Ulcerative colitis

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Abstract | Ulcerative colitis (UC) is a chronic inflammatory bowel disease of unknown aetiology affecting the colon and rectum. Multiple factors, such as genetic background, environmental and luminal factors, and mucosal immune dysregulation, have been suggested to contribute to UC pathogenesis. UC has evolved into a global burden given its high incidence in developed countries and the substantial increase in incidence in developing countries. An improved understanding of the mechanisms underlying UC has led to the emergence of new treatments. Since the early 2000s, anti-tumour necrosis factor (TNF) treatment has significantly improved treatment outcomes. Advances in medical treatments have enabled a paradigm shift in treatment goals from symptomatic relief to endoscopic and histological healing to achieve better long-term outcomes and, consequently, diagnostic modalities have also been improved to monitor disease activity more tightly. Despite these improvements in patient care, a substantial proportion of patients, for example, those who are refractory to medical treatment or those who develop colitis-associated colorectal dysplasia or cancer, still require restorative proctocolectomy. The development of novel drugs and improvement of the treatment strategy by implementing personalized medicine are warranted to achieve optimal disease control. However, delineating the aetiology of UC is necessary to ultimately achieve disease cure.

Stricture
An abnormal narrowing of the digestive tract.

Fistula
An abnormal connection between two organs or spaces.

Moon face
A medical sign of facial swelling with deposition of fat.

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Ulcerative colitis (UC), first described in 1859, is one of two major forms of inflammatory bowel disease (IBD)[1]. UC is characterized by mucosal inflammation initiating in the rectum and extending proximally in the colon in a continuous fashion[2–6]. By contrast, inflammation in Crohn's disease (CD), the other type of IBD, demonstrates patchy lesions that are potentially scattered anywhere in the gastrointestinal tract[2]. The inflammation in UC is typically limited to the mucosal layer, causing superficial damage of the bowel wall, whereas CD is characterized by transmural inflammation (involving all layers of the bowel wall) that leads to fibrosis, stricture and fistula. The exact pathogenesis of UC is still unknown but several factors, including a dysregulated immune response, altered gut microbiota, genetic susceptibility and environmental factors, have been implicated[2]. A bloody diarrhoea is the most common symptom of UC, although diagnosis is made from a combination of symptoms, endoscopy and histology.

Until the use of corticosteroids was introduced in 1955, the natural disease course in patients with moderate-to-severe UC was devastating, with mortality of >50%[5]. However, increased use of corticosteroids, in turn, can result in several adverse effects, including osteoporosis, depression, moon face, type 2 diabetes mellitus and cataracts[5]. To date, treating steroid-refractory patients (that is, corticosteroid dependent or corticosteroid resistant) remains a challenge. However, the introduction of biologics targeting cytokines and adhesion molecules have enabled a dramatic improvement in long-term outcomes, including the achievement of corticosteroid-free remission[6,7]. However, many patients still require surgery because of therapy failure or owing to the development of dysplasia[8].

The incidence and prevalence of UC is increasing worldwide. Similar to CD, UC is now considered a progressive disease owing to the risks of proximal extension, strictures, gut dysmotility, anorectal dysfunction, need for colectomy, hospitalization, colorectal cancer, disability and impaired quality of life. Given its potentially progressive and debilitating disease course, the therapeutic goals for UC have changed over the past decade, from treating symptoms to mucosal healing, with the aim of modifying the natural history of the disease and improving long-term outcomes[9,10]. Indeed, histological remission is associated with lower risks of hospitalizations, colectomy and colorectal cancer than endoscopic healing[11–13].

This Primer provides a comprehensive overview of the current knowledge of the epidemiology, pathogenesis, diagnosis and therapeutic options of UC. In addition, we discuss outstanding questions in the field that

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will direct future research and the numerous potential emerging therapeutic options for the management of UC.

Epidemiology

The burden of IBD is rising substantially worldwide. Although the incidence of UC and CD is high in Western countries, it might be plateauing. For example, in the 2000s, the incidence of both UC and CD was reported to be ~15 cases per 100,000 persons in Canada[14], yet new population-based data on incidence from three provinces in Canada have shown a decrease in the incidence of UC and CD in adults[15–17]. Nonetheless, the prevalence continues to rise in Western jurisdictions, for example, with 1% of the Canadian population estimated to be affected by IBD by 2030 (REF.[18]). The incidence of UC is much lower in developing jurisdictions than in developed jurisdictions, but emerging data reveal an increase in the incidence in developing jurisdictions[19]. Among the developing regions of the world, India has the highest reported incidence of 9.31 cases per 100,000 persons for IBD and an incidence of 5.41 cases per 100,000 persons for UC[20]. Interestingly, a predominance of CD is observed in southern India whereas a predominance of UC is observed in northern India[21]. Considering its vast population, within a few years, India might likely have the highest burden of IBD in terms of overall numbers[22]. As mortality is generally low, the burden of disease will continue to grow worldwide.

UC has been reported to occur across all ages. Globally, Scandinavia and Canada have the highest incidence of paediatric IBD (occurring in children <16 years of age); the incidence of paediatric IBD is 10.6 cases per 100,000 persons in Norway, 12.8 cases per 100,000 persons in Sweden and 9.68 cases per 100,000 persons in Canada[23,24]. A Canadian study reported no significant rise in the incidence of paediatric IBD overall. However, the study reported that the incidence of very-early-onset IBD (occurring in children 0–5 years of age) significantly increased by 7.2% per year[25]. Ongoing studies on very-early-onset IBD suggest that the pathophysiology might be different to that of older onset IBD despite having the same phenotype[26]. CD is predominantly observed in male sex in childhood but becomes predominant in women in adulthood, whereas the incidence of UC is reported to be equal between the sexes from childhood to adulthood[27]. Although more research is warranted, ethnicity might not play an important part in the epidemiology of IBD. For example, children of people who migrated from low-incidence areas to high-incidence areas have been reported to have the same incidence as in the new migrated area[28]. Furthermore, the increasing incidence in the developing world and the similar phenotype among Asians and Westerners with IBD[21] suggest that ethnicity may not be an important driver of UC[29]. As the phenotype of UC is largely homogeneous worldwide, environmental changes are likely to underlie the observed epidemiological trends[30].

The rising incidence in selected populations can facilitate hypothesis generation to understand the disease aetiology (FIG. 1). By tracking the worldwide epidemiology of IBD, health-care providers and policy-makers will be informed of the management and economic burden of this disease, especially as evidence seems to point to expensive biologics being the optimal care in moderate and severe disease.

Risk factors

Although cigarette smoking is an important environmental risk factor in CD, quitting smoking has been a risk factor in UC[30]. The pathogenesis as to how smoking either triggers UC or protects an individual against developing UC is unknown. Whether the rising incidence of UC reflects any trends in smoking cessation is unknown. However, studies from India show neither an association between ex-smoking status and the incidence of UC nor between active smoking and the incidence of CD[31,32]. Furthermore, a vegetarian diet has been shown to be protective against the development of UC in India[32], suggesting that a shift from plant-based diets towards processed foods might be a risk factor for UC in the developing world[33]. Urbanization is no longer considered a risk factor based on studies from both Western and developing jurisdictions[32,34,35]. Other crucial risk factors of UC that are relevant globally include factors that affect the gut microbiota and, in turn, the gut immune response, such as antibiotic use[36], dietary changes, including the widespread use of food additives[33,37], and psychiatric comorbidity[38]. The gut–brain axis is complex and some of the effects of psychiatric comorbidity in the disease course of UC might possibly be mediated through the gut microbiota, although more research is required in this area[39]. Appendectomy is a protective factor in UC for unclear reasons[40], yet appendectomy after a UC diagnosis has been shown to actually worsen the disease course[41].

Colorectal cancer risk. Patients with longstanding and/or extensive UC have an increased risk of colorectal cancer (CRC) compared with the general population. A meta-analysis demonstrated that the cumulative probabilities of developing CRC among all persons with UC were 2% by 10 years of disease, 8% by 20 years of disease and 18% by 30 years of disease[42]. The relative risk of CRC was reported to be twofold higher in individuals with UC than in the general population in Scandinavia and North America[43,44], and this increased risk has also been observed in China and India[45,46]. In addition to the

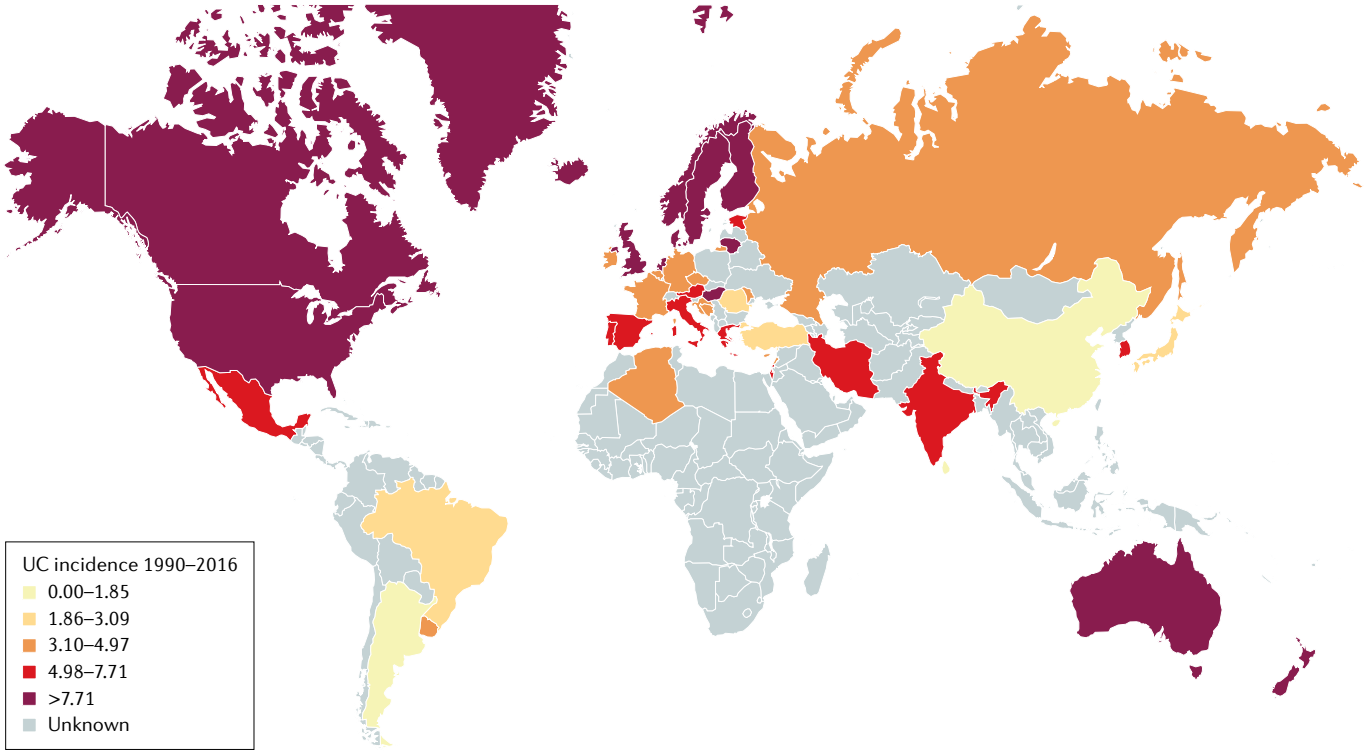

Fig. 1 | **Global incidence of ulcerative colitis.** Incidence of ulcerative colitis (UC) from 1990 to 2016 in different jurisdictions is shown. The authors acknowledge G. Kaplan for providing the data for this figure[230].

duration and extent of disease, several factors, such as concomitant primary sclerosing cholangitis, younger age of onset, and personal and family history of CRC, have also been reported to increase the risk of UC-associated CRC[47]. In addition, treatment with 5-aminosalicylic acid (5-ASA, which is routinely used to treat patients with UC) might be protective against the development of CRC[48,49]. However, patients with UC-associated CRC are reported to have worse outcomes than patients with sporadic CRC[47,50], resulting in an increased mortality.

