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REVIEW ARTICLE

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German guideline diverticular disease/diverticulitis

Part II: Conservative, interventional and surgical management

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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

interdisciplinary challenge. To meet theses considerations the German Societies for Gastroenterology and Visceral Surgery decided to create joint guidelines addressing all aspects in a truely 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, inflammation, treatment

CHAPTER 5: PROPHYLAXIS AND CONSERVATIVE TREATMENT: PHARMACOTHERAPIES, DIET, LIFESTYLE

Foods and stimulants: Dietary fibre

Recommendation 5.1 A high-fibre diet (≥30 g/day) rich in fruit, vegetables and cereals, should be recommended for men and women, regardless of age, for primary prophylaxis of diverticular disease and in accordance with general dietary recommendations.	Evidence level 1, recommendation grade A, strong consensus
Recommendation 5.2 A recommendation to avoid nuts, grains, corn and popcorn should not be made for the primary prophylaxis of diverticular disease.	Evidence level 2, recommendation grade B, strong consensus
Recommendation 5.3 Limitation of red meat consumption is advisable for primary prophylaxis of diverticular disease. When consumption is greater than 105–135 g/week, the risk increases linearly by about 50%, plateauing at approx. 540 g/week.	Evidence level 2, recommendation grade B, strong consensus
Statement 5.4 Other than avoiding red meat and consuming plenty of fibre, there is currently insufficient evidence for other specific dietary recommendations.	Evidence level 2, strong consensus
Recommendation 5.5 Nicotine abstinence should be recommended for primary prophylaxis of diverticular disease	Evidence level 1, recommendation grade A, strong consensus
Statement 5.6 An increased risk for diverticular disease has been documented for acute alcohol intoxication, for alcohol abuse and for alcohol dependence syndrome.	Evidence level 2, strong consensus

(Continued)

There are currently no data indicating that low-risk or even risky alcohol consumption lead to an increased risk of developing diverticular disease.	
Recommendation 5.7 There are no data that show an association of coffee consumption with the occurrence of diverticular disease. Therefore, a recommendation to this effect regarding coffee consumption should not be made.	Evidence level 2, recommendation grade B, strong consensus
Recommendation 5.8 Maintenance of normal weight should be recommended to prevent diverticular disease.	Evidence level 1, recommendation grade A, strong consensus
Recommendation 5.9 Physical activity can reduce the likelihood of developing diverticular disease or diverticulitis. The most benefit can be gained from over 50 MET-h (metabolic equivalent)/week, corresponding to about 12 h walking at 5 km/h, 6 h cycling at 24 km/h or 4.5 h jogging at 11 km/h. At a minimum, however, in accordance with the DGE, 30–60 min of moderate physical activity per day should be recommended (10 guidelines of the DGE).	Evidence level 1, recommendation grade A, strong consensus
Recommendation 5.10 A healthy lifestyle should be recommended for primary prophylaxis of diverticular disease. A lifestyle incorporating reduced red meat intake, increased consumption of dietary fibre and vigorous physical activity, while maintaining a normal BMI and abstaining from smoking, reduces the risk of developing diverticulitis by up to 50%.	Evidence level 2, recommendation grade A, strong consensus

(Continued)

Recommendation 5.11 Use of NSAIDs, corticosteroids, opioids, and postmenopausal hormone replacement therapy, but not aspirin or coxibs, is associated with an increased risk of developing diverticular disease, diverticulitis, and complicated diverticulitis. The risk association for paracetamol exists primarily with respect to diverticular bleeding. In view of these risks, the corresponding medications should only be administered after careful risk-benefit assessment.	Evidence level 1–2, recommendation grade A, strong consensus

All Statements and Recommendations commented in Supplemental Material.

Pharmacological, dietary and probiotic therapies in active disease

Recommendation 5.12
Segmental colitis associated with diverticulosis (SCAD) can be treated with mesalazine.
Evidence level 5, recommendation grade 0, strong consensus

Comment—Recommendation **5.12**

SCAD is characterised by differing manifestations of colitis between non-inflamed diverticula. In contrast to ulcerative colitis, the rectum is not affected. The prevalence of this clinical condition has been reported to be 0.3%–1.3% in patients with diverticula[1]; SCAD is therefore quite rare, not least because it is probably often overlooked or incorrectly diagnosed (differential diagnosis e.g., IBD). The prognosis seems favourable, without a need for long-term therapy. Formal therapy studies are not available. Acute therapy usually consists of medications used in IBD, with oral mesalazine as first-line therapy.[2,3]

Acute diverticular disease/diverticulitis

Recommendation 5.13
Acute uncomplicated diverticular disease/diverticulitis (CDD types 1a and 1b) should primarily be treated conservatively.
Expert consensus, strong recommendation, strong consensus

Comment—Recommendation 5.13

Acute uncomplicated diverticulitis is practically always treated conservatively.There is no indication for a first-line surgical approach. Studies comparing a conservative versus a surgical approach in the acute situation are not available. In various prospective and retrospective case series, conservative treatment of acute uncomplicated diverticulitis has shown high rates of success, and recurrence rates were also low.[4]

Recommendation 5.14
Patients with confirmed uncomplicated diverticular disease/diverticulitis (CDD1a/b) can be treated on an outpatient basis if there are no signs of serious disease and/or increased risk, and provided they can be closely medically monitored.
Evidence level 1, recommendation grade 0, strong consensus

Comment—Recommendation 5.14

In a systematic review with a literature search in 2011, Friend & Mills found four studies investigating whether outpatient oral antibiotic therapy is adequate for the treatment of uncomplicated diverticulitis.[5] Besides one randomised controlled trial (RCT) with 79 patients, there were two prospective cohort studies (each with 70 patients) and one retrospective cohort study (693 patients). On the basis of these studies, the authors concluded that outpatient treatment is possible under the following conditions: (1) oral intake (fluids, medication, etc.) is possible; (2) there are no significant comorbidities; (3) oral antibiotics are available; (4) adequate pain control is possible; (5) adequate follow-up is accessible and, if necessary, support in the social environment is available; and (6) ultrasound or CT shows diverticulitis without any significant abscess.

A very well-designed systematic review came to the conclusion that outpatient treatment of acute uncomplicated diverticulitis is possible in selected patients, that is, if complications, comorbidities and immunosuppression are ruled out and there is adequate oral intake and social integration. However, the authors also critically note that well-designed randomised studies are lacking, with almost all the evidence coming from observational studies and only three studies existing in which there was no use of antibiotics. Therefore, there is a need for better studies without antibiotics.[6]

Before outpatient treatment of diverticulitis can be considered, complicated diverticulitis must be ruled out. This requires reliable, rapid predictors that are universally available. One candidate is CRP. In a cohort study of 247 patients, only CRP was significantly correlated with perforation in the regression model. The best accuracy was found for a CRP of 150 mg/L, with a sensitivity of 44% and a specificity of 81%. A CRP value < 50 mg/L (normal value: < 5 mg/dl) was shown to have a negative predictive value of 0.79, while a CRP of >150 mg/L had a positive predictive value of 0.57.[7] Notably, however, perforations were also found in patients with normal CRP levels in this study. It should also be borne in mind that inflammation parameters usually take 1–2 days to develop as a distinguishing feature of complicated disease; therefore, clinical and laboratory (CRP) re-evaluation of the patient is recommended after 48 h (48-h rule).[8] Further studies confirm the correlation of CRP with more severe

diverticulitis[9] and with therapy failure.[10,11] In contrast, leucocytes and body temperature fail to differentiate perforating from non-perforating diverticulitis. Since clinical parameters cannot differentiate with sufficient sensitivity and specificity between uncomplicated and complicated diverticulitis, the use of imaging techniques (sonography or CT) is essential before deciding on outpatient therapy. Conversely, it may be concluded that all patients who do not meet the requirements for outpatient treatment should be treated as inpatients.

Diet and lifestyle in symptomatic uncomplicated diverticular disease

Recommendation 5.15

There is insufficient evidence for a recommendation to use a high-fibre diet or fibre supplements in the management of symptomatic uncomplicated diverticular disease.

Nevertheless, a high-fibre diet can be recommended on the basis of general nutritional recommendations (see 2.1.1).

Evidence level 4, recommendation grade 0, strong consensus

Comment—Recommendation 5.15

A systematic review examined the role of a high-fibre diet or fibre supplements in the management of symptomatic uncomplicated diverticular disease (SUDD).[12] The aim of the intervention was to reduce abdominal symptoms and/or prevent flares of acute diverticulitis. Nineteen studies, involving a total of 2443 patients, were included in the review, including all those discussed in Ünlu's earlier review (2012).[13] On the Jadad study quality scale, only one study achieved the highest score of 5 points, 12 studies scored between 1 and 3 points, and six studies zero points. Due to the low quality of the studies and their heterogeneity with regard to the quantity and quality of dietary fibre used, a meta-analysis was not possible. Consequently, although individual studies suggested a positive effect of dietary fibre, it was impossible to make a statement regarding the effectiveness of dietary fibre in the reduction of abdominal symptoms or prevention of acute diverticulitis in patients with SUDD.

Pharmacological therapy of acute (symptomatic) uncomplicated diverticular disease (CDD 1a)

The aim of pharmacotherapy is to improve symptoms and, in particular, to reduce pain. A further aim is to prevent the development of diverticulitis, especially complicated diverticulitis.

Recommendation 5.16

Mesalazine may be considered for the treatment of acute episodes of uncomplicated diverticular disease (CDD 1a).

Evidence level 2, recommendation grade 0, consensus

Comment—Recommendation 5.16

Alongside open observations of mesalazine treatment in acute (active) uncomplicated diverticular disease[14] that show positive results for symptomatic improvement, there are also three RCTs. In a placebo-controlled 4-week study (n = 123), 1000 mg tid mesalazine was described to have various effects on pain.[15] In another randomised, 12-week study, two doses of mesalazine were compared to two doses of rifaximin (n = 170). A significant improvement in pain was recorded in both groups, whereby mesalazine (1600 mg/d) had a significantly more pronounced effect than rifaximin.[16] In another randomised study (n = 268) with a similar design (mesalazine vs. rifaximin), the effects of mesalazine on symptoms were confirmed, and here too, its significant superiority over rifaximin was shown.[17] All studies confirm the drug to have good tolerability, with few side effects.

Despite these various studies, it must be kept in mind that their very different and limited individual quality, very different designs and different endpoints devalue the formal evidence level and preclude a stronger recommendation.

Recommendation 5.17

Therapy of acute uncomplicated diverticular disease with rifaximin or with probiotics cannot be recommended.

Evidence level 3, recommendation grade 0, consensus

Comment—Recommendation 5.17

Based on evidence suggesting that the microbiome plays an essential role in the pathogenesis of uncomplicated diverticular disease, several studies have investigated the use of antibiotics and probiotics.

The effectiveness of the poorly absorbable broad-spectrum antibiotic rifaximin in uncomplicated diverticular disease was examined in a meta-analysis.[18] There were 4 controlled studies, three of them with an open design (Jadad Score 2–3) and one placebo-controlled. All comparisons were made with a combination therapy consisting of rifaximin plus dietary fibre. In the only placebo-controlled trial, there was no difference in symptomatic improvement between the rifaximin plus fibre and the fibre plus placebo groups within the first 3 months.[19] Recently, a controlled open-label study was published that compared rifaximin 400 mg bid for 10 days per month with a fibre supplement. The randomisation was questionable, since imaging was not among the inclusion criteria. After 3 months, a global symptom score improved in both groups. However, no statistics were reported for the inter-interventional difference.[20] Data on the treatment of acute uncomplicated diverticular disease are therefore so few and so incongruent that it is not possible to make an evidence-based recommendation.

Several other double-blind, placebo-controlled studies of probiotics in uncomplicated diverticular disease are discussed in two systematic reviews.[21,22] The study protocols are characterised by a high degree of heterogeneity, for example, very diverse

combinations are tested against different controls, each with different microorganisms and dosages. The studies are mostly of a preliminary nature and of very limited quality. A meta-analysis was therefore not possible; rather, the need for further and better studies was pointed out.[21] Thus, a recommendation for probiotics cannot be given.

Acute uncomplicated diverticulitis with surrounding tissue reaction (CDD 1b)

Mesalazine

Recommendation 5.18
Mesalazine should not be prescribed for acute uncomplicated diverticulitis (CDD 1b).
Evidence level 1, recommendation grade B, consensus

Comment—Recommendation 5.18

In contrast to acute symptomatic uncomplicated diverticular disease, there are hardly any therapeutic studies of mesalazine in CT-verified acute diverticulitis. A retrospective, single-centre cohort study found no significant benefits of mesalazine.[23] In the most recent systematic review on mesalazine in diverticular disease, one RCT in acute diverticulitis is cited.[14] This study also showed no significant benefit.[24] The negative recommendation is therefore based not only on the sparse availability of study data, but also on the negative results reported in the cited studies.

Recommendation 5.19
Therapy of acute uncomplicated diverticulitis with probiotics cannot be recommended.
Evidence level 2, recommendation grade 0, strong consensus

Comment—Recommendation 5.19

There are several studies on probiotic therapy in acute uncomplicated diverticulitis. Two systematic reviews and meta-analyses[21,22] list 3 studies, of which one will not be considered here because diverticulitis was not confirmed by a cross-sectional imaging procedure.[25] A double-blind RCT showed no significant difference in a global symptom score after 12 weeks' treatment with a combination of probiotics and mesalazine compared with placebo.[24] Another blinded, placebo-controlled RCT compared the therapeutic effect of 10 days' treatment with *Lactobacillus reuteri* versus *placebo*. Both groups had additionally received antibiotic therapy with ciprofloxacin/metronidazole for 1 week.[26] The combination with *L. reuteri* resulted in a significant improvement in terms of pain reduction and inflammatory markers and a shorter hospital stay in comparison to placebo. Due to the sparse and inconsistent data, no recommendation can be made for the use of probiotics in acute uncomplicated diverticulitis.

