# Colonic diverticular disease

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Abstract | Diverticula are outpouchings of the intestinal wall and are common anatomical alterations detected in the human colon. Colonic diverticulosis (the presence of diverticula in the colon; referred to as diverticulosis) remains asymptomatic in most individuals but ~25% of individuals will develop symptomatic diverticulosis, termed colonic diverticular disease (also known as diverticular disease). Diverticular disease can range in severity from symptomatic uncomplicated diverticular disease (SUDD) to symptomatic disease with complications such as acute diverticulitis or diverticular haemorrhage. Since the early 2000s, a greater understanding of the pathophysiology of diverticulosis and diverticular disease, which encompasses genetic alterations, chronic low-grade inflammation and gut dysbiosis, has led to improvements in diagnosis and management. Diagnosis of diverticular disease relies on imaging approaches, such as ultrasonography, CT and MRI, as biomarkers alone are insufficient to establish a diagnosis despite their role in determining disease severity and progression as well as in differential diagnosis. Treatments for diverticular disease include dietary fibre, pharmacological treatments such as antibiotics (rifaximin), anti-inflammatory drugs (mesalazine) and probiotics, alone or in combination, and eventually surgery. Despite being effective in treating primary disease, their effectiveness in primary and secondary prevention of complications is still uncertain.

Diverticula, that is, sac-like protrusions in the wall of large bowel, are the most frequent anatomical alteration in the human colon. Colonic diverticulosis (hereafter referred to as diverticulosis) refers to the presence of diverticula in the colon. For many years, the western lifestyle has been considered a key factor in the development of diverticulosis, owing to its comparatively high prevalence in developed areas. Indeed, the global prevalence of diverticulosis is increasing in both developed and developing jurisdictions, presumably as a result of changes in diet and lifestyle[1]. The pathogenesis of diverticulosis is not completely understood but several changes are known to occur in the architecture of the colon wall, including loss of elasticity function and deposition of immature collagen fibres in the extracellular matrix[2]. The colonic wall consists of mucosa, submucosa, muscular and serosal layers. In western populations, the outpouchings involve eversion of the mucosal and submucosal layers, but not the muscular layer of the colon wall (FIG. 1) and, therefore, are termed 'false' diverticula or pseudodiverticula[3]. In eastern populations, the eversion can involve all layers of the colon wall and these diverticula are, therefore, referred to as 'true' diverticula. Diverticulosis involving both false and true diverticula are generally asymptomatic, but might result in diverticulitis (inflammation of the diverticula), and colonic bleeding, which is more commonly observed in eastern populations[3].

Colonic diverticular disease (hereafter referred to as diverticular disease) develops when diverticulosis becomes symptomatic, which typically involves bloating, abdominal pain and changes in bowel habit and is estimated to occur in ~25% of individuals with diverticulosis[3]. Diverticular disease can range in severity from symptomatic uncomplicated diverticular disease (SUDD) to symptomatic complicated disease such as acute diverticulitis or diverticular haemorrhage. SUDD is a distinct entity in which symptoms, particularly abdominal pain, can be attributed to diverticula in the presence of low-grade inflammation detected on histology but without macroscopic signs of inflammation (FIG. 1). Acute diverticulitis can range in severity from peridiverticular inflammation limited to the colonic wall (acute uncomplicated diverticulitis) to peritonitis (inflammation of the lining of the abdominal cavity; complicated diverticulitis) resulting from perforations of diverticula. Diverticular haemorrhage occurs as a consequence of rupture of diverticula-associated arteries, leading to colonic bleeding. The pathogenesis of diverticular disease is less well understood than that of diverticulosis but is thought to involve genetic predisposition, gut microbiota imbalance, neuromuscular abnormalities, chronic low-grade inflammation or acute inflammation, as well as altered colonic motility[2] (FIG. 1).

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Diverticulosis is usually detected incidentally in patients undergoing endoscopy or radiological examinations. Diagnosis of diverticular disease requires combined assessment of clinical signs and biomarkers. Diagnosis of acute diverticulitis relies on cross-sectional imaging such as ultrasonography, CT and MRI, as biomarkers are often not sufficient to establish a diagnosis. Colonoscopy is generally not recommended in individuals with acute diverticulitis owing to the risk of bowel perforation but is currently advised 6–8 weeks after an episode of acute diverticulitis to rule out colorectal cancer (CRC). Consensus is lacking regarding the optimal treatment options for diverticular disease, although treatment usually includes dietary fibre supplementation, pharmacological therapies (such as antibiotics and anti-inflammatory drugs) and probiotics, alone or in combination[3].

In general, acute diverticulitis occurs less frequently than previously thought[2] and the long-standing recommendation to treat acute diverticulitis with antibiotics has been disputed of late[4]. Although diverticula can occur throughout the gastrointestinal tract (including the oesophagus[5], the stomach[6] and the small bowel[7]), those arising in the colon are the most frequent.

In this Primer, we review the current knowledge of the epidemiology, pathogenesis, diagnosis, prevention and management of colonic diverticulosis and colonic diverticular disease. In addition, current and evolving tools for predicting disease outcome are discussed.

## Epidemiology

The 'true' prevalence and incidence of diverticulosis and diverticular disease is unknown. Indeed, epidemiological data come from papers or registries, which often do not report the specific phenotype of the disease and include any condition of the whole spectrum of diverticular disease unless specified otherwise.

### *Prevalence and incidence*

***Diverticulosis.*** Colonic diverticula can manifest in various clinical presentations[8]. As diverticulosis is usually asymptomatic and detected incidentally, accurate estimates of its true incidence and prevalence are lacking. Nevertheless, the incidence of diverticulosis seems to be increasing globally, especially in developed regions, where approximately two-thirds of adult populations (>18 years of age) eventually develop diverticulosis[1]. Age and geographic location, which is associated with different lifestyles (that is, diet and physical activity), are the two most important determinants of diverticulosis prevalence.

The prevalence of diverticulosis is very low among individuals <40 years of age and high among those >65 years of age, although, it is currently increasing, particularly among younger individuals (<40 years of age)[1]. For example, in the USA, diverticulosis is the most frequent finding in routine colonoscopy[9] and was the eighth most frequent outpatient gastrointestinal diagnosis in 2010 (REF.[10]). In 2009, in the USA, the reported prevalence of diverticulosis was 32.6% in individuals 50–59 years of age and 71.4% in those ≥80 years of age[9]. In Mexico, the prevalence of diverticulosis is in the range 1.9–9.2%, whereas in Africa the prevalence ranges from 2% in Egypt to 9.4% in Nigeria[1]. Among Asian jurisdictions, the prevalence is 12.5% in South Korea and 70.1% in Japan; in Europe, the lowest prevalence has been reported in Romania (2.5%) and highest prevalence has been found in Italy (51.4%)[1].

In western regions, diverticulosis was detected in the sigmoid or left colon in 90% of patients, whereas in Japan[11] and South Korea[12], diverticulosis was found more frequently in the ascending or right colon (75–85% of patients). Additionally, black individuals have a higher proportion of diverticula (both in distribution and total number) in the right colon than white individuals[13,14]. The prevalence of diverticulosis detected on colonoscopy has also increased in Asia, from 13% in the period 1990–2000 to 24% in the period 2001–2010 (REF.[15]). Furthermore, the frequency of right-sided diverticulosis is also increasing in the western world[16].

***Diverticular disease.*** Approximately 25% of individuals with diverticulosis develop SUDD, and an even smaller proportion develop acute diverticulitis[1]. Progression to diverticulitis occurred in only ~1% of individuals with diverticulosis over 11 years of observation[17]. One-fifth of patients with incident diverticulitis (first occurrence of an inflamed diverticulum) will have at least one recurrent episode[10]. Approximately 12% of patients presenting with diverticulitis will have a complication such as perforation, abscess (accumulation of pus within the diverticulum) or fistula (a tunnel or an abnormal connection between two body parts). Diverticular haemorrhage is the most common cause of lower gastrointestinal bleeding[18], with ~200,000 admissions in the USA annually. Fewer than 5% of patients with diverticulosis experience diverticular haemorrhage[18].

A study involving veterans in Los Angeles, CA, reported that only 4.3% of patients (a rate of 6 cases per 1,000 patient-years) with diverticulosis developed acute diverticulitis. The median time to develop an acute episode of diverticulitis was 7.1 years and the risk of diverticulitis increased with lower age at the time of diverticulosis diagnosis[15]. The highest reported prevalence of diverticular disease has been reported in Japan (13–28 cases per million individuals), the USA (12–22 cases per million individuals) and western Europe (8–12 cases per million individuals)[1]. Conversely, the prevalence of diverticular disease is low (0.1–5 cases per million individuals) in Africa and in Asia (with the exception of Japan)[1]. In Europe, prevalence varies across

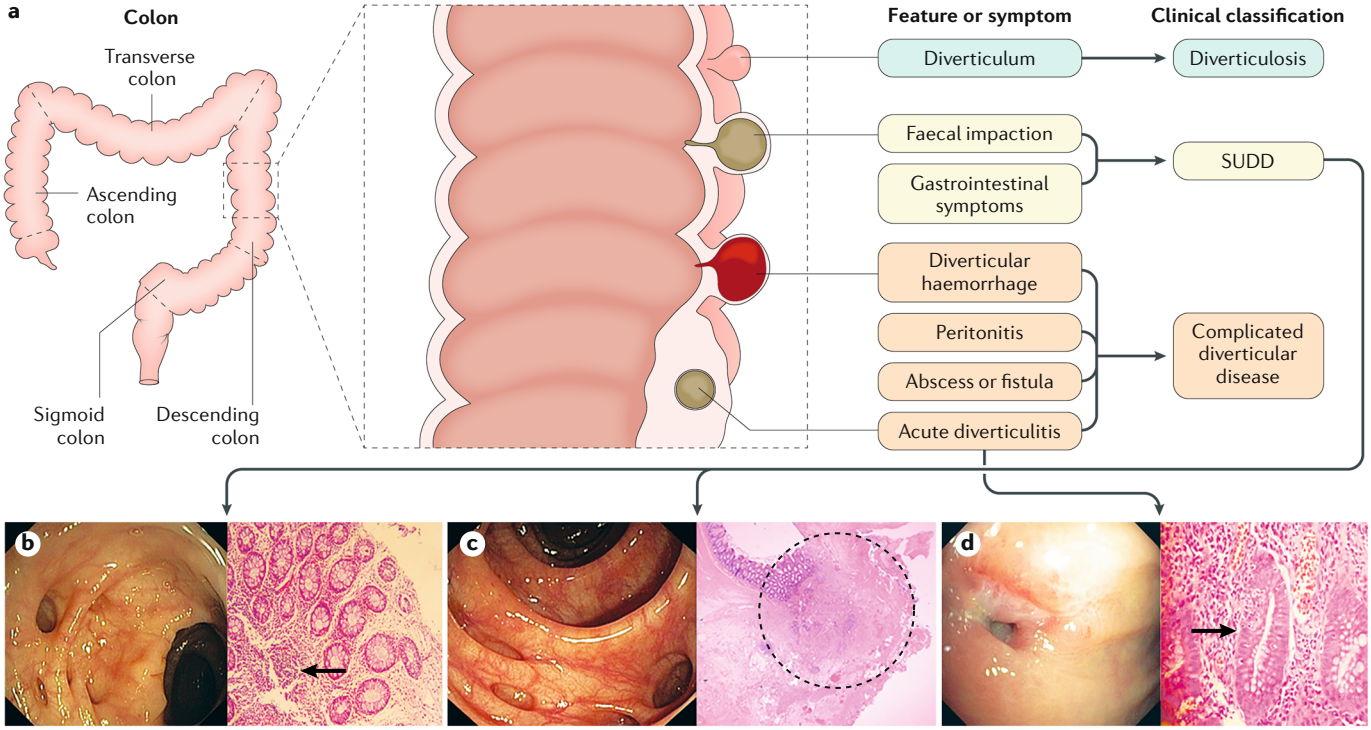


Fig. 1 | **Diverticulosis and diverticular disease. a** | Diverticulosis can occur in any part of the colon. However, in western jurisdictions it generally occurs in the left (descending and sigmoid) colon involving the mucosa and submucosa, whereas in eastern jurisdictions, protrusion generally occurs in the right (ascending) colon involving all colonic layers. Faecal stasis and faecal impaction in the diverticulum might lead to gut dysbiosis, resulting in the development of symptoms (symptomatic uncomplicated diverticular disease (SUDD)) and, sometimes, macroscopic evidence of diverticular inflammation (acute diverticulitis). Diverticular haemorrhage might also occur and is more commonly observed in eastern than in western populations. **b** | SUDD is characterized by the absence of macroscopic evidence of inflammation (left panel), but histology often shows patchy lymphoplasmacytic inflammation with lymphoid follicles that expand the lamina propria (arrow, right panel; ×40). **c** | Sometimes patients have persisting abdominal pain following acute diverticulitis, a clinical situation called post-diverticulitis SUDD. In these patients, endoscopy may not show signs of inflammation (left panel), and inflammation is generally located at the bottom of colonic crypt by histology (circled, right panel; ×10). **d** | Diverticular inflammation in acute diverticulitis can be observed on endoscopy (left panel), and acute and chronic inflammatory infiltrate, as well as cryptitis (arrow; right panel) on histology (×100). All histological images are of paraffin-fixed sections stained with haematoxylin and eosin. Images in parts **b** and **d** courtesy of C. D. Inchingolo, L. Bonomo Hospital, Andria, Italy. Image in part **c** courtesy of M. Walker, University of Newcastle, Australia.

regions, but does not follow any geographical pattern. For example, in Italy, Austria and Sweden low prevalence has been reported, whereas in Germany, France and the UK a higher prevalence than other European countries has been reported[19]. However, these differences might, at least in part, be owing to disparities in the methodology used to collect epidemiological data.

