[Au: Queries are meant to draw your attention to edits, inconsistencies or issues that are unclear. If we just ask you to confirm edits are correct, a simple yes/ok between the brackets will do [Au: OK? Is this what you meant? Edits OK? yes]. If questions are asked, please rephrase/update the manuscript text when addressing queries, so that the message is conveyed to the reader (do NOT just type your answer to our query).]

[Au: Throughout the manuscript, please use consistent terminology. For example, acute diverticulitis is diverticular disease and in several instances, they are mentioned separately. For clearer understanding, please use consistent terminology and define cleary what diverticular disease refers to. Similarly, there is a slight ambiguity between the terms diverticulosis and asymptomatic diverticulosis. My understanding is that diverticulosis is always asymptomatic. Please refer to them consistently if they are used to refer to the same condition. Is acute uncomplicated diverticulitis as in some instances, its refered to as uncomplicated acute diverticulitis? Please also use the abbreviation, AUD, if this terminology is widely accepted in the field. Just wanted to flag these here to make it easier for you to address.]

[Au: Important! As I am managing the references for this manuscript, it is essential that changes to references are noted to me in a comment rather than edited manually (as this will likely unlink the references and cause much confusion). If a reference needs to be added, include the full reference details (at a minimum, PMID or DOI are needed) and precise location to be cited. If a reference needs to be deleted, state which reference (author, year) and not just the reference number (as this will change with every change to the references).

You can move text around, including the references associated with any given statement, but please don't edit the reference list at the end of the document.]

Diverticular disease

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[Au: This is the last opportunity to check if your names are correct, and as you would like them in PubMed, and the affiliations are correct. Please check carefully as we cannot make changes after publication. I have 'unbolded' A.T and C.S and mentioned their equal first authorship in the author contributions according to our in house journal style, ok?]

[Au: I have removed all ORCID information from here as you have now incorporated them in your profile as discussed]

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[Au: I have removed the equal first authorship from here and mentioned it in the author contributions, ok?] **Acknowledgements**

[Au: Edited for house style and brevity ok?] The authors thank Prof. Richard H. Hunt (McMaster University) for critical reading of the manuscript, useful discussions and suggestions and Dr Gian Andrea Binda (Biomedical Institute, Genoa) for useful discussion and reviewing the section devoted to surgical management. **[Au: optional; do you want to thank any not-for-profit funders?]**

Author contributions

[Au: Please double check that all author contributions are correct as C.S. wasn't listed for the Outlook section in the online portal.]

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. & S.D.); Overview of Primer (A.T.). A.T. and C.S. contributed equally and are co-first authors **[Au:OK?]**.

74

75 **Competing interests**

76 **[Au: Edited for house style.]** C.S. and A. Lanas are members **[Au:OK?]** of the Speakers'
77 Bureau and of the Scientific Advisory Board of Alfasigma SpA. W.K. served as speaker,
78 consultant and/or advisory board member for Abbvie, Ardeypharm, Falk, Ferring,
79 Genetic Analysis, Gräfe & Unze, Institut Allergosan, Nikkiso, Otsuka and Tillots. **[Au: I**
80 **combined A. Lanas membership with C.S. for brevity, ok?]** S.D. served as speaker,
81 consultant, and/or advisory board member for Abbvie, Allergan, Alfa Wassermann,
82 Biogen, Boehringer Ingelheim, Celgene, Celltrion,Ferring, Gilead, Hospira, Johnson and
83 Johnson, Merck, MSD, Mundipharma, Pfizer Inc, Sandoz, Takeda, Tigenix, UCB Pharma,
84 Vifor. . The remaining authors declare no competing interests.

85

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Abstract [Au: Shortened slightly to fit within 200 words; please check carefully]

Colonic diverticula are outpouchings of the intestinal wall and are common anatomical alterations detected in the human colon. Diverticulosis (the presence of diverticula in the colon) remains asymptomatic in most individuals but ~25% of individuals will develop symptomatic diverticulosis, termed 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 and in differential diagnosis**[Au: edited for brevity, ok?]**. Treatments for diverticular disease include dietary fibre, pharmacological treatments such as antibiotics (rifaximin), anti-inflammatory drugs (mesalazine) and probiotics, alone or in combination, and surgery **[Au:OK?]**. Despite being effective in treating primary disease, their effectiveness in primary and secondary prevention of complications is still uncertain **[Au:OK?]**.

[H1] Introduction

Diverticula, that is, sac-like protrusions **[Au:OK?]**in the wall of large bowel **[Au: ok?]**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. **[Au: I moved the definition of diverticulosis separately from the next sentence for easy flow, ok?] [Au: moved statements on diverticulosis from second paragraph to here for flow, ok?]** For many years, the western lifestyle has been considered a key factor for the development of diverticulosis), owing to its comparatively high prevalence in developed countries. Indeed, the global prevalence of diverticulosis is increasing in both developed and developing countries, 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]. **[Au: Please mention the implication of these changes?] [Au: A sentence describing the anatomy of intestinal wall is warranted here for readers understanding, please include it here. Please also cite Figure 1 here to be concise?]** In western populations, the outpouchings involve eversion of the mucosal and submucosal layers but not the muscular layer of the colon wall 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 **[Au:OK?]** are generally asymptomatic, but might result in diverticulitis (inflammation of the diverticula) **[Au: definition ok?]**, and colonic bleeding, which is more commonly observed in eastern populations[3]. **[Au:OK?]**

[Au: Moved sentences on diverticulosis up for flow.] Diverticular disease develops when diverticulosis becomes symptomatic, which typically involves bloating, abdominal pain and changes in bowel habit **[Au:OK?]**and is estimated to occur in ~25% of individuals with diverticulosis **[Au: please provide a reference for this statement]**. Diverticular disease can range in severity from symptomatic uncomplicated diverticular disease (SUDD) to symptomatic complicated disease **[Au:OK?]**such as acute diverticulitis

or diverticular haemorrhage **[Au: Edited to mention the conditions first and to include definitions later for flow, ok? Do chronic cases of diverticulitis exist?]**. SUDD is a distinct entity in which symptoms, particularly abdominal pain, can be attributed to diverticula in the presence of low-grade inflammation visible on histology (such as xxx **[Au: please provide an example for completeness]**) but with no macroscopic signs of inflammation (such as xxx**[Au: please provide an example for completeness]**). Acute diverticulitis can range in severity from peridiverticular inflammation (acute uncomplicated diverticulitis)**[Au:OK?]** to peritonitis (inflammation of the lining of abdominal cavity; complicated diverticulitis) **[Au: definitions ok?]**resulting from perforations of diverticula. Diverticular haemorrhage occurs as a consequence of rupture of diverticula-associated arteries, resulting in 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, and altered colonic motility[2] (Figure 1) **[Au: included the missing factors from the Mechanisms section to avoid repetition later, ok?]**.

Asymptomatic diverticulosis **[Au: Are not all diverticulosis asymptomatic? Please clarify. If this is not a different condition, please use consistent terminoloy]** is usually detected incidentally in patients undergoing endoscopy or radiological examinations. Diagnosis of diverticular disease requires combined assessment of **[Au:OK?]** clinical signs **[Au: such as?]**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 **[Au: removed incorrect figure callout from here, ok?]**. Endoscopy **[Au: do you mean colonoscopy? Since we also discuss upper GI endoscopy and colonoscopy in other sections of the Primer, for the benefit of readers, please use the terminology lower endoscopy or colonoscopy (where appropriate) for clearer understanding.]**is generally not recommended in individuals with acute diverticulitis owing to risk of bowel perforation **[Au: removed the figure call out from here to introduce it in the appropriate section to be concise]** but is currently advised 6–8 weeks

after an episode of acute diverticulitis to rule out colorectal cancer. Consensus is lacking regarding the optimal treatment options for diverticular disease **[Au:OK?]**, although treatment usually includes dietary fibre supplementation, pharmacological therapies (such as antibiotics and anti-inflammatory drugs) and probiotics, alone or in combination **[Au: please cite a ref]**.

In general, acute diverticulitis occurs less frequently than previously thought[2] and **[Au: We avoid using recent or recently as it unnecessarily ages the Primer, hence edited it]** the long-standing recommendation to treat acute diverticulitis with antibiotics has been disputed of late[4].

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

[H1] Epidemiology

[H2] Prevalence and incidence

[H3] Diverticulosis.

Colonic diverticula can manifest in various clinical presentations[5] **[Au: edited to avoid repetition]** OK 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 countries, where approximately two-thirds of adult populations eventually develop diverticulosis **[Au: please cite a ref. (Antonio, see commnet) Please specify the age range of adult population that is discussed. > 18 years old]**. 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 in individuals <40 years of age and high among those >65 years of age, although, prevalence is currently increasing, particularly

Comentado [UdMO1]:

Comentado [UdMO2]: Antonio, I would put here one of the references previously cited (e.g. reference 1). This will avoid introducing new cites)

among younger individuals[1] **[Au: Do you mean individuals <40 years or even younger? Yes, younger than 40]**. For example, in the USA, diverticulosis is the most frequent finding in colonoscopy procedures[6] and the eighth most frequent outpatient gastrointestinal diagnosis in 2010 (Ref[7]).**[Au: Our style is to add 'Ref' when references follow a number, OK]** 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[6]. In Mexico, the prevalence of diverticulosis is in the range 1.9–9.2% **[Au: moved prevalence of Mexico to here for flow, OK]**, whereas in Africa the prevalence ranges from 2% in Egypt to 9.4% in Nigeria[1]. **[Au: do you mean to say that Egypt reported the lowest prevalence and Nigeria the highest prevalence?, No, this means that in Africa there is a low prevalence which ranges from the very low 2% to an also low 9.4% in Nigeria]** Among Asian countries, the prevalence is 12.5% in South Korea and 70.1% in Japan; **[Au: moved and edited the statement on Mexico after USA as it is not South America, ok?, OK]** in Europe, the lowest prevalence was reported in Romania (2.5%) and highest prevalence was reported in Italy (51.4%)[1] **[Au: is this what you meant? Yes Please clarify,]**.