Genetic factors

Although environmental factors are hypothesized to play a vital part in determining the risk of developing UC, genetic factors have also been identified to be associated with UC. The risk of UC is increased in first-degree relatives but this risk might be due either to genetically or to environmentally driven associations or reflective of both[51].

A genome-wide association study analysis from 2012 revealed that several disease-associated loci are shared between CD and UC[52]. The associated risk with most susceptibility loci is small, emphasizing that numerous loci, along with additional factors, such as smoking status, contribute to the disease[53]. This finding was also illustrated by twin studies that compared the concordance rates between monozygotic and dizygotic twins. The concordance was higher in monozygotic twins (up to 17% in UC and up to 55% in CD) than in dizygotic twins (6% in UC and 4% in CD)[54–57], implying that the genetic trait is more important in CD than in UC. In addition, the disease-associated loci involve genes with different functions, including the innate and adaptive immune systems, cytokine signalling, lymphocyte activation and responses to bacterial molecules[52], which are discussed in detail in the sections below. In another subsequent analysis, the Montreal classification (which includes the age at onset of disease, extent of disease and phenotype) was applied to determine the IBD class in 34,819 patients with either CD or UC. The ImmunoChip array was used for genotyping the patient cohorts and a genotype–phenotype association was tested across 156,154 genetic variants, generating a risk score that classified individuals into three IBD disease groups: ileal CD, colonic CD and UC[58]. This new classification is now being further supported by more immunological data that are in line with the genetic classification. In fact, several studies have reported similar morphological findings and T cell infiltrates in the lamina propria and underscore the similarities between UC and Crohn's colitis in comparison to ileal CD[59]. In addition, genetic risk factors seem to be different between Western regions and Asian regions in both CD and UC[60,61]. Thus, these data fully support the concept suggested by the genetic consortium, namely that the disease location, which is partly genetically determined, drives disease behaviour over time[58]. However, this requires more detailed future analysis.

Mechanisms/pathophysiology

The pathophysiology of UC is multifaceted and is not completely understood. However, the currently available data allow for establishing a current working model consisting of different factors and structures that contribute

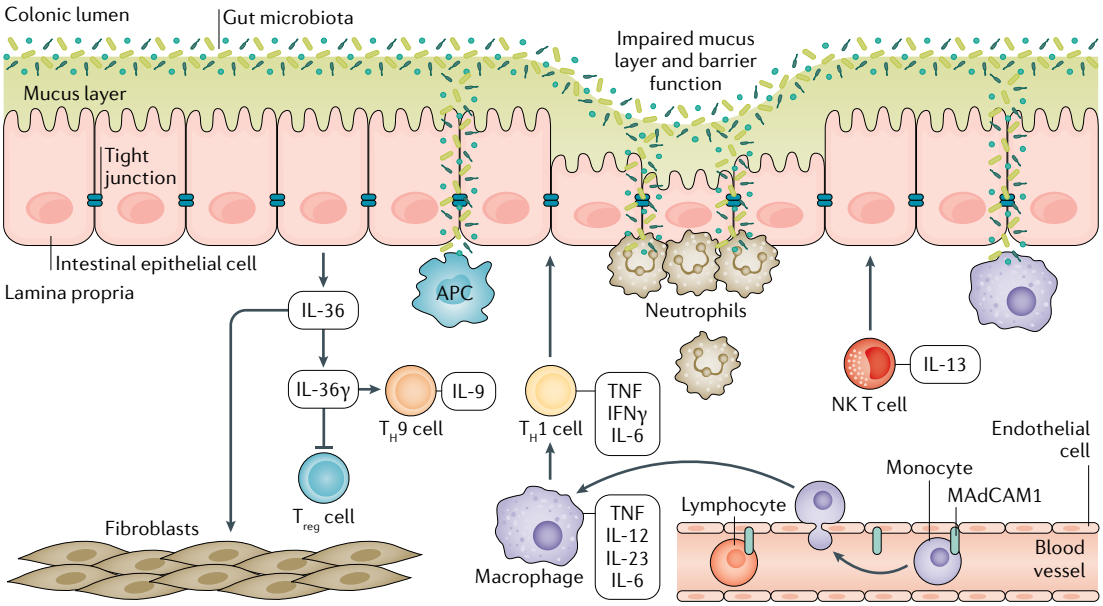

Fig. 2 | **Pathophysiology of ulcerative colitis.** Multiple factors contribute to the pathophysiology of ulcerative colitis (UC). The gut microbiota shows decreased diversity and a change in metabolic profile, which is indicated by a decrease in short-chain fatty acids. The mucus layer in UC is characterized by a decreased synthesis of the colon mucin, mucin 2. The changes in the microbiota as well as the decreased mucus layer result in a barrier breach, facilitating the approach of the microbiota to the epithelial barrier. The intestinal epithelium is disrupted owing to apoptotic foci and an altered expression of tight junction proteins, thereby permitting more microbiota to cross the barrier, activating macrophages and antigen-presenting cells (APCs) and resulting in the expression of chemokines that ultimately attract neutrophils. Neutrophils build the first line of cellular response by forming neutrophil extracellular traps, and immune cells infiltrate by binding to the adhesion molecule expressed by the blood vessel endothelium. Infiltrating monocytes that mature to macrophages produce tumour necrosis factor (TNF), IL-12, IL-23 and IL-6, resulting in a polarization of type 1 T helper (T_H1) cells. In addition, IL-36γ derived from the epithelium inhibits regulatory T (T_{reg}) cells and induces the polarization of IL-9-producing T helper (T_H9) cells, and IL-36 has been shown to induce fibrogenesis genes. Furthermore, IL-13 released by natural killer (NK) T cells has been shown to contribute to barrier dysfunction.

to the pathophysiology of the disease (FIG. 2). UC is an intestinal barrier disease driven initially by either an epithelial cell or structural intestinal epithelial dysfunction. Alternatively, the barrier might be disrupted by strong inflammatory mediators and cells in the lamina propria, which then consecutively result in barrier disruption; this inflammatory cascade then leads to the chronicity of the disease.

The maintenance of barrier function should be the primary therapeutic aim, which can probably be achieved using different strategies. Thus, therapeutic strategies can either target the epithelial cell layer or the inflammatory cells in the lamina propria and intestinal barrier function can be restored by both means, resulting in clinical remission.

Intestinal homeostasis

Intestinal homeostasis is based on a delicate equilibrium maintained by a number of components[62]. Beginning at the luminal surface, the key contributor is the intestinal microbiota, which provides nutritional factors and dietary components that serve to enhance barrier function. The intestinal lumen is followed by the mucus layer and the underlying epithelium, which together form the first line of defence. The innermost layer is the lamina propria, which is responsible for preserving the non-inflamed state in a healthy individual. Intestinal homeostasis can be disrupted at several levels: a primary dysbiosis of the intestinal microbiota, a defect in the mucus layer, a primary defect of the epithelium, or an inflamed state of the lamina propria. The contribution of these factors to the pathogenesis of UC will be discussed in the following sections.

Impaired barrier function

Early on in the pathogenesis of UC, an epithelial barrier defect is observed. For example, the thickness of the mucin-containing mucosal layer of the colon has been shown to be decreased in patients with UC with active disease, predominantly mediated through decreased synthesis of mucin 2 (REF.[63]) (FIG. 2). In addition, in the early stages of UC, although the epithelium looks normal endoscopically, apoptotic foci can already be observed[64]. Indeed, a study indicated a decrease in intestinal barrier function in patients with UC, which was evaluated using an oral sugar test (using sucrose for gastroduodenal permeability, lactulose/mannitol for intestinal permeability and sucralose for colon permeability). In addition, unaffected relatives revealed a higher intestinal permeability than the general population. This impaired barrier function can be because of a primary genetic defect but can also be due to environmental factors, including changes in the microbiota. Remarkably, a study evaluating the barrier defect in UC during remission found that the

barrier defect was an issue in the small intestine and not, as expected, in the colon[65]. The intestinal epithelium has a key role in the innate immune system, as it acts as the interface between the host immune response repertoire and the intestinal microbiota. Thus, the intestinal epithelium is particularly sensitive to changes that impair the resolution of endoplasmic reticulum stress, which can be driven by genetic as well as environmental and microbial factors[66]. Unresolved endoplasmic reticulum stress is a mechanism that contributes to the pathophysiology of both UC and CD. However, a discussion of these mechanisms is beyond the scope of this review; an excellent overview on this topic is presented in REF.[67].

In addition, altered expression of tight junction proteins that results in impaired barrier function has been implicated in the development of UC[62]. For example, tricellulin, a protein that contributes to the maintenance of barrier function against macromolecules and luminal antigens, has been shown to be specifically downregulated in patients with UC[68]. A study demonstrated that IL-13 (a cytokine important in regulating barrier function) and signalling via its receptor, IL-13Rα2, mediated the downregulation of tricellulin, whereas IL-13 signalling upregulated the pore-forming protein claudin 2, which was specifically found in patients with UC[68] (FIG. 2).

Why is the intestinal barrier of such importance for intestinal homeostasis? In the presence of a functioning intestinal barrier, consisting of intestinal epithelial cells and the mucus layer on top, only few luminal antigens find their way into the lamina propria. The existing tolerance mechanisms prevent the immune cells within the lamina propria from developing a pro-inflammatory immune response. However, when the barrier breach increases and more luminal antigens cross this barrier, these tolerance mechanisms fail, resulting in the stimulation of local immune cells, the production of chemokines and the subsequent infiltration of immune cells that further exacerbates this inflammatory process[69].

Neutrophilic immune response

Neutrophil extracellular traps (NETs, extracellular meshes composed of chromatin and neutrophil granular proteins) have been implicated in inflammation in addition to their function in host defence[70]. Proteins, including protein-arginine deiminase type 4, neutrophil elastase and myeloperoxidase, which are all associated with neutrophils and NETs, are upregulated in the colonic mucosa of patients with UC, even in remission[71,72]. The implication of this finding is not clear at this point but might be an indicator for a quiescent disease state. Thus, future work might need to consider these upregulated NET-associated proteins as therapeutic targets (FIG. 2) to reduce inflammation in UC.

