Diverticular Disease: Emerging Evidence in a Common Condition
Diverticular disease – a frequent disorder with nowhere to call home

Diverticular disease is by no means rare but actually occurs with a fairly high frequency. This frequency, however, is hardly reflected in the scientific literature and in medical discussions, and diverticula and their health consequences are only rarely a topic of congresses and symposia. There is also a corresponding dearth of data on diagnosis and therapy and even the definitions of the different forms of the disease remain unsettled. Thus the terms diverticulosis, diverticulitis, symptomatic or asymptomatic diverticular disease are often used imprecisely or even synonymously. “In surveys, every respondent has an answer to the question of what diverticula are and how to treat them. The answers that one gets, however, are fundamentally different,” W. Kruis (Cologne) said in assessing the situation.

More clarity in the area of diverticular disease and defining state-of-the-art thinking on this topic was the objective of the 148th International Falk Symposium in Munich, which was attended by more than 450 participants from 31 nations. The symposium was chaired by A. Forbes (Harrow), K.-W. Jauch (Munich), W. Kruis (Cologne) and S.D. Wexner (Weston).
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Diverticulosis and diverticulitis: The available data are unsatisfactory

There is a dearth of confirmed data on the diagnosis and therapy of diverticular disease. This, as speaker after speaker noted, is puzzling given the frequency of diverticula in the general population. Correspondingly frequent is the entity of diverticular disease, whereby the incidence of both diverticulitis and diverticulosis increases with advancing age.

Speakers at the symposium were in agreement that, because of a lack of well-controlled studies, significant uncertainty remains, especially with regard to conservative treatment of diverticular disease, but also concerning the indications for surgical management. “The data on diverticular disease is generally unsatisfactory” – this was the most commonly heard remark at the symposium in Munich. Another universal complaint related to the fact that this widespread clinical entity does not receive the medical or scientific attention it deserves.

The pathogenesis of diverticular disease is still not exactly understood

N.Y. Haboubi (Manchester) suggested, for better understanding of the pathology of diverticular disease, a classification according to changes that suggest ulcerative colitis, those that point to Crohn’s disease and finally disease forms characterized by herniation of the mucosa as the predominant anatomic feature. Mucosal herniation is seen in up to 90% of patients, while about one in ten patients exhibit proliferation of the mucosa around the diverticulum. Inflammatory processes are also frequently seen, N.Y. Haboubi said.

It is probable that several factors operate simultaneously in the pathogenesis of diverticular disease. One factor relates to changes in connective tissue and smooth muscle as an effect of aging. Others include dietary and structural changes, as explained by T. Wedel (Lübeck), and also motility disturbances (figure 1).
**Enteric neuropathy and diverticular disease**

**Classic pathogenetic concepts**

- **Aging** ⇒ predominant in elderly
- **Diet** ⇒ low fiber intake
- **Connective tissue disorder** ⇒ elastosis
- **Smooth muscle disorder** ⇒ myochosis
- **Enteric neuropathy** ⇒ ?

**Hypersensitivity caused by damage to the enteral nervous system**

Changes in the enteral nervous system may also play a role. These may be responsible for an increase in intraluminal pressure, resulting in increased motility. Hypersensitivity might also explain the pain sensations (figure 2).

That diverticular disease may actually represent a "neuromuscular derangement" has, according to T. Wedel, been described in the literature, pointing to reports on the formation of giant ganglia and a general hypertrophy of nerve cells in the submucosa (figure 3). Such intestinal neuronal dysplasia is found in about 20% of patients.
**Enteric neuropathy and diverticular disease**

**Why should enteric nerves be involved?**

- intraluminal pressure
- motor activity
- painful sensations

... mediated by the enteric nervous system (ENS)

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**Structural alterations of the ENS**

- submucous giant ganglia
- submucous nerve fiber hypertrophy

↓

**Intestinal neuronal dysplasia**

(20% of cases)

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*Structural alterations of the ENS (T. Wedel, Lübeck)*

*Wedel T et al. Viszeralchirurgie 1999; 34: 307-311*
High pressure in the sigmoid colon triggers diverticulosis

These neural changes, however, are certainly not the sole basis of this disease. Diverticular disease is best understood as a multifactorial entity, M. Kreis (Munich) said. “There is a widely held opinion that motility disturbances leading to high pressure in the sigmoid colon are the actual cause of this disease,” M. Kreis observed.

