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Review article: the pathophysiology and medical management of diverticulosis and diverticular disease of the colon

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SUMMARY

Background
The incidence of diverticulosis and diverticular disease of the colon, including diverticulitis, is increasing worldwide, and becoming a significant burden on national health systems. Treatment of patients with diverticulosis and DD is generally based on high-fibre diet and antibiotics, respectively. However, new pathophysiological knowledge suggests that further treatment may be useful.

Aim
To review the current treatment of diverticulosis and diverticular disease.

Methods
A search of PubMed and Medline databases was performed to identify articles relevant to the management of diverticulosis and diverticular disease. Major international conferences were also reviewed.

Results
Two randomised controlled trials (RCT) found the role of antibiotics in managing acute diverticulitis to be questionable, particularly in patients with no complicating comorbidities. One RCT found mesalazine to be effective in preventing acute diverticulitis in patients with symptomatic uncomplicated diverticular disease. The role of rifaximin or mesalazine in preventing diverticulitis recurrence, based on the results of 1 and 4 RCTs, respectively, remains unclear. RCTs found rifaximin and mesalazine to be effective in treating symptomatic uncomplicated diverticular disease. The use of probiotics in diverticular disease and in preventing acute diverticulitis occurrence/recurrence appears promising but unconclusive. Finally, the role of fibre in treating diverticulosis remains unclear.

Conclusions
Available evidence suggests that antibiotics have a role only in the treatment of complicated diverticulitis. It appears to be some evidence for a role for rifaximin and mesalazine in treating symptomatic uncomplicated diverticular disease. Finally, there is not currently adequate evidence to recommend any medical treatment for the prevention of diverticulitis recurrence.

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INTRODUCTION

Diverticulosis of the colon is the most frequent anatomical colonic alteration, frequently detected during colonoscopy.[1] It is a structural alteration of the colonic wall characterised by the presence of pockets called 'diverticula'. These diverticula are characterised by herniation of the colonic mucosa and sub-mucosa through defects in the muscle layer at the weakest point in the colonic wall: the sites of penetration by blood vessels of the colon wall.[2] These types of diverticula, which are actually pseudodiverticula as herniation is not through all colonic layers, occur typically in the left colon. The real prevalence of diverticulosis is unknown. In Europe, it is largely age-dependent and is uncommon (prevalence of 5%) in those under the age of 40 years, increasing up to 65% in those aged 65 years or more.[3] For many years, it has been thought that this type of diverticulosis exclusively affected the westernised world and was due to a lack of fibre in the diet and increased pressure at the colonic wall.[4, 5] However, recent data have revealed an increase in the prevalence of colonic diverticulosis throughout the world.[6, 7] Colonic diverticulosis occurring in the right colon is characterised by true diverticula, in which there is herniation of all colonic wall layers.[2] Right-sided diverticulosis is quite common in Asian people. For example, Yamada *et al.* recently found right-sided colonic diverticulosis in 21.6%, and left-sided or bilateral diverticulosis in 18.6% of Japanese people undergoing colonoscopy.[8]

Although most people with colonic diverticulosis remain asymptomatic, about 20% of patients will develop symptoms, developing so-called 'diverticular disease' (DD) [1] of whom 15% will ultimately develop complications.[9–11] DD imposes a significant burden on westernised National Health Systems. In the USA, the prevalence of DD increases with age, with about 70% of people aged ≥80 years showing diverticulosis,[1] and DD accounts for more than 300 000 hospital admissions, 1.5 million in-patient care days, and 2.4 billion dollars in direct costs each year.[1] The incidence of DD and its complications appears to be increasing, and the number of patients with DD can be expected to increase in coming years in accordance with current trends as the population continues to age. In the USA, overall annual age-adjusted admissions for acute diverticulitis increased from 120 500 in 1998 to 151 900 in 2005 (26% increase). Rates of admission increased more rapidly within patients aged 18–44 years (82%) and 45–74 years (36%). The number of elective operations for diverticulitis rose from 16 100 to 22 500 per year during the same time period (29%), along with a more rapid increase (73%) in rates of surgery for individuals aged 18–44 years.[12] Finally, in Europe DD accounts of about 13 000 death per year.[3]

TERMINOLOGY

To aid in the discussion of diverticulosis, it is important to first define some key terms, including DD, symptomatic diverticulosis and symptomatic uncomplicated diverticular disease (SUDD). According to current accepted definitions,[13–21] the following terminology is used in describing different scenarios in which diverticula may be detected. 'Diverticulosis' is merely the presence of colonic diverticula; these may, or may not, be symptomatic or complicated. 'Diverticular disease' is defined as clinically significant and symptomatic diverticulosis; this may be from true diverticulitis or from other less well-understood manifestations (e.g. visceral hypersensitivity in the absence of verifiable inflammation).[22] The overarching term 'diverticular disease' implies that the pathologic lesion (diverticulosis) rises to the level of an illness. 'Symptomatic Uncomplicated Diverticular Disease' is a subtype of DD in which there are persistent abdominal symptoms attributed to diverticula in the absence of macroscopically overt colitis or diverticulitis. In contrast, 'diverticulitis' is the macroscopic inflammation of diverticula with related acute or chronic complications. Diverticulitis can be uncomplicated or complicated. It is uncomplicated when computerised tomography (CT) shows colonic wall thickening with fat stranding, while it is complicated when CT finds complicating features of abscess, peritonitis, obstruction, fistulas or haemorrhage. Segmental colitis associated with diverticulosis (SCAD) is a unique form of inflammation that occurs in areas marked by diverticulosis. Endoscopic and histological characteristics describe it as a forerunner of inflammatory bowel disease (IBD).[23–25] Our primary focus in this article is acute and chronic forms of DD, including SUDD, and diverticulitis.

All definitions used in this review are reported in Table 1.

METHODS

A literature search was performed using PubMed, up until December 2014. Original articles and reviews were identified using PubMed search terms: 'diverticular disease', 'diverticulitis', 'diverticulosis' in association with each of the following terms: 'treatment', 'therapy', 'mesalazine', 'rifaximin', 'probiotics', 'antibiotics' and 'fibre'. Additional articles were identified through review of the

Table 1 | Terminology used in describing different scenarios in which diverticula may be detected

Diverticulosis. It is the presence of colonic diverticula; these may or may not be symptomatic or complicated
Diverticular disease. It is defined as clinically significant and symptomatic diverticulosis; this may be from true diverticulitis or from other less well-understood manifestations (e.g. visceral hypersensitivity in the absence of verifiable inflammation)
i *Symptomatic Uncomplicated Diverticular Disease (SUDD).* It is the presence of persistent abdominal symptoms attributed to diverticula in the absence of macroscopically overt colitis or diverticulitis
ii *Diverticulitis.* It describes macroscopic inflammation of diverticula with related acute or chronic complications
a Uncomplicated. CT may show colonic wall thickening with fat stranding
b Complicated. Complicating features of abscess, peritonitis, obstruction, fistulas or haemorrhage (CT not likely to show haemorrhage)
Segmental colitis associated with diverticulosis (SCAD). It is a unique form of inflammation that occurs in areas of diverticulosis. Endoscopic and histological characteristics show features suggestive of inflammatory bowel disease (IBD)

reference lists of select pertinent articles. Data presented at major international conferences were also reviewed. The articles returned by the searches were selected based on English language and relevance to this review.

CURRENT PATHOPHYSIOLOGY OF DIVERTICULOSIS AND DIVERTICULITIS

The underlying pathological mechanisms that cause the formation of colonic diverticula remain unclear. These are likely to be the result of complex interactions among diet, colonic microbiota, genetic factors, colonic motility, microscopic inflammation and structure. All these factors have to be considered as potential targets of treatment.

Colonic motility

Neural degeneration with age may also contribute, with several studies suggesting reduction in neurones in the myenteric plexus[26] and decreased myenteric glial cells and interstitial cells of Cajal.[27] Denervation hypersensitivity has also been reported,[28] and these abnormalities of enteric nerves might lead to uncoordinated contractions and high pressure, producing diverticulosis. The associated muscular hypertrophy and altered enteric nerves[29] may result from remodelling after acute inflammation, which numerous animal studies have shown to be associated with muscular hypertrophy, abnormal motility,[30] visceral hypersensitivity and altered neurochemical coding.[31, 32] Such changes may account for the common experience of the development of recurrent abdominal pain and disturbed bowel habits following acute diverticulitis,[33] and the finding of visceral hypersensitivity in patients with symptomatic DD.[22, 34]

Microbiota alterations

Disease-specific variations in intestinal microbiome composition have been found for a number of intestinal disorders, and preliminary information on colonic microbiota alteration is also becoming available. Using a polymerase chain reaction-based profiling technique on DNA isolates from faecal samples, Daniels *et al.* recently compared the faecal microbiota of diverticulitis patients with control subjects from a general gastroenterological practice. They found that Firmicutes/Bacteroidetes ratios and Proteobacteria load were comparable among patients and controls ($P = 0.20$), while a higher diversity in diverticulitis for Proteobacteria ($P < 0.00002$) and all phyla combined ($P = 0.002$) were found.[35]

Genetic factors

Hereditary factors also seem to play a role in the development of DD.