Immune response in the lamina propria

Although UC was thought to be a type 2 T helper (T_H2) cell-driven disease and CD was postulated to be T_H1-driven disease[73], studies demonstrate that many key cytokines, including TNF, are shared between the two conditions. For several cytokines that originate from the pro-inflammatory immune cell infiltrate in the lamina propria, a central function in the pathogenesis of UC has been proposed; the key cytokines are discussed below.

IL-13. IL-13 has been reported to be upregulated in the lamina propria of patients with UC[68,74]. Indeed, strategies targeting IL-13 have been investigated in a mouse model of oxazolone-mediated colitis, in which colitis was induced by hapten sensitization, and IL-13 blockade demonstrated an amelioration of disease severity[68,74]. A study identified natural killer T cells as the IL-13-producing cell population, suggesting a significant role for this cell population in the pathogenesis of UC[75]. However, a phase II clinical trial of an anti-IL-13 antibody reported no therapeutic benefit or amelioration of disease severity in patients with moderate-to-severe UC[76]. Although no further anti-IL-13 strategies are being developed, the specific function of this cytokine in the pathogenesis of UC remains to be understood.

TNF. TNF, a key cytokine that is elevated in CD and is responsible for granuloma development in this disease[77], is also elevated in patients with UC[78]. In addition, TNF has been shown to induce a substantial decrease in intestinal barrier resistance and, therefore, TNF produced in the lamina propria results in a barrier defect that is characteristic for UC[78]. Indeed, studies have shown that anti-TNF treatment is efficacious in a subgroup of patients with CD as well as in those with UC[79,80].

IL-23. The role of IL-23 (a heterodimeric cytokine that shares the p40 subunit with IL-12 and is mainly produced by macrophages) and its receptor have been genetically and functionally linked to intestinal inflammation in various mouse models and in patients with UC[81,82]. Evidence from experimental animal models and phase II clinical trials indicates that the blockade of IL-23 rather than IL-12 is important for the anti-inflammatory effects observed with anti-p40 antibodies[81,83]. Originally, IL-23 blockade was believed to be effective only in CD. However, a phase III trial of ustekinumab (an antibody targeting the shared subunit IL-12/IL-23p40) in patients with UC has demonstrated efficacy and an anti-inflammatory effect in UC[84].

IL-9. In mouse models of oxazolone-induced colitis and in mucosal T cells of patients with UC, increased expression levels of IL-9 as well as of its transcription factor PU.1 were observed. The stimulation of T cells by TGFβ induces the expression of PU.1, which binds directly to the *IL9* promoter, forming a complex with the histone acetyltransferase, GCN5, resulting in an induction of the *IL9* promoter. In line with these findings, IL-9 knockout, PU.1-deficient T cells or antibody-mediated neutralization of IL-9 was sufficient to ameliorate inflammation in experimental colitis[85]. These data strongly point to a possible role of IL-9-producing T helper (T_H9) cells in the pathophysiology of UC, although a clinical study is required to confirm the functional relevance in humans.

IL-36. Expression levels of IL-36 (a cytokine of the IL-1 family) and its receptor, IL-36R, are also increased in patients with UC[86,87]. Additional studies showed that the

increased expression of IL-36γ was localized to fibrotic intestinal tissue of patients with UC as well as of those with CD. IL-36 has been known to induce fibrogenesis in fibroblasts, for example, by upregulation of α-smooth muscle actin expression (FIG. 2). Blockade of IL-36 signalling in experimental colitis was associated with less severe colitis and intestinal fibrosis than in controls[88]. These findings are of importance in UC, as a considerable degree of fibrosis and muscularis mucosae thickening was described in chronic UC[89]. Furthermore, IL-36γ has been shown to inhibit regulatory T (T_{reg}) cell development. T_{reg} cells form a key subpopulation of T cells that maintain intestinal homeostasis and, therefore, a decrease of T_{reg} cell abundance indirectly promotes inflammation. In addition, IL-36γ enhances the differentiation of T_H9 cells, a pro-inflammatory T_H cell subpopulation that drives inflammation. In line with these observations, mice deficient in IL-36γ were protected from colitis[90]. Future studies and clinical trials are warranted to understand the clinical effect of these pathways (FIG. 2).

Luminal factors

The intestinal microbiota, which can be closely linked to environmental changes[91], has been implicated to have a regulatory function in UC. A lower abundance of some gut bacteria, such as *Roseburia hominis* and *Faecalibacterium prausnitzii* (the most abundant commensals in the healthy human gut), has been reported in patients with UC[92]. Although microbial dysbiosis (decreased microbial diversity) could be linked to active UC, the individual contribution of single bacterial species is less well defined[93]. In addition, the production of short-chain fatty acids (SCFAs) was reported to be reduced in patients with UC. Studies have shown that SCFAs exert barrier-protective actions and have anti-inflammatory properties[94]. Remarkably, in contrast to *Clostridioides difficile*-induced colitis, the simple substitution of a 'diseased' microbiota with a 'healthy' microbiota by a single faecal microbiota transplantation does not induce cure in patients with UC. However, studies have demonstrated that remission can be achieved in a limited number of patients with UC by repeated faecal transplantation[95–97]. Interestingly, patients who achieved remission were characterized by a significant increase in microbial diversity[96,97] and some donors seemed to be more suitable than others to help achieve remission; however, the markers that would enable identification of these subsets of individuals are currently lacking[95,96].

Increasing evidence suggests that various bacterial metabolites, such as SCFAs (for example, butyrate), rather than the microbiota itself, are important to maintain the intestinal barrier and, thus, mucosal homeostasis[92]. For example, butyrate, a histone deacetylase inhibitor, has been shown to maintain intestinal barrier function by an IL-10-mediated downregulation of the pore-forming protein claudin 2 (REF.[98]), which increases the permeability of the tight junctions. In experimental models of colitis, butyrate substitution by pharmacologically designed histone deacetylase inhibitors resulted in an amelioration of colitis[99]. Thus, prospectively, a 'smart metabolite cocktail' might be sufficient to provide the niche that allows the microbiota to maintain its natural diversity (FIG. 2).

Intestinal T cell homing

Gut homing of T cells has a key role in the pathophysiology of UC[100]. Vedolizumab, an antibody to α4β7 integrin, has shown beneficial effects in the treatment of UC[101]. However, the detailed effects of adhesion molecules on single immune cell subpopulations have not been entirely deciphered. A study investigating the functional effect of α4β7 integrin and the G protein-coupled receptor GPR15 for intestinal homing of either effector T (T_{eff}) cells or T_{reg} cells indicated that α4β7 is crucial for the homing of T_{reg} cells, whereas both α4β7 and GPR15 mediate the homing of T_{eff} cells. Indeed, patients treated with vedolizumab showed a decrease in homing of T_{reg} cells as well as T_{eff} cells[100]. This result implies that, in particular, fewer inflammatory cells enter the lamina propria when gut homing is blocked, ultimately resulting in decreased inflammation. Further studies on other immune cell subpopulations are required to completely understand the mechanisms underlying the therapeutic efficacy observed for vedolizumab (FIG. 2).

Diagnosis, screening and prevention

Diagnosis

An accurate and timely diagnosis of UC is important to start the appropriate treatment. The current diagnostic criteria for UC have not altered much over the past few decades and are based on the combination of clinical symptoms, endoscopic appearance, histological analysis and the exclusion of potential differential diagnoses, such as infection and other forms of colitis[5,6,102] (TABLE 1). Nonetheless, various biomarkers, such as faecal calprotectin or faecal lactoferrin, as well as bowel ultrasonography are being increasingly used for non-invasive diagnosis and monitoring. In addition, artificial intelligence might be a helpful tool to increase diagnostic accuracy in the near future. No single gold-standard modality for diagnosing UC exists; therefore, a UC diagnosis has to be made by integrating patient history, endoscopy, histopathology, laboratory testing and imaging studies when necessary and appropriate[5,6,102].

Patient history. A careful documentation of a patient's medical history is the first step towards establishing a correct diagnosis of IBD, including UC. The chronicity of symptoms is an important factor that needs to be considered. A diagnosis of UC in patients with acute-onset symptoms and a definite time frame should raise concern, as infection and bowel ischaemia would be more likely diagnoses than IBD, especially if the symptoms have manifested only over a short period of time. Typical symptoms in UC include blood and/or mucus in the stool, increased bowel movement frequency, tenesmus or urgency presenting for months in patients between 20 and 50 years of age. Despite technological progress, patient medical history continues to be the foundation of diagnosis and cannot be replaced. Occasionally, patients present with profound bloody diarrhoea associated with anaemia, tachycardia and fever; in these cases, acute severe colitis should be considered and prompt therapy indicated accordingly.

Tenesmus
An abnormal feeling of incomplete defecation.

Table 1 | **Differential diagnosis of ulcerative colitis**

Differential diagnosis[a]	Diagnostic tool	Distinguishing features
Infection		
Bacteria (*Salmonella* spp. or *Shigella* spp., *Escherichia coli*, *Clostridioides difficile*, *Campylobacter* spp., Mycobacteriaceae, *Yersinia* spp.)	History plus stool culture	Acute onset, positive stool culture
Protozoa (amoebic colitis and strongyloidiasis)	Stool ova and protozoa study	Positive stool test
Virus (cytomegalovirus)	Colonic histopathology with IHC	Positive IHC
Immune related		
Crohn's disease	Endoscopic picture	Skipped lesions, longitudinal ulcers
Graft versus host disease	History plus endoscopic picture	History of transplantation
Immune therapy-related colitis	History plus endoscopic picture	History of immune-checkpoint inhibitor use
Eosinophilic colitis	Colonic histopathology	Eosinophilic infiltration
Vascular		
Ischaemic colitis	History plus endoscopic picture	Acute onset, ischaemic change in the watershed area
Vasculitis	History plus other lab data	Anti-neutrophil cytoplasmic antibody
Exposures		
Radiation colitis	History plus endoscopic picture	Localized in the exposed area
Bowel preparation-related colitis	History plus endoscopic picture	Acute onset after bowel preparation
Malignancy		
Lymphoma	Colonic histopathology	Lymphoma cells
Primary adenocarcinoma	Colonic histopathology	Adenocarcinoma
Metastatic cancer	Colonic histopathology	Tumour cells depending on the primary site
Miscellaneous		
Diverticulum-associated colitis	Endoscopy	Presence of inflammation within a diverticulum involved segment
Diversion colitis	History plus endoscopic picture	History of colonic diversion surgery

IHC, immunohistochemistry. [a]All differential diagnoses are diagnosed by colonic histopathology.