Studies of motility in healthy controls and in patients with different types of diverticular disease appear to confirm this hypothesis. For example, while there was no difference between control persons and patients with asymptomatic diverticulosis, a significantly increased motility was seen in patients with symptomatic, complicated diverticular disease. Still more pronounced were the motility disturbances in patients with symptomatic, non-complicated diverticular disease, both under normal conditions (figure 4) and following ingestion of a meal (figure 5).

Persistence of these motility disturbances over a long period of time together with increased pressure in the colon appears to play an essential role in diverticular disease, M. Kreis said. It remains unclear whether this triggers the formation of diverticula or whether these represent a secondary phenomenon as a consequence of structural changes in the bowel wall.

Motility studies in subgroups of patients with diverticular disease under basal conditions (M. Kreis, Munich)

ADD = asymptomatic diverticular disease
SUDD = symptomatic uncomplicated diverticular disease
SCDD = symptomatic complicated diverticular disease
Motility studies in subgroups of patients with diverticular disease following a meal (gastro-colic response) (M. Kreis, Munich)

ADD = asymptomatic diverticular disease
SUDD = symptomatic uncomplicated diverticular disease
SCDD = symptomatic complicated diverticular disease

Diverticula: There may be a genetic predisposition
Independent of these factors, according to A. Forbes (Harrow), there is good evidence for a genetic predisposition to diverticular disease, although no specific gene has been implicated as triggering the development of this disease. The possibility of a significant genetic component is supported not only by observations that diverticula occur more frequently in some families, but also by studies of twins.

There also appears to be a close association with genetically caused disorders such as polycystic kidney disease, with 83% of patients also exhibiting signs of diverticular disease. “This is a significant finding, since normally a prevalence of only 20–50% would be expected,” A. Forbes said in Munich.
Incidence and prevalence are age-dependent

Because the majority of patients remain asymptomatic, the exact prevalence of intestinal diverticula is difficult to estimate, A. Fingerhut (Poissy) said. It is clear, however, that both incidence and prevalence increase with advancing age. At age 40, diverticula are rare and affect only about 5% of persons. Past 65 years, however, a prevalence above 65% shows that they are a common phenomenon, A. Fingerhut said. It is important to differentiate between diverticulosis, defined as the presence of diverticula with no associated disease signs or symptoms, and diverticular disease, in which the diverticula have become symptomatic.

The precision of the clinical classification can be further enhanced by differentiating between "symptomatic, non-complicated disease", "recurrent symptomatic disease" and a "complicated disease form" in which bleeding and, in extreme cases, perforation occur.

According to A. Fingerhut, the Hinchey classification of diverticulitis has found wide acceptance. It assigns patients with this clinical entity to one of four stages. Hinchey I is diverticulitis with localized abscess; Hinchey II is characterized by extensive mesenteric abscess; Hinchey III has progressed to free perforation; while Hinchey IV represents peritonitis after free perforation (figure 6).

Fig. 6

<table>
<thead>
<tr>
<th>Localized pericolic abscess (Hinchey stage I)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large mesenteric abscess (Hinchey stage II)</td>
</tr>
<tr>
<td>Free perforation (Hinchey stage III)</td>
</tr>
<tr>
<td>Free perforation causing fecal peritonitis</td>
</tr>
<tr>
<td>(Hinchey stage IV)</td>
</tr>
</tbody>
</table>

*Hinchey classification (A. Fingerhut, Poissy)*
Right-sided and left-sided diverticular disease – two different entities?

Diverticular disease may manifest itself in a predominantly left-sided or right-sided pattern of localization and it has been suggested that these two localizations may actually be evidence of two different disease entities. For example, the left-sided form, which often manifests itself with pain and is frequently associated with complications, such as fistulae and obstructions, less often with bleeding, is most common in Europe.

The situation is somewhat different for right-sided diverticular disease, which, according to R. Cohen (Harrow), is most often described in Asian patients and in which bleeding is the primary symptom. Right-sided diverticular disease is also more common in younger patients, which points to a genetic predisposition, while the left-sided localization is more common at higher ages. This suggests that environmental factors and especially dietary factors such as a low-fiber diet may be important in the pathogenesis (figures 7 and 8).

Fig. 7

Uncomplicated diverticular disease (R. Cohen, Harrow)
Differentiating between complicated and non-complicated diverticulitis

In about 70% of patients, diverticular disease presents as diverticulosis, which is asymptomatic, S. Hollerbach (Celle) said. About 10–25% of patients, however, go on to develop diverticulitis, which, in 75% of cases, remains non-complicated. Patients usually complain of non-specific pain and frequently constipation, and may also experience incontinence or changed bowel habits.