The Swedish Twin Registry was cross-linked with the Swedish Inpatient Registry, and a diagnosis of DD was found among all twins, born between 1886 and 1980 and not dead before 1969. Of a total of 2296 twins having a diagnosis of DD, the odds ratio of developing the disease if one twin was affected was 7.15 for monozygotic and 3.20 for dizygotic twins. Similarly, concordance rates and tetrachoric correlations were higher in monozygotic than in dizygotic twins. The heritability was estimated to be 40%, and the nonshared environmental effects to be 60%.[36] Similar results were obtained in a similar population-based study conducted in Denmark.[37]

Specific genes able to predict the occurrence of complications have also recently been investigated. The TNFSF15 gene has been associated with other inflammatory diseases affecting the colon, such as medically refractory ulcerative colitis (UC), aggressive Crohn's disease (CD) and pouchitis after restorative proctocolectomy.[38] This gene has recently been investigated in patients undergoing surgical treatment of diverticulitis, and matched with three separate groups: healthy controls, CD control patients and UC control patients. In the discovery phase, the TNFSF15 SNP rs7848647 was significantly associated with diverticulitis compared with

all control groups studied ($P = 0.0003$). The risk allele for this SNP (G substituted for A) was found in all SD patients. The homozygous GG allele was found in 62% (13/21) of diverticulitis patients versus only 5% (1/21) of healthy controls ($P = 0.001$) and 24% (10/42) of all UC + CD controls ($P = 0.002$). In the test group, the homozygous GG genotype was found in 56% of SD patients compared with 17% of healthy controls ($P = 0.006$). Risk of diverticulitis seemed to increase with number of the G alleles, with 8% of diverticulitis patients having AA homozygosity, 35% of diverticulitis patients having AG heterozygosity and 56% of diverticulitis patients having GG homozygosity.[39]

Inflammation

In recent years, several findings have supported a significant role of inflammation in determining symptom and complication occurrence in those patients:

i DD shows a significant microscopic inflammatory infiltrate.[40, 41] This microscopic inflammation, ranging from increased chronic lymphocytic infiltration to active neutrophilic infiltrate, seems to be linked to the severity of the disease[41, 42];

ii DD shows an enhanced expression of pro-inflammatory cytokines as TNFα.[29, 34, 43] Moreover, the overexpression of this cytokine decreases parallel to response to therapy[44, 45];

iii Obesity is a risk factor for diverticulitis recurrence, due to the pro-inflammatory effect of adipokynes and chemokynes[46];

iv Both persisting endoscopic and histological inflammation have recently been identified as significant risk factors for diverticulitis recurrence[47];

v Up to 20% of patients complain of persistent abdominal pain after surgical treatment of diverticulitis, and quality of life of patients is significantly worse after surgery.[48] It has been hypothesised that persistent symptoms are linked to increased neuropeptides in mucosal biopsies, which may reflect resolved prior acute inflammation and persistent chronic inflammation.[49]

DIAGNOSIS OF DD

Radiology

Barium enema was once considered the best tool for demonstrating the extent and severity of colonic DD.[50] This is because this radiological technique allows examination of the entire colon, including all anatomical alteration (e.g. stenosis) that may affect endoscopic exploration. However, the use of BE is now discouraged due to poor patient compliance, long examination time, high risk of complications and radiation exposure.[51] There are now more sophisticated and sensitive methods that provide greater information about the characteristics of the colonic wall and the pericolonic tissues. The diagnostic accuracy of barium enema for DD is similar to that of computer tomograpy colonography (CTC), but use of barium enema should only be considered if CTC is unavailable. CTC is easy, standardised and much less labour-intensive and invasive than barium enema or colonoscopy (Figure 1).[52] CTC can provide a balanced view of the disease by incorporating visual analysis with quantitative analysis by using a CTC-based DD severity score; this score appears to correlate with relevant coexisting lesions and can potentially influence therapeutic decision making.[52] CTC is strongly advisable in cases where colonoscopy is incomplete, has failed, or is unfeasible, but is contraindicated in acute abdominal conditions, such as acute diverticulitis, because of the high risk of complications (i.e. perforations).[53]

Abdominal computed tomography (CT) plays an important role in the diagnosis of diverticulosis, but it is particularly helpful in diagnosing acute diverticulitis.[50] Moreover, a CT scan is able to differentiate between uncomplicated (acute diverticular inflammation without stenoses, and/or fistulas and/or abscesses) (Figure 2a) and complicated diverticulitis (acute diverticular inflammation with stenoses, and/or fistulas and/or abscesses) (Figure 2b).

Ultrasound has also been successfully used for diagnosis, and magnetic resonance imaging has significant potential as a radiation-free imaging test for acute colonic diverticulitis. However, results from these imaging modalities remain inconclusive in terms of their ability to provide clinical direction.[53]

Colonoscopy

Colonoscopy remains the main tool used for the diagnosis and management of diverticulosis and DD. Diverticulosis is the most commonly reported finding on routine colonoscopy.[1] Endoscopic diagnosis of diverticulosis is generally incidental and does not affect the safety or accuracy of colonoscopy. However, detection of massive diverticulosis, especially in the sigmoid, may increase the risk of perforation, because of rigidity of the colon and potential confusion between diverticular lumen and true colonic lumen when multiple large diverticular openings are detected. Colonoscopy is also able to detect the first

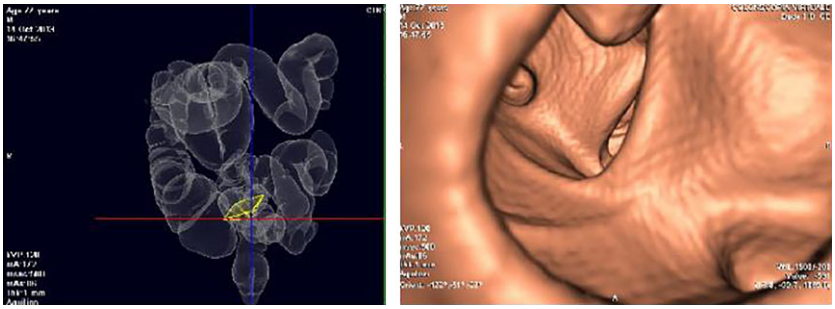
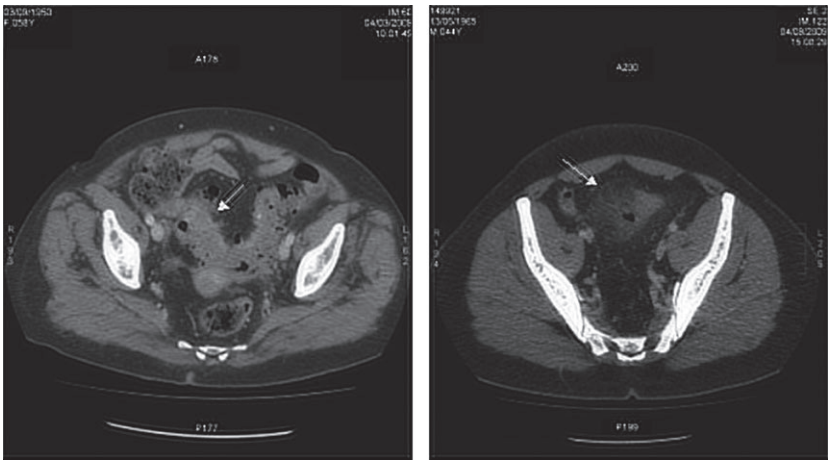


Figure 1 | Colonic diverticulosis on CT colonography. This technique is strongly advised when colonoscopy is incomplete, failed, or unfeasible.



Panel **(a)** Panel **(b)**

Figure 2 | Acute diverticulitis on computerised tomography. (a) Uncomplicated disease. Thickening of the colonic wall with fat stranding in pericolic tissue (arrow). (b) Complicated disease. Thickening of the colonic wall with the presence of an abscess (arrow).

occurrence of acute diverticulitis. Ghorai *et al.* found that endoscopic findings of diverticular inflammation were reported in about 0.8% of patients undergoing colonoscopy without clinical evidence of diverticulitis.[54] More recently, Tursi *et al.* found that endoscopic signs of diverticulitis may be detected in 2% of people undergoing colonoscopy.[55]

Colonoscopy is currently advised in managing DD of the colon, ranging from treatment to diverticular bleeding to differential diagnosis with IBDs or colorectal cancer (Figure 3).[56]

THE CLINICAL PICTURE OF DD

The term 'diverticular disease' describes the symptoms linked to the anatomical–structural changes in the colon that harbour diverticula.

