



REVIEW ARTICLE

German guideline diverticular disease/diverticulitis

Part I: Methods, pathogenesis, epidemiology, clinical characteristics (definitions), natural course, diagnosis and classification

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Abstract

Diverticulosis and diverticular disease are ranked among the most common gastroenterological diseases and conditions. While for many years diverticulitis was found to be mainly an event occurring in the elder population, more recent work in epidemiology demonstrates increasing frequency in younger subjects. In addition, there is a noticeable trend towards more complicated disease. This may explain the significant increase in hospitalisations observed in recent years. It is not a surprise that the number of scientific studies addressing the clinical and socioeconomic consequences in the field is increasing. As a result, diagnosis and conservative as well as surgical management have changed in recent years. Diverticulosis, diverticular disease and diverticulitis are a complex entity and apparently an

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interdisciplinary challenge. To meet these considerations the German Societies for Gastroenterology and Visceral Surgery decided to create joint guidelines addressing all aspects in a truly interdisciplinary fashion. The aim of the guideline is to summarise and to evaluate the current state of knowledge on diverticulosis and diverticular disease and to develop statements as well as recommendations to all physicians involved in the management of patients with diverticular disease.

KEYWORDS

colon, diagnosis, diverticular disease, diverticulitis, treatment

CHAPTER 1: INTRODUCTION AND METHODOLOGY

Background

Diverticulosis and diverticular disease are ranked among the most common gastroenterological diseases and conditions. In Germany, one in every two to three individuals will develop diverticula at some point during their lifetime. Moreover, there is a noticeable trend towards increasingly complicated disease. As a result, a significant increase in hospitalisations has been observed in Germany in recent years.¹

Several pivotal trials have been conducted focussing on surgical indications and complications. Diverticular disease prophylaxis is described in detail, with specific dietary recommendations and suggestions for lifestyle modifications in those affected. These are derived not only from large cohort studies, but also from insights into the disease pathogenesis. Another focus, a subject of intense discussion, is symptomatic uncomplicated diverticular disease, which is characterised by pain related to the affected bowel segment without visual morphological or laboratory evidence of diverticulitis.

Objectives of the guideline

The aim of the guideline is to summarise and evaluate the current state of knowledge on diverticular disease and to develop statements as well as recommendations to all physicians involved in the diagnosis and therapy of patients with diverticular disease.

Organisational procedure of the consensus process

All procedures, working groups and participants of the guideline are described in detail in 'Supplemental methods'.

Evidence evaluation

The literature evaluation was conducted on the basis of the 2011 Oxford Centre for Evidence-Based Medicine Levels of Evidence for interventional, diagnostic and prognostic studies.² Experts from the respective Working Groups (WGs) assessed the methodological

quality of each study according to checklists, using the 'Critical Appraisal Tools' of the Oxford CEBM³ or, in the case of non-randomised (cohort and case-control) studies, the Newcastle-Ottawa Scale.⁴

Recommendations

The recommendations and background information were drafted by the WG leaders based on the evidence, and adopted within the individual WGs by means of an e-mail circulation procedure. The grading of the recommendations was based on the formulation should, should, can (Table 1).

All recommendations were voted upon according to a Delphi procedure by all guideline participants using a 3-option decision scale (yes, abstention, no). In the second Delphi vote, all but 9 recommendations received 95% approval. The remaining recommendations also achieved a high level of agreement, at over 90%. In consultation with the Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (Working Group of the Scientific Medical Societies in Germany), it was decided to forego a consensus conference (SARS CoV-2 pandemic). The strength of consensus was defined as set out in Table 2. Following the second Delphi vote, the comments underwent final revision by the WGs and the guideline was editorially compiled by the coordinators.

TABLE 1 Grading scheme for recommendations

Recommendation grade	Description	Syntax
A	Strong recommendation	Should
B	Recommendation	Should
0	Open	Can

TABLE 2 Classification of degrees of consensus

Consensus	% Approval
Strong consensus	>95
Consensus	>75-95
Majority approval	>50-75
No consensus	≤50

Statements

“Statements” are explanations or observations regarding specific facts or questions without an immediate call for action. The statements have been adopted as part of a formal consensus procedure in accordance with that used for the recommendations, and can be based either on study results or on expert opinions.

CHAPTER 2: ANATOMY, PATHOLOGY, PATHOGENESIS, RISK FACTORS, COMORBIDITIES

Statement 2.1 Expert consensus, strong consensus
Colonic diverticula are acquired protruberances of the mucosa and submucosa through hiatal weak points in the muscle of the colon wall.

Statement 2.2 Expert consensus, strong consensus
Pathologically, diverticulitis is characterised by an inflammatory process that originates from colonic diverticula (peridiverticulitis) and spreads to the intestinal wall (focal pericolitis). This inflammation can result in severe complications (abscess and/or fistula formation, covert perforation, overt perforation with peritonitis, stenosis, diverticulitic tumour). Colonic diverticular haemorrhage is a further complication of diverticular disease.

Statement 2.3 Expert consensus, strong consensus
A thickening of the muscles of the bowel wall is often found in diverticulosis and diverticular disease.

Statement 2.4 Expert consensus, strong consensus
There are indications that diverticulosis and diverticular disease are associated with changes in the content, composition and linkage of connective tissue fibres and a faulty metabolism of the connective tissue matrix.

Statement 2.5 Expert consensus, strong consensus
There is evidence that diverticulosis and diverticular disease are accompanied by enteric neuropathy, which is characterised by structural changes in the enteric nervous system and disturbances

(Continued)

of the enteric neurotransmitter system.

Statement 2.6 Expert consensus, strong consensus
Congruent with the neuropathic and myopathic changes in the bowel wall, at least a proportion of patients with diverticulosis and diverticular disease show disturbances in colonic motility and sensitivity.

Statement 2.7 Expert consensus, strong consensus
The prevalence of diverticulosis or diverticular disease increases sharply with age. However, the incidence is currently increasing more rapidly in younger age groups.

Statement 2.8 Expert consensus, strong consensus
Alongside environmental factors, genetic predisposition also plays an important role in the development of diverticulosis and diverticulitis.

Statement 2.9 Expert consensus, strong consensus
The intestinal microbiome does not seem to be involved in the development of diverticula. It could, however, represent a pathogenic cofactor in the progression to diverticular disease.

Statement 2.10 Expert consensus, strong consensus
It is currently unknown whether mucosal/subclinical inflammation (low grade inflammation) plays a pathogenic role in diverticulosis or whether it can develop into diverticulitis.

Statement 2.11 Expert consensus, strong consensus
The development of diverticula and the course of diverticular disease are determined by non-influenceable pathogenetic factors and by influenceable risk factors.

Recommendation 2.12 Expert consensus, strong recommendation, strong consensus
Comorbidities should be taken into account in diagnostic and therapeutic decision-making due to associated risks for diverticulosis and diverticular disease/diverticulitis.

All statements and recommendations are commented in supplemental material.

CHAPTER 3: CLINICAL CHARACTERISTICS (DEFINITIONS), NATURAL DISEASE COURSE, COMPLICATIONS, EPIDEMIOLOGY

Definitions

Statement 3.1.1 Evidence level 1, consensus
 “Diverticular disease” of the colon is present when symptoms, inflammation and/or complications arise in patients with existing diverticulosis.

Statement 3.1.2 Evidence level 1, strong consensus
 Diverticulitis is the inflammation of diverticula. Acute “diverticulitis” occurs when the pseudodiverticula and adjacent structures become inflamed. Acute, complicated diverticulitis describes diverticulitis accompanied by a perforation, fistula, and/or abscess.

Statement 3.1.3 Evidence level 1, strong consensus
 Chronic diverticulitis is characterised by recurrent or persistent flares of inflammation, as a result of which complications (stenosis, fistulas) can occur.

Statement 3.1.4 Evidence level 1, consensus
 Symptomatic uncomplicated diverticular disease (SUDD) is characterised by pain related to the diverticulum-bearing segment.

All Statements commented in supplemental material.

Epidemiology

Statement 3.2.1 Evidence level 1, strong consensus
 The prevalence of diverticulosis in the general population of western industrialised nations is high, especially among older adults.

Statement 3.2.2 Evidence level 1, strong consensus
 The rate of hospitalisation due to diverticular disease (diverticulitis, bleeding) increases with age. In the western industrialised nations, the hospitalisation rate has noticeably increased over the past few decades.

Statement 3.2.3 Evidence level 4, strong consensus
 Right-sided diverticulosis differs from left-sided diverticulosis in terms of geographical distribution, clinical symptoms and disease course.

Statement 3.2.4 Evidence level 2, strong consensus
 After acute diverticulitis, quality of life can be impaired.

All statements commented in supplemental material.

Disease course/risk of recurrence/

Statement 3.3.1 Evidence level 1, strong consensus
 The majority of diverticulitis flares are mild and can be treated conservatively and on an outpatient basis. The recurrence rate after acute diverticulitis depends on the severity of the initial diverticulitis, whereby the relapse is no more severe than the initial diverticulitis.

Statement 3.3.2 Evidence level 1, strong consensus
 Increased complication rates during relapse after initial acute diverticulitis are associated with younger age, multimorbidity, and immunosuppression or complicated initial diverticulitis, especially abscess formation.

All statements are commented in supplemental material.

Mortality

Statement 3.3.3
 Complicated acute diverticulitis is associated with considerable mortality. Patients under immunosuppressive therapy are particularly at risk.
 Evidence level 3, strong consensus

Statement 3.3.4
 The lethality of acute diverticular haemorrhage depends primarily on comorbidity. Haemorrhage is usually not the cause of death.
 Evidence level 3, strong consensus

Comment on both statements

Data on mortality from diverticulitis are very heterogeneous and of relatively poor quality. Complicated diverticulitis, in particular, has a relevant mortality rate. This increases with age and the extent of comorbidity.^{5,6} In addition, the presence of ascites in patients with liver cirrhosis is associated with increased perioperative mortality.⁷ Immunosuppression represents a special situation in which steroid therapy, especially, increases the rate of postoperative complications.⁸⁻¹¹ Similarly, in diverticular haemorrhage, mortality depends to a large extent on comorbidity. In most cases, the cause of death is not the bleeding per se.¹²⁻¹⁷

Associated diseases

Statement 3.4.1 Evidence level 2, strong consensus
 The probability of a diagnosis of adenoma or carcinoma is significantly increased in patients with a history of diverticulitis.

(Continued)

However, there is no conclusive evidence of a heightened risk of colorectal cancer in diverticulosis.

Statement 3.4.2 Evidence level 2,
There is no conclusive evidence for an associ- strong consensus
ation of diverticulosis with the occurrence
of inflammatory bowel disease.

Statement 3.4.3 Evidence level 2,
Diverticulosis can be associated with strong consensus
segmental colitis.

Statement 3.4.4 Evidence level 2,
There is no evidence of an association between strong consensus
mucosal inflammation markers and diver-
ticulosis with clinical symptoms.

All statements commented in supplementary materials.

CHAPTER 4: DIAGNOSIS AND CLASSIFICATION

Background; medical history, basic diagnosis, differential diagnosis

Recommendation 4.1 Evidence level 3,
The medical history contributes recommendation grade A,
fundamentally to the assessment strong consensus
of the disease potential of diver-
ticulosis and should therefore al-
ways be recorded.

Recommendation 4.2 Evidence level 3,
Calprotectin can be used for differ- recommendation grade 0,
ential diagnosis. strong consensus

Recommendation 4.3 Evidence level 2,
If diverticulitis is suspected, a phys- recommendation grade A,
ical examination and laboratory strong consensus
tests including leucocytes,
C-reactive protein and urinary
status should be performed.

Recommendation 4.4 Evidence level 2,
Diverticulitis should be considered as recommendation grade B,
a differential diagnosis of acute strong consensus
abdominal pain even in younger
patients (<40 years of age).

Recommendation 4.5 Expert consensus, strong
Diverticulitis should be considered as recommendation, strong
a differential diagnosis of acute consensus
abdominal pain, even if the local-
isation of the pain is right-sided or
suprapubic.

All recommendations commented in supplemental material.

Ultrasound / CT Imaging

Recommendation 4.6

To confirm the diagnosis of diverticulitis, a cross sectional imaging procedure should be carried out.

Evidence level 1, recommendation grade A, strong consensus

Comment—Recommendation—4.6

Different studies have consistently shown clinical diagnosis (without imaging procedures) of diverticulitis to have a substantial error rate. The studies of Toorenvliet et al.¹⁸ and Laméris et al.¹⁹ reported a sensitivity of 68% and a positive predictive value of 65%, and a sensitivity of 71%, respectively. Laurell et al.²⁰ found a similar sensitivity (64%), despite the already mentioned limitations. Schwerk et al.²¹ report a false positive purely clinical assessment of “highly suspected diverticulitis” in 9/28 cases and 44/68 cases with a less clear clinical suspicion (“possible but equivocal diverticulitis”), as well as a false negative assessment in 9/34 cases (“diverticulitis very unlikely”).

Recommendation 4.7

Ultrasound or computed tomography (CT) should be used as diagnostic procedures upon suspicion of diverticulitis.

Evidence level 1, recommendation grade A, strong consensus

Comment—Recommendation—4.7

Both sectional imaging methods (ultrasound, CT) illuminate the extraluminal structures, enabling a comprehensive differential diagnostic assessment of diverticulitis and related complications.

The colonic barium enema should no longer be used to diagnose diverticulitis.

Special technical preparations are not required for sonography in diverticulitis; in fact, acute diverticulitis is the most easily learnable ultrasound diagnosis of the intestinal tract.

The use of a high-resolution scanner head (>= 5 MHz) ensures optimal resolution with, as a rule, sufficient soundability under well-dosed compression. The advantage of sonography is that imaging can be directly targeted according to the patient's description of the maximum point of pain and the palpation findings, where the diverticulitis and its complications, if applicable, will be localised. The characteristic findings can usually be found at this site; alongside the precisely localisable pressure pain, these include

- (1) the (depending on the extrusion of the causative faecalith²²) variable (i.e., +/- half-moon-shaped gas reflex in the inflamed

- diverticulum) hypoechoic appearance of the inflamed diverticulum, surrounded by
- (2) an echogenic mesenteric cap (pericolonic, inflammatory reaction of the fatty tissue) and
 - (3) a hypoechoic, initially asymmetrical wall thickening (>5 mm) with loss of wall layering, reduced deformability under pressure and constriction of the lumen, and
 - (4) occasionally hypoechoic strands of inflammation²²⁻²⁴

The hypoechoic diverticular protrusion with an echogenic centre has also been referred to as the dome sign (in patients with right-sided diverticulitis).²⁵

The sonographic criteria of an abscess are hypoechoic/anechoic paracolic or intramural foci formation with echogenic reverberation echoes or comet tail artefacts; on the other hand, gas reflexes within hypoechoic band-shaped structures are characteristic of fistulas. Key structures of overt perforation are evidence of free air and free, mixed echogenically reflecting fluids.

Using high-resolution sound frequencies (≥ 7.5 MHz), it is possible to reliably visualise the layers of the intestinal wall, which can be helpful for the differential diagnostic evaluation of diverticulitis. Muscle hypertrophy and elastosis, as well as nutritive vessels that thus run perpendicularly through the sigmoid wall, are regular findings that are prerequisite to (left-sided) diverticula formation. In about 85% of cases, endoscopically verified diverticulosis (without indication of the focus of pain) can be correctly detected sonographically, whereby the number of diverticula detected in ultrasound is always lower than in colonoscopy.²⁶

In acute diverticulitis, at the hands of an experienced examiner, the sensitivity and specificity of abdominal sonography with directed questions and prospective evaluation are each 98%.²¹ Direct visualisation of the inflamed diverticulum is possible with a sensitivity of 96% in uncomplicated acute diverticulitis, but noticeably more difficult in the case of complicated findings (overall sensitivity 77%, specificity 99%).²⁴ Whereas ultrasound is mostly primarily focussed on the (painful) inflamed diverticulum, the detection of an inflamed diverticulum as sole criterion in computed tomography (CT) diagnostics achieves a sensitivity of only 43%.²⁷

An early systematic prospective comparative study from France shows an accuracy of 84% for both sonography and CT; the sensitivity was 85 versus 91%, specificity 84 versus 77%, Positive Predictive Value (PPV) 85 versus 81%, and Negative Predictive Value 84 versus 88%. With regard to other, alternative diagnoses, the sensitivity of CT was higher, at 50% versus 33% (ultrasound), as was also the case for the detection of pericolonic abscesses.²⁷ A retrospective analysis from Spain shows a sensitivity of 86% in operated patients with acute diverticulitis, but 94% sensitivity in all patients with acute diverticulitis. The difference shows that uncomplicated acute diverticulitis, in particular, is a domain of sonography; however, this older study also found that 10 of 34 patients who underwent emergency surgery had false negative ultrasound findings (sensitivity 70%).²⁸

Due to developments in equipment, techniques and thematic know-how standards, both investigations must be regarded as no longer representative.

In a comparative prospective study from Germany with 4 experienced ultrasound examiners and the CT facilities of a university clinic, sonography showed a sensitivity of 100% (CT 98%), while the specificity of both methods was 97%. In cases of extensive diverticulitis and covert perforations, CT showed a clear tendency towards overstaging, whereas sonography showed a somewhat less pronounced tendency towards understaging. Overt perforations or abscesses were not missed by either procedure.²⁹

Like sonography, CT is a practicable and valuable examination where there is suspicion of acute diverticulitis. Both are suitable techniques to visualise the diagnosis and the severity of diverticulitis, to identify important differential diagnoses, and to guide the surgical approach in a stratified manner.

Diagnostic criteria for diverticulitis are the direct detection of inflamed diverticula, thickening of the intestinal wall to over 3 (5) mm and increased contrast medium absorption in CT and MRI (and, where appropriate, in contrast-enhanced ultrasound/CEUS). Indirect signs are perifocal mesenteric injection and free abdominal fluid as an expression of inflammation. Covert or overt perforations or evidence of abscesses detected by any imaging procedure are signs of complicated diverticulitis.

For CT, older studies still using a single-line detector configuration showed sensitivities and specificities of 87%–100% and 90%–100%, respectively.^{27,30-32} The technique was found to be highly suited as a means of determining disease severity and, if necessary, of initiating further surgical consequences.^{33,34} In initially conservatively treated patients, the severity of changes in the CT scan is an indicator of the likely necessity for surgery in the further disease course; however, even in the case of severe CT findings (pericolonic air, abscess), there was no indication for surgery in the majority of patients during the course of disease.³³ Complications such as abscesses and covert or overt perforations can be evaluated by CT with a high degree of certainty.³⁵ Early studies showed CT to be superior to sonography.²⁸ CT-guided, interventional abscess relief can improve patient outcomes prior to surgery.³⁶⁻³⁸

Recommendation 4.8

The technical implementation of CT can be modified depending on the clinical situation. A suitable methodology should be chosen and everything possible undertaken to minimise radiation exposure. Evidence level 2, recommendation grade A, strong consensus

Comment—Recommendation 4.8

Computed tomography is currently performed in most German clinics as an examination with positive intravenous and oral contrast using diluted iodine-containing contrast agents. In addition, for better assessment of the rectum and sigmoid colon, rectal contrast via

enema with a water-soluble contrast agent is recommended. The examination is carried out as a regular abdomen CT in the portal venous phase, with a tube voltage of 100–120 kVp and a tube current of around 120 mAs.

In recent years, studies have been conducted that dispensed with not only intravenous, but also oral and rectal contrasting; in addition, the use of modern multi-line CTs, which employ a low-dose technique with 30 mAs, can achieve the same diagnostic results as regular CT.³⁹ Theoretically, this could reduce radiation exposure from an average of 10 mSv to around 3 mSv, which would broaden the usability of the investigation. A comparison between single-line and multi-line technology in CT has not been conducted. Since studies using the single-line technique already achieved sensitivities and specificities of almost 100%, there is no relevant benefit to be expected from multi-line diagnostics.