Hospitalization rates for diverticular disease have also increased in most parts of the world. For example, in the USA, >216,000 hospital admissions were reported for acute diverticulitis without haemorrhage in 2012, a 21% increase from 2003 (REF.[10]). In the UK, the hospital admission rate for diverticular disease increased from 0.56 per 1,000 person-years in 1996 to 1.20 per 1,000 person-years in 2006 (REF.[20]). In Italy, the hospitalization rate for acute diverticulitis constantly increased in the period 2008–2015, with an annual change of ~1.9%[21]. Patients were mainly younger individuals (<40 years of age), particularly men. A significant increase was also noted in in-hospital mortality, especially among women (>18 years of age), the elderly (>70 years of age) and during the first hospitalization[21]. All the above findings call for the need for increased awareness and clinical skills in the management of this common condition.

### *Risk factors*

***Diverticulosis.*** Differences in the prevalence of diverticulosis between regions might be owing to the low-fibre diet consumed in the western world, which has been pathogenetically linked to increased colonic intraluminal pressure that results in the formation of a diverticulum[2]. However, findings from one study question the role of fibre in affected individuals[22]. A Japanese study found that age, male sex, tobacco use, weight gain in adulthood, pre-diabetic conditions, alcohol consumption and increased serum triglyceride levels were risks factors for diverticulosis[11]. Most of these factors in addition to a low-fibre diet are also risk factors for diverticulosis in other areas of the world[22].

***Diverticular disease.*** Numerous risk factors for diverticular disease have been identified including non-modifiable factors, such as age, sex and genetics[23], and modifiable risk factors, such as lifestyle (diet and physical activity) and the use of prescription drugs[22,24] (TABLE 1). In one study, people from non-western regions who migrated to Sweden had a decreased risk of hospitalization for diverticular disease compared with individuals born in Sweden, but, after a short period of

Table 1 | **Modifiable factors associated with incident diverticulitis**

| Risk factor | Category[a] | Relative risk (95% CI)[b] | Recommendation for prevention |
|---|---|---|---|
| ***Diet*** | | | |
| Fibre | Highest quintile | 0.59 (0.46–0.78) | Increase consumption |
| Nuts | >2 times per week | 0.80 (0.63–1.01) | Increase consumption |
| Popcorn | >2 times per week | 0.72 (0.56–0.92) | Increase consumption |
| Vegetarian diet | Yes or no | 0.69 (0.55–0.86) | Implement or adopt |
| Western dietary pattern | Highest quintile | 1.55 (1.20–1.99) | Reduce fat and refined foods |
| Red meat | Highest quintile | 1.58 (1.19–2.11) | Reduce consumption |
| ***Lifestyle*** | | | |
| Physical activity | Highest quintile | 0.75 (0.58–0.95) | Increase physical activity |
| BMI | BMI ≥30 kg/m$^2$ | 1.78 (1.08–2.94) | Reduce BMI |
| Waist-to-hip ratio | Highest quintile | 1.62 (1.23–2.14) | Reduce fat consumption |
| Smoking | Current or ≥15 cigarettes per day | 1.56 (1.42–1.72) | Quitting |
| ***Medication*** | | | |
| Non-aspirin NSAIDs | ≥2 times per week | 1.72 (1.40–2.11) | Avoid intake |
| Aspirin | Ever or ≥2 times per week | 1.25 (1.05–1.47) | Avoid intake |
| All NSAIDs | ≥2 times per week | 1.65 (1.36–2.01) | Avoid intake |
| Corticosteroids | Current use | 2.74[c] (1.63–4.61) | Avoid intake |
| Opiate analgesics | Current use | 2.16[c] (1.55–3.01) | Avoid intake |
| Postmenopausal hormones | Past use | 1.35 (1.25–1.45)[d] | Caution in taking hormonal replacement therapy[d] |

Effect estimates are from selected large population-based cohorts or case–control studies (modified from REF.[22]). [a]When compared with lowest category; [b]Adjusted for potential confounders; [c]Represents odds ratio; [d]Data from REF.[24].

acculturation to the western lifestyle, the risk increased in the immigrant population, becoming similar to that in the native Swedish population[25]. On the basis of these data, ethnicity seems to be less important than lifestyle as a risk factor for diverticular disease.

The risk of hospitalization for diverticular disease, especially acute diverticulitis, is associated with modifiable risk factors. In western regions, factors that increase the risk of hospitalization include obesity, high intake of red meat, hypertension, hyperlipidaemia, use of oral contraceptives, hormone replacement therapy, smoking and the use of some medications (such as aspirin, NSAIDs and corticosteroids). Similarly, factors that decrease the risk of hospitalization include vigorous and regular physical activity, high educational attainment, high intake of fibre and a vegetarian diet[26,27]. One study found that adherence to a low-risk lifestyle, defined as low intake of red meat, high intake of fibre, vigorous and regular physical activity, a BMI of 18.5–24.9 kg/m$^2$ and no tobacco use, was associated with a reduced incidence of acute diverticulitis[28].

## Mechanisms/pathophysiology

A number of hypotheses have been postulated to explain the pathogenesis of diverticulosis and the various manifestations of diverticular disease. Although evidence in support of some of these hypotheses is accumulating, the biological mechanisms that underlie the development of these conditions have not been fully elucidated. As mentioned earlier, the aetiology of diverticular disease is likely to be multifactorial and the mechanisms are likely to differ for different disease manifestations (FIG. 2). For example, connective tissue abnormalities, such as altered elastin (a key extracellular matrix protein that provides resilience and elasticity to tissue and organs) crosslinking, might predispose individuals to the development of asymptomatic diverticulosis[29], whereas additional changes or precipitating factors, such as gut microbial dysbiosis or medication use, might be necessary for the development of symptoms or complications such as acute diverticulitis and diverticular haemorrhage. Burgeoning evidence from genome-wide association studies (GWAS) promises to guide future research and improve our understanding of underlying biological mechanisms.

### *Faecal stasis and faecal impaction*

A long-standing hypothesis for the development of diverticulitis suggests that faecal stasis and faecal impaction (trapping of faeces in a diverticular sac) can result in formation of a faecalith (a hard stony mass of faeces), which might obstruct a diverticulum. This obstruction can lead to bacterial stasis and local trauma, followed by ischaemia, microperforation, inflammation and infection. In support of this hypothesis, resection specimens from patients with acute diverticulitis often contain a faecalith[30]. In addition, diverticulitis shares many clinical and histopathological features with acute appendicitis, including obstruction of the appendix by a faecalith (an appendicolith). However, despite faecal impaction causing gut dysbiosis, no evidence directly links faecalith obstruction of diverticula to diverticulitis.

### *Chronic inflammation*

In addition to the overt acute inflammation that occurs in acute diverticulitis, chronic low-grade inflammation in individuals with diverticulosis might predispose to the development of diverticulitis and SUDD. Many of the risk factors for diverticulitis such as a low-fibre diet[26], high red meat consumption[31], obesity[32,33], smoking[34] and physical inactivity[35], which are also risk factors for cardiovascular disease[36] and diabetes mellitus[37], are known to be associated with chronic, low-grade inflammation. Thus, chronic inflammation might be the underlying mechanistic link between diet and lifestyle factors and diverticulitis. In a large, prospective study that only included men (40–75 years of age), the inflammatory potential of diet was correlated with the risk of diverticulitis after adjusting for other known risk factors, including dietary fibre intake and red meat consumption[38]. The inflammatory potential of diet was assessed using the validated empirical dietary inflammatory pattern score, which is a weighted index of nine pro-inflammatory and nine anti-inflammatory food groups, predictive of the levels of three markers of inflammation, CRP, IL-6 and TNFRSF1B. In addition, in a nested case–control study within the same cohort, plasma levels of CRP and IL-6 were associated with the risk of diverticulitis,

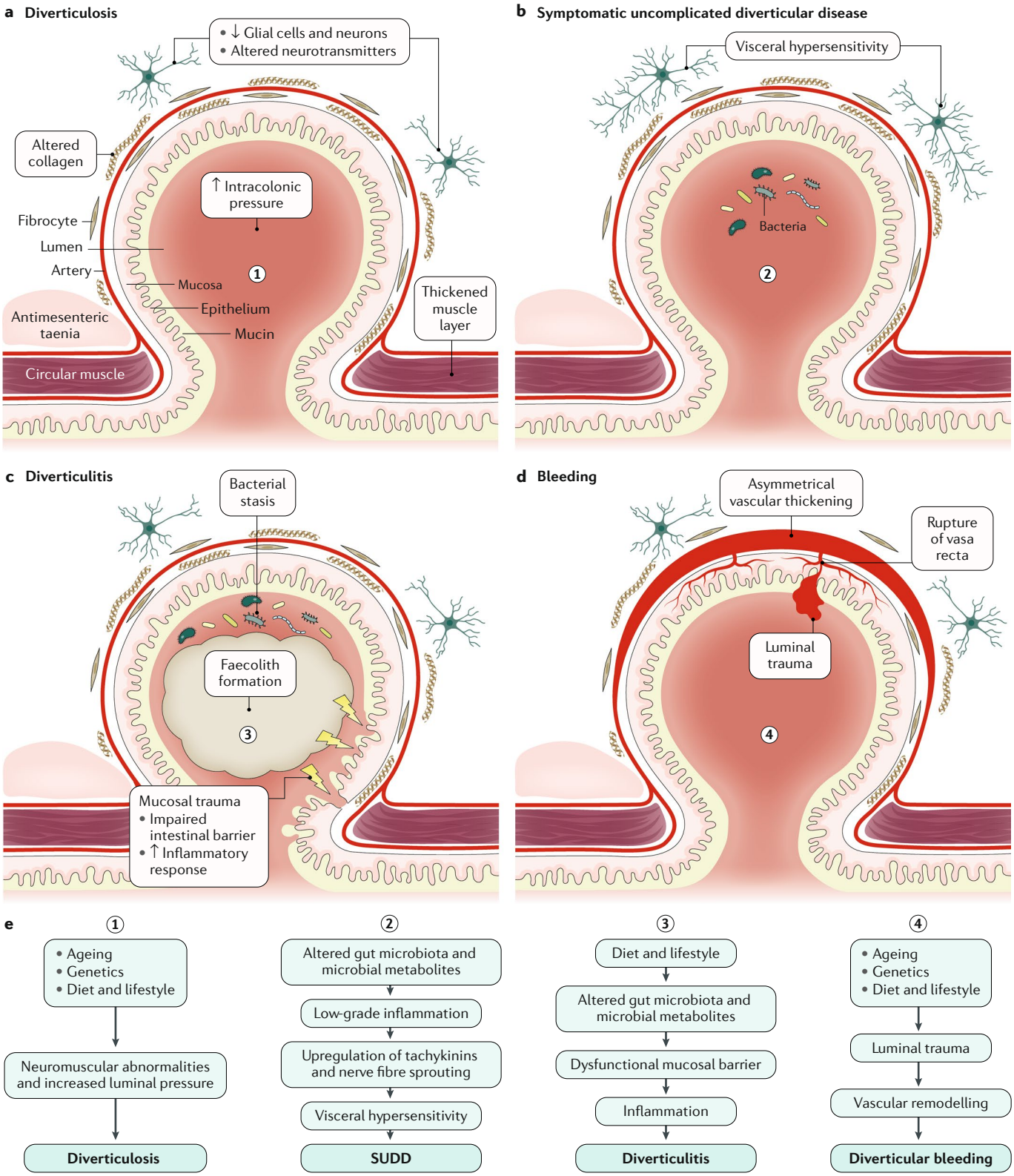


Fig. 2 | **Proposed biological mechanisms for diverticular disease. a** | Diverticulosis is hypothesized to be the result of neuromuscular abnormalities such as alterations in collagen and the enteric nervous system, in the setting of increased intraluminal pressure. **b** | Symptomatic uncomplicated diverticular disease (SUDD) can arise from an altered intestinal microbiota leading to chronic, low-grade inflammation mediated by tachykinins. Increased nerve sprouting leads to subsequent visceral hypersensitivity. **c** | Alterations in the intestinal microbiota leading to mucosal barrier dysfunction and inflammation and/or local trauma from a faecalith are proposed mechanisms for diverticulitis. **d** | Diverticular haemorrhage occurs at sites of asymmetrical vascular thickening. Risk factors for vascular injury such as obesity and hypertension and luminal trauma contribute to bleeding. **e** | Summary of mechanisms underlying different spectrum of diverticular disease.

further supporting the link between chronic systemic inflammation and diverticulitis[38].