Clinical classification of DD is still currently based on the 1999 EAES (European Association for Endoscopic Surgery) criteria, which subdivided DD as symptomatic uncomplicated disease, recurrent symptomatic disease and complicated disease.[15]

Symptomatic uncomplicated diverticular disease is characterised by nonspecific attacks of abdominal pain without evidence of an inflammatory process. This pain is typically colicky in nature, but can be constant, and is often relieved by passing flatus or having a bowel movement. Bloating and changes in bowel habits also can occur due to bacterial overgrowth, and constipation is more common than diarrhoea. Fullness or tenderness in the left lower quadrant, or occasionally a tender palpable loop of the sigmoid colon, is often discovered on physical examination.

Recurrent symptomatic disease is associated with the recurrence of the symptoms described above, and it may occur several times per year. As recently underlined, these symptoms may resemble irritable bowel syndrome (IBS).[8, 57] Moreover, it has been recently described that IBS occurs 4.7-fold more likely in patients after an episode of acute diverticulitis than controls.[58] Several factors seem to explain persistence of symptom in those patients (significant attenuation in serotonin-transporter expression,[5] increased neuropeptides expression in colonic mucosa,[59] persistence of low-grade inflammation[60]). Hence, in this way, it seems to be appropriate to speak of IBS-like symptoms rather than IBS in those patients.[61]

On the contrary, it may be quite difficult to differentiate SUDD from IBS. Clinical and laboratory parameters may be useful. Cuomo *et al.* found recently that only a minority of DD patients (10%) fulfilled criteria for IBS

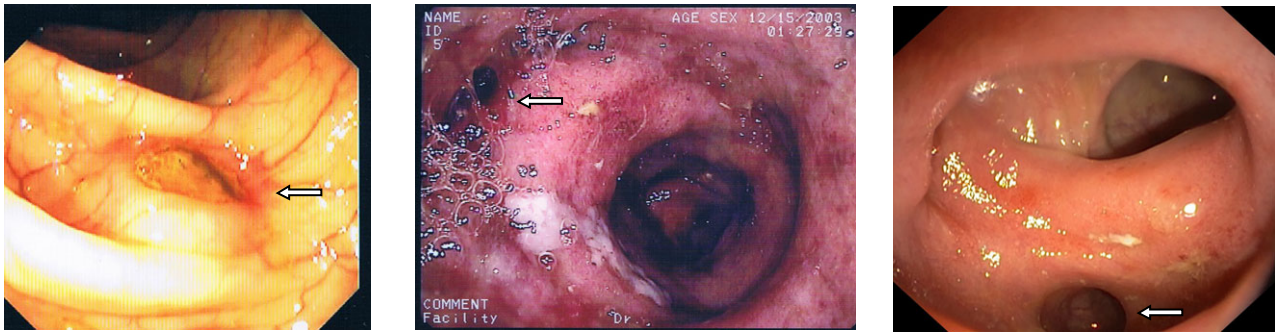


Figure 3 | Endoscopic appearances of inflammation in association with diverticula. (a) Inflammation affects only the diverticulum (indicated by the arrow). This is diverticulitis. (b) Inflammation affects the entire colonic mucosa. This is ulcerative colitis in a patient with diverticulosis (diverticulum indicated by the arrow). (c) Inflammation affects only inter-diverticular mucosa, with sparing of the diverticulum (indicated by the arrow). This is segmental colitis associated with diverticulosis (SCAD).

diagnosis and that abdominal pain >24 h was more prevalent in SUDD than in IBS patients ($P < 0.01$). It was also demonstrated that, compared with IBS, DD patients had more episodes of pain lasting 24 h requiring medical attention ($P < 0.01$).[62] More recently, we investigated 72 patients suffering from abdominal pain with diverticula identified on colonoscopy, of whom 42 were classified as having SUDD (abdominal pain for at least 24 consecutive hours in the left lower abdomen), and 30 were classified as having IBS-like symptoms fulfilling Rome III criteria. All patients underwent faecal calprotectin (FC) determination and it was found that FC levels were elevated in 64.3% of SUDD patients and in no patients in the IBS-like group ($P < 0.0001$). Moreover, the severity of the abdominal pain and the FC score correlated significantly in SUDD patients ($P = 0.0015$).[63] FC is particularly useful in this setting, because raised FC may be detected in SUDD, acute diverticulitis and SCAD but not in IBS.[64, 65] Hence, the characteristic of abdominal pain (left lower quadrant pain lasting >24 h), and the detection of raised FC are very useful for achieving a correct differential diagnosis between IBS and DD in a patient with diverticulosis of the colon.[66]

European Association for Endoscopic Surgery criteria classifies as 'complicated disease' all complications related to DD, ranging from haemorrhage to peritonitis and strictures. Acute diverticulitis (DD with signs and symptoms of diverticular inflammation) is included in complicated disease.

Regarding treatment, symptomatic uncomplicated and recurrent symptomatic forms of colonic DD generally require medical treatment. Uncomplicated diverticulitis is also generally treated medically, and complicated diverticulitis generally requires surgical treatment.[1] This has been recently confirmed by Lamb *et al.,* who found that urgent surgery, elective surgery and no surgery are required in 30%, 36% and 35% of uncomplicated diverticulitis patients, respectively.[67]

MEDICAL TREATMENT OF DIVERTICULOSIS AND DD

National and International Guidelines and Consensus Conferences have provided therapeutic advice for patients with DD.[15–21, 68, 69] However, such advice is often conflicting, so we will describe herein current practice for the treatment of diverticulosis and DD.

Symptomatic uncomplicated DD

Fibre. According to current WGO Guidelines, many clinicians advise spasmolytics and a high-fibre diet or fibre supplementation, which still represent first-line treatment for SUDD.[68] However, a recent systematic review found that high-quality evidence for a high-fibre diet in the treatment of DD is lacking, and most recommendations are based on inconsistent level 2 and mostly level 3 evidence.[70] Only three randomised, placebo-controlled trials of adequate quality were identified, giving contradictory results.[71–73] This systematic review did not found a significant difference between soluble versus insoluble fibre. Only one randomised, placebo-controlled study compared insoluble (bran, 6.99 g/daily) with soluble fibres (ispaghula 9.04 g/daily) and placebo (2.34 g/daily), taken for 16 weeks. There were no significant differences in pain, lower bowel symptoms or total symptom scores taking crisp bread, ispaghula drink and

Table 2 | Adequate quality controlled trials in using fibre in diverticulosis and symptomatic diverticular disease

Study	Trial design	No. of patients	Randomisation	Outcomes assessed	Length of follow-up	Results
Brodibb[71]	Double-blind, randomised	18	Wheat crispbread 0.6 g/day vs. bran crisp bead 6.7 g/day	Reduction in global symptom score in SUDD	3 months	High fibre vs. low fibre group has significant reduction in symptoms score (34.3–8.1 vs. 42.0–35.1, $P < 0.002$)
Ornstein *et al.*[72]	Randomised, cross-over, double-blind, placebo-controlled	58	Bran (6.99 g/day) vs. ispaghula (9.04 g/day) vs. placebo (2.34 g/day)	Reduction in global symptom score in SUDD	16 weeks	No difference was found between the three arms (from 16.3, 18.4 and 15.6–5.9, 6.7 and 6.3, P = n.s.)No difference between bran and ispaghula consumption (5.9 vs. 6.7)
Hodgson[73]	Double-blind, randomised, placebo-controlled	30	Methylcellulose 2 tablets/day vs. placebo 2 tablets/day	Reduction in global symptom score in SUDD	3 months	Symptom score decreased significantly in the methylcellulose group (from 19 ± 6 to 13 ± 4, $P < 0.01$) but not in the placebo group (from 21 ± 7 to 17 ± 9, P = n.s.)
Crowe *et al.*[94]	Prospective, cohort study	47 033	Vegetarian vs. nonvegetarian dietHigh (≥25.5 g/day for women and ≥26.1 g/day for men) vs. lower fibre consumption	Occurrence of DDHospital admission for DD complications	11.6 years	Vegetarians had a 31% lower risk of DD occurrence ($P = 0.001$)High fibre intake had a 26% lower risk of developing DD ($P = 0.018$) Hospital admission or death for DD was 4.4% for meat eaters and 3.0% in vegetarians or vegans
Peery *et al.*[74]	Cross-sectional study	2104	Fibre or high Fibre consumption (>50 g/day) vs. normal diet	Diverticulosis occurrence	12 years	High fibre consumption had higher risk to develop diverticulosis ($P = 0.004$)Soluble fibre had higher risk to develop diverticulosis ($P = 0.038$)
Strate *et al.*[37]	Prospective cohort study	47 228	Lower (less than once per month) vs. Higher (at least twice per week) nut, corn, or popcorn consumption	Diverticulitis occurrenceDiverticular bleeding occurrence	18 years	Higher nut, corn or popcorn consumption had lower risk of diverticulitis occurrence ($P = 0.034$)No difference in diverticular bleeding occurrence between higher or lower consumption of nut, corn or popcorn ($P = 0.56$, 0.64 and 0.52 respectively)
Leahy *et al.*[93]	Prospective case–control study	56	Lower (<25 g/day) vs. High (>25 g/day) fibre diet	Symptoms recurrenceOccurrence of complicationsSurgery due to DD	66 months	High fibre diet has significantly lower symptom recurrence (19.35% vs. 44%, $P < 0.05$), occurrence of complications (6.45% vs, 20.25%, $P < 0.05$) and surgery due to DD (6.45% vs. 32%) than low fibre diet