As regards technology, therefore, it can be asserted that all modern CTs appear to be adequate and suitable for diagnosis. On the question of contrast, be it intravenous, oral or rectal, there are few publications suggesting that it may be possible to dispense with any type of contrast agent.³⁹ As yet, the evidence level of these few studies is insufficient for general application. Currently, if there are no contraindications, the technique with contrast should be used.

In the older, surgically dominated literature, CT is often the only cross-sectional imaging method that is used. A study from the Netherlands gives cause for critical consideration in this context: The study examined the validity of preoperative CT in all patients ($n = 75$) who underwent emergency surgery for perforated diverticulitis, after having been examined by CT within 24 h prior to the operation. The assessment was carried out retrospectively by two independent radiologists on the basis of the CT data sets, taking no account of the clinical presentation. The accuracy of the CT for different stages of perforation unexpectedly turned out to be only 71%–92% (PPV 45%–89%), and thus considerably lower than generally assumed. In 42% of patients with Hinchey stage 3, the study showed understaging in the CT (Hinchey stage 1 or 2) (indicating that CT has a PPV of only 61% for Hinchey stages 1 and 2).⁴⁰

In a comparable study from Germany, the preoperative CT was compared with intraoperative findings and histology in 204 patients. In patients with Hansen & Stock (HS) stage IIa (phlegmon), correct detection was found in 52% (intraoperative findings) and 56% (histology). Understaging was found in 12 (11%) and overstaging in 36 (33%). The accuracy of staging for abscessing (HS IIb, Hinchey I/II) was 92% (intraoperative findings) and 90% (histology), with understaging in 3% and 0%, respectively, and overstaging in 5 (10%). Overt perforation (HS IIc, Hinchey III/IV) was recorded correctly in 100%, yielding a PPV for CT of 52 (56)%, 92 (90)% and 100 (100)% for HS IIa, HS IIb and HS IIc, respectively.⁴¹ The value of the radiological assessment thus seems to be clearly examiner-dependent in the (important) HS stage IIa/IIb (understaging in the Netherlands, overstaging in Germany). For the preoperative differential diagnosis of phlegmonous diverticulitis (HS IIa) versus perforated diverticulitis (HS IIb/IIc), CT cannot universally be considered the gold standard.

Recommendation 4.9

MRI examinations can be performed on a case-by-case basis, but should not be used for routine diagnosis of diverticulitis
Expert consensus, recommendation, strong consensus

Comment- Recommendation—4.9

The use of MRI to assess colonic diverticulitis is not yet widespread, either in practice or in studies. There are several problems concerning its practical implementation: Severe abdominal pain during the long procedure required for data acquisition often results in motion artefacts. Occasionally, claustrophobia prevents the examination from being adequately conducted. MRI is also associated with higher costs than CT and, in many clinics, MRI is not available around the clock for emergency examinations. What is more, the clinically and therapeutically very important issue of small air pockets around the colon when diagnosing overt or covert perforation is especially difficult to assess with MRI; as a result, its usefulness in complicated diverticulitis is very limited. To date, a systematic evaluation of the limit of detectability of small quantities of abdominal air is lacking in the literature. The technique has only been evaluated in small, usually specially chosen patient collectives.^{42–45} Based on the results of these studies, it can only be concluded that similar results are achievable using MRI with oral or rectal contrast, or with intravenous contrast agent administration, as can be achieved by CT. However, it must be noted that there are no available studies dedicated to complicated diverticulitis or the detection of small pockets of free air in covert perforation.

In the absence of study data, it is not possible to give a definitive recommendation for the technical implementation of MRI in diverticulitis. Currently, analogous to CT imaging, a contrast-enhanced MRI examination with intravenous, oral and rectal contrast should be performed. The protocol should include high-resolution T1 weighted 3D gradient echo sequences as well as T2 sequences to allow assessment of acute inflammatory situations. The question as to whether intraluminal contrast using the dark-lumen technique⁴⁴ or T1 positive contrast can achieve a better differential diagnosis of abscesses⁴³ has not yet been answered in the literature.

Colon MRI for diagnosis of diverticulitis should therefore only be carried out in centres conducting controlled studies and in certain specific cases (e.g., examinations in pregnant women or paediatric patients, for reasons of radiation reduction).

Endoscopy, haemorrhages, interventions, fistulas

Colonoscopy in acute diverticulitis.

Recommendation 4.10

Colonoscopy should not be used to diagnose acute diverticulitis.
Evidence level 2, recommendation grade B, strong consensus

Comment—Recommendation 4.10

Colonoscopy can explain abdominal complaints, is able to detect lower Gastrointestinal (GI) bleeding and to rule out tumours. It is suited for the differentiation between diverticula and mucosal inflammation and polypoid findings or diverticulosis with an atypical or symptomatic course.⁴⁶

Colonoscopy is not required to detect acute diverticulitis⁴⁷; an increased risk of perforation, although unproven, cannot be ruled out.

Endoscopically visible inflammatory changes at the diverticular neck are detected in about 0.8% of colonoscopies without the presence of acute diverticulitis.⁴⁸

Luminal changes are secondary in the pathogenesis of diverticulitis, since the disease begins as a bacterial penetration into the depths of the diverticulum, and crucial complications (phlegmon, microperforation, fistula, abscess) are transmural. If sonography indicates the intestinal wall to be thickened by >11 mm, colonoscopy shows the spontaneous drainage of pus from inflamed diverticula.⁴⁹

Recommendation 4.11

In certain situations (e.g., uncharacteristic clinical picture or disease course), colonoscopy (probably with a slightly increased risk of perforation) can be performed in acute diverticulitis, provided covert perforation and abscesses have been ruled out.

Evidence level 4, recommendation grade 0, strong consensus

Comment—Recommendation—4.11

Due to insufficient data, opinions regarding the safety and importance of colonoscopy differ considerably.

In a series of 54 patients with diverticulitis, perforation occurred during colonoscopy in 1.9%; however, in a further 39 patients in whom covert perforation or abscess had been excluded by CT, no perforations were observed. A total of two CT-negative adenocarcinomas and a bone fragment in the inflamed diverticulum were detected as relevant findings.⁵⁰ The colonoscopies were carried out 4–12 days after hospital admission (median 5.8 days). The rate of total colonoscopies (reaching the caecum or tumour stenosis in 81.7% of cases) was lower than in an elective situation.

In the same clinic, a study was conducted to investigate early (in the hospital stay) versus postponed (after 6 weeks) colonoscopy for CT-confirmed diverticulitis. The authors identified neither perforations, nor any diagnostic gain.⁴⁷ They did, however, recognise a benefit for patients with an atypical disease course who had persistent symptoms after a week of antibiotic therapy or a relapse within 2 months. In this situation (23/224 patients), a therapeutically relevant diagnosis was made by colonoscopy in 4/23 cases (17%): in 3 cases, an adenocarcinoma, and in one case, a chicken bone lodged in a diverticulum, which was successfully endoscopically removed.⁵¹

Statement 4.12

In patients with fully healed conservatively treated diverticulitis (usually after 6–8 weeks), the indication for colonoscopy should be based on clinical and anamnestic factors (protracted disease, persistent symptoms, patient age, imaging).

Evidence level 3, recommendation grade B, strong consensus

Comment—Recommendation—4.12

Until now, colonoscopy has often been recommended (a) in principle after conservatively treated acute diverticulitis and (b) before sigmoid resection. This recommendation is based firstly on the differential diagnosis of other diseases with similar symptoms, and secondly, on coincidence of synchronous carcinoma or adenoma in predominantly older patients.

However, the importance and necessity of colonoscopy has been called into question by several studies in differing healthcare systems, due to the quality of consistent CT diagnostics of diverticulitis (and doubtless also on the grounds of health-economic considerations).

In a retrospective longitudinal study of 205 patients with a CT-guided diagnosis of acute uncomplicated diverticulitis, colonoscopy revealed adenomas in 9.3% of patients, 5.4% of which were advanced neoplasms.⁵² One patient was diagnosed with sigmoid carcinoma and one with Inflammatory Bowel Disease (IBD) (however, these two patients reported symptoms that would in any case have prompted colonoscopy). This rate of adenoma and carcinoma detection is somewhat lower than would be statistically expected based on the evaluation of data from screening colonoscopies.

In 100 patients four to six weeks after hospital treatment for acute diverticulitis (CT-based diagnosis), colonoscopy revealed at least one polyp in 32%, advanced adenoma in only one case and not a single malignancy; therefore, there were only a few (directly) relevant findings in only a small number of cases.⁵³

Though, prognostically, even findings of non-advanced adenoma should generally be considered a relevant pathology of the colon, other investigations allow detection of coincidental colon carcinoma on a larger scale. A widely cited retrospective study from the USA found that 5 out of 73 (7%) patients who underwent surgery for acute diverticulitis at the University Hospital of St. Louis between 1992 and 2001 had a previously undetected colon carcinoma.⁵⁴

In addition, a database analysis from Australia⁵⁵ found a slightly increased rate (2.1%) of colon carcinoma within one year after CT-based diagnosis of left-sided diverticulitis (evaluation of 1088 patients; comparison with the national cancer registry). In 319 patients, colonoscopy was performed within one year after diverticulitis was diagnosed: In nine of these patients, a colon carcinoma was identified (2.8%).

A systematic literature search on the usefulness of colonoscopy with respect to colon carcinoma detection up to 24 weeks after CT diagnosis of diverticulitis identified only 10 studies, with 771 documented patients.⁵⁶ The rate of colorectal cancer was 2.1% (95% Confidence Interval 1.2%–3.2%), and thus well above the expected prevalence (0.68%) in US citizens aged >55 years.

In another meta-analysis⁵⁷ that included 1796 patients after resolution of diverticulitis, the prevalence of carcinoma was 1.6% and the rate of detected polyps 20.2%. A systematic review by Meyer et al.⁵⁸ showed almost identical results, with a 1.9% prevalence of colorectal cancer (polyps 22.7%, advanced adenomas 4.4%, adenomas 14.2%). This review also showed that Colorectal Carcinoma was found significantly more frequently in patients with complicated than with uncomplicated diverticulitis (7.9% vs. 1.3%).

In a prospective, multicentric study,⁵⁹ no differences were observed in the prevalence of carcinoma or adenoma in patients who had had diverticulitis compared with a group undergoing routine screening.

Thus, the recommendation for total colonoscopy in patients >50 years of age with clinically conspicuous diverticular disease who have not undergone colonoscopy <5 years previously equates to a special situation of preventive colonoscopy; that is, colonoscopy is useful, despite reports of discrepant views from other health care systems.

This recommendation also serves to decisively counter the patients' subjective view that ultrasound or CT examination carried out due to the diverticulitis might be sufficient to rule out malignancy or dysplasia.

Indisputably, colonoscopy makes an essential contribution to further diagnostic clarification of CT-detected thickening of the colon wall.^{60,61} Likewise, in the case of bowel stenosis, that is, including patients with recurrent diverticulitis with an indication for surgery, colonoscopy should generally be performed to ascertain the dignity (malignant vs. benign) of the stenosis. Since diverticulitis can also occasionally mask IBD, in patients with persistent pain, blood and/or mucus in the stool and signs of inflammation, it seems appropriate to confirm the diagnosis by colonoscopy, regardless of the patient's age.⁶²

Medical history and clinical findings

Recommendation 4.13

Medical history taking in patients with suspected diverticular haemorrhage should include questioning on the severity of the bleeding, as well as risk factors for prolonged bleeding and recurrent bleeding.

Evidence level 2, recommendation grade A, strong consensus

Recommendation 4.14

In addition to a shock index assessment, the examination should include evaluation of signs of anaemia, cardiovascular risk factors and other comorbidities, as well as abdominal palpation and rectal examination.

Evidence level 2, recommendation grade A, strong consensus

Comment—Recommendation—4.13 and 4.14

Painless lower GI bleeding is predominantly ascribable to arterial diverticular bleeding (35%) and angiodysplasia (21%)⁶³; in elderly patients with diverticula, diverticular bleeding accounts for up to 50% of lower GI bleeding,^{64,65} whereby diverticular bleeding is, however, usually a complication of diverticulosis rather than diverticulitis.

The aims of diagnosis and therapy of arterial diverticular haemorrhage are to clearly localise the source of bleeding, assess its severity and the probability of recurrence, and stop the bleeding - if possible as a definitive therapy, that is, also in respect of subsequent rebleeding.

Details of earlier bleeding severity are based on the patient's (only limitedly reliable) description of the amount of blood. Blood pressure and pulse rate (shock index) indicate the circulatory impact of the bleeding.⁶⁴ Validated scores like those used in upper GI bleeding (Rockall, Glasgow Blatchford) have not been reported. While spontaneous descriptions of the colour of lower GI bleeding are often questionable, a colour comparison chart can be helpful.⁶⁶

Recurrent bleeding is more often found in patients with endoscopically detected active bleeding or evidence of a vascular stump and coagulum-covered bleeding site, as well as those with arterial hypertension (RR 4.2), platelet aggregation inhibition (RR 2.4) or NSAIDs (RR 2.6).⁶⁷

Anticoagulant drugs also constitute a risk for more severe bleeding and rebleeding.⁶⁸

In accordance with the S2k guideline "Gastrointestinal Bleeding",⁶⁹ if diverticular bleeding is suspected, gastroscopy should be performed early to rule out severe upper GI bleeding as the cause of haematochezia.⁶⁴

Recommendation 4.15a

In patients with lower gastrointestinal bleeding with haemodynamic instability, alongside measures to stabilise the circulation and having ruled out anorectal or gastric sources of bleeding (procto-rectoscopy, gastroscopy), a colonoscopy should be performed within 12 h of admission. Bowel cleansing should be shortened and intensified.

Evidence level 2, recommendation grade B, strong consensus

Recommendation 4.15b

In patients who are haemodynamically stable, a colonoscopy should be performed within 12–24 h.

Evidence level 1, recommendation grade A, strong consensus

Comment- Recommendation—4.15a and 4.15b

In the case of acute peranal bleeding, upper GI bleeding must be considered as a differential diagnosis; thus, gastroscopy should be performed as early as possible. If the gastroscopy findings fail to explain the bleeding, a sigmoidoscopy should be carried out in order to rule out an anorectal source of bleeding.

Haematochezia with fresh blood arouses high suspicion of a bleeding source in the lower GI tract. However, peranal passage of

fresh blood can also be a manifestation of heavy upper GI bleeding with a rapid transit time.

Diverticular bleeding is clinically indistinguishable from severe colonic bleeding of other origins; a priori, therefore, the situation is one of lower (i.e., colonic) GI bleeding. In this context, it should be noted that upper and mid-GI bleeding describes bleeding not only from within the gastroscopically visible segment, but also from anywhere within the whole small bowel. Heavy bleeding from the upper and mid-GI tract can mimic lower GI bleeding by causing the passing of brighter-coloured blood. Therefore, alongside colonoscopy, esophagogastroduodenoscopy is also part of the diagnostic concept, and additionally, if no evidence is found of a probable source of bleeding, (capsule) endoscopy of the small bowel (in haemodynamically stable patients) or angiography (in unstable patients).

Since diverticular bleeding stops spontaneously in 90% of cases, early colonoscopy is generally recommended in order to precisely identify the source of bleeding. Early colonoscopy (here, <24 h; OR 8.4), an experienced endoscopist (>1000 colonoscopies; OR 3.0), use of an Endo-Cap (OR 3.4) and use of a water jet rinse (OR 5.8) were proven to be prognostically favourable factors in lower GI bleeding.⁷⁰ Reliable identification of the bleeding source is achieved in 22% of early elective colonoscopies, that is, 7.5 times more frequently than after 24 h ($p < 0.01$) and 22 times more frequently than after 48 h ($p < 0.01$). In addition to the detection and localisation of the bleeding source, however, the application of endoscopic therapy should also be a primary aim.⁷¹ In patients with active haematochezia and diverticula, early colonoscopy (<12 h) with antegrade irrigation allows bleeding diverticula to be identified and interventionally treated in at least 20% of cases.⁷² Therefore, in patients with haemodynamical instability, having ruled out upper GI and anorectal bleeding, it seems necessary to perform colonoscopy after shortened bowel prep (4–6 L polyethylene glycol solution; if required, via a gastric tube over up to 12 h), applying additional cleaning methods such as enemas, and using an endowasher, as required. In stable patients, it is sufficient to use conventional preparation (split dosage) and perform the examination within 12–24 h. The detection rate of certain or probable sources of bleeding decreases over time.

Indication for and techniques of endoscopic haemostasis in diverticular bleeding

Statement 4.16

(Definitive) identifiable diverticular bleeding during colonoscopy is an indication for endoscopic haemostasis.
Expert consensus, strong consensus

Comment—Statement—4.16

The following are considered stigmata of definitive diverticular bleeding:

- (a) endoscopically visible, active bleeding from the diverticulum,
- (b) a blood clot adherent to the diverticulum, and
- (c) a visible vascular stump,^{63,72}

while, on the other hand, diverticular bleeding is considered presumptive if

- (a) fresh blood is found segmentally in the proximity of diverticula during total colonoscopy, or
- (b) in patients with brightly coloured lower GI bleeding, a colonoscopy pinpoints colonic diverticula as the sole source of bleeding and upper GI bleeding (including capsule endoscopy) can be ruled out, or if
- (c) in the multidetector CT, a leakage of contrast medium is clearly attributable to a diverticulum.^{63,72,73}

Poncet et al.⁷⁴ reported spontaneous cessation of bleeding in 92.4% of a population of 133 patients with definitive or probable diverticular haemorrhage (among 1145 patients undergoing colonoscopy due to lower GI bleeding) over a period of 8½ years. An intervention was required in only 10/133 patients, 3 endoscopic, 4 radiological, and 3 surgical; additionally, 4 of the 7 patients initially receiving an endoscopic/radiological intervention required surgery as a secondary measure.

Although, in the light of these data, diverticular haemorrhage may appear prognostically favourable, it must not be trivialised, since there is a considerable tendency for recurrence, risk factors for rebleeding (including age, hypertension, low-dose American Society of Anesthesiologists (ASA), and NSAIDs) are widespread, and emergency surgery without exact localisation of the bleeding is associated with relevant morbidity and mortality.

The current literature, predominantly from Asia, shows that endoscopic band ligation (EBL) is superior to endoscopic clipping in terms of the rebleeding rate (6% vs. 33%; $p = 0.018$), while both procedures achieve an initial haemostasis rate of 100% without complications due to the respective techniques.⁷⁵ In another Japanese multicentre study, the rebleeding rate under EBL was 10%, compared with 31% after endoscopic clipping ($p < 0.01$).⁷⁶ Early rebleeding was shown to emanate mainly from the same diverticulum as the initial bleeding. The main risk factor for earlier recurrence was the localisation of diverticular bleeding in the right colon, a peculiarity in Asia; it is thus unclear whether these results are transferable to the sigmoidal pseudodiverticula that are predominant in Western Europe.

As an alternative to rubber band ligation, the application of a so-called “over-the-scope clip” (OTSC) may be considered. In some case series, this procedure also seems to have a favourable effect on the further course of disease.^{77,78}

Although afflicted with many uncertainties, the questionnaire-based retrospective study of Mizuki et al.⁷⁹ at least suggests that left-sided diverticula are less likely to bleed recurrently than right-sided or bilateral diverticula. The finding of this study, that non-

interventionally treated patients had fewer rebleeding episodes (38.7% vs. 61.5%, $p < 0.05$) than those in the endoscopic intervention arm (clipping or adrenaline injection at the diverticular neck) should not be understood as an indication that the intervention increases the bleeding risk, but rather as an expression of the limitations of such an analysis. The detection of definitive bleeding stigmata was linked to therapeutic intervention, while the absence of a clear source of bleeding was associated with conservative treatment. In addition, no statement was made concerning the severity of bleeding (shock index, transfusions, haematocrit); therefore, despite having similar epidemiological data, the groups do not appear by any means comparable.