Endoscopy. In patients presenting with the above-mentioned cardinal symptoms, initial endoscopic evaluation is an indispensable tool for establishing an accurate disease diagnosis and to evaluate the extent and severity of disease[103]. The evaluation of disease extent affects the treatment choices (local versus systemic treatment) and prognosis (possibility for proximal extension). Several guidelines recommend a full colonoscopy (FIG. 3) with ileal intubation in all patients with a clinical presentation suggestive of IBD. However, it is contraindicated by the presence of severe colitis or toxic megacolon, in which the risk of bowel perforation should be weighed against the diagnostic value of endoscopy[5,102,104]. When perforation risk is a concern, cross-sectional imaging studies, such as computed tomography, MRI or bowel ultrasonography, are reasonable alternatives[102].

In UC, the earliest response to tissue injury is an increased blood flow in the colonic mucosal surface, leading to erythema, vascular congestion and oedema, which can appear as 'wet sandpaper' during visualization[105]. Hallmark endoscopic features of UC include the presence of continuous inflammation extending proximally from the anal verge, often characterized by erythema, oedema and ulceration. The degree of inflammation classically, but not invariably, increases in a proximal to distal pattern. There is often a line of demarcation at the proximal extent of disease, with an abrupt transition to normal mucosa[104].

Histopathology. At the time of diagnosis, systematic biopsies from each segment of the large bowel are highly recommended to make a correct and thorough diagnosis because the macroscopic appearance often underestimates the histological extent of UC[6,102,103]. The histopathological features of UC mostly include changes in the mucosal architecture (including changes

Megacolon
Dilation of the colon without any mechanical obstruction.

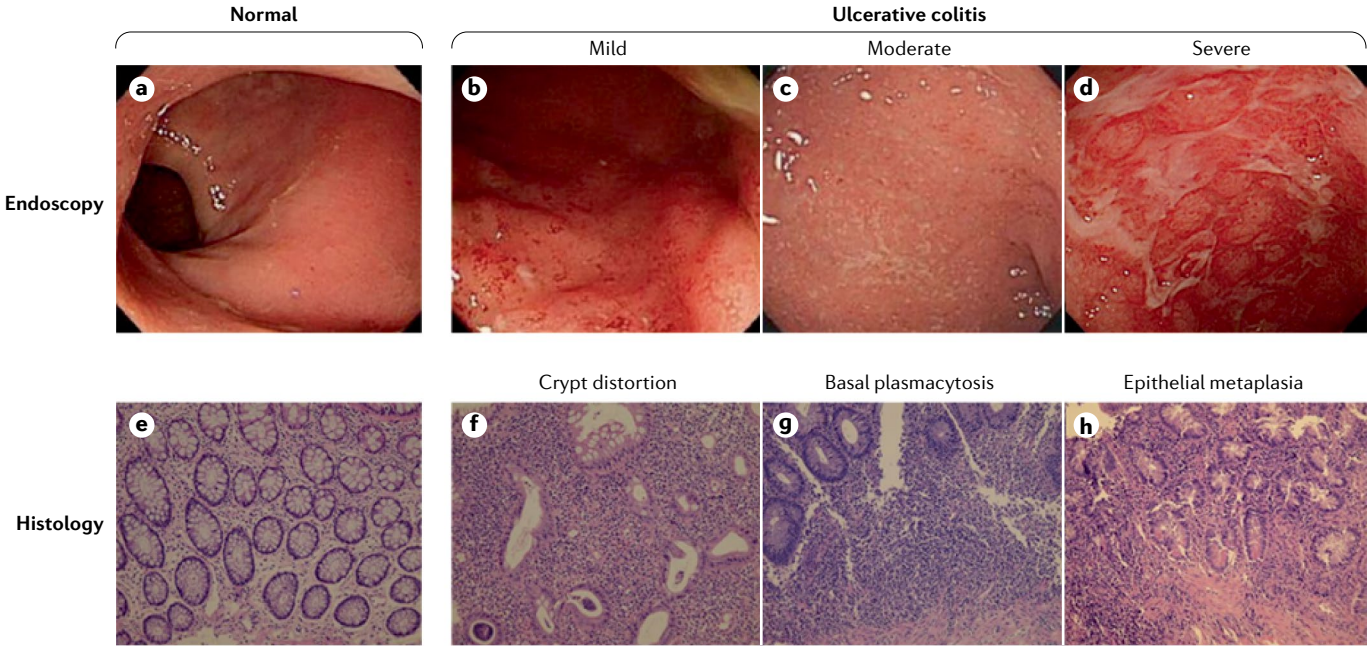

Fig. 3 | **Endoscopic and histological features of ulcerative colitis.** Endoscopic and histological findings are essential for the differential diagnosis of ulcerative colitis (UC). Endoscopic image of a normal colon (part **a**). Endoscopic images of colons with increasing severity of UC (parts **b**–**d**); obliterated vascular patterns, mucosal friability, erythema, bleeding, erosions or ulcerations can be observed according to the severity of inflammation. Normal histology of the colon (part **e**). Histological findings in UC can be non-specific, however, crypt distortion (part **f**), basal plasmacytosis (part **g**), and epithelial metaplasia and goblet cell depletion (part **h**) are the histological characteristics of UC. Haematoxylin and eosin staining was performed in parts **e**–**h**, magnification ×200. Histology images courtesy of T.-A. Chang.

in colonic crypt morphology and decreased crypt densities), alterations in the lamina propria cellularity, immune cell infiltration (crypt abscess and basal plasmacytosis) and epithelial abnormality (including epithelial metaplasia and loss of goblet cells)[106] (FIG. 3). In addition to providing a confirmation of diagnosis, another important role of histopathology is that it can be useful to rule out other aetiologies, such as infection, ischaemia and malignancies[102] (TABLE 1).

Laboratory testing. Biochemical test results, including elevated CRP, anaemia and hypoalbuminaemia, might be useful additional parameters of disease severity[102,107]. However, these parameters cannot be used to establish a diagnosis, as most patients with UC have a normal biochemistry with only mild or no anaemia at presentation, unless the disease severity is high.

Severity stratification

Various scoring instruments integrating clinical symptoms, physical findings and endoscopic analysis have been used to assess the disease severity of UC. These scores are used as objective indices to guide therapy and monitor the disease condition[108]. The most commonly used scoring instrument in clinical practice or in clinical trials is the Mayo Score (also known as the Mayo Clinic Score or the Disease Activity Index), first described in 1987 (REF.[109]). The instrument measures disease severity by integrating clinical symptoms, such as bowel movement (score 0–3; symptoms ranging from normal, 1–2 more bowel movements a day, 3–4 more bowel movements a day or ≥5 more bowel movements a day), blood in stool percentage (score 0–3; no blood, streaks of blood with stools appearing in <50% of the bowel movements, bloody stools in >50% of the bowel movements or frank blood mostly), physicians' global assessments (score 0–3) and endoscopic findings (score 0–3; normal, inflammation, erosion or ulcer). The total Mayo score ranges from 0 to 12, with remission having a score of 0–2 (no sub-scores >1), mild disease activity having a score of 3–5, moderate to severe disease activity having a score of 6–10, and severe disease activity having a score of 11–12 (REF.[110]).

Diagnostic workflow in current clinical practice. The confirmation of a UC diagnosis is usually made after the patient achieves clinical, endoscopic and, in some cases, even histological improvement. Thus, after induction therapy, follow-up to assess the improvement would provide diagnostic confirmation. If a patient does not improve or improves only slightly, re-evaluation of the diagnosis and treatment modifications are essential to confirm the diagnosis and apply the 'treat-to-target' approach (BOX 1) to achieve better outcomes.

Emerging diagnostic modalities

Faecal biomarkers. Faecal biomarkers, such as faecal calprotectin and lactoferrin, have emerged as a new diagnostic tool to detect and monitor intestinal inflammation[111,112]. These two faecal biomarkers are now being used in clinical practice to differentiate irritable bowel syndrome from IBD, to monitor disease activity and the response to treatments, and even to predict symptomatic flares, allowing an earlier intervention[6,11,113].

Colonic crypt
A repetitive invagination of colonic surface epithelium.

Crypt abscess
A collection of neutrophils in an intestinal crypt.

Basal plasmocytosis
The presence of plasma cells beneath the base of the crypts.

Metaplasia
A transformation of one differentiated cell type to another.

Goblet cells
A type of colonic epithelial cell that secrete mucus.

Faecal calprotectin is a neutrophil cytosolic protein that is released into the bowel lumen during active intestinal inflammation[114]. Faecal calprotectin is a reliable biomarker owing to its homogeneous distribution in the stool, its stability at room temperature for up to 7 days and the consistent correlation of its levels with endoscopic index[115]. According to previous studies and meta-analyses, the sensitivity of faecal calprotectin for detecting IBD is 80–98% and the specificity is 68–96%, with the cut-offs ranging from 30 µg/g to 100 µg/g (REFS[113,116]). Faecal lactoferrin is an iron-binding glycoprotein and a major component of the secondary granules of intestinal mucosal neutrophils. During the inflammatory process, neutrophil degranulation occurs and the faecal concentration of lactoferrin increases proportionally[117]. Although lactoferrin is a stable molecule and resistant to proteolysis in the faeces, lactoferrin is less stable than faecal calprotectin, with a stability of up to 2–5 days at room temperature[118].

Faecal calprotectin and faecal lactoferrin levels can be quantitatively assessed using ELISA, and a point-of-care test (POCT) has been developed to measure both biomarkers. In paediatric patients, the sensitivity of both the calprotectin and the lactoferrin POCTs has been shown to be 0.94 (95% CI 0.72–0.99), with specificities of 0.93 (95% CI 0.84–0.97) and 0.99 (95% CI 0.92–1.00), respectively. The study showed that the calprotectin and lactoferrin POCTs reduced the referral rate by 76% and 81%, respectively, although the biomarkers missed one child with IBD (6%). Nonetheless, these biomarkers have the potential to reduce the need for referral for further diagnostic workup in a specialist care centre, with a very low risk of missing a child with IBD[119]. Similarly, in adults, faecal calprotectin levels of <100 µg/g have been shown to have a very high negative predictive value for IBD in differentiating from irritable bowel syndrome, justifying its use as a screening test to reduce the number of endoscopies and thereby the costs of health-care management. This strategy has been shown to delay the diagnosis in only a small proportion (7%) of patients[120]. Faecal calprotectin levels of >250 µg/g identify patients who are most likely to have intestinal inflammation and might need further endoscopic examination[121]. Faecal lactoferrin cut-off values of <7.25 µg/g are considered normal, but lactoferrin remains minimally investigated to date[122].

Of note, both faecal calprotectin and faecal lactoferrin are also elevated in other inflammatory intestinal disorders, such as gastrointestinal malignancies, NSAID enteropathy, infectious gastroenteritis and diverticulitis. Hence, the implication of increased levels should be correlated with the appropriate clinical condition after careful consideration[123].