Recommendation 5.20
In acute uncomplicated left-sided diverticulitis (CDD 1b) without risk indicators for complicated disease, antibiotic therapy need not to be prescribed, provided the patient is under close clinical monitoring.
Evidence level 1, recommendation grade 0, strong consensus

Comment—Recommendation 5.20

The question of whether to use antibiotic therapy in acute uncomplicated diverticulitis continues to be a topic of heated national and international debate. In addition to numerous retrospective and smaller prospective studies, two large, randomised multicentric studies have been conducted. The largest study, of 623 patients with CT-confirmed uncomplicated left-sided diverticulitis, revealed no statistically significant differences between the group treated with antibiotics and those who received no antibiotics, in respect of rates of complications (perforation, need for resection, length of hospital stay) during hospitalisation or rates of readmission for recurrence of diverticulitis after 1 year of follow-up.[27] Abscess formation was statistically higher in the group not receiving antibiotics (1% vs. 0%; $p = 0.08$). The study has several methodological weaknesses: The antibiotic therapy (type of drug, administration route) was not standardised, and there was no blinding and no placebo control. CRP on admission was statistically higher in the antibiotics group (100 vs. 90 mg/L; $p = 0.07$). Comorbidities were not classified according to a validated comorbidity index and were based on data from surgical medical records. Several exclusion criteria (e.g., sepsis) were inadequately defined.[27] There is now a follow-up publication with a median follow-up of 11 years that essentially confirms these results.[28] Another open-label study included 528 patients with Hinchey stages 1a/b.[29] The patients were randomised to 2 groups, one with standardised antibiotic administration (initially amoxicillin/clavulanic acid i.v. for at least 4 days with the possibility to switch to oral administration (amoxicillin/clavulanic acid or ciprofloxacin/metronidazole) thereafter, for a total of 10 days), and for comparison, a group that was only observed. The median time to clinical improvement (composite endpoint) was 12 days (7–30 days) in the antibiotic group and 14 days (6–35) in the observation group. Secondary endpoints similar to those of the AVOD study[27] also showed no significant differences. Only the hospital stay was shorter in the observation group. A follow-up study of these patients yielded findings similar to those of the initial study.[29] This study was also subjected to criticism. An up to date, very thorough and critically well-balanced systematic review[30] arrived at the conclusion that treatment of acute uncomplicated diverticulitis without broad-spectrum antibiotics is feasible, safe, and effective. However, as the authors point out, the subgroup analysis of only the randomised studies shows a significantly higher failure rate in patients not treated with antibiotics. The authors also note that the influence of certain risks, for example, comorbidity, on the question of the need for antibiotic therapy has not been sufficiently investigated. Indeed, this points to a crucial aspect that is often overlooked: All of these studies examine a strictly selected (inclusion criteria) patient population with generally mild disease. This

TABLE 6 Lists risk indicators that play a role in the individual indication for antibiotic therapy in acute uncomplicated diverticulitis.[31]

Risk indicators		
Clinical risk indicators	**Laboratory risk indicators**	**Drug-induced risk indicators**
Patient under immunosuppression	High CRP	Immunosuppression
Comorbidity	Leucocytosis	NSAID
Poor overall condition		Corticosteroids
High fever/sepsis		
Complications: Peritonitis, abscess		

is illustrated by some of the exclusion criteria from the AVOD[27] and DIABOLO studies[29]: Poor general condition (ASA > III), high fever, clinical suspicion of bacteraemia, sepsis, peritonitis, immunosuppression. In large studies of antibiotics, in addition to the exclusion criteria mentioned here, a number of clinical and drug-related risk indicators must be taken into account that are associated with more severe diverticulitis and possibly with the risk of a worse course of disease. Overall, comorbidity (Charlson Index ≥3) and immunosuppression play a particularly important role in the disease course.

The results of a recently-published randomised, placebo-controlled, double-blind comparative study with 201 patients, which has yet to be included in any meta-analysis, underline that the jury is still out on whether antibiotic therapy should be given in acute uncomplicated diverticulitis.[32] The therapeutic efficacy of rifamycin SV, a barely absorbable, topically acting antibiotic, was investigated. While antibiotic therapy showed only a statistically marginal ($p = 0.06$) effect after 10 days, the effect was seen much earlier in the antibiotic group than in the placebo group. After 3 days, a significant improvement was observed. In the group of patients with prolonged clinical symptoms, the antibiotic was significantly superior after 10 days. It has also been shown previously that a short, 4-day course of antibiotics (ertapenem) is not inferior to a therapy of longer duration.[33]

In summary, treatment of acute uncomplicated diverticulitis is frequently possible without the use of antibiotics. The limited assessability not only of risk factors, but also of clinical disease severity in the acute situation, indicate that there is scope for individual case-based decision-making, leading to a "can" recommendation (Table 6). This level is corroborated by the fact that while there is good evidence against 10 days of antibiotic therapy, there is strong evidence that a shorter course of treatment with antibiotics may have clinical benefits.

Recommendation 5.21

When diagnosing acute diverticulitis, the patient's general health status and risk indicators should be evaluated and the prognosis assessed.

Evidence level 1, recommendation grade A, strong consensus

Comment—Recommendation 5.21

Since there are various options for the therapy of acute uncomplicated diverticulitis, it is necessary to assess the severity and risks of each specific case. This also allows a prognosis to be made about the possible disease course. Algorithms can assist in estimating the future course of acute diverticulitis that

Supportive therapy in acute, uncomplicated diverticulitis

Recommendation 5.22

Adult patients hospitalised due to acute uncomplicated diverticulitis require no special dietary restrictions.

Evidence level 2, recommendation grade 0, strong consensus

Comment—Recommendation 5.22

Supportive therapy in acute, uncomplicated diverticulitis with low-fibre diet or starvation is often recommended for a short period of time, in the assumption that a less active or "resting" bowel has a beneficial effect with regard to irritation or inflammation of the bowel. Data from studies comparing a liberal versus a restricted diet in acute, uncomplicated diverticulitis in the outpatient and inpatient setting, with or without the use of antibiotic treatment, were assessed in a systematic review.[34] Five studies investigating the effect of dietary fibre were included in the analysis—three randomised controlled studies and two observational studies. Overall, the study quality was very low and meta-analyses could not be conducted due to the inconsistent and divergent data. Patients on a liberal diet had a shorter hospital stay; no differences were found with regard to symptoms, treatment failure or disease recurrence.[34]

Secondary prophylaxis of acute, uncomplicated diverticulitis

Recommendation 5.23

There is insufficient evidence for a recommendation to use a high-fibre diet or fibre supplements as secondary prophylaxis following a flare of acute, uncomplicated diverticulitis. Nevertheless, a high-fibre diet should be recommended on the basis of general nutritional recommendations

Expert consensus, strong recommendation, strong consensus

Comment—Recommendation 5.23

A systematic review identified three studies examining the effect of altered dietary fibre intake on prevention of a further episode of diverticulitis or GI symptoms after an episode of acute uncomplicated diverticulitis.[34] Two of the three studies lacked control groups with a low fibre intake. The authors concluded that the evidence that a high-fibre diet or fibre supplementation has a protective effect against diverticulitis recurrence or improves GI symptoms is very limited. On the other hand, there is also no evidence that a low-fibre diet is superior.[34] Although evidence to support fibre intervention as a secondary prophylaxis after acute, uncomplicated diverticulitis is lacking, the authors recommend long-term consumption of a fibre-rich diet in accordance with generally accepted nutritional recommendations.[34]

A dietary fibre intake of 25–32 g/day for adult women and 30–35 g/day for adult men is recommended throughout Europe. In Germany, ≥30 g/day is recommended for adults, regardless of age and gender. In some countries, recommendations for dietary fibre intake are lowered in older adults to reflect their reduced calorie requirement (e.g., in the USA; for men aged 19–50 years 38 g/day, and for men aged >51 years 30 g/day). In large meta-analyses of prospective cohort studies, a beneficial effect of a high-fibre diet has been documented for for example, mortality regardless of cause, coronary heart disease, arterial hypertension, stroke, hyperlipidaemia, type 2 diabetes, obesity, constipation, diverticular disease and various cancers inside and outside the GI tract.[35]

The American Gastroenterological Association Institute Technical Review on the Management of Acute Diverticulitis addresses, amongst other things, whether a high-fibre diet should be recommended for secondary prophylaxis of acute diverticulitis, whether corn, nuts and popcorn should be avoided, and whether aspirin or non-aspirin NSAIDs should be avoided. In all four instances, the authors are unsure whether the corresponding measure reduces the risk of recurrence of diverticulitis, a related complication, the need for surgery, or abdominal pain.[36] Only with regard to the high-fibre diet were studies found that investigated the question in a population previously affected by acute diverticulitis (included in Carabotti's 2017 systematic review[12]). The very low data quality allowed no firm conclusions to be drawn. Data from prospective cohort studies in collectives without previous diverticulitis (see 2.1.1 and 2.4.1) were considered of insufficient value to solve the question of secondary prophylaxis.[36]

Treatment of acute complicated diverticulitis (CDD 2a)

Recommendation 5.24
Patients with complicated diverticulitis should be hospitalised and monitored.
Evidence level 2, recommendation grade A, strong consensus

Comment—Recommendation 5.24

Acute complicated diverticulitis (CDD 2a, b, c) is a serious illness associated with relevant morbidity and mortality.[37,38] In a multicentric study, 743 patients with acute left-sided diverticulitis were hospitalised. In 67.4% of the patients, the primary treatment was conservative, while 32.6% initially underwent surgery. Postoperatively, complicated diverticulitis of Hinchey grade 0–1 was confirmed in 60.7% of patients, Hinchey 2 in 11.6%, and the most severe complications, Hinchey 3 and 4, in 27.7%.[39]

Of 528 patients with acute diverticulitis initially diagnosed as uncomplicated, 16 (3.0%) went on to develop complicated disease forms with perforations, abscesses and obstructions.[40] This percentage is very probably an underestimate, since the patients comprised a study population rather than a "real world situation", and were thus recruited and initially diagnosed at specialised centres. The American PRACTICE Guidelines assume that 15%–30% of patients hospitalised with acute diverticulitis develop complications requiring an operation shortly after admission.[41]

The prospective DIABOLO substudy identified pericolic fluid accumulation and an inflamed colon segment >8.6 cm in length in the initial CT as prognostic parameters for the progression of diverticulitis initially assessed as uncomplicated. On the other hand, detection of pericolic extraluminal air had no prognostic value.[40]

In summary, complicated diverticulitis is a serious illness with an uncertain course that requires permanent, interdisciplinary monitoring and differentiated (conservative/interventional/surgical) therapeutic strategies. The corresponding diagnostic procedures must therefore be immediately available. Constant monitoring, including the review of risk indicators for complicated disease, is a prerequisite for rapid intervention in the event of deterioration (see also Statements and Comments 4.2.0 and 4.2.1).[42–44]

Recommendation 5.25
If oral fluid intake is insufficient, parenteral fluid substitution should be administered.
Evidence level 3, recommendation grade B, strong consensus

Comment—Recommendation 5.25

Complicated diverticulitis is a severe intraabdominal infectious event. There are no specific studies on the value of intravenous fluid replacement; however, general recommendations apply in this situation and clearly call for fluid substitution.[45]

Recommendation 5.26
Oral feeding can be adapted individually depending on the clinical situation.
Evidence level 5, recommendation grade 0, strong consensus

There is no evidence for a negative effect of situatively adapted enteral nutrition in complicated diverticular disease. A smaller prospective study of 25 patients showed no disadvantage of a careful stepwise liquid diet during the course of treatment.[46]

Recommendation 5.27
In patients with complicated diverticulitis, antibiotic therapy should be administered.
Evidence level 3, recommendation grade B, strong consensus

Comment—Recommendation 5.27

The evidence on this topic is weak, probably because there is a broad clinical consensus. For this reason, the recommendation for antibiotic therapy is not evidenced by targeted studies in this patient group, but must be extrapolated for example, from older studies[47–49] which, however, only sought to compare different antibiotic regimens with one another. Additional pertinent data can be found in a subgroup analysis of the DIABOLO study.[29] Due to the small numbers of cases, the authors are unable to draw any firm conclusions. They do, however, make the recommendation that antibiotic therapy should not be withheld in patients with complicated diverticulitis (in this case Hinchey 1b, no information on comorbidity).

From two study cohorts (including the prospective DIABOLO study), all patients with Hinchey 1a diverticulitis (thickening of the colonic wall >4 mm with limited pericolic inflammation) and free extraluminal, pericolic air were retrospectively selected. The median volume of free air detected in the 109 selected patients was 1.5 cm^3. 92% of the cases were treated conservatively. 48% of the patients received antibiotic therapy. In the antibiotics group, the median CRP tended to be higher, at 142 versus 115 mg/L, and the median free air volume was significantly greater than in patients who received no antibiotics, at 2.0 versus 1.5 cm^3. Treatment failure was observed in 7/52 (13%) in the antibiotics group versus 2/57 (4%) in the non-antibiotics group. In the multivariate analysis, antibiotic therapy had no influence on treatment failure; an effect was identified only for increased CRP, with an OR of 1.01 for each mg/L.[10]

The antibiotics recommended for the treatment of complicated diverticulitis are those that cover the expected polymicrobial spectrum of pathogens. There are currently no data indicating a combination therapy to be superior to monotherapy. There is also insufficient evidence as regards the route of administration (intravenous or oral). However, smaller studies have demonstrated the possibility of success with a sequential intravenous/oral therapy.[50,51] The selection and administration route of antibiotic therapy require an individual decision, taking into consideration the patient's overall condition and risk profile as well as any local resistance. Drugs used in clinical routine are cefuroxime, ceftriaxone and ciprofloxacin, as well as metronidazole, ampicillin/sulbactam, piperacillin/tazobactam and moxifloxacin. When making this selection, it should be noted that there is an official warning for fluoroquinolones.

Overall, these statements are derived from general recommendations of guidelines for antibiotic administration in complicated intraabdominal infections,[45] which also offer guidance on the administration route—intravenous or oral—(no preference) and therapy duration. In this case, 4–7 days are recommended, at least in those patients who respond to therapy.

Chronic uncomplicated diverticular disease (CDD 3a)

Mesalazine

Recommendation 5.28
Intermittent mesalazine therapy can be given to improve symptoms and prevent symptomatic episodes in chronic uncomplicated diverticular disease.
Evidence level 2, recommendation grade 0, consensus

Comment—Recommendation 5.28

Patients with persistent symptoms (over months to years), often after initial episodes of acute diverticulitis, are classified as having chronic uncomplicated diverticular disease, also known as symptomatic uncomplicated diverticular disease (SUDD). The disease is characterised by typical symptoms (persistent pain of undulating intensity, flatulence, irregular stools), but not by clear inflammatory changes (fever, CRP, tomographic imaging). The therapeutic goal is therefore to improve symptoms or prevent their exacerbation. Two recently published systematic reviews discuss a number of RCTs, some of them placebo-controlled, according to the PRISMA standard.[14,52]

In,[52] the authors analyse 7 publications that describe the symptomatic effects seen in 6 RCTs, of which 4 had a duration of between 12 and 48 months.[52] One placebo-controlled trial is available.[53] In this 4-armed study, patients received intermittent (10 days/month) treatment with either mesalazine 1.6 g/d or *Lactobacillus casei* subsp. DG 24 billion/d or *Lactobacillus casei* subsp. DG 24 billion/d plus mesalazine or placebo, for 12 months. Several interesting findings emerged. Following treatment, 93.3% of patients on mesalazine were symptom-free, compared with 54.0% in the placebo group. A total of 7 (3.1%) patients developed acute diverticulitis, of whom 6 were in the placebo group. A further symptomatic episode of diverticular disease occurred in 8 patients (14.5%) on mesalazine therapy compared with 23 (46.0%) of those on placebo. The effect for maintenance of remission of symptoms after 12 months, as primary endpoint, was thus significant and an NNT of 3 was given by the authors. The review[52] concludes that mesalazine is superior to placebo and other therapies in achieving remission of symptoms in SUDD. However, the quality of the data, especially with regard to the inclusion criteria used in the studies, is criticised.