Furthermore, in a small study, patients with SUDD showed increased expression of the neuropeptide receptor $NK_1$ (also known as tachykinin 1, which is known to be involved in smooth muscle contraction and inflammation) and the pro-inflammatory cytokine TNF compared with individuals with asymptomatic diverticulosis, indicating that symptoms in SUDD might be mediated by chronic, low-grade inflammation and upregulation of tachykinins[39]. In another study, patients with SUDD demonstrated elevated levels of faecal calprotectin (which mirrors neutrophil infiltration in the intestinal mucosa), whereas individuals with diverticulosis did not[40]. However, two large, community-based studies evaluating patients undergoing routine colonoscopy found no evidence of mucosal inflammation, based on immune markers such as IL-6, IL-10, TNF and serum CRP or histopathology, in patients with diverticulosis, regardless of symptoms[41,42]. Differences in the patient population in these population-based studies can account for discrepancies in findings. For example, detection of inflammation in small case–control studies might be the result of prior episodes of diverticulitis that were not explicitly excluded. In fact, persistent endoscopic and/or histological inflammation after resolution of acute diverticulitis has been associated with increased risk of recurrent diverticulitis[43,44].

### *Alterations in the intestinal microbiota*

Some risk factors for diverticulitis including low-fibre diet, obesity and physical inactivity, are known to influence the composition and function of the intestinal microbiota[45–47]. For example, dietary fibre intake increases intestinal microbial diversity via bacterial production of short-chain fatty acids (SCFAs)[48–50], which enhance mucosal barrier and immune function[51]. Indeed, the SCFA butyrate, when delivered to the colon via a microencapsulated formulation, might decrease the risk of recurrent diverticulitis[52].

Preliminary studies have indicated that the intestinal microbiota in patients with a history of acute diverticulitis differs from that in individuals with diverticulosis and those with various other intestinal conditions. Two cross-sectional studies found decreased levels of bacteria associated with SCFA production such as *Clostridium* spp. and increased levels of bacteria with pro-inflammatory effects, including *Marvinbryantia* spp. and *Subdoligranulum* spp.[53,54], in patients with acute diverticulitis compared with controls. Carbohydrate metabolism and biosynthesis of secondary metabolites was predicted to be reduced based on a survey of marker genes in the intestinal microbial communities in patients with a history of acute diverticulitis compared with individuals with diverticulosis[53]. Another study found that the diversity of Proteobacteria was higher in patients with acute diverticulitis than in individuals with diverticulosis. Few studies have focused on the intestinal microbiota in patients with SUDD. A study involving eight patients with SUDD found lower levels of the SCFA-producing bacterial spp. *Clostridium* cluster IX, *Fusobacterium* spp. and Lactobacillaceae than in individuals with diverticulosis. Moreover, biopsy samples from the area of diverticulosis (that is, within 1 cm of a diverticulum in patients with SUDD) had lower levels of *Akkermansia muciniphila* (a mucin-degrading bacterium that promotes epithelial barrier integrity by suppressing inflammation) than biopsy samples obtained from a distant (at least 20 cm from a diverticulum) colonic site[55]. Another study involving 28 patients with SUDD found a higher abundance of *Pseudobutyrivibrio* spp., *Bifidobacterium* spp. and Christensenellaceae in patients with a history of acute diverticulitis than in those without a history[56]. Alterations in the faecal and urinary metabolome have also been observed in patients with SUDD[55,57]. However, one study, comparing 226 individuals with incidental diverticulosis (asymptomatic) and 309 individuals without diverticulosis on screening colonoscopy, found that the mucosa-adherent bacterial community did not differ between these two groups[58].

### *Neuromuscular alterations*

***Diverticulosis.*** The development of diverticulosis has historically been attributed to a combination of increased intracolonic pressure and weakness in the colon wall. Higher intracolonic pressure has been attributed to low intake of fibre, whereas weakness in the colon wall might be associated with ageing[59]. GWAS have identified diverticulosis risk loci that contain genes involved in connective tissue integrity and intestinal motility, highlighting the importance of neuromuscular abnormalities in the development of diverticulosis[60]. However, the increase in the incidence of diverticulosis with age suggests that, in most cases, these neuromuscular alterations might be linked to ageing rather than genetic factors.

Individuals with diverticulosis have altered colonic connective tissue composition and collagen metabolism. Morphologically, the longitudinal and circular muscle layers become hypertrophic, which appears on colonoscopy as thickened colonic folds and a reduced lumen calibre, termed myochosis coli[30]. Levels of tissue-degrading matrix metalloproteinases are higher in areas of the colon with diverticula than in those without[61]. Alterations in the enteric nervous system[30], such as reduced numbers of glial cells, nerve cells[62] and intestinal pacemaker cells[63], as well as changes in the levels of neurotransmitters, neurotransmitter receptors and neurotrophic factors[64,65], are also observed in individuals with diverticulosis. Colonic motility studies using 24-hour manometry (which measures the pressure and pressure waves in the colon), have indicated that patients with diverticulosis have increased intraluminal pressure, increased colonic response to eating and increased numbers of high-amplitude contractions in segments involved with diverticula compared with individuals without diverticulosis[66]. These findings suggest that motor abnormalities either contribute to the development of diverticulosis or are the result of diverticulosis.

***Diverticular disease.*** Neuromuscular disturbances are also associated with symptoms in patients with diverticular disease. Patients with SUDD, but not individuals with diverticulosis, have heightened perception of distension in colonic segments involved with diverticulosis

and in the rectum[67]. This visceral hypersensitivity might be mediated by chronic, low-grade inflammation and upregulation of tachykinins[39]. Furthermore, in patients with SUDD but not in individuals with diverticulosis, nerve fibre sprouting was found to be increased in the region of diverticulosis, which might be the cause of visceral hypersensitivity and, therefore, be involved in symptom generation[68]. Additionally, the ratio of type I to type III collagen, crosslinking of collagen fibres[69] and levels of tissue-degrading matrix metalloproteinases[61] are increased in patients with diverticular disease. However, it is not clear whether these changes are related to the development of diverticulosis itself or to symptoms and complications of diverticular disease.

### *Genetics*

Several lines of indirect evidence suggest a genetic basis for diverticulosis and diverticular disease. First, as discussed earlier, the higher prevalence of diverticulosis and the left versus right colon distribution in western versus eastern parts of the world might have an underlying genetic basis[25]. Second, diverticular disease is common in several genetic syndromes that are caused by mutations in genes that are also implicated in the development of diverticular disease. For example, early-onset, extensive diverticulosis occurs in patients with inherited connective tissue disorders such as Marfan syndrome, Ehlers–Danlos syndrome, Coffin–Lowry syndrome and Williams–Beuren syndrome[70–72]. Third, two large population-based familial aggregation studies in Scandinavia found that the risk of hospitalization for diverticular disease was higher in the siblings of individuals with diverticular disease than in the general population and higher in monozygotic twins than in dizygotic twins; these studies estimated that ~50% of the risk of diverticular disease requiring hospitalization is inherited[73,74].

Case–control studies have identified genetic variants within candidate genes implicated in diverticulosis and diverticulitis. A study of 433 individuals with diverticulosis and 285 individuals without diverticulosis identified an association between rs3134646 (a variant of *COL3A1*, encoding type III collagen) and diverticulosis in white men[75]. Two smaller case–control studies identified an association between rs7848647, a variant within *TNFSF15* (encoding a cytokine of the TNF family) and diverticulitis requiring surgery[76]. Another study found that a variant in *RPRM* (encoding reprimo, a protein involved in cell cycle regulation and DNA repair), is linked to the presence of diverticulosis[77]. Finally, a rare SNP in *LAMB4* (encoding laminin subunit β4, a constituent of the extracellular matrix) was identified in five family members with young-onset (<52 years of age) diverticulitis[78].

Three GWAS have identified susceptibility loci for diverticular disease[79]. In a study from Iceland, variants in *ARHGAP15* (encoding proteins that regulate GTPase activity) and *COLQ* (encoding the collagen-tail subunit of acetylcholinesterase in the neuromuscular junction) were associated with diverticular disease in hospitalized patients, and variants in *FAM155A* (encoding a protein of unknown function) were associated specifically with complicated diverticulitis or diverticulitis requiring surgery[80]. A larger GWAS involving >27,000 individuals with diverticular disease and 382,000 individuals without diverticulitis, diverticular haemorrhage or known diverticulosis from the UK Biobank identified 40 loci with significant associations with diverticular disease and 112 loci with suggestive associations[60]. In a separate American cohort of 2,572 individuals with diverticular disease and 28,649 healthy individuals without these diagnoses, eight significant and two suggestive loci were replicated[60]. The identified risk loci contain genes involved in the immune system, intestinal motility, cytoskeleton organization, cellular adhesion, the extracellular matrix and membrane transport. The association with *COLQ* variant was confirmed in the UK study and the associations with *ARHGAP15* and *FAM155A* variants were confirmed in both the UK and the American cohorts, but not the association with *TNFSF15* (REF.[60]). The UK Biobank was again used in a slightly larger GWAS with replication in a European sample involving 3,893 individuals with diverticular disease or diverticulosis and 2,829 healthy controls[81]; 48 loci with significant associations were identified, of which 12 were novel and 35 were replicated. For most loci, the associations were similar for diverticulosis and diverticulitis, and no overlap was identified between genome-wide significant variants for diverticular disease and those previously identified for inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS). However, mutations in 12 of the lead candidate genes associated with diverticular disease are involved in 18 monogenic syndromes[79]. The functions of the identified candidate genes further support a role for impaired neuromuscular, mesenteric smooth muscle and connective tissue function in the pathogenesis of diverticular disease[79]. In addition, one of the identified candidate genes, *PHGR1*, which is involved in gastrointestinal epithelial cell function, was specifically associated with diverticulitis[81].

## Diagnosis, screening and prevention

### *Diagnosis*

The aims of the diagnostic process are not only to merely diagnose diverticular disease, but also to identify the different phenotypes, namely diverticulosis, SUDD and diverticulitis. In diverticulitis, it is important to recognize the severity and complications (that is, distinguish uncomplicated disease from complicated disease, which has abscess, fistula and stricture). Exact diagnosis is a prerequisite for appropriate treatment strategies. Although recognizing chronically recurrent or complicated episodes of diverticulitis is straightforward, diagnosis of chronic SUDD can be challenging. Unspecific symptoms like bloating, pain and altered bowel movements, without macroscopic pathology on colonoscopy and/or imaging might make the differential diagnosis with IBS difficult. Here, biomarkers (for example, faecal calprotectin) might be of help.

If diverticular disease (including acute diverticulitis) is suspected, the first step is to obtain a detailed medical history and perform a physical examination, to assess factors that affect disease outcomes and treatment such as comorbidities and medications and to assess indicators of disease severity such as fever and peritonitis[82].