In Asia, bilateral diverticula increase the risk of acute diverticular haemorrhage ($p = 0.0021$), as do obesity, arterial hypertension, coronary sclerosis and low-dose ASA.⁸⁰

Indication for radiological or surgical therapy

Recommendation 4.17

In patients with persistent bleeding or clinically relevant rebleeding after initially successful endoscopic haemostasis, endoscopic, surgical, or radiologic-interventional therapy should be performed.

Expert consensus, strong recommendation, strong consensus

Comment—Recommendation—4.17

Today, it is generally accepted that in the therapeutic management of GI bleeding, the possibilities of endoscopic diagnostics and therapy should be first exploited.^{72,81–84} In the case of repeated or persistent bleeding without an endoscopically clearly identifiable source, a CT angiography (or angiography) should be performed for localisation diagnostics during the suspected active bleeding.

Computed tomography angiography and conventional angiography (+/–Digital Subtraction Angiography [DSA]) are valid options for localising diverticular haemorrhage during active bleeding. In practice, however, their use is rarely required. Computed tomography angiography enables reliable localisation of a haemorrhage if bleeding is still sufficiently active at the time of examination.⁸⁵ The same applies to conventional angiography, which offers the additional advantage of possible intervention (haemostasis through arterial embolisation: transcatheter arterial embolisation, TAE).

In a retrospective study, transarterial embolisation was performed in 52 patients with lower GI bleeding. The source of bleeding could only be clearly localised in 32/52 cases. Technical success was reported in 100%; however, there was a 30-day rebleeding rate of 27% and a 30-day mortality of 29%. In two patients, postinterventional intestinal ischaemia occurred.⁸⁶

Thus, the availability of technical equipment and personnel with sufficient expertise are of greater importance in acute severe haemorrhage than in less severe cases; this is particularly relevant when considering whether to transport patients if the appropriate equipment/expertise is lacking. In this situation - although there are no studies to confirm this - experience has shown that if endoscopic

therapy is insufficiently effective, emergency surgery, as an option that is both reliable and well proven, should be given preference.

In a retrospective study, the mortality rate associated with emergency colectomy for diverticular haemorrhage was 17% and the rate of non-fatal complications 20%.⁸⁷

Recommendation 4.18

In patients with recurrent, haemodynamically effective diverticular haemorrhage and a need for lifelong anticoagulation, there may be an indication for elective partial colectomy during the remission interval.

Expert consensus, recommendation open, strong consensus

Comment—Recommendation—4.18

There are no data available from clinical studies for this scenario. The individual decision must be made by the attending physician after detailed discussion with the patient, taking into account the perioperative risk of elective surgery compared with the perioperative risk of emergency surgery in the event of diverticular bleeding that cannot be stopped endoscopically.

Severe, endoscopically not manageable bleeding

Statement 4.19

In the threatening situation of severe active bleeding that cannot be either endoscopically or angiographically located, surgical exploration, possibly with colectomy (dissection at the terminal ileum and in the upper third of the rectum), is justifiable.

Expert consensus, strong consensus

Comment—Statement—4.19

There are no clinical data to show what is the most suitable surgical procedure. If the bleeding cannot be endoscopically and interventionally localised and brought under control, there is a vital indication for urgent surgical therapy. Since these patients are critically ill and often multimorbid, laparotomy should be followed by colectomy, this being the fastest procedure. Whether to perform an anastomosis by means of ileorectostomy, or a discontinuity resection with closure of the anorectal stump and creation of a terminal ileostomy, is an individual decision in which the bleeding activity and intensity (previous transfusions) and the patient's comorbidity must be taken into account. In view of the fact that patients in the emergency situation are predominantly critically ill, discontinuity resection is usually the procedure of choice. In the study by Plummer et al., for instance, anastomotic leak was the most common cause of postoperative mortality.⁸⁷

Likewise, in very rare cases of non-localised recurrent haemorrhage requiring repeated transfusions, subtotal resection can be indicated. If this intervention is performed electively, the choice of

procedure should be made individually, based on the characteristics of the patient and the experience of the surgeon. Studies comparing laparoscopic and conventional resection in this situation are not available.^{88,89}

Recommendation 4.20

If diverticular bleeding is recurrent or not to stop but clearly localisable, segmental resection can be performed.

Expert consensus, recommendation open, strong consensus

Comment—Recommendation 4.20

Few clinical data are available on the extent of surgical resection in patients with localisable diverticular bleeding. In a retrospective study of 42 consecutive patients with diverticular haemorrhage in the years 1993–2000, bleeding was localisable in 6 patients by colonoscopy ($n = 2$) or angiography ($n = 4$). Ten patients were treated by segmental resection and 32 patients underwent colectomy. In 5 of the 10 patients with segmental colon resection, the bleeding was localisable by colonoscopy, whereas this was achieved in only one of the 32 subtotal colectomised patients. The patients who underwent segmental resection were 10 years younger ($65+/-13$ vs. $75+/-12$ years; $p = 0.03$), while there was no difference in the duration of surgery ($208+/-77$ vs. $212+/-58$ min). Intraoperative blood loss was higher for subtotal resection ($578+/-347$ ml) than for segmental resection ($305+/-146$ ml; $p = 0.02$). No difference was found with regard to in-hospital morbidity (20 vs. 19%), mortality (10 vs. 3%), rebleeding (12.5 vs. 0%), stool frequency ($2.4+/-1$ vs. $3.5+/-2$), the Cleveland Clinic incontinence score ($0.6+/-1$ vs. $2+/-3.6$) or patient satisfaction over a mean follow-up period of 4.1 (0.5–7.4) years (p in each case >0.05).⁸⁸ Older studies essentially confirm these results.⁸⁹ Against this background, segmental and total colectomy are justifiable procedures in certain individual cases.

In surgical practice, if the site of the bleeding is clear, segmental colectomy is more frequently performed.

Diagnostic procedures upon suspicion of sigmoidesical or colovaginal fistula

Recommendation 4.21

If there is clinical suspicion of sigmoidesical fistula and the fistula has not already been described morphologically (ultrasound, CT, MRI, colonoscopy), a poppy seed test should be performed.

Evidence level 2, recommendation grade B, strong consensus

Comment - Statement 4.21

Fistulas to the urinary bladder or vagina are a relevant complication of diverticulitis. About 90% of fistulas in diverticulitis involve these two entities, while fistulas to the small bowel, skin, uterus or ovaries,

psoas muscles or hip joints are less common findings.⁹⁰ The vast majority of patients (ca. 85%) with a sigmoidesical fistula are male.

In patients with sigmoidesical fistula, sonography or CT often shows a focal wall thickening of the (filled) bladder; evidence of air in the bladder in this situation confirms the fistula. Affected patients often report the presence of air bubbles in the urine (“champagne urine”) only when questioned; on the other hand, recurrent or therapy-refractory urinary tract infections and dysuria are characteristic and show the diagnostic path forward. No matter which tomographic technique is used, direct fistula detection is only realisable in a certain proportion of cases. If the symptoms are clear (pneumaturia, recurrent urinary tract infection), suspicion of an enterovesical fistula in the cross-sectional imaging is a sufficient indication for sigmoid resection.

While colonoscopy can detect residual inflammatory activity, Crohn's disease as an important differential diagnosis, and stenosis, endoscopic diagnosis of fistulas succeeds only rarely ($<10\%$)⁹⁰. Similarly, detection rates of cystoscopy (10%), cystography (17%), colonic barium contrast imaging (36%), MRI (60%) and CT (61%) are disappointing. Qualitative detection of a fistula is best performed (sensitivity 95%) by the so-called poppy seed test, in which 250 g natural poppy seeds are taken in the evening and the urine is examined for the appearance of poppy seeds over the next 48 h.^{91,92}

The extent to which urological diagnostics are useful or necessary before sigmoid resection and fistula excision must therefore be decided on a case-by-case basis, and is consequently more often determined by local factors.

In another modification, 35 g poppy seeds were consumed in 160 g yoghurt or with 340 ml liquid; here, too, the poppy seed test, with a sensitivity of 100%, was significantly ($p = 0.03$) superior to CT examination (70% sensitivity) – at 8.2% of the cost.⁹³

In principle, the poppy seed test is also suitable for detecting a colovaginal fistula; it is recommended to insert a tampon or cotton wool pad for detection after ingestion of the test substance. In individual cases, colposcopy and vaginal transrectal endosonography can be useful supplementary techniques in addition to sonography and CT; general or comparable information on the respective detection rates of these methods is not available.

Classification

Recommendation 4.22a

The diagnosis of diverticular disease should include a classification. Evidence level 1, recommendation grade A, consensus

Comment—Recommendation 4.22

The Classification of diverticular disease (CDD) allows different degrees of severity and different situations to be categorised. This is useful if it is linked with different diagnostic and/or therapeutic pathways and recommendations, the provision and use of different

measures, and the possibility to improve safety for both patient and physician.

In principle, therefore, a classification should cover all facets of diverticular disease without becoming impractical by being excessively detailed and structurally emphasising rare situations. In addition, it should allow the disease course to be easily and correctly described according to the specific situation.

Statement 4.22b

The guidelines conference continues to recommend the use of the CDD (Table 3), which in this new version takes into account not only the discussions concerning SUDD, but also the practicalities of diagnostics in diverticulitis.

Evidence level 2, consensus

Comment—Recommendation 4.22b

In 2014, the DGVS and DGAV adopted a new classification, the CDD (Table 3), which has since found its way into the literature and clinical practice.⁹⁴

As evidenced by diverse classifications that accommodate national circumstances and take into account not only diagnostics and therapy, but also new aspects of aetiology, pathogenesis and the

nosological understanding of the disease, the classifications of Hinchey (including the modifications by Sher and Wasvary), Ambrosetti and Hansen/Stock (and their modifications by Köhler and Siewert) can now be considered outdated in terms of their practical relevance and/or content.

The scope of the more recent (since 2011) guidelines and classifications, and the relative weighting of different content, is presented in a thorough review by Galetin et al. (2018),⁹⁵ in which the previous S2k guideline of the DGVS/DGAV (2014).⁹⁶

Numerous classifications and modifications describe the various stages of diverticular disease. For current critical reviews, see^{97,98} and.⁹⁵

While Hinchey's classification was primarily aimed at stratifying surgical procedures appropriate to different manifestations of macroscopically perforated diverticulitis with abscess or overt perforation, and has subsequently undergone various modifications, the aim of a CDD and diverticulitis applicable in visceral medicine today must be

- (a) to describe the different forms of diverticular disease, independent of surgery, and
- (b) to enable stratification for different prognoses and therapy forms (outpatient/inpatient; need for antibiotic therapy;

TABLE 3 Classification of diverticular disease (CDD)

Classification of diverticular disease (CDD)		
Type 0	Asymptomatic diverticulosis	
	Incidental finding; asymptomatic	Not a disease
Type 1	Uncomplicated diverticular disease/diverticulitis	
Type 1a	Diverticulitis/diverticular disease without phlegmonous reaction of the surrounding tissue	
	Diverticulum-associable symptoms	
	Signs of inflammation and/or	
	Evidence of inflammation in the imaging (wall thickening, inflamed diverticulum)	
Type 1b	Diverticulitis with phlegmonous reaction of the surrounding tissue	
	Signs of inflammation; phlegmonous diverticulitis (colon wall, mesentery)	
	In the imaging: Possibly with strands of fluid (without air)	
Type 2	Complicated diverticulitis	
Type 2a	Microabscess	Covert perforation, small abscess (≤ 3 cm); minimal paracolic air
Type 2b	Macroabscess	Paracolic or mesocolic abscess (> 3 cm)
Type 2c	Overt perforation	Overt perforation, free air/fluid, generalised peritonitis
Type 2c1	Purulent peritonitis	
Type 2c2	Faecal peritonitis	
Type 3	Chronic diverticular disease	
Type 3a	Persistent/recurrent symptoms associated with diverticulitis (SUDD)	
Type 3b	Recurrent diverticulitis without complications	
Type 3c	Recurrent diverticulitis with complications	(Stenosis, fistula, conglomerate)
Type 4	Diverticular haemorrhage	Evidence of bleeding source

conservative/interventional/surgical) at initial diagnosis and in recurrent disease. It also needs to serve as a basis for adequate case depiction in diagnosis-based remuneration.

Both of these goals are achieved primarily by the Hinchev classification as modified by Wasvary,^{99,100} and by the classification of HS.¹⁰¹ However, the former includes only the different manifestations of diverticulitis with a category of mild clinical diverticulitis (relevant for outpatient treatment), while the classification by HS does not further differentiate perforated disease (micro/macroporforation, abscess size and site).

An advantage of the HS classification was the inclusion of chronic relapsing (recurrent) disease. However, it does not differentiate between chronic recurrent disease without complications (individual indication for elective surgery) and chronic recurrent disease with complications (obligatory indication for surgical therapy). In the Hansen-Stock classification, acute diverticulitis with accompanying phlegmon falls under the category of complicated diverticulitis.

The CDD classification correctly classifies this disease type as uncomplicated, with a good prognosis under conservative therapy. In particular, the sonographic finding of a hyperechoic mesenteric cap as a correlate of peridiverticular changes is found in both stages HS I and HS IIa (without being categorised as complicated diverticulitis). The boundary between HS I and HS IIa is difficult to visualise with CT (or with sonography) and a differentiation between microperforation and macroperforation, which would be desirable, is lacking.

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CONFLICT OF INTEREST

Honoraria for talks AllergoSan, Graz, Austria. Falk, Freiburg, Germany. Ferring Arzneimittel, Kiel, Germany. Nikkiso, Langenhagen, Germany. Consultation and studies Falk Pharma, Freiburg, Germany. Ferring Arzneimittel, Kiel, Germany. No other conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Supplemental materials

Chapter 1 Introduction and Methodology

1.1. – 1.3.1 Background, Objectives of the guideline and period of validity, Organisational procedure of the consensus process, see also the main manuscript

1.3.1. Composition of the guideline group and participation of professional societies

The guideline was steered by the German Society for Gastroenterology, Digestive and Metabolic Diseases (DGVS) in association with the German Society for General and Visceral Surgery (DGAV), who assigned its coordination to Prof. Christoph-Thomas Germer (DGAV), Würzburg, Prof. Wolfgang Kruis (DGVS), Pulheim, and Prof. Ludger Leifeld (DGVS), Hildesheim. Responsible for the methodology were PD Dr. Petra Lynen Jansen and Ms. Pia Lorenz, DGVS Head Office, Berlin. Dr. Susanne Blödt and Dr. Monika Nothacker, of the Working Group of the Scientific Medical Societies in Berlin, Germany (AWMF registration number: 021-20), provided methodological advice. The literature work was supported by the librarial services of Ms. Elisabeth Friedrich-Würstlein. Dr. Nadine Steubesand conducted the systematic research and provided support to the guideline group on methodological issues. Mr. Torsten Karge administered the guideline portal.

The guideline project was announced in the Zeitschrift für Gastroenterologie and on the AWMF website so that other specialist societies/representatives could apply to collaborate. Specialist societies and patient groups relevant to the field were approached and asked to name representatives.

A total of seven working groups (WGs) were formed, each headed by one to three leaders (Table S1).

University and non-university physicians, clinicians and practitioners, gastroenterologists, internists, surgeons, neurogastroenterologists, proctologists, pathologists, radiologists and nutritionists participated in the working groups.

Table S1: Members of the guideline group

WG 1: Anatomy, pathology, pathogenesis, risk factors, comorbidities, pharmacotherapies	WG leading coordinator	W. Kruis, Pulheim (DGVS)
	WG members	H. Allescher, Garmisch-Partenkirchen (DGNM) J. Hampe, Dresden (DGVS) J. Keller, Hamburg (DGVS) J. Langhorst, Bamberg (DGNM) J. Neumann, Munich (DGP/BDP) B. Siegmund, Berlin (DGVS)
WG 2: Clinical appearance (definitions), natural disease course, complications, epidemiology	WG leaders	F. Dumoulin, Bonn (DGVS) T. Frieling, Krefeld (DGVS)
	WG members	U. Helwig, Oldenburg (DGVS) J. Hoffmann, Ludwigshafen (DGVS)
WG 3: Diagnostics and staging	WG leaders	B. Lembcke, Frankfurt (DEGUM) A. Schreyer, Brandenburg an der Havel (DRG)
	WG members	J. Lauscher, Berlin (DGAV)

		A. Meining, Würzburg (DGVS) A. Schäfer, Leipzig (DRG) W. Schwenk, Solingen (DGAV)
WG 4: Conservative treatment, pharmacotherapies, diet, lifestyle	WG leaders	S. Böhm, Bülach (DGVS) W. Kruis, Pulheim (DGVS) L. Leifeld, Hildesheim (DGVS)
	WG members	A. Madisch, Hanover (DGVS) D. Rubin, Berlin (DGEM) C. Sander, Berlin (DCCV) M. Reinshagen, Braunschweig (DGVS)
WG 5: Indications for surgical therapy	WG leaders	C. Germer, Würzburg (DGAV) J. Labenz, Siegen (DGVS)
	WG members	F. Hartmann, Frankfurt (DGVS) J. Lock, Würzburg (DGAV) J. Pelz, Hildesheim (DGAV) C. Reissfelder, Mannheim (DGAV) U. Tappe, Hamm (DGVS) S. Willis, Ludwigshafen am Rhein (DGAV)
WG 6: Surgical procedures	WG leaders	M. Kreis, Berlin (DGAV, DGK) J. Ritz, Schwerin (DGAV)
	WG members	F. Aigner, Berlin (DGAV) C. Eckmann, Hannover Münden (DGAV) T. Schiedeck, Ludwigsburg (DGAV) W. Schwenk, Solingen (DGAV)
WG Quality indicators	WG leaders	L. Leifeld, Hildesheim (DGVS) J. Ritz, Schwerin (DGAV)
	WG members	F. Aigner, Berlin (DGAV) F. Dumoulin, Bonn (DGVS) T. Frieling, Krefeld (DGVS) U. Helwig, Oldenburg (DGVS) A. Madisch, Hannover (DGVS) C. Reissfelder, Mannheim (DGAV) U. Tappe, Hamm (DGVS)
Methodology		P. Lynen Jansen P. Lorenz N. Steubesand T. Karge E. Friedrich Würstlein
Coordination		C. Germer, Würzburg (DGAV) W. Kruis, Pulheim (DGVS) L. Leifeld, Hildesheim (DGVS)

Participating professional societies could each nominate at least one expert representative. In addition, the DGVS allowed its members to apply to participate in preparing the guideline. A balanced relationship between the individual specialist representatives was established, so that not only office-based physicians were involved, but also doctors from clinics of all levels of care.

Representativeness of the guideline group: Participating professional societies

- German Society for Ultrasound in Medicine [Deutsche Gesellschaft für Ultraschall in der Medizin (DEGUM)]
B. Lembcke (Frankfurt)
- German Nutrition Society [Deutsche Gesellschaft für Ernährungsmedizin e.V. (DGEM)]
D. Rubin (Berlin)
- German Society for Coloproctology [Deutsche Gesellschaft für Koloproktologie e.V. (DGK)]
M. Kreis (Berlin)
- German Society for Neurogastroenterology and Motility [Deutsche Gesellschaft für Neurogastroenterologie und Motilität (DGNM)]
H. Allescher (Garmisch-Partenkirchen), J. Langhorst (Bamberg)
- German Society for Pathology [Deutsche Gesellschaft für Pathologie e.V. (DGP)] /Federal Association of German Pathologists [Bundesverband Deutscher Pathologen e.V. (BDP)]
J. Neumann (Munich)
- German Radiological Society [Deutsche Röntgengesellschaft e.V. (DRG)]
A. Schäfer (Leipzig), A. Schreyer (Brandenburg an der Havel)

Representativeness of the guideline group: Involvement of patient associations

Direct collaboration of a representative (C. Sander) of the German Crohn's Disease/Ulcerative Colitis Association (DCCV) e.V.