About 25% of patients with diverticulitis experience a complicated form of the disease with abscess formation, obstructions, fistulation and even perforation (figure 9).

High complication rate

According to S. Hollerbach, the prognosis in patients with a first episode of uncomplicated diverticulitis is good, since they very often do not experience disease recurrence. It is treated conservatively and 85% of patients respond with complete remission. Long-term, however, about 15% of patients will eventually require surgery.

Should diverticulitis recur, the rate of surgery jumps to 30–40%, associated with a drastic increase in the rate of complications and of mortality, which S. Hollerbach put at 1.3–5%. Risk factors for severe disease course include male sex and obesity. In addition, young patients
may be especially at risk for a “virulent” disease course with an increased risk of recurrent disease flares and complications. “In patients under 40 with diverticulitis, elective surgery should be considered,” S. Hollerbach said in Munich.
Careful differential diagnosis is essential
A patient presents to your office with symptoms suggestive of diverticular disease. In these cases, according to R. Jones (London), a comprehensive consideration of differential diagnoses is crucial. This will include, R. Jones said, the gamut of dietary intolerances and food poisoning to entities such as irritable bowel syndrome, inflammatory bowel disease and vascular causes of symptoms, such as ischemic colitis. The differential also includes malignancies, but also urinary tract infections.

Laboratory tests are not very helpful
Laboratory tests that are reliably diagnostic in diverticular disease are not available, C. Gasché (Vienna) said. Some help is provided by inflammation markers, such as C-reactive protein (CRP) and hemoglobin concentration, which, if low, may indicate bleeding complications.

In emergencies, prompt surgical exploration is required
Timely recognition of emergencies is crucial. These include fistulae, obstruction and especially perforations. “In such cases, exploratory laparoscopy must be obtained without delay,” J.M. Müller (Berlin) said (figures 10 and 11).

Fig. 10

Diverticulitis

- uncomplicated
  - symptomatic first manifestation
  - symptomatic recurrent

- complicated
  - Fistulae
  - Perforation
  - Stenosis
    - Ileus
      - free
      - covered
    - Peritonitis
      - local
    - Abscess
      - general
The diagnosis can also be difficult in a patient presenting with lower gastrointestinal bleeding, J. Schölmerich (Regensburg) said. Although diverticular bleeding resolves spontaneously in 80–85% of cases, mortality, the gastroenterologist said, is high at 2–4%.

Diverticulitis is the most common cause of bleeding in the lower gastrointestinal tract, followed by neoplasms and ischemic colitis (figure 12). Prognosis depends on the definitive identification of the source and localization of the bleeding.

The rupture of a localized peridiverticular abscess into the peritoneal cavity did not result in gross peritonitis, presumably because the diverticular neck was obstructed by a fecolith.

**Acute diverticulitis stage III (J.M. Müller, Berlin)**

![Image](Fig. 11)

56 year-old male with 6 weeks obstipation and pelvic pain

J. Schölmerich

![Image](Fig. 12)

Lower gastrointestinal bleeding – etiology (J. Schölmerich, Regensburg)
Close parallels to inflammatory bowel diseases
In the diagnostic work-up of diverticular disease, it is important to think not only about the possible complications of the disease but also about potential gastrointestinal comorbidity, H.-J. Krammer (Mannheim) said. Patients may be simultaneously suffering from inflammatory bowel disease. These entities may be difficult to differentiate, because diverticular disease may be associated with extensive inflammation and may even present the picture of “diverticular colitis”.

There are other parallels between inflammatory bowel diseases (IBD) and diverticular disease. For example, both entities may present with fairly similar patterns of symptoms, dominated by pain, stool irregularities, weight loss and fever. In addition, with both disorders, many patients respond well to treatment with mesalazine.

Overlap with irritable bowel syndrome
In addition, there may be overlap with irritable bowel syndrome and H.-J. Krammer sees close parallels between these two entities. Patients complain of partially comparable symptoms such as constipation, meteorism and flatulence, as well as mucus admixture in the stool and abdominal pains. Because both diverticular disease and irritable bowel syndrome are very common, a high comorbidity must be expected, H.-J. Krammer said.