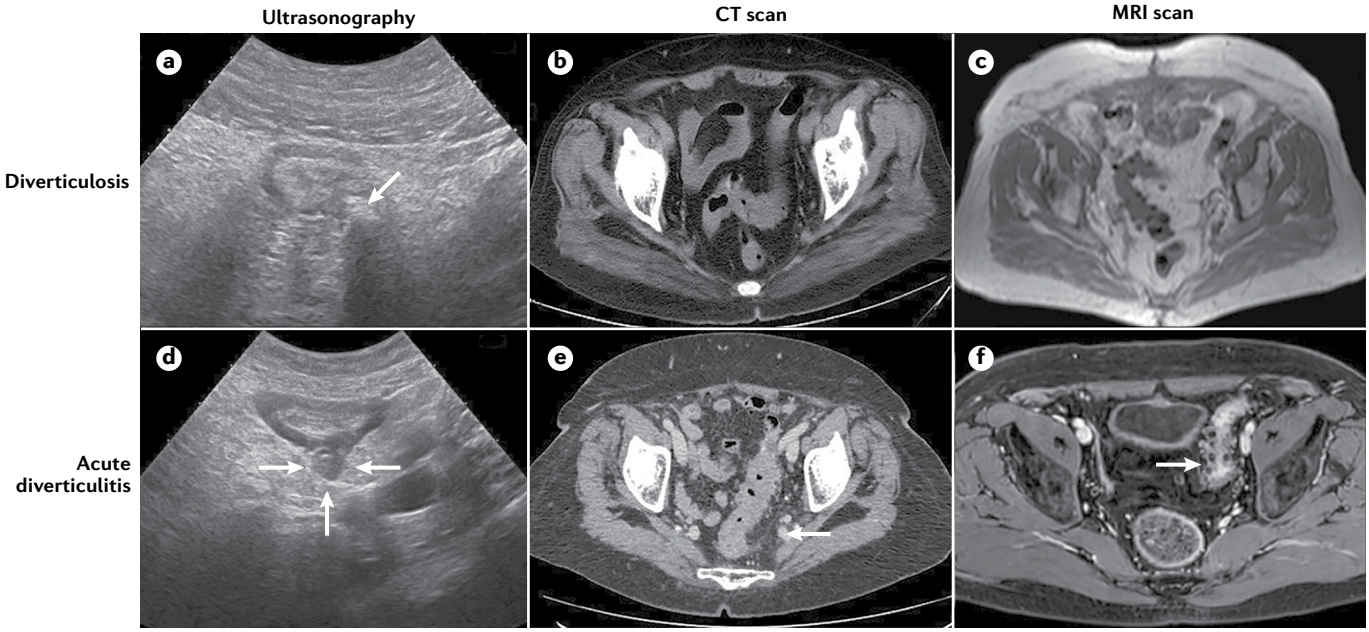


Fig. 3 | **Cross-sectional imaging of diverticulosis and diverticular disease.** Colonic diverticulosis can be clearly visualized using ultrasonography (part **a**), CT (part **b**) and MRI (part **c**). On ultrasonography, the absence of pericolonic involvement (namely absence of thickening of the diverticular wall and absence of involvement of pericolic fat) is indicative of a lack of inflammation (part **a**, transverse section of the sigmoid colon characterized by a thickened muscularis propria, with a diverticulum appearing as a hyperechoic lesion (arrow) with a posterior hypoechoic halo). Ultrasonography can also be very useful in detecting acute inflammation of diverticula (part **d**, transverse section of the sigmoid colon characterized by a thickened muscularis propria, with an inflamed diverticulum appearing as a hypoechoic protrusion (arrows) surrounded by hyperechoic mesenteric tissue). CT can reveal thickening of the diverticular wall with inflammation of the pericolonic fat (so-called fat stranding; part **e**, arrow), and MRI can also show diverticular inflammation (part **f**, arrow). Images in parts **a** and **d** courtesy of G. Maconi, University of Milan, Italy. Images in parts **b**, **c**, **e** and **f** courtesy of M. Maiorano, L. Bonomo Hospital, Italy.

Clinical evaluation, including laboratory tests alone, is not accurate enough to establish a diagnosis of diverticular disease. A large study conducted in the Netherlands has indeed demonstrated that clinical evaluation has limited sensitivity (68%; positive predictive value 65%)[83]. Furthermore, clinical evaluation alone resulted in an incorrect diagnosis in 34–68% of patients[84,85], which might delay appropriate treatment, lead to redundant investigations and result in unjustified hospitalization. Moreover, biomarkers are not specific enough for an initial diagnosis (see below).

***Cross-sectional imaging.*** Traditionally, imaging of diverticula and related disease was performed using barium enema. Although the detection rate of colonic diverticula is high and more accurate than that obtained by colonoscopy[86], barium enema is not an appropriate imaging technique to diagnose acute diverticulitis. Indeed, one systematic review found low sensitivity and specificity of barium enema in comparison with modern cross-sectional imaging[87]. However, in selected patients (for example, those with intestinal stenosis), barium enema can still be indicated.

In contrast to barium enema and colonoscopy, cross-sectional imaging modalities such as ultrasonography, CT and MRI can display the whole colonic wall, thereby enabling the visualization of peridiverticular tissue and alterations in the bowel wall[88]. Thus, these methods are the mainstay in the diagnosis of diverticular disease and mandatory for an accurate diagnosis of diverticulitis[82] (FIG. 3).

Although CT is currently the widely adopted diagnostic approach, technological advances have led to an increasing use of ultrasonography worldwide[89–91]. An early comparison of ultrasonography and CT found very similar diagnostic accuracy for these two approaches[84]. In fact, a systematic review with meta-analysis confirmed that ultrasonography and CT did not differ substantially in sensitivity (92% and 94%, respectively) or specificity (90% and 99%, respectively)[92,93]. However, pathological conditions other than diverticular disease were more often described with CT[92]. A drawback of this meta-analysis is that the studies included patients across the whole spectrum of diverticular disease. A study comparing the diagnostic accuracy of ultrasonography and CT in patients with SUDD, acute uncomplicated or complicated diverticulitis found a clear superiority of CT in diagnosing complicated diverticular disease, whereas the two approaches had comparable diagnostic accuracy in patients with SUDD[94]. Data regarding the diagnostic accuracy of MRI in diverticular disease are sparse but promising. The only comparative study between CT and MRI in patients admitted to the emergency department with clinically suspected acute diverticulitis found a sensitivity of 94% and a specificity of 88% for MRI. Interestingly, the diagnostic accuracy

of MRI was found to be better in younger (<60 years of age) than in older patients[95].

Typical ultrasonography findings in acute diverticulitis include hypoechogenic thickening of the bowel wall, diverticula with surrounding inflammation that appears as a hyperechogenic rim, fluid collection, abscesses or fistulas[92,93,96,97]. In addition to these features, CT can also detect distant abscesses (for example, in the pelvis), fat stranding (to detect mesenteric inflammation) and contrast extravasation (to detect perforation). However, the diagnostic yield of ultrasonography and CT might differ in some aspects, the two being complementary rather than competing techniques. For example, ultrasonography is a dynamic investigational tool that provides information on the motor activity of the bowel. As a matter of fact, the pressure of the ultrasonography probe can cause pain, which can lead the operator to focus on the given abdominal area. By contrast, CT has a superior penetration depth and can better display the retroperitoneal and pelvic space, regardless of the presence of intestinal gas or obesity. After an episode of acute diverticulitis, findings from CT, in contrast to ultrasonography, have substantial prognostic value[98]. Indeed, colonic wall thickness and severity of diverticulitis detected by CT were predictive of the need for elective partial colectomy[99]. In contrast to ultrasonography and MRI, CT involves exposure to radiation, which limits its repeated use. Acute diverticulitis might progress rapidly (in <12 hours). By nature, inflammation is a dynamic process and an appropriate visualization would require reiterative examinations. For example, the size of a visible abscess can be closely followed, which may lead to escalating procedures such as drainage or even surgery. Ultrasonography can be replicated as often as it is useful for difficult decision making.

In principle, for all imaging methodologies (especially ultrasonography), diagnostic accuracy is operator-dependent and is better performed in referral centres (where all diagnostic procedures are usually available) than in a general hospital setting[89,100]. The choice of diagnostic procedure is usually determined by local availability and skill. Ideally, ultrasonography might be used as a first step, followed by CT if needed[89].

***Colonoscopy.*** Traditionally, colonoscopy is avoided in patients with acute diverticulitis because of perceived hazards from the procedure[101], especially an increased risk of local or distant perforation, although this risk was not confirmed in one small study[102]. As the main pathophysiological features of acute diverticulitis take place outside the colonic wall, colonoscopy has only a minor role in the initial diagnosis of acute diverticulitits. In a prospective study, all patients with confirmed acute diverticulitis had an initial colonoscopy. Patients improving rapidly within some days demonstrated no pathologies on colonoscopy, whereas four out of 23 patients with persistent diverticulitis (>1 week) benefited from early colonoscopy[102], which helped identify the reason for persistent diverticulitis or change the final diagnosis in these patients. Differential diagnoses for diverticular disease include IBD, IBS, appendicitis, microscopic colitis, cancer or segmental colitis associated with diverticula (SCAD). SCAD is not discussed in this Primer as it is now considered a forerunner of IBD rather than a complication of diverticular disease[3]. Colonoscopy is, however, advisable prior to elective surgery in patients with acute diverticulitis to rule out other colonic findings, including neoplastic lesions[82].

Diverticular haemorrhage typically presents as painless, intermittent and large volume of lower gastrointestinal bleeding[103], which often stops spontaneously but can also be life threatening[103–105]. Diagnostic and interventional modalities available to diagnose and treat diverticular haemorrhage include colonoscopy, angiography, radionuclide scintigraphy (tagged red blood cell scanning) and CT. Colonoscopy can precisely identify the origin of bleeding and offers a range of effective interventions for haemostasis. In prospective studies and in a nationwide database study, colonoscopy within 24 hours of acute lower gastrointestinal bleeding was related to shorter hospital stay and lower hospitalization costs[106,107]. High-volume upper gastrointestinal bleeding leads to acute-onset haematochezia (fresh blood in stool), which needs differential diagnosis before investigation of the colon. At this time, it is recommended either to insert a gastric tube or to perform upper gastrointestinal endoscopy prior to colonoscopy[108]. Furthermore, several guidelines recommend colonoscopy within 24 hours after bowel cleansing in patients with severe haematochezia[107].

Where there is an identifiable source of bleeding, endoscopic haemostasis must be attempted. If endoscopic treatment is not possible, angiography with embolization can be performed following identification of the bleeding. In all other cases of persistent bleeding or in the event of a clinically relevant bleeding relapse after initial endoscopic or angiographic haemostasis, surgical therapy must be undertaken urgently[18,82,104,108]. If surgery is inevitable, precise knowledge of the localization is crucial for any surgical procedure that is required. Colonic resections in patients with diverticular haemorrhage with unclear localization of bleeding showed a postoperative mortality of 43% in comparison with 7% in patients with well-defined localization of bleeding[109].

The need for routine colonoscopy in asymptomatic patients after a flare of acute diverticulitis is intensly debated owing to the long-standing discussion on the association between diverticular disease and simultaneous colonic neoplastic lesions. A large meta-analysis involving 50,445 patients with acute diverticulitis analysed 31 studies conducted worldwide and showed substantial heterogeneity between the study results ($I^2 = 57\%$, $P < 0.01$)[110]. The meta-analysis included a pooled prevalence of associated CRC of 1.9%. Notably, the risk of CRC was sixfold higher in patients with complicated diverticulitis than in patients with uncomplicated diverticulitis. Additionally, the meta-analysis showed that colonoscopy detected polyps with a pooled prevalence of 22.7% (4.4% of which were advanced adenomas, 14.2% were adenomas and 9.2% were hyperplastic polyps).

Since diverticular disease and CRC share some risk factors (such as age, diet and body weight), the coexistence of both diseases in the general population is expected. The clinically relevant issue is that the

symptoms of diverticular disease might mask signs of CRC, which was significantly associated with longer diagnostic intervals[111]. Taking all these considerations into account, colonoscopy should be considered after an episode of acute diverticulitis, provided that it has not already been performed[111]. Owing to risks of perforation, a delay of 6–8 weeks after treatment is generally recommended[112]. According to two meta-analyses[112,113], in most studies colonoscopy was performed within 6–8 weeks (and in any case within 6 months) after the index episode. However, the rate of detecting CRC via endoscopy is relatively low, especially after an episode of uncomplicated acute diverticulitis[114]; a meta-analysis of 11 studies[113] showed a low risk of malignancy after a CT-proven episode of acute uncomplicated diverticulitis (0.7%, 95% CI 0.4–1.4) in comparison with 1.6% (95% CI 1.6–2.8) in patients with complicated diverticulitis on subsequent colonic evaluation. According to a meta-analysis of 17 studies, routine colonoscopy can be omitted in patients with uncomplicated diverticulitis if CT imaging is otherwise clear[115]. However, as the prevalence of precursor lesions, such as adenomas, is large and the procedure is relatively safe, colonoscopy should be offered to all patients (especially those >50 years of age) after an episode of acute diverticulitis.

***Biomarkers.*** Biomarkers might substantiate clinical suspicion and can be useful for assessing disease severity and for disease monitoring[116]. For example, pro-inflammatory markers, such as CRP, erythrocyte sedimentation rate and leukocyte count, faecal calprotectin and procalcitonin, might have a role as biomarkers of diverticular disease, given the importance of inflammatory processes in the disease pathophysiology.

On the basis of the available data, CRP is the most useful biomarker for diverticulitis. A comparative study found that a high index CRP value was the best predictor of severe complications in patients with acute diverticulitis[116]. Additionally, serum CRP concentrations are closely related to clinical and histological severity of diverticulitis. Low CRP levels (<50 mg/l) are indicative of acute uncomplicated diverticulitis, whereas CRP >200 mg/l can indicate complications such as perforation with peritonitis or abscesses.

Faecal calprotectin is a useful biomarker to follow up therapy outcomes; its levels decrease in patients responding to treatment, whereas persistently high levels indicate treatment failure[117]. A systematic review examining the use of faecal calprotectin to distinguish IBS from IBD[118] showed that faecal calprotectin levels >50 mg/g detected IBD with a pooled sensitivity of 93% (range 83–100%) and a pooled specificity of 94% (60–100%)[119]. Faecal calprotectin testing seems to be the most sensitive preliminary test for discriminating IBD from IBS and is superior to serum CRP in its diagnostic accuracy[120], suggesting that faecal calprotectin can also be a valuable tool to discriminate IBS and SUDD[40]. Typical symptoms of SUDD are pain localized in the left lower abdomen without macroscopic signs of inflammation[121]. Though the clinical signs of IBS and SUDD might show some similarities, an in-depth history (such as the course of pain) and faecal calprotectin levels might help clarify the diagnosis[122]. A prospective study comparing faecal calprotectin levels in patients with SUDD and IBS according to Rome III criteria found significantly higher faecal calprotectin levels in SUDD than in IBS, which decreased after successful treatment[40]. Although faecal calprotectin is a well-established biomarker of inflammatory activity in IBD, its utility for the diagnosis of diverticulitis remains to be fully established.