1.3.2. Literature search

Execution of the search

The systematic literature search was carried out in the Medline database via the PubMed search interface <https://pubmed.ncbi.nlm.nih.gov/> and in the Cochrane Library <https://www.cochranelibrary.com/>. The PubMed search period directly follows on from that applied in the previous version of the guideline [1], and thus covers the time period from 01 January 2012 to 26 April 2019. Since the Cochrane Library was not included in the 2013 literature search, the current search period for the Cochrane Library was extended to 10 years, from April 2009 to 24 April 2019.

In the first German S2k guideline from 2014 [1], the results of the PubMed search were viewed in a first screening step without formal evaluation of the literature. Therefore, the literature found at that time was combined with the newly added literature after the first screening step, for joint review and evaluation.

Further details of the literature search can be found in the guideline report.

Screening and manual search

Evidence was selected by means of a multi-step screening process. In the title - abstract screening, studies identified in the literature search were screened by Prof. L. Leifeld for potential relevance, based on the given inclusion and exclusion criteria. Of the 1163 articles found, 493 were classified as potentially relevant. These were combined with the 489 studies from the 2013 PubMed search and assigned to the individual WGs according to relevance. In a second screening step, full texts of the selected publications were assessed by the individual WGs for compliance with the aforementioned exclusion criteria. Further details on the procedure can be found in the guideline report.

At any time during the research process, up until the experts had completed full-text screening, WG members were free to check the researched collections for completeness and nominate additional topic-related studies.

These were directly added to the respective collections to be submitted for evidence assessment.

1.3.3 Evidence selection

The literature review was carried out via the guideline portal of CGS Clinical Guideline Services GmbH (CGS). After removal of duplicates, the articles identified in the searches were deposited as a literature collection in the guideline portal (<https://www.guideline-service.de>).

Inclusion and exclusion criteria

The following inclusion and exclusion criteria were defined for the search and the selection of evidence:

- Published in German or English
- Human clinical trials (no animal experiments)
- Publication available as full text
- Published between April 2009 and the time of the last search (26 April 2019)
- Case reports, case series, in vitro studies

General criteria for exclusion were also applied:

- Presence of a duplicate publication
- Availability of a more recent version (follow-up publication, update)
- Previous inclusion of the primary study in a review article
- Narrative reports in which the methodology is not described
- Study design description or protocol only (without results)

Evidence evaluation

The literature evaluation was conducted on the basis of the 2011 Oxford Centre for Evidence-Based Medicine (Oxford CEBM) Levels of Evidence for interventional, diagnostic and prognostic studies [2]. Experts from the respective WGs assessed the methodological quality of each study according to checklists, using the 'Critical Appraisal Tools' of the Oxford CEBM [3] or, in the case of non-randomised (cohort and case-control) studies, the Newcastle-Ottawa Scale [4].

If appropriate, the level of evidence of the studies lacking quality, precision or directness and/or with significant heterogeneity was downgraded by one level. On the other hand, the evidence level of studies with a large effect could be upgraded by one level. After evaluation of the studies, the literature was assigned to the respective relevant key question. Using this method, all references selected by full-text screening were

evaluated, together with additional references added after manual searches by the WGs. In the next step, data was extracted from all selected studies and summarised in the form of evidence tables [5-7].

Compilation of evidence tables

Following the positive assessment of the literature, the most important data were extracted from all the studies included. These data were summarised in the form of evidence tables in the guideline portal, sorted according to study type. Further details on the evidence tables can be found in the guideline report.

1.3.4 Formulation of recommendations and structured consensus building

The recommendations and background information were drafted by the WG leaders based on the evidence, and adopted within the individual WGs by means of an e-mail circulation procedure. The grading of the recommendations was based on the formulation should, should, can (in German; soll, sollte, kann) (see main manuscript Table 2).

All recommendations, including those adopted unchanged from the 2014 guideline, were then voted upon according to the Delphi procedure by all guideline participants using a 3-option decision scale (yes, abstention, no). Members of the Delphi committee who voted other than “yes” for a particular recommendation were required to comment and provide a reason for their decision. Recommendations for which more than 95% of the participants voted “yes” were adopted at this point in time.

The Delphi committee’s comments and suggestions for changes were reviewed by the WGs and coordinators, and the recommendations revised accordingly. Subsequently, all revised recommendations were subject to a second Delphi vote, again using the 3-option decision scale. In the second Delphi vote, all but 9 recommendations received 95% approval. The remaining recommendations also achieved a high level of agreement, at over 90%. In consultation with the AWMF, it was decided to forego a consensus conference. The strength of consensus was defined as set out in Table 3 (main manuscript). Following the second Delphi vote, the comments underwent final revision by the WGs and the guideline was editorially compiled by the coordinators.

Statements

“Statements” are explanations or observations regarding specific facts or questions without an immediate call for action. The statements have been adopted as part of a formal consensus procedure in accordance with that used for the recommendations, and can be based either on study results or on expert opinions.

Expert consensus

“Expert consensus” is used to describe recommendations for which no systematic literature search was carried out, or for which no suitable literature could be found in a corresponding search. The grading of each recommendation is derived exclusively from the wording used (should/should/can), according to the grading scheme shown in Table 2.

Choosing Wisely

Recommendations marked “Choosing Wisely” were selected for the “Choosing Wisely” initiative of the German Society for Internal Medicine (DGIM). These recommendations are intended to provide concrete assistance in assessing indications for diagnostic and therapeutic measures, in order to avoid over- or undertreatment. Further information (in German) can be found here: <https://www.klug-entscheiden.com/>.

1.3.5 Timeline

August 2018 AWMF registration completed

October 2018 Coordinators commissioned by the DGVS

April 2019	Invitations issued to the professional societies and experts to be involved
April 2019 to October 2020	Revision of the recommendations and background information
November 2020 to	
December 2020	Delphi vote
Until end of February 2021	Revision of the recommendations
March 2021	2. Delphi vote
April 2021 to October 2021	Full manuscript prepared
October to November 2021	Approval procedure

1.4. External review and approval

1.4.1. Adoption by the governing boards of the issuing professional societies/organisations

The completed guideline was reviewed and approved by all participating professional societies within 3½ weeks (21 October 2021 to 15 November 2021), and was simultaneously available to the scientific community for comment as a consultation version on the DGVS and AWMF websites. A request for comments was issued via the DGVS newsletter. No suggestions for changes were received.

1.4.2. Editorial independence and funding of the guideline

Editorial independence was maintained with regard to the guideline creation. The DGVS financed the use of the guideline portal, the systematic search and the evaluation of evidence. The DGAV financed the librarial support. No funding was received from third parties. All representatives and experts worked exclusively on a voluntary basis.

1.4.3. Declaration and handling of conflicts of interest

In line with the AWMF regulations on handling conflicts of interest, all participants submitted their declarations on the corresponding AWMF form (2018 version). Conflicts of interest were first assessed for thematic relevance to the guideline and categorised according to the AWMF criteria as being of low, moderate or high relevance with regard to the individual recommendation.

Highly relevant conflicts of interest with regard to the guideline were not found for any of the participants. The following conflicts of interest were classified as moderately relevant:

- Consultancy, advisory work or paid work as member of the scientific advisory board of a company in the health industry (e.g., pharmaceutical industry, medical device industry), a commercially oriented contract service provider or an insurance company
- Participation in a scientific advisory board
- Research projects/execution of clinical studies: financial grants (third-party funds) for research projects or direct funding of facility employees by a company in the health industry, a commercially oriented contract service provider or an insurance company
- Ownership interests (patent, copyright, shareholding): Ownership of shares, stocks or investment funds with holdings in companies of the health industry

Paid lecturing or training activities and paid author- or co-authorship were rated as minor conflicts of interest.

The influence of conflicts of interest was additionally reduced by the creation of interdisciplinary WGs.

The conflict-of-interest declarations of all experts are presented in the appendix to the guideline report.

1.5. Distribution and Implementation

1.5.1. Distribution and implementation concept

The German guideline has been published not only in the Zeitschrift für Gastroenterologie (German) and Digestion (englisch; [1]), but also on the websites of AMBOSS, the DGVS (www.dgvs.de) and the AWMF (www.awmf.de).

1.5.2. Validity period and updating procedures

The guidelines will be valid for approximately five years (15th October 2026). A revision will be initiated by the guidelines delegate of the DGVS. The guideline steering group will annually review the need to update the guideline. Correspondence and queries may be sent to Pia Lorenz (leitlinien@dgvs.de) at the DGVS head office.

Editorial note

Gender neutrality

In order to improve legibility, gender-specific terminology has not been used in this document. All personal designations are therefore to be interpreted as gender neutral.

Participatory decision-making

All recommendations contained in these guidelines are to be understood as recommendations intended to be discussed and implemented in the form of a participatory decision-making process involving the physician and the patient and/or the patient's family members.

Special remark

Medicine is subject to a continuous process of development, as a result of which all information, particularly that related to diagnostic and therapeutic procedures, can only correspond to the state of knowledge at the time the guideline went to press. Recommendations pertaining to therapies and the selection and dosage of drugs were prepared with utmost care. Nevertheless, the user should always refer to the manufacturer's package insert and expert information, and consult a specialist in case of doubt. In the public interest, it is kindly requested that any discrepancies be reported to the DGVS. The use of any diagnostic and therapeutic application, medication or dosage remains the personal responsibility of the user. Registered trademarks (protected trade names) are not specifically identified in this guideline. Therefore, the absence of a corresponding sign does not allow the conclusion to be drawn that it represents a free trade name. The work is protected by copyright in all its parts. Any use outside of the provisions of the copyright law without the written consent of the DGVS is inadmissible and punishable. No part of this article may be reproduced in any form without written permission. This applies in particular to any copying, translation and microfilming of the work and its storage, processing or utilisation in electronic systems, intranets or the internet.

Quality indicators

Quality indicators (QI) are measurable variables whose collection serves to assess the quality of the underlying structures, processes or results. The aim of their use is to continuously improve care by describing treatment outcomes, critically evaluating them and improving them, if necessary. A "Quality Indicators Working Group" was set up for the deduction process. The extensive communication and discussion took place via an e-mail circulation procedure. A set of quality indicators was created by mutual agreement.

QI 1: (Recommendation 4.22a)

A diagnosis of diverticular disease should include a classification.

Quality goal: to use a classification as often as possible

QI 2: (Recommendation 4.7) – Choosing wisely

Ultrasound or computed tomography (CT) should be used as diagnostic tools upon suspicion of diverticulitis.

Quality goal: to use ultrasound or CT as often as possible

QI 3: (Recommendation 6.10)

Patients with overt perforation and peritonitis in acute complicated diverticulitis should be operated on within 6 hours after diagnosis (emergency surgery).

QI 4: (Recommendation 5.3)

In perforated sigmoid diverticulitis with generalised peritonitis (CDD type 2c1/2), sigmoid resection with primary restoration of continuity with anastomosis and proximal ileostomy should preferentially be performed as the standard surgical procedure. In patients who are unstable or have sepsis, the Hartmann procedure should be performed.

Quality goal: to use the most appropriate surgical procedure for perforated sigmoid diverticulitis as often as possible

QI 5: (Recommendation 6.4)

Patients with acute diverticulitis with microabscess (CDD type 2a) should be hospitalised and treated with antibiotics. There is no indication for elective surgery after successful conservative therapy.

Quality goal: in patients with diverticulitis with microabscess, to give inpatient antibiotic therapy as often as possible

Chapter 2 Anatomy, Pathology, Pathogenesis, Risk Factors, Comorbidities, Pharmacotherapies

Statement 2.1

Colonic diverticula are acquired protuberances of the mucosa and submucosa through hiatal weak points in the muscle of the colon wall.

Expert consensus, strong consensus

Comment - Statement 2.1.

The herniation of the mucosa, along with parts of the submucosa, occurs via preformed weak points ("Loci minoris resistentiae") along intramural blood vessels (vasa recta) [8-11]. A so-called pseudodiverticulum that extends into the muscle layer is known as an incomplete intramural colonic diverticulum [12]. If, however, the herniation crosses all layers of the colonic wall, right through to the serosal surface of the bowel, it is described as a complete, extramural colonic diverticulum. Whereas in western countries, colonic diverticula arise predominantly in the left-sided colon, in the Asian population, the right-sided colon is more frequently affected [13-15]. The increased occurrence of colonic diverticula in the sigmoid colon is attributed to the fact that this bowel segment contains a large number of vasa recta, the intraluminal pressure is high, and the peristaltic waves break, as though buffered, just ahead of the rectum.

2.2. Pathology 2.2.

Statement 2.2

Pathologically, diverticulitis is characterised by an inflammatory process that originates from colonic diverticula (peridiverticulitis) and spreads to the intestinal wall (focal pericolitis). This inflammation can result in severe complications (abscess and/or fistula formation, covert perforation, overt perforation with peritonitis, stenosis, diverticulitic tumour). Colonic diverticular haemorrhage is a further complication of diverticular disease.

Expert consensus, strong consensus

Comment – Statement 2.2.

Colonic diverticula are particularly prone to inflammatory changes, since the blood vessels passing through the herniation are compressed, resulting in locally inadequate supply to the prolapsed mucosa [16]. In addition, a narrowed diverticular neck can lead to longer retention of bacteria-loaded stool in the diverticular lumen, and to the formation of faecal stones, which can cause pressure ulcerations through mechanical irritation at the rim of the diverticulum [17]. Histopathological characteristics include prominent mucosal protrusions with impaired crypt architecture and cryptitis, ulcerations with lymphocytic and neutrophilic infiltrates, fibrosis of the lamina propria mucosae, and hyperplasia and fragmentation of the lamina muscularis mucosae [18]. In the long run, recurrent flares of inflammation can cause not only localised fibrosis, wall thickening and stenosis, but also, in some cases, cancer (diverticulitic tumour) [19]. Clinically, symptoms of subileus or complete occlusion of the large bowel (ileus) may occur. Covert perforations arise as a result of localised inflammatory processes and form outlets for abscess and fistula formation in neighbouring organs. An open diverticular rupture in the free abdominal cavity can occur even without inflammatory changes, and is usually caused by a weakening of the thin-walled diverticular dome [19].

The tautened blood vessels at the diverticular neck and dome are particularly susceptible to mechanically-induced ruptures or arrosions, which are largely responsible for the high bleeding tendency in diverticular disease and usually occur without accompanying inflammatory changes [20].

In some cases, histopathological findings can be observed to overlap with those typically found in inflammatory bowel disease (IBD) (e.g., granuloma, transmural inflammatory infiltrates, lymphoid aggregates, paneth cell metaplasia) [21]. Additional differential diagnoses include various forms of colitis (lymphocytic, collagenous, ischemic or infectious colitis) and sigmoiditis, which is rarely associated with diverticular disease (segmental colitis associated with diverticulosis "SCAD"). SCAD is characterised by the fact that whereas the interdiverticular mucosa is affected by inflammation, the peridiverticular mucosa is spared, except in cases of severe inflammation [22].

2.3. Pathogenesis

The pathogenetic mechanisms of diverticulum formation and diverticular disease are complex, and many aspects have yet to be fully investigated. Factors that play an important role in the current scientific discussion will be discussed below.

Statement 2.3

A thickening of the muscles of the bowel wall is often found in diverticulosis and diverticular disease.

Expert consensus, strong consensus

Comment – Statement 2.3.

The thickening of the tunica muscularis affects both the circular and the longitudinal muscle layers [23-28]. Muscle thickening has been described as a common finding in the diverticulum-bearing colonic segment and can also occur in non-symptomatic diverticulosis [23, 28]. While muscle thickening correlates with the extent of the diverticulosis, it does not correlate with the severity of clinical symptoms [23]. Histopathologically, muscle thickening has been observed to be mostly ribbon-like and less often circumferential [23, 28]. Herringbone-like and aberrant muscle traction has been observed [26]. This muscle thickening, considered myostatic ("myochosis coli"), is probably less the result of hyperplasia than of hypertrophy of the contracted myocytes [24, 27, 28]. Based on evidence showing increased elastin storage in the longitudinal muscles [25, 26, 29], it is assumed that this leads to contraction of the taenia, causing the intestinal tube to shorten ("concertina colon") [26-28]. As a result, excess folds of mucous membrane are pushed outwards through the intestinal wall to protrude as pseudodiverticula.

Statement 2.4

There are indications that diverticulosis and diverticular disease are associated with changes in the content, composition and linkage of connective tissue fibres and a faulty metabolism of the connective tissue matrix.

Expert consensus, strong consensus

Comment – Statement 2.4.

As a result of the general age-related slackening of connective tissue and decrease in tissue turgor, blood vessel tunnels flanked by connective tissue are allowed to expand, thus promoting the increased development of diverticula with advancing age. A pathogenetic significance of connective tissue changes is evidenced by the increased occurrence of colonic diverticula in patients with systemic connective tissue diseases resulting from genetic defects (e.g., the Marfan and Ehlers-Danlos syndromes) [30, 31]. Individual studies have shown an increase in the total collagen content [25, 29] and the cross-linkage of collagen fibres [32] in diverticular disease. This is assumed to reduce the ability of the intestinal tube to adapt to changes in intraluminal pressure. In addition, a shift from type I collagen to the less stable type III collagen has been described [33, 34], which might lead to a local mechanical weakening of the bowel wall. Two studies indicated that the enzymes primarily responsible for the breakdown of connective tissue are changed in diverticular disease (diminished matrix metalloproteinase 1, increased matrix metalloproteinase tissue inhibitors 1 and 2) [35, 36]. Older investigations showed an increased content of elastin fibres within the muscles of the taenia (elastosis coli), which can lead to longitudinal contracture of the intestinal tube, and thus to a surplus of mucous membrane [25, 26, 29].

Statement 2.5

There is evidence that diverticulosis and diverticular disease are accompanied by enteric neuropathy, which is characterised by structural changes in the enteric nervous system and disturbances of the enteric neurotransmitter system.

Expert consensus, strong consensus

Comment – Statement 2.5.

Several studies have shown that in diverticular disease, the intramural ganglia are reduced in size and contain fewer nerve cells (oligoneuronal hypoganglionosis) [37-41]. In one study, the authors found histopathological correlates of a so-called intestinal neuronal dysplasia [42]. In addition, changes in both excitatory (acetylcholine, substance P) and inhibitory (nitric oxide, vasoactive intestinal polypeptide) neurotransmitters, and in neurotransmitter receptors (serotonin receptor 4, muscarinic receptor 3), have been described [43-48]. Bassotti et al. also reported a considerable reduction in certain associated cell systems that are likewise involved in the regulation of stimulus creation and transmission within the bowel wall, namely the interstitial cells of Cajal (ICC) and the glial cells [38]. More recent studies confirm disruptions in the glial cell line-derived neurotrophic factor (GDNF) system, not only in diverticular disease, but also in the early stages of diverticulum formation, before any morphometric myenteric changes are to be found [49].

Statement 2.6

Congruent with the neuropathic and myopathic changes in the bowel wall, at least a proportion of patients with diverticulosis and diverticular disease show disturbances in colonic motility and sensitivity.

Expert consensus, strong consensus

Comment – Statement 2.6.

It has been hypothesised that the neuropathic and myopathic changes lead to intestinal motility disturbances that promote the development of diverticulosis. The evidence supporting this hypothesis has so far only been investigated in a few studies in patients with non-symptomatic diverticulosis prior to development of diverticulitis. Even in this patient group, a loss of ganglion cells and/or change in regulatory mediators was already detectable [39, 49]. An increased response of the isolated bowel muscles to excitatory mediators has also been described in patients with non-symptomatic diverticulosis [50].