In western countries, diverticulosis was detected **[Au:OK?, OK]** in the sigmoid or left colon in 90% of cases, whereas, in Japan[8] and South Korea[9], diverticulosis was found more frequently in the ascending or right colon (75–85% of cases). Additionally, black individuals **[Au: generally, in all countries? In studies performed in western countries with different etnic populations]** have a higher proportion of diverticula (both in distribution and the total number) in the right colon than white individuals[10,11] **[Au: Sentence moved up to have 'location' discussion together; OK? OK].** 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[12])**[Au: Our style is to add 'Ref' when references follow a number.OK]**. Furthermore, incidence of **[Au: ok? or is this prevalence? Increases affects both incidence and prevalence, you can use the word "frequency"]**right-sided diverticulosis is also increasing in western countries[13].

[H3] Diverticular disease.

Approximately 25% of individuals with diverticulosis develop SUDD, and an even smaller proportion develop acute diverticulitis[1]. **[Au: moved statement on progression to diverticulitis from Prevention section to keep related facts together.OK]** Progression to diverticulitis occurred in only ~1% of individuals with diverticulosis over 11 years of observation[14]. **[Au: moved statements on incident diverticulitis from the figure legend to here, ok? Ok]**One-fifth of patients with incident diverticulitis (first occurance of an inflamed diverticulum) **[Au: definition ok? OK]**will have at least one recurrent episode **[Au: ref] reference 7**. Approximately 12% of patients presenting with diverticulitis will have a complication, including perforation, abscess (accumulation of pus within the diverticulum) or fistula (a tunnel or an abnormal connection between two body parts). **[Au: definitions ok? OK] [Au: moved epidemiology data on diverticular bleeding from the the Diagnosis section to here for flow, ok? OK]** Diverticular haemorrhage **[Au: for consistent use of terminology, ok? Ok]**is the most common cause of lower gastrointestinal bleeding[15], with ~200,000 admissions in the USA annually. Fewer than 5% of patients with diverticulosis experience diverticular haemorrhage. **[Au: please cite a ref. same reference 15]**

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**[Au: symptomatic or asymptomatic? both]** developed acute diverticulitis **[Au: ref? not needed]**. The median time to develop an acute episode of diverticulitis was 7.1 years and risk of **[Au: acute? ok]** diverticulitis increased with lower age at the time of diverticulosis diagnosis[12] **[Au:OK? yes]**. The highest reported prevalence of diverticular disease **[Au: Could you please clarify whether it is specifically SUDD or acute/ chronic diverticulitis or diverticular haemorrhage? Or does prevalence mean any one of these complications? Please clarify and please mention this explicitly in the text. It refers to all types - symptomatic and asymptomatic colonic diverticuli-]**is 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) **[Au: please cite a ref 16]**. **See comment Antonio** Conversely, the prevalence **[Au: please mention specifically which condition if**

Comentado [UdMO3]: Antonio, I belive that some of these figures were introduced by you in the final version. As Imentiones in my previous reply to referees. I could see that these figures were extracted from one of your reviews. Please consider whether we should enter taht reference)I believe it is ref 1) or just introduce the actual references where you got those figures

the information is available. It is prevalence here]is low (0.1–5 cases per million individuals) in Africa and in Asia (with the exception of Japan) **[Au: ref 1]**. In Europe, prevalence varies across countries, but do not follow any geographical pattern. For example, Italy, Austria and Sweden reported low prevalence, whereas Germany, France and the UK reported a higher prevalence than other European countries[16].**[Au: please mention explicitly if this prevalence include any spectrum of diverticular disease. All spectrum]** However, these differences might, at least in part, be owing to disparities in the methodology used to collect epidemiological data.

Hospitalization rates **[Au: to be consistent, ok?, OK]** for diverticular disease have also increased in most countries. For example, in the USA, >216,000 hospital admissions were reported for acute diverticulitis without haemorrhage in 2012, a 21% increase from 2003 (Ref[7]). In the UK, the hospital admission rate for diverticular disease **[Au: Is it diverticulitis or hemmorhage or both? The study does not specify, but the logical thinking implies that it should include both]** increased from 0.56 per 1,000 person-years in 1996 to 1.20 per 1,000 person-years in 2006[17]. **[Au: edits for brevity ok?. Ok]** . In Italy, in the period 2008–2015, the hospitalization rate for acute diverticulitis has been constantly increasing[18] **[Au: please mention the increase rate? Around 1.9% of annual percentage change Any information on hospitalization rates for SUDD or diverticular hemmorhage in Italy?, I am not aware of]**. Patients were mainly younger individuals **[Au: could you please mention the age range of the patients? < 40]**, particularly men. A significant increase was also noted in in-hospital mortality, especially among women, **[Au: why? And in which country? please specificy the age range of women. Are these subsequent hospitalizations?]**, **Antonio see comments** the elderly **[Au: >65 years of age? yes]**and during the first hospitalization **[Au: including men? At what age range was mortality high during first hospitalization?] [Au: please cite a ref]**. All the above findings call for the need of increased awareness and clinical skills in the management of this common condition.

Comentado [UdMO4]: Antonio, a lot of new text has been introduced in this section, I did not write these entences and tehrefore I have not those references to check. Furthermore, I see that reference 18 it is not in PUbmed. Did you introduced this. Please can you answer these multiple and repetitive questions from the text reviewer?)

[H2] Risk factors

[H3] Diverticulosis.

Differences in the prevalence of diverticulosis between countries might be owing to the low-fibre diet consumed in western countries, which has been pathogenetically linked to increased colonic intraluminal pressure that results in the formation of a diverticulum[2]. **[Au:OK? ok]** However, findings from one study question the role of fibre in these individuals[19] **[Au: could you please mention the actual findings of the study? I do not think it is necessary. It is just that there was not association between fiber intake and the prevalence of diverticulosis]**. A Japanese study reported age, male sex, tobacco use, weight gain in adulthood, pre-diabetic conditions **[Au: do yo mean hyperglycaemia? It is what the authors refer, and it is what they mean]**, alcohol consumption and increased serum triglyceride levels as risks factors for diverticulosis[8]. Most of these factors in addition to low-fibre diet **[Au:OK? Ok]**are also risk factors for diverticulosis in other areas of the world **[Au: Please cite a ref, 19]**.

[H3] Diverticular disease.

Numerous risk factors for diverticular disease have been identified including non-modifiable factors such as age, sex and genetics[20]and modifiable risk factors such as lifestyle (diet and physical activity) and the use of prescription drugs[19,21] (Table 1). **[Au: moved sentence on risk factors from Prevention section to here for flow, ok? ok]** In one study, people from non-western countries 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 acculturation to the western lifestyle, the risk increased in the immigrant poplation, becoming similar to the native Swedish population[22]. On the basis of these data, ethnicity seems to be less important than lifestyle as a risk factor for diverticular disease.

[Au: new paragraph] The risk of hospitalization for diverticular disease, especially acute diverticulitis**[Au: is this what you meant? Yes If not, it is ambiguous what you mean with diverticular disease and acute diverticulitis as acute diverticulitis is diverticular disease. Please clarify]**, is associated with modifiable risk factors. In western countries, factors that increase 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 risk of hospitalization include vigorous **[Au: and regular? yes]** physical activity, high educational attainment, high intake of fibre and a vegetarian diet[23,24]. One study reported that adherence to a low-risk lifestyle, defined as low intake of red meat, high intake of fibre, vigorous **[Au: and regular? yes]**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[25]**[Au: Does low-risk lifestyle also reduce hospitalization? What is the impact of diet and lifestyle on SUDD and diverticular haemorrhage? Data on diet and lifestyle refer to overall diverticular disease, both symptomatic and asymptomatic, I ma not aware of data on these risk factors and specific types of diverticular disease]**.

[H1] 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 multifactorialand the mechanisms are likely to differ for different disease manifestations (Figure 2) **[Au: moved the figure call out here to be concise]**. For example, connective tissue abnormalities such as altered elastin (a key extracellular matrix protein that provides resilience and elasticity to tissue and organs **[Au: definition ok?]**) cross-linking, might

predispose individuals to the development of asymptomatic diverticulosis **[Au: please cite a ref]**, whereas additional changes or precipitating factors such as gut microbial dysbiosis or medication use, might be necessary for the development of symptoms or complications **[Au: such as?]**. Burgeoning evidence from genome-wide association studies (GWAS) promises to guide future research and improve our understanding of underlying biological mechanisms **[Au: moved the figure call out above]**.

[H2] Faecal stasis and faecal impaction

A long-standing hypothesis of 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 **[Au: ok?]**often contain a faecalith[26]. In addition, diverticulitis shares many clinical and histopathological features with acute appendicitis, including obstruction of the appendix by a faecalith (an appendicolith). However, no evidence directly links faecalith obstruction of diverticula to diverticulitis. **[Au: Could you please explain how faecal impaction can cause or is associated with SUDD, as implied in figure 1?]**

[H2] Chronic inflammation

In addition to the acute inflammation that occurs in overt acute diverticulitis **[Au:OK?]**, chronic, low-grade inflammation in individuals with diverticulosis **[Au:OK?]** might predispose these individuals **[Au:OK?]** to the development of diverticulitis and SUDD. Many of the risk factors for diverticulitissuch as a low-fibre diet[23], high red meat consumption[27], obesity[28,29], smoking[30] and physical inactivity[31], which are also risk factors for cardiovascular disease[32] and diabetes mellitus[33], are known to be associated

with chronic, low-grade inflammation. **[Au: edited for brevity]**Thus, chronic inflammation might be the underlying mechanistic link between diet and lifestyle factors and diverticulitis **[Au: is this what you meant?]**. In a large, prospective study that only included men **[Au:OK? what is the age range of men in this study?]**, the inflammatory potential of diet was correlated **[Au:OK?]** with the risk of diverticulitis after adjusting for other known risk factors, including dietary fibre intake and red meat consumption[34]. The inflammatory potential of diet was assessed using the validated empirical dietary inflammatory pattern (EDIP) score, which is predictive of the levels of three markers of inflammation, CRP, IL-6 and TNFR2 **[Au: do you mean TNF? As TNFR2 is a receptor is not freely soluble in the plasma, please clarify] [Au: Our house style is to not expand abbreviations of proteins and genes, so I have removed the names of proteins, ok?].[Au: could you please mention the finding of this study? Was the EDIP score higher for red meat? Higher the on-going, chronic inflammation, higher the risk of diverticulitis. Although, this is implied, the message is not explicit.]**In addition, in a nested case–control study within the same cohort, plasma levels of CRP and IL-6 were associated with risk of diverticulitis, further supporting the link between chronic systemic inflammation and diverticulitis[34].