MicroRNA expression profiling. In addition to faecal biomarkers, serum biomarkers may also be used for an early diagnosis of UC. A study evaluated the combination of machine learning techniques and systemic microRNA (miRNA) expression profiling as a non-invasive test for the diagnosis of IBD[91]. Based on microarray technology, expression levels of 863 miRNAs were determined in whole blood samples from 40 patients with CD, 36 patients with UC and 38 healthy individuals[124]. The study further discriminated between disease-specific inflammation and general inflammation by analysing miRNA expression levels from 130 patients with other inflammatory diseases as well as 70 healthy individuals. According to the findings, levels of the miRNAs miR-103–2*, miR362-3p and miR-532-3p were elevated in patients with UC compared with healthy individuals. Furthermore, a combination of expression levels of eight miRNAs (miR-28-5p, miR-103–2*, miR-149*, miR-151-5p, miR-340*, miR-505*, miR-532-3p and miR-plus-E1153) was useful in discriminating between active CD and active UC[125]. However, the diagnostic value of serum miRNA levels should be further evaluated in large, independent, clinically well-characterized cohorts.

Bowel ultrasonography. Transabdominal bowel ultrasonography (BUS) is a well-tolerated, non-invasive, radiation-free, cheap, easy-to-use tool in clinical practice. Two prospective studies[126,127] showed that the findings from BUS correlated well with the colonoscopic findings of UC disease activity and severity. One of these studies proposed the Humanitas Ultrasound Criteria for assessing disease activity and severity, grading colonic wall thickening (>3 mm), colonic wall flow at power Doppler and colonic wall pattern (normal (0 points), multilayered (1 point), prevalently hypoechogenic (2 points), prevalently hyperechogenic (2 points), and loss of the multilayers and presence of lymph nodes (3 points))[126]. Transperineal ultrasonography is reported to be a useful tool to visualize rectal inflammation to compensate for the limitations of transabdominal BUS; operator dependency is the major limitation of BUS[128].

Box 1 | **Treat-to-target strategy**

'Treat-to-target' is a principle or an approach that has been successful in treating certain chronic diseases by determining a target and continuing to treat patients until the target is achieved. Initially, this approach was used to treat hypertension, diabetes mellitus and hyperlipidaemia to avoid progression and the development of complications. Recently, this scope has been broadened to include other chronic disorders, including inflammatory bowel disease.

A discrepancy between clinical symptoms and endoscopic severity has been observed, and endoscopic severity is more closely associated with the clinical course of ulcerative colitis. Thus, the current gold standard definition of the treatment target is endoscopic resolution of inflammation, referred to as mucosal healing. The diverse ways to measure mucosal healing include resolution of symptoms and a Mayo endoscopic sub-score of 0–1 (absence of ulcers, erosions, friability and spontaneous bleeding). As faecal calprotectin has been shown to correlate well with endoscopic disease activity, this faecal biomarker could be used as an adjunctive measure in monitoring the disease status.

In contrast to Crohn's disease, high-quality randomized trials for ulcerative colitis employing the treat-to-target approach are lacking. Several important questions remain to be answered to determine whether the treat-to-target strategy can be pursued in clinical practice. For example, which patients would benefit from this strategy and how can treatment be optimized? Should one always step-up to more robust treatment to treat endoscopic lesions, even in asymptomatic patients? Furthermore, whether treatment escalation enables a patient to reach the target is also unclear.

Several studies suggest that achievement of mucosal healing results in sustained remission but the long-term outcomes over the years are still unknown. One should be aware that the ultimate goal of the treat-to-target approach is to allow patients to experience a normal daily life whilst minimizing costs and invasiveness.

Colon capsule endoscopy. Colon capsule endoscopy (CCE) has been used recently to detect colonic polyps or cancer. Increasing data suggest that CCE can also be used to monitor mucosal inflammation in patients with active IBD[129,130]. Preliminary studies demonstrate good correlation between CCE and optical colonoscopy for the assessment of colonic disease activity in IBD. Despite the advantages of its non-invasive nature, patient comfort and safety, CCE has limitations, including the lack of ability to obtain biopsies and no control over its movement inside the body[131]. Hence, the use of CCE in the diagnosis of UC requires further investigation.

Artificial intelligence. With the advancements in information technology and the application of artificial intelligence in medicine, a fully automated diagnostic system employing artificial intelligence that uses endocytoscopy to determine the histological remission of UC has been reported[132]. With the further progress in research and training, one can assert that the combination of artificial intelligence, CCE and/or endocytoscopy will be implemented in the future for diagnosing UC (FIG. 4). Another possible integrated use of artificial intelligence in IBD diagnosis could be in assisting histological reading to exclude mimics of IBD, such as in detecting acid-fast bacilli, granulomas or giant cells with inclusion bodies.

Screening

Chronic inflammation in UC has been shown to promote the development of colon cancer, and chronic inflammation is the main pathogenetic factor of IBD-induced CRC, although the mechanisms involved are not yet clear[133]. According to a Cochrane review, colonoscopic screening or surveillance in patients with IBD might reduce the development of CRC and the rate of CRC-associated death through early detection[50]. All guidelines recommend screening or surveillance colonoscopies 8 years after the onset of pancolitis or 12–15 years after the onset of left-sided colitis to assess disease extent and other endoscopic risk factors[47]. This recommendation is especially highlighted in patients with a family history, younger age of onset and/or other comorbidities, such as primary sclerosing cholangitis. However, discrepancy exists among guidelines in terms of the interval duration and the recommended method used for screening (random biopsy versus targeted biopsy[134] with the use of chromoendoscopy or narrow band imaging). In the real world, another factor that influences the effectiveness of CRC screening is the

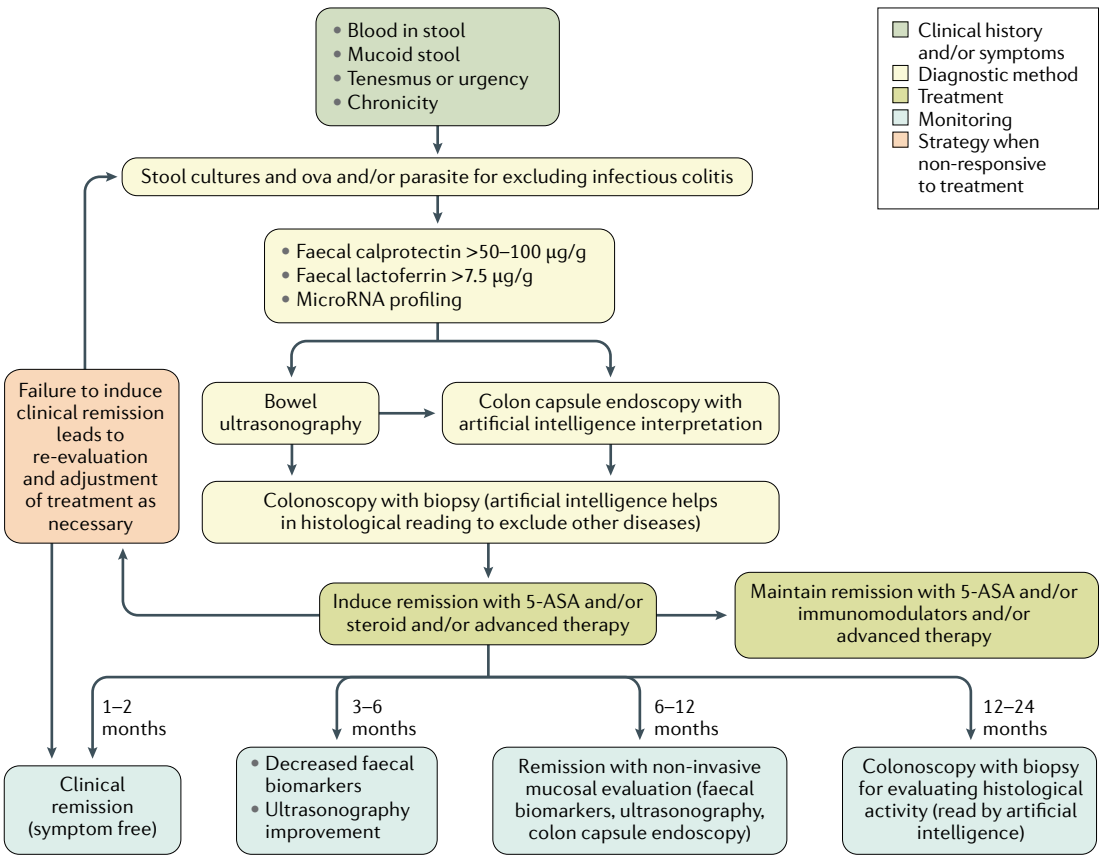

Fig. 4 | **Proposed diagnostic flow for ulcerative colitis in the future.** Current standard diagnosis of ulcerative colitis (UC) is made from a combination of patient history and endoscopy with biopsy. Less-invasive techniques, such as faecal biomarkers, microRNA profiling and abdominal ultrasonography, should be incorporated in future in clinical practice. The diagnostic assessment should also be repeated for frequent monitoring so that treatment can be optimized to achieve better long-term outcomes via the treat-to-target strategy. Advanced therapy includes anti-tumour necrosis factor (TNF) therapy, vedolizumab, ustekinumab and tofacitinib. 5-ASA, 5-aminosalicylate.