While a causal relationship between enteric neuromyopathy and motility disorders in diverticular disease has not yet been clearly established, numerous studies have shown altered intestinal motility, especially in the rectosigmoid colon: A number of older studies found that contractile activity was increased both at rest and in response to meal intake [51-55]. Similar changes have also been shown in right-sided colonic diverticular disease [56]. The resulting increase in intraluminal pressure can promote the development of diverticula. However, since studies also exist that showed no such changes, this phenomenon may only be relevant in a subgroup of patients with diverticular disease [57, 58]. Changes in motility in patients with diverticula have also been detected in more recent investigations using 24-hour manometry of the entire colon. These include, for example, increased contractile activity in diverticula-bearing bowel segments, a heightened spastic increase in postprandial tonus and an increased number of high amplitude propagated contractions (HAPC), which are believed to be the manometric correlate of mass movements in the bowel [59, 60]. The propagation of these HAPCs is frequently retrograde, which may be taken either as a sign of impaired motor coordination or even as a response to a distal (spastic?) constriction [59-61].

In addition, disruption of intestinal innervation is considered responsible for pain-related symptoms, which arise particularly frequently in patients with chronic diverticular disease. In these cases, an increase in pain-mediating neurotransmitters (galanin, neuropeptide K) and a proliferation of pain-conducting nerve fibres have

been observed, probably as a post-inflammatory response. This would suggest the presence of visceral hypersensitivity in chronic diverticular disease - similar to that observed in post-infectious irritable bowel syndrome (IBS) [62, 63].

On a genetic level, the evidence supports a pathogenetic connection between the intestinal nerve function of connective tissue and diverticular disease through the association of variants in e.g., S100A10 (S100 calcium binding protein A10, regulator of the remodelling of the extracellular matrix), BMPR1B (bone morphogenetic protein receptor type 1B), ELN (elastin) and EFEMP1 (epidermal growth factor containing fibulin-like extracellular matrix protein 1) [64, 65].

In line with this, sensorimotor examination of the rectum and sigmoid colon of symptomatic diverticulum carriers compared to healthy subjects, using the barostat technique, showed a heightened sensory sensitivity to balloon distension with unchanged compliance of the colorectal wall [66]. This hypersensitivity was found not only in the diverticulum-bearing sigmoid colon, but also in the unaffected rectum [66].

Faecal stasis and impaction

Ultimately, motility disorders could also explain the long-discussed hypothesis of faecal stasis with faecal impaction and formation of so-called faecaliths. Faecaliths, which are frequently observed during colonoscopy, and obstruction of the diverticula can promote bacterial stasis, mucosal trauma, localised ischaemia and inflammation. The intraoperative detection of faecaliths in acute diverticulitis may support this hypothesis [67]. A similar pathomechanism can be seen in acute appendicitis. However, there is no further evidence for this hypothesis.

2.7. Influence of Age

Statement 2.7

The prevalence of diverticulosis or diverticular disease increases sharply with age. However, the incidence is currently increasing more rapidly in younger age groups.

Expert consensus, strong consensus

Comment – Statement 2.7.

Since the presence of diverticula does not necessarily cause symptoms, the prevalence of diverticulosis is difficult to define. On the basis of colon contrast examinations and autopsies, both of which might lead to an overestimation, the prevalence of diverticulosis in western industrialised nations has been estimated as follows: approximately 13% for people under 50 years of age, 30% for 50-70 year-olds, 50% for 70-85 year-olds and 66% among those over 85 years of age [68-71].

While the incidence of diverticular disease is also clearly age-dependent, data from the last decade show a trend towards an increase in younger patients [72]. In a US study based on the nationwide registry of all hospitalised patients, inpatient admissions for treatment of diverticular disease were found to have increased by 26% between 1998 and 2005. The average age of those affected fell from 64.6 to 61.8 years during this period. In 1998, the incidence was highest among those aged 75 years and over, at 2,447/million, followed by 1,360/million among 65-74-year-olds, 659/million among 45-64-year-olds and 151/million among 18-44-year-olds [73]. However, during the period studied, the incidence rose most in adults aged 18-44 years (to 251/million), followed by those aged 45-64 years (to 777/million), whereas the incidence among those aged 65-74 years remained stable and a reduction was observed in persons of 75 years and over [73]. In a similar analysis covering the period from 2002 to 2007, 29.6% of patients admitted for diverticulitis were younger than 50 years, 40.2% between 50 and 70 years and 30.2% older than 70 years. During this period, too, admissions decreased by 4.8% in persons of 75 years and over, whereas increases of 1.3% in adults under 50 years and

3.5% in persons of 50 to 70 years were observed [74]. In a new study, 2,127 individuals diagnosed with diverticulosis during colonoscopy were followed up for a median of almost 7 years. The cumulative probability of developing diverticulitis over a period of 10.8 years was 4.3%; it was highest for 40-year-olds, at 11%, and decreased by 24% with every additional decade of increasing age [75]. While some authors have described a more aggressive course of diverticular disease in younger patients [76, 77], this does not appear to be borne out by more recent investigations [78-80]. Data on gender distribution in diverticulosis are inhomogeneous [69, 71]. While early studies reported a predominance of males among patients with diverticular disease [72], the 1998/1999 US studies found that the proportion of women among hospital admissions for diverticular disease was 60.7%, a proportion that fell to 57.8% in 2007 [72, 74].

2. Genetics

Statement 2.

Alongside environmental factors, genetic predisposition also plays an important role in the development of diverticulosis and diverticulitis.

Expert consensus, strong consensus

Comment – Statement 2.

Several rare genetic syndromes are associated with a strong predisposition for the development of colonic diverticula. These include Marfan syndrome, Ehlers-Danlos syndrome, Williams-Beuren syndrome, Coffin-Lowry syndrome and polycystic kidney disease [71, 81-83]. Those affected develop colonic diverticula at an early age [69, 84, 85]. Common to these syndromes are defects in a component of the extracellular matrix and/or connective tissue fibres, suggesting that these structures also play a role in the pathogenesis of spontaneous diverticulosis (see comment on statement 2.4).

Clinical case reports have previously detected familial risk factors for the development of diverticulosis/diverticular disease in the general population [71]. A study of 104,552 twins identified a clear genetic risk for the development of diverticular disease, with an odds ratio (OR) of 7.15 for a monozygotic twin and 3.20 for a same-sex dizygotic twin. The influence of genetic factors on the development of diverticular disease was estimated at 40%, compared with 60% for environmental factors [82]. Based on these epidemiological findings, it is clear that diverticulosis is a polygenic disease that results from an interaction of hereditary and environmental risk factors.

Between 2017 and 2019, three genome-wide association studies were able to capture an overview of the genetic risk profile of non-syndromic diverticulosis [64, 65, 86]. Overall, the findings of the genome-wide association studies are consistent with those of the replication studies [87]. Up to 48 risk genes with genome-wide significance have been identified [65], of which at least 35 were replicated in at least one independent cohort. The results of these studies further elucidate existing pathophysiological concepts and identify specific molecular signalling pathways. The identified genes can be assigned to a surprising degree to molecular mechanisms and show an interesting overlap with the monogenic and syndromic forms of diverticulosis [65, 87]: A number of loci, such as COLQ, COL6A1, GDNF and GPR158, indicate neuromuscular dysfunction. Three loci show pathophysiological connections to the calcium signalling pathway in the smooth muscle cells of the small bowel (CPI-17, CECNB2, ANO1). The homeobox transcription factor Hlx plays an important role in neuromuscular development. Another group of confirmed risk loci comprises genes of connective tissue function and morphogenesis such as ELN, BMPR1B, EFEMP1, CRISPLD2 and S100A10. The mesenteric vascular function is influenced by CALCB and PPP1R16B.

Only four of the genes so far identified (PHGR1, FAM155A, CALCB, S100A10) showed an association with the risk for diverticulitis. Interestingly, PHGR1 - a risk gene for both diverticulosis and diverticulitis - is the only one of these genes that is clearly functionally linked to the intestinal epithelial function. Furthermore, there is no overlap with the risk genes for IBD and also, overall, no genetic immune signature for diverticulitis [64, 65, 86]. In order to fully elucidate the underlying pathomechanisms, further mechanistic studies are required.

Visceral fat

New findings suggest a role for visceral adipose tissue as an immuno- and endocrine-active organ. Indeed, CT studies show significantly more visceral fat in patients with diverticulosis and diverticulitis compared with controls. Interestingly, there was no association between visceral and general subcutaneous fat content in the patients, in contrast to controls. Fatty degeneration of the muscle layers was found only in diverticulosis [88]. Another study, while failing to confirm these differences in fat content, found negative and positive correlations between serum levels of adiponectin and leptin in diverticulosis and diverticular disease. Since stool calprotectin levels were increased, these findings were interpreted as proinflammatory status [89].

Clinically, obesity and overweight pose a risk for diverticular disease progression (see Chapter 5), suggesting that visceral fat may play a pathogenetic role. Overall, however, scientific background knowledge in this area is not yet sufficient to define the pathogenetic role of visceral fat.

2.9. Intestinal microbiome

Statement 2.9

The intestinal microbiome does not seem to be involved in the development of diverticula. It could, however, represent a pathogenic cofactor in the progression to diverticular disease.

Expert consensus, strong consensus

Comment – Statement 2.9.

The gut microbiome is now a central focus of scientific research. In this context, there is increasing interest in clinical interrelationships, not least with respect to diverticulosis, diverticular disease and diverticulitis. Current knowledge has been summarised very concisely in a very recent review [90]. Numerous examinations of the faecal microbiota have detected a number of abnormalities. However, the results are inconsistent and largely unconfirmed. The same applies to microbiological findings from mucosal biopsies of the bowel.

A summary of these innumerable descriptions of changes in the microbiota of patients with colonic diverticula comes to the conclusion that the microbiome does not play a decisive role in the development of diverticula. In contrast, however, the progression to diverticular disease appears to be linked to dysbiosis [91]. It is presumed that the microbial changes are not monocausal, but that co-events lead to pathogenic changes in the microbiota. Such co-events might be, for example, specific dietary habits and food additives or medication (e.g., antibiotics). The effects of physical activity on the intestinal microbiome are of particular interest in this context.

Findings related to microbial changes in diverticular disease have prompted attempts to alter the microbiota for therapeutic reasons, in order to create a “favourable” microbiome. These studies have largely been carried out with poorly resorbable antibiotics and probiotics (for more details, see Chapter 5).

2.10 Inflammation (chronic inflammation, low grade inflammation)

Statement 2.10

It is currently unknown whether mucosal/subclinical inflammation (low grade inflammation) plays a pathogenic role in diverticulosis or whether it can develop into diverticulitis.

Expert consensus, strong consensus

Comment – Statement 2.10

The question as to whether mucosal inflammation plays a role in diverticulum-dominant colon segments has been the subject of intense scientific debate for some years. Alongside the microbiome and nutritional factors, obesity and physical inactivity are prejudicial factors for a subliminally pro-inflammatory intestinal environment. Genetic evidence suggests not. For methodological reasons, histological findings are not really helpful, while investigations into the immune reaction of the bowel wall have revealed very controversial findings. Scientific research has tended to focus on the role of "chronic" inflammation in the progression of the disease. The few attempts to gain further insights through the effects of direct anti-inflammatory therapy have so far been unsuccessful [91-93].

Risk factors for disease progression, complications, prognosis

Data concerning the frequency of diverticular disease/diverticulitis development in patients with existing diverticula should be interpreted with caution. Definitions and diagnostic methods have changed over time, and prospective observational follow-up studies are rare. Older data (which have repeatedly been passed on uncritically) suggest a lifelong prevalence of symptomatic diverticulosis of up to 25% of the population, i.e., around 75% of those with diverticula never have symptoms causing them to visit a doctor [94].

In a more recent study following up 2,222 patients with confirmed diverticulosis, 23 - 95 patients (1% - 4.3%, depending on the strictness of the definition) developed acute diverticulitis. Overall, a progression incidence of 1.5 patients per 1,000 patient years was observed. Acute diverticulitis developed after a median of 7.1 years [95].

About 15% of patients with uncomplicated acute diverticulitis develop complications in the form of abscesses [96]. A population-based study in England found that among patients with complicated diverticulitis, first-year mortality was 20%, compared to 4% in controls [97].

A small subgroup of patients with acute diverticulitis show persistent symptoms (pain, sometimes with signs of inflammation in laboratory and imaging tests), known as smouldering diverticulitis [98]. After the first episode of acute uncomplicated diverticulitis, around 15% - 30% of patients will have a relapse [93]. Interestingly, a recent population-based study reported the occurrence of recurrent diverticulitis in only 11.2% of patients. However, this took into account only those patients who were admitted to hospital due to the disease relapse [99]. This is fully consistent with the fact that the first episode is the most severe, and subsequent episodes clinically milder.

Statement 2.11

The development of diverticula and the course of diverticular disease are determined by non-influenceable pathogenetic factors and by influenceable risk factors.

Expert consensus, strong consensus

Comment – Statement 2.11

Besides (risk) factors already mentioned in the pathogenesis of diverticular disease/diverticulitis, a number of other factors are under discussion as risks affecting the course and severity of the disease (Table 3).

Table 3

Influenceable risk factors

Favourable diet

- avoidance of red meat
- high in dietary fibre
- individual substances: fruit, vegetables, whole grains, legumes

Unfavourable stimulants

- damaging alcohol intake
- nicotine

Favourable lifestyle

- physical activity

Unfavourable nutritional status

- overweight/obesity

The influenceable risk factors give cause for treatment recommendations, the principles and details of which are discussed in Chapter 5.

Comorbidity plays a special role, being influenceable only to a limited extent, and will be discussed here as a special risk factor for the course of diverticular disease.

2.12 Comorbidity as a risk factor

When discussing the role of comorbidity in diverticular disease, a number of different aspects need to be considered. Comorbidity can not only influence the formation of diverticula (diverticulosis), but also determine disease severity in the sense of multimorbidity ("risk indicator"). In addition, diverticular disease can lead to comorbidity. Due to inadequate data, and also commonalities, associations between diverticular disease and other diseases are discussed below.

Recommendation 2.12

Comorbidities should be taken into account in diagnostic and therapeutic decision-making due to associated risks for diverticulosis and diverticular disease/diverticulitis.

Expert consensus, strong recommendation, strong consensus

Comment – Recommendation 2.12

The following associations have been described in detail:

Hypothyroidism

In an Israeli retrospective case-control study with 3,175 patients, previous diagnosis of hypothyroidism in the anamnesis was linked to a 2.4-fold risk of diverticulosis [100]. In the USA, an association between hypothyroidism and diverticulitis was described in a very large cohort [101].

Diabetes mellitus

Diabetes mellitus (DM) was reported to be a protective factor for the existence of diverticulosis, with an OR of 0.49 [100]. In a Japanese cross-sectional study with 954 patients, the prevalence of type II DM among subjects with diverticula (mostly right-sided) was statistically significantly higher than in diverticulum-free subjects, at 21.6% versus 14.0% [102]. (See also below, under "immunosuppression").

Arterial hypertension

In the Japanese study, the prevalence of arterial hypertension in patients with diverticula was found to be statistically significantly higher, at 30.9% vs. 19.8% in people without diverticula [102]. The Israeli study, in contrast, found no connection between arterial hypertension and the existence of diverticulosis [100].

Polycystic kidney disease

From six case series including a total of 186 patients with polycystic kidney disease (PKD) [103-108], three reported the prevalence of diverticulosis. Scheff et al. [103] found a prevalence of 10/12 (83%), Dominguez Fernandez et al. [105] 15/28 (53.5%) and Sharp et al. [106] 28/59 (47%). Scheff et al. found a prevalence of 10/31 (32%) for diverticula in a comparison group with kidney failure but without PKD, and a comparable prevalence of 45/120 (38%) in an age-matched comparison group without kidney failure. Sharp et al. [106], on the other hand, reported a prevalence of 35/59 (59%) for diverticula in their control group without PKD and without kidney failure, and thus came to the conclusion that patients with PKD do not have a higher risk of diverticulosis or diverticular disease than the general population.

Comorbidity and acute uncomplicated and complicated diverticular disease/diverticulitis

Arterial hypertension

A Swedish prospective cohort study of 7,500 men found, in the univariate analysis, a 1.8-fold increased risk of developing complicated diverticular disease in men with a systolic blood pressure (RR) of 146-162 mmHg or > 162 mmHg compared with men with a systolic RR < 133 mmHg. The univariate analysis also showed that an increased diastolic RR of > 102 mmHg was associated with a 2.2-fold heightened risk compared to patients with a diastolic RR < 88 mmHg. In the multivariate analysis, only diastolic RR was determined to be a significant risk factor, with a hazard ratio of 1.02 for each mmHg [109]. Although bleeding was taken into account in this research, it was not shown separately.

Renal disease

A study from the UK retrospectively documented 202 patients with perforated diverticular disease. The mortality rate was 24.3%. Pre-existing kidney disease was a risk factor for death, with an OR of 18.7 [110]. Of six case series with a total of 186 patients with PKD [103-108], four report the incidence of diverticular disease. Scheff et al. [103], Lederman et al. [107] and Pourfarziani et al. [108] report especially high incidences of severe diverticular disease, at 4/12 (33%), 12/59 (20%) and 3/18 (17%), respectively. Only Lederman et al. stated the incidence of diverticular disease in a comparison group of patients with kidney failure but without PKD, reporting that 4/125 (3%) were affected. Dominguez Fernandez et al. found no increased incidence of diverticular disease even in patients with PKD, at 1/28 (4%) [105]. Diverticular disease management in patients with PKD should not differ from that recommended in the general population [111].

Patients with a variety of end-stage renal diseases on dialysis treatment (n = 32,000) were found to have a remarkably increased cumulative incidence of acute diverticulitis in comparison to matched controls. After adjustment for all possible risk factors, the risk was increased by a factor of 11.2 [112].

Immunosuppression

Various studies indicate a more severe course of diverticular disease in patients under immunosuppression [108, 113-116].

A literature review by Hwang et al. identified 25 studies on diverticulitis in patients with immunosuppression. These were exclusively retrospective cohort studies. Twenty-one were studies on organ transplantees, 13 were on kidney transplantees, and the remaining 8 on heart, lung, or combined heart-lung transplantees. 4 studies involved patients receiving chronic corticosteroid therapy. A total of 12,729 patients were included in the studies [117]. Within differing follow-up periods of between 1 month and 17.3 years, the incidence of acute diverticulitis in the immunosuppressed patients was 1%, and thus higher than in the general population. A

report describing fatal complications of diverticular disease in M. Cushing makes a clinically interesting contribution to the literature on problems associated with immunosuppression [118].

Only one study directly compared the incidences in patients under immunosuppression with those of the general population, reporting rates of 0.94 vs. 0.02% [119]. The incidence of diverticulitis in the subgroup of patients whose diverticulosis was known prior to initiation of immunosuppression was 15.1% within variable follow-up periods [117]. The mortality of all conservatively or surgically treated patients with diverticulitis was 25%, while for patients who had undergone surgery, this figure was 23%. Mortality in these patients was thus significantly higher than the 1-5% reported for the general population [73, 120].

Since very few data are available for non-transplanted patients under immunosuppression [117], no statements can be made regarding the effects of different immunosuppressive regimens. Similarly, no studies were found on patients undergoing chemotherapy or with HIV/AIDS [117]. Sachar summarised 15 studies of HIV-positive patients undergoing emergency abdominal surgery. He concluded that diverticular disease does not occur more frequently in patients with HIV/AIDS, and that its course does not differ from that of the general population as long as CD4 cells do not fall below 50-200/ μ L and the viral load does not exceed 10,000-30,000 copies/mL [121].