[Au: deleted statement on inflammation and SUDD to avoid repetition, ok?]Futhermore, in a small study, patients with SUDD showed increased expression of the neuropeptide receptor NK1 (also known as tachykinin 1, which is known to be involved in smooth muscle contraction and inflammation)**[Au: definition ok? I have changed neuropeptide to neuropeptide receptor from the cited reference. Can you please double check?]** and the proinflammatory cytokine TNF compared with individuals with asymptomatic diverticulosis **[Au:OK?]**, indicating that symptoms in SUDD might be mediated by chronic, low-grade inflammation and upregulation of tachykinins[35]. In another study, patients with SUDD demonstrated elevated levels of faecal calprotectin (which is an indication of neutrophil infiltration in the intestinal mucosa) **[Au: explanation ok?]**, whereas individuals with **[Au: asymptomatic?]** diverticulosis did not[36]. However, two large, community-based studies evaluating

patients undergoing routine colonoscopy found no evidence of mucosal inflammation, either based on immune markers **[Au: such as?]**, serum CRP or histopathology, in patients with diverticulosis, regardless of symptoms[37,38]. Differences in the patient population in these population-based studies **[Au:OK?]**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[39,40].

[H2] 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[41–43]. For example, dietary fibre intake increases intestinal microbial diversity via bacterial production of short chain fatty acids (SCFAs)[44–46], which enhance mucosal barrier and immune function[47]. Indeed, the SCFA butyrate, when delivered to the colon via a microencapsulated formulation, might decrease **[Au: Rearranged for flow, ok?]**the risk of recurrent diverticulitis[48].

Preliminary studies indicate that the intestinal microbiota in patients with a history of acute diverticulitis differs from that of 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 *Clostridiales* species and increased levels of bacteria with pro-inflammatory effects, including *Marvinbryantia* species and *Subdoligranulum* species[49,50], in patients with xxx **[Au: Please mention in whom the bacteria levels were different]**. Carbohydrate metabolism and biosynthesis of secondary metabolites **[Au: such as?]**was predicted to be reduced **[Au: Was it only predicted or was it actually reduced? Please clarify]**in the intestinal microbial communities **[Au:OK?]**in patients with a history of acute diverticulitis **[Au:OK?]** compared with individuals with diverticulosis[49]. Another study found that the diversity of Proteobacteria was higher in patients with acute diverticulitis than in individuals with

diverticulosis and species of the Enterobacteriaceae family such as *Escherichia coli*, provided the highest discriminative value[50] **[Au: please explain what this means][Au: I have removed the information on E.coli and IBD as this information is not warranted here. Please note that this deleted references 50 and 51]**. Few studies have focused on the intestinal microbiota in patients with SUDD. A study involving 8 patients with SUDD found lower levels of the SCFA-producing bacterial species *Clostridium* cluster IX, *Fusobacterium* species and Lactobacillaceae than in individuals with diverticulosis. Moreover, biopsy samples from the area of diverticulosis **[Au: Does this also include area surrounding a diverticulum? Please mention what the area of diverticulosis consists of?]**in patients with SUDD had lower levels of *Akkermansia muciniphila* (a mucin-degrading bacterium that promotes epithelial barrier integrity by suppressing inflammation) than in biopsy samples obtained from the more proximal colon **[Au: or 'right-sided' to be consistent with earlier?]**[51].**[Au: I moved the function of A. muciniphila next to its description and removed the statement on negative correlation with IBD to be consistent as we don't mention the association of all microbial species wrt IBD in this section, ok? Please note that this deleted the appropriate reference.]** Another study involving patients with SUDD **[Au: number of patients?]**found a higher abundance of *Pseudobutyrivibrio* species*, Bifidobacterium* species and Christensenellaceae in patients with a history of diverticulitis **[Au: acute?]**than in those without a history of acute diverticulutis[52] **[Au: Is this what you meant? Is this condition SUDD post-acute diverticulitis?]**. Alterations in the faecal and urinary metabolome **[Au: or microbiota? Were the genomics assessed or just the species diversity?]** have also been observed in patients with SUDD[51,53]. However, one study, comparing 226 individuals with incidental diverticulosis (asymptomatic) **[Au:OK?]**and 309 individuals without diverticulosis **[Au: are these healthy control individuals?]**, found that the mucosal-adherent bacterial community did not differ between these two groups[54]. **[Au: removed summary statement to avoid repetition, ok?]**

[H2] Neuromuscular alterations

[H3] 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 associatedwith ageing[55]. GWAS have identified diverticulosis risk loci that contained genes involved in connective tissue integrity and intestinal motility, highlighting the importance of neuromuscular abnormalities in the development of diverticulosis **[Au: ref?]**. **[Au: removed sentence on enteric nervous system to avoid repetition as it is explained in detail later in this section, ok?]** However, 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 metabolism. Morphologically, the longitudinal and circular muscle layers become hypertrophic, which appears on endoscopy **[Au: colonoscopy?]**as thickened colonic folds and a reduced lumen caliber, termed myochosis coli[26] **[Au: is this what you meant? Edits ok?]**. Alterations in the enteric nervous system[26] such as reduced number of glial cells, nerve cells[56] and intestinal pacemaker cells[57] as well as changes in the levels of neurotransmitters, neurotransmitter receptors and neurotrophic factors[58,59] are also observed in individuals with diverticulosis. Colonic motility studies using 24-hour manometry (which measures the measures strength and muscle coordination **[Au: description ok?]**), indicate that patients with diverticulosis have increased intraluminal pressure, increased colonic response to eating and increased number of high-amplitude contractions compared with individuals without diverticulosis[60] **[Au: what is the implication of this?]**.

[Au: could you please explain how colonic metabolism is altered, as mentioned at the beginning of this paragraph?]

[H3] 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 distention in colonic segments involved with diverticulosis and in the rectum[61] **[Au:OK?]**. This visceral hypersensitivity might be mediated by chronic, low-grade inflammation and upregulation of tachykinins[35]. 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[62]. Addiyionally, the type I to type III collagen ratio, cross-linking of collagen fibrer[63] and levels of tissue-degrading matrix metalloproteinases[64] are increased in patients with diverticular disease. **[Au: Please explain the implication of these structural changes towards the development of the disease in a sentence or two.] [Au: Is visceral hypersensitivity also present in patients with acute diverticulitis?]**

[H2] Genetics

Several lines of indirect evidence suggest a genetic basis for diverticulosis and diverticular disease. First, as discussed earlier, the high prevalence of sigmoidal diverticulosis in western contries verus prevalence of right-sided diverticulosis in eastern countries might have an underlying genetic basis[22] **[Au: Is this what you meant? Edited to avoid repetition, ok?]**. 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, severe diverticulosis **[Au: Please define severe diverticulosis? If this is SUDD or other symptomatic diverticular disease, please use consistent terminology]**occurs in patients with inherited connective tissue disorderssuch as Marfan syndrome, Ehlers–Danlos syndrome, Coffin–Lowry syndrome and Williams–Beuren syndrome, or with inherited intestinal motility disorders[65–67] **[Au: please give an example of inherited intestinal motility disorder]**. 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 general population and higher in monozygotic twins than in dizygotic twins; these studies estimated that ~50% of the risk for diverticular disease **[Au: is this a risk for incidence or for hospitalization?]**was inherited[68,69].

Case–control studies have identified genetic variants **[Au:OK?]** within candidate genesimplicated in diverticulosis and diverticulitis **[Au:OK?]**. 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) **[Au:OK?]**and diverticulosis in white men[70]. 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[71] **[Au: Is this acute complicated diverticulitis? Please use consistent terminology]**. Another study found that a variant in *RPRM* (encoding reprimo, a protein involved in cell cycle regulation **[Au: is this what you meant?]** and DNA repair), was linked to the presence of diverticulosis[72] **[Au: Does this also include women?]**. Finally, a rare SNP in *LAMB4* (encoding laminin subunit β4, a constitutent of the extracellular matrix) was identified in five family members with young-onset diverticulitis[73] **[Au: please mention what age is considered young-onset]**.

Three GWAS have identified susceptibility loci for diverticular disease[74]. 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) **[Au: definitions ok?]** were associated with diverticular disease **[Au: do you specifically mean SUDD or haemorrhage as you mention diverticulits in the latter part of this sentence]**and variants in *FAM155A* (encoding a protein of unknown function **[Au:OK?]**) were associated with diverticulitis[75] **[Au: Do you mean to say that this was absent from SUDD etc?]**. A larger GWAS involving >27,000 individuals with diverticular disease **[Au: which includes SUDD, diverticulitis or diverticular haemorrhage? If so, please mention this explicitly]**and 382,000 healthy individuals **[Au: Edited for brevity; any information if these individuals presented diverticulosis?]**from the UK Biobank identified 40 loci with significant associations with diverticular disease and 112 loci with

suggestive associations **[Au: Please citethe ref]**. In a separate American cohort of 2,572 individuals with diverticular disease **[Au: please mention which type]** and 28,649 healthy individuals without these diagnoses, eight significant and two suggestive loci were replicated **[Au: Were no new loci identified from this study? Please cite a ref]**. The identified risk loci contain genes involved in the immune system **[Au:OK?]**, intestinal motility, cytoskeleton organization, cellular adhesion, the extracellular matrix and membrane transport. The associations with *ARHGAP15*, *COLQ* and *FAM155A* variants were confirmed in this larger study **[Au: Study from the UK biobank or the American cohort?]**, but not the association of *TNFSF15* (Ref[76]). 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 individuals[77]; 48 loci with significant associations were identified **[Au: edited for consistency, ok?]**, 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[74]**[Au: is this what you meant?]**. The functions of the identified candidate genes further supported **[Au: edits ok? as we have discussed these factors earlier in this section.]** a role for impaired neuromuscular, mesenteric smooth muscle and connective tissue function in the pathogenesis of diverticular disease[74]. In addition, one of the identified candidate genes, *PHGR1*, which is involved in gastrointestinal epithelial cell function **[Au:OK?]**, was specifically associated with diverticulitis[77].

[Au: Removed the sentence on referring readers to review for brevity and I have cited the reference earlier in the section and when the gene functions are mentioned, ok?]

[H1] Diagnosis, screening and prevention

[Au: Please include a description to explain the various clinical presentations of diverticular disease. Currently, an explanation of features distinguishing acute uncomplicated diverticulitis and acute complicated diverticulitis is missing. In some sections of the main text, you also describe persistent diverticulitis. Please explain these spectrum of conditions and their symptoms.]

[H2] Diagnosis

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[78].