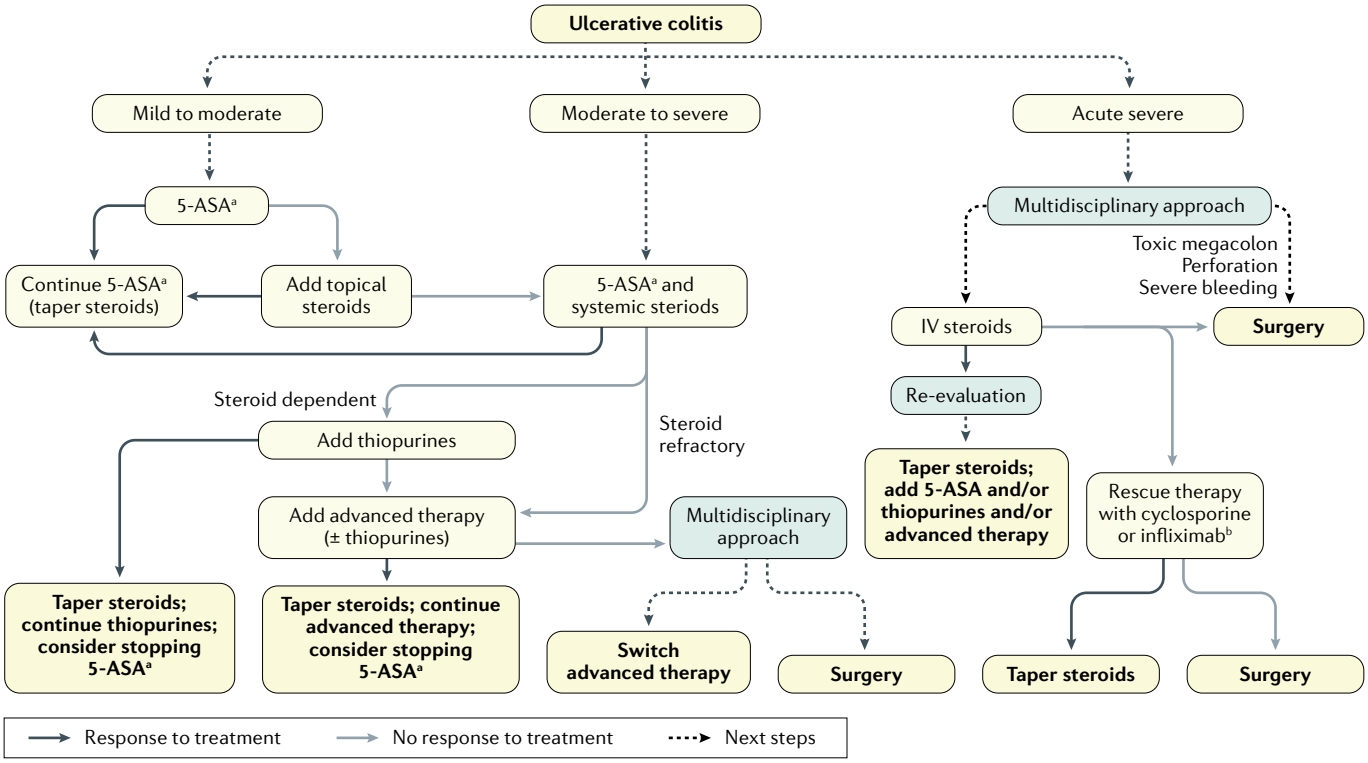

Fig. 5 | **Management of ulcerative colitis according to disease severity.** The conventional treatment approach is to step-up from 5-aminosalicylate (5-ASA) with or without topical therapy followed by thiopurines, steroids and advanced therapy according to disease severity and patient response to systemic steroids. Advanced therapy includes anti-tumour necrosis factor (TNF) therapy, vedolizumab, ustekinumab, tofacitinib, tacrolimus and cyclosporine. The multidisciplinary team approach involves physicians, surgeons, nurses, pharmacists and dieticians, and such an approach has an important role in making critical decisions. IV, intravenous. [a]5-ASA could probably be discontinued once endoscopic response (that is, Mayo subscore 0 or 1) has been achieved. [b]Consider other advanced therapies.

compliance of doctors and patients to the surveillance programme.

Management

The therapeutic approach in patients with UC mainly depends on the severity of the disease, the extent of inflammation and its evolution over time[5,135]. However, the treatment goal should be rather similar for all patients, namely, achieving resolution of rectal bleeding and diarrhoea as well as of mucosal friability and ulceration at lower endoscopy, all within 3 months after starting therapy[11].

In patients with acute severe colitis, prompt hospital admission is required[136]. A multidisciplinary approach is fundamental, and contacting a colorectal surgeon at the moment of admission is recommended. Sometimes, emergency surgery might be required early on in case of toxic megacolon, perforation or massive bleeding. Although treatment initiation should not be postponed in severe cases, excluding differential diagnoses, including *C. difficile* infection, is crucial. A limited flexible sigmoidoscopy without bowel preparation should be performed to assess disease severity as well as to acquire mucosal biopsies to rule out cytomegalovirus. In most cases, screening for latent tuberculosis and hepatitis B virus at the moment of admission is indicated to prevent delaying eventual rescue therapy with an anti-TNF agent. Most patients should be managed with aggressive medical therapy, starting with intravenous corticosteroids[7] (FIG. 5). As patients with active UC have an increased risk of thromboembolism (that is, obstruction of a blood vessel by a blood clot)[137], anticoagulants, such as low-molecular-weight heparin, and calcium and vitamin D supplements should be initiated in addition to adequate fluid and electrolyte replacement. Hospitalized patients should be re-evaluated regularly in a multidisciplinary way involving physicians, surgeons, radiologists, specialist nurses, pharmacists and dieticians. Failure of intravenous corticosteroids at day 3–5 should prompt rescue therapy with cyclosporine, infliximab or surgery[7,135,136,138].

The principles of management are basically the same among older and younger adults and paediatric patients. However, in paediatric patients, the nutritional and psychological aspects require greater attention, whereas comorbidities should be considered when treating older adult patients[5,139]. In addition, some advanced therapies, such as tofacitinib and ustekinumab, have not been approved for use in paediatric patients, although the majority of paediatric-onset UC presents as extensive colitis, affecting the entire colon, with a more aggressive course[140]. By contrast, although the severity of late-onset disease in adult patients is comparable with that in early-onset patients[139], the influence of comorbidities, which might lead to a more critical disease course and disease-related complications, needs to be considered[141].

Mucosal friability
An abnormally fragile surface of the intestine due to inflammation.

Pharmacological management

Most patients with UC can be managed at the outpatient clinic and treated successfully with a symptom-focused step-up approach comprising 5-ASA, corticosteroids and thiopurines, such as azathioprine and 6-mercaptopurine[135] (FIG. 5). Indeed, patients with mild-to-moderate, left-sided or extensive colitis will benefit most from a combination therapy consisting of oral 5-ASA and rectal 5-ASA or steroids[142]. In patients failing this first-line therapy, oral corticosteroids are recommended. Topical agents, such as beclomethasone dipropionate and budesonide MMX, are preferred over systemic steroids owing to their superior safety profile[143]. However, corticosteroids should be tapered after achieving clinical remission (defined as a lack of bleeding and increased bowel movements) to prevent adverse effects, whereas 5-ASA therapy is continued for maintenance of remission. Patients with corticosteroid-refractory or corticosteroid-dependent UC should be reassessed to initiate additional medical therapy[5,135]. Although thiopurines are effective in maintaining remission in corticosteroid-dependent UC, methotrexate is not as effective as induction or maintenance therapy[144,145]. However, the use of thiopurines is increasingly questioned owing to their slow onset of action as well as the increasing evidence of potentially serious adverse effects, such as bone marrow and liver toxicity, pancreatitis, increased risk of non-melanoma skin cancer and lymphoma[135].

Advanced therapies

Anti-TNF therapies. Since the early 2000s, several biological therapies and small molecules have shown efficacy in patients with moderate-to-severe UC. However, in most jurisdictions, these efficacious drugs are only available for patients who previously failed to improve with corticosteroids and/or thiopurines. Anti-TNF therapies, including infliximab, adalimumab and golimumab, have become indispensable in the management of UC. In a pivotal placebo-controlled, active-controlled trial, a significant proportion of patients with moderate-to-severe UC receiving intravenous infliximab achieved clinical response, clinical remission and mucosal healing at 8, 30 and 54 weeks following treatment, respectively[80]. Of note, patients who achieved short-term mucosal healing (defined as a Mayo endoscopic sub-score of 0 or 1 at week 8) had a better long-term outcome, including longer relapse-free and colectomy-free survival[146]. Furthermore, a combination therapy of infliximab and azathioprine was superior to infliximab monotherapy in achieving corticosteroid-free clinical remission at week 16 (REF.[147]). In the ULTRA 2 trial, significantly more patients treated with subcutaneous adalimumab achieved clinical response with clinical remission at 8 weeks and mucosal healing at 52 weeks compared with placebo, especially, in anti-TNF-naive patients[148]. In addition, adalimumab treatment was associated with lower UC or drug-related hospitalization rates than placebo. Finally, in the PURSUIT trial, subcutaneous golimumab was associated with significantly higher clinical response and mucosal healing remission rates at 6 weeks than with placebo[149].

Anti-adhesion therapy. The GEMINI 1 study clearly showed the efficacy of intravenous vedolizumab, an anti-α4β7-integrin antibody, in inducing and maintaining clinical remission and mucosal healing in patients with moderate-to-severe UC[101]. However, patients previously failing anti-TNF therapy showed lower efficacy rates with vedolizumab. Although significant differences compared with placebo were already observed at week 6, the onset of action of vedolizumab is generally regarded as slower than anti-TNF agents. In the entire phase III programme, vedolizumab treatment up to 5 years ($n = 2,830$, of whom 1,107 with UC) demonstrated a favourable safety profile[150]. Vedolizumab was not associated with an increased risk of serious or opportunistic infections but enteric infections did occur more frequently than with placebo. In addition, infusion reactions (hypersensitivity that develops following drug administration) were rare, highlighting the low immunogenicity risk of this molecule. In a new head-to-head trial, vedolizumab was shown to be superior to adalimumab in achieving remission at week 54[151]. A subcutaneous formulation of vedolizumab has been developed and was confirmed to be as efficacious as intravenous vedolizumab as a maintenance treatment throughout week 52 (REF.[152]).

Anti-IL-12/IL-23p40 therapy. Ustekinumab is an anti-IL-12/IL-23p40 antibody that is generally used in the treatment of psoriasis, psoriatic arthritis and CD. A phase III clinical trial (UNIFI) involving patients with moderate-to-severe active UC showed that ustekinumab was effective in inducing clinical remission at 8 weeks[84]. Subcutaneous ustekinumab every 8 or 12 weeks was also effective as maintenance therapy in patients who responded to the intravenous induction dosing. Patients who previously failed anti-TNF treatment demonstrated lower response and remission rates, as consistently observed with other biologics. The safety and immunogenicity of ustekinumab have been shown to be comparable with those of vedolizumab[81].

JAK inhibitors. Tofacitinib, an orally administered small molecule preferentially targeting JAK1 and JAK3, showed efficacy in patients with moderate-to-severe UC. In the OCTAVE trials, clinical remission and mucosal healing rates were significantly higher in the tofacitinib group than in the placebo group[153]. Furthermore, anti-TNF-naive patients demonstrated the best remission and healing rates but tofacitinib was also significantly efficacious in anti-TNF-experienced patients. Although the safety profile of JAK inhibitors is generally acceptable, long-term safety studies have reported a high risk for the reactivation of herpes zoster. A trial involving patients with rheumatoid arthritis showed a fivefold increase in pulmonary embolisms in patients treated with high-dose tofacitinib (10 mg twice daily) compared with patients treated with infliximab[154]. Of note, all patients included in this trial needed to have substantial cardiovascular comorbidities and an absolute risk of thrombosis was not shown. Therefore, the risk specifically in UC are currently unknown[155].

Surgical management

Despite advances in medical therapy, ~20–25% of patients with UC eventually require surgical intervention. In an epidemiology study conducted between 1970 and 2004 from Olmsted County, Minnesota, USA, the cumulative probability of colectomy from time of diagnosis was 13.1%, 18.9% and 25.4% at 5, 10 and 20 years, respectively[156]. A population-based study conducted between 1987 and 2008 from Manitoba, Canada, showed the cumulative incidence of colectomy in patients with UC to be 7.5%, 10.4% and 14.8% at 5, 10 and 20 years, respectively[157]. However, the 10-year colectomy rates have significantly decreased over time (12.2% between 1987 and 1991, 11.2% between 1992 and 1996, and 9.3% between 1997 and 2001)[158]. Interestingly, this downward trend antedated the use of biological therapy. A population-based study from the Calgary Health Zone, Canada, conducted between 1997 and 2009, also showed a significant drop in elective colectomies for UC, with an average annual change of −7.4% (95% CI −10.8% to −3.9%)[159]. A Swedish population study conducted in the current biologics era observed a similar trend, with reduced colectomy rates[160]. However, the rate of emergency colectomies have remained stable, with an average annual change of −1.4% (95% CI −4.8% to 2.0%)[159]. The extensive use of immunomodulators and biological agents is speculated to contribute further to the decline in current colectomy rates, although this speculation needs to be verified.