As a consequence of the increased incidence and mortality of diverticular disease in patients under immunosuppression, screening for diverticulosis before the initiation of immunosuppressive therapy has been discussed [117]. However, McCune found that colonoscopic screening of patients over the age of 50 for post-transplant colonic complications is ineffective [104]. Screening, or even prophylactic sigmoid or colon resection, are not recommended [111, 117]. DM is associated with immunosuppression. In a study from Australia, 349 patients with DM and at least known diverticulosis were retrospectively analysed. Compared to patients with diverticulitis, those with diverticulosis were more frequently treated with antidiabetic agents. A significant reduction in the incidence of diverticulitis was noted in the group taking metformin [122]. A systematic review of prospective studies found a 1.2-fold increase in morbidity (95% CI, 1.135–1.270) in patients with diverticular disease and DM. The risk of diverticular haemorrhage was increased by 53% [123]. A study from Taiwan showed a significant risk of individuals with diabetes requiring emergency surgery for diverticulitis [124]. Such reports highlight DM as a risk indicator for diverticular disease.

Allergic predisposition

A study group operated on 101 consecutive patients, either for complicated (covert perforation, overt perforation, phlegmonous diverticulitis; $n = 57$) or for non-complicated (chronic recurrent diverticulitis, elective due to comorbidities; $n = 44$) diverticular disease. The group reported that 39% of the patients had an anamnestic allergic predisposition against grass, pollen, foods, medications, pets or other allergens. Patients with an allergic predisposition had an OR of 3.2 with regard to surgery for complicated diverticulitis [125].

Other comorbidities

In summary, the literature includes studies on a diverse range of disorders associated with diverticular disease, e.g., liver disease (cirrhosis) [126], diseases of the cardiovascular system [127] chronic obstructive pulmonary disease [128], rheumatic diseases (polymyalgia rheumatica) [129], dementia [130], and others. In some cases, the data are inconsistent, the definitions unclear, or the risks marginal. In many cases, a confirmatory study would be beneficial.

Multimorbidity

Multimorbidity must be considered as a separate risk factor of considerable importance. This is evidenced by studies based on the Charlson Comorbidity Index (> 3) as a risk indicator for diverticular disease [112]. A further publication confirms the predictive value not only of the Charlson Index for the severity of diverticulitis, but also of the American Society of Anesthesiologists' (ASA) Physical Status Classification Scores [131]. Comorbidity is a determining factor for mortality in diverticular disease [132].

Drugs and Diverticular bleeding

Diverticula are the most common source of bleeding from the colon. Diverticular haemorrhage ceases spontaneously in over 90% of cases [133]. The remaining 10% can be life-threatening and require interventional or surgical treatment. The frequency of rebleeding ranges from low to well over 50%, depending on the initial clinical situation and the type of treatment given for the primary bleeding [134, 135].

Diverticular haemorrhage is usually painless. Bleeding originates from arterial vessels around the diverticular neck that rupture as a result of mechanical impacts. This process is not usually preceded by inflammation, i.e., it occurs in the context of diverticulosis [136].

Diverticular haemorrhage is linked with numerous risk factors, which are summarised in Table 5. Special mention should be made of a recent US case-control study in which a number of risk factors for primary and recurrent haemorrhage were identified [137].

Arterial hypertension and diverticular haemorrhage

Four studies have investigated the role of arterial hypertension in diverticular haemorrhage. In a case-control study, Yamada et al. found diverticular bleeding in 44 of 1753 patients with diverticulosis. The OR for diverticular bleeding in patients with arterial hypertension was 6.6 [138]. In another Japanese case-control study, 45 of 254 patients with diverticulosis had diverticular bleeding. The OR reported for diverticular bleeding in patients with arterial hypertension was 2.2 [139]. A third Japanese case-control study analysed 51 patients with diverticulum-related lower gastrointestinal (GI) bleeding and found a significant risk for patients < 65 years of age with arterial hypertension [140]. In a retrospective case series reported by Jansen et al., 30 patients with diverticular bleeding were identified from 140 patients with diverticular disease. In this analysis, the authors found not arterial hypertension itself to be an independent risk factor for bleeding, but rather, a drug containing calcium antagonists that can be used to treat arterial hypertension [141].

Hyperlipidaemia and haemorrhage

The Japanese case-control study by Tsuruoka et al. found an OR of 2.2 for diverticular haemorrhage in patients with hyperlipidaemia [140].

Coronary heart disease and haemorrhage

The Japanese case-control studies by Tsuruoka et al. and Niikura et al. found respective ORs of 1.9 and 2.4 for diverticular haemorrhage in patients with coronary artery disease [139, 140].

Chronic kidney failure and haemorrhage

In the Japanese case-control study by Niikura et al., an OR of 6.4 was found for diverticular haemorrhage in patients with chronic kidney failure [139].

Hyperuricaemia and haemorrhage

In a study by Jansen et al., the authors described an increased risk of diverticular bleeding in patients with uricaemia. Of 30 patients with diverticular bleeding, 6 (20%) suffered from hyperuricaemia or were taking allopurinol. Of the 110 patients without bleeding, only 8 (7.3%) were documented to have hyperuricaemia or be taking a uric acid-reducing drug [141].

NSAIDs, aspirin as risk factor for diverticular haemorrhage

Since Langman's report on the possible role of NSAIDs as a risk factor for diverticular haemorrhage [142], two Japanese case-control studies have reported a 7.5- to 15.6-fold increased risk of diverticular bleeding [138, 140]. The first evaluation of the large Health Professionals Follow-Up Study (HPFS) cohort by Aldoori determined a 4.64-fold increased risk for NSAID users [143]. In the update of the prospective cohort study of Strate et al., the risk of diverticular bleeding was increased 1.74-fold for regular intake of NSAIDs alone, 1.70-fold for aspirin alone, and 2.02-fold for the combination of NSAIDs and aspirin [144]. For aspirin, an astonishingly lacking linear dose-effect relationship has emerged, with the highest risk associated with an intake of 2 - 5.9 325 mg tablets per week (HR 2.32), whereas intakes of 0.1 - 1.9 or ≥ 6 325 mg tablets are linked to lower risks of similar magnitude, with HRs of 1.58 and 1.65, respectively. As regards the frequency of aspirin use, its intake 4 - 6 times per week (HR 3.13) was associated with a significantly higher bleeding risk than daily intake (HR 1.57) or intake 2 - 3.9 times a week (HR 1.21) [137, 144].

Acetaminophen (Paracetamol) and haemorrhage

In the first analysis of the HPFS cohort, Aldoori et al. reported a 13.63-fold increased risk of diverticular bleeding while taking acetaminophen [143].

Aspirin (low-dose) and other anticoagulants

A single study has examined the risk of diverticular haemorrhage associated with the 100 mg aspirin dose that is widely used today. In their hospital-based case-control study, Yamada et al. reported an OR of 3.7 in the univariate analysis [138]. Other platelet aggregation inhibitors, such as cilostazol, sarpogrelate and dipyridamole reached an OR of 2.3 in the univariate analysis. In the multivariate analysis, ASA 100 and other platelet aggregation inhibitors showed a combined OR of 3.0 [120]. A Spanish population-based study identified 2,130 cases of diverticular bleeding. In 189 cases, concomitant medication was documented. The study showed "low-dose" aspirin (in 21.7%) to be the most common concomitant medication, while the prevalence of NSAID (14.8%) and anticoagulant (14.3%) intake was roughly similar [137, 145].

Corticosteroids and haemorrhage

In the hospital-based case-control study by Jansen et al., of 140 patients with diverticular disease, 30 were identified as having diverticular bleeding. Four of the 30 (13.3%) patients with diverticular bleeding were using steroids compared with 4/110 (2.7%) of the group without bleeding. In a multivariate analysis, steroid intake was shown to be an independent risk factor for diverticular haemorrhage [141].

Calcium antagonists and haemorrhage

Jansen and colleagues further reported that 10/30 (33.3%) of the patients with diverticular bleeding were taking calcium antagonists, compared with 23/110 (20.9%) in the group without bleeding. In a multivariate analysis, use of calcium antagonists was found to be an independent risk factor for diverticular bleeding [137, 141].

Table 4: Diverticular disease and Diverticula bleeding associated to comorbidity

Diverticulosis	Diverticular disease	Diverticular bleeding				
	Risk	Study evidence	Risk	Study evidence	Risk	Study evidence
Hypothyroidism	+	CC	+	C	n.s.	
Diabetes mellitus	+/-	CC	+		+	CC
Arterial hypertension	+/o	CC	+	C	+/o	CC
Polycystic and other kidney diseases	+/o	CS	+	CS	+	CC

Immunosuppression	n.s.	+	CC-SR	n.s.
Allergic predisposition	n.s.	+	CS	n.s.
Hyperlipidaemia	n.s.	n.s.		+ CC
Hyperuricaemia	n.s.	n.s.		+ CS
Coronary heart disease	n.s.	n.s.		+ CC

+ indicates that the risk for the corresponding condition is increased by the influencing parameter
o indicates that the risk for the corresponding condition is not changed by the influencing parameter
- indicates that the risk for the corresponding condition is reduced by the influencing parameter
a combination of signs indicates that existing studies have conflicting conclusions

The following abbreviations were chosen for the underlying study evidence:

C = cohort study/studies

CC-SR = systematic review of several case control studies

CC = case control study/studies

CS = one or more case series

n.s. = not specified

Chapter 3 Clinical Characteristics (Definitions), Natural Disease Course, Complications, Epidemiology

3.1 Definitions

Statement 3.1.1

"Diverticular disease" of the colon is present when symptoms, inflammation and/or complications arise in patients with existing diverticulosis.

Evidence level 1, consensus

Comment - Statement 3.1.1

This statement was intensely debated. Since both abdominal symptoms and diverticulosis are very common, it is difficult to differentiate between coincidence and causal relationship.

There is currently no generally accepted definition of diverticular disease. National and international guidelines show major differences, and many recommendations are supported by only moderate or low evidence [146-153]. The term diverticular disease is associated in the literature with a spectrum of symptoms. In some reports, a distinction is made between diverticular disease and diverticulitis as separate entities, while in others, diverticulitis and diverticular bleeding are subsumed under the term diverticular disease [98]. Some authors differentiate asymptomatic or uncomplicated from symptomatic or complicated colonic diverticulosis, whereby patients with (chronic) persistent pain, acute colonic diverticulitis and diverticular bleeding fall into the diagnostic category of complicated or symptomatic colonic diverticulosis [154].

Statement 3.1.2

Diverticulitis is the inflammation of diverticula. Acute "diverticulitis" occurs when the pseudodiverticula and adjacent structures become inflamed. Acute, complicated diverticulitis describes diverticulitis accompanied by a perforation, fistula, and/or abscess.

Evidence level 1, strong consensus

Comment - Statement 3.1.2

Diverticulitis is inflammation of the diverticula, usually due to faecal impaction at the diverticular neck. This can cause disruption of the local microcirculation [147, 155]; prolonged retention of bacteria-filled stool, with the formation of faecaloliths can also cause pressure ulceration [17]. The inflammatory process originates from the

colonic diverticula and invades adjacent structures. Histopathological characteristics include prominent mucosal protrusions with impaired crypt architecture and cryptitis, ulcerations with lymphocytic and neutrophilic infiltrates, fibrosis of the lamina propria mucosae, and hyperplasia and fragmentation of the lamina muscularis mucosae [18]. Possible complications include not only covert perforation, abscess, fistula, and stenosis, but also overt perforation with peritonitis. Segmental colitis associated with diverticulosis (SCAD) is a clearly differentiable diagnosis, in which inflammation is strictly limited to the mucosa of the diverticulum-bearing bowel segment [22].

In acute diverticulitis, uncomplicated (non-perforated) diverticulitis is differentiated from complicated (with covert or overt perforation) diverticulitis [146, 154]. Covert perforations arise as a result of local inflammatory processes and can serve as outlets for abscedation and fistulation. Overt perforation to the abdominal cavity is usually caused by a weakening of the thin-walled diverticular dome [155]. Recurrent flares of inflammation can lead to fibrosis,

<p>Statement 3.1.3</p> <p>Chronic diverticulitis is characterised by recurrent or persistent flares of inflammation, as a result of which complications (stenosis, fistulas) can occur.</p> <p>Evidence level 1, strong consensus</p>	
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Comment - Statement 3.1.3

The term chronic diverticulitis with stenosis or fistula formation is not uniformly applied in the literature or in some classifications, e.g., those of Hinchey or Ambrosetti [156, 157] (see 2.2.1). In the current guideline, this situation is classified as CCD type 3a-c. In diverticulitis CDD type 3a (symptomatic uncomplicated diverticular disease, SUDD), similarities exist with functional disorders [150]. Other patients develop recurrent ('smouldering') diverticulitis, sometimes in the context of relevant underlying organic complications such as stenosis, stricture or fistula. 40% of patients with uncomplicated diverticulitis treated with antibiotics had persistent mild symptoms [158]. Moreover, these patients showed an increased risk of IBS [159]. A recent study did not find inflammation in this type of patients [160].

<p>Statement 3.1.4</p> <p>Symptomatic uncomplicated diverticular disease (SUDD) is characterised by pain related to the diverticulum-bearing segment.</p> <p>Evidence level 1, consensus</p>

Comment - Statement 3.1.4

The 2014 German guideline classified SUDD as diverticular disease CDD type 3a [134]. However, SUDD cannot be definitely differentiated from IBS [161]. Controlled studies are lacking, as is a clear distinction between symptoms persisting after acute uncomplicated diverticular disease and SUDD without previous diverticulitis [149, 162-164].

It is simple to separate asymptomatic diverticulosis from diverticulitis. However, despite intensive scientific efforts and growing partial insights [165, 166] the designation of symptoms to the existence of diverticula remains unclear. Terms used include symptomatic diverticulosis or - most commonly - (symptomatic) uncomplicated diverticular disease (SUDD).The contentious issue revolves around the question of whether this is a symptomatic manifestation of IBS with coincident diverticula, or whether the IBS-like symptoms constitute an independent clinical picture in the context of existent diverticulum formation.

SUDD is characterised as a syndrome in which patients with diverticula experience abdominal pain, without typical mucosal alterations [149, 162]. The symptom complex SUDD includes abdominal discomfort, flatulence, changes in defaecation patterns. The patients comprise a large patient group, making up approximately 20% of patients with diverticulosis [167]. SUDD leads to a reduced quality of life [168].

The pathophysiology of SUDD is unclear [98, 169]. Among the features described are visceral hypersensitivity with hyperalgesia in the diverticulum-bearing sigmoid colon, a reduction in interstitial cells of Cajal (ICC) or glial cells in the colon without evidence of neuronal abnormalities, and a decrease in electrical slow wave activity with consequent transit retardation. Overgrowth of nerve fibres in the enteric nervous system has also been demonstrated [170, 171].

Differentiation of SUDD from IBS is challenging [75, 98, 147, 148, 162, 172-174]. In a large retrospective analysis of US veterans, the risk of IBS following diverticulitis or functional bowel symptoms, respectively, was 5 and 2.5 times higher, compared with patients without diverticulitis [159]. In another large prospective study, no association was found between IBS and diverticulosis [175].

It remains unclear whether the development of symptoms is related to a prior inflammatory reaction. Furthermore, in patients with SUDD, minimally elevated inflammation markers (calprotectin) can be detected in the stool, as distinct from IBS [176]. Data concerning the obligatorily preceding inflammatory reaction prior to the development of SUDD are incongruent.

3.2.1. Epidemiology

Statement 3.2.1

The prevalence of diverticulosis in the general population of western industrialised nations is high, especially among older adults.

Evidence level 1, strong consensus

Comment - Statement 3.2.1

The prevalence of diverticulosis has been reported to be 28% at screening colonoscopy [68, 177], 45% in patients undergoing barium contrast enema [178-181], and in autopsy studies, over 60% in persons over 70 years of age [23].

Its prevalence increases with age: e.g., from 0.17/1,000 in the age group 15 – 44 years to 5.74/1,000 in those > 75 years [68, 172], or from 5% for 30 – 39-year-olds to 60% in adults over 80 years [182]. A large Japanese study analysed 62,503 “check-up” colonoscopies performed over 20 years. Diverticulosis was found in 11,771 individuals (18.8%). The prevalence increased with age. In addition, the incidence of diverticulosis increased during the course of the observation period, from 13% (between 1990 and 2000) to 23.9% (between 2001 and 2010). While a right-sided localisation was observed more frequently in younger patients (< 60 years), left-sided diverticulosis predominated in older patients. In this study, the prevalence of diverticulosis was found to be significantly higher in men than in women, possibly due to the cohort examined (“check-up” colonoscopy) [183].

Statement 3.2.2

The rate of hospitalisation due to diverticular disease (diverticulitis, bleeding) increases with age. In the western industrialised nations, the hospitalisation rate has noticeably increased over the past few decades.

Evidence level 1, strong consensus

Comment - Statement 3.2.2

Numerous population-based retrospective and prospective cohort studies and meta-analyses based on registry data from Europe and the USA show increasing hospitalisation rates for acute diverticulitis [73, 173, 184-189]. The relative increase is highest in younger patients between 40 and 49 years of age [188]. In persons of up to 60 years of age, acute diverticulitis is more common in men [188, 190]. The hospitalisation rate is highest among white Americans, similarly high among Americans of African or Spanish origin, and lowest among Asians [189]. The prevalence of diverticulitis is higher in city dwellers than in those who live in rural areas [191]. It is also associated with lower levels of income and education [128], and more common in developed countries [179].

From 2000 to 2010, the Scottish National Health Service documented hospital admissions of 90,990 patients for diverticulum-related complaints, including diverticular haemorrhage. Over the study period of 10 years, the annual rate of admissions increased by 4.5% (from 6,591 cases in 2000 to 10,228 cases in 2010). This increase was due not least to single-day stays (3,618 cases in 2000 to 6,925 cases in 2010). Inpatient stays of more than one-day duration also increased by 11% (2,973 - 3,303). Sixty percent of these patients were women. Admissions increased proportionally in younger patients and showed no association with physical impairments. Although the rate of complicated diverticular disease increased from 22.9% in 2000 to 27.1% in 2010, with 16.8% of these being emergency admissions, the rate of surgical intervention decreased during the observation period [192].

In England, too, increasing hospitalisation rates for acute diverticulitis have been reported, although the findings of some studies are limited by coding ambiguities [186, 187]. However, a large, prospective population-based study conducted in England from 1996 to 2006 estimated the incidence of hospital admissions and one-day admissions due to diverticular disease to have increased during this period from 0.56 to 1.2 per 100,000 inhabitants [192]. In two large prospective cohort studies from England and the USA with follow-up periods of 18 and 11.6 years, respectively, the incidence of diverticulitis was between 1 and 2% [193, 194]. In a large prospective Italian study [197], a total of 174,436 patients hospitalised for acute diverticulitis between 2008 and 2015 were analysed [195]. Women were more often hospitalised (54.9%). The median age was 70 years. During the study period, a significant increase of 30% (from 18,797 to 24,342) ($p < 0.001$) was observed in hospitalisations for acute diverticulitis, in contrast to all-cause hospitalisations, which decreased significantly by 25% (from 9,890,961 to 7,827,402) ($p < 0.001$). Overall, annual hospital admissions for acute diverticulitis increased significantly by 3% ($p < 0.001$), from 39/100,000 inhabitants in 2008 to 48/100,000 in 2015. The rate per 100,000 hospitalisations increased annually by 7.5%, from 248/100,000 in 2008 to 310/100,000 in 2015 ($p < 0.001$). Women had a higher rate of inpatient admissions than men ($p < 0.001$), whereby the increase in admissions ($p < 0.001$) was seen in both sexes, but more so in men (3.9% vs. 2.1%). The admission rate was increased for older patients aged over 80 years (mean number of admissions $152.94 \pm \text{SD } 2.87/100,000$ population) and aged 70–79 years ($99.23 \pm \text{SD } 1.49/100,000$). These numbers remained stable throughout the study period, from 2008–2015, with a non-significant increase of 0.2% per year observed in these age groups. The lowest number of hospitalisations was seen in patients aged 18 to 39 ($6.32 \pm \text{SD } 0.93/100,000$ inhabitants). However, a significant ($p < 0.001$) annual increase of 6.6% was observed in this age group. Patients between 60 and 69 years (mean annual increase 2.7%), 50–59 years (5.1%) and, highest of all, 40–49 years (7.1%) also showed significant yearly increases. As regards the gender ratio, in the patient group under 60 years of age, men were predominant (ratio of males to females; 4.32 (95% CI 4.09–4.58), 2.44 (95% CI 2.36–2.52) and 1.24 (95% CI 1.21–1.27), for patients aged 18–39, 40–49 and 50–59 years, respectively).