DD, diverticular disease; SUDD, symptomatic uncomplicated diverticular disease.

placebo.[72] Surprisingly, Peery *et al.* found recently that high intake of soluble fibre had a higher risk of diverticulosis occurrence ($P = 0.038$).[74]

Nevertheless, a high-fibre diet is still recommended. Adequate quality controlled studies in using fibre in such patients are reported in Table 2.

Antibiotics. Since 1992, the use of rifaximin has been investigated in the treatment of SUDD. This is a poorly absorbable antibiotic with a broad spectrum of action, including action against Gram-positive and -negative bacteria, aerobes and anaerobes.[75] It has been successfully used in recent years in the treatment of SUDD,[76]

and also seems to be effective in maintaining SUDD remission.[77] A recent meta-analysis examined four prospective randomised trials (only one conducted in double-blind placebo-controlled fashion) including 1660 patients. The pooled rate of difference for symptom relief was 29.0% in favour of rifaximin (rifaximin vs. control; 95% CI 24.5–33.6; $P < 0.0001$) with a clinically significant Number Needed to Treat (NNT = 3).[78] Controlled studies of rifaximin in such patients are reported in Table 3.

Mesalazine. Controlling inflammation with mesalazine is another option for the treatment of SUDD. Although this drug has been effectively used for many years in the treatment of IBDs, the mechanisms of action are not yet well understood. Mesalazine acts in the gastrointestinal epithelium, through N-Ac-5ASA, the active metabolite of 5-ASA (mesalazine), but the molecular mechanisms of its action are not clear. It is thought that mesalazine inhibits some key factors of the inflammatory cascade (Cyclo-oxygenase, thromboxane-synthetase and PAF-synthetase), inhibits the production of interleukin-1 and free radicals, and has intrinsic antioxidant activity.[79] In the light of new data on the role of inflammation in the pathogenesis of SUDD, it was inevitable that researchers would attempt to use to apply mesalazine in this indication.

Although limited by the open-label design, the favourable effect of mesalazine on SUDD has been demonstrated by several open-label studies.[80–85]

Three double-blind, placebo-controlled studies have also recently assessed the role of mesalazine in treating those patients.

The first trial investigated the efficacy and safety of mesalazine granules 3 g/daily vs. placebo in patients with lower abdominal pain as a symptom of SUDD. Change in lower abdominal pain to week 4 (baseline defined using pain score from 7 days pre-treatment) was significantly lower in mesalazine group ($P = 0.05$) in the per-protocol (PP) but not on intention-to-treat ($P = 0.374$) population. *Post hoc* adjustment for confounding factors resulted in $P = 0.005$ (PP). Safety was comparable.[86]

Table 3 | Controlled trials in using rifaximin in treating diverticular disease

Study	Trial design	No. of patients	Randomisation	Outcomes assessed	Length of follow-up	Results
Papi *et al.*[95]	Open-label, prospective, randomised	217	RFX 800 mg/plus GM 2 g/day for 7 days vs. GM 2 g/day for 7 days each month	Reduction in global symptomatic score in SUDD	12 months	RFX + GM 63.9% reduction score vs. GM alone 47.6% ($P < 0.001$)
Papi *et al.*[76]	Double-blind, randomised, placebo-controlled	168	RFX 800 mg/plus GM 2 g/day for 7 days vs. Placebo plus GM 2 g/day for 7 days each month	Reduction in global symptomatic score in SUDDPrevention of diverticulitis occurrence	12 months	RFX + GM 68.9% reduction score vs. placebo + GM 39.5% ($P = 0.001$)No difference in preventing diverticulitis occurrence (1.3% vs. 1.5%, P = n.s.)
Latella *et al.*[77]	Prospective, randomised, open-label	968	RFX 800 mg/plus GM 4 g/day for 7 days vs. GM 4 g/day for 7 days each month	Reduction in global symptomatic score in SUDDPrevention of DD complications (acute diverticulitis and diverticular bleeding)	12 months	RFX + GM 56.5% reduction score vs. GM alone 29.2%, $P < 0.001$)RFX + GM 1.34% occurrence of DD complications vs. GM alone 3.22% ($P < 0.05$)
Lanas *et al.*[111]	Open-label, prospective, randomised	165	RFX 800 mg/plus fibre 7 g/day for 7 days vs. fibre 7 g/day for 7 days each month	Prevention of diverticulitis recurrence	12 months	RFX/fibre 10.4% diverticulitis recurrence vs. fibre alone 19.3% ($P = 0.025$)

RFX, Rifaximin; GM, Glucomannan.

The second trial assessed the effectiveness of mesalazine, with or without probiotic vs. placebo in maintaining remission in SUDD patients. Four groups were randomly enrolled: Group M (active mesalazine 1.6 g/day plus *Lactobacillus casei* subsp. DG placebo), Group L (active *L. casei* subsp. DG 24 billion/day plus mesalazine placebo), Group LM (active *L. casei* subsp. DG 24 billion/day plus active mesalazine), Group P (*L. casei* subsp. DG placebo plus mesalazine placebo). SUDD recurred in no (0%) patient in group LM, in 7 (13.7%) patients in group M, in 8 (14.5%) patients in group L and in 23 (46.0%) patients in group P (LM group vs. M group, $P = 0.015$; LM group vs. L group, $P = 0.011$; LM group vs. P group, $P = 0.000$; M group vs. P group, $P = 0.000$; L group vs. P group, $P = 0.000$). No adverse events were recorded during the study.[87]

Another double-blind, placebo-controlled trial not yet published assessed the efficacy of mesalazine in controlling abdominal pain in SUDD as a secondary endpoint. Patients with SUDD underwent flexible sigmoidoscopy and biopsies at baseline and after 12 weeks' treatment, completing diaries of pain and bowel habits. Patients were randomised to receive mesalazine 3 g/day (group M) or placebo (group P) for 12 weeks with follow-up visits at 2 and 4 weeks. In Group M but not in Group P there was a significant reduction in the duration of abdominal pain ($P = 0.0413$).[44] Controlled studies of mesalazine use in such patients are reported in Table 4.

Probiotics. Using probiotics is a third choice for the treatment of SUDD. Probiotics are living micro-organisms, which can exert host health benefits beyond those of inherited basic nutrition.[88] The physiopathological actions of probiotics include pathogen adherence inhibition, increasing IgA secretion in Peyer's patches, increasing immune system activity inhibiting the release of anti-inflammatory cytokines and inhibiting pro-inflammatory cytokines.[88] Moreover, these 'good' bacteria may interfere with pathogen metabolism by a mechanism of metabolic competition.[88]

It is generally though that DD is affected by bacterial overgrowth in the diverticula, and that this may cause ischaemic phenomena, diverticular and peri-diverticular inflammation, increased exposure to intraluminal antigens and toxins, and bacterial flora changes related to stasis.[89] Therefore, a therapeutic manipulation of the colonic flora may be useful in controlling colonic inflammation, and finally in controlling symptoms in those patients. Widespread use of antibiotics can control bacterial overgrowth and prevent translocation of gut bacteria. However, some bacteria may provide specific health benefits when consumed as a food component or in the form of specific preparations of viable micro-organisms, without the risk of antibiotic resistance. This considered, recent studies investigated the effect of probiotics on the course of SUDD. All found different probiotic strains effective in treating SUDD patients,[82, 85, 90, 91] but the open-label designs limit the usefulness of these results.

Finally, the double-blind, placebo-controlled trial was already mentioned. In this study, the combinations of mesalazine with *L. casei* subsp. DG (group LM) or *L. casei* subsp. DG alone (group L) were significantly better than placebo in preventing SUDD recurrence (LM group vs. P group, $P = 0.000$; L group vs. P group, $P = 0.000$).[87] Controlled studies of probiotics in such patients are reported in Table 5.

