the patient.
    - Are not resulting in an **effective** disease response.
    - Are not resulting in **any** disease response.

Ozanimod [19]

- Ozanimod is a sphingosine-1-phosphate receptor modulator, which prevents movement of lymphocytes out of lymph nodes, thereby limiting inflammation in the central nervous system and intestine.
- NICE has recommended ozanimod as an option for treating moderately to severely active ulcerative colitis in adults. It has been shown to be just as effective as conventional treatments.

- It can only be used if:
    - Conventional treatment cannot be tolerated or is not working well enough and infliximab is not suitable; or
    - Biological treatment cannot be tolerated or is not working well enough.

Upadacitinib [20]

- NICE has recommended upadacitinib, a selective and reversible inhibitor of the Janus-associated tyrosine kinase JAK1 more commonly used for rheumatoid arthritis, as an option for treating moderately to severely active ulcerative colitis in adults.
- It can only be used if conventional treatments are not tolerated or have stopped working. It is thought to be just as effective as other treatments available.

Mirikizumab [14]

- Mirikizumab is a humanised monoclonal antibody that selectively binds to cytokine interleukin-23 (IL-23) and inhibits the release of pro-inflammatory cytokines.
- Mirikizumab is recommended by NICE as an option for treating moderately to severely active ulcerative colitis in adults when conventional or biological treatment cannot be tolerated, or the condition has not responded well enough or lost response to treatment, but only if:
    - A tumour necrosis factor (TNF)-alpha inhibitor has not worked (inadequate response or has lost response to treatment) or
    - A TNF-alpha inhibitor cannot be tolerated or is not suitable.

Surgery

20-30% of patients will ultimately require colectomy for ulcerative colitis.

- Colectomy is an option for patients who do not respond to, or are intolerant of, medical treatment, or in those with complications such as colorectal neoplasia. [21]

- Because ulcerative colitis is confined to the colorectum, colectomy is curative.[21]
- The usual procedure is a restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA).[21]
- There may be an increased likelihood of needing surgery for people with any of the following:[4]
    - Stool frequency of more than eight per day.
    - Pyrexia.
    - Tachycardia.
    - An abdominal X-ray showing colonic dilatation.
    - Low albumin, low haemoglobin, high platelet count or CRP >45 mg/L.

Complications of ulcerative colitis

- Colorectal cancer:

- - Patients with ulcerative colitis have about double the incidence of colorectal cancer than people without the disorder.
  - Children who are diagnosed as having IBD in childhood have an increased risk of cancer, especially gastrointestinal cancers, both in childhood and later in life. The increase has not fallen since the introduction of modern drug therapies for IBD. However the absolute risk is low.[22]
  - In the UK, colonoscopic surveillance is recommended for all patients, starting about ten years after the onset of symptoms, except for those with ulcerative proctitis that is documented on two consecutive endoscopic examinations, who do not require surveillance.[2]
  - The surveillance interval depends on the extent of disease. See the separate Screening for the Early Detection of Colorectal Cancer article.
  - The evidence base for this regime is not robust and NICE recommends further research in this area.[23]
- Other bowel complications include:

  - Pouchitis: up to 45% of patients who undergo ileal pouch surgery for ulcerative colitis have pouchitis. Metronidazole or ciprofloxacin for two weeks is the first-line therapy. Mesalazine or corticosteroids may be used in acute pouchitis if antibiotics are ineffective. Long-term, low-dose metronidazole or ciprofloxacin are potentially effective for chronic pouchitis.
  - Post-IPAA complications include leakage and pelvic abscess.
  - Toxic megacolon may be triggered by hypokalaemia, opiates, anticholinergics and barium enemas. The colon becomes acutely dilated and patients are severely ill. IV fluids, IV steroids, antibiotics and IV ciclosporin are the mainstay of conservative treatment but total colectomy may be required.

- Management of extra-intestinal manifestations: those that are associated with active intestinal disease largely respond to therapy aimed at controlling disease activity, whereas those that occur whether disease is inactive or quiescent, run a course independent of therapy for intestinal disease.
- Osteoporosis:[2]
    - This is common, although the absolute fracture risk, contribution of steroids and role of prophylaxis remain a subject for debate.
    - The use of corticosteroids should be minimised by optimising 5-ASA treatment and introducing thiopurines early in the disease course if 5-ASAs do not control disease activity.
    - In the UK, guidelines recommend bisphosphonate prophylaxis in patients aged over 65 years who need corticosteroids.
    - In patients aged under 65 years who need more than three months of glucocorticoids, bone densitometry measurement is recommended and a bisphosphonate started if the T score is 1.5 or less.
    - See the separate Osteoporosis Risk Assessment and Primary Prevention article.
- Psychosocial and sexual problems may arise.[24]

Prognosis[1]

- Ulcerative colitis is a lifelong condition, with unpredictable relapses and remissions.
- Mortality is slightly higher than in the general population. The slightly increased mortality is greatest in the first two years after diagnosis.
- Up to 90% will have one or more relapses after the first attack. Early relapse or active disease in the first two years is associated with a worse disease course.

- One study in Norway found that:[25]
    - The cumulative colectomy rate after ten years was 9.8%.
    - 83% of people initially had relapsing disease but half were relapse-free after five years.
    - About 20% of people with proctitis or left-sided colitis progressed to extensive colitis.
- Factors which may suggest a poor prognosis include:
    - Severe symptoms at presentation.
    - Extensive disease.
    - Raised inflammatory markers.
    - Age less than 50 years, especially childhood-onset disease.
    - Poor compliance with drug treatment.

Further reading

- Primary Care Society for Gastroenterology
- British Society of Gastroenterology
- Crohn's and Colitis UK

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