Clinical evaluation including laboratory tests alone **[Au:OK?]**, 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%; a positive predictive value of 65%)[79]. Furthermore, clinical evaluation alone resulted in an incorrect diagnosis in 34–68% of cases[80,81], which might delay appropriate treatment, cause redundant investigations and result in unjustified hospitalization. Moreover, biomarkers are not specific enough for an initial diagnosis (*see below*).

[H3] Cross–sectional imaging.

Traditionally, imaging of diverticula and related disease was performed by barium enema. While the detection rate of colonic diverticula is high and more accurate than that obtained by colonoscopy[82], barium enema**[Au: for consistency, ok?]** is not an appropriate imaging technique to diagnose acute diverticulitis. Indeed, one systematic review found low sensitivity and specificity of barium enema in comparison to modern cross–sectional imaging[83]. However, in selected cases (for example, in patients with intestinal stenosis), barium enema can be still 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[84]. Thus, these methods are the mainstay for the diagnosis of diverticular disease and mandatory for the accurate diagnosis of diverticulitis[78] (Figure 3). **[Au: edited for brevity and to avoid repetition, ok?]**

Although CT is currently the widely-adopted diagnostic approach, technological advances have led to an increasing use of ultrasonography worldwide[85–87]. **[Au: Moved statement on features identified below for flow.]** An early comparison of ultrasonography and CT found very similar diagnostic accuracy for these two approaches[80]. In fact, a meta-analysis confirmed that ultrasonography and CT did not differ substantially in sensitivity (92% and 94%, respectively) and specificity (90% and 99%, respectively) **[Au: Ref?]**. Of note, alternative diseases **[Au: what do you mean with alternative diseases?]**were more often described with CT[88]. A drawback of this meta-analysis is that the studies included patients across the whole spectrum of diverticular disease **[Au: please explain why this is a drawback]**. A study comparing the diagnostic accuracy of ultrasonography and CT in SUDD and complicated diverticular disease **[Au: could you please mention if this study included diverticulitis and diverticular haemorrhage?]**found a clear superiority of CT in diagnosing complicated diverticular disease whereas the two approaches had comparable diagnostic accuracy in SUDD[89]. **[Au: deleted statement on diagnostic superiority of CT to avoid repetition]** Data regarding the diagnostic accuracy of MRI in diverticular disease are sparse but promising. Most interestingly, the only comparative study between CT and MRI in patients admitted to the emergency room with clinically suspected acute diverticulitis **[Au: for consistency, ok?]** reported a sensitivity of 94% and a specificity of 88% for MRI. Interestingly, the diagnostic accuracy of MRI was found to be better in younger patients (<60 years of age) than in older patients[90].

[Au: Moved sentence on features identified from previous paragraph to here for flow] Typical ultrasonography findings in diverticular disease include hypoechogenic thickening of the bowel wall, diverticula with surrounding inflammation that appears as

a hyperechogenic rim, fluid collection, abscesses or fistulas[88,91–93]. In addition to thesefeatures, 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 mightdiffer in some aspects, the two are complementary rather than competing techniques. For example, ultrasonography is a dynamic investigational tool that provides information on the motor activity **[Au: motility?]**of the bowel. However, the pressure of the ultrasonography probe can cause pain, which can lead the operator to focus on the given abdominal area **[Au: do you mean to say that pain might indicate the area of diverticulosis? What is the implication of only focusing on one 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[94]. Indeed, colonic wall thickness and severity of diverticulitis detected by CT were predictive of the need for elective partial colectomy[95]. **[Au: deleted sentence on MRI and diverticulitis to avoid repetition, ok?]** In contrast to ultrasonography and MRI, CT involves exposure to radiation, which limits its repeated use. Acute diverticulitis might progress rapidly **[Au: how rapid? Hours or days or weeks?]**. By nature, inflammation is a dynamic process and an appropriate visualization would require reiterative examinations **[Au: It is unclear why acute diverticulitis requires repetitive imaging, please explain]**. Ultrasonography can be replicated as often as it is useful for difficult decision making **[Au: But is this true for diverticular disease as you mention earlier in the section, while ultrasonography is useful for diagnosing SUDD, it is less useful for complicated diverticular disease. So, it is not clear how ultrasound will help difficult decision making, please clarify]**.

[Au: new paragraph] In principle, for all imaging methodologies (especially ultrasonography), diagnostic accuracy is operator-dependent and is better in referral centres (where all diagnostic procedures are usually available) than in a general hospital

setting[85,96]. 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[85] **[Au: edited for brevity and to avoid repetition]**.

***[H3] Colonoscopy*. [Au: Could you please briefly mention in a sentence or so that colonoscopy is being increasingly used in diverticular disease of late and not CT is the most widely accepted method for diagnosis?]**

Traditionally, colonoscopy is avoided in patients with acute diverticulitis because of perceived risks from the procedure[97], especially an increased risk of local or distant perforation, although this risk was not confirmed in one small study[98]. As the main pathophysiological features of acute diverticulitis take place outside the colonic wall **[Au:OK?]**, colonoscopy has only a minor role in the initial diagnosis of acute diverticulitits **[Au:OK?]**. In a prospective study, all patients with confirmed acute diverticulitis had initial colonoscopies. Patients with a 'regular' course of diverticulitis **[Au: please define regular course; is this different from acute diverticulitis?]**demonstrated no pathologies on colonoscopy, whereas four out of 23 patients with persistent diverticulitis **[Au: please define]**benefited from early colonoscopy[98], which helped to identify the reason for persistent diverticulitis or to change the final diagnosis in these patients **[Au:OK?]**. Differential diagnoses for diverticular disease include IBD, IBS, appendicitis, microscopic colitis, cancer **[Au: added all the conditions from the differential diagnosis section below to avoid repetition later, ok?]** or segmental colitis associated with diverticula (SCAD). SCAD will not be discussed in this review because it is now considered as a forerunner of IBD rather a complication of diverticular disease[3]. Colonoscopy is however advisable prior to elective surgery in patients with acute diverticulitis **[Au:OK?]** to rule out differential diagnoses and neoplastic lesions[78].

[Au: moved epidemiology data on diverticular hemorrhage from here to the Epidemiology section for flow, ok?] Diverticular haemorrhage typically presents as

painless, intermittent and large volume of lower gastrointestinal bleeding[99], which often stops spontaneously but can also be life threatening[99–101].**[Au: merged paragraphs and rearranged information for flow of text. Please check carefully.]** 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[102,103]. High volume upper gastrointestinal bleeding**[Au: Does diverticular haemorrhage present also as upper gastrointestinal bleeding? If yes, please mention this at the beginning of the paragraph where you mention the symptoms; sentence highlighted in yellow.]** 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[104]. Furthermore, several guidelines recommend colonoscopy within 24 hours after bowel cleansing in patients with severe haematochezia[103].

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 site **[Au: Are these patients not referred to for colonoscopy?]**. 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[15,78,100,104]. If surgery is inevitable, precise knowledge of the localization is crucial for any surgical process that is required **[Au: in what cases is localization of bleeding not possible in patients?]**. Colonic resections in patients with diverticular haemorrhage with unclear localization of bleeding showed a postoperative mortality of 43% in comparison to 7% in patients with well-defined localization of bleeding[105].

[Au: Since this section has to discuss diagnosis of diverticular disease, a detailed discussion on CRC is unwarranted in this Primer. Please consider shortening the discussion to include the most relevant information and the most important findings; I have tried to do some shortening for you but I suggest more is needed.] 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 of diverticular disease with simultaneous colonic neoplastic lesions. **[Au: removed for brevity]**A large meta-analysis involving 50,445 patients with acute diverticulitis analysed 31 studies conducted worldwide and reported substantial heterogeneity between the study results (I^2=57%, P<0.01)[106]. The meta-analysis reported a pooled prevalence of 1.9% of associated colorectal cancer (CRC). Notably, the risk for CRC was sixfold higher in patients with complicated diverticulitis than in patients with uncomplicated diverticulitis **[Au: is this SUDD? If yes, please use the terminology SUDD for consistency]**. Additionally, the meta-analysis reported that endoscopy **[Au: any information on which endoscopy?]** detected a pooled prevalence of 22.7% of polyps, (4.4% of the 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, leading to a substantial diagnostic delay (although not reported in length **[Au: what do you mean by length?]**) of CRC in patients with both conditions[107]. Taking all these considerations into account, colonoscopy should be considered after an episode of acute diverticulitis **[Au:OK?]**, provided that it has not already been performed[107]. Owing to risks of perforation, a delay of 6–8 weeks after treatment is generally recommended[108]. According to two meta-analyses[108,109], most studies performed colonoscopy within 6–8 weeks (and in any case within 6 months) after the index episode. **[Au: merged paragraphs]** However, the rate of detecting CRC via endoscopy is relatively low, especially after an episode of uncomplicated acute diverticulitis[110] ; a meta-analysis of 11 studies[109] reported a low risk of malignancy after a CT-proven **[Au: edited for**

consistency as you report this in all other sections of the manuscript, ok?]episode of acute uncomplicated diverticulitis (0.7%, 95% CI 0.4–1.4)in comparison to patients with complicated diverticulitis **[Au: do you mean complicated diverticular disease? Please use consistent terminology.]**(1.6%, 95% CI 1.6–2.8) at subsequent colonic evaluation. Routine colonoscopy might not be necessary after an episode of uncomplicated diverticulitis, but 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.

[Au: moved section on DICA classification below for flow]

[H3] Biomarkers.

[Au: deleted statement on biomarkers and diagnosis to avoid repetition]Biomarkers might substantiate clinical suspicion and can be useful for assessing disease severity and for disease monitoring[111]. For example, proinflammatory 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 process in the disease pathophysiology.

On the ground 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[111]. Additionally, serum CRP concentrations are closely related to clinical and histological severity of diverticular disease **[Au: diverticulitis?]**. Low CRP levels (<50 mg/l) are indicative of acute uncomplicated diverticulitis **[Au: is this different from SUDD?]**, 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 persistent high levels indicate treatment failure[112]. **[Au: deleted function of calprotectin to avoid repetition, ok?]** A systematic review examining the use of faecal calprotectin to distinguish IBS from IBD[113] reported that faecal calprotectin levels >50mg/g detected IBD with pooled sensitivity of

93% (range 83–100%) and pooled specificity of 94% (60–100%)[114]. 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[115], suggesting that faecal calprotectin can also be a valuable tool to discriminate IBS and SUDD[36]. Typical symptoms of SUDD are pain localized in the left lower abdomen without signs of inflammation[116]. 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 to clarify the diagnosis[117]. A prospective study comparing faecal calprotectin levels in patients with SUDD and IBS according to Rome III criteria described significantly higher faecal calprotectin levels in SUDD **[Au: compared with patients with IBS?]**, which decreased after successful treatment[36]. Although faecal calprotectin is a well-established biomarker of inflammatory activity in IBD, its utility for diverticulitis remains to be established.