Primary prevention of acute diverticulitis

Primary prevention of acute diverticulitis, namely prevention of the first episode of acute diverticulitis, is a very important topic, even if a more recent, colonoscopy-based study hypothesised a lower rate of diverticulitis occurrence from diverticulosis.[92] However, results of studies investigating such prevention are often conflicting.

Fibre. Data on the role of fibre in primary prevention of diverticulitis are particularly conflicting.

Patients with a history of diverticulosis or DD commonly seek dietary and lifestyle recommendations to reduce their risk of occurrence/recurrence of the disease and/or complications. The traditional recommendation has been to consume a high-fibre diet. Using data from a single case–control study that included 56 participants, it is estimated that a high-fibre diet might reduce the number of complications (by 52 cases per 1000 patients treated) and need for surgery (by 100 cases per 1000 patients treated).[93]

Using data from a prospective cohort study that examined the association of dietary fibre intake and risk of incident hospitalisation for DD,[94] it is approximated that a high-fibre diet may reduce the risk of acute diverticulitis by 59 cases per 1000 patients on a high-fibre diet. We rated the quality of this evidence as very low based on substantial differences between our target population (those with a history of diverticulitis) and those in the cohort study (those without a history of diverticulitis).

Only three randomised trials analysed the role of fibre in preventing diverticulitis occurrence in those

Table 4 | Fully published placebo-controlled trials in using mesalazine in diverticular disease

Study	Trial design	No. of patients	Randomisation	Outcomes assessed	Length of follow-up	Results
Kruis *et al.*[86]	Double-blind, randomised, placebo-controlled	117	Mesalazine granules 3 g/day vs. Placebo in SUDD	Pain control in SUDD	4 weeks	Mesalazine had higher percentage of pain control (62.5% vs. 50.81%, $P = 0.374$ on ITT and $P = 0.05$ on PP)
Tursi *et al.*[87]	Double-blind, randomised, placebo-controlled	210	Mesalazine Eudragit L 2.4 g/day vs. Mesalazine 2.4 g/day + *Lactobacillus casei* 750 mg/day vs. *Lactobacillus casei* 750 mg/day vs. placebo in SUDD	Maintaining remissionPreventing diverticulitis occurrence	12 months	Mesalazine, alone or in combination, had high remission rate (93.33% and 85.45% vs. 54%, $P = 0.0001$)*Mesalazine, alone or in combination, had lower diverticulitis occurrence (0% and 1.81% vs. 12%, $P = 0.003$)*
Stollman *et al.*[113]	Double-blind, randomised, placebo-controlled	117	Mesalazine Eudragit L 2.4 g/day vs. Mesalazine 2.4 g/day + *Bifidobacterium infantis 35624* vs. placebo following acute diverticulitis	Reducing gastrointestinal symptomsPreventing diverticulitis recurrence	12 months	Mesalazine, alone or in combination, had higher symptoms' improvement rate (59.3% and 54.8% vs. 27.3%, $P = 0.0346$)* Mesalazine, alone or in combination, had no higher remission rate in preventing diverticulitis recurrence (28.1%, 37% vs. 31% placebo, P = n.s.)*
Parente *et al.*[114]	Double-blind, randomised, placebo-controlled	92	Mesalazine Eudragit L 2.4 g/day for 10 days/month vs. placebo following acute diverticulitis	Preventing diverticulitis recurrenceImprovement quality of life	24 months	Mesalazine had higher but no significant remission rate in preventing diverticulitis recurrence (13% vs. 28%, $P = 0.1011$)*Mesalazine had higher quality of life score ($P = 0.022$)*
Raskin *et al.*[115]	Double-blind, randomised, placebo-controlled	1182 in two different trials (590 in PREVENT 1 and 592 in PREVENT 2)	Mesalazine MMX 1.6 g/day vs. 2.4 g/day vs. 4.8 g/day vs. placebo following acute diverticulitis	Preventing diverticulitis recurrence	24 months	Mesalazine did not reduce the rate of diverticulitis recurrence both in PREVENT 1 (53–63% vs. 65%, P = n.s.)* and in PREVENT 2 (59–69% vs. 68%, P = n.s.)*

ITT, intention-to-treat analysis; PP, per-protocol analysis.

*All results reported are on ITT analysis.

patients.[71–73] Unfortunately, their sample size is far too small to demonstrate a significant effect of high-fibre supplementation in preventing the occurrence of acute uncomplicated diverticulitis or other complications of DD (e.g. abscess, perforation, stenosis, fistula or bleeding).

Rifaximin. Data from three open randomised trials (comprising a total of 1492 patients) and four comparing rifaximin plus glucomannan or fibre supplementation vs. glucomannan or fibre alone, reported that rifaximin led to a slight benefit in preventing acute diverticulitis, but only the largest study showed significant results.[56] Cumulative

Table 5 | Controlled trials in using probiotics for symptomatic diverticular disease

Study	Trial design	No. of patients	Randomisation	Outcomes assessed	Length of follow-up	Results
Annibale *et al.*[90]	Prospective, randomised, open-label	50	Group A, high-fibre diet alone; group B, twice daily 1 sachet of probiotic *Lactobacillus paracasei sub. paracasei F19* for 14 days/month + high-fibre diet); group C twice daily 2 sachets of probiotic *Lactobacillus paracasei sub. paracasei F19* for 4 days/month+ high-fibre diet	Decrease in VAS score after treatment in SUDD	6 months	Bloating decreased significantly in Groups B and C (group B: 4.6 ± 2.6 vs. 2.3 ± 2.0, $P < 0.05$, group C: 3.9 ± 2.9 vs. 1.8 ± 2.1, $P < 0.05$)
Dughera *et al.*[120]	Prospective, randomised, open-label	83	Polybacterial lysate suspension of *Escherichia coli* + *Proteus Vulgaris* for 2 weeks every month plus fibre 15 g/day vs. fibre 15 g/day alone	Prevention of diverticulitis recurrence	3 months	Polybacterial lysate plus fibre had significant superiority to fibre alone at 1 and 3 months in controlling symptoms and preventing diverticulitis recurrence ($P < 0.05$ and $P < 0.01$ respectively)
Lahner *et al.*[91]	Prospective, randomised, open-label	30	Methylcellulose 2 tablets/day vs. placebo 2 tablets/day	Reduction in global symptom score in SUDD	3 months	Symptom score decreased significantly in the methylcellulose group (from 19 ± 6 to 13 ± 4, $P < 0.01$) but not in the placebo group (from 21 ± 7 to 17 ± 9, P = n.s.)
Tursi *et al.*[87]	Double-blind, randomised, placebo-controlled study	210	Mesalazine 800 mg twice a day and Mesalazine 800 mg twice a day + *Lactobacillus casei* 750 mg a day vs. *Lactobacillus casei* 750 mg a day vs. Placebo	Maintain remission of SUDDPrevention of acute diverticulitis occurrence	12 months	Remission was maintained in 93.33% in combined treatment group, 85.45% in probiotic group and 54% of placebo group ($P = 0.0001$)Acute diverticulitis occurred in 0% in combined treatment group, 1.82% in probiotic group and 12% in the placebo group ($P = 0.003$)
Tursi *et al.*[119]	Prospective, randomised, open-label study	30	Balsalazide 2.25 g daily for 10 days every month plus probiotic mixture *VSL#3* 450 billions/day for 15 days every month (Group A) vs. *VSL#3* alone 450 billions/day for 15 days every month (Group B)	Prevention of diverticulitis recurrence	12 months	6.66% of group A and 13.33% of group B pts had recurrence of the disease (P = n.s.)

DD, diverticular disease; SUDD, symptomatic uncomplicated diverticular disease.

data from placebo-controlled and unblinded trials[76, 77, 95, 96] showed that the rate of acute diverticulitis were significantly less frequent in patients treated with rifaximin plus fibre supplementation than with fibre alone (11/970 (1.1%) vs. 20/690 (2.9%; $P = 0.012$). According to these results, the number needed to be treated to prevent an attack of acute diverticulitis in 1 year with the rifaximin plus fibre supplementation regimen reached 57. Only one double-blind, placebo-controlled trial assessed the prevention of acute diverticulitis as a secondary end-point. This was a 1-year follow-up trial in which all patients received glucomannan (2 g/day); one arm received rifaximin (400 mg twice a day for 7 days each month), and the other arm received a placebo. Rifaximin failed to show superiority over placebo in preventing acute diverticulitis, which occurred in 2.4% of patients in both study arms.[76]

Mesalazine. Data from five randomised open trials (comprising more than 400 patients)[80–84] comparing mesalazine alone or in combination with probiotics, and probiotics alone in preventing acute diverticulitis, did not show a significant difference among treatments. However, there were only seven episodes of acute diverticulitis per year (yearly incidence rate, 2%).