The main indications for colectomy in patients are medically refractory UC, poor drug tolerance and UC-associated neoplasia. Surgical treatment modalities include colectomy or proctocolectomy with permanent Brooke end ileostomy and restorative proctocolectomy (RPC) with the construction of a pelvic or an abdominal pouch. RPC has become the surgical treatment of choice for UC and staged RPC has become conventional in the treatment of UC requiring colectomy. The two-stage surgery normally consists of a total proctocolectomy with the construction of an ileal pouch and diverting ileostomy, followed by ileostomy closure. By contrast, the three-stage surgery consists of colectomy and the Hartmann procedure with diverting ileostomy as stage 1, completion proctectomy, construction of an ileal pouch and diverting loop ileostomy as stage 2, and closure of loop ileostomy as stage 3. The three-stage RPC and pouch surgery are reserved for patients with a risk of postoperative complications. Commonly reported risk factors for postoperative complications include fulminant colitis[157], severe hypoalbuminaemia and anaemia[161], and immunosuppression from hypoproteinaemia, preoperative blood transfusion, and the use of corticosteroids or biological agents[161–163]. However, the findings on the influence of preoperative use of anti-TNF agents[164–166] or anti-integrin agents[167] on the postoperative complications are inconsistent. The three-stage RPC is believed to reduce the risk of postoperative adverse outcomes related to previous use of anti-TNF therapy or systemic corticosteroids[168].

Since the early 1990s, surgical doctrines and techniques have evolved alongside a better understanding of disease processes and the effect of the underlying disease and pelvic anatomy on surgical outcomes. A variety of configurations of the ileal pouch have been designed (FIG. 6), with J-pouch, S-pouch and K-pouch being the most common. The J-pouch procedure is commonly performed in patients with refractory UC or UC-associated neoplasia. Mucosectomy of the rectal cuff is often performed in patients with UC with dysplasia of the rectum or sigmoid colon during the pouch construction. A laparoscopic approach for RPC and for the construction of ileal pouch-anal anastomoses (IPAAs) has gained momentum[169]. Although the laparoscopic approach offers a shorter incision and quicker recovery time than open surgery, no significant differences in mortality or complications were reported in a pooled analysis[170]. In addition, during RPC and IPAA, intramesorectal proctectomy and total mesorectal excision have been performed; however, their long-term outcomes need to be explored.

Restorative proctocolectomy with IPAA has become the surgical treatment of choice for patients with UC or familial adenomatous polyposis who require colectomy. IPAA surgery has been shown to substantially improve patients' quality of life as it preserves the natural route of defecation. However, surgery-associated adverse sequelae can occur and are classified into five main categories: structural complications, such as stricture, anastomotic leak, abscess, presacral sinus and vaginal fistula; inflammatory conditions, such as pouchitis, de novo CD of the pouch and cuffitis (inflammation of the cuff, created during an IPAA); functional disorders, such as irritable pouch syndrome and dyssynergic defecation; neoplastic conditions, such as adenocarcinoma of the rectal cuff or anal transition zone; and metabolic abnormalities, such as iron or vitamin D deficiency and nephrolithiasis[171]. The frequent occurrence of such adverse sequelae of RPC and IPAA should be considered when exploring the surgical options in patients with medically refractory UC or UC-associated neoplasia.

Quality of life

Patients with UC experience disabling digestive symptoms (diarrhoea, rectal bleeding and abdominal pain) in everyday life and >30% of patients also experience extraintestinal manifestations. UC can also affect the psychological, familial, social and professional dimensions of a patient's life. These effects can be symptom-related or owing to bowel damage, even in the absence of disease activity, or because of postoperative complications, adverse events and constraints associated with specific therapies or monitoring.

Health-related quality of life

The health-related quality of life (HRQOL) is a multidimensional concept of disease-related patient perceptions involving physical, psychological and social components[172]. The earliest assessment of HRQOL in IBD dates back to 1971 (REF.[173]). In 1989, the IBD Questionnaire (IBDQ) was developed[174,175] and, subsequently, its short version (SIBDQ)[176] was a major breakthrough. Ever since, the assessment of HRQOL has been a frequently measured secondary end point in clinical trials in both CD and UC. Many studies have

Ileostomy
A surgically created opening of the small intestine in the abdominal wall.

Sinus
A space or a cavity in a bone.

Nephrolithiasis
The process of formation of a kidney stone.

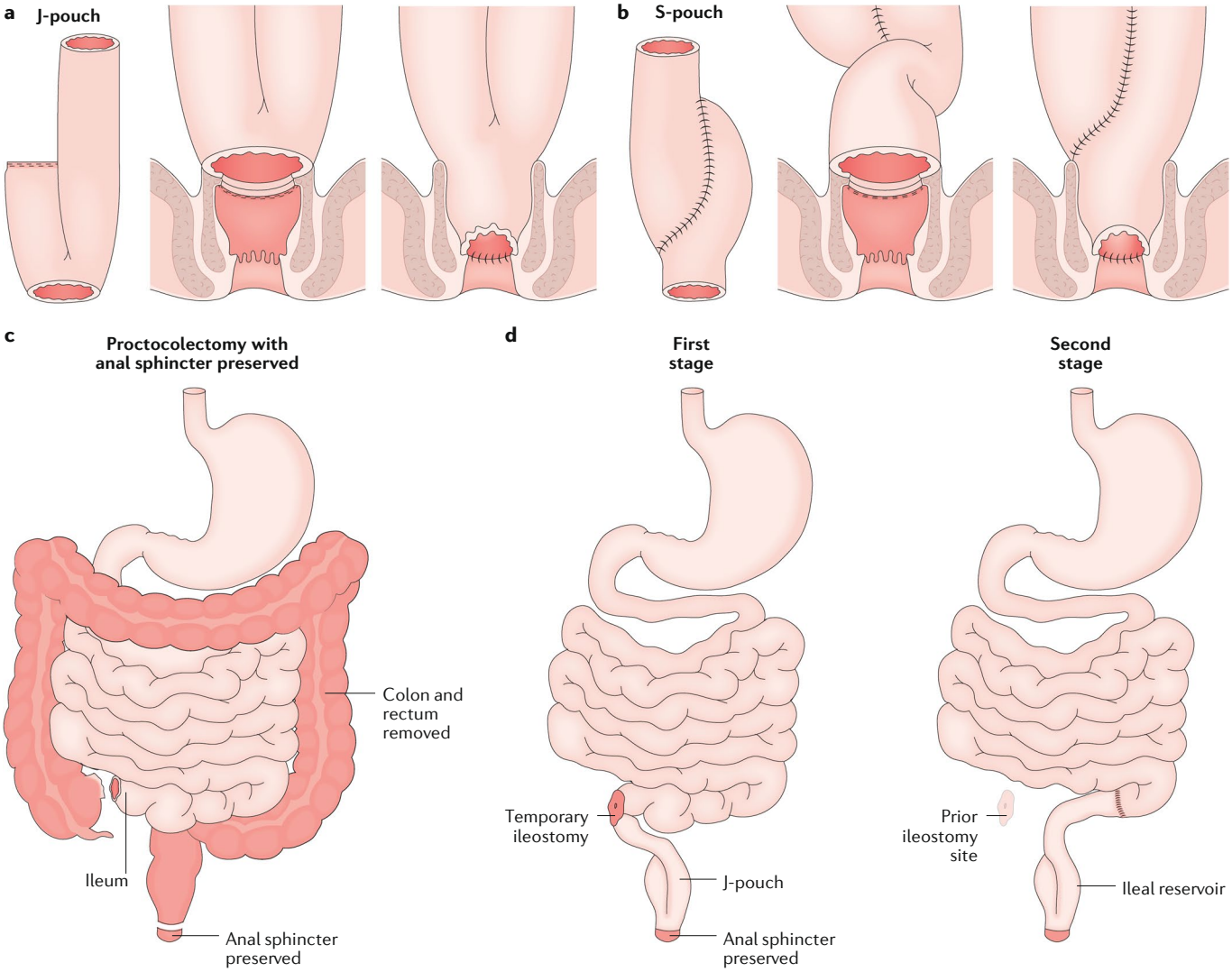

Fig. 6 | **Ileal pouch-anal anastomoses.** The choice among pelvic pouches (J-pouch or S-pouch) versus abdominal pouches (K-pouch) is determined by the patient's anatomy (for example, BMI, length of mesentery and functioning of anal sphincter) and the available surgical expertise. Various forms of construction of ileal pouch-anal anastomosis pattern include hand-sewn versus stapled and with mucosectomy versus without mucosectomy. **a** | J-pouch (left) with a stapled anastomosis and without mucosectomy (middle) is the preferred surgical modality, which is easier to perform and provides better functional outcome than hand-sewn anastomosis with mucosectomy. J-pouch with mucosectomy and hand-sewn anastomosis are commonly performed in patients with ulcerative colitis with dysplasia in the rectum or sigmoid colon (right). **b** | S-pouch (left) with a stapled anastomosis and without mucosectomy (middle) reserved for those with a short mesentery. S-pouch with mucosectomy and hand-sewn anastomosis can also be performed (right). **c** | Total proctocolectomy with preservation of the anal sphincter. **d** | Two-stage restorative proctocolectomy with total proctocolectomy, construction of the J-pouch, and diverting loop ileostomy as stage 1 (left) and closure of the loop ileostomy as stage 2 (right).

highlighted the substantial impact of UC on HRQOL, notably because of the bowel-related symptoms (most patients experienced symptoms weekly, even when in remission) and systemic symptoms (fatigue, feeling unwell and having trouble sleeping) that affected patients' social (for example, avoiding events without toilet access) and emotional life[177,178]. However, HRQOL remains subjective, describing a patient's experience about disease-related limitations. Furthermore, none of the existing tools measuring quality of life in IBD was developed according to FDA guidelines that enable the development of patient-reported outcome measures[179]. These limitations make the use of HRQOL difficult in clinical trials in the absence of a regulatory framework.

Disability

In contrast to HRQOL, disability refers to the objective problems that a patient might have in different domains. According to the WHO, disability is an umbrella term for impairments, activity limitations and participation restrictions[180]. Disability denotes the negative aspects of the interaction between an individual with an illness and that individual's contextual factors (environmental and personal factors)[181,182]. Although both UC and CD are known to be chronic diseases leading to reduced function, disability was not measured in patients with IBD before 2012, with work disability being an exception[183]. Thus, until now, disability was poorly explored in IBD compared with HRQOL. Conversely, disability has been

well investigated in other inflammatory disorders, such as in rheumatoid arthritis, using the Health Assessment Questionnaire[184,185], and in multiple sclerosis, using the expanded disability status scale, assessing, among other things, aids or devices that patients must use or their need for assistance from another person to perform activities[186,187]. These tools have been used in numerous disease-modification trials and in randomized, controlled trials as primary or secondary end points.