According to guidelines, the diagnostic algorithm for a range of bacterial infectious diseases comprises measurement of serum procalcitonin (to identify sepsis)[123] before commencing antibiotic therapy[124,125]. Its use has led to a decrease in antibiotic prescription[126], a goal that is also pursued in the treatment of diverticulitis. One study demonstrated a high diagnostic accuracy of procalcitonin in differentiating uncomplicated and complicated diverticulitis[127]. However, the role of procalcitonin needs to be further investigated.

To date, among many other proteins that have been studied as potential biomarkers for diverticular disease, none has achieved clinical significance[117]. Also serum vitamin D levels have been shown to be associated with the severity of endoscopic mucosal alterations in diverticular disease[128]. However, overall, CRP remains the most useful biomarker to date.

### *Classification*

***DICA.*** A study found that the persistence of mucosal alterations after an episode of acute diverticulitis might have a prognostic role in determining the risk of diverticulitis recurrence, showing for the first time that endoscopic examination can be useful in predicting the outcome of the disease[44]. The Diverticular Inflammation and Complication Assessment (DICA)[129], developed on the basis of colonoscopy, is a three-stage severity score that classifies the disease into mild, moderate or severe[129] (FIG. 4). DICA takes into account several main features and sub-features: the four main items are extension of diverticulosis (left or right and the length of colon involved), the number of diverticula in each colonic segment (≤15 or >15), the presence of inflammation (oedema and/or hyperaemia, erosions and SCAD) and the presence of complications (rigidity, stenosis, pus and bleeding). SCAD, although now considered a precursor of IBD, was included in the original DICA classification. The results of a prospective ongoing study will allow to establish whether SCAD should be excluded from the classification[130]. When diverticula are detected during colonoscopy, they are described as 'scattered', 'scanty', 'diffuse' or 'numerous'. Each feature and sub-feature has a numerical point score, and the sum of the point scores leads to three different DICA scores: DICA 1 (≤3 points), DICA 2 (4–7points) and DICA 3 (>7 points)[129] (FIG. 4). This classification might be predictive of disease outcome; for example, in a 2016 retrospective study, the DICA score was predictive of the risk of acute diverticulitis occurrence and/or recurrence and the risk of surgery[131]. A 3-year prospective, international validation study is currently ongoing[130] and preliminary analysis of the results at 1 year have confirmed the results of the retrospective study[132]. The DICA score needs further validation. Provided early results (at 1 year) can be

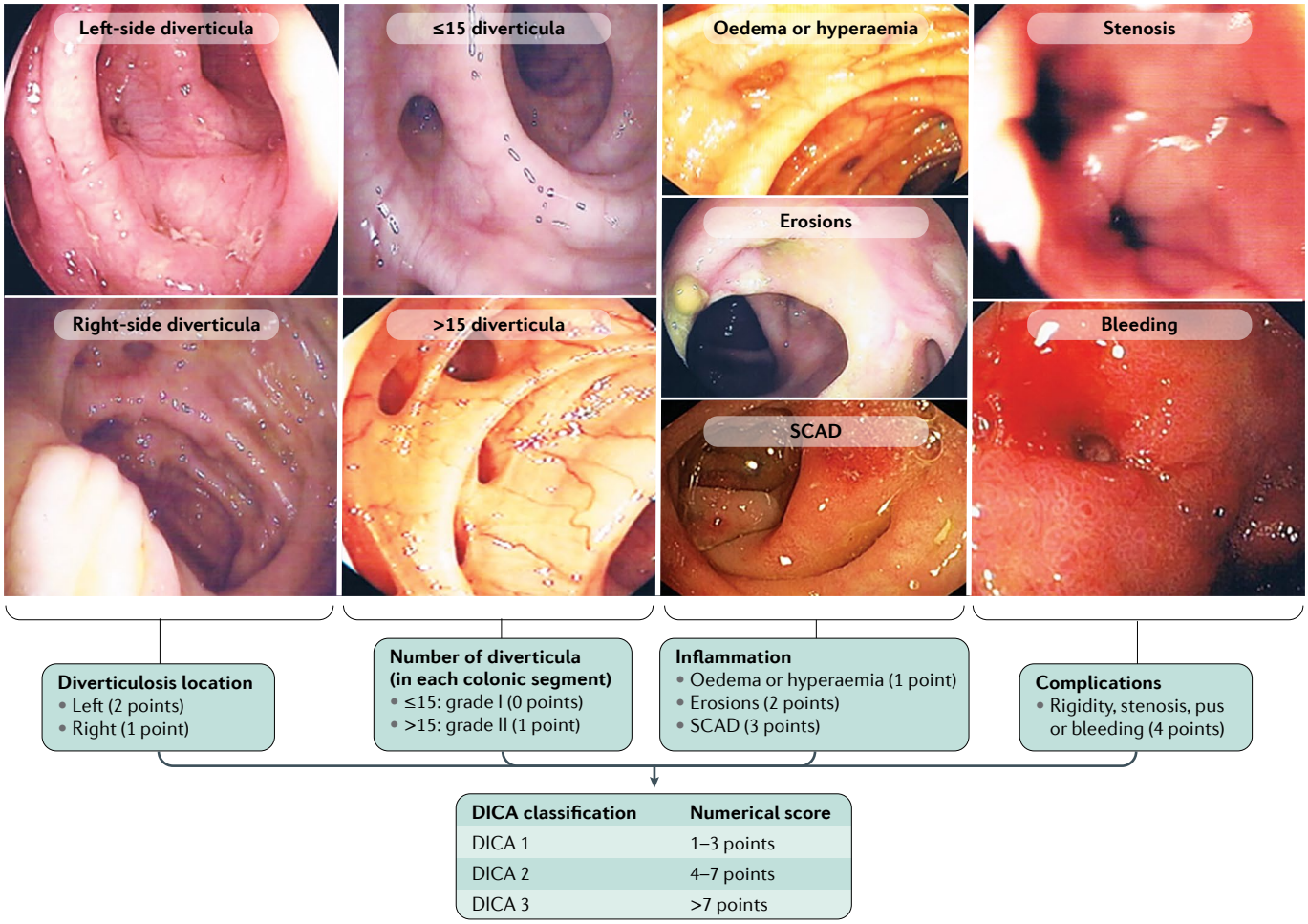


Fig. 4 | **The DICA classification system.** The Diverticular Inflammation and Complication Assessment (DICA) classification is the first endoscopic classification developed specifically to objectively describe the presence of diverticulosis in the colon and signs of current or past diverticular inflammation. This classification consists of four main colonic characteristics (the location of diverticulosis, the number of diverticula in each colonic segment, the presence or absence of inflammation, including segmental colitis associated with diverticula (SCAD), and the presence or absence of complications). Sub-features are considered and scored. If two different grades of severity are detected at the same time (for example, some diverticula with hyperaemia and others showing erosions), the more severe grade of inflammation (for example, erosions instead of hyperaemia) must be scored and the sum of the scores leads to three different DICA scores: DICA 1, DICA 2 and DICA 3.

confirmed, follow-up colonoscopy after acute diverticulitis can provide additional benefits to the existing classification.

***Diverticulitis.*** Several classification systems for diverticulitis are available, including two clinical (Hansen–Stock and Köhler classifications) and three radiological (modified Hinchey, Ambrosetti and Dharmarajan classifications)[99]. The modified Hinchey classification is the most commonly used owing to its high sensitivity (94%) and specificity (99%) and gives a good overview often with important additional information on other pathologies[133]. Apart from diagnosing diverticulitis, CT has become important in determining the severity of the disease.

The original classification developed by Hinchey et al. is a surgical classification of the perforated acute diverticulitis with four individual stages based on intraoperative findings[134] (FIG. 5). This classification is very simple with good prognostic value, but yields limited correlation with CT findings. A modified version of this classification, which is now the most commonly used, consists of five (instead of four) categories[135]. When present, abscesses are differentiated depending on their location as confined, pericolic abscesses (Ib) and distant (intra-abdominal or intra-peritoneal) abscesses (II). The initial goal of this modification was to discriminate between patients manageable with image-guided percutaneous drainage and those requiring surgery.

### *Prevention*

As already discussed, diverticulosis has been hypothesized as being the result of a low-fibre diet[136]. More modern scientific work including population-based studies of twins and siblings[74] as well as GWAS[81] have higlighted the genetic background of the disease indicating a multifactorial aetiology, which is difficult to modify. Indeed, there are currently no evidence-based

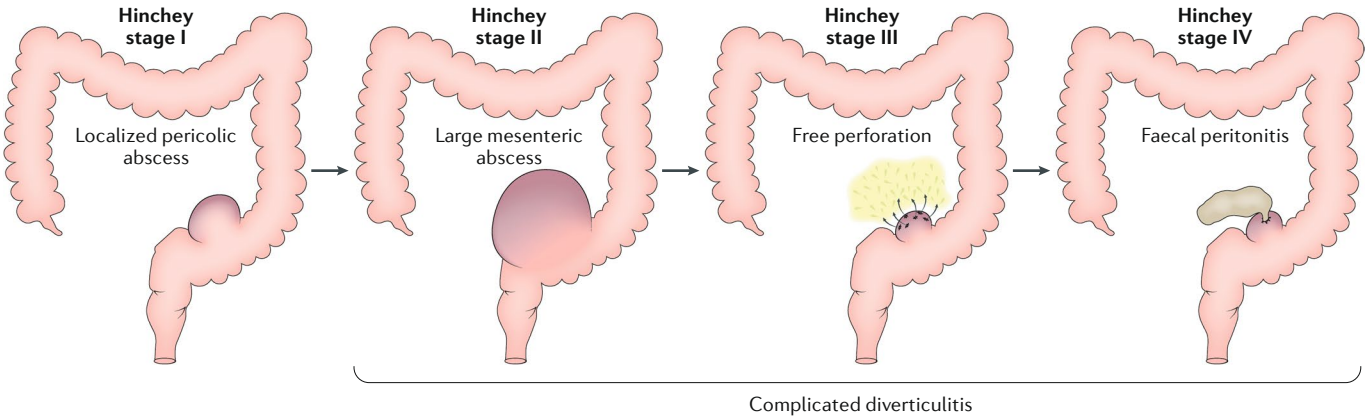


Fig. 5 | **Clinical presentations of acute diverticulitis.** The clinical presentation of diverticulitis, in which diverticula become inflamed and/or infected, depends on the location of the affected diverticulum, the severity of the inflammatory process and the presence of complications. Colonic diverticula have a narrow neck that can be easily obstructed by faecal matter. Obstruction of the neck initiates a cascade of events that might lead to distension of the sac, bacterial overgrowth, vascular compromise and perforation. Most perforations are localized and contained, so that uncomplicated diverticulitis is present as a small localized pericolic abscess. Complicated diverticulitis usually results from worsening of the infection. If this is the case, large perforations develop with consequent mesenteric abscesses, free perforation and faecal peritonitis. This description, which classifies acute diverticulitis in four stages, was first developed by Hinchey et al.[134]. Fistulas and obstruction might suddenly develop during an episode of diverticulitis or can be a late complication. However, diverticular haemorrhage represents a non-infective complication.

measures for the primary prevention of diverticulosis. Although only a small proportion of individuals with diverticulosis develop diverticular disease, the absolute number of individuals affected by diverticular disease is sufficient to place an enormous burden on national health systems, which makes primary prevention highly desirable. Modifiable risk factors offer opportunities for primary prevention of diverticular disease in patients with known diverticulosis[23]. Of note, as risk factors have typically been identified in retrospective observational studies, these weak data only allow recommendations for prevention to be made (TABLE 1).

## Management

The therapeutic approach to diverticular disease is tailored to the severity of the disease. The presence of diverticula is not an indication for pharmacological therapy, as in most individuals diverticulosis will not progress to symptomatic disease.

### *SUDD*

In patients with SUDD, pharmacological therapy should aim to reduce both the intensity and frequency of symptoms and to prevent complications[137,138]. Although patients with SUDD complain of mild to moderate pain and bloating as well as bowel changes, their quality of life is markedly impaired and can be improved by medical treatment[139]. Treatments for SUDD include fibre, antibiotics (including the poorly absorbed antibiotic, rifaximin), anti-inflammatory drugs such as mesalazine or balsalazide and probiotics, alone or in combination[3,138].

***Fibre.*** A high-fibre diet has been and is still recommended for patients with diverticular disease. However, a systematic review[140] concluded that the level of evidence supporting alleviation of symptoms in patients with SUDD with a high-fibre diet or dietary supplements of fibre is very low. Indeed, most studies had substantial methodological limitations (for example, the experimental design was not always suitable to answer the clinical question) and the therapeutic regimens used were heterogeneous[140]. Thus, the benefit of dietary or supplemental fibre in the treatment of SUDD needs to be established.