The most recent systematic review, by Iannone, which also applies the PRISMA methodology, comes to very similar conclusions.[14] After a rigorous selection process, 13 RCTs were included in the

analysis. Six RCTs explicitly concerned patients with uncomplicated diverticular disease, while 7 focussed on uncomplicated diverticulitis (not considered here). Four of the 6 RCTs on SUDD demonstrated a significantly greater reduction in a global symptom score after treatment with mesalazine compared with the control groups. The authors[14] conclude that mesalazine might reduce the frequency of symptomatic episodes and improve quality of life in patients with SUDD.

Non-absorbable antibiotics (rifaximin)

Recommendation 5.29
Rifaximin cannot be recommended for the treatment of chronic uncomplicated diverticular disease.
Evidence level 2, recommendation grade 0, strong consensus

Comment—Recommendation 5.29

Rifaximin is a practically non-absorbable antibiotic approved for a variety of indications including hepatic encephalopathy and travellers' diarrhoea, and has been prescribed off-label for diverticular disease for almost 20 years. It has a broad antimicrobial spectrum of action against gram-positive and -negative as well as aerobic and anaerobic pathogens. The available systematic reviews and meta-analyses date back several years.[18,54] National recommendations on the use of rifaximin in uncomplicated diverticular disease vary widely.[55] Whereas in Italy, Poland and Denmark, there are clear recommendations for a combination therapy consisting of rifaximin and dietary fibre, in other guidelines, rifaximin is either not mentioned or not recommended.

The only existing meta-analysis examined the results of 4 RCTs, all of which investigated a combination therapy with rifaximin/fibre.[18] With regard to the goal of preventing new symptomatic episodes, there was a pooled difference of −2% (95% CI: −3.4 to −0.6; $p = 0.0057$; NNT = 50) versus controls. In the only double-blind study (rifaximin 2x400 mg/d for 7 days/month plus glucomannan 2 g/d compared to glucomannan only), there was no difference in effectiveness.[19]

In the same study,[19] a global symptom score showed significant improvement in both therapy arms; however, after 12 months, the effect was significantly greater in the group treated with rifaximin plus glucomannan. This difference was also found in three open-label studies with a similar design.[18]

A large retrospective study presents findings from an observation of patients with chronic uncomplicated diverticular disease who received intermittent therapy with rifaximin or rifaximin-free treatment. The two groups showed no significant differences in terms of recurrence of a symptomatic episode, need for surgery, or mortality. Likewise, no difference was seen in the intensity of abdominal pain; however, the results for bowel habits and bloating were significantly better in the rifaximin group. No adverse effects were reported in the rifaximin group.[56]

Recommendation 5.30
Probiotics cannot be recommended for maintenance of remission in chronic uncomplicated diverticular disease.
Evidence level 2, recommendation grade 0, strong consensus

Comment—Recommendation 5.30

The role of the intestinal microbiome in diverticular disease is increasingly the subject of interest in the scientific literature, and as a result, a growing focus of scientific research. The therapeutic use of probiotics is based on data describing dysbiosis in diverticular disease.[56]

A current systematic review identified 13 studies of probiotics in all types of diverticular disease that met the PRISMA standard.[22] Four of the 13 studies were uncontrolled. Six of the 9 controlled trials tested a combination of a probiotic and (mostly) mesalazine. The remaining 3 studies compared a probiotic monotherapy twice versus placebo.

In a small study, while *Lactobacillus casei* achieved a similar proportion of symptom-free patients compared with mesalazine after 12 months, the combination of both treatments was significantly superior.[57]

In another RCT,[25] 14.3% of patients in the *Lactobacillus casei* group remained free of symptoms (pain) throughout the 12-month study period, compared to 4.0% in the placebo group. Episodic symptom recurrence occurred in 14.5% on probiotics compared to 46.0% on placebo ($p = 0.0$). During the study, a total of 7/210 patients developed acute diverticulitis, one in the probiotic group and six on placebo.

The most recent RCT is a double-blind study ($n = 143$) from England that compares a multispecies preparation versus placebo in patients with a confirmed diagnosis of uncomplicated diverticular disease (SUDD) and pain that had persisted for at least 3 months.[58] The primary outcome of the study, pain intensity over 3 months of therapy, did not differ significantly between the probiotic and placebo groups. Also, the study yielded unconvincing results for the investigational product versus placebo in 8 different, typical symptoms of SUDD.

Recurrent diverticulitis without complications (CDD 3b)

Recommendation 5.31
Mesalazine should not be used for secondary prophylaxis of recurrent diverticulitis.
Evidence level 1, recommendation grade A, strong consensus

Comment—Recommendation 5.31

There are four prospective, randomised, double-blind, placebo-controlled phase 3 studies on the use of mesalazine to prevent relapse of recurrent diverticulitis. The Prevent 1 and Prevent 2 studies, which included 590 and 592 subjects, respectively, had identical study protocols and were published together.[59] The studies included patients who had experienced at least one episode of diverticulitis that had responded to conservative treatment, without surgery, during the last 24 months. The patients were randomised into 4 arms to receive therapy with 1.2 g/day, 2.4 g/day or 4.8 g multimatrix mesalazine or placebo for 104 weeks. The primary endpoint was CT-confirmed recurrence of diverticulitis. In the Prevent 1 study, 53%–63% of patients on mesalazine had no recurrence of diverticulitis, compared with 65% on placebo; in the Prevent 2 study, 59%–69% of patients on mesalazine versus 68% on placebo had no relapse. There was no statistical difference between the 1.2 and 2.4 g groups, respectively, and placebo (p = 0.159–0.780), in either study. In the 4.8 g group of Prevent 1, however, there was a statistical difference (52.7% vs. 64%, p = 0.047), which was not confirmed in Prevent 2 (67% vs. 64%, p = 0.778). In the Prevent 2 study, the time until relapse was statistically even shorter under mesalazine 1.2 and 2.4 g (but not 4.8 g) therapy than under placebo (p = 0.013, p = 0.044, p = 0.179). In Prevent 1, no differences were observed in the time until relapse.

Two jointly published studies, SAG-37, which randomised 345 subjects to 3 g mesalazine granules or placebo for 48 weeks, and SAG-51, which randomised 330 subjects to 1.5 g, 3 g or placebo for 96 weeks, also showed no effect in preventing relapse.[60] The study populations consisted of patients who had experienced at least one episode of uncomplicated diverticulitis confirmed by CT or sonography. The primary endpoint was disease relapse confirmed by clinical and laboratory evaluation within 48 and 96 weeks, respectively. In the SAG-37 study, 67.9% of patients receiving mesalazine were relapse-free, that is, the proportion was not significantly higher than under placebo (74.4%). In the SAG-51 study, the proportion of relapse-free patients on 1.5 g mesalazine (46%) or 3 g mesalazine (52%) after 96 weeks was also not higher than in the placebo group (58%).

In the DIVA trial, a 12-week study of 117 subjects with acute uncomplicated diverticulitis who received placebo, mesalazine (2400 mg) or a combination of mesalazine and Bifidobacterium infantis in three arms, there was no difference in a global symptom score after 12 weeks; a significant difference in favour of mesalazine was seen only in the analysis at 52 weeks. The therapy had no significant influence on the number of recurrences during the follow-up period.[24]

In a placebo-controlled study, intermittent intake of mesalazine for 10 days/month for 1 year also failed to produce any recurrence-preventing effect.[61]

Two meta-analyses confirm the lack of effect of mesalazine in the secondary prevention of uncomplicated diverticulitis.[62,63]

Recommendation 5.32
Rifaximin should not be used for secondary prophylaxis of recurrent diverticulitis.
Evidence level 5, recommendation grade B, strong consensus

Comment—Recommendation 5.32

The use of rifaximin to prevent recurrent flares of acute diverticulitis is another topic of intense debate. However, the effect of rifaximin monotherapy on remission maintenance has yet to be examined in a controlled study. There is evidence to suggest that the combination of rifaximin and dietary fibre may have a positive effect with regard to remission maintenance.[64] Most of the trials with rifaximin were conducted in Italy. A position paper of the Italian Society for Gastroenterology concludes that the concept of a therapy with rifaximin is promising, but that its effectiveness still requires investigation.[65]

Probiotics are the subject of much debate. However, there are no reliable studies on the intake of probiotics in stage 3b. (See also review[22]).

It might be speculated that dietary fibre intake could be effective not only in primary prophylaxis but also in secondary prophylaxis, in stage 3b. Unfortunately, there are not enough data to verify this. There is only one study, a small retrospective analysis of 72 subjects, that shows an effect.[66]

There are also no studies investigating the effectiveness of physical exercise, a low-meat diet, or the avoidance of overweight. However, in view of the general health benefits and the high plausibility of a positive effect with regard to chronic diverticular disease, these measures should not be discouraged.

CHAPTER 6: CHOICE OF OPERATIVE INTERVENTIONS

Conservative versus operative approach

Recommendation 6.1 After acute uncomplicated diverticulitis (CDD 1b), elective sigmoid resection should not be performed in symptom-free patients, regardless of their medical history.	Evidence level 2, recommendation grade B, strong consensus
Recommendation 6.2 In patients with acute uncomplicated diverticulitis CDD 1b with persistent symptoms (“smouldering diverticulitis”), elective sigmoid resection can lead to an improvement in quality of life.	Evidence level 2, recommendation grade 0, strong consensus
Statement 6.3 To distinguish between micro and macro abscesses, a threshold value of approximately 3 cm can be applied, since this reflects the	Evidence level 3, recommendation grade 0, consensus

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possibility of interventional drainage and the risk of recurrence correlates with the size of the abscess.	
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.	Evidence level 3, recommendation grade B, strong consensus
Recommendation 6.5 Larger retroperitoneal or paracolic abscesses (>3 cm) can be interventionally drained (sonography, CT).	Evidence level 3, recommendation grade 0, strong consensus

All recommendations and statements commented in Supplemental Material.

Complicated acute diverticulitis 6.

Complicated acute diverticulitis

Statement 6.6

Patients with acute diverticulitis with macroabscess (CDD 2b) should be hospitalised for antibiotic therapy and referred to a surgeon for examination/co-evaluation.

Evidence level 2, recommendation grade A, strong consensus

Comment—Statement 6.6

Complicated acute diverticulitis with macroabscess is a potentially life-threatening condition. A Danish registry analysis of 3148 patients reported a 30-day mortality rate of 8.7%. Only a small proportion, 6%, of patients was reported to have undergone surgery during the initial inpatient stay.[67]

The proportion of patients who fail to show adequate clinical improvement, or even deteriorate, under first-line non-surgical therapy and go on to require surgery during the initial inpatient stay, varies greatly in the available literature, ranging from 5%[68] to 33%.[69]

A current multi-centric retrospective study from the Netherlands reports that 8.9% of patients require urgent emergency surgery after initial conservative therapy.[70] The only prospective randomised study available on complicated acute diverticulitis found that 11% of patients with treatment failure required emergency surgery.[71]

The risk increases with the size of the abscess and the need for percutaneous drainage. A meta-analysis of 22 studies including 1051 patients, 50% of whom had percutaneous drainage, showed a 30% failure rate of primary conservative therapy.[72] The risk of failure of primary conservative therapy is higher in patients with abscesses than in patients with evidence of extraluminal air (15.6%).[73] A large American registry study showed that twice as many patients required surgery during the first hospital stay due to failure of initial conservative therapy of an abscess compared with an overt perforation, since the latter occurs correspondingly less frequently.[74]

It is not possible to predict the success of primary non-surgical therapy based on the radiological criteria of the initial CT.[75]

In patients who fail primary conservative therapy, urgent surgery has a relevant mortality risk (5.8%); however, antibiotic therapy alone was reported to have a 30-day mortality rate of 10.1%.[76] It is therefore vitally important that failure of primary conservative therapy is recognised in good time, so that the indication for surgery can be quickly made and the procedure performed without delay, in order to avoid subsequent complications. An American registry-based cohort study with 2119 patients reported a significant increase in postoperative morbidity depending on the timing of surgery within the first week after admission (from 38% within the first 24 h to 61.8% after more than one week; 0.001) and an increase in the postoperative length of stay (from 10.72 ± 9.35 days to 22.73 ± 12.06 days; $p < 0.001$).[77]

As yet, however, there are no evidence-based and clearly defined criteria to define the failure of conservative therapy. There are also no reliable predictors for the failure of conservative therapy. Close monitoring with interdisciplinary follow-up, including the involvement of a surgeon, is therefore recommended.

Statement 6.7

About a third of patients with acute complicated diverticulitis are readmitted due to a recurrence of diverticulitis, usually within a year.

Evidence level 2, strong consensus

Comment—Statement 6.7

A systematic review on the frequency of recurrence after acute diverticulitis, including 35 studies with 396,676 patients, described an abscess to be the main risk factor for relapse, with a risk approximately double that observed after uncomplicated diverticulitis. Furthermore, >50% of relapses were again complicated, while 88% of recurrences after uncomplicated diverticulitis were also uncomplicated. Abscess size (≥5 cm), drainage placement and a retroperitoneal localisation have been described as risk factors for a recurrence of diverticulitis.[78]

A systematic review from 2016 specifically focussing on complicated acute diverticulitis with abscess reported an overall recurrence rate of 25.5% (7653 patients) from 23 evaluated studies with 1206 patients. In this collective, the risk of relapse in patients who had had additional percutaneous drainage was lower than after antibiotic therapy alone (15.9% vs. 22.2%, 560 vs. 126 patients).[79]

Another systematic review from 2014, also specifically examining complicated acute diverticulitis with abscess, evaluated comparatively more patients with additional percutaneous drainage (49%). The

authors found a recurrence rate of 28% in this collective; ultimately, only 28% of the patients were able to avoid surgery in the long term.[72]

In the first published, prospective, randomised study on complicated acute diverticulitis with abscess (or extraluminal air), the reported rate of recurrence within 3 years of conservative therapy was 32%, whereby all relapses were complicated.[71]

However, a few cohort studies have reported considerably lower (10%[80]) or higher (60%[81]) recurrence rates.

In addition, large-scale registry-based cohort studies with a large number of cases are available from Denmark, Canada and the USA. The Danish study, with 3148 patients, reports relapse rates of 15.5% after antibiotic therapy alone and 23.6% in patients with additional percutaneous drainage,[67] while the Canadian study of 14,124 patients reports a 12% relapse rate.[82] In the American study, which analysed the records of 237,879 patients, abscesses were identified as the main influencing factor for relapse (OR 1.67, risk 14.0%–18.2%) and poor outcome (OR 3.84, risk 10.2%–13.7%).[83] Across all studies, >50% of recurrences were reported within 1 year of complicated diverticulitis.