According to the WHO's International Classification of Functioning, Disability and Health[181], the first IBD Disability Index (IBD-DI) was developed in 2012, specifically devoted to evaluating disability in patients with IBD[188]. This index comprises 14 questions assessing, amongst others, body image and difficulties in regulating defecation, in maintaining a balanced diet, in performing household activities, and in maintaining personal relationships or those at work. This score ranges from 0 to 100 and has been validated for use in clinical trials and epidemiological studies[189]. Subsequently, the IBD-DI has been used in several studies. A French cohort involving >1,000 patients with IBD showed that 50% of patients reported poor quality of life, severe fatigue and/or depression as measured by SIBDQ, Functional Assessment Chronic Illness Therapy-Fatigue, and Hospital Anxiety Depression Scale–Depression, respectively. In the same study, approximately one-third of patients reported anxiety and/or moderate-to-severe disability, measured by Hospital Anxiety Depression Scale–Anxiety and the IBD-DI, respectively[190]. In these studies, the level of disability was generally similar in patients with CD and UC. Another study conducted in patients after RPC with IPAA demonstrated a good correlation between the IBDQ and the IBD-DI and that the level of disability was lower in the RPC with IPAA group than in pharmacologically treated patients. Although this could be an argument in favour of surgery in UC, notably, only five patients on biological therapy were compared in this study[190]. Earlier studies have also demonstrated a substantial improvement of HRQOL in patients with severe UC after IPAA[191]. However, early and late complications, such as faecal incontinence, pouchitis or sexual dysfunction, occur in approximately one-third of patients undergoing colectomy[192] and will therefore require a permanent ileostomy[191,192]. Although surgery can be a good alternative in some patients, it does not always normalize all aspects of disability and, therefore, quantifying disability is essential.

Despite its robustness and being developed according to FDA guidelines, the responsiveness to change of the IBD-DI is unknown. The IBD-DI questionnaire needs the attendance of a health-care professional for documentation and therefore seems to be difficult to apply in clinical practice. A self-report version of the IBD-DI has been validated in a population-based cohort of patients with IBD[193]. In addition, based on the PSODisk (used in psoriasis)[194,195], the IBD Disk, a shortened and self-administered questionnaire, has been developed. The IBD Disk was adapted from the validated IBD-DI to give the gastroenterologist an immediate and visual representation of a patient's disability[196], exploring abdominal pain, regulating defecation, interpersonal interactions, education and work, sleep, energy, emotions, body image, sexual functions, and joint pain. This tool could be used to follow disability over time, which enables the monitoring of treatment efficacy in routine practice.

Psychological stress. Increasing evidence suggests a link between psychological stress and IBD[197–200]. Furthermore, the psychological component is not only an important part of HRQOL but impaired HRQOL can also trigger or worsen psychological disorders, such as depression and anxiety[198], which may then lead to clinical flares of UC[199,200]. As a result, this multidimensional complexity mutually affects the quality of life as well as disease outcomes.

Outlook

Outstanding mechanistic questions

Despite the advances in understanding the pathophysiology of the disease, critical questions remain to be answered. The most pressing problem in the field is to identify the most critical cause and the triggers that lead to the development of UC. Understanding the aetiology of UC can help in the development of treatments that can cure or prevent disease development and flare-up. Another potential step forwards that the field might benefit from would be re-classifying IBD based on the aetiology, which includes genetics, microbiota or cytokine imbalances. A combination of omics and bioinformatics might contribute to a further understanding of the disease aetiology. Furthermore, ongoing epidemiological studies will hopefully point researchers towards understanding and identifying the key environmental causal factors of the diseases. Thus, narrowing the gaps between basic, clinical and translational research is further warranted.

New concepts in treatment goals

Until the late 1990s, the management of UC aimed at resolving symptoms and achieving short-term improvement of patients' quality of life. However, advances in medical treatment since the 2000s have enabled physicians and patients to aim for better long-term outcomes. In this regard, a treat-to-target approach (BOX 1) has been proposed and, so far, the target is to achieve endoscopic mucosal healing, which might reduce future relapse of disease and the need for treatment escalation, hospitalization and surgery[11,146]. In addition, histological healing has received attention as a deeper remission as well as a better treatment target to achieve further improvement of clinical course[12,13,201]. Whether a reduction in biomarker levels can be an alternative treatment target is being investigated. In this regard, a study showed that faecal calprotectin-targeted treatment optimization improved the clinical outcomes in CD[202].

In various clinical trials, higher serum concentrations of biologics have been reported to be associated with better clinical status and future outcome[203–205]. Thus, therapeutic drug monitoring has been utilized to tailor the dose or interval of administration to optimize drug levels[206–208]. This monitoring might be expanded to other treatment options in the future, but the impact on

	Anti-TNF	Anti-adhesion molecules	JAK inhibitors	Anti-IL-12 and/or anti-IL-23	Immunosuppressants	S1P receptor modulators	Anti-cytokines (others)
Phase I and/or II		• AJM347	• Peficitinib • TD-1473 • Deucravacitinib		• Apremilast • GSK2831781 • Ravagalimab	• Amiselimod	• Spesolimab • PF-06480605
Phase III		• AJM300 • Ontalizumab • Etrolizumab	• Filgotinib • Upadacitinib	• Brazikumab • Risankizumab • Guselkumab • Mirikizumab		• Etrasimod • Ozanimod	• Spesolimab
Launched	• Adalimumab • Golimumab • Infliximab	• Vedolizumab	• Tofacitinib	• Ustekinumab	• Tacrolimus • Cyclosporine		

• Oral administration • Intravenous or subcutaneous

Fig. 7 | **Main ulcerative colitis drugs in the pipeline and their targets.** Ulcerative colitis (UC) drugs under development are listed according to the development phase and their mechanisms of action. Anti-tumour necrosis factor (TNF) agents that are approved include infliximab, adalimumab and golimumab; anti-adhesion molecules that are in various trials include AJM347 (α4β7-integrin inhibitor), etrolizumab (anti-β7-integrin antibody), AJM300 (anti-α4-integrin antibody) and ontalizumab (anti-MadCAM1 antibody), and vedolizumab (anti-α4β7-integrin antibody) has been launched. JAK inhibitors, such as peficitinib (JAK3 inhibitor), deucravacitinib (TYK2 inhibitor) and TD-1473 (gut-selective pan-JAK inhibitor), are in phase I/phase II trials; filgotinib (JAK1 inhibitor) and upadacitinib (JAK1 inhibitor) are in phase III trials, and tofacitinib (JAK1–3 inhibitor) has been approved. Anti-IL-12/IL-23 antibodies that are being studied include ustekinumab (IL-12/IL-23p40) and brazikumab, risankizumab, guselkumab and mirikizumab (anti-IL-23p19 antibody). Other drugs include immunosuppressants, such as apremilast (phosphodiesterase 4 inhibitor), GSK2831781 (anti-LAG3 antibody), ravagalimab (anti-CD40 antibody), tacrolimus and cyclosporine, sphingosine 1 phosphate (S1P) receptor modulators, such as amiselimod, etrasimod and ozanimod, and molecules targeting cytokines, such as spesolimab (anti-IL-36R antibody) and PF-06480605 (anti-TNFSF15 antibody). Data retrieved from REF.[231].

clinical outcomes as well as cost-effectiveness should be further confirmed for each treatment.

Emerging therapeutics

Since the early 2000s, many novel therapies have been introduced for the management of IBD. By applying oral small molecules and/or gut selectivity, the new treatments have potential advantages, including higher efficacy as well as safety and patient acceptability. Nevertheless, even the newest drugs have a remission rate of <50% and many drugs also develop secondary loss of response in patients who initially responded[80,209,210]; therefore, a substantial unmet need persists for more advanced therapies.

Treatments targeting cytokines, including anti-TNF agents, have been the mainstream of biologics over the past two decades. Several clinical trials targeting IL-23 using antibodies to the IL-23p19 subunit (for example, guselkumab, tildrakizumab, brazikumab, risankizumab and mirikizumab) have demonstrated clinical benefits in both UC and CD[211–213]. Understanding the physiological role of IL-36 signalling in tissue remodelling and inflammation has led to the development of an anti-IL-36R antibody (B655130) as a possible treatment for UC (FIG. 7). Next generation anti-adhesion therapies, including an anti-MadCAM1 antibody (PF-00547659) and an anti-β7-integrin antibody (etrolizumab), are under development[214,215]. In a phase II clinical trial, the oral α4-integrin inhibitor AJM300 was shown to be efficacious in treating patients with UC[216], although this strategy might not be used for maintenance therapy owing to the risk of progressive multifocal leukoencephalopathy, which was previously described in patients treated with natalizumab (an anti-α4-integrin antibody)[217] (FIG. 7).

Another molecule that is frequently targeted to reduce the recruitment of inflammatory cells is sphingosine 1 phosphate receptor 1 (S1PR1), which facilitates the migration of T cells from the lymph nodes to areas of inflammation and therefore its inhibition 'traps' the lymphocytes in the lymph nodes. In the phase II TOUCHSTONE trial, ozanimod has been shown to be effective for moderately to severely active UC[218] and phase III trials are ongoing. The long-term safety of ozanimod is still unknown and is yet to be determined.

The novel JAK1-selective inhibitors upadacitinib and filgotinib are being tested in both UC and CD[219,220]. Although the pan-JAK inhibitor tofacitinib was the first marketed drug of this class for UC, information on which combination of JAK inhibition is the most efficient for UC is missing, alongside maintaining safety (FIG. 7).

Progress in understanding the role of the gut microbiota in IBD have led to trials investigating the efficacy of faecal microbiota transplantation; however, the results so far have been controversial and the findings less impressive than for *C. difficile*-associated diarrhoea[95]. Nevertheless, these findings have augmented our knowledge and might enable the development of pills enriched with beneficial bacteria[96,97]. Manipulating the gut microbiota might not only help treat UC but might also be useful in disease prevention in the future[221].

Personalized medicine

Another important area of research in UC involves personalized medicine. Several drugs with a different mechanism of action exist for the treatment of UC, many of which have been discussed in the sections above. However, to date, which drugs to use and in which order is not entirely apparent. Therefore, one

cannot take full advantage of the broad range of treatment options unless the right treatment is chosen for the right patient. A deeper understanding of the immunopathogenesis of UC and treatment could inform such decision-making. Hence, more research is needed to determine which gene signatures, biomarkers or, even, microbiota might be able to predict whether a particular patient will respond to a particular drug[222–229]. Tools to stratify patients based on their personal disease course and prognosis to appropriately plan the long-term treatment strategy are desired[171,172]. The need for personalized medicine is becoming increasingly important with the rapidly expanding range of treatment options.

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Introduction (T.H., T.K. and S.D.); Epidemiology (C.N.B.); Mechanisms/pathophysiology (B. Siegmund); Diagnosis, screening and prevention (S.C.W.); Management (M.F. and B. Shen); Quality of life (C.L.B. and L.P.-B.); Outlook (T.K.); Overview of Primer (T.K. L.P.-B and T.H.).

Competing interests
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