In contrast, female patients predominated in the age groups 60 to > 80 years, the male to female ratios being 0.87 (95% CI 0.85–0.89), 0.78 (95% CI 0.77–0.80), and 0.80 (95% CI 0.78–0.81) for the age groups 60–69, 70–79 and ≥ 80 years, respectively. In the USA, between 1998 and 2005, the annual age-adjusted increase in hospital admissions due to acute diverticulitis (acute inflammation, abdominal pain, systemic reaction) was estimated at 26% [73, 186]. Another study from the US showed a 9.5% increase in hospitalisation for acute diverticulitis between 2002 and 2007, 85% of these being emergency admissions that were treated with drug therapies [74]. One US study also described geographical differences [173], showing that age-adjusted hospitalisation for diverticulitis was lower in the West (50.4/100,000) compared to the Northeast (77.7/100,000), South (73.9/100,000) and Midwest (71.0/100,000) of the USA.

Many studies show an increasing prevalence of diverticulitis, especially in younger people. The risk of developing diverticulitis is lower in elderly patients than in younger ones [75]. In another study, the “relative” increase in the hospitalisation rate for acute diverticulitis was found mainly for younger patients, with 44 to 120 patients per 100,000 inhabitants treated annually as inpatients for diverticulitis [196]. Other investigations have identified a significant increase in the prevalence of diverticulitis over the past decade, especially in patients under 45 years of age [73, 173, 185, 197].

Whereas in the case of diverticulitis in younger patients, the majority are men, in patients > 50 years, most are female [154, 195]. Some studies found that the disease course was more severe in younger patients [198, 199], while others found no correlation with age [78, 196, 200–204]. Data on the frequency of complicated diverticulitis (with phlegmon, abscess, peritonitis, obstruction, fistula or perforation) are available from numerous countries, based on their own populations [110, 184, 205, 206]. Complications can be expected to occur in around 12% of cases, with 70% of patients developing phlegmon or abscess [97, 188]. After diverticular perforation, the one-year mortality rate was 19.2%, i.e., higher than the mortality of the general population of similar age and gender (4%). Mortality reached its highest level (13.7%) within a period of 3 months after diverticular perforation [97]. Diverticulitis under immunosuppressive therapy [207] and/or after organ transplantation takes a more severe course. A systematic review on this topic indicates - with different follow-up periods - an incidence of acute diverticulitis of 1% (and as high as 8% if diverticula are previously known); the mortality rate of diverticulitis in this patient group was up to 25% [117].

Statement 3.2.3

Right-sided diverticulosis differs from left-sided diverticulosis in terms of geographical distribution, clinical symptoms and disease course.

Evidence level 4, strong consensus

Comment – Statement 3.2.3

In Japan, there is a higher prevalence of right-sided versus left-sided diverticula [208]; the aetiology, however, seems to be similar [15]. A study comparing 207 Vietnamese with 299 Caucasians showed that the Vietnamese had a significantly higher frequency of right-sided diverticulosis (30 versus 3%) [209]. In another case-control study including 30 vs. 70 Caucasians with right-sided vs. left-sided diverticulosis, patients with right-sided diverticulosis were younger, less obese, more frequently had only focal inflammation, and had fewer complications [210].

Statement 3.2.4

After acute diverticulitis, quality of life can be impaired.

Evidence level 2, strong consensus

Comment – Statement 3.2.4

A smaller study, in which structured interviews were carried out with 50 patients with symptomatic diverticular disease, found evidence of a significant reduction in quality of life compared to healthy individuals [168]. In a meta-analysis of 21 studies with 1858 patients, GI symptoms were present in 36% of patients after conservative treatment of diverticulitis [211]. In addition, a follow-up of the prospective randomised DIABOLO study showed that a third of the 528 patients had a relevant reduction in quality of life - regardless of whether they had been treated with antibiotics or simply observed [212]. Possible correlates were found with increased neuropeptide levels, which were detectable in colon biopsies from patients with symptomatic diverticular disease [62] or increased anticipated pain perception, detectable in functional MRI [213].

3.3. Disease course/risk of recurrence/mortality

Statement 3.3.1

The majority of diverticulitis flares are mild and can be treated conservatively and on an outpatient basis. The recurrence rate after acute diverticulitis depends on the severity of the initial diverticulitis, whereby the relapse is no more severe than the initial diverticulitis.

Evidence level 1, strong consensus

Comment – Statement 3.3.1

About 4-10% of patients develop smouldering inflammation with pain, leucocytosis, signs of inflammation, fever, and/or signs of inflammation in computed tomography in spite of antibiotic therapy [214, 215]. However, data on the recurrence rate of acute diverticulitis are inconsistent. The assessment of recurrence rates in the literature is of limited value due to inadequate documentation of the natural course of the disease and the frequency of surgery after 2 episodes of acute diverticulitis [90]. Recurrence rates after pharmacologically treated diverticulitis have been reported to be between 13.3% and 36%, depending on the population studied and the duration of follow-up [216]. These numbers may be an underestimate, since cases of diverticulitis flares not requiring inpatient hospital treatment were not recorded [216]. In addition, stringent imaging and reference tests are often lacking. The majority of diverticulitis recurrences are mild and can be treated conservatively and on an outpatient basis [198, 200, 217-222]. Also, most perforations occur with the first instance of diverticulitis rather than during relapse, and multiple recurrences are not associated with a higher rate of complications [154, 223-229]. The recurrence rates reported in the above referenced literature range between 9 and 47%. Recurrence rates after acute drug-treated diverticulitis range from 18.8% (60/320) over a median control period of 101 months [230], to 20.8% (46/221) [78] and 26% (78/297) with a 46% recurrence rate (36/78) within the first year [221]. More recent studies show recurrence rates of around 8% within the first year and 20% within 10 years after initial diverticulitis [98]. Two studies with stringent reference testing describe recurrence rates of 9% [222] and 23% [200]. The risk is highest within the first year, at 10%, falling subsequently to 3% [219]. In a more recent retrospective study including 672 patients, a 5-year recurrence rate of 36% (95% CI, 31.4-40.6%) was recorded [231], while in a prospective study of 280 patients with verified uncomplicated diverticulitis, a recurrence rate of 16.4% (n = 280) was observed over an observation period of 24 months [232]. A recent literature review showed a recurrence rate after acute diverticulitis of 25-35%, with a low risk of severe complications (e.g., perforation); the risk of requiring emergency surgery was 2 - 14% and the risk of ostomy or death was 0 - 2.7%, within an observation period of 5 years [195]. In a prospective study of 320 patients after initial acute diverticulitis, 61% were subsequently asymptomatic, while 22% reported

chronic symptoms. The risk of recurrence within an observation period of 12 years was 21.2% for relapse, 8.3% for emergency surgery, 1% for ostomy and 0% for death [195].

Statement 3.3.2

Increased complication rates during relapse after initial acute diverticulitis are associated with younger age, multimorbidity, and immunosuppression or complicated initial diverticulitis, especially abscess formation.

Evidence level 1, strong consensus

Comment- Statement 3.3.2

Earlier data suggested that diverticulitis was a progressive disease with an increasing risk of complications. In contrast, however, recent studies show that complications, with the exception of fistulas, predominantly occur during the first manifestation of diverticulitis. For example, a prospective study of 900 patients showed that whereas the risk of perforation during initial diverticulitis was 25%, it decreased to 0% by the third relapse [97, 233]. Population-based studies have also shown that the risk of recurrence after drug-treated initial diverticulitis was no higher than after uncomplicated diverticulitis, and that the morbidity and mortality of recurrent diverticulitis did not correlate with the number of previous episodes of diverticulitis [188, 199, 223]. In a linear logistic regression analysis conducted as part of a retrospective cohort study, initial uncomplicated diverticulitis was not associated with an increased risk of complications during relapse (OR 1.58; CI 0.52–4.81). Furthermore, multiple recurrences after uncomplicated diverticulitis were not associated with an increased risk of complicated diverticulitis (level 3) [158]. Similar results are to be found in a large, recent retrospective literature review [234]. From 1985 to 2006, discharge reports of inpatients in New York, collected by the New York Statewide Planning and Research Cooperative System (SPARCS) database, were systematically examined. SPARCS is a robust registry in which patient data including demographics, patient characteristics, diagnoses and treatments for each hospital stay in New York State are recorded, using the international DRG International Classification of Diseases V9th Rev. (ICD-9) for coding [234]. In this analysis, after initial inpatient admission due to acute uncomplicated diverticulitis, most of the patients (91.3%) had no further related admissions. In another population-based study, however, patients with a recurrence of diverticulitis were shown to have an increased risk for further episodes. The risk of a further episode of diverticulitis was 18% in the first year, 55% within 10 years and after a third relapse, 40% within 3 years [188].

Younger age

When considering possible age-dependency in connection with the recurrence of diverticulitis, it must be taken into account that the higher recurrence rate reported in the literature for younger patients may be caused by a higher accumulated risk due to increased life expectancy [154, 195, 216]. A population-based study of 314 conservatively treated patients showed a recurrence rate of 13.3% over an observation period of 8.9 years, with patients > 50 years exhibiting a lower, and patients with comorbidities a higher, rate of relapse [198, 235]. A meta-analysis of 23,078 patients from eight studies also showed a higher probability of recurrence in patients under 50 (RR 1.73; 95% CI 1.40–2.13) compared with patients over 50 years of age.

Other studies also indicate a strong influence of younger age in recurrent diverticulitis [199, 236, 237]. Twenty-two studies including a total of 387,027 patients have investigated the association between age and relapse: three prospective investigations [202, 232, 238], a study of prospective and retrospective data [239], and 18 retrospective studies [78, 80, 188, 198, 204, 218, 234, 240-250]. While the three prospective studies found no significant association [202, 238, 251], the retrospective study [239] showed a higher risk for younger patients

< 40 years of age (multivariate HR 5.01, 95% CI 1.25–20.08). Ten of the other retrospective studies showed a relationship between age and risk of recurrence [80, 188, 198, 218, 234, 241, 242, 244, 246, 247]. These data indicate with significance that age < 50 years is associated with a higher risk (multivariate HR 1.24, 95% CI 1.09–1.41 [244]; multivariate OR 1.20, 95% CI 1.15–1.26) [234] and age >50 years with a lower risk (multivariate HR 0.68, 95% CI 0.53–0.87 [198]; multivariate HR 0.69 per increasing decade, 95% CI 0.59–0.66 [188]; multivariate HR 0.83 for ages 50–64 years, 95% CI 0.80–0.87) [246]. The remaining studies showed a higher recurrence rate in younger patients (age < 50, 40%; 50–70, 17%; age > 70, 19% [218]; age ≤ 50, 26%; age > 50, 11% [80]), and described age as an independent risk factor [80]. In another study, the age of patients with recurrent diverticulitis was younger than that of patients with only one episode of diverticulitis (59 vs. 66 years)[247], while in another study, age > 80 years was described as a protective factor against recurrence of diverticulitis (multivariate HR 0.47, 95% CI 0.37–0.60) [242]. In another nine unadjusted studies, no significant effect was observed [78, 204, 240, 241, 243, 245, 248, 249]. Similarly, in two retrospective studies including 1,441 and 636 patients, respectively, no difference in severity and recurrence rate of acute diverticulitis was found between patients < 50 and > 50 years [196, 204].

Obesity

Published data on BMI and recurrent diverticulitis are inconsistent. There are studies that show BMI to have no significant influence on the recurrence rate after diverticulitis [236]. In three retrospective studies including a total of 898 patients, no influence was found [228, 238, 243]. A further retrospective analysis [228] and a prospective study also failed to find an association (multivariate HR 0.97, 95% CI 0.91–1.03) [232]. In contrast, another retrospective study found an increased recurrence rate in patients with BMI > 30 (univariate OR 1.69, 95% CI 1.08–2.64) [243]. In line with this, a small retrospective case control study with 61 patients including 11 with recurrent diverticulitis and 18 healthy subjects showed that recurrent diverticulitis was significantly associated with a higher BMI ($p = 0.002$) [205]. In a further retrospective analysis of 347 ethnically diverse patients in New York, USA, overweight patients with a BMI > 30 had a higher risk of recurrent diverticulitis than patients without obesity (OR, 1.69; 95% CI, 1.08–2.64; $p = 0.02$) [208]. A further study from New York investigated 265,724 patients with diverticulitis for risk factors for recurrence. It was reported that overweight was associated with an 11% increased risk for at least two inpatient admissions for diverticulitis ($p < 0.0001$) [15]. A similar retrospective analysis from Birmingham, UK, in 65,162 patients with initial diverticulitis found a rate of 11.2% for subsequent inpatient admissions for recurrent diverticulitis. By logistic regression analysis, overweight was demonstrated to be a risk factor for recurrent diverticulitis (OR 1.38 (95% CI 1.26 - 1.52)) [209]. Finally, an analysis of 1,048 patients from the Nurses' Health Study also showed an association between overweight and recurrent diverticulitis. Women with a BMI ≥ 30.0 kg/m² were found to have a higher risk of recurrent diverticulitis (HR 1.66), (95% CI, 1.09–2.51; $p = 0.002$) in comparison to women with BMI < 22.5 kg/m², HR 1.44 (95% CI, 1.16–1.79; $p = <0.001$) [167, 252].

Multimorbidity as a risk factor

In primary care (general practice), the highest prevalence of diverticular disease is found in elderly and multimorbid patients and in connection with polypharmacy [253]. In a current literature review, it was shown that, alongside a first manifestation of diverticulitis, predictors of severe, complicated diverticulitis were the use of non-steroidal anti-inflammatory drugs (NSAIDs) and/or cortisone, high CRP levels on admission, significant changes in radiological imaging, as well as multimorbidity with a Charlson Index score > 3 [131]. In another analysis of 65,162 patients with a diverticulitis recurrence rate of 11.2%, in addition to younger age, risk factors characterised for recurrent diverticulitis were female sex, smoking, overweight, dyslipidaemia or initially

complicated diverticulitis, as well as increased comorbidities with a Charlson Comorbidity Index > 20 [99]. However, the recurrence rate is not generally increased in older patients [242], but probably heightened due to comorbidities associated with older age. Thus, a significant relationship has been shown between age and comorbidity with COPD or heart failure.

Multimorbidity is also associated with an increased risk of mortality, morbidity and complications in patients undergoing elective diverticular surgery. In a retrospective cohort study of 22,752 patients, a comparison of 3,907 (17.2%) multimorbid patients (17.2% COPD, 5.8% heart failure, 1.9% COPD and heart failure) identified these to have a higher probability of anus praeter, wound infection and lung or postoperative complications and a longer hospital stay, compared with non-comorbid patients. The patients were also older, had a higher Charlson Index, and incurred higher hospital costs [254]. In a multivariate analysis, the authors were able to show that patients with COPD with an increased rate of wound infections (OR 1.4, 95% CI 1.19–1.67) or lung complications (OR 2.2, 95% CI 1.94–2.52), and patients with heart failure, had a three-fold higher hospital mortality rate (OR 3.5, 95% CI 2.59–4.63), an almost two-fold increased rate of ostomy (OR 1.9, 95% CI 1.68–2.27) and an increased rate of postoperative complications. Overall, older age, especially > 75 years, COPD and heart failure were significantly associated with increased morbidity and mortality.

Other studies showed that not only mortality, but also the risk of ostomy and of readmission after elective or emergency surgery are increased in elderly individuals [255-257]. In a large review on recurrent diverticulitis, it was shown that wound infections, which occur in 10-20% of these patients, are responsible for the highest morbidity (mortality < 5%) after operative therapy, and that comorbidities and the need for emergency surgery are the main causes of mortality [258].

Immunosuppression as a risk factor

In a population-based retrospective analysis, increased complication rates in recurring diverticulitis were associated not only with a younger age (OR 1.04; CI 1.00–1.08), but also with immunosuppressive therapy (OR 4.71; CI 1.21–18.28) [259]. A large meta-analysis of 11 studies found on Medline, EMBASE and CENTRAL [260] analysed and compared 2,977 immunosuppressed and 780,630 immunocompetent patients undergoing surgery for diverticular disease. The mortality of patients under immunosuppression was increased for emergency surgery, but not for elective surgery. After elective surgery, morbidity was higher in the immunosuppressed (RR 2.18) than in the immunocompetent patients (RR 1.40). Another large meta-analysis from Medline, EMBASE, CINAHL and the Cochrane database [261], including 11,966 patients after organ transplantation, found a diverticulitis rate of 0.1% to 3.5%. In 10 studies giving the proportion of cases of complicated diverticulitis, the pooled incidence of acute uncomplicated diverticulitis in transplantees was 1.7% (95% CI 1.0 to 2.7%), while that of complicated diverticulitis was 40.1% (95% CI 32.2 to 49.7%). Overall, about one in 100 transplant recipients had complicated diverticulitis. Another literature review on transplantees and patients under cortisone therapy, including 25 studies [117], found that the incidence of diverticulitis was 8%, with a mortality rate of 23% under surgical therapy and 56% under conservative therapy. The overall mortality was 25%. The authors conclude that patients who undergo transplantation or receive cortisone therapy have higher rates of both acute diverticulitis and mortality than the general population.

Complicated initial diverticulitis, particularly abscess formation, as a risk factor

Many studies show that the severity of initial diverticulitis is relevant for the disease course and/or risk of relapse. Patients with initially complicated diverticulitis, and especially with abscesses, have a higher risk of recurrence and worse outcomes [234]. In the aforementioned study, data were collected for year of illness, size of hospital, race, health insurance and income. Risk factors (OR 95% CI) for recurrence and other

outcomes were calculated and adjusted for these parameters: The risk of recurrence (OR) for the factor age < 50 vs. > 50 years was 1.18 (1.13-1.24); for a severe course of disease, 1.13 (1.04-1.23); for non-age-dependent uncomplicated vs. complicated diverticulitis, 1.24 (1.16-1.32) vs. 2.51 (2.30-2.74); for complicated diverticulitis < 50 years vs. > 50 years, 1.63 (1.40-1.89) vs. 2.95 (2.43-3.58); for age-independent abscess drainage vs. no abscess drainage, 1.84 (1.60-2.11) vs. 4.89 (4.15-5.76); and for abscess drainage < 50 years vs. abscess drainage > 50 years, 2.27 (1.74-2.95) vs. 5.58 (4.14-7.53). Based on their data, the authors recommend that patients with complicated initial diverticulitis, especially those with abscess formation, should be offered elective surgery, as should younger patients (< 50 years) after two inpatient admissions for diverticulitis [234].