***Poorly absorbed antibiotics.*** The rationale for the use of poorly absorbed antibiotics, which display a high intraluminal availability, relies on the evidence that diverticula, in predisposed individuals, might favour faecal entrapment. This will be followed by bacterial overgrowth and potential breakdown of the epithelial lining, leading to bacterial translocation, mucosal inflammation and complications[141], which leads to complicated diverticular disease. Studies showing the presence of dysbiosis in patients with SUDD[55,57] and diverticulitis[142] strongly support this hypothesis. Antimicrobial drugs have been shown to reduce colonic $H_2$ production and gas-related symptoms[143]. In addition, antimicrobial therapy causes a rise in mean stool weight in subjects with a constant fibre intake, most likely because of reduced fibre degradation as a consequence of a decline in the bacterial population[144]. Both these findings provide an additional rationale for antibiotic use in diverticular disease. The reduction in gas production and the increase in faecal mass both reduce the intraluminal pressure, therefore, improving symptoms and decreasing the enlargement and stretching of diverticula as well as the generation of new diverticula[145].

In a double-blind, placebo-controlled, randomized clinical trial (RCT)[141] as well as open studies[146] and their meta-analyses[147,148], the combination of rifaximin and (soluble or insoluble) fibre was more effective in reducing symptoms in patients with SUDD than fibre alone.

As the number needed to treat (NNT) was found to be three, the treatment should be considered cost-effective. Rifaximin is a poorly absorbed, gastrointestinal tract-targeted, antibiotic that displays both eubiotic and anti-inflammatory properties[149,150]. It is also very effective and safe in the treatment of small intestine bacterial overgrowth (SIBO; the most widely detected form of gut dysbiosis)[151], which underlies several (organic and functional) gastrointestinal disorders[152]. The combination of rifaximin (given for 7–10 days, every month) and soluble fibre such as glucomannan (a plant extract capable of absorbing up to 200 times its weight in water) was very effective in treating SUDD, a finding confirmed in real-life studies from both gastroenterology and general practice[153,154]. One trial found that rifaximin alone (800 mg/day, 10 days a month) was more effective than dietary fibre in improving symptoms and quality of life in patients with SUDD[155]. The efficacy of this drug seems to be maintained in the long term, as shown by a large retrospective study with an 8-year follow-up[156]. Indeed, as the diverticula do not disappear (if anything, increase), the SIBO can recur after months if predisposing conditions are not eliminated[157]. SUDD is a chronic relapsing disease and needs a cyclic (7–10 days a month) treatment. Indeed, several guidelines[158–164] recommend long-term cyclic administration of rifaximin for the treatment of SUDD.

According to the European Pharmacopoeia, rifaximin shows crystal polymorphism with five distinct crystal forms, namely α, β, γ, δ and ε[165]. In vitro studies have demonstrated different dissolution and solubility rates of these polymorphs, and in vivo investigations in dogs found significantly different pharmacokinetic patterns amongst the various crystal forms, with the γ polymorph displaying the highest systemic bioavailability[165]. In addition to crystal polymorphs, an amorphous form of rifaximin also exists. All the above-mentioned clinical studies were performed with rifaximin-α. It is worthwhile emphasizing that the therapeutic results obtained with this polymorph should not be simply translated to the generic formulations of rifaximin, which do not claim to contain only rifaximin-α, will display significantly higher systemic absorption in both healthy individuals and patients with SUDD, and will not show the features (especially safety) of a poorly absorbed antibiotic[166].

The spread of antimicrobial resistance is one of the leading public health problems worldwide, and has been accelerated by the overuse and misuse of antimicrobial drugs[167]. Antimicrobial stewardship programmes have been shown to improve patient outcomes, reduce antimicrobial adverse events and decrease antimicrobial resistance[168]. In digestive diseases, such programmes have mainly been implemented in the treatment of patients with cirrhosis, who are widely considered 'frail' and susceptible to health-care-associated infections[169]. Being poorly absorbed, rifaximin is associated with a very low risk of systemic resistance[136]. Microbial resistance within the gastrointestinal tract is rare and transient, owing to the high local concentration of the drug and the absence of horizontal transmission. *Clostridium difficile* infection is not usual in patients receiving rifaximin in the absence of predisposing conditions such as hospitalization and immunosuppression, which are uncommon in patients affected by SUDD[170]. In the TARGET 3 trial, short-term repeat treatment with rifaximin had no apparent long-term effects on stool microbial susceptibility to rifaximin, rifampicin or non-rifamycin antibiotics[171].

***Anti-inflammatory drugs.*** Mesalazine (5-aminosalicylic acid) is an established anti-inflammatory drug with multiple pharmacological effects, although the mechanism(s) of action have not been fully elucidated[172]. In diverticular disease, mesalazine might exert anti-inflammatory activity, thereby improving chronic low-grade inflammation[172] or could modulate nociception[172]. In patients with SUDD, one double-blind study showed the efficacy of mesalazine in providing pain relief during symptomatic flares[173] whereas another study found that mesalazine was more effective in maintaining remission[174] than placebo. A systematic review[175] found that mesalazine provided better symptom relief than placebo, a high-fibre diet or low-dose rifaximin in patients with SUDD.

***Probiotics.*** Compared with antibiotic treatment, probiotics are a less invasive and provide a more physiological approach to the treatment of microbial dysbiosis in patients with diverticular disease. The most widely used probiotic mixtures contain lactobacilli and bifidobacteria, but yeasts (such as *Saccharomyces boulardii*) are also used with good clinical results. Probiotics restore the intestinal microecology by competitively inhibiting pathogenic bacterial overgrowth at the mucosa, decrease bacterial translocation by enhancing tight junction integrity and downregulate pro-inflammatory cytokines (such as TNF). All of these actions lead to improvement of mucosal defence, a feature that is potentially beneficial in the treatment of diverticular disease[176].

Despite these potential benefits, the available evidence for efficacy of probiotics in treating SUDD is poor. Indeed, the designs of the 11 published studies were very heterogeneous and only two of these studies were double-blinded and randomized[177]. For example, some trials investigated symptom improvement whereas others assessed the maintenance of remission of abdominal symptoms. Furthermore, the patient populations were small and the duration of follow-up was short (never >12 months). Inclusion criteria and the probiotic formulations that were used (single strain or multi-strain) were different, making any comparison of the results from different studies difficult. Accordingly, a critical analysis of the available data suggests a beneficial effect in treating SUDD, but does not permit any evidence-based definite conclusion[176,177]. Indeed, the Italian Consensus Conference on Diverticular Disease[160] and the guidelines of the Italian Society of Colon and Rectal Surgery[161] stated that there is insufficient evidence to conclude that probiotics show efficacy in reducing symptoms in patients with diverticular disease. However, probiotics might be useful in combination with other therapies. In one double-blind, randomized, placebo-controlled study, combination therapy with cyclic mesalazine and a probiotic (*Lactobacillus casei* DG) seemed to be more

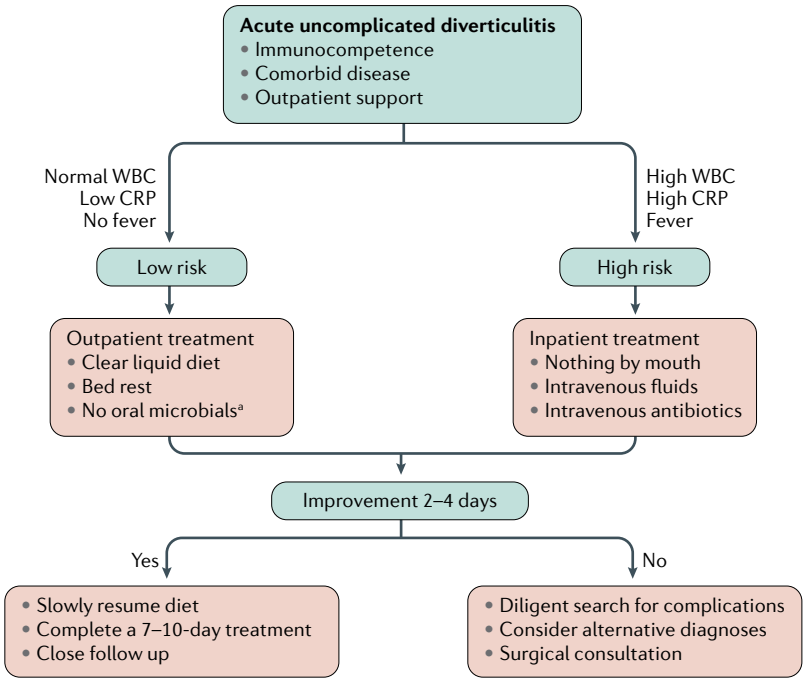


Fig. 6 | **Algorithm for the management of acute uncomplicated diverticulitis.** The clinical suspicion of acute diverticulitis needs to be confirmed by imaging (ultrasonography and/or CT scan) and laboratory parameters (leukocyte count, erythrocyte sediment rate and CRP, which correlates with the severity of the disease). In the setting of acute uncomplicated diverticulitis (with or without immunocompetence, comorbid disease and outpatient support), normal white blood cell count (WBC) and low CRP (together with absence of fever) characterize patients as low-risk, in whom outpatient treatment is feasible and omission of antimicrobial therapy is safe. Besides comorbidities, immunosuppression and the availability of outpatient support need to be taken into account in risk evaluation. Outpatients should be treated with a clear (low-fibre) liquid diet and antimicrobials should only be given in selected patients. For patients needing admission, intravenous fluids and intravenous antimicrobials should be administered. In both patients with low-risk and patients with high-risk disease, improvement of symptoms is expected within 2–3 days, and then a normal diet can be resumed. If improvement continues, patients might be discharged to complete a 7–10-day antibiotic course at home, if deemed necessary. Failure of conservative medical treatment warrants a diligent search for complications, consideration of alternative diagnoses and surgical consultation. [a]On a case-to-case basis.

effective than placebo or either treatment alone in maintaining remission of SUDD[174]. Owing to the small sample size of this study, larger trials are required to confirm this interesting observation.

### *Primary prevention of acute diverticulitis*

Progression from SUDD to diverticulitis is uncommon because the disease course is often benign. In a prospective, long-term study[178], 97% of patients with SUDD had mild or no symptoms after a median follow-up of 66 months and only 2.5% of patients developed acute diverticulitis. Prevention (both primary and secondary) of acute diverticulitis is challenging. Although studies on medical therapies to reduce occurrence and recurrence of diverticulitis are available, most of them are of poor quality and management is often empirical rather than evidence-based.

A vegetarian diet and high intake of dietary fibre lowered the risk of hospitalization and mortality from diverticular disease[26]. Both rifaximin and mesalazine have been used in an attempt to prevent the occurrence of diverticulitis in patients with SUDD, but the evidence in favour of their use is low. Two meta-analyses[147,148] found that rifaximin in combination with fibre is more effective than fibre alone in preventing acute diverticulitis, a trend that is also observed in daily clinical practice[156]. However, the therapeutic value of rifaximin was quite low (NNT 59)[148]. A meta-analysis[179] found that mesalazine also prevented diverticulitis occurrence in patients with SUDD. However, the analysis included only two RCTs and 221 patients and showed a moderate level of heterogeneity between trials, precluding definite conclusions.

### *Acute diverticulitis*

Management of acute diverticulitis depends on the severity of the condition (such as uncomplicated diverticulitis or diverticulitis complicated with abscess, perforation or peritonitis) as well as on the presence of comorbidities[22,23,180,181]. Most patients admitted with acute diverticulitis respond to conservative treatment, although 10–20% of patients will eventually require surgery.

***Acute uncomplicated diverticulitis.*** In most patients with uncomplicated diverticulitis (that is, patients who are immunocompetent, display no comorbidity, can tolerate oral intake and have outpatient support), outpatient management is possible (FIG. 6). In the setting of acute uncomplicated diverticulitis, in patients with low-risk disease, a normal leukocyte count and a low CRP level (and absence of fever), outpatient treatment is feasible and omission of antimicrobial therapy is safe[182]. A large study that analysed >1,000 patients with CT-proven acute uncomplicated diverticulitis found that patients with a systemic comorbidity, vomiting, symptoms lasting >5 days or CRP levels >140 mg/l at initial presentation had a higher risk of developing a 'complicated course of initially uncomplicated diverticulitis', requiring intensive treatment and eventually surgery[183]. Two studies confirmed high CRP concentrations as a factor predicting a worse outcome (that is, development of complicated disease)[184,185]. These studies also found that a systemic inflammatory response syndrome (which is an exaggerated defence response of the body to a noxious stressor such as infection, trauma, surgery, acute inflammation, ischaemia or reperfusion, or malignancy, to name a few), a high pain score and pharmacologically-induced immunosuppression predict a worse outcome of uncomplicated diverticulitis.