According to guidelines, the diagnostic algorithm for a range of bacterial infectious diseases comprises measurement of serum procalcitonin (to identify sepsis[118]) before commencing antibiotic therapy[119,120]. **[Au: removed the information on procalcitonin and its diagnostic algorithm in various infectious conditions as such detailed information is unwarranted here, ok? This removed one reference with respect to peritonitis]** Its use has led to a decrease in antibiotic prescription[121], 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[122]. However, the role of procalcitonin needs to be further investigated.

To date, among many other proteins that were studied as potential biomarkers for diverticular disease, none has achieved clinical significance[112]. Serum vitamin D levels are shown to be associated with the severity **[Au: is this what you meant? Higher levels correlating with more alterations?]**of endoscopic alterations in diverticular disease[123]. Overall, CRP remains the most useful biomarker to date.

[H2] Classification

[Au: Please also include a section to describe Hinchey classification system as this is discussed later in the manuscript. I have include a call out for (Figure 4) which explains the Hinchey staging as a call out for this figure is currently missing.]

[Au: I moved information on DICA from colonoscopy to here for flow, ok?]

A study investigated the prognostic role of persistent mucosal alterations after an episode of acute diverticulitis[40] **[Au: please explain the findings of this study and its implication]**. The Diverticular Inflammation and Complication Assessment (DICA)[124], developed on the basis of colonoscopy, a three-stage severity score that classifies the disease into mild, moderate or severe [124](Figure 5). DICA takes into account several main features **[Au:OK?]** and sub features: the four main items are extension **[Au: do you mean localisation?]** of diverticulosis (left or right), the number of diverticula in each colonic segment (≤15 or >15 diverticula), the presence of inflammation (edema and/or hyperemia, erosions, SCAD **[Au: Ealier in the Diagnosis section, you mention SCAD as a separate entity and not related to diverticular disease. Its relevance in DICA score suggests otherwise. Could you please explain why SCAD needs to be assessed to score diverticular disease?]**) and the presence of complications (rigidity, stenosis, pus and bleeding). When diverticula were detected during colonoscopy, they were described as 'scattered', 'scanty', 'diffuse' or 'numerous'. **[Au: moved a statement classifying the diverticula from Outlook section to here to related facts together, ok?]** Each feature and sub-feature **[Au:OK?]** have a numerical score, and the sum of the scores leads to three different DICA scores: DICA 1 (≤3 points), DICA 2 (4–7 points), and DICA 3 (>7 points)[124] (Figure 5). 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[125]. A 3-year *prospective*, international validation study is currently ongoing[1] **[Au: you had wanted to cite this clinical trial but I am unable to find the trial. Could you please double check if the trial ID is correct and provide me with the correct details so that I can update the reference? *"US National Library of Medicine. ClinicalTrials.gov, https://clinicaltrials.gov/ ct2/show/NCT0275886 (2016)"*]** (118) and preliminary

analysis of the results at one-year follow up confirmed the results of the retrospective study[126]. The DICA Score still needs further validation. Provided early results **[Au: what do you mean with early results?]**can be confirmed, follow-up colonoscopy after acute diverticulitis may provide some additional benefits.**[Au: do you mean for additional classification?]**

[Au: I have removed the section on differential diagnosis to avoid repetition. I have listed all the conditions at the first explanation of differential diagnosis discussed under colonoscopy. This will also enable more space for you to discuss the classification which I have requested.]

[H2] Prevention

[Au: I have shortened the following text to avoid repetition as most of the information discussed below has been mentioned in other sections above. Please check carefully]

As already discussed, diverticulosis has been hypothesized as being the result of a low-fibre diet[127]. However, population-based studies of twins and siblings[69] as well as GWAS[77] have higlighted the genetic background of the disease confirming a multifactorial aetiology, which is difficult to modify. Indeed, there are currently no evidence-based measures for primary **[Au:OK?]** prevention of diverticulosis. **[Au: merged paragraphs]** 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 prevention **[Au: of the disease or of symptoms of the disease?]**[20]. 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) **[Au: for Table 1 to be even more useful, I suggest adding a 'recommendations for prevention' column that translates these risk to potential prevention recommendations; see below]** .

[Au: moved statement on percentage of patients developing diverticulitis to Epidemiology section, ok?]

[H1] Management

The therapeutic approach to diverticular disease **[Au: for consistency ok?]** is tailored to the severity of the disease. The presence of diverticula is not an indication for pharmacological therapy, as most individuals with diverticulosis will not progress to symptomatic disease. **[Au: removed the sentence on preventive measures to avoid repetition, ok?]**

[H2] SUDD

In patients with SUDD, pharmacological therapy should aim to reduce both the intensity and frequency of symptoms and to prevent complications[128,129]. Although patients with SUDD complain of mild to moderate pain and bloating **[Au:OK?]**, their quality of life is markedly impaired and can be improved by medical treatment[130]. Treatments for SUDD include fibre, **[Au: prophylactic?]** antibiotics (including the poorly absorbed antibiotic, rifaximin), anti-inflammatory drugs such as mesalazine or balsalazide and probiotics, alone or in combination[3,129].

[H3] Fibre.

A high-fibre diet has been and is still recommended for patients with diverticular disease. However, a systematic review[130,131] concluded that 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[131]. Thus, the benefit of dietary or supplemental fibre in the treatment of SUDD needs to be established. **[Au: added the inference of the systematic review here for completion, ok?]**

[H3] Poorly absorbed antibiotics.

[Au: Could you please add a sentence that antibiotics in SUDD is prophylactic to prevent infectious complication? Or is the reason for antibiotic therapy purely to treat dysbiosis? Please explain the rationale for using antibiotics explicitly in the text for readers understanding. When SUDD patients develop infections, is it considered a complicated disease?]

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 favor faecal entrapment. This will be followed by bacterial overgrowth and potential breakdown of the epithelial lining, leading to bacterial translocation, mucosal inflammation and complications[132], which leads to complicated diverticular disease **[Au:OK?]**. Studies showing the presence of dysbiosis in patients with SUDD[51,53] and diverticulitis[133] strongly support this hypothesis. In a double-blind, placebo-controlled, randomized clinical trial (RCT)[132] as well as open studies[134] and their meta-analyses[135,136], the combination of rifaximin (a poorly absorbed, gastrointestinal tract-targeted antibiotic that has both eubiotic and anti-inflammatory properties[137,138]) **[Au: moved statement on properties of rifaximin from below to here, ok?]** and soluble or insoluble fibre was more effective in reducing symptoms in patients with SUDD than fibre alone. The combination of rifaximin (given for 1 week every month) **[Au: for how many months? Until symptoms disappeared?]**and soluble fibre such as glucomannan (extracted from root of the konjac plantthat can absorb up to 200 times its weight in water), was most effective in treating SUDD, which are confirmed in real-life studies from both gastroenterology and general practice[139,140].

In addition, rifaximin is also very effective in the treatment of small intestine bacterial overgrowth (SIBO, the most widely detected form of gut dysbiosis)[141] and related (organic and functional) gastrointestinal disorders[142] and safe in clinical practice[143]. Indeed, several national guidelines[144–150] recommend long-term cyclic administration **[Au: do you mean repeated administration?]** of rifaximin for the treatment of SUDD **[Au: I have merged sentences on rifaximin and SIBO here for brevity and have mentioned SUDD as we are discussing management of SUDD here, edits ok?]. [Au: can you comment on antimicrobial stewardship and risk of resistence? Is this an area of concern for the field and for these patients?]**

[H3] Topical anti-inflammatory drugs. **[Au: why topical? How is the anti-inflammatory drug delivered in patients?]**

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[151]. In diverticular disease, mesalazine might exert anti-inflammatory activity, thereby improving chronic, low-grade inflammation[151]or it can modulate nociception[151]. In patients with SUDD, one double-blind study showed its efficacy in providing pain relief during symptomatic flares[152] whereas another study found mesalazine was effective in maintaining remission[153] than placebo. A systematic review[154] found that mesalazine provided better symptom relief than placebo, a high-fibre diet or low-dose rifaximin in patients with SUDD.

[H3] Probiotics.

In contrast to antibiotic treatment, probiotics are a less invasive and more physiological approach to treat the intestinal microbial dysbiosis in patients with diverticular disease. The most widely used probiotic mixtures contain *Lactobacilli* and *Bifidobacteria*, but yeasts (such as *Saccharomyces boulardi*) 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 defense, a feature that is potentially beneficial in the treatment of diverticular disease[155].

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 2 of these studies were double-blinded and randomized[156]. 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 of in treating SUDD, but does not permit any evidence-based definite conclusion[155,156]. Indeed, the Italian Consensus Conference on Diverticular Disease[146] and the guidelines of the Italian Society of Colon and Rectal Surgery[147] stated that there is insufficient evidence to conclude the efficacy of probiotics in reducing symptoms of patients with diverticular disease **[Au: SUDD?]**. However, probiotics might be useful in combination with other therapies. In one study, combination therapy with cyclic mesalazine and a probiotic (*Lactobacillus casei DG*) seemed to be more effective than placebo or either treatment alone in maintaining remission of SUDD[153]. Owing to the small sample size of this study, larger trials are required to confirm this interesting observation.

[H2] 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[157], 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[23]. Both rifaximin and mesalazine have been used in the attempt of preventing the occurrence of diverticulitis in patients with SUDD, but the evidence in favor of their use is low. Two meta-analyses[135,136] found that rifaximin in combination with fibre is more effective than fibre alone in preventing acute diverticulitis, a trend that is also observed in clinical practice[143]. The therapeutic value of rifaximin was however quite low (number needed to treat (NNT) = 59)[136]. A meta-analysis[158] found that mesalazine also prevented diverticulitis occurrence in patients with SUDD. However, the analysis only included only two RCTs and 221 patients and showed a moderate level of heterogeneity between trials precluding definite conclusions **[Au:OK?]**.