In summary, despite the heterogeneity of the data, it can be concluded that the risk for complicated relapse after successful antibiotic or interventional therapy of acute complicated diverticulitis with macroabscess is significantly higher than after uncomplicated diverticulitis. The absolute risk of recurrence was reported in the systematic reviews and the one available randomised study to be between 25% and 28%.

Recommendation 6.8

Patients who have been successfully treated conservatively or interventionally for complicated acute diverticulitis with macroabscess (CDD 2b) can be offered surgery in the inflammation-free interval.

Evidence level 2, recommendation grade 0, strong consensus

Comment—Recommendation 6.8

Numerous cohort studies report that in the long term, the majority (56%–83%) of patients with initial complicated acute diverticulitis with macroabscess underwent surgery.[71,80,84] However, the indication for elective surgery is often not described in detail. Whether surgery was indicated because of recurrent inflammatory flares, persistent symptoms or primarily as a result of the initial flare is unclear.

Larger registry-based cohort studies report a significantly lower rate of elective surgery in the longer term (e.g., 16% of 3148 patients[76,79]; 18.6% of 10,342 patients[85]). In the past, the indication for elective surgery after complicated diverticulitis was based, among other things, on the presumed risk of overt perforation in the event of relapse. However, newer studies have shown that the risk of perforation is at its highest during the initial flare.[86]

The only available prospective, randomised study on complicated acute diverticulitis shows that long-term conservative therapy is also possible without the risk of perforation or urgent surgery; on the other hand, the risk of recurrence is considerably increased (32% vs. 9%; all relapses complicated[71]). However, this study has important limitations: in addition to its monocentric design and the low number of cases, only 49/107 (45%) randomised patients had an abscess, whereas in the majority of cases, only extraluminal air beads without abscess formation were described. Neither the symptoms, nor the quality of life of the patients were analysed in this study.

An American registry study with 10,342 patients found that the 5-year mortality risk for a recurrence of diverticulitis was 1.9% for patients treated conservatively and 0.6% for patients who underwent surgery. In this study, the postoperative 30-day mortality rate was 0.2%.[85]

A US registry analysis with 210,268 patients reported a mortality risk of 2.2% for recurrent diverticulitis with repeated conservative therapy, compared to 4.6% with urgent surgical therapy. In contrast, postoperative in-hospital mortality after elective surgery was 0.3%.[86] Results of the Danish registry analysis, with 1248 patients, indicate a 5-year mortality risk from recurrent diverticulitis of 2.0% after conservative therapy with percutaneous drainage, compared with 1.1% after antibiotic therapy alone and 0.6% after surgery ($p = 0.24$).

Overall, these data show that elective surgery can significantly reduce the risk of death due to recurrence of diverticulitis, provided that patients with a low surgical risk are operated on by surgeons with the appropriate expertise.

Galentin's review summarises the 11 internationally available guidelines on diverticulitis[87]: Five of the guidelines recommend elective surgery after complicated diverticulitis, four give qualified recommendations for elective surgery after complicated diverticulitis, and two make no statement on this issue. The most recent NICE Guideline, from the UK National Institute for Health and Care Excellence, recommends considering surgery if symptoms of diverticular disease persist after successful conservative therapy.

In addition to further investigating the risks of relapse, perforation or emergency surgery, more recent studies focus increasingly on patient quality of life.[88,89] In a German cohort study with 290 patients, albeit with a low follow-up rate (47.6%) and a correspondingly high selection bias, patients who had undergone elective sigmoid resection for complicated diverticulitis with macroabscess had a significantly better quality of life than patients treated conservatively.[89] The first prospective randomised study on the effectiveness of elective resection for persistent symptoms after diverticulitis also includes a high proportion of patients with primary abscess formation.[88]

In summary, due to the relevant risks of relapse and mortality and the frequent improvement in quality of life, patients whose overall condition is good can be offered elective surgery. The advantages and disadvantages of surgery, as well as the risks of a wait-and-see tactic, should be discussed with the patient, based on the individual risks of surgery, recurrence and complications. This particularly applies to patients whose symptoms persist after conservative therapy.

Statement 6.9
An elective operation after successful initial conservative therapy of acute complicated diverticulitis with macroabscess should be performed ca. 6 weeks after completion of the conservative therapy.
Evidence level 2, recommendation grade B, strong consensus

Comment—Statement 6.9

All of the studies mentioned above show that the highest incidence of relapse is within the first year after index diverticulitis. The available Kaplan-Meier curves for recurrence of diverticulitis also clearly show that the risk of relapse is significantly higher during the first 6 months than in months 7–12.[67,82,86] In a cohort study with 210 patients, the median time interval until recurrence was 3.5 months.

Accordingly, on the basis of their retrospective registry study, Gregersen et al. recommend that elective surgery should be performed as soon as possible after the acute symptoms of inflammation have subsided.[67]

Regarding the optimal timing of elective surgery, a systematic review compared patients who underwent surgery within 6 weeks with those operated after a longer interval, on the basis of 4 cohort studies. No differences were found with regard to the risks of anastomotic insufficiency or postoperative mortality. However, based on moderately heterogeneous study data, the authors found both a longer duration of operation and a higher risk of conversion to open surgery in patients who underwent early elective surgery.[90]

In summary, elective surgery should be performed early to minimise the risk of a recurrence of diverticulitis. However, since (too) early operation can be associated with difficult operating conditions, an interval of 6 weeks should be allowed after the infection has entirely cleared, with a corresponding convalescence period.

Conservative versus operative approach—Complicated (recurrent) Diverticulitis

Recommendation 6.10 Patients with overt perforation and peritonitis in acute complicated diverticulitis should be operated on within 6 h after diagnosis (emergency surgery).	Evidence level 3, recommendation grade B, consensus
Recommendation 6.11 Symptomatic uncomplicated diverticular disease (CDD 3a) should not be treated surgically.	Evidence level 4, recommendation grade B, strong consensus
Recommendation 6.12 The risk of recurrence in chronic recurrent diverticulitis CDD 3b increases with each flare. The risk of perforation is highest during the first episode and decreases with each subsequent relapse. Therefore, the indication for surgery should not be determined by the number of previous flares.	Evidence level 2, recommendation grade B, strong consensus

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Recommendation 6.13 Elective sigmoid resection can significantly improve quality of life in patients with chronic recurrent diverticulitis CDD 3b. Impairment of quality of life due to recurrent disease should be an important determinant in decision-making when considering elective surgery in these patients.	Evidence level 2, recommendation grade B, strong consensus
Statement 6.14 The risk factors for a complicated postoperative course in patients with chronic recurrent sigmoid diverticulitis CDD 3b correspond to the general risk factors for elective colon resection.	Evidence level 1, strong consensus
Statement 6.15 Chronic recurrent diverticulitis CDD 3c with evidence of fistulas should be treated surgically.	Evidence level 3, recommendation grade B, strong consensus
Recommendation 6.16 Chronic recurrent diverticulitis CDD 3c with evidence of symptomatic colonic stenosis should be treated surgically.	Evidence level 3, recommendation grade B, strong consensus

All statements and recommendations commented in Supplemental Material.

CHAPTER 7: CHOICE OF OPERATIVE INTERVENTIONS

Recommendation 7.1
If technically possible, minimally invasive sigmoid resection should be favoured over open surgery.
Evidence level 2, recommendation grade B, strong consensus

Comment—Recommendation 7.1

The minimally invasive approach has been shown to be superior with respect to minor complications. In addition, the patients' quality of life is postoperatively better in the short-term after minimally invasive surgery.[91] Other outcomes of the open and laparoscopic procedures (major complications, long-term quality of life) are considered comparable.[92] Minimally invasive sigmoid resection is also technically feasible in patients with colovesical fistula[93,94] or right-sided diverticulitis.[95]

Statement 7.2
The total laparoscopic operation, the laparoscopy-assisted operation, the robot-assisted operation, and hand port procedures are all proven, safe, and effective.
Evidence level 3, strong consensus

Comment—Statement 7.2

Comparative studies on different minimally invasive procedures are available only with a low level of evidence and show no relevant differences.[96] It is therefore not possible to make a relative assessment of the individual procedures.

Recommendation 7.3 In perforated sigmoid diverticulitis with generalised peritonitis (CDD 2c1/2), sigmoid resection with primary restoration of continuity, with anastomosis and protective ileostomy, should preferentially be performed as the standard surgical procedure. In patients who are unstable or have sepsis, the Hartmann procedure should be performed.	Evidence level 2, recommendation grade B, strong consensus
Recommendation 7.4 In patients with perforated diverticulitis with purulent peritonitis (CDD 2c1), primary sigmoid resection should be performed. A potential alternative therapeutic strategy is laparoscopic peritoneal lavage and drainage, without resection.	Evidence level 2, recommendation grade B, strong consensus
Recommendation 7.5 The "damage control" procedure, with sigmoid resection and blind closure of the ends of the bowel, and abdominal vacuum therapy with two-stage anastomosis max. 72 h after successful treatment of the abdominal infection, can be used as a treatment strategy for diverticulitis CDD 2c1/2.	Evidence level 3, recommendation grade 0, strong consensus
Recommendation 7.6 The oral resection margin for sigmoid resection should be chosen directly proximal to the acutely or chronically inflamed bowel segments. Additional diverticulum-bearing bowel segments without inflammatory or post-inflammatory changes should not be resected.	Evidence level 3, recommendation grade B, strong consensus
Recommendation 7.7 The aboral resection margin should be situated in the upper rectum.	Evidence level 3, recommendation grade B, strong consensus
Recommendation 7.8 A tension-free, well-perfused and leak-tight anastomosis should be created. If this requires mobilisation of the left flexure, this should be performed.	Expert consensus, strong recommendation, strong consensus
Recommendation 7.9 Ligation of the inferior mesenteric artery central to the origin of the left colic artery should not be performed.	Evidence level 3, recommendation grade B, strong consensus

(Continued)

Statement 7.10 Provided the anastomosis is technically correctly performed, stapler and hand sutures are to be regarded as equivalent.	Evidence level 1, strong consensus
Recommendation 7.11 Anastomotic insufficiency after sigmoid resection should be treated using a step-by-step approach, depending on clinical severity. If diffuse peritonitis occurs, reoperation with (protective or terminal) stoma creation should be performed.	Evidence level 4, recommendation grade B, strong consensus

All recommendations and statements commented in Supplemental Material.

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CONFLICT OF INTEREST

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

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in [repository name for example, "figshare"] at http://doi.org/[doi], reference number [reference number].

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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 Material:

Chapter 5 Prophylaxis and Conservative Treatment: Pharmacotherapies, Diet, Lifestyle

Foods and Stimulants: Dietary fibre

Recommendation 5.1

A high-fibre diet (≥ 30 g/day) rich in fruit, vegetables and cereals, should be recommended for men and women, regardless of age, for primary prophylaxis of diverticular disease and in accordance with general dietary recommendations.

Evidence level 1, recommendation grade A, strong consensus

Comment – Recommendation 5.1.

The question of whether the quantity and type of dietary fibre consumed influences the risk of developing diverticular disease is addressed by a recent meta-analysis which includes five prospective cohort studies with a total of 865,829 participants and 19,282 patients [398]. The included studies and cohorts are the Health Professionals Follow-up Study (HPFS) (47,888 men) [399], the EPIC-Oxford study (47,033 men and women) [193], the Million Women's Study (690,075 women) [400], the Swedish Mammography Cohort (36,110 women) [401] and the Cohort of Swedish Men (44,723 men) [401].

Overall, the authors determined a relative risk (RR) of 0.74 (95% CI 0.71-0.78) per 10 g fibre intake per day. Compared to a consumption of 7.5 g fibre/day, intakes of 20, 30 and 40 g/day had an RR of 0.77 (95% CI 0.74 - 0.79), 0.59 (95% CI 0.55 - 0.64) and 0.42 (95% CI 0.35 – 0.51), respectively.

With respect to fibre sources, the RR per 10 g intake/day was 0.74 (95% CI 0.67-0.81) for cereals, 0.56 (95% CI 0.37-0.84) for fruits and 0.80 (95% CI 0.45-1.44) for vegetables.

A number of other prospective cohort studies have examined the relationship between dietary fibre consumption and the risk of developing diverticulitis. The HPFS of 45,203 men found an RR of 0.77 (95% CI 0.60 - 0.98) for fibre consumption in the highest quintile (≥ 23g/day) versus the lowest quintile [402]. With an RR of 0.86 (95% CI 0.78 – 0.95), the Nurses' Health Study of 50,019 women demonstrated a lesser effect for fibre consumption in the highest quintile (mean 28.5g/day) versus the lowest quintile (Q) (mean 12.5 g/day) (402). According to this study, dietary fibre from cereals, fruits and especially whole apples, pears and plums has a protective effect, whereas vegetable fibre does not. The 1998 evaluation of the HPFS cohort also showed a favourable effect, especially for insoluble dietary fibre, but with diverticular disease as the endpoint [403].

The importance of a high-fibre diet for health, above and beyond its implications for diverticular disease, is well documented by systematic reviews and meta-analyses [404-406]. This evidence is reflected in the recommendations of the German, Austrian and Swiss societies for nutrition [407].

Foods and Stimulants: Nuts, grains, corn and popcorn

Recommendation 5.2

A recommendation to avoid nuts, grains, corn and popcorn should not be made for the primary prophylaxis of diverticular disease.

Evidence level 2, recommendation grade B, strong consensus

Comment Recommendation 5.2.

Contrary to the previously frequently expressed notion that undigested rests of nuts, corn and popcorn can get stuck in the diverticular neck and lead to increased complications, the analysis of the HPFS cohort showed that regular consumption of these foods can actually even reduce the risk of developing diverticular disease. Compared to those with the lowest consumption (less than 1x/month), men with the highest consumption (at least 2x/week) had an RR of 0.80 (95% CI 0.63-1.01) for nuts and 0.72 (95% CI 0.56-0.92) for popcorn [194].

5.3. Red meat

Recommendation 5.3

Limitation of red meat consumption is advisable for primary prophylaxis of diverticular disease. When consumption is greater than 105-135 g/week, the risk increases linearly by about 50%, plateauing at approx. 540 g/week.

Evidence level 2, recommendation grade B, strong consensus

Comment – Recommendation 5.3.

Evidence that red meat consumption represents a risk factor for the development of diverticular disease or diverticulitis, or the consequent need for hospitalisation, has been consolidated by the publication of two recent, prospective cohort studies [402, 408].

In the 1994 HPFS cohort analysis, increased red meat consumption led to a 1.5-fold increased risk of developing diverticular disease, albeit without evidence that this increase was dose-dependent. An intake of 39.4, 65.9, 97.4, or 144.4 g red meat/day resulted in the same risk as an intake of 16.0 g/day. On the other hand, individuals who consumed at least one meat dish daily as a main meal (113-170 g beef, pork, lamb) had a 3.23-fold higher risk of developing diverticular disease than those who consumed less than one meat-based main meal per month [399]. In the EPIC cohort analysis published in 2011, the RR for diverticular disease in vegetarians in comparison to meat eaters was 0.69 (95% CI 0.55–0.86). The cumulative probability of diverticular disease-related hospitalisation or death was 4.4 for 50 to 70-year-old meat eaters vs. 3.0% for vegetarians [193].