More recently, a double-blind, double-dummy placebo-controlled trial assessed the prevention of acute diverticulitis occurrence as secondary end-point. This was a 1-year follow-up trial in which patients received mesalazine (1.6 g/day for 10 days/month), a probiotic (*L. casei* subsp. DG 24 billion/day for 10 days/month), mesalazine plus probiotic, or placebo. This study found mesalazine significantly better than placebo in preventing acute diverticulitis, which occurred in no patients in the mesalazine group, in 1.78% and in 12% of patients in probiotic and placebo study arms respectively.[87]

Figure 4 shows advice on how to manage such patients based on the above mentioned data.

Acute diverticulitis

As stated, acute diverticulitis (namely DD with signs and symptoms of diverticular inflammation) is mild in the vast majority of cases. Patients with uncomplicated diverticulitis, are generally treated as out-patients with a clear liquid diet and antibiotics.[97] In out-patients, broad-spectrum antibiotics are usually given for 7–10 days. Various antibiotics may be used in the treatment of acute diverticulitis, ranging from ampicillin to third-generation cephalosporins,[68, 97, 98] ensuring complete coverage against Gram-positive and -negative, and aerobic–anaerobic bacterial strains.[68, 97, 98]

The combination of ciprofloxacin and metronidazole is a commonly used treatment for uncomplicated diverticulitis,[68, 97, 98] both intravenously and orally. According to the American Society of Colon and Rectal Surgeons (ASCRS), ampicillin–sulbactam is a good option in this group of patients.[99]

If opioid analgesics are required for pain control, meperidine is the preferred option since morphine causes colonic spasm and may accentuate colonic hypersegmentation.[68, 97, 98]

Out-patient treatment is effective in most cases, and less than 10% of patients are re-admitted at the emergency room for diverticulitis within 60 days of the initial evaluation.[68, 97, 98]

Hospitalisation, with intravenous antibiotic treatment, is usually recommended by current guidelines[15–21, 68] if the patient is unable to take oral therapy, is affected by severe comorbidity, if the patient fails to improve with out-patient therapy, or if patient is affected by complicated diverticulitis.[15–21, 68] Clinical improvement in patients affected by acute diverticulitis is generally observed within 34 days. If patients are hospitalised, a 7–10 day course of oral antibiotics is usually given following discharge.[15–21, 68]

A recent, retrospective study evaluated the proportion of patients able to be managed as out-patients at the first episode of acute diverticulitis.[100] The diagnosis of acute diverticulitis was confirmed by abdominal CT scan. The

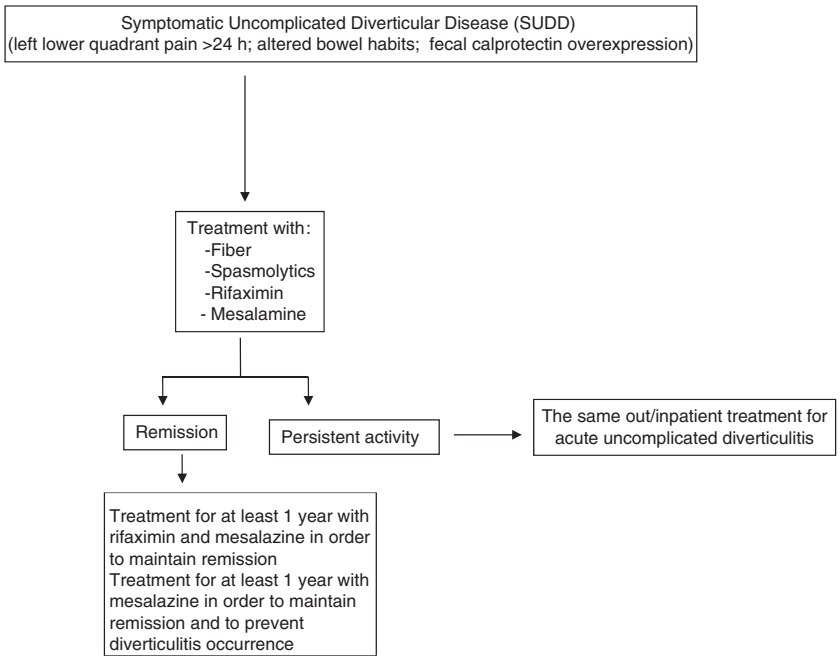


Figure 4 | Management of symptomatic uncomplicated diverticular disease according to the current literature data.

endpoints included length of stay, need for surgery, percutaneous drainage and mortality. Patients were considered to have had a minimal hospitalisation, defined as survival to discharge without needing a procedure, hospitalisation of ≤3 days and no re-admission for diverticulitis within 30 days after discharge. On a cohort of 639 patients, 368 (57.6%) had a minimal hospitalisation. Female gender and CT scan findings of free air/fluid were negatively associated with the likelihood of minimal hospitalisation. The presence of an abscess <3 cm and stranding on CT did not predict the need for a higher level of care. Unfortunately, authors failed to identify patients likely to need only minimal hospitalisation, and only free air/liquid in a patient admitted for acute diverticulitis indicated a more severe clinical course.[100]

The few high-quality randomised trials that have been published in this field are summarised in Table 5. All found that out-patient treatment is as safe and effective as in-patient treatment, with significant cost savings.[101–103] Figure 5 provides advice regarding management of these patients in accordance with these data.

These trials confirm that out-patient treatment is safe and effective in selected patients with uncomplicated acute diverticulitis. Out-patient treatment allows important costs saving to health systems without negative influence on the quality of life of patients with uncomplicated diverticulitis, reducing healthcare costs by more than 60%.

Unfortunately, evidence of antibiotic use in acute diverticulitis, uncomplicated disease included, isn't 'evidence-based'. Notably, three recent randomised studies failed to show that antibiotic treatment was superior to simple support therapy in obtaining clinical resolution and in preventing diverticulitis recurrence[104–106] (see Table 6).

Failing out-patient treatment of uncomplicated diverticulitis. Out-patient treatment is effective in most cases, with a low risk of emergency room re-admission for diverticulitis within 60 days of the initial evaluation (less than 10%).[48, 80, 81] However, recurrence rate in out-patients is quite high, occurring in up to 18% of patients at 10 years.[107]

Secondary prevention of acute diverticulitis

We know that the long-term recurrence rate of diverticulitis is up to 20%.[47–52, 89, 108] In particular, recurrence rates seems to increase in patients having at least three episodes of acute uncomplicated diverticulitis,[104] although multiple episodes of uncomplicated diverticulitis do not seem to increase the risk of developing complicated diverticulitis or surgery.[109]

At present, no consensus is available regarding the optimal strategy for secondary prevention of acute diverticulitis, that is, preventing acute diverticulitis recurrence.

High-fibre diet. Once the acute episode has resolved, patients are generally advised to maintain a high-fibre diet to optimise their bowel movements.[15–21, 68] However, the collective literature investigating the role of dietary modification in preventing DD or a recurrence of

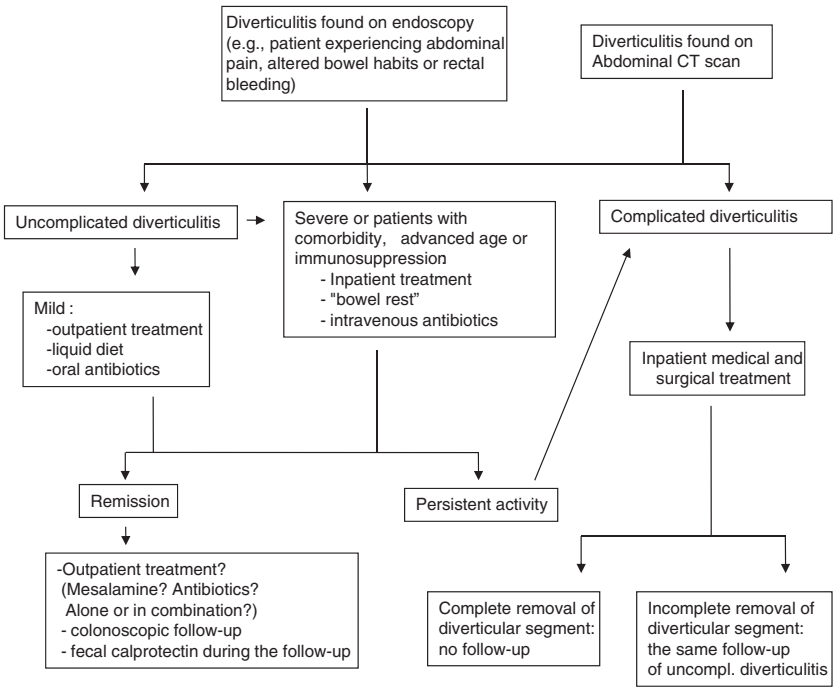


Figure 5 | Management of acute diverticulitis according to the current literature.