This position was supported whole-heartedly by his colleague, L.M.A. Akkermans (Utrecht), who confirmed the significant overlap between the individual clinical pictures. This may go so far that in patients with diverticular disease it may no longer be possible to determine which symptoms are due to the diverticula and which are caused by other structural or functional changes. This differential diagnostic problem must also be considered when planning the patient’s future management.
Colonoscopy: only after the acute phase has passed?

Diverticular disease can also be hard to pin down with diagnostic imaging methods. Hence, it has become usual, S. Bar-Meir (Tel Hashomer) said, to refer the patient for colonoscopy following resolution of the acute disease phase. The reason normally given for not performing colonoscopy in the acute stage is that there may be an increased risk of bowel perforation. “This worry, however, is not evidence-based,” S. Bar-Meier said.

First experiences with 93 patients, according to S. Bar-Meir, suggest that colonoscopy is possible, even in the acute stage of the disease. Early colonoscopy, however, should be limited to patients with recurrent disease phases and to those in whom computed tomography imaging shows no free air in the vicinity of the diverticula. S. Bar-Meir is currently conducting a randomized study comparing the benefits and potential risks of early colonoscopy compared with first examination six weeks after resolution of the acute disease phase.

Include ultrasound in the work-up

Diagnostic ultrasound also has a role in the work-up of diverticular disease, S. Schanz (Cologne) said. With a sensitivity and specificity of 97%, the method is, in his opinion, comparable to CT and examiners with the appropriate experience can even reliably detect diverticula in patients with diverticulosis of the left colon. Advantages of ultrasound, according to S. Schanz, are the wide availability of the method and the fact that the examination is non-invasive and inexpensive. Beyond the limits of ultrasound are large and complex fistular systems, involvement of the distal sigmoid colon in diverticular disease and overlap with other gastrointestinal disorders, especially with IBD or colon carcinoma.

In the opinion of S. Feuerbach (Regensburg), CT remains the most reliable imaging method for diagnosing diverticular disease.
Individual clinical course determines choice of therapy

The management of diverticular disease is determined to a great extent by the patient's individual disease course. Risk factors for a complicated clinical course, according to M.Z. Panos (Athens) include low patient age, obesity, male sex and, especially, immunosuppression.

Even in the absence of such risk factors, diverticular disease is something that must not be taken lightly. Recurrence rate within one year of the first disease flare is 2% and this figure rises long-term by 33% per year. In fact, 90% of patients with two disease flares can reckon with a recurrence of acute diverticulitis.

Nutrition can trigger diverticula

Nutritional behavior plays a contributory role in the pathogenesis of diverticular disease. This statement is supported, M.Z. Panos said, by observations that diverticular disease is widespread in Western industrial nations, but is

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence (%)</th>
<th>n</th>
<th>Year</th>
<th>Reference</th>
<th>Method</th>
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<tbody>
<tr>
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<td>35</td>
<td>109</td>
<td>1967</td>
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<td>1985</td>
<td>Burkitt</td>
<td>BE</td>
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<td>Thailand</td>
<td>4</td>
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<td>1980</td>
<td>Vajrabukka</td>
<td>BE</td>
</tr>
<tr>
<td>China</td>
<td>1</td>
<td>909</td>
<td>1983</td>
<td>Guo-Zong</td>
<td>C</td>
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<tr>
<td>Japan</td>
<td>8</td>
<td>12505</td>
<td>1982</td>
<td>Kubo</td>
<td>BE</td>
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<tr>
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<td>4</td>
<td>592</td>
<td>1978</td>
<td>Archmpong</td>
<td>BE</td>
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<tr>
<td>Kenia</td>
<td>6</td>
<td>226</td>
<td>1978</td>
<td>Calder</td>
<td>BE</td>
</tr>
<tr>
<td>Nigeria</td>
<td>0</td>
<td>1420</td>
<td>1987</td>
<td>Jhekwaba</td>
<td>A</td>
</tr>
</tbody>
</table>

hardly ever seen in developing countries, where people consume diets high in fiber (figure 13). Also, the fact that younger persons are almost never affected while the incidence increases drastically with age suggests that dietary factors may play a decisive role.

**Abdominal pains are the main clinical symptom**

While diverticulosis remains asymptomatic in about one-third of all cases, the remaining two-thirds develop repeated episodes of pain and bowel irregularities, R.C. Spiller (Nottingham) said (figure 14). The cause for this phenomenon may be related to increased tension in the bowel wall. The pain may, however, simply be a direct consequence of the inflammatory process.