In the 2017 HPFS cohort analysis, men in the highest quintile for red meat consumption (14 portions/week; 150g/day) had an RR of 1.43 (95% CI 1.10–1.85) compared with those in the lowest quintile (1.2 portions/week; 15g/day) for the occurrence of diverticulitis [402].

A paper published in 2018, also using data from the HPFS cohort, found an RR of 1.58 (95% CI 1.19 – 2.11) for diverticulitis development in men in the top quintile for red meat consumption (12.4 portions/week) compared with those in the lowest quintile (1.5 portions/week) [408]. As in the 1994 study, the increase in risk was not linear, but plateaued at 6 portions/week. The association was stronger for unprocessed red meat (RR for Q5 vs. Q1: 1.51 95% (1.12 – 2.03)) than for processed red meat (RR for Q5 vs. Q1: 1.03 (95% CI 0.78 – 1.35)). Increased consumption of poultry or fish showed no association with the risk for diverticulitis; however, replacing one serving of unprocessed red meat by one serving of poultry or fish per day reduced the risk of developing diverticulitis, with an RR of 0.80 (95 % CI 0.63 – 0.99) [408].

How can nutritional recommendations be derived from these data?

The 10 rules of the German Society of Nutrition (DGE, https://www.dge.de/ernaehrungspraxis/ vollwertige-ernaehrung/10-regeln-der-dge/) recommend intake of around 300g of meat/sausage per week for individuals with a low calorie requirement and around 600g of meat/sausage per week for those with a high calorie requirement, with no differentiation made between red and white meat:

However, if the risk of developing diverticular disease is to be reduced, the results of the above-mentioned cohort studies underline the need for more restrictive intake recommendations on red meat intake. Maximum protective effects were reported for 7 x 16g = 112g/week (64), 7 x 15g = 105g [402] and, with an average portion size of 90g, for 1.5 x 90g = 135g/week [408]. Two studies reported that the risk of developing diverticular disease plateaued with a given quantity of red meat, and that the risk did not further increase when even higher amounts were consumed. This plateau effect was seen at 7 x 39.4 = 275.8 g/week in one study (64) and 6 x 90g = 540 g/week in the other [408]. The protective effects described are 50% [399], 43% [402] and 58%.

Statement 5.4

Other than avoiding red meat and consuming plenty of fibre, there is currently insufficient evidence for other specific dietary recommendations.

Evidence level 2, strong consensus

Comment – Statement 5.4.

Another analysis of the HPFS cohort examined the effect of more complex dietary patterns, rather than individual nutritional components, on the risk of developing diverticulitis [410]. The so-called Western diet is defined in this study as a diet that includes high proportions of red and processed meats, refined flour, sweets/candies, French fries and high-fat dairy products, while the recommended diet includes plenty of fruit, vegetables, wholemeal products, legumes, poultry and fish. For the Western diet, men in the highest quintile had a multivariate hazard ratio (HR) of 1.55 (95% CI 1.20-1.99) for the development of diverticulitis compared to those in the lowest quintile. For those consuming the recommended diet, men in the highest quintile had a reduced risk of diverticulitis compared to those in the lowest quintile (multivariate HR 0.74 (95% CI 0.60-0.91). The effects of the dietary patterns were primarily attributable to their dietary fibre and red meat content. Total fat content and saturated fats had no influence on the risk. The data also indicate that recent intake (1-4 years) of the Western diet, in particular, increases the risk of developing diverticulitis [410].

The Western diet is associated with higher plasma concentrations of inflammatory markers such as CRP, IL-6, TNFαR2 or adiponectin in comparison to the recommended diet. Chronically active inflammation plays an important role in the development of chronic disease, including cardiovascular disease, type 2 DM and carcinoma.

In the HPFS cohort, men in the highest quintile of the Western diet had a multivariate HR of 1.31 (95% CI 1.07-1.60) compared with those in the lowest quintile for developing diverticulitis. Plasma samples were collected for determination of CRP and IL-6 a median of 7.9 years before diverticulitis was diagnosed. Men with the highest CRP concentrations had an RR of 1.85 (95% CI 1.04-3.30) for developing diverticulitis in comparison to those with the lowest concentrations. The corresponding RR for IL-6 was 2.04 (95% CI 1.09 - 3.84) [411].

5.5. Smoking

Recommendation 5.5

Nicotine abstinence should be recommended for primary prophylaxis of diverticular disease.

Evidence level 1, recommendation grade A, strong consensus

Comment – Recommendation 5.5.

The relation between cigarette smoking and the development of diverticulitis or complications of diverticulitis was examined in a meta-analysis [412]. The link between current smoking and the development of diverticular disease was analysed from the results of four prospective cohort studies with 363,205 participants and 5,964 cases. The RR was determined to be 1.36 (95% CI 1.15 – 1.61). The same data were used to analyse this risk for former smokers. The RR for the development of diverticular disease was 1.17 (95% 1.05 - 1.31). Five cohort

studies with 370,699 individuals and 6,076 cases were available for the analysis of the association between “ever smoked” and diverticular disease. The resulting RR was 1.33 (95% CI 1.21 – 1.47). For an examination of the dose-response relationship, four cohort studies were available. The RR was found to be 1.11 (95% CI 0.99 - 1.25) per 10 cigarettes/day, whereby the risk increased more steeply for the first five cigarettes, becoming linear thereafter.

For the analysis of the risk of complications such as perforation or abscess, two cohort studies were available for current smokers and former smokers, and three for "ever smoked". The respective RRs for current smokers, past smokers, and ever smoked were 2.54 (95% CI 1.49-4.33), 1.26 (95% CI 0.81-1.95), and 1.83 (95% CI 1.25-2.67) [412].

The analysis of the Swedish construction workers’ cohort on the association between cigarette smoking and hospitalisation for diverticular disease was not included in the meta-analysis. The cohort included 232,685 men and 14,592 women [413]. Men who smoked 15 or more cigarettes per day had an RR of 1.56 (95% CI 1.42-1.72) for the development of diverticular disease requiring inpatient treatment compared to non-smokers. The RRs for moderate smokers and ex-smokers compared to non-smokers were 1.39 (95% CI 1.27-1.52) and 1.14 (95% CI 1.04-1.27), respectively. The ratios were similar for women, but were less precise due to the smaller number of cases. Men who had ever smoked had an RR of 2.73 (95% CI 1.69 - 4.41) for the development of complicated diverticular disease with perforation or abscess. The available data did not allow confounders such as lifestyle, medication or comorbidities to be taken into account in the analysis [413].

The analysis of the HPFS cohort from 2017 found a multivariate RR of 1.27 (95% CI 1.01 – 1.58) for the occurrence of diverticulitis in men with a smoking history of ≥ 40 pack years compared to men who had never smoked [402].

A case control study of 176 patients who required emergency hospitalisation due to diverticulitis found that smokers and ex-smokers had a distinctly increased risk of needing surgical therapy, in the form of partial colectomy [414].

5.6. Alcohol

Statement 5.6

An increased risk for diverticular disease has been documented for acute alcohol intoxication, for alcohol abuse and for alcohol dependence syndrome.

There are currently no data indicating that low-risk or even risky alcohol consumption lead to an increased risk of developing diverticular disease.

Evidence level 2, strong consensus

Comment – Statement 5.6.

Low-risk alcohol consumption equates to a consumption of ≤ 24 g alcohol/day for men and ≤ 12 g alcohol/day for women, with at least 2 alcohol-free days/week; risky alcohol consumption means consumption of > 24 g/day for men and > 12 g/day for women. Alcohol abuse is used to describe consumption at a level causing demonstrable consequential damage to mental or physical health. In accordance with general nutritional recommendations, and in view of the general health risks of alcohol consumption, recommendations for low-risk alcohol consumption should be in line with the thresholds indicated in the German S3 guideline [415] or the 10 guidelines of the DGE (≤ 20 g/day for men and ≤ 10 g/day for women).

In the 1995 analysis of the HPFS cohort, a statistically insignificant RR of 1.36 (95% CI 0.94 – 1.97; p for trend = 0.37) was found for the development of diverticular disease in men with a daily alcohol intake of > 30 g compared with men who abstained from alcohol. In the subgroup analysis, no link was identifiable between

consumption of beer or wine and the development of diverticular disease. Consumption of 1-3 units of spirits/month resulted in a 50% increased risk of diverticular disease; the dose-response relationship was weak, so that an intake of 2-3 units of spirits/day led to a risk increase of 65% [409].

In the EPIC cohort, no effect of alcohol consumption was found on the necessity for hospitalisation due to diverticular disease [193].

A Danish working group analysed a cohort of 21,094 men and 7,723 women discharged from hospital after inpatient therapy due to a diagnosis of alcoholism or alcohol-induced psychosis, with respect to their subsequent need for diverticulitis-related hospitalisation [416]. The national inpatient admission rate for diverticulitis served as a control. The results showed RRs of 2.0 for the men with alcohol-related illness, and 2.9 for the women. The risk decreased only very slightly over time, and was still 1.9 for men and 2.5 for women 5 years after the diagnosis of alcohol abuse.

A Taiwanese working group studied a cohort diagnosed with alcohol intoxication. In a 1:4 ratio, 51,866 patients with alcohol intoxication were matched according to age and sex with 207,464 persons without a history of alcohol intoxication [417]. The multivariate HR for development of diverticular disease during the observation period was calculated to be 3.21 (95% CI 2.76-3.74), whereby the value for women, at 3.44, was slightly higher than for men (3.19). The effect was more pronounced for patients < 45 years, with an HR of 4.95 (95% CI 3.91 - 6.27), compared with individuals ≥ 45 years, whose HR was 2.34 (95% CI 1.89 - 2.88). When the severity of intoxication was divided into tertiles, the HR was 1.98 (95% CI 1.64 - 2.39) for the group with mild intoxication, 4.73 (95% CI 3.86 - 5.79) for the group with moderate intoxication, and 10.3 (95% CI 8.27 – 12.7) for those with severe intoxication [417].

5.7. Coffee

Recommendation 5.7.

There are no data that show an association of coffee consumption with the occurrence of diverticular disease. Therefore, a recommendation to this effect regarding coffee consumption should not be made.

Evidence level 2, recommendation grade B, strong consensus

Comment – Recommendation 5.7.

In the 1995 HPFS cohort analysis, no association was found between coffee consumption and the occurrence of diverticular disease [403].

Body weight, physical activity, healthy lifestyle

5.8. Overweight

Recommendation 5.8

Maintenance of normal weight should be recommended to prevent diverticular disease.

Evidence level 1, recommendation grade A, strong consensus

Comment – Recommendation 5.8.

Available data indicate that the risk of developing diverticular disease or diverticulitis is at its lowest at a BMI of 20.0-22.5 kg/m^2 and that the relationship between increasing BMI and risk is linear.

The BMI is not in all respects a perfect measure of unhealthy overweight, since it overlooks, for example, the important aspect of fat distribution and muscle mass and does not take into account categories of normal weight vs. overweight and age-related development [418, 419]. There are also conflicting data concerning the mortality risk for persons in the category "overweight" (25 - < 30 kg/m^2) [420].

According to the S3 guideline for the prevention and treatment of obesity [421], individuals with obesity (BMI ≥ 30 kg/m^2) or overweight (25 - < 30 kg/m^2) with obesity-related health disorders (e.g., arterial hypertension,

type 2 DM), abdominal obesity, or diseases that are aggravated by overweight or high levels of psychosocial stress, should strive to lose > 5% of their initial body weight within 6 - 12 months.

The association between BMI and diverticular disease, diverticulitis, and complications such as perforation, abscess and bleeding, was examined in a meta-analysis [422]. The analysis of the association between BMI and diverticular disease drew data from six cohort studies with 1,636,777 participants and 28,915 cases. The RR for the highest vs. the lowest BMI was 1.78 (95% CI 1.48 - 2.14). A linear dose-response relationship was found even within the normal BMI range, with an RR of 1.28 (95% CI 1.18 - 1.40) for a BMI increase of 5 kg/m^2. In the analysis of the relation between BMI and diverticulitis, 2 cohort studies with 89,798 participants and 1,159 cases were included. The RR for the highest vs. the lowest BMI category was 2.09 (95% CI 1.63 - 2.68). The dose-response analysis showed a threshold-free linear relationship with an RR of 1.31 (95% CI 1.09 – 1.56) for a BMI increase of 5 kg/m^2.

Three studies with 93,699 participants and 2326 cases were included in the analysis of the association between BMI and complications of diverticular disease, such as perforation, abscess and bleeding. The RR for a BMI increase of 5 kg/m^2 was 1.20 (95% CI 1.04 - 1.40). The dose-response relationship showed signs of non-linearity, with the lowest risk shown for a BMI of 22 kg/m^2 [422].

As only one study [423] reported details on waist circumference and waist-to-hip ratio, a meta-analysis of these data was not possible [422]. In the analysis of the HPFS cohort, with 47,228 participants, it was found that men in the highest quintile for waist circumference had a multivariable RR of 1.56 (95% CI 1.18 - 2.07) for the occurrence of diverticulitis compared to those in the lowest quintile [423]. After adjustment for BMI, the waist-to-hip ratio remained an independent risk factor for the occurrence of complications. Pathogenetically, through the release of pro-inflammatory cytokines from visceral fat, central obesity may play a role in diverticular disease [423].

An analysis of the Nurses' Health Study cohort published in 2018, with 46,079 participants and 1,084 cases of diverticulitis, was not included in the meta-analysis [424]. In a multivariate analysis, women with a BMI ≥ 35.0 kg/m^2 had an HR of 1.42 (95% CI 1.08-1.85) versus those with a BMI < 22.5 kg/m^2 for development of diverticulitis. For women in the highest quintiles for waist circumference and waist-to-hip ratio, respectively, the RRs for development of diverticulitis compared with the lowest quintile were 1.35 (95% CI 1.02-1.78) and 1.40 (95% CI 1.07-1.84). When BMI was included as a variable in these calculations, the association was found to be reduced. Compared to women who were able to maintain a constant weight from the age of 18 up until the time of analysis, women who gained ≥ 20 kg in weight had an RR of 1.73 (95% CI 1.27-2.36) for the development of diverticulitis.

Recommendation 5.9

Physical activity can reduce the likelihood of developing diverticular disease or diverticulitis. The most benefit can be gained from over 50 MET-h (metabolic equivalent)/week, corresponding to about 12 h walking at 5 km/h, 6 h cycling at 24 km/h or 4.5 h jogging at 11 km/h. At a minimum, however, in accordance with the DGE, 30 to 60 minutes of moderate physical activity per day should be recommended (10 guidelines of the DGE).

Evidence level 1, recommendation grade A, strong consensus

Comment – Recommendation 5.9.