When patient classification was accurate, the outpatient approach proved to be safe and cost-effective[186–189]. Treatment usually consists of 7–10 days of oral broad-spectrum antimicrobial therapy, including coverage against anaerobic microorganisms. The most popular combination is ciprofloxacin plus metronidazole, but other regimens are also effective. A Cochrane review[190] found non-inferiority between different antibiotic regimens (cefoxitin versus gentamicin–clindamycin combination) and treatment duration (24–48 hours intravenous antibiotic treatment versus longer treatments). In uncomplicated sigmoid diverticulitis, a study

found no difference in symptom improvement between a short 4-day antibiotic course and a 7-day course[191]. Although not rigorously studied, a low-fibre liquid diet is commonly recommended as fibres can be entrapped in diverticula. However, this is based more on tradition than on evidence. In recent years, two studies have shown that an unrestricted diet is not associated with an increase in diverticular complications[192,193].

Although antimicrobial therapy has long been the cornerstone of acute diverticulitis treatment, routine use of this therapy in patients with uncomplicated diverticulitis has been challenged[194] owing to the evolving concepts in the pathogenesis of the disease (shifting from bacterial infection to an inflammatory process), the growing concerns about antibiotic overuse and the results of several studies. Two RCTs[195,196] led to the questioning of antimicrobial use and showed that observational treatment can be considered appropriate in patients with uncomplicated diverticulitis. Five meta-analyses (including RCTs, cohort studies and case–control studies)[197–201] demonstrated that clinical outcomes between patients treated with and those treated without antimicrobials are not significantly different. Indeed, no substantial differences were evident in the proportion of patients requiring additional treatment or intervention, rate of readmission or deferred admission, need for surgical or radiological intervention, and recurrence or complication rate. One meta-analysis[197] found that the only variable that was significantly associated with treatment failure in the non-antibiotic treatment group was associated comorbidities, an expected finding in clinical practice that is likely to apply to immunocompromised patients and pregnant women. Post hoc analysis of the DIABOLO trial[202] (a multicentre RCT that compared antibiotic treatment and observational treatment in 528 patients with uncomplicated acute diverticulitis)[203] found more patients with fluid collections and a longer inflamed colonic segment in the group of patients with a complicated course of initially uncomplicated diverticulitis.

Avoiding antimicrobial agents in the treatment of patients with uncomplicated acute diverticulitis is associated with a substantially shorter hospital stay[199,204]. Omitting antibiotics in the treatment of acute uncomplicated diverticulitis did not result in a higher incidence of complicated diverticulitis, recurrent diverticulitis or the need for surgical intervention even in the long term[205]. As a consequence, the guidelines from Italian medical[160] and surgical[161] societies and from the World Society of Emergency Surgery[204] as well as from the American Gastroenterological Association (AGA)[206] recommend selective use of antimicrobial drugs rather than routine administration in patients with acute uncomplicated diverticulitis.

Patients with severe presentations of uncomplicated diverticulitis (that is patients with high CRP levels, high fever, vomiting or long-lasting symptoms), those unable to tolerate oral intake or without outpatient support should be hospitalized, and should receive intravenous fluids and intravenous antimicrobial drugs (such as a β-lactam antibiotic with β-lactamase inhibitor, or metronidazole and a third-generation cephalosporin)[22,23,180,181].

In both patients with low-risk disease and patients with high-risk disease, symptoms usually improve within 2–3 days on conservative therapy, after which a solid diet can be resumed. Upon continued improvement, patients can be discharged and can continue their oral antimicrobial course at home for a total of 7–10 days. One study[207] found that patients failing to improve after 48 hours of treatment required prolonged hospitalization or surgery. When conservative medical treatment fails, a diligent search for complications is warranted and alternative diagnoses as well as surgical consultation need to be considered (FIG. 6).

***Complicated diverticulitis.*** Abscess is the most common complication of diverticulitis (occurring in ~10% of patients). Patients with small abscesses (<3–4 cm in diameter), phlegmons (localized areas of inflammation or swelling of the soft tissues) or small amounts of extraluminal air can usually be managed with antimicrobial drugs alone[208] (FIG. 7). Larger abscesses are generally treated with percutaneous drainage when antimicrobial therapy is insufficient. Percutaneous drainage can transform emergency surgery into an elective operation, reducing the need for a two-stage procedure[180,181]. In carefully selected patients (those who are immunocompromised or those with severe cardiac or pulmonary disease), observation (with no surgery) after percutaneous drainage of colonic diverticular abscess might be attempted[209,210]. However, current evidence suggests that complicated diverticulitis with abscess is associated with a high probability of requiring resective surgery, and conservative management alone can frequently result in chronic or recurrent diverticular symptoms[209,211].

The surgical approach to complicated diverticulitis is evolving and is generally becoming less aggressive[212]. Surgical resection is usually necessary to relieve symptoms when diverticulitis is complicated by a fistula or chronic obstruction due to stricture. Urgent surgical intervention is required in patients with sepsis and diffuse peritonitis (Hinchey stages III and IV) (FIG. 5) or in those who do not respond to conservative therapy[22,23,180,181]. Historically, sigmoid colectomy with end colostomy (Hartmann procedure, which brings one end of the large intestine out through the intestinal wall) was performed, but this approach is associated with the need for subsequent major surgery to restore bowel continuity. This procedure is also associated with a significant rate of perioperative complications and a risk of a permanent stoma, albeit related to the patient's disease and comorbidity rather than the surgical procedure itself. Alternatively, sigmoid colectomy with primary anastomosis (with or without diverting loop ileostomy), that seems to be associated with a lower overall mortality, has been proposed[213]. Some European studies[213] have compared the Hartmann procedure to primary anastomosis and found comparable results. However, the difficulty in applying RCT principles to studies in acute surgical settings and the intrinsic limitations of the studies do not allow definite conclusions[22].

Laparoscopic lavage has also been proposed as a means to control purulent (not faeculent) peritonitis, enabling subsequent elective resection with

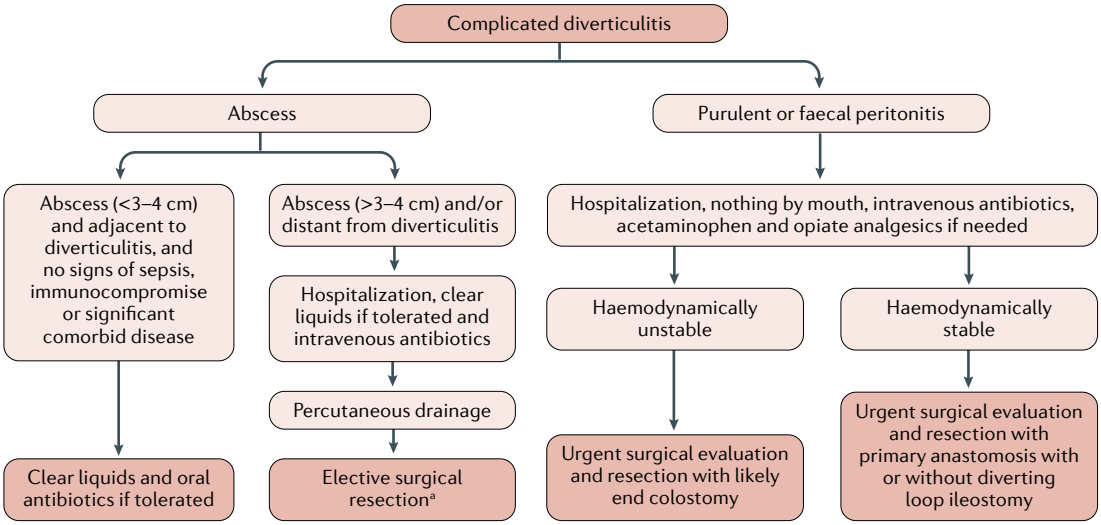


Fig. 7 | **Management of acute complicated diverticulitis.** Evaluation and treatment approach of complicated disease depends on the severity of presentation, presence of complications (peritonitis, abscess) and comorbid conditions. Abdominal CT is very useful to diagnose diverticular complications according to the Hinchey classification. Patients with small abscesses are usually managed by antimicrobial drugs and a liquid diet. If antimicrobial therapy is ineffective, larger abscesses need to be treated by percutaneous drainage, which can enable subsequent elective surgery. In addition to medical treatment, in case of diffuse peritonitis, resection surgery is mandatory. The most suitable surgical approach needs to be selected on a case-by-case basis, according to individual factors such as the extent of the inflammation in the area of the proposed anastomosis and patient stability and comorbidity. Modified from REF.[22]. [a]Recommended by current guidelines, but some evidence to suggest good outcomes without resection in selected patients.

primary anastomosis, reducing the risk of a permanent stoma[214,215]. However, at present, its use is not recommended outside clinical trials[22]. Indeed, a systematic review[216] concluded that laparoscopic lavage has an increased risk of major complications[217] compared with primary resection for Hinchey stage III diverticulitis. Primary resection with anastomosis remains the optimal management approach for complicated diverticulitis with perforation, as the rate of stoma reversal and of complications is lower than with the Hartmann procedure[216]. However, that the most suitable surgical approach needs to be selected on a case-by-case basis according to individual factors, such as the localization and extent of inflammation as well as patient stability and comorbidity[218] (FIG. 7).

### *Secondary prevention of acute diverticulitis*

After an episode of acute diverticulitis, patients might present with recurrent or smouldering diverticulitis, stricture and fistula and often develop chronic gastrointestinal and non-gastrointestinal symptoms[219]. For example, one study found that, after a follow-up of 1 year, 40% of patients with CT-confirmed acute diverticulitis complained of mild to moderate abdominal pain and/or changes in bowel habit[195]. The overall risk of acute diverticulitis recurrence is ~36% at 5 years[220]. Recurrence usually occurs <12 months after the initial episode and the risk of complications is very low[221]. In a retrospective analysis of patients over an average follow-up period of 6.3 years, patients with acute diverticulitis had a 4.7-fold increased risk of being diagnosed subsequently with IBS[222]. The infection-associated gut dysbiosis and the resulting chronic low-grade mucosal inflammation might underlie the so-called post-diverticulitis IBS (more appropriately termed as 'post-diverticulitis SUDD'), which has a pathophysiology similar to that of post-infection IBS[223]. Several strategies have been applied to prevent recurrence of diverticulitis.

***Dietary interventions.*** The AGA guidelines on the management of acute diverticulitis[206] conditionally recommend a high-fibre diet or fibre supplementation in patients with a history of acute diverticulitis, although a systematic review[224] found that the evidence for this approach is of very low quality. After resolution of an episode of acute diverticulitis, a high-fibre diet was not effective in preventing recurrence or treating recurring gastrointestinal symptoms compared with a standard or low-fibre diet. Thus, in clinical practice, dietary restrictions could be substituted with less-strict diets. A lack of evidence for the efficacy of probiotics precludes recommending their use for secondary prevention of diverticulitis[176,206].

***Pharmacological therapies.*** A meta-analysis of six trials, which evaluated the efficacy of mesalazine in the prevention of recurrent diverticulitis in 2,461 patients, showed no significant difference in the rate of recurrent diverticulitis with mesalazine treatment[225]. However, mesalazine use after an episode of diverticulitis should not be precluded. Indeed, in the DIVA trial, mesalazine treatment resulted in fewer and less-severe symptoms than placebo, a benefit that persisted at the 9-month follow-up[226]. In addition, a small retrospective study of patients with acute uncomplicated diverticulitis found that mesalazine treatment led to faster recovery[227].

In a proof-of-concept study[228], the combination of cyclic rifaximin treatment and fibre supplements reduced the risk of diverticulitis recurrence in patients in remission (HR 2.64, 95% CI 1.08–6.46), a trend later confirmed in an observational study[229]. Due to the intrinsic limitations of both studies, the current evidence favouring rifaximin use is low. An international, multicentre RCT[230] with a new rifaximin formulation (extended intestinal release) for secondary prevention of acute diverticulitis is ongoing and the results are eagerly awaited. Furthermore, a combination of mesalazine and rifaximin (both administered 7 days per month for 12 months) seems to be more effective than rifaximin alone for resolution of symptoms and prevention of diverticulitis (recurrence rate 2.7% versus 13.0%, respectively, at the end of follow-up)[231]. Furthermore, the normalization of the inflammatory indices was faster with the combined treatment[231]. Although rifaximin use can be considered promising, the AGA guidelines do not consider the available evidence to be sufficient to recommend its use for the secondary prevention of diverticulitis[206].

A 2012 systematic review concluded that the evidence on medical therapy to prevent recurrent diverticulitis is poor[232]. Thus, no recommendation of any non-operative relapse prevention therapy for diverticular disease could be made at that time. Unfortunately, little progress has been made since then. Indeed, no disease-modifying pharmacological treatment for the prevention of acute diverticulitis and/or for treating patients with symptomatic diverticular disease is currently approved in North America or Europe.

***Surgery.*** Surgery is also considered on an elective basis in patients with recurrent, uncomplicated diverticulitis. In the past, surgery was recommended after two occurrences and potentially sooner in younger patients (<50 years of age)[233]. However, accumulating data on the natural history of the disease have led to the abandonment of this recommendation as most complications (except fistulas and obstruction) occur during the first or second episode and emergency surgery is rarely needed in recurrent disease[22]. As a consequence, several reviews[234–236] concluded that there is no evidence to support the practice of elective surgery after two episodes of diverticulitis.