[H2] Acute diverticulitis

[Au: This particular H2 is section is too long. I initially considered giving H3 subheadings to include uncomplicated diverticulitis and uncomplicated diverticulitis. But in this flow of text, we might to rearrange the flow of text in such a way. If you agree, please use H3 subheadings as suggested by me or something which you consider appropriate to break up this long section]

Management of acute diverticulitis depends on the severity of the condition (such as complicated or uncomplicated diverticulitis with abscess, perforation or peritonitis) as well as on the presence of comorbidities[19,20,159,160]. Most patients admitted with acute diverticulitis respond to conservative treatment, although, 10–20% of patients will eventually require surgery. **[Au: Edited to avoid repetition as we discuss this also later, ok?]**

For 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 (Figure 6). In the setting of acute uncomplicated diverticulitis, for low-risk patients characterized by normal leukocyte count and low CRP (together with absence of fever), outpatient treatment is feasible and omission of antimicrobial therapy is safe[161] **[Au: is this what you meant?]**. A large study that analysed >1,000 patients with CT-proven acute uncomplicated diverticulitis found that patients with a systemic comorbidity **[Au: such as?]**, 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'[162] **[Au: Does this have a different disease course compared to general complicated diverticulitis?]**. Two studies confirmed high CRP concentrations as the predictive factor for a worse outcome[163,164] **[Au: please explain worse outcome – is it development of complicated disease or a different kind of complication?]**. These studies also found that systemic inflammatory response syndrome (which xxx **[Au: please add a description of SIRS]**), high pain score and pharmacologically-induced immunosuppression predict a worse outcome of uncomplicated diverticulitis.

When patient classification was accurate **[Au: is this what you meant?]**, the outpatient approach proved to be safe and cost-effective[165–168]. 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[169] found a non-inferiority between different antibiotic regimens (cefoxitin versus gentamicin-clindamycin combination) and treatment lengths (24–48 hours intravenous antibiotic treatment versus longer treatments **[Au: longer oral treatments or IV?]**). In uncomplicated sigmoid diverticulitis, a study reported no difference symptom improvement between a short 4-day course and a 7-day antibiotic course[170] **[Au: is this**

what you meant?]. Although not rigorously studied, a low-fibre liquid diet is commonly recommended **[Au: in patients with uncomplicated diverticulitis? why?]**.

Although antimicrobial therapy has long been the cornerstone of acute diverticulitis treatment, routine use of this therapy in patients with uncomplicated diverticulitis **[Au: for consistency, ok? Or do you mean SUDD?]** has been challenged[171] 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[172,173] questioned the antimicrobial use and showed that observational treatment can be considered appropriate **[Au: how long was observational treatment sufficient?]**in patients with uncomplicated diverticulitis. Five meta-analyses (including RCTs, cohort studies and case–control studies)[174–178] **[Au: removed information on publication year for brevity]** demonstrated that clinical outcomes between patients treated with and those treated without antimicrobials are not substantially 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[174] 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 will likely apply to immunocompromised patients and pregnant women. Post-hoc analysis of the DIABOLO trial[179] (a multicentre RCT that compared antibiotic treatment and observational treatment in 528 patients with uncomplicated acute diverticulitis[180]) **[Au: moved this information from the QoL section ok?]** 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 **[Au:OK?]**- **[Au: what is the implication of this finding?]**.

Avoiding antimicrobial agents in the treatment of patients with uncomplicated acute diverticulitis is associated with a substantially shorter hospital stay[176,181]. Omitting antibiotics in the treatment of acute uncomplicated diverticulitis did not result in a higher incidence of **[Au:OK?]** complicated diverticulitis, recurrent diverticulitis **[Au: complicated or uncomplicated?]** or surgical intervention **[Au:OK?]**even at long-term follow-up[182]. As a consequence, the guidelines from Italian medical[146] and surgical[147] societies and from the World Society of Emergency Surgery[181] and the American Gastroenterological Association (AGA)[183] recommend selective use of antimicrobial drugs rather than routine administration in patients with acute uncomplicated diverticulitis.

Patients with severe presentations of uncomplicated diverticulitis **[Au: Please explain what the severe presentations are and how it is different to complicated diverticulitis.]** or those unable to tolerate oral intake or without outpatient support should be hospitalized, should receive intravenous fluids intravenous antimicrobial drugs (such as a beta-lactam antibiotic with beta-lactamase inhibitor, or metronidazole and a third-generation cephalosporin)[19,20,159,160].

In both low-risk and high-risk patients, symptoms usually improve within 2–3 days of 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[184] found that patients failing to improve at 48 hours of treatment required prolonged hospitalization or surgery **[Au: edited for brevity]**. When conservative medical treatment fails, a diligent search for complications is warranted and alternative diagnoses as well as surgical consultation need to be considered (Figure 6). **[Au: deleted statement on 10–20% needing surgery to avoid repetition.]**

Abscess is the most common complication of diverticulitis (in ~10% of patients) **[Au: is this complicated diverticulitis?]**. Patients with small abscesses (<3–4 cm in diameter), phlegmons (localized inflamed area or swelling) **[Au: definition ok?]**or small amounts of

extraluminal air can usually be managed with antimicrobial drugs alone[185] (Figure 7). Larger abscesses are generally treated with percutaneous drainage when antimicrobial therapy alone is insufficient. Percutaneous drainage can transform emergency surgery into an elective operation, reducing the need for a two-stage procedure[159,160]. 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[186,187]. However, current evidence suggests that complicated diverticulitis with abscessis associated with a high probability of requiring resective surgery and conservative management alone can frequently result in chronic or recurrent diverticular symptoms[186,188].

The surgical approach to complicated diverticulitis is evolving and is generally becoming less aggressive[189]. 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 for patients with sepsis and diffuse peritonitis (Hinchey stages III and IV (Figure 4)) or for those who do not respond to conservative therapy[19,20,159,160]. 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 also brings about a significant rate of perioeperative complications and a risk of permanent stomas albeit related to the patient's disease and comorbidity rather than the surgical procedure itself. Alternatively, sigmoid colectomy with primary anastomosis and diverting loop ileostomy has been proposed **[Au: ref?]**. Some European studies have compared the Hartmann procedure to anastomosis with diverting loop ileostomy and found comparable results **[Au: in terms of associated risks?]**. However, the difficulty of applying RCT principles to studies in acute surgical settings and the intrinsic limitations of the studies do not allow definite conclusions[19].

Laparoscopic lavage has also been proposed as a means to control purulent (not faeculent) peritonitis, allowing for a subsequent elective resection with primary anastomosis, reducing the risk of permanent stoma[190,191]. However, at present, its use is not recommended outside clinical trials[19]. **[Au: merged paragraphs]** Indeed, a systematic review[192] concluded that laparoscopic lavage has an increased risk of major complications **[Au: such as?]**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[192]. It is evident, 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[193](Figure 7).

[H2] Secondary prevention of acute diverticulitis

After an episode of acute diverticulitis, patients might present with recurrent or smoldering diverticulitis **[Au: do you mean chronic?]**, stricture and fistula and often develop chronic gastrointestinal and non-gastrointestinal symptoms **[Au: Please explain what non-gastrointestinal symptoms include]**. For example, one study found that, at 1-year follow-up, 40% of patients with CT-confirmed acute diverticulitis complained of mild to moderate abdominal pain and/or changes in bowel habit[172]. **[Au: removed statement on quality of life from here for flow.]** The overall risk of acute diverticulitis recurrence is ~36% at 5-year follow-up[194]. Recurrence usually occurs <12 months of the initial episode and the risk of complications is very low[195]. **[Au: moved this information on diverticulitis recurrence from the Outlook section for flow]**In a retrospective analysis of patients over an average follow-up period of 6.3 years, patients with diverticulitis **[Au: acute?]** had a 4.7-fold increased risk of being diagnosed subsequently with IBS[196]. The infection-associated gut dysbiosis and the resulting chronic, low-grade mucosal inflammation might underlie this so-called post-diverticulitis IBS (more

appropriately termed as "post-diverticulitis SUDD") **[Au: In the rebuttal, you mention that the accepted terminology is SUDD post-acute diverticulitis, if this is the case, could you please rephrase this?]**, which has a pathophysiology similar to that of post-infection IBS[197]. Several strategies have been undertaken to prevent recurrence of diverticulitis.

[H3] Dietary interventions.

The AGA guidelines on management of acute diverticulitis[183] conditionally recommends a high-fibre diet or fibre supplementation in patients with a history of acute diverticulitis,although, a systematic review[198] found that the evidence for this approach was of very low quality. After resolution of an episode of acute diverticulitis **[Au: is this what you meant?]**, 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[155,183].

[H3] Pharmacological therapies.

In a meta-analysis, six trials that 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[199]. 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[200]. In addition, a small retrospective study of patients with acute uncomplicated diverticulitis found that mesalazine led to faster recovery[201].

In a proof-of-concept study[202], 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[203]. Due to the intrinsic limitations of both studies, the current evidence favoring rifaximin use is low. An international, multicenter RCT[204] with a new rifaximin formulation (extended

intestinal release) for secondary prevention of acute diverticulitis is ongoing and 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)[205]. Furthermore, the normalization of the CRP levels **[Au:OK?]** was faster with the combined treatment[205]. Although rifaximin use can be considered promising, the AGA guidelines do not consider the available evidence to be sufficient to recommend the use of rifaximin for the secondary prevention of diverticulitis[183].

A 2012 systematic review concluded that the evidence on medical therapy to prevent recurrent diverticulitis is poor[206]. 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 **[Au: do you mean for treating recurrent diverticular disease?]**is currently approved in North America or Europe.

[H3] Surgery.

Surgery is also considered on an elective basis for patients with recurrent, uncomplicated diverticulitis. In the past, surgery was recommended after 2 occurrences and potentially sooner in younger (<50 years of age) patients[207]. However, accumulating data on the natural history of the disease have led to the abandonment of this recommendationas most complications (except fistulas and obstruction) occur during the first or second episode and emergency surgery **[Au: do you mean elective surgery?]** is rarely needed in recurrent disease[19]. As a consequence, several reviews[208–210] concluded that there is no evidence to support the practice of elective surgery after two attacks of diverticulitis.