The association between physical activity and diverticular disease or diverticulitis was also investigated in a meta-analysis [422]. Five cohort studies with 147,869 participants and 2,080 cases were included in an analysis of the association between physical activity and the occurrence of diverticular disease. The RR for high vs. low physical activity was 0.76 (95% CI 0.63 - 0.93). Because data pertaining to measurements of

physical activity varied from study to study, it was not possible to carry out a dose-response analysis [422]. In general, however, the data from these studies showed that vigorous physical activity leads to stronger effects than less vigorous activity, and that for the maximum effect, > 50 MET-h/week were generally required [422, 425].

Two cohort studies with 89,798 participants and 1,158 cases reported data on vigorous physical activity and the risk of developing diverticulitis. The RR for vigorous physical activity vs. low physical activity was 0.74 (95% CI 0.57 - 0.97) [422].

Recommendation 5.10

A healthy lifestyle should be recommended for primary prophylaxis of diverticular disease.

A lifestyle incorporating reduced red meat intake, increased consumption of dietary fibre and vigorous physical activity, while maintaining a normal BMI and abstaining from smoking, reduces the risk of developing diverticulitis by up to 50%.

Evidence level 2, recommendation grade A, strong consensus

Comment – Recommendation 5.10

There are a number of cohort studies providing relatively few, but methodologically good, data on the effect of a lifestyle that minimises several risk factors ("healthy lifestyle") with regard to the development of diverticular disease.

In the 2017 analysis of the HPFS cohort, including 51,529 men and 907 cases, the effect of a combination of different lifestyle factors on the risk of developing diverticulitis was investigated [402]. A low-risk lifestyle was defined as red meat consumption < 51 g/day, fibre consumption in the top 40% of the cohort (approximately 23 g/day), vigorous physical activity in the top 50% of those participants who engaged in vigorous physical activity at all (roughly 2 hours of activity/week), a normal BMI (between 18.5 and 24.9 kg/m^2) and being a “never-smoker”. An inverse, linear relationship was found between the number of low-risk lifestyle factors and the incidence of diverticulitis. Compared to men with no low-risk lifestyle factors, the RR for developing diverticulitis for those with 1 factor was 0.71 (95% CI 0.59-0.87), with 2 factors 0.66 (95% CI 0.55-0.81), with 3 factors 0.50 (95% CI 0.40 - 0.62), with 4 factors 0.47 (95% CI 0.35 - 0.62) and with 5 factors 0.27 (95% CI 0.15 - 0.48) [402].

The authors estimate that about 50% of diverticulitis cases could be avoided by adopting a low-risk lifestyle. Since the HPFS cohort consists of a group of individuals who live more healthily than the general population, the effect may be even larger in the latter [402].

In a Norwegian cohort of 42,750 people, 358 were found to have been hospitalised with a diagnosis of acute diverticulitis. In addition to age, BMI ≥ 30 kg/m^2 (HR = 2.58), dyspnoea (HR = 2.57) and living in a rural area (HR = 1.74) were found to be risk factors in men; in women, the identified risk factors were BMI ≥ 30 kg/m^2 (HR = 2.06) and prior or current cigarette smoking (HR = 1.65). On the other hand, no effect was found for education level, physical activity, presence of constipation or preferred type of bread eaten [426]. The study has weaknesses, such as the rough categorisation of risk factors (e.g., bread - fine, coarse, or mixed, as a measure of fibre intake) and missing data for at least one risk factor in approximately 50% of participants.

An interesting perspective was provided by the study of a cohort of 43,772 Swedish military recruits drafted between the ages of 18 and 20 and thoroughly screened at that time. Over the following 39 years, with the help of the National Patient Register, 444 men were identified who were discharged from inpatient hospitalisation with a diagnosis of diverticular disease. This allowed the identification of lifestyle factors of young adulthood that manifest as risks for the development of diverticular disease in later life [427]. Men with

a BMI ≥ 25 kg/m^2 had an HR of 2.02 (95% CI 1.50 - 2.73) in comparison to the reference group with a BMI of 18.5 - 22.5 kg/m^2. A high level of cardiovascular fitness was found to be protective, with an HR of 0.94 (95% CI 0.87-0.99), while smoking was associated with an increased risk, which was most pronounced for 1-5 cigarettes/day, with an HR of 1.60 (95% CI 1.18 – 2.18). Whereas alcohol consumption per se, up to a consumption of 250 g alcohol/week, did not increase the risk of developing diverticular disease in later life, risky alcohol consumption was identified as a risk factor, with an HR of 1.43 (95% CI 1.09 - 1.88). Contrary to the definition given in 2.1.6, cited from the German literature, risky alcohol consumption was defined as self-reported consumption of alcohol to alleviate a hangover, arrest for drunkenness and/or frequent drunkenness [427].

Another possible lifestyle factor could be to consciously seek exposure to UV light even during the winter months, in order to maintain higher serum concentrations of vitamin D. A US nationwide study initially observed a seasonal, sinusoidal course of non-elective hospital admissions for diverticulitis, with the lowest numbers in February and an increase of 25.2% up until August [428]. An analysis of 25-hydroxyvitamin D serum concentrations in 9,116 individuals with diverticulosis and 922 patients hospitalised for diverticulitis showed significantly higher vitamin D levels in the people with diverticulosis (29.1 vs. 25.3 ng/mL; $p < 0.0001$). The multivariate RR of hospitalisation due to diverticulitis for those in the highest versus those in the lowest vitamin D quintile was 0.49 (95% CI 0.38-0.62) [429]. Another study showed a higher incidence of diverticulitis-related hospitalisations in areas of the USA with lower UV light exposure. Admissions were observed to peak from June to August, and thus with a latency of several months from the lowest UV light exposure [191]. Finally, research carried out in Australia described a seasonal peak in April for diverticulitis cases in the southern hemisphere [430].

Recommendation 5.11

Use of NSAIDs, corticosteroids, opioids, and postmenopausal hormone replacement therapy, but not aspirin or coxibs, is associated with an increased risk of developing diverticular disease, diverticulitis, and complicated diverticulitis. The risk association for paracetamol exists primarily with respect to diverticular bleeding. In view of these risks, the corresponding medications should only be administered after careful risk-benefit assessment.

Evidence level 1-2, recommendation grade A, strong consensus

Comment – Recommendation 5.11

A meta-analysis of eight case-control studies found NSAID use to be associated with an increased risk of diverticular perforation (OR 2.49; 95% CI 1.98-3.14) [431]. The largest of these case-control studies reported similarly high risks for current and prior use, with ORs of 1.51 and 1.62, respectively, but only the value for “ever use” was statistically significant [207].

The 1998 analysis of the HPFS cohort, with 35,615 male participants, determined that subjects taking NSAIDs had an increased risk of diverticular disease, with an RR of 2.24 (95% CI 1.28-3.91) [143].

In the later analysis of the 2011 HPFS cohort, including 47,210 participants, the RR for the development of diverticulitis in NSAID users was 1.72 (95% CI 1.40 - 2.11) [144].

A German study examined 194 patients who underwent colonoscopy, of whom 144 had diverticulosis without a previous episode of diverticulitis, while 50 had previously been diagnosed with diverticulitis. Whereas the use of NSAIDs (OR 3.2; 95% CI 1.5 -6.9) increased the risk for diverticulitis, aspirin use did not [432].

A meta-analysis of three case-control studies found no increased risk of diverticular perforation for aspirin (OR 1.03; 95% CI 0.69-1.55) [431].

The 1998 analysis of the HPFS cohort showed that the risk of developing symptomatic diverticular disease was not increased in subjects taking aspirin more than twice a week (RR 0.80; 95% CI 0.55–1.18) (143). In contrast, the 2011 analysis reported an RR of 1.25 (95% CI 1.05 – 1.47) for the occurrence of diverticulitis in men taking aspirin ≥ 2x/week. However, no linear dose-response relationship was found. For example, individuals who took 2-5.9 325 mg tablets of aspirin per week had a higher risk of diverticulitis (HR 1.26) than those who took ≥ 6 tablets (HR 1.11). On the other hand, daily aspirin use at an unspecified dose resulted in a higher risk of diverticulitis (HR 1.46) than aspirin use 4 to 6 times a week (HR 1.24) [144].

Using the data of the Swedish mammography cohort of 36,586 women, 44.2% of whom were taking aspirin, showed no increase in the risk of hospitalisation for diverticular disease [433].

Paracetamol

In the first analysis of the HPFS cohort, from 1998, individuals who regularly took paracetamol were found to have an increased risk of developing symptomatic diverticular disease, with an RR of 1.81 (95% CI 0.79 – 4.11). The main risk was in connection with increased bleeding [143].

COX-2 inhibitors (coxibs)

In a population-based case-control study, Humes et al. [207] found that the use of coxibs was rare. Only 7.8% of cases and 3% of controls had ever used these substances. In contrast, 66% of cases and 52% of controls reported a history of NSAID use. After correction for confounding factors, current intake of a coxib was no longer significantly associated with an increased risk of perforation.

Corticosteroids

The meta-analysis of 5 case-control studies examining the association between corticosteroid use and diverticular perforation reported a greatly increased risk, with an OR of 9.08 (95% CI 3.49 - 23.62) [431]. Humes et al. reported a higher risk of diverticular perforation for current versus “ever” steroid use: OR 2.74 (95% CI 1.63 - 4.61) vs. 1.69 (95% CI 1.41 - 2.04) [207].

In the Swedish mammography cohort, the risk of symptomatic diverticular disease was increased, with an RR of 1.37 (95% CI 1.06-1.78) for oral steroid intake and 1.71 (95% CI 1.36-2.14) for inhaled steroids, the latter having an RR for diverticular disease-related hospitalisation of 1.44 (CI 95% 1.06 - 1.97) after 1 - 10 years, 1.95 (CI 95% 1.01 - 3.77) after 11 - 20 years, and 6.07 (95% CI 3.00 - 12.3) after ≥ 21 years of use [433].

In Denmark, a population-based analysis was performed, including all patients ≥ 18 years of age who were hospitalised for perforated diverticulitis between 2005 and 2013. The cohort consisted of 4,640 patients. Of these, 897 (19.3%) had used corticosteroids in the past year, 725 of whom were on systemic therapy. The mortality rate of patients who used systemic steroids was calculated at 7, 30, and 90 days, and at 1 year. In comparison with the group who had not previously taken steroids, mortality rates after 7 days and 1 year were slightly increased in patients who had recently used steroids (91-365 days before admission), with HRs of 1.11 and 1.23, respectively; mortality was also increased in patients with current steroid use, with respective HRs of 2.10 and 2.05, and was highest, with HRs of 2.88 and 2.89, respectively, in patients who had recently started steroid medication (≤ 90 days before the event) [434].

On the other hand, a Taiwanese case-control study described a protective effect of long-term steroid use with regard to the need for inpatient therapy for right-sided diverticulitis. The OR was 0.60 (95% CI 0.35-1.06) for current steroid use and 0.80 (95% CI 0.64-1.008) for previous steroid use. This study raises the question of whether right-sided diverticulosis/-itis and the left-sided diverticulosis/-itis that is prevalent in the western world are comparable entities [436].

Oestrogen/progesterone

65,367 postmenopausal women were included in the prospective Nurses' Health Study cohort and the association of menopausal hormone therapy with the occurrence of diverticulitis was investigated. A total of 5,435 cases were identified. The risk of diverticulitis was increased with both current (HR 1.28; 95% 1.18-1.39) and past (HR 1.35; 95% 1.21-1.42) hormone intake, regardless of whether a pure oestrogen preparation or an oestrogen-progesterone combination was used. The risk did not increase with a longer duration of use [437].

Opioids

A meta-analysis of three case-control studies found a pooled OR of 2.52 (95% CI 1.77-3.57) for diverticular perforation in patients using opioid drugs [431]. The study by Humes et al. found a 2.16-fold increased risk for current opiate analgesic use and a 1.88-fold increased risk for past opiate use [207]. The data reported by Morris et al. show a higher risk associated with daily than with occasional use [438].

Calcium antagonists

While individual studies reported a protective effect of calcium antagonists on the risk of diverticular perforation, this effect was not confirmed in a meta-analysis of three case-control studies, which showed a pooled OR of 0.70 (95% CI 0.37-1.34) [431].

Statins

In a population-based case-control study with 899 cases and 8,980 controls, current use of statins was associated with a reduced risk of perforated diverticulitis (OR = 0.44; 95% CI 0.20-0.95). However, past use of statins had no effect [207].

A possible association between use of statins and the occurrence of diverticular disease was recently investigated in a population-based case-control study of 13,127 hospitalised cases and 128,442 controls in Sweden. Current statin use was defined as intake within the last 125 days; intake ending more than 125 days previously was considered former use. The study identified neither an increased nor a reduced risk for the development of diverticular disease in current statin users (OR = 1.00; 95% CI 0.94-1.06); however, they required emergency surgery significantly less frequently (OR = 0.70; 95% CI 0.55-0.89) [438].

Use of NSAIDs, corticosteroids, opioids, and postmenopausal hormone replacement therapy, but not aspirin or coxibs, is associated with an increased risk of developing diverticular disease, diverticulitis, and complicated diverticulitis. The risk association for paracetamol exists primarily with respect to diverticular bleeding.

Tocilizumab and tofacitinib have been reported to be associated with an increased risk of colonic perforation in patients with rheumatoid arthritis, particularly in patients with a history of diverticulosis/diverticulitis.

In the light of this risk, these drugs should only be administered after careful risk-benefit assessment.

Chapter 6 Choice of Operative Interventions

Conservative versus operative approach

6.1. Conservative versus operative approach - Diverticulitis CDD 1b

Recommendation 6.1

After acute uncomplicated diverticulitis (CDD 1b), elective sigmoid resection should not be performed in symptom-free patients, regardless of their medical history.

Evidence level 2, recommendation grade B, strong consensus

Comment – Recommendation 6.1.

About 20% of conservatively treated patients with diverticulitis go on to have at least one relapse; however, the complication rate after conservative treatment of uncomplicated diverticulitis is low, at < 5% over the course

of 10 years. In a population-based retrospective study from Sweden [259], 809 patients had acute uncomplicated diverticulitis (642 new-onset, 167 recurrence). About 2% developed complications, irrespective of initial/recurrent diverticulitis, gender, inflammatory parameters and prior conditions, e.g., DM. Only immunosuppressive therapy was found to be associated with an increased risk of complications. In 2012, a large retrospective Spanish study documented an increased risk of complications in patients under immunosuppression, especially steroids [498], although the frequency of emergency surgery was no higher than in patients without immunosuppression.