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**Incidence (R.C. Spiller, Nottingham)**

35% of > 50 year old have diverticulosis in UK


Onset of painful DD at mean age 55 years was 1.8/1000 patient years (6% over next 30 years)
The cause of “post-diverticulitis pain” is still unclear
According to R.C. Spiller, these pains occur episodically and usually continue for about seven days. Even after the inflammation resolves, many patients continue to report abdominal pains an average of five days per month. The cause of these “post-diverticulitis pains” is unclear, R.C. Spiller said. The thickened bowel wall (figure 15) could be to blame, but the pain may also be due to an increased sensitivity to pain, possibly caused by the inflammation.

There are not correlations with patients’ age or sex or with their radiological findings. Manometric studies have also found no differences in bowel contractions between healthy controls and patients with symptomatic, non-complicated diverticular disease.

Do not ignore extraintestinal comorbidity
The management of diverticular disease depends not only in the disease course but also on the question of whether there is concomitant extraintestinal morbidity, B. Lembcke (Gladbeck) said. For example, obesity contributes significantly to surgical risk. In addition, as J.C. Hoffmann (Berlin) noted, other factors must also be considered, such as a potential immunosuppression.

**Fig. 15**
Circular muscle hypertrophy in acute diverticulitis (AD) and symptomatic complicated diverticular disease (SCDD)

<table>
<thead>
<tr>
<th>Thickness (mm)</th>
<th>Control</th>
<th>AD</th>
<th>SCDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 cm</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Kruskal-Wallis p < 0.000


I Thickened bowel wall (R.C. Spiller, Nottingham)
A central issue in the treatment of diverticular disease, in his opinion, is that to date there is a dearth of well-planned controlled studies of the different treatment methods and patients’ outcome. “Most of the literature consists of retrospective case studies,” J.C. Hoffmann warned.

**Therapy recommendations are not evidence-based**

There are very few prospective studies and there is also no clear, internationally accepted definition or classification of the individual disease stages. This makes it difficult to assess the respective treatment option in the individual case and it makes the formulation of generally applicable recommendations difficult. For example, J.C. Hoffmann said, it is usually recommended to refer the patient for elective surgery after the second episode. “The studies do not support this recommendation,” he emphasized.

This is of even greater importance since the associated morbidity of each operation must be considered. This includes not only the direct complications of surgery but also the risk of anesthesia as well as potential postoperative complications (figure 16).

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**Fig. 16**

- **Conservative treatment**
  - Antibiotic-associated complications (e.g. pseudomembranous colitis)
  - General complications: DVT, PE, pneumonia, catheter sepsis, pneu etc.
  - Recurrence in high-risk groups (e.g. immunosuppression)
  - Sepsis

- **Operative treatment: anesthesia-related**
  - Respiratory failure, pneumonia
  - General complications: DVT, PE, pneumonia, catheter sepsis, pneu etc.

- **Operative treatment: surgery-related**
  - Anastomotic leakage
  - Uncontrolled sepsis
  - Bleeding, wound infections, incisional hernia
  - Fistula
  - Abscess

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*Treatment-related morbidity (J.C. Hoffmann, Berlin)*
Sigmoid resection after the second diverticulitis flare

If the conservative management of diverticular disease proves unsuccessful, sigmoid resection may be considered, N. Senninger (Münster) said, noting that more than 50% of diverticula are localized to this bowel segment (figure 17). At surgery, complications, such as bleeding, can be handled and surgery in general can help prevent the development of complicated diverticular disease.

Sigmoid resection essentially removed the “high pressure zone” of the colon. Ideally, N. Senninger explained, the acute situation should be controlled by conservative methods and several weeks after resolution sigmoid resection, if still indicated, should be performed as an elective operation.

Laparoscopic resection is feasible

According to A. Fingerhut (Poissy), sigmoid resection, while it can be done as a conventional open procedure, is definitely feasible as a laparoscopic procedure: “The laparoscopic procedure is just as efficient as conventional open surgery.” This is no longer the case, he cautioned, if complications, such as fistulae or strictures, have already occurred, or when there is bleeding, whose source may not be known.

In favor of a laparoscopic approach, said K.-W. Jauch (Munich), is also the fact that the procedure is usually less stressful for the patient. Laparoscopy is also less expensive, because patients’ hospitalizations are shorter. On this point, however, there are conflicting data and a final assessment is probably not possible at this time. Whether laparoscopy is really gentler and, hence, less stressful is a question that, according to V. Schumpelick (Aachen), cannot yet be answered.