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Table 6 | Controlled trials of antibiotics in acute uncomplicated diverticulitis

Study	Trial design	No. of patients	Randomisation	Outcomes assessed	Length of follow-up	Results
Schug-Pass *et al.*[101]	Open-label, randomised, prospective study	123	Short (4 days) vs.standard (7 days) ertapenem 1 g/day for AUD	Obtaining diverticulitis remissionMean hospital stay. Acute diverticulitis recurrence	12 months	No difference in obtaining remission (98% vs. 98.2%, P = n.s.) and in diverticulitis recurrence rate (94% vs. 96.2%, P = n.s.)Short treatment is better in reducing hospital stay (7.8 vs. 9.7 days, P = 0.002)
Moya *et al.*[102]	Open-label, randomised, prospective study	66	Intravenous in-patient treatment vs. oral out-patient treatment for AUD	Obtaining diverticulitis remission. Saving money	1 month	No difference in obtaining remission (98% vs. 94%, P = 0.86)Oral out-patient treatment saves about 1600€ (P < 0.05)
Biondo *et al.*[103]	Open-label, randomised, prospective study	132	Intravenous in-patient treatment vs. oral out-patient treatment for AUD	Treatment failure rate of the out-patient protocol. Overall healthcare costs	1 month	No difference in treatment failure rate (4.54% vs. 6.06%, P = 0.619)Oral out-patient treatment saves about 1124€ (P < 0.005)
De Korte *et al.*[104]	Retrospective, case–control study	272	Antibiotic vs. no treatment for AUD	Treatment failure rate	12 months	No difference in treatment failure rate (4% vs. 6%, P = 0.350)
Chabok *et al.*[105]	Multicentre, randomised, prospective, open-label study	623	Antibiotic vs. no treatment for AUD	Occurrence of complications. Recurrence rate	12 months	No difference in both occurrence of complications (1% vs. 1.9%, P = 0.302) and recurrence rate (16% vs. 15%, P = 0.881)
Daniels *et al.*[106]	Multicentre, randomised, prospective, open-label study	528	Antibiotic vs. no treatment for AUD	Recovery rate. Median time to recovery (in days)	6 months	No difference in both recovery rate (89.3% vs. 93.2%, P = 0.183) and median time to recovery (14 days vs. 12 days, P = 0.291)

AUD, acute uncomplicated diverticulitis.

diverticulitis is inconsistent. Looking at more recent studies, the results are conflicting,[74, 94] and there is not consistent support for recommending a high-fibre diet. Despite this lack of evidence, a high-fibre diet is still commonly recommended to reduce the likelihood of diverticulitis recurrence.[15–21, 68]

Another interesting point is related to the classical advice to avoid consuming seeds, popcorn and nuts, which is based on the assumption that such substances could theoretically enter, block or irritate a diverticulum and result in diverticulitis, and possibly increase the risk of perforation. However, there is no evidence to date to support this practice.[110]

Rifaximin. No placebo-controlled studies have been conducted to investigate the prevention of acute diverticulitis recurrence.

A recent randomised, open-label, proof-of-concept study compared 3.5 g of high-fibre supplementation b.d. with or without 1 week per month of the nonabsorbable antibiotic rifaximin (400 mg b.d.) for 1 year. Acute diverticulitis recurred in 10.4% of patients given rifaximin plus fibre vs. 19.3% of patients receiving fibre alone.[111] Further larger, double-blind, placebo-controlled studies are necessary to confirm these preliminary results.

Mesalazine. As mesalazine has been found to be effective for controlling SUDD and in preventing diverticulitis occurrence from SUDD,[63, 65] its use in preventing diverticulitis recurrence has been investigated.

In symptomatic patients with a history of recent attacks of acute diverticulitis, open randomised trials showed that acute diverticulitis was significantly reduced with the use of mesalazine (800 mg twice a day 1 week/

month) plus rifaximin (400 mg twice a day 1 week/month) compared with rifaximin alone (400 mg twice a day 1 week/month) (2.8% vs. 18%; $P = 0.001$).[112] It is noteworthy that the 1-year prevalence of diverticulitis, observed with rifaximin in one of these studies (18%), is higher than that reported in previous randomised trials (1.1%), suggesting that the occurrence of this complication may be affected by features of the patients investigated in the study.

Seven double-blind placebo-controlled trials (four published, three unpublished) evaluating the use of mesalazine vs. placebo in preventing acute diverticulitis recurrence were identified.[113–117] Mesalazine was used in doses ranging from 0.8 g for 10 days every month to 4.8 g daily. Most failed to find mesalazine significantly superior to placebo in preventing diverticulitis recurrence. However, mesalazine Eudragit-L was found to be significantly better than placebo in reducing abdominal symptoms following acute diverticulitis in both trials (DIVA trial: $P = 0.045$; DIV/04 trial: $P = 0.021$).[113, 114]

Only an unpublished trial conducted in Romania found that mesalazine (514.7 ± 30.5 mg/day) was better than placebo in terms of reducing the risk of developing diverticulitis ($P = 0.044$) over a 40-month period, as well as the number of diverticulitis flares ($P = 0.001$) and the need for surgery ($P = 0.02$). The relative risk of developing diverticulitis was 2.47 times higher (95% CI 1.38–4.43) in the placebo group compared to the mesalazine group.[118]

Controlled studies of mesalazine use in such patients are reported in Table 4.

Probiotics. No placebo-controlled study has been conducted to investigate the use of probiotics in the prevention of acute diverticulitis recurrence.

Two small prospective studies investigated theprobiotic mixture VSL#3 (composed by eight different bacterial strain: *L. casei*, *L. plantarum*, *L. acidophilus*, *L. delbrueckii subsp. Bulgaricus*, *B. longum*, *B. breve*, *B. infantis*, *Streptococcus salivarius* subsp. *thermophilus*) and the polybacterial lysate suspension of *Escherichia coli* + *Proteus Vulgaris* in preventing recurrence of diverticulitis (see Table 5). Both studies found this approach effective,[119, 120] but the absence of a placebo arm litim the importance of these results.

Surgery. Although the description of the surgical treatment of DD is beyond the scope of this review we briefly report that surgery is a therapeutic option after an attack of diverticulitis.

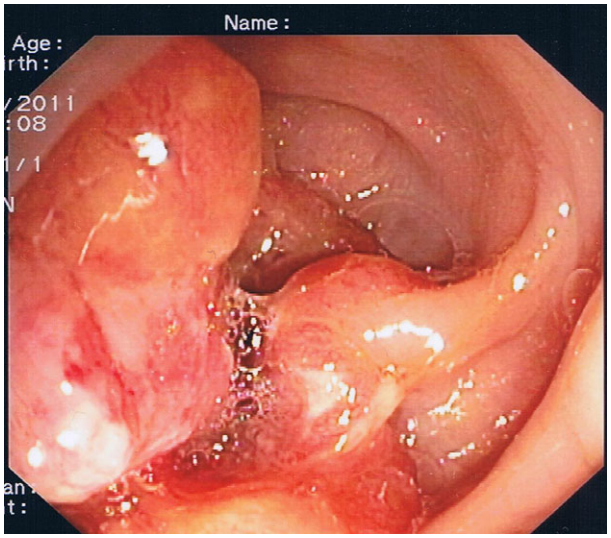

Figure 6 | Colonoscopy following acute diverticulitis is strongly advised when a patient does not improve or has complicated diverticulitis. This was a 78-year-old woman admitted for acute diverticulitis: due to persistent abdominal pain, she underwent colonoscopy 10 days later and sigmoid carcinoma was detected.

Indeed, according to the ASCRS guidelines[98] as well as various other guidelines,[15–21, 68] elective resection should be considered after one or two well-documented attacks of diverticulitis, depending on the severity of the attack and on the age and medical fitness of the patient. Although the recurrence rate of diverticulitis after surgery is currently considered quite low (about 7% at 10 years),[98] other recently published data indicate that of patients who had elective surgery for diverticulitis, 25% experienced persistent abdominal symptoms.[121] Neither the stage of disease (complicated or uncomplicated) nor the surgical technique (laparotomy or laparoscopy) were significantly related to the occurrence of symptoms.[122] A more individualised approach taking into account the frequency, severity of the attacks and their impact on quality of life should guide the indication for surgery.[121]

HOW TO MANAGE DD AFTER DIAGNOSIS

How to manage DD of the colon after diagnosis is still under debate.

A clinical approach may still be advisable. However, as yet there is no validated clinical score system, and clinical assessment remains based on the clinicians' experience.