Two meta-analyses specifically examining patients who have undergone organ transplantation [117, 261] show an increased incidence of diverticulitis overall and an increased proportion of complicated disease types. Several current retrospective cohort studies point to increased postoperative risks in these patients and do not recommend elective resection in general [499-501]. A review of national and international guidelines [152] reveals that only 5 of 11 guidelines specify elective resection in immunocompromised patients with complicated diverticulitis. None of the guidelines contains an indication for prophylactic sigmoid resection due to diverticulosis. Similarly, a cohort study [274] concluded that elective sigmoid resection is not to be recommended in patients undergoing chemotherapy, as these patients have an increased risk of postoperative complications and no increased risk of relapse.

A total of three meta-analyses have addressed the question in younger patient populations. A meta-analysis on diverticulitis in young Israelis [262] found a relative risk of 1.7 in patients under the age of 50; at the same time, the risk for urgent operations was not increased. A systematic review [236] points to an increased risk of recurrence in younger people. The most recent meta-analysis [502] confirms the overall higher risk of relapse in younger patients; however, the study also shows that there is no increase in the risk of complicated diverticulitis, indicating that the therapeutic strategy should not be modified in younger patients.

Finally, data are also available for patients with obesity, who are known to have an increased risk of diverticulitis. A retrospective cohort study [503] with evaluation of CT imaging reported that the risk of recurrence in patients with a BMI >30 was not increased.

6.2. Conservative versus operative approach – Diverticulitis CDD 1b - smoldering diverticulitis

Recommendation 6.2

In patients with acute uncomplicated diverticulitis CDD type 1 with persistent symptoms ("smouldering diverticulitis"), elective sigmoid resection can lead to an improvement in quality of life.

Evidence level 2, recommendation grade 0, strong consensus

Comment – Recommendation 6.2.

Some 4-10% of patients with diverticulitis have so-called "smouldering diverticulitis", defined as persistent symptoms after acute diverticulitis with initially increased inflammatory parameters, fever and CT-detectable inflammation [214]. However, the definition is not standardised in the literature and in certain cases, it is difficult to clearly differentiate persistent symptoms after acute diverticulitis from chronic recurrent diverticulitis.

A meta-analysis [211] investigating the quality of life after elective sigmoid resection showed an improvement compared with patients receiving conservative therapy; however, the underlying cohort studies were of poor quality. On the basis of this analysis, a first prospective randomised study was initiated with this objective. The Dutch DIRECT trial [504] compared the therapeutic effect of elective sigmoidectomy (n=53) with conservative therapy (n=56) in an open-label, randomised, prospective multicentric study in patients with recurrent diverticulitis or persistent symptoms (smouldering diverticulitis) after acute diverticulitis (initial diagnosis confirmed by CT or endoscopy). The primary endpoint was the quality-of-life index (QoL), measured according

to the Gastrointestinal Quality-of-Life Index (GIQLI) after 6 months. This was significantly higher in the surgically treated patients (114.4 vs. 100.4). After 5 years of follow-up [505], the GIQLI was still significantly better in the surgically treated group, at 118.2 vs. 108.5. Ultimately, 26 patients (46%) in the initially conservatively treated group had to undergo surgery because of persistent symptoms. A cost-effectiveness analysis after 5 years showed an advantage in favour of surgical treatment [505]. Unfortunately, the results of the DIRECT trial were not differentiated for recurrent diverticulitis vs. smouldering diverticulitis.

In a German retrospective study [506], a significant improvement in quality of life was described in 44 patients with smouldering diverticulitis who had undergone surgery, with a Gastrointestinal Quality of Life Index (GIQLI) of 115 (72-143) compared to GIQLI 98 (56-139) in the preoperative situation (p = 0.018). Eighty percent of the patients were satisfied with the result of the operation.

The authors of a recently published cohort study suggest an increased incidence of undiagnosed intramural or pericolic abscesses in the course of acute diverticulitis as a possible cause of persistent symptoms [507].

Conservative versus operative approach – Diverticulitis CDD 2a

Statement 6.3

To distinguish between micro and macro abscesses, a threshold value of approximately 3 cm can be applied, since this reflects the possibility of interventional drainage and the risk of recurrence correlates with the size of the abscess.

Evidence level 3, recommendation grade 0, consensus

Comment – Statement 6.3.

An evidence-based distinction between micro and macro abscesses is not available in the literature. In the majority of available studies, diverticulitis CDD 2a and 2b have been combined into a joint cohort, as patients with covert perforation. The earlier guideline proposed a limit of 1 cm. A distinction based on the therapy, such as the possibility of interventional drainage, or on prognostic significance, would seem more suited. The reported diameters of percutaneously-drained abscesses vary considerably in the available studies (6 cm [3-18cm][508]; 6cm [3-18cm] [509]; 6.7 (3-15) [510]; > 4 cm [511]; 5.6 ± 2cm, 85% > 4cm [512]; 6·4 (5.0-8·5); 6.4cm [5.0-8.5cm] [513]; 8.5 ± 0.9cm [342]).

Recommendation 6.4

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

Evidence level 3, recommendation grade B, strong consensus

Comment – Recommendation 6.4.

Specific analyses of patients with microabscesses are not yet available in the literature. Therefore, initial treatment analogous to CDD 2b seems appropriate. Since there is no evidence for the effectiveness of elective resection, especially for small abscesses, and since the risk of recurrence is lower with smaller abscesses, there is currently no indication for elective resection after successful conservative therapy.

6.5. Conservative versus operative approach – Diverticulitis CDD 2b

Recommendation 6.5

Larger retroperitoneal or paracolic abscesses (> 3cm) can be interventionally drained (sonography, CT).

Evidence level 3, recommendation grade 0, strong consensus

Comment – Recommendation 6.5.

The level of evidence on the indication for percutaneous abscess drainage in complicated acute diverticulitis is still low. Recommendations are based exclusively on retrospective cohort studies. Indications for drainage

are resultantly heterogeneous. They can depend on abscess size and localisation, and on the response to antibiotics as sole therapy.

As a consequence, the proportion of patients with percutaneous drainage compared to those treated with antibiotics alone varies widely in the individual studies (from 78% with drainage at an abscess size ≥ 3cm [510]; 26.7% in [513]; and only up to 11% in [240].

There are also reports of multiple interventions in patients with initially insufficient abscess drainage or inadequate clinical response [514]. However, this approach was associated with an increasing risk of treatment failure with conversion to surgery. Therefore, the authors did not recommend more than 2 attempts. Moreover, in a small cohort study [342], a 38% risk of faecal fistula development was reported. Due to the lack of data, it is not possible to estimate the technical success rate of percutaneous drainage placement. The duration of drainage also varied widely (8 days [1–18 days] [508]; 36 days [511]; 8 days [1-18 days] [509]; 28 days [510]; 6 days [3-16 days] [513]).

Those non-randomised studies that examined the effectiveness of percutaneous drainage versus antibiotic therapy alone for the avoidance of surgery showed them to have a comparable risk of treatment failure [508, 510, 513, 515].

Overall, there is still no conclusive evidence that percutaneous abscess drainage is effective as a reinforcement of antibiotic therapy and can actually obviate urgent surgical intervention. The recommendation is therefore based on general principles of abscess treatment. It is also unclear whether abscess drainage should be performed as a primary therapy or only when antibiotic treatment has failed. Since this procedure can also have relevant complications, it should only be carried out in patients with larger abscesses situated so that they allow safe interventional access, and with subsequent close clinical monitoring. The drainage procedure should be selected according to the site of the abscess and the locally available expertise (sonography, CT).

6.10. Conservative versus operative approach –Chronic complicated Diverticulitis (CDD 2c)

Recommendation 6.10

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

Evidence level 3, recommendation grade B, consensus

Comment – Recommendation 6.10

Only a few studies have examined the indication for conservative treatment of perforated sigmoid diverticulitis. In particular, the question as to whether surgery is indicated in patients with free extraluminal air without accompanying peritonitis, or purulent (CDD 2c1) or faecal (CDD 2c2) peritonitis, has been little investigated. One reason for this is that, in the past, many studies have used the Hinchey classification, which does not describe the presence of free air without major abscesses or signs of sepsis/peritonitis. Similarly, the CDD classification does not currently allow for overt perforation without peritonitis.

In a retrospective cohort study by Sallinen et al. [527], however, overt perforation without the presence of a macroabscess was explicitly examined. A total of 132 patients were examined in 3 groups according to different manifestations of extraluminal air: In group I (n = 82), only paracolic air was detectable; in group II (n = 29), intraabdominal free air was detected; in group III (n = 14), the gas bubbles were generalised retroperitoneally. In the course of follow-up, conservative therapy was successful in groups I-III in 99%, 62% and 43% of the patients, respectively, with a mortality rate of 0%, 5% and 7%. Although the authors considered the results to

be limited due to their retrospective nature, a conservative approach in patients with little intraperitoneal or paracolic air and without clinical signs of peritonitis remains under discussion.

In the case of overt perforation with purulent or faecal peritonitis (CDD 2c1 and 2c2), the indication for surgery is generally given.

Thorisson et al. [528] described similar results in 107 patients treated conservatively for perforated diverticulitis. However, the success rate of conservative therapy when free air was diagnosed was only 34%. If, in addition, a macroabscess was present, the success rate dropped to 17%.

Colas et al. [529] also examined reasons for the failure of conservative therapy in this patient group. Of 91 patients, only 29 (31.9%) were identified as treatment failures. The amount of free intraabdominal air and the presence of abscesses were significant risk factors.

A very high success rate of 84.4% was reported by Titos-Garcia et al. [518] with regard to the conservative therapy of overt perforation. In this study, too, far better results were achieved in patients with paracolic air only, with a 90.2% success rate, in contrast to 61.5% in patients with generalised intraabdominal free air.

Overall, the available data and the quality of the studies justify a conservative approach only in very selected cases. A conservative approach can be considered as an individual therapeutic trial, particularly in patients with no signs of peritonitis and only local paracolic air. Surgical treatment remains the therapy of choice.

Since the indication for surgery in these patients is based on peritonitis or sepsis, the general surgical criteria for emergency laparotomy for hollow organ perforations should be applied. This is backed up by the study of Mozer et al. [521]. The authors observe that when there is a need for surgical therapy, the earlier the operation is performed, the better the outcome.

Conservative versus operative approach – Uncomplicated Diverticulitis CDD 3a

Recommendation 6.11

Symptomatic uncomplicated diverticular disease should not be treated surgically.

Evidence level 4, recommendation grade B, strong consensus

Comment – Recommendation 6.11

Symptomatic uncomplicated diverticular disease (SUDD) CDD 3a is a default diagnosis, i.e., there are no objective criteria to confirm this diagnosis. In many cases, it is impossible to clinically differentiate from IBS. There are no controlled studies that unequivocally prove the effectiveness of surgical therapy. In a retrospective cohort study, 47 patients with “atypical smouldering diverticular disease", who had symptoms for at least 6 months during a 10-year period, underwent sigmoid resection [530]. Data from 12-months’ follow-up were available for 68% of the patients. Of these, 76.5% were completely symptom-free and 88% were pain-free.

There is evidence from a randomised, placebo-controlled conservative interventional study that patients with SUDD may have an increased risk for acute diverticulitis [485]. The rate in the placebo arm was 12% in the first year. This rate was significantly reduced under conservative therapy with probiotics +/- mesalazine. In this situation, an operation would be a primary prophylaxis against a diverticular complication. Again, there is no supporting evidence for this clinical scenario. If patients become or remain symptomatic after diverticulitis or recurrent flares of diverticulitis, it is not classified as SUDD in the narrower sense.

In summary, if the pathogenesis/pathophysiology is unclear, the diagnosis is uncertain and there is no conclusive evidence for the effectiveness of an operation that would allow a benefit-risk assessment, such an intervention is currently inadvisable.

Conservative versus operative approach – Chronic recurrent Diverticulitis CDD 3b

Recommendation 6.12

The risk of recurrence in chronic recurrent diverticulitis CDD 3b increases with each flare. The risk of perforation is highest during the first episode and decreases with each subsequent relapse. Therefore, the indication for surgery should not be determined by the number of previous flares.
Evidence level 2, recommendation grade B, strong consensus

Comment – Recommendation 6.12.

After the first episode of diverticulitis, the risk of recurrence is around 8% and increases with each subsequent relapse; after the fifth flare, it is about 45% [236]. However, the risk of perforation is highest, at about 5-25%, during the first episode of diverticulitis, and decreases with each additional flare; during the fifth flare, the risk of perforation is below 1% [233, 531]. This roughly corresponds to a halving of the perforation risk with each subsequent episode of acute diverticulitis. The cause of this has yet to be conclusively clarified; adhesions caused by previous episodes of inflammation may play a role.

Only about 5% of patients hospitalised for recurrent diverticulitis require emergency surgery [154, 532]. In principle, recurrent episodes of diverticulitis lead neither to a higher complication rate nor to a higher failure rate of conservative therapy [228]. However, risk factors for a complicated relapse (steroid medication, abscess) have been described [245]. In a retrospective cohort study of 210 patients, the risk of recurrence with perforation was 0.7% [533]. Another retrospective cohort study focussed on long-term outcomes (follow-up 13 years); 252 patients with conservatively treated sigmoid diverticulitis showed a 34% relapse rate and a 0.8% rate of fatal diverticulitis-related complications [250]. The previously propagated recommendation for resection after the second inflammatory flare is therefore to be regarded as obsolete; instead, the decision must be made on an individual basis [498]. The impairment of quality of life due to recurrent inflammation plays a decisive role in this decision, according to a multicentric RCT from the Netherlands (DIRECT trial) [504, 505]. Three out of four patients in whom conservative therapy fails benefit from elective resection [147, 534].

Recommendation 6.13

Elective sigmoid resection can significantly improve quality of life in patients with chronic recurrent diverticulitis CDD 3b. Impairment of quality of life due to recurrent disease should be an important determinant in decision-making when considering elective surgery in these patients.
Evidence level 2, recommendation grade B, strong consensus

Comment – Recommendation 6.13.

There is only one multicentric RCT that compares conservative versus operative therapy for recurrent diverticulitis (DIRECT trial). In this study from the Netherlands, a total of 109 patients with recurrent or persistent symptomatic diverticular disease were randomised to a conservative or surgical treatment arm. Short- and long-term results are now available from this study, as well as data on cost-effectiveness [504, 505, 535]. The study's primary endpoint was the subjective health-related quality of life of the patients. Surgical intervention was found to be significantly superior to conservative therapy, after both 6 months and 5 years of follow-up. Furthermore, 23% of patients in the conservative treatment arm underwent surgery within 6 months as a result of persistent abdominal symptoms. There was no mortality in either study arm, while 6-month morbidity was comparable (surgical arm, 34%; conservative arm, 40%). Although the study was terminated prematurely due to recruitment difficulties, its findings represent the best available evidence in the treatment of chronic recurrent sigmoid diverticulitis type 3b. In conclusion, in these patients, elective surgery can lead to a significant improvement in quality of life. Therefore, impairment of quality of life due to recurrent disease should be an important determinant in decision-making when considering elective surgery in these patients. Even before publication of the DIRECT trial, retrospective cohort studies indicated that patients with chronic,

diverticulitis-related symptoms often benefit from elective resection and, in 75-88% of cases, become non-symptomatic [147, 211].