Morbidity is common after elective resection (10–15%) and surgery does not eliminate risk of diverticulitis recurrence[211]. **[Au: unfortunately, we can't include the meta-**

analysis figure you suggested because this would require re-engagement of the referees to check the methodology and we are too tight for time to accommodate this. Additionally, publication of this analysis here would preclude your ability to publish the full analysis elsewhere, which I assume is your aim. Overall, the message is clear and supported by the AGA technical review cited here, so readers of the Primer will have sufficient information on this point.] Recurrence rate in patients with persistent diverticulitis **[Au: chronic? Or is it complicated diverticulitis?]**is likely to be higher. In the DIRECT trial[163], 11% of surgically-treated patients had anastomotic leakage and 15% of surgically-treated patients required reintervention at 5-year follow-up. However, conservative management (pharmacological treatment combined with dietary and lifestyle changes) resulted in more re-admissions because of recurrence than surgery **[Au: Ref?]**. Both short-term and long-term outcomes of the DIRECT Trial[163,212] 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 basistaking 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[19].

Notably, in the setting of acute diverticulitis (excluding patients with generalized peritonitis **[Au: what do you mean by generalized?]**, which does represent a surgical emergency), medical and surgical treatments have not been directly compared in RCTs. In the absence of clear evidence in favor of surgery (which is invasive and not devoid of morbidity and mortality), it is reasonable to favor (whenever possible) conservative medical therapy in most patients[211,213]. **[Au: removed statement on discussion with patient to avoid repetition, ok?]**

[H1] 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[214]. 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[1,36], studies assessing the effect of diverticular disease on the quality of life are surprisingly rare (**[Au: My suggestion is to remove table 2 as everything in the table has been described in detailed in the main text. So I removed the callout]**. 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[116,117]. In addition, both during and after bouts of acute diverticulitis, patients with SUDD **[Au: This statement implies bouts of diverticulitis in SUDD patients. Do you mean bouts of symptoms?]** attributed a wide range of negative psychological, social, and physical symptoms to their condition, which impaired their quality of life[215]..

In a 2003 study[216] involving 50 patients with SUDD and 50 healthy individuals, personal interview and the IBD quality of life questionnaire[216] 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 (P<0.003) in all aspects, with lowest scores for systemic and gastrointestinal symptoms than healthy individualsdemonstrating that diverticular disease negatively affected patients' quality of life **[Au: edited for brevity]**. An Italian study involving 58 patients with SUDD[130]employed the 36-question short form (SF-36) questionnaire[217], 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 general Italian population and 6 months of treatment with

rifaximin or mesalazine improved all quality of life measures. **[Au: deleted summary statement for brevity]**

The diverticulitis quality of life (DV-QOL), a disease targeted questionnaire[215] developedbased on a cross–sectional validation study involving 197 patients with SUDD, contains 17 items **[Au: questions?]**addressing four major disease-specific aspects—physical symptoms, concerns, emotions and behavioural change **[Au: do you mean habitual changes?]**. The study concluded that the range of symptoms in patients with SUDD adversely affected their physical, psychological and social well-being, which can be effectively monitored using the DV-QOL.

A long-term extension of the DIABOLO trial[218] assessed the effect of persistent symptoms on HRQOL using the visual analog scale (VAS) score from the EuroQol 5D (EQ5D) survey, a general HRQOL questionnaire[219], the SF-36 survey[217] 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[219]. At 2-year follow-up, 32–38% of patients reported that persistent symptoms negatively affected the quality of life **[Au: Ref?]**. The quality of life was not different between patients treated with antibiotics for acute diverticulitis and the observation group.

Finally, two studies, one in Britain **[Au: do you mean England and Wales, or the UK?]** and one in Germany, revealed higher rates of anxiety and depression in patients with diverticular disease than in healthy individuals[220,221]. **[Au: removed summary for brevity and to avoid repetition.]**

[H1] Outlook

Optimal management of diverticular disease requires defined prognostic factors, which can be clinical, laboratory or instrumental measurements (Figure 8). Knowledge on prognostic factors will be crucial in predicting the main complication of the disease, namely acute diverticulitis **[Au:OK?]**. **[Au: merged paragraphs]** **[Au: removed**

epidemiology data on progression of diverticulosis to diverticulitis to avoid repetition] 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 that contain diverticula) are at higher risk of developing acute diverticulitis[153,196]. **[Au: merged paragraphs]** Prognostic factors for recurrence of acute diverticulitis are also important. **[Au: moved statement on recurrence to secondary prevention]** 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)[194] 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[36], although additional studies are needed to identify the ideal cut-off for faecal calprotectin for identifying active inflammation in these patients. In addition, persistent endoscopic and histological inflammation following acute diverticulitis[40] are well established prognostic factors for recurrence of acute diverticulitis.

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 (Figure 5), based on colonoscopy became available only in 2015, which is surprising, given the high frequency of incidental detection of diverticulosis during routine colonoscopy **[Au: removed prevalence data to avoid repetition]**. **[Au: moved information on diverticula classification to the Diagnosis section, ok?]** The DICA classification will potentially **[Au:OK?]**be an important tool for providing a personalized approach in patients with diverticular disease, in particular in preventing acute diverticulitis occurrence and/or recurrence[124]. The first retrospective study evaluating this tool found that treatment was not able to influence **[Au: is this what you meant?]**the outcomes in patients with either DICA1 or DICA3 in terms of acute diverticulitis occurrence and/or recurrence: this means that patients classified DICA1 are at lower risk of acute diverticulitis and patients classified DICA3 are at higher risk of

acute diverticulitis despite a scheduled treatment during the follow-up. Conversely, only patients classified as DICA2 benefitted from a scheduled treatment during the follow-up, being at lower risk of acute diverticulitis occurrence or recurrence compared with those not receiving any treatment during follow-up[125]. As medical treatments did not show significant advantagein preventing acute diverticulitis occurrence or recurrence, or preventing need for surgical intervention in patients classified as DICA1 and DICA3**[Au: edits ok?]**, targeting medical treatments only to those classified under DICA2 might save considerable economic resources that could be directed to other purposes**[Au: rephrased it to a theory as it is not proved, ok?]**. In this regard, a study estimated that in Italy, adopting such DICA-driven approach to manage diverticular disease would save >475 million euros per year[222].

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'[37,38], SUDD is a distinct disease entity with clearly defined clinical characteristics, mainly specific characteristics of the abdominal pain[223]. Consequently, patients with diverticulosis who have symptoms resembling those having IBS should be diagnosed as having 'IBS-like diverticulosis'[224] **[Au: is this an established classification?]**. Although other characteristics of patients with SUDD such as increased faecal calprotectin, presence of low-grade mucosal inflammation and increased levels of some pro-inflammatory cytokines[224]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 **[Au:OK?]**. Although some pathophysiological mechanisms that trigger the occurrence of symptoms (such as environmental factors, colonic dysmotility and visceral hypersensitivity) have been well-studied, understanding of 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

reported lower levels of *A. muciniphila* in patients with SUDD than in healthy individuals[51], whereas another study reported the opposite[53]. Interestingly, an increased abundance of *A. muciniphila* was observed in older individuals compared with younger individuals[225], an observation which overlaps with the general population **[Au: is this what you meant?]**. Furthermore, a pilot study found that treatment resulted in a lower abundance of *A. muciniphila*, which was restored to pre-treatment levels within 60 days after stopping treatment[226]. These changes in *A. muciniphila* abundance correlate with abdominal pain in the left lower quadrant and with the faecal metabolome[226].

Current studies concerning both faecal and mucosa-associated microbiota in diverticular disease do not allow drawing definite conclusions on the precise alterations (if any) of intestinal microecology associated with the disease. Many studies present drawbacks and limitations including reduced sample size, not having a well-defined inclusion criteria, different patient populations and the methodology adopted. Results across different studies are not always consistent and sometimes actually conflicting[129,227]. Asymptomatic diverticulosis does not seem to be associated with substantial changes of 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[129,227].

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 involved the hippurate and kynurenine pathways, and six urinary biomarkers provided diagnostic value to distinguish patients with SUDD from healthy individuals[51]. The fecal 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 provided discriminatory value for distinguishing between patients with SUDD and healthy individuals[228]. Metabolomic

signatures will likely represent a key aspect for the future characterization of different phenotypes of diverticular disease.

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[Au: for Table 1 to be even more useful, I suggest adding a 'recommendations for prevention' column that translates these risk to potential prevention recommendations]

Table 1. Modifiable factors associated with incident diverticulitis.

Risk factor	Category[a]	RR or OR (95% CI)[b]	Recommendation for prevention [Au: Please consider adding potential recommendations for prevention. See first example below]
Diet			
Fibre	Highest quintile	0.59 (0.46–0.78)	Increase dietary fibre
Nuts	>2 times/week	0.80 (0.63–1.01)	
Popcorn	>2 times/week	0.72 (0.56–0.92)	
Vegetarian diet	Yes/no	0.69 (0.55–0.86)	
Western dietary pattern	Highest quintile	1.55 (1.20–1.99)	
Red meat	Highest quintile	1.58 (1.19–2.11)	
Lifestyle			
Physical activity	Highest quintile	0.75 (0.58–0.95)	
BMI	BMI ≥30 kg/m^2	1.78 (1.08–2.94)	
Waist-to-hip ratio	Highest quintile	1.62 (1.23–2.14)	
Smoking	Current or ≥15 cigarettes/day	1.56 (1.42–1.72)	
Medication			
Non-aspirin NSAIDs	≥2 times/week	1.72 (1.40–2.11)	
Aspirin	Ever or ≥2 times/week	1.25 (1.05–1.47)	
All NSAIDs	≥2 times/week	1.65 (1.36–2.01)	
Corticosteroids	Current use	2.74 (1.63–4.61)	
Opiate analgesics	Current use	2.16 (1.55–3.01)	
Postmenopausal hormones	Past use	1.35 (1.25–1.45)[c]	

Effect estimates are from select large population-based cohort or case–controls studies (modified to from Ref#17). OR, odds ratio; RR, relative risk
[a]Highest category when compared with lowest category.

[b]Adjusted for potential confounders. [c]Data from Ref 18.

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[Au: As all the information mentioned in the table is included and described in detail in the main text, my suggestion is to remove this table to avoid unnecessary repetition.]

Figure legends

[Au: Figure legends must be ~200 words, otherwise they won't fit in the in house style layout. I have provided some suggestions for shortening the text. Could you please work on this further?]