Performing colonoscopy following diagnosis of DD is controversial. Safe colonoscopy to exclude colorectal can-

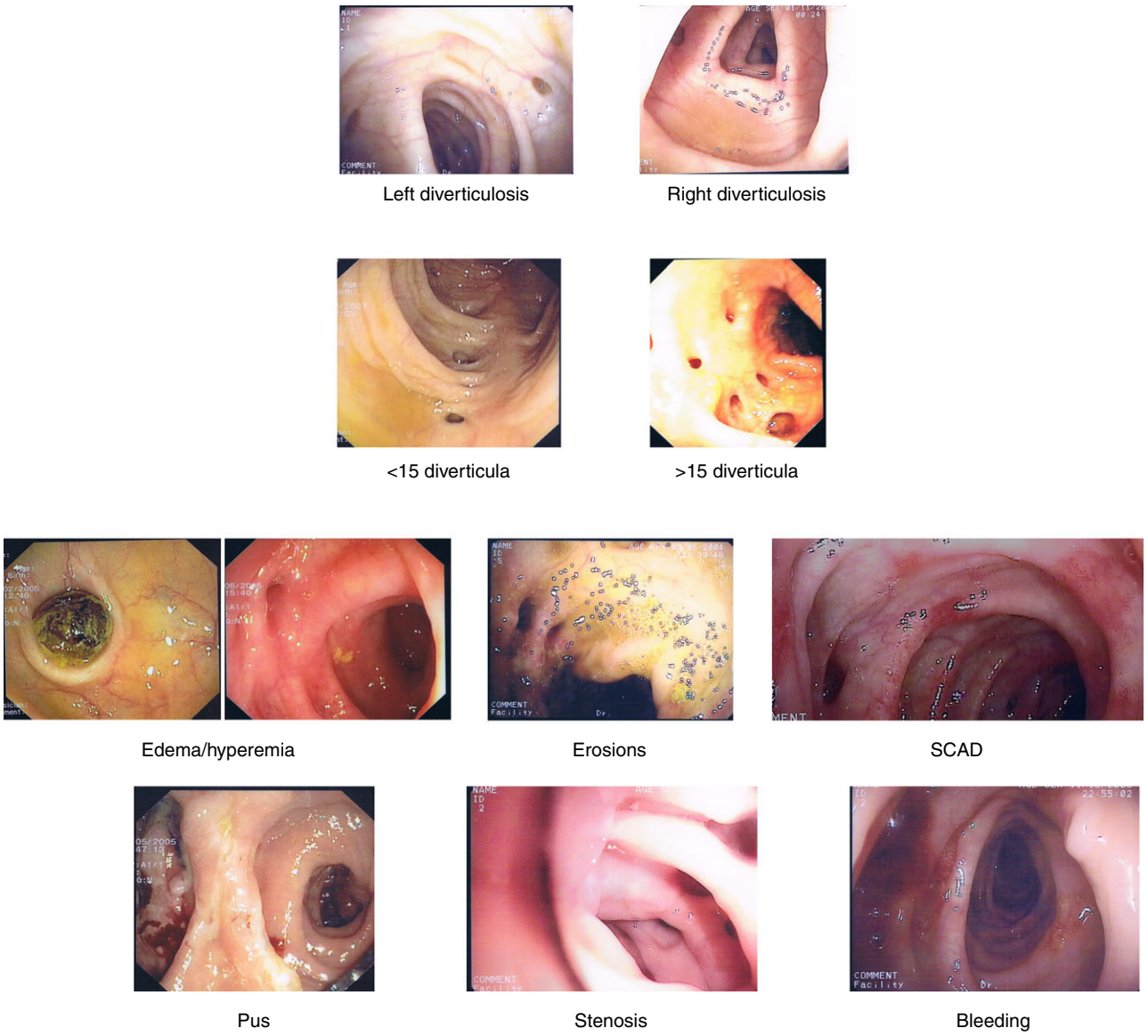

Figure 7 | DICA Classification. This classification scores diverticular disease according to the endoscopic finding of the colon harbouring diverticula. Each of those findings gives a specific scoring (see Table 6 for scoring).

cer is generally advised at least 6 weeks after an episode of acute diverticulitis due to the risk of perforation or bleeding.[56] However, an early colonoscopy (for example, 7–10 days after an episode of uncomplicated diverticulitis) seems to be safe and effective compared with late colonoscopy (4–6 weeks after hospital discharge).[123] This approach may be particularly useful in patients with persistent symptoms (Figure 6). The vast majority of studies concluded that colonoscopy after radiologically confirmed uncomplicated diverticulitis is unnecessary to exclude malignancy,[124–129] while it seems to be necessary after radiologically confirmed complicated diverticulitis because the risk of malignancy in those patients is higher.[130, 131]

Other noninvasive tools may be useful in clinical practice. FC is a protein excreted in the faeces, and widely used in managing IBDs.[132] A rapid test has been successfully used in differentiating between SUDD, IBS and acute uncomplicated diverticulitis.[63, 64] It also appears to be useful in surveillance for acute diverticulitis after remission, since diverticulitis recurrence seems strictly related to the presence of abnormal FC test during follow-up.[133]

FUTURE TRENDS IN MANAGING DD

A currently active topic of debate is that of the ways in which to treat acute diverticulitis. Controlled trials show

that antibiotic treatment for acute uncomplicated diverticulitis neither accelerates recovery nor prevents complications or recurrence. Thus, antibiotics should be reserved for the treatment of uncomplicated diverticulitis with comorbidities and complicated diverticulitis. The reason why antibiotic treatment does not appear to work remains unknown, but given study results to date, the use of antibiotics in treating both SUDD and acute diverticulitis is becoming questionable. Many specific points should be considered regarding the treatment of acute diverticulitis patients with antibiotics, ranging from the selection of an antibiotic based on minimum effective concentrations and bacterial sensitivity, to assessment of pharmacokinetics and pharmacogenomics of antibiotics in this specific population. Future clinical trials investigating antibiotic therapy in acute diverticulitis patients need to provide additional strategies to achieve individualisation.

Another point currently under debate is how to prevent diverticulitis recurrence. Although promising in open-label trials, both rifaximin and mesalazine were found to be ineffective in secondary prevention of diverticulitis in RCT. The reasons for this lack of effect remain to be elucidated, with the lack of effect surprising, particularly considering that both drugs are effective in placebo-controlled studies in controlling symptom of SUDD, and that mesalazine is also effective in primary prevention of acute diverticulitis. Heterogeneity in the population enrolled, heterogeneity in the type of mesalazine investigated linked to the mechanism of discharging through the colon, and heterogeneity in endpoints assessed, may be detected in all trials published, with all of these factors able to influence results.

Improvement in selecting patients according to the colonic characteristics may be an option to increase therapeutic efficacy. To this end, an endoscopic classification of DD has recently been developed and validated.[134] This classification, called DICA (Diverticular Inflammation and Complications Assessment), assesses four main items (diverticulosis extension, number of diverticula in each district, presence of inflammation, presence of complications) and some sub-items (Figure 7), and scores the disease as three grades: DICA 1, DICA 2 and DICA 3[134] (see Table 7). Preliminary retrospective data found this classification able to predict the outcome of the disease according to the severity of the score.[134] In other words, simple and/or asymptomatic diverticulosis does not appear to need any maintenance treatment to prevent occurrence of complications, while a colon with signs of recurrent inflammatory attack may be unresponsive to maintenance treatment to prevent recurrence of complications. On the contrary, DICA 2 seems to be very responsive to scheduled treatment. In other words, symptomatic diverticulosis with/without signs of inflammation responds very well to maintenance treatment for the prevention of occurrence/recurrence of complications. If further, prospective studies confirm these results, then we will have a clear subgroup of patients that can be expected to benefit from scheduled maintaining treatment.

Table 7 | Diverticular inflammation and complication assessment (DICA) classification

Items	Points
Diverticulosis extension	
Left colon	2
Right colon	1
Number of diverticula (in each district)	
Up to 15: grade I	0
15: grade II	1
Presence of inflammatory signs	
Oedema/hyperaemia	1
Erosions	2
SCAD	3
Presence of complications	
Rigidity of the colon	4
Stenosis	4
Pus	4
Bleeding	4

SCAD, segmental colitis associated with diverticulosis.

DICA 1: from 1 to 3 points; DICA 2: from 4 to 7 points; DICA 3: >7 points. For complete description and explanation of this classification, please read the text.

In conclusion, DD is a multifactorial disease in which optimal patients' stratification according to the severity of the disease may guarantee therapeutic success. Recent radiological and endoscopic classifications could be the optimal tool to reach this target. Furthermore, prospective studies adopting these classification are therefore urgently required, to have a tailored therapeutic strategy.

AUTHORSHIP

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