The importance of the severity of the initial diverticulitis, especially abscess formation, with regard to disease outcomes and recurrent diverticulitis has also been emphasised in other studies [231, 262-265]. In a retrospective cohort study, 3,148 patients with a mean age of 65.1 years, 25.6% with previous admission for diverticulitis and 48.1% with multimorbidity, had a mortality rate of 8.7% within 30 days of hospital admission and 2.5% after discharge, while 23.8% were readmitted within 30 days of discharge [264]. A literature analysis showed that diverticulitis outcomes were no more severe in younger than in older people, but that the disease tended to recur more frequently in younger people [262]. In a further literature analysis, the authors evaluated the importance of the severity of initial diverticulitis with regard to the disease course [236]. The relation of abscess formation during initial diverticulitis to subsequent disease course was analysed in 14 studies including 368,452 patients. Four retrospective studies showed an increased risk of relapse (Hinchey Ib and II; multivariate HR 2.6, 95% CI 1.51–4.33, multivariate OR 1.67, 95% CI 1.45–1.94; Hinchey Ib, OR 2.04, 95% CI 1.13–3.67, Hinchey II, OR 6.05, 95% CI 2.62-13.99; multivariate HR 2.02, 95% CI 1.92-2.13). One retrospective study reported an increased risk with more than one abscess (abscess \geq 1, multivariate HR 5.29, 95% CI 2.11–13.3) [241].

In addition, an increased risk of recurrence has been reported after conservatively treated perforated diverticulitis with free air in the CT (Hinchey III) [204]. Furthermore, initial diverticulitis without abscess reduced the risk of relapse (univariate HR 23.2, 95% CI 7.57–71.28 [240]; multivariate HR 6.2, 95% CI 2.5–15.7) and complicated relapse (univariate HR 0.15, 95% CI 0.06–0.4) [245]. A significant correlation with the relapse rate was also described after initial diverticulitis with retroperitoneal abscess (multivariate HR 4.5, 95% CI 1.1–18.4) [231]. The size of the initial abscess, if > 5 cm, also correlated with the recurrence rate [266, 267]. In contrast, a further investigation failed to demonstrate any relation [268]. The probability of readmission, however, correlated with abscess drainage (multivariate HR 4.01, 95% CI 2.72–5.90) and was more than doubled in patients without abscess drainage (multivariate HR 2.38, 95% CI 1.93–2.95) [244]. Compared with initial uncomplicated diverticulitis, severe diverticulitis (Hinchey Ib-IV) was significantly more frequently associated with relapse in the first year of remission [241]. In this study, 54.5% of patients with initially severe diverticulitis also had a severe recurrence of diverticulitis, while 88.5% of patients with mild initial diverticulitis also had a mild relapse. After 5 years, the readmission rate was unrelated to the initial abscess therapy (drainage — multivariate HR 1.56, 95% CI 1.08–2.26; no drainage — multivariate HR 1.42, 95% CI 1.21–1.65). The risk of emergency surgery during relapse correlated with abscess occurrence during initial diverticulitis (drainage — multivariate HR 8.47, 95% CI, 4.55–15.77; no drainage — multivariate HR 4.03, 95% CI 2.73–5.93) [244]. In addition, initial diverticulitis and relapse were of comparable severity according to the Hinchey classifications [238, 269].

3.4.1. Associated diseases

Statement 3.4.1

The probability of a diagnosis of adenoma or carcinoma is significantly increased in patients with a history of diverticulitis. However, there is no conclusive evidence of a heightened risk of colorectal cancer in diverticulosis.

Evidence level 2, strong consensus

Comment – Statement 3.4.1

Concurring evidence from three quite large registry studies (Sweden, Taiwan, Denmark) and a meta-analysis addressing this question shows that diverticulitis is associated with an increased risk for a diagnosis of colorectal cancer [270-273]. Two further meta-analyses show additionally that this risk increase primarily applies to the subgroup of patients with a history of complicated diverticulitis [274, 275]. However, since the association only exists for the first 12-18 months after diverticulitis is diagnosed [270 271], diverticulitis is more likely to be a symptom of carcinoma than a risk factor for its development.

Statement 3.4.2

There is no conclusive evidence for an association of diverticulosis with the occurrence of inflammatory bowel disease.

Evidence level 2, strong consensus

Comment – Statement 3.4.2

A retrospective comparison of 100 patients with inflammatory bowel disease (IBD) with and 100 without concurrent diverticulosis showed a higher mean age and more inflammatory changes in the sigmoid colon/rectum in the group with IBD and diverticulosis [276]. In another study, 314 patients with IBD were compared with 1023 matched controls: Diverticula were found markedly less frequently in the IBD group (3 vs. 15%) [277]. Diverticula were also found less frequently in patients with ulcerative colitis than in matched controls (11 vs. 28%) [278].

Statement 3.4.3

Diverticulosis can be associated with segmental colitis.

Evidence level 2, strong consensus

Comment - Statement 3.4.3

Segmental colitis associated with diverticulosis (SCAD) is a term used to describe inflammatory mucosal lesions in between unattached diverticula. Endoscopy and histology are often similar to findings in IBD [279, 281]. A summary of 486 published cases yielded a prevalence of around 1%. SCAD can be asymptomatic or associated with hematochezia, diarrhoea or abdominal pain [281-283]. In two observational studies, 15 patients were followed up for seven years and 37 patients for 5 years [283, 284]. Five of the 15 patients had symptoms, two of whom were diagnosed with Crohn's disease during the observation period. Several patients had recurrent disease and required immunosuppressive therapy [284]. The endoscopic findings correlated with histological severity [282, 284].

Statement 3.4.4

There is no evidence of an association between mucosal inflammation markers and diverticulosis with clinical symptoms.

Evidence level 2, strong consensus

Comment – Statement 3.4.4

In two current prospective studies, no association was found between diverticulosis and mucosal inflammation: Peery et al. analysed mucosal biopsies taken during a screening colonoscopy in 619 patients (255 with diverticula) [160]. There was no association between mucosal inflammation markers and the presence of diverticulosis or clinical symptoms. Similar data were collected in another case-control study of 254 participants undergoing screening colonoscopy. Although abdominal symptoms and soft stools were somewhat more frequent in patients with diverticula, these symptoms did not correlate with mucosal or serological signs of inflammation [285].

Chapter 4 Diagnosis and Classification

Background

An exact diagnosis of diverticular disease is not only the basis for appropriate therapy, but also a prerequisite for the avoidance of inadequate or excessive therapeutic options. This seems trivial, but it is absolutely relevant and of practical significance [286].

In an older analysis of the resected tissue of 100 consecutive patients undergoing elective diverticulitis surgery, 24% of samples showed no histological signs of inflammation [287]. On the other hand, even histologically normal biopsies from patients with symptomatic diverticulosis show significant changes in the expression of neuropeptides by the intestinal nervous system [62]. Moreover, histological examination of resected tissue from (CT-evident) “phlegmonous” diverticulitis after antibiotic therapy usually shows successful healing, whereas in resected specimen from patients with covert perforation after antibiotic therapy, serious histological structural anomalies remain [288].

Diagnostically, it is important not only to precisely capture the diagnosis of each relevant state within the spectrum of diverticulitis and the differential diagnostic demarcation of diverticular symptoms (pain, inflammation, bleeding) from a multitude of other (extra)intestinal causes, but also - bearing in mind the frequency of diverticulosis - to consider coincidence with other defined entities (e.g., microbial enteritis, colorectal carcinoma, IBD and IBS).

4.1 – 4.5. Medical history, basic diagnosis, differential diagnosis

Recommendation 4.1

The medical history contributes fundamentally to the assessment of the disease potential of diverticulosis and should therefore always be recorded.

Evidence level 3, recommendation grade A, strong consensus

Comment – Recommendation 4.1

By definition, asymptomatic diverticulosis (CDD type 0) has no symptoms; it is therefore not deemed pathologically significant in its own right. In rare cases, even inflamed diverticula can be asymptomatic. In the former classification according to Hansen and Stock, asymptomatic diverticulosis was classified as Stage 0 [289].

Diverticulosis is of prognostic importance due to an increased risk of perforation under NSAIDs, corticosteroids and opiates [207] as well as an increased risk of bleeding under ASA/NSAIDs, direct oral anticoagulants (DOACs) and vitamin K antagonists [144].

In smokers, the risk of diverticular perforation is increased [290]. A medical history of prior diverticulitis can be important with regard to complications (perforation) under immunosuppression (transplantation, IBD, autoimmune diseases) [132]. Bleeding from diverticula/diverticular vessels usually takes the form of painless arterial bleeding that occurs spontaneously.

The anamnesis should clarify

- a) whether there are diverticulosis-related symptoms, and
- b) whether the diverticulosis can be expected to have complications. However, this is only possible on the basis of subtly nuanced signs and without aspiration to diagnostic reliability.

In the anamnesis, the patient should be questioned about medications with harmful potential (including NSAIDs, immunosuppressants) and tobacco use.

Differential diagnosis

Clinically, symptomatic diverticulosis is not reliably differentiable from IBS. Both are diseases, not subjective indispositions or ailments [291]. The patients have symptoms, and although laboratory work-up (CRP, leucocytes), endoscopy and cross-sectional imaging are unremarkable, subtle micromorphological and inflammatory changes are detectable [292]. The laboratory correlate of symptomatic diverticulosis is a discretely increased calprotectin concentration in the stool [293]. However, this parameter is unspecific (with pathological findings in e.g., IBD, NSAID intake, colon carcinoma/adenoma) and diagnostically not sufficiently discriminatory to serve as evidence of SIDD or diverticulitis. However, it can be usefully applied in the differential diagnosis between inflammatory diseases (diverticulitis, infections, or IBD) and IBS.

Recommendation 4.2

Calprotectin can be used for differential diagnosis.

Evidence level 3, recommendation grade 0, strong consensus

Comment – Recommendation 4.2

Patients with symptomatic diverticulosis usually describe pain in the lower left quadrant (LLQ) - possibly cutting, sometimes recurring, occasionally persistent, and often in connection with meteorism and changes in bowel habits. However, as described even in early clinical reports, localisation in the left lower abdomen is significantly relativised by the variability of the position of the sigmoid colon and the occurrence of diverticulitis in the right colon (14% of diverticulitis cases) [294, 295]. Symptomatic diverticulosis is classified as diverticular disease.

Flatulence and/or defaecation bring relief. The sigmoid colon is sensitive to pressure on palpation, occasionally distended, and tympanitic upon percussion. Palpable resistance due to a thickened mass, or objective evidence of inflammation, are seldom findings.

IBS patients tend to be younger, whereas patients with diverticulosis-associated symptoms are generally older; in individual cases, however, this is not helpful. Furthermore, since changes in enterochromaffin cells and neurohumoural transmitter substances have also been described in post-infectious IBS [296], microbially-triggered visceral hypersensitivity can be considered a common denominator.

Surgical inpatient readmission has been reported to occur in 6.1% (n = 19/317; R = 0-48%) of patients after emergency sigmoid resection and in 26.4% (n = 141/534; R = 0-55%) after primary conservative therapy [182]. These data, drawn from a subgroup of a large patient collective (21 studies with n = 31,366 patients), are a

reflection of diverse aspects: on the one hand, residual or recurrent disorders, and on the other, the need of some conservatively treated patients for elective or postponed surgery. However, these findings contribute little when considering, for example, the differential diagnosis of IBS, since these patients are not generally readmitted as surgical inpatients.

Persistence of symptoms after sigmoid resection indicated by diverticular disease is described in about 22-25% of cases [227, 297]. Besides recurring diverticulum development with symptoms and surgery-related adhesion issues, the presence of IBS should be strongly considered, symptoms of which may have promoted the indication for surgery. An occasionally helpful sign that can be taken as evidence of functional or psychosomatic symptoms rather than inflammatory disease/diverticulitis is the closing of the eyes during abdominal palpation (closed eye sign) [298].

According to the German IBS guideline, a diagnosis of IBS is based on abdominal symptoms (pain, flatulence) that both doctor and patient consider bowel-related, that last for more than 3 months, that impair the quality of life, thus prompting medical examination, and that are not explained by other findings in symptom-guided diagnostics [299].

In this context, it is important to note that the Rome II criteria for IBS are often found (OR 1.8; at age > 65 years: OR 9.4) in patients with diverticulosis (women 17%; men 9%), but not in patients with diverticulitis [300]. Accordingly, the term "diverticulitis" should not be used unless imaging methods show evidence of inflammatory changes affecting the diverticula [301].

Basic diagnostics

Recommendation 4.3

If diverticulitis is suspected, a physical examination and laboratory tests including leucocytes, CRP and urinary status should be performed.

Evidence level 2, recommendation grade A, strong consensus

Comment - Recommendation 4.3.

Acute onset, localised, increasing pain in the left lower abdomen, in connection with pathological inflammation parameters (temperature increase > 37.6 - 38°C, CRP > 5mg/100mL, leucocytosis > 10-12000/ μ L) are typical symptoms of diverticulitis [302], whereby the inflammation parameters usually only develop over a period of 1 - 2 days. As the latter are, to a certain degree, also a discriminatory feature of an abscessing/complicated disease course, clinical observation of the patient (palpation findings, temperature) and laboratory testing (CRP) over a period of 48 hours (48-hour rule) ensures diagnostic reliability in the interest of the patient [303]. Additional follow-up after 24 hours is advisable.

Outpatient diagnostics are based on the same criteria. However, collection of the necessary data often fails to withstand critical evaluation, as shown by a study in which body temperature (52.4%) or leucocytes (65.5%) were not recorded in > 50% of the patients. In > 75% of outpatient diagnoses classified as "diverticulitis", at least one of the 3 criteria (LLQ pain, fever, leucocytosis) was missing [286].

The clinical manifestation is sometimes described as "left-sided appendicitis" due to the symptomatology. Additional symptoms can include rectal air leakage, spontaneous defaecation, nausea, constipation and diarrhoea. pollakisuria, dysuria, pneumaturia or even haematuria, as well as pain in the genital area/dyspareunia, indicate local complications (fistula, bladder perforation, irritation of the plexus sacralis). Although vomiting is less common in diverticulitis than unspecific symptoms (e.g., gastroenteritis) [304, 305], it is certainly, as a vegetative symptom, also part of the symptomatology of complicated diverticulitis.

Movement-dependent pain is more suggestive of sigmoid diverticulitis. The weighting of the anamnestic and clinical findings (i.e., age > 50 years [OR 2.15], previous episodes [OR 5.67], LLQ pressure pain [OR 2.96], aggravation of pain on movement [OR 3.28], CRP > 50 mg/L [OR 5.18], localisation of the pain in the left lower abdomen [OR 1.73] and the absence of vomiting [OR 1 vs. 0.38]) depicts the typical diagnostic constellation in diverticulitis, allowing a nomogram to be created that achieves an accuracy of 86% for the clinical diagnosis. In future, use of this scoring system may reduce the rate of false negative clinical findings [305].

Leucocytosis > 10 -12000/ μ L, an increase in C-reactive protein (CRP) > 5 mg/100mL (0.8 mg/100mL) and an accelerated ESR > 15 mm/hour reflect the presence of inflammation, as does increased calprotectin in the stool. For acute diagnostics in an admission setting, determination of calprotectin in the stool is not beneficial; the same applies to other inflammatory markers such as fibrinogen, acidic alpha1-glycoprotein or interleukin-6 and LPS (lipopolysaccharide-binding protein). While LPS has been found to be increased early in stenosing diverticulitis, this is also the case in bacterial gastroenteritis [306, 307].

CRP appears to be most reliably able to objectify diverticulitis in a clinical context. Levels of CRP tend to correlate with complicated/perforated disease.

While values > 5 mg/100 mL reflect diverticulitis, a CRP > 20 mg/100 mL arouses suspicion of perforation (PPV 69%). CRP concentrations < 5 mg/100 mL have a negative predictive value (NPV) of 79% for perforation [308]. However, the specification of such cut-off concentrations requires qualification in the context of method-specific normal values.

On the other hand, a fixation on CRP values as proof/exclusion criterion for diverticulitis is not permissible; its sensitivity is approximately 0.85 and its diagnostic accuracy no higher than 0.93. Furthermore, CRP levels can be influenced by age, NSAIDs or statins [309].

Procalcitonin (PCT) as a one-off measurement is less informative than when repeated serially; PCT can be used as an indicator of a complicated course of diverticulitis (see below) [310]. In contrast, leucocytes and temperature fail to differentiate perforating from non-perforating diverticulitis [311].

Data on the frequency of positive CRP findings vary considerably; while an Italian study group [312] found an increased CRP in 62% of patients with diverticulitis (ESR 57%; leucocytosis 21%), in the publication by Toorenvliet from the Netherlands, 56/57 patients diagnosed with diverticulitis had at least one indication of infection (leucos > 12000/ μ L, CRP > 0.8 mg/100mL, ESR > 15 mm/hour or temp > 38°C). However, it is not known how many patients had each of the individual parameters mentioned.

In the analysis by Laurell et al. [311], a normal CRP value was recorded for 16% of patients with the discharge diagnosis of diverticulitis; in 25%, leucocytes were normal, in 29%, body temperature. It is striking, and must be seen as a limitation, that imaging methods played practically no role in this study: in uncomplicated diverticulitis, CT was performed in only 4% of cases, in complicated diverticulitis (perforation), in 36%. Since the authors are not familiar with ultrasound diagnostics, it remains to be seen how correct the classification "discharge diagnosis diverticulitis" as gold standard actually is.

The most sensitive indicator of complicated diverticulitis is CRP, which had a sensitivity of 84% in a series of 101 operated patients (95% CI 71.7-92.4), compared with 79% for leucocytes (66.1-88.6) and 38.6% for temperature > 37.5°C (95% CI 26.0-52.4%) [313]. PCT can be used as an indicator of complicated diverticulitis if the highest values of consecutive measurements (at admission, and after 24 and 48 hours) are taken (sens. 81%, spec. 91%) [310]. Due to the reiterative, cost-intensive measurements, however, it is clearly less valuable than CRP determination.

A urine status analysis is required to capture differential diagnoses of the urinary tract (e.g., cystitis, ureterolithiasis) or complications of diverticulitis (sigmovesical fistula, accompanying cystitis).

Recommendation 4.4

Diverticulitis should be considered as a differential diagnosis of acute abdominal pain even in younger patients (< 40 years of age).

Evidence level 2, recommendation grade B, strong consensus

Comment – Recommendation 4.4

Although the majority of patients with manifest diverticulitis are > 40 years old, the problem of diverticulitis in younger patients (18 - 44 years) has significantly increased [73]. In women, the differential diagnosis of disorders of the internal genitalia (e.g., midpain, adnexitis/salpingitis, endometriosis, ovarian cyst +/- haemorrhage, ectopic pregnancy) should be considered on the basis of a gynaecological anamnesis and, if necessary, elucidated by means of imaging procedures (ultrasound) and specialist gynaecological examination. Palpation generally reveals a (left-sided) primarily locally defined tenderness, and additionally, in the case of peritoneal irritation, muscular guarding and rebound pain in the lower abdomen (absent if, e.g., the inflamed diverticulum is in a dorsal, retrovesical position). The presence of an inguinal hernia is ruled out as a differential diagnosis through examination of the hernial openings. Rectal examination can be painful if the diverticulitis is located deep down. Closing of the eyes during palpation (closed eye sign) is considered an indication of functional or psychosomatic disorders [298]. While tympany is not uncommon, it is unspecific. It is important to look out for signs of existing ileus (paralysis with overt perforation), especially in seriously ill patients; however, clinical assessment should always include auscultation findings. Diffuse peritonitis through a perforation into the free abdominal cavity comprises an acute abdomen.

Recommendation 4.5

Diverticulitis should be considered as a differential diagnosis of acute abdominal pain, even if the localisation of the pain is right-sided or suprapubic.

Expert consensus, strong recommendation, strong consensus

Comment – Recommendation 4.5

Right-sided symptoms can arise not only from right-sided diverticulitis (diverticulitis in the right hemicolon), but also from a sigmoid loop that extends far to the right. Moreover, a suprapubic localisation is not uncommon [294].

Table 3: Factors and risks affecting the course and severity of Diverticular Disease and Diverticulitis

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