Figure 1. Diverticulosis and diverticular disease. **[Au: moved statement on incident diverticulosis to the Epidemiology section for brevity, ok?] [Au: For all histological images provided below, would it be possible for you to provide images of similar maginification as it will make comparison between similar structures easy for readers and to better understand the distintion between conditions?]** **a|** Diverticulosis can occur in any part of the colon . However, in western countries it generally occurs in the left (descending) colon **[Au:OK?]**involving the mucosa and submucosa, whereas in eastern countries protrusion generally occurs in the right colon (ascending)involving all colonic layers **[Au: edited for brevity]**. 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 **[Au: for consistency, ok?]** might also occur and is more commonly observed in eastern than in western populations. **b|**SUDD is characterized by 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). Magnification 40×. **c|** Sometimes patients have persisting abdominal pain following acute diverticulitis, a clinical situation called SUDD post-acute diverticulitis. **[Au: I adopted this terminology from the rebuttal as this was the terminology that you mentioned is now being accepted in the community, ok? Please revert my changes if you disagree]** 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). Magnification 10×. **d |** Diverticular inflammation in acute diverticulitis can be observed at endoscopy (left panel) **[Au: could you please explicitly indicate the inflammation in the endoscopic image with an arrow head for the readers easy understanding?]**, and acute and chronic inflammatory infiltrate, as well as cryptitis (thick white arrow; right panel) by histology. Magnification 100×. All histological images are haematoxylin and eosin staining of paraffin-fixed samples **[Au:OK?]**. Histological images provided by C. D. Inchingolo (Andria, Italy) and M. Walker (Newcastle, Australia).

Figure 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 lead 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 hemorrhage **[Au: for consistency, ok?]** occurs at sites of asymmetrical vascular thickening. Risk factors for vascular injury such as obesity and hypertension and luminal trauma contribute to bleeding

Figure 3. Cross–sectional imaging of diverticulosis and diverticular disease. [Au: edited to fit our in house style]Colonic diverticulosis can be clearly visualized using ultrasonography (panel **a**), CT (panel **b**) and MRI (panel **c**). Absence pericolonic involvement (thickening of the diverticular wall) is indicative of a lack of inflammation (white arrow; panel **a [Au: could you please also indicate the areas of lack of inflammation in panel b and c?]** Ultrasonography can also very useful in detecting acute inflammation of diverticula with complications, such as the occurrence of abscesses

(white arrow; panel d). CT can reveal thickening of diverticular wall with inflammation of the pericolonic fat (the so-called fat stranding)(white arrow, panel e) MRI canshow diverticular inflammation (thin white arrow, panel f). In this image, acute diverticulitis is detected in the right colon **[Au: is this what you meant?]**. **[Au: since we don't discuss computerized tomography colonography in the main text and since it is not majorly used for diagnostic purposes, my suggestion is to remove images in panel g and h.]** Images in panel a was provided by G. Makoni (Milan, Italy); images in panel b and c were provided by M. Majorna (Andria, Italy); image in panel d was provided by D. Lisa (Rome, Italy) and panel e was provided by N. Flor (Milan, Italy).

Figure 4. Clinical presentations of acute diverticulitis [Au:OK?]. [Au: Please include a description of the perforations that are shown in this image. This figure legend should include a mention the Hinchey system and name the stages and explain the features. My suggestion is also to remove the endoscopic images from this Hinchey classification figure to avoid repetition as the DICA image shows all the endoscopic features]

The clinical presentation of diverticulitis, in which diverticula become inflamed or infected, depends on the location of the affected diverticulum, the severity of the inflammatory process, and the presence of complications. **[Au: deleted sentence on CT in diagnosis as it is not represented in the figure, ok?]**Colonic diverticula have narrow necks that can be easily obstructed by fecal matter. Obstruction of the neck initiates a cascade of events that might lead to distention of the sac, bacterial overgrowth, vascular compromise, and perforation. Most perforations are localized and contained, so that uncomplicated diverticulitis is present as 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 fecal peritonitis. Fistulas and obstruction might suddenly develop during an episode of diverticulitis or can be a late complication. Diverticular haemorrhage, however, represents a non-infective complication.

Figure 5. The DICA e classification system. The Diverticular Inflammation and Complication Assessment (DICA) classification is the first endoscopic classification developed specifically to describe objectively the presence of diverticulosis in the colon **[Au: is this what you meant?]** and signs of current or past diverticular inflammation. This classification consists of four main colonic characteristics (the location **[Au: as mentioned in the figure, ok?]** of diverticulosis, the number of diverticula in each colonic segment **[Au:OK?]**, the presence or absence of inflammation, and the presence or absence of complications). Subfeatures 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 **[Au: The image also mentions SCAD and this information and its description should be included here.]**), 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: DICA1, DICA 2, and DICA 3. **[Au: removed results of retrospective studies to avoid redundancy.]**

Figure 6. Algorithm for the management of acute uncomplicated diverticulitis. [Au: as the figure abbreviates to AUD, ok?]

The clinical suspicion of acute diverticulitis needs to be confirmed by imaging (US 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, normal WBC and low PCR (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 **[Au: do you mean immunocompetency?]**and the availability of outpatient support need to be taken into account. Outpatients should be treated with a clear liquid diet **[Au: do you mean complete liquid diet?]**and antimicrobials should only be given in selected cases. For patients needing admission, intravenous fluids and intravenous antimicrobials should be

administered. In both low-risk and high-risk patients, improvement of symptoms is expected within 2–3 daysand then, normal diet can be resumed. If improvement continues, patients might be discharged to complete a 7–10 days 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. **[Au: If this image was adapted or reproduced from elsewhere, please cite the reference.]**

Figure 7. Management of acute complicated diverticulitis. [Au:OK?]

[Au: I have edited the flowchart to include only management of complicated diverticulitis. Could you please expand the legend to describe the figure?] Evaluation and treatment approach of complicated disease depends on the severity of presentation, presence of complications (peritonitis, abscess), and comorbid conditions. **[Au: Please expand the legend slightly.]**

[a]Recommended by current guidelines, but some evidence to suggest good outcomes without resection in selected patients **[Au: If this image was adapted or reproduced from elsewhere, please cite the reference.]**

[Au: As mentioned earlier in the main text, we have removed the original Figure 7.]

Figure 8. Current and future predictors of outcome in diverticular disease. Predictors of outcome in diverticular disease have been identified, including family history, imaging characteristics (such as length of the involved colon, or retroperitoneal abscesses) and laboratory parameters (raised fecal calprotectin during the follow up). Future predictors include endoscopic characteristics of the affected according to the Diverticular Inflammation and Complication Assessment (DICA) classification. Other future predictors, which need further studies to confirm the preliminary results, are the

identification of changes in the colonic microbiota and in the faecal and urinary metabolomes **[Au: or microbial diversity?]** in patients with diverticular disease. These predictors will help to identify patients with diverticulosis who will develop diverticular disease.

Highlighted references [Au: I have included the highlighted references here and edited for in house style. I will add them in the library after in the final version of the bibliography]

8) Yamamichi, N. et al. Trend and risk factors of diverticulosis in Japan: age, gender, and lifestyle/metabolic-related factors may cooperatively affect on the colorectal diverticula formation. *PLoS One* **10**: e0123688 (2015)

This study assesses the characteristics and the risk factors for diverticulosis in a far east nation.

11) Shahedi, K. et al. Long-term risk of acute diverticulitis among patients with incidental diverticulosis found during colonoscopy. *Clin Gastroenterol Hepatol* **11**: 1609-1613 (2013)

This is a long-term study showing that the risk of acute diverticulitis occurrence in incidental diverticulosis is lower than expected.

16) Hjern, F., Johansson, C., Mellgren, A., Baxter, N.N. & Hjern A. Diverticular disease and migration--the influence of acculturation to a Western lifestyle on diverticular disease. *Aliment Pharmacol Ther* **23**: 797-805 (2006)

This paper is an epidemiological study assessing the role of changing lifestyle on the risk of diverticular disease occurrence.

19) Crowe, F.L., Appleby, P.N., Allen, N.E. & Key, T.J. Diet and risk of diverticular disease in Oxford cohort of European Prospective Investigation into Cancer and Nutrition (EPIC): prospective study of British vegetarians and non-vegetarians. *BMJ* **343**: d4131 (2011)

This paper is a large study that found fibre was a significant predictive factor for occurrence of diverticular disease.

46) Daniels, L. et al. Fecal microbiome analysis as a diagnostic test for diverticulitis. *Eur J Clin Microbiol Infect Dis* **33**, 1927-1936 (2014)

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51) Kvasnovsky, C.L. et al. Clinical and symptom scores are significantly correlated with fecal microbiota features in patients with symptomatic uncomplicated diverticular disease: a pilot study. *Eur J Gastroenterol Hepatol* **30**, 107-112 (2018)

This is the first study that found that changes in microbiota features are linked to symptom's expression in SUDD patients.

76) Schafmayer, C. et al. Genome-wide association analysis of diverticular disease points towards neuromuscular, connective tissue and epithelial pathomechanisms. *Gut* **68**, 854-865 (2019)

This is a large study assessing the role of several genes coding for neuromuscular, connective tissue and epithelial functions in predisposing to the occurrence of diverticular disease.

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This paper is a clinical study showing how clinical characteristics, together with faecal calprotectin expression, might be useful in differentiating SUDD from IBS.

144) Papi, C., Ciaco, A., Koch, M. & Capurso. L. Efficacy of rifaximin in the treatment of symptomatic diverticular disease of the colon. A multicentre double-blind placebo-controlled trial. *Aliment Pharmacol Ther* **9**, 33-39 (1995)

This paper is a controlled double-blind study showing the efficacy and safety of cyclic treatment with rifaximin versus placebo in controlling symptoms in SUDD.

165) Tursi, A. et al. Randomised cinical trial: mesalazine and/or probiotics in maintaining remission of symptomatic uncomplicated diverticular disease – a double-blind, randomised, placebo-controlled study. *Aliment Pharmacol Ther* **38**, 741-751 (2013)

This study is a controlled double-blind study showing the efficacy and safety of cyclic treatment with mesalazine, with or without probiotics, versus placebo in controlling symptoms in SUDD and in preventing acute diverticulitis occurrence in patients with SUDD.

205) Spiegel, B.M. et al. Development and validation of a disease-targeted quality of life instrument for chronic diverticular disease: the DV-QOL. *Qual Life Res* **24**, 163-179 (2015)

Con formato: Español (España)

Con formato: Español (España)

This is the first study that developed and validated a specific quality of questionnaire for diverticular disease.

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This paper demonstrated the influence of the current SUDD treatments on faecal microbiota and on urinary and faecal metabolome.

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