Morbidity is common after elective resection (10–15%) and surgery does not eliminate risk of diverticulitis recurrence[237]. The recurrence rate in patients with persistent diverticulitis is likely to be higher. In the DIRECT trial[184], 11% of surgically treated patients had anastomotic leakage and 15% of surgically treated patients required reintervention at 5 years. However, conservative management (pharmacological treatment combined with dietary and lifestyle changes) was associated with more re-admissions because of recurrence than surgery[184]. Both short-term and long-term outcomes of the DIRECT trial[184,238] showed that elective sigmoidectomy, despite its inherent risk of complications, results in better quality of life than conservative management in patients with recurrent and persistent abdominal complaints after an episode of diverticulitis. Taking these findings into account, elective surgery is recommended for recurrent, uncomplicated diverticulitis on a case-by-case basis, taking into consideration factors such as severity and frequency of symptoms, effect of surgery on the quality of life, need for immunosuppression, surgical risk profile and patient preference[22].

Notably, in the setting of acute diverticulitis (excluding patients with generalized peritonitis, which does represent a surgical emergency), medical and surgical treatments have not been directly compared in RCTs. In the absence of clear evidence in favour of surgery (which is invasive and not devoid of morbidity and mortality)[239], it is reasonable to favour (whenever possible) conservative medical therapy in most patients[237,240].

## Quality of life

Health-related quality of life (HRQOL) is specified as an individual's or a group's perceived physical and mental health over time[241]. By definition, HRQOL refers to the chronic effects of a disease rather than effects during an acute phase. Although patients with diverticular disease face a prolonged disease course and recurrent symptoms owing to prolonged subclinical inflammation[1,40], studies assessing the effect of diverticular disease on the quality of life are surprisingly rare. During the disease course, a substantial proportion of patients with diverticular disease have recurrent abdominal pain, change in bowel habits and bloating but without overt symptoms of acute diverticulitis[121,122]. In addition, both during and after acute diverticulitis recurrences, patients with SUDD attributed a wide range of negative psychological, social and physical symptoms to their condition, which impaired their quality of life[219].

In a 2003 study[242] involving 50 patients with SUDD and 50 healthy individuals, personal interview and the IBD quality of life questionnaire[242] were used to evaluate HRQOL. The IBD questionnaire addressed four aspects of the patients' quality of life — emotional function, social function, systemic symptoms and gastrointestinal symptoms. Although detailed clinical data describing disease severity were lacking, patients with SUDD had significantly lower scores than healthy individuals ($P < 0.003$) in all aspects, with the lowest scores for systemic and gastrointestinal symptoms, demonstrating that diverticular disease negatively affects patients' quality of life. An Italian study involving 58 patients with SUDD[139] employed the 36-question short form (SF-36) questionnaire[243], a general HRQOL questionnaire that measures eight different aspects of a patient's health status and well-being (four domains each for physical health and for mental health), to evaluate the efficacy of pharmacological treatment in improving patients' quality of life. Baseline scores in all eight quality of life domains were lower in patients with SUDD than in the general Italian population and 6 months of treatment with rifaximin or mesalazine improved all quality of life measures.

The diverticulitis quality of life (DV-QOL) questionnaire, a disease-targeted questionnaire[219] developed based on a cross-sectional validation study involving 197 patients with SUDD, contains 17 items addressing four major disease-specific aspects: physical symptoms, concerns, emotions and behavioural changes. The study concluded that the range of symptoms in patients with

SUDD adversely affects their physical, psychological and social well-being, which can be effectively monitored using the DV-QOL questionnaire.

A long-term extension of the DIABOLO trial[244] assessed the effect of persistent symptoms on HRQOL using the visual analogue scale (VAS) score from the EuroQol 5D (EQ5D) survey, a general HRQOL questionnaire[245], the SF-36 survey[243] and the Gastrointestinal Quality of Life Index (GIQLI), a HRQOL questionnaire for gastrointestinal diseases that contains 36 items assessing the four major aspects of a patient's life: physical, social and emotional function, and gastrointestinal symptoms[245]. At 2 years, 32–38% of patients reported that persistent symptoms negatively affected their quality of life[244]. Quality of life was not different between patients treated with antibiotics for acute diverticulitis and the observation group.

Finally, two studies, one in the UK and one in Germany, revealed higher rates of anxiety and depression in patients with diverticular disease than in healthy individuals[246,247].

## Outlook

Optimal management of diverticular disease requires defined prognostic factors, which can be clinical, laboratory or instrumental measurements (FIG. 8). Knowledge on prognostic factors will be crucial in predicting the main complication of the disease, namely acute diverticulitis. Although there are no clear clinical features that are predictive of this progression, patients with SUDD, who have extensive diverticulosis (both in terms of the number of diverticula per segment and the number of colonic segments with diverticula), are at higher risk of developing acute diverticulitis[174,222]. Prognostic factors for recurrence of acute diverticulitis are also important. When acute diverticulitis occurs, some clinical and radiological factors such as family history of diverticulitis (HR 2.2, 95% CI 1.4–3.2), >5 cm length of inflamed colon (HR 1.7, 95% CI 1.3–2.3) and presence of retroperitoneal abscess (HR 4.5, 95% CI 1.1–18.4)[220] might be easily identified as risk factors for recurrence. Other predictive factors identified include persistent increased faecal calprotectin levels after an episode of acute diverticulitis[40], although additional studies are needed to identify the ideal cut-off level for faecal calprotectin for detecting active inflammation in these patients. In addition, persistent endoscopic and histological inflammation following acute diverticulitis[44] are well-established prognostic factors for recurrence of acute diverticulitis.

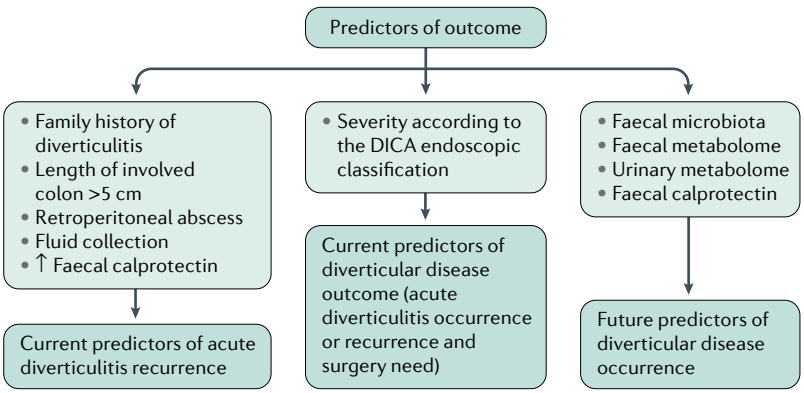


Fig. 8 | **Current and future predictors of outcome in diverticular disease.** Predictors of outcome in diverticular disease have been identified and include family history, imaging characteristics (such as length of the involved colon or retroperitoneal abscesses) and laboratory parameters (raised faecal calprotectin during follow-up). Future predictors include endoscopic characteristics of the affected colon, according to the Diverticular Inflammation and Complication Assessment (DICA) classification. Other future predictors, which need further studies to confirm preliminary results, are the identification of changes in the colonic microbiota and in the faecal and urinary metabolomes in patients with diverticular disease. These predictors might help identify patients with diverticulosis who will develop diverticular disease.

Taking all these risk factors into account, it is evident that endoscopic features have an important role in predicting both the occurrence and recurrence of acute diverticulitis. The DICA classification (FIG. 4), based on colonoscopy became available only in 2015, which is surprising, given the high frequency of incidental detection of diverticulosis during routine colonoscopy. The DICA classification could be an important tool for providing a personalized approach in patients with diverticular disease, in particular in preventing acute diverticulitis occurrence and/or recurrence[129]. The first retrospective study evaluating this tool found that treatment was not able to influence the outcomes in patients classified as either DICA 1 or DICA 3 in terms of acute diverticulitis occurrence and/or recurrence. This means that patients classified as DICA 1 are at lower risk of acute diverticulitis and patients classified as DICA 3 are at higher risk of acute diverticulitis despite a scheduled treatment during follow-up. Conversely, only patients classified as DICA 2 benefited from a scheduled treatment during follow-up, being at lower risk of acute diverticulitis occurrence or recurrence compared with those not receiving any treatment during follow-up[131]. As medical treatments did not show significant advantage in preventing acute diverticulitis occurrence or recurrence, or avoiding the need for surgical intervention in patients classified as DICA 1 and DICA 3, targeting medical treatments only to those classified as DICA 2 may save considerable economic resources that could be directed to other health purposes. In this regard, a study estimated that, in Italy, adopting such a DICA-driven approach to manage diverticular disease would save >475 million euros per year[248].

Another area requiring additional investigation is the correct diagnosis of patients with SUDD. Although in some studies patients with diverticulosis and IBS-like abdominal symptoms continue to be categorized as having 'symptomatic diverticular disease'[41,42], SUDD is a distinct disease entity with clearly defined clinical characteristics, mainly specific characteristics of the abdominal pain[249]. Consequently, patients with diverticulosis who have symptoms resembling those in patients with IBS should be diagnosed as having 'IBS-like diverticulosis'[250]. Although other characteristics of patients with SUDD such as increased faecal calprotectin levels, presence of low-grade mucosal inflammation and increased levels of some pro-inflammatory cytokines[250] enable an accurate differential diagnosis, additional studies are needed to establish clear clinical features that are easily identifiable in clinical practice.

Factors that promote progression of diverticulosis to SUDD need to be further elucidated. Although

some pathophysiological mechanisms that trigger the occurrence of symptoms (such as environmental factors, colonic dysmotility and visceral hypersensitivity) have been well-studied, understanding the role of gut microbial dysbiosis is fairly new and is of pivotal importance. However, as discussed earlier, the findings of preliminary studies have not always been consistent. For example, one study found lower levels of *A. muciniphila* in patients with SUDD than in healthy individuals[55], whereas another study found the opposite[57]. Interestingly, an increased abundance of *A. muciniphila* was observed in older individuals compared with younger individuals[251], an observation that overlaps with the general population. Furthermore, a pilot study found that treatment resulted in a lower abundance of *A. muciniphila*, which returned to pretreatment levels within 60 days of stopping treatment[252]. These changes in *A. muciniphila* abundance correlate with abdominal pain in the left lower quadrant and with the faecal metabolome[252].

Current studies concerning both faecal and mucosa-associated microbiota in diverticular disease do not allow definite conclusions to be drawn on the precise alterations (if any) of intestinal microecology associated with the disease. Many studies have drawbacks and limitations including reduced sample size, not having well-defined inclusion criteria, different patient populations and the methodology adopted. Results across different studies are not always consistent and are sometimes actually conflicting[138,253]. Asymptomatic diverticulosis does not seem to be associated with substantial changes in the gut microbiota. However, considerable changes occur in the microbiota composition when diverticulosis evolves into SUDD or acute diverticulitis (in particular, depletion of microbial taxa with purported anti-inflammatory activity). These findings are consistent with the idea that microbiota could be involved in the progression of diverticulosis to SUDD and diverticulitis, but not in the pathogenesis of diverticula. Microbiota-directed therapies might, therefore, represent a rational approach to diverticular disease[138,253].

Characterization of the faecal and urinary metabolome is a research area that is likely to improve diagnostic accuracy. The changes in the urinary and faecal metabolome in patients with SUDD involve the hippurate and kynurenine pathways, and six urinary biomarkers provide diagnostic value to distinguish patients with SUDD from healthy individuals[55]. The faecal metabolome in patients with SUDD is characterized by low levels of valerate, butyrate and choline, and by high levels of N-acetyl derivatives, whereas hippurate, methanol and 3,5-dihydroxybenzoate provide discriminatory value for distinguishing between patients with SUDD and healthy individuals[254]. Metabolomic signatures are likely to represent a key aspect of the future characterization of different phenotypes of diverticular disease.

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Introduction (A.T. and S.D.); Epidemiology (A. Lanas); Mechanisms/pathophysiology (L.L.S.); Diagnosis, screening and prevention (W.K.); Management (C.S.); Quality of life (A. Lahat); Outlook (A.T., C.S. and S.D.); Overview of Primer (A.T.). A.T. and C.S. contributed equally and are co-first authors.

**Competing interests**
C.S. and A. Lanas are members of the Speakers' Bureau and of the Scientific Advisory Board of Alfasigma SpA. W.K. served as speaker, consultant and/or advisory board member for Abbvie, Ardeypharm, Falk, Ferring, Genetic Analysis, Gräfe & Unze, Institut Allergosan, Nikkiso, Otsuka and Tillots. S.D. served as speaker, consultant, and/or advisory board member for Abbvie, Allergan, Alfa Wassermann, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Ferring, Gilead, Hospira, Johnson and Johnson, Merck, MSD, Mundipharma, Pfizer Inc., Sandoz, Takeda, Tigenix, UCB Pharma, Vifor. The remaining authors declare no competing interests.

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