The predictive factors and recommendations that apply to elective sigmoid resection are equally applicable as predictors of good postoperative outcomes in chronic recurrent diverticulitis type 3b. The aim of surgery is a sigmoid resection with primary anastomosis. In centres with the appropriate expertise, surgery should be performed laparoscopically, since this is usually associated with faster postoperative recovery [315]. Mobilisation of the left flexure has become the generally accepted practice; to prevent postoperative persistence of symptoms, the anastomosis is created in the upper rectum [315, 498]. With regard to the proximal resection margin, it is recommended to make the detachment in a healthy part of the bowel, i.e., in the non-inflamed colon, whereby it is not necessary to resect all diverticulum-bearing bowel segments [534].

Statement 6.14

The risk factors for a complicated postoperative course in patients with chronic recurrent sigmoid diverticulitis CDD 3b correspond to the general risk factors for elective colon resection.

Evidence level 1, strong consensus

Comment – Recommendation 6.14.

Specific risk factors for a complicated postoperative course in chronic recurrent diverticulitis type 3b have not been investigated. The known perioperative risk factors of colorectal interventions can be assumed also to apply to these patients (e.g., comorbidities, hypalbuminaemia). In a retrospective cohort study of 576 patients, the overall rate of postoperative complications after intended laparoscopic elective sigmoid resection in patients with diverticulitis was reported to be 14.2% [536]. The multivariable analysis in this study identified a BMI > 35 kg/m^2 (RR 2.10), conversion to open surgery (RR 2.21) and intraoperative blood loss > 100 mL (RR 1.06) as independent risk factors for a complicated postoperative course. Patients under immunosuppression who undergo elective sigmoid resection due to diverticulitis have an increased risk of morbidity (major surgical complications, wound dehiscence) compared to immunocompetent patients, while the mortality rate is comparable [501]. Some authors have discussed the possibility that younger patients (< 50 years) may have both a higher perioperative risk and an increased risk of relapse; overall, however, the data are inconclusive. Therefore, a younger age cannot be taken as a predictive factor for a complicated postoperative disease course [498]. With regard to the timing of surgery, early elective resection brings no advantage in comparison to delayed surgery [526].

Conservative versus operative approach – CDD 3c

Statement 6.15

Chronic recurrent diverticulitis CDD 3c with evidence of fistulas should be treated surgically.

Evidence level 3, recommendation grade B, strong consensus

Comment – Statement 6.15.

The evidence for the treatment of fistulas in chronic diverticulitis is derived from case reports and retrospective case series. Diverticulitis-associated fistulas can extend to the bladder, to other bowel segments, to the skin, or to the vagina. As a rule, the symptoms can only be alleviated by surgical intervention [537]. Consequently, the majority of guidelines recommend surgery in patients with chronic recurrent diverticulitis type 3c with evidence of fistulas [147, 154, 315]. Creation of a primary anastomosis is successfully achieved in > 90% of resection procedures in patients with type 3c and diagnosed fistulas, albeit with an increased risk of conversion when primarily laparoscopic surgery is performed [315, 537, 538]. In patients with colovesical fistulas, the rationale behind the surgical indication is additionally based on the potential risk of urosepsis, even though this

may have been overestimated in the past. Individual case series show that patients with benign colovesical fistulas can be conservatively treated for many years [539, 540]. In these cases, the decision to operate should be made dependent on the symptoms and the individual suffering of the patient. However, it is essential that a malignant process be ruled out with certainty. If this is not possible, surgery is recommended [147].

Recommendation 6.16

Chronic recurrent diverticulitis CDD 3c with evidence of symptomatic colonic stenosis should be treated surgically.

Evidence level 3, recommendation grade B, strong consensus

Comment – Recommendation 6.16.

There are no prospective data on the treatment of symptomatic diverticulitis-related colonic stenosis. As a rule, diverticulitis-related colonic stenosis is only considered clinically relevant if it causes an obstruction of stool transit that requires treatment. In this case, surgery is the only appropriate causal therapy [147, 154, 315, 531]. Interventional endoscopic therapy using a stent is experimental in nature and should be reserved for palliative situations [541, 542].

Chapter 7 Choice of Operative Interventions

Recommendation 7.3

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

Evidence level 2, recommendation grade B, strong consensus

Comment – Recommendation 7.3.

According to the majority of prospective randomised studies, systematic meta-analyses and the world's largest cohort analyses, mortality and morbidity after primary anastomosis with protective ileostomy are comparable with those of the Hartmann procedure [549-554]. However, two-thirds of the RCTs also showed that the rate of patients requiring stoma reversal or reconnection surgery is higher after primary anastomosis with protective ileostomy [550, 551]. A meta-analysis of RCTs did not confirm this advantage of stoma reversal or reanastomosis [552], in contrast to meta-analyses that analysed RCTs together with cohort studies [555, 556]. This infers that primary anastomosis with protective ileostomy could be advantageous for these patients.

Recommendation 7.4

In patients with perforated diverticulitis with purulent peritonitis (CDD 2c1), primary sigmoid resection should be performed. A potential alternative therapeutic strategy is laparoscopic peritoneal lavage and drainage, without resection.

Evidence level 2, recommendation grade B, strong consensus

Comment – Recommendation 7.4.

Prospective randomised studies have now shown that, in perforated sigmoid diverticulitis with purulent peritonitis, laparoscopic lavage represents a minimally invasive organ-preserving alternative to the Hartmann procedure and to primary resection with restoration of continuity and protective ileostomy. Nevertheless, in most studies, the reoperation rate after lavage alone was significantly higher than that observed after definitive

sanitation of the source of infection [557]. This was particularly the case in type IIc2 disease, where the conversion rate to the resective procedure was up to 45% [558]. In 35% of cases, laparoscopic lavage was performed in a two-stage procedure with consecutive early elective laparoscopic sigmoid resection, which explains why this procedure was inferior to primary sigmoid resection with restoration of continuity.

The prospective randomised studies comparing laparoscopic lavage with the Hartmann discontinuity resection (DILALA trial) or resection with primary anastomosis (SCANDIV trial) showed a slightly, albeit not significantly, higher 1-year complication rate (difference 7.2% (95% CI -6.5 to 20.4); P = 0.323) in the lavage group [559]. For type IIc1, the DILALA trial even showed a significantly lower rate of follow-on operations after laparoscopic lavage (mean 0.63 versus 1.08), reduction of 49% (ratio 0.51, 95% CI 0.31 - 0.87; P=0.024) [560].

Recommendation 7.5

The "damage control" procedure, with sigmoid resection and blind closure of the ends of the bowel, and abdominal vacuum therapy with two-stage anastomosis max. 72 hours after successful treatment of the abdominal infection, can be used as a treatment strategy for diverticulitis CDD 2c1/2.

Evidence level 3, recommendation grade 0, strong consensus

Comment – Recommendation 7.5.

Uni- and multicentric observational studies were able to prove that use of the damage control concept led to a significant reduction in the rate of Hartmann procedures and permanent stomas [561-567]. In overtly perforated sigmoid diverticulitis with purulent or faecal peritonitis, damage control consists of a two-step procedure: In a first step, without delay, resection is performed sparingly to remove the perforated bowel segment, leaving blind ends and creating a vacuum seal of the abdomen to allow negative pressure treatment of the peritonitis. The second step takes place after clinical stabilisation of the usually septic patient: After not less than 48 hours, a second-look procedure is carried out, in which sigmoid resection is completed and an anastomosis or Hartmann stump created, with or without reapplication of a negative pressure system, depending on the local findings. The advantage of this concept is twofold: on the one hand, the primary operation (sigmoid resection with blind closure of the ends of the colon and application of an abdominal vacuum system) does not necessarily need to be performed by a visceral surgeon with colorectal experience; on the other hand, the decision as to whether to restore continuity (73% in a systematic review by Sohn et al. [567]) or apply the Hartmann procedure is adjourned, and can then be performed by a specialist under early elective conditions. This allows the rate of permanent ostomy to be kept relatively low (about 20%) [561]. Persistent peritonitis at the time of second-look surgery is an independent prognostic factor and correlates significantly with the rate of organ failure and the duration of the first surgical procedure. In the observational study by Sohn et al., patients with persistent peritonitis despite negative pressure therapy had a significantly longer hospital stay, higher stoma rates at discharge and a higher rate of follow-on surgery. Rates of mortality and complications were also increased, although not significantly [566]. To date, there are no prospective randomised studies.

Recommendation 7.6

The oral resection margin for sigmoid resection should be chosen directly proximal to the acutely or chronically inflamed bowel segments. Additional diverticulum-bearing bowel segments without inflammatory or post-inflammatory changes should not be resected.

Evidence level 3, recommendation grade B, strong consensus

Comment – Recommendation 7.6.

Evidence on localisation of the oral resection margin is extremely weak. The resection level depends on intraoperatively-identified inflammatory/post-inflammatory changes, and should be located in a

macroscopically normal bowel segment [568]. A sufficiently wide end-to-end stapled anastomosis cannot be safely created if the bowel wall is insufficiently elastic due to persisting acute or chronic induration of the bowel wall [569]. Whether the presence of detectable signs of inflammation at the upper dissection margin promotes relapse is questionable. Thaler, in 2003, found an inflammatory reaction in only 1 of 12 relapses [570]. To ensure the maximum result of the anastomosis, the area around the anastomosis itself should be free of diverticula [568].

The extent to which diverticula that are left in the rest of the proximal colon may influence recurrent diverticulitis has not been sufficiently investigated. There is an older analysis on this dating back to 1984. In this study, after sigmoid resection, diverticulitis recurred in 11.4% of the 61 included patients after a follow-up period of at least 5 years. The rate of relapse was independent of the number of diverticula initially left [571].

Recommendation 7.7

The aboral resection margin should be situated in the upper rectum.

Evidence level 3, recommendation grade B, strong consensus

Comment – Recommendation 7.7.

There is limited evidence regarding the influence of the aboral resection margin on the recurrence rate after sigmoid resection and anastomosis.

Individual studies show that anastomosis to the rectum is associated with a reduced probability of relapse compared to anastomosis to the distal sigmoid colon. The authors suggest this to be related to indications that there is a zone of high pressure at the rectosigmoid junction [572, 573]. Their relevance in the development of recurrent colonic diverticulitis remains speculative.

Benn compared patients with colosigmoidal versus colorectal anastomosis and found 10-year relapse rates of 20% for the sigmoid group versus 8% for the rectum group ($p<0.05$) [574].

In 2003, Thaler examined the influence of different anastomotic techniques on the relapse rate after uncomplicated sigmoid diverticulitis. Patients with colosigmoidal anastomosis showed a 4-fold increased risk of recurrence compared to those with colorectal anastomosis [575]. Other investigators do not confirm this connection with the site of the anastomosis [227].

Recommendation 7.8

A tension-free, well-perfused and leak-tight anastomosis should be created. If this requires mobilisation of the left flexure, this should be performed.

Expert consensus, strong recommendation, strong consensus

Comment – Recommendation 7.8.

The need to mobilise the left colonic flexure when creating a colorectal anastomosis has primarily technical reasons. In order to uphold the basic surgical principles of good blood circulation and achieve tension-free sutures, mobilisation of the left flexure can be necessary. No relevant systematic studies are available. Therefore, there is actually still no evidence supporting a mobilisation of the left colon flexure. Nonetheless, one investigation shows an inverse result: Avoiding mobilisation of the left flexure leads to an increased risk that sections of the descending colon or sigmoid colon that are affected by inflammation will be left around the proximal resection margin. As a result, the risk of diverticulitis recurrence is increased [576]. This has been incorporated into the British/Irish guidelines. The US and Danish guidelines make no explicit recommendations, due to the uncertainty of the evidence.

In principle, many authors' studies have shown that mobilisation of the left colonic flexure is possible, both laparoscopically and via the open technique, without increasing the rate of major complications [577, 578].

Recommendation 7.9

Ligation of the inferior mesenteric artery central to the origin of the left colic artery should not be performed.

Evidence level 3, recommendation grade B, strong consensus

Comment – Recommendation 7.9.

Evidence concerning removal of the inferior mesenteric artery is still inconsistent.

The main arguments for tubular resection with preservation of the superior rectal artery are a better perfusion of the anastomotic region and, consequentially, a lower rate of anastomotic insufficiency. In addition, tubular resection has a decreased risk of injury to the hypogastric plexus and thus, hypothetically, a better functional result.

The main advantage attributed to a high ligature of the inferior mesenteric artery is an improved mobility in the area of the descending colon, resulting in a tension-free anastomosis.

Assessment of the study data is problematic, not least because they compare several different techniques: complete ligation of the inferior mesenteric artery, sparing of the superior rectal artery, and exclusive resection of the sigmoid arteries.

A 2012 meta-analysis of diverse studies found no difference in the anastomotic insufficiency rate after complete ligation of the inferior mesenteric artery compared with deeper ligation [579]. However, alongside three clinical cohort studies, this meta-analysis included only one randomised study [580], and this showed the preservation of the superior rectal artery to be advantageous with regard to a clinical anastomotic insufficiency rate. These results were backed up in 2017 [581] by another retrospective analysis of 267 patients, which demonstrated a significant advantage when the superior rectal artery was preserved. The anastomotic leakage rate with preserved arterial perfusion was 1.9%, in comparison to 7% (p=0.053). The last published results date from the year 2018 [582]. This study compared radical ligation of the inferior mesenteric artery to resection of the branches of the sigmoid arteries (preserving the superior rectal artery). The retrospective analysis of 1,016 patients found no difference between the two groups, whereby the overall rate of anastomotic insufficiency (1.2 vs 1.4%, p = 0.794) was very low. In order to be able to prove such a difference with sufficient power, it would be necessary to have a collective of 100,000 patients.

Statement 7.10

Provided the anastomosis is technically correctly performed, stapler and hand sutures are to be regarded as equivalent

Evidence level 1, strong consensus

Comment – Statement 7.10.

Numerous publications [583, 584] indicate that there is no difference in the rates of mortality, anastomotic insufficiency, bleeding, reoperation, wound infections or strictures, or in the length of hospital stay, for stapled anastomosis versus hand suture. This was proven by a Cochrane systematic review, updated in 2012, on the evidence of 9 RCTs [584].

Recommendation 7.11

Anastomotic insufficiency after sigmoid resection should be treated using a step-by-step approach, depending on clinical severity. If diffuse peritonitis occurs, reoperation with (protective or terminal) stoma creation should be performed.

Evidence level 4, recommendation grade B, strong consensus

Comment – Recommendation 7.11.

There are no RCTs on the management of anastomotic insufficiency after sigmoid resection. If peritonitis occurs, there are different treatment options that can be selected, depending on the clinical findings. These include the damage control concept (see Statement 5), anastomosis removal with creation of a Hartmann stump, or forming a new anastomosis/oversewing the anastomosis with a proximal protective ileo- or colostoma.

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