### Fig. 17

<table>
<thead>
<tr>
<th>Location</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sigmoid</td>
<td>51.3%</td>
</tr>
<tr>
<td>Sigmoid + Descending</td>
<td>14.7%</td>
</tr>
<tr>
<td>Descending</td>
<td>14.7%</td>
</tr>
</tbody>
</table>

(These data are from Jansen und Kaden, 1974.)

I Localization of colonic diverticula
(N. Senninger, Münster)
Surgical success also depends on the experience of the surgeon

It is also clear that the success of a procedure and the rate of complications depends to a great extent on the experience of the surgeon. Laparoscopic surgery, in addition, has significant limitations. According to V. Schumpelick, it is not indicated in the presence of fistulae, perforation or peritonitis. In addition, in an emergency situation, conventional open surgery should generally be selected. Without doubt, however, the laparoscopic procedure gives better cosmetic results.
The therapeutic effects of roughage
The conservative management of diverticular disease depends directly on its clinical course. Because of the probable close relationship to a low-fiber diet in the pathogenesis of diverticular disease, 75% of gastroenterologists surveyed reported recommending a high-fiber diet or the direct addition of dietary fiber (e.g. with psyllium) to their patients, J.O. Lindsay (London) said. “In terms of evidence-based data supporting this recommendation for therapy with dietary fiber,” he admitted, “there is little.” There are, however, some first controlled studies that do show advantages, although, to date, only about 250 patients have been included.

Preventive effects are also probable
Furthermore, there is also epidemiological evidence suggesting that there actually is a close correlation between consumption of a diet low in fiber and the occurrence of diverticulosis. In a survey of 47,000 American men, the relative risk was only 0.58 in the group with the highest intake of fiber, suggesting that nutrition may be very effective in preventing diverticular disease. This leads J.O. Lindsay to postulate that dietary fiber may be the key to a conservative strategy with both therapeutic and preventive ramifications. The basis for this may be the increase in stool weight secondary to increased fiber intake as well as the fact that colon transit time may be cut in half, which effectively prevents constipation.

Finally, J.O. Lindsay cited first studies that suggest that dietary fiber may reduce the severity of complaints in patients with diverticular disease. For example, in a study with 40 patients treated for six months with increased dietary fiber, a significant reduction in symptoms was reported by 60% of patients in the high-fiber group. The therapeutic importance of treatment is primarily in the group of patients with non-complicated diverticular disease. The more complicated the clinical course, the lower the significance of nutritional factors (figure 18).
Antibiotics in symptomatic disease forms

While asymptomatic diverticular disease remains the domain of treatment with dietary fiber, antibiotics take center stage in the management of symptomatic diverticular disease. If there is no evidence of inflammation (figure 19), it is the practice in some countries to treat with rifaximine, a poorly absorbed antibiotic that is not currently licensed in Germany. In this area, too, truly “evidence-based” medicine is not possible. “There simply are no comparison studies between antibiotics or of antibiotic versus placebo,” G. Latella (L’Aquila) emphasized.

“The choice of antibiotic depends mostly on the clinical scenario,” he added. While he generally does not see an indication for antibiotics in asymptomatic patients, the situation is different in the case of diverticulitis with suspected bacterial overgrowth. Patients with mild disease can be treated on an outpatient basis. Broad-spectrum antibiotics, especially the imidazoles and fluoroquinolones, are prescribed and avoidance of oral food intake is essential.

Patients with severe diverticulitis require inpatient hospitalization. Beside absolute avoidance of oral intake, a combined antibiotic therapy is required in most cases. Typically used antibiotics include the imidazoles (especially metronidazole) as well as clindamycin, aminoglycosides such as gentamycin and third-generation cephalosporins. If patients do not respond to therapy, G. Latella said, an intense work-up for complications must be initiated. The diagnosis must be reconsidered and, where required, referral to a surgeon should follow (figure 20).
Fig. 19

Antibiotic treatment of diverticular disease

**Symptomatic without inflammation**

Gut microflora in determining symptoms:
- ↑ fibre fermentation ⇒ constipation, cramps
- ↑ excessive production of bowel gas ⇒ bloating, pain, discomfort
- ↑ bacterial overgrowth ⇒ diarrhea

---

Fig. 20

**Diverticular Disease**

- Asymptomatic (80%)
  - Without inflammation
  - With inflammation (10–25%) (Diverticulitis)
    - Perforation
      - Abdomen
      - Abscess – Peritonitis
      - Fistulae
    - Fibrosis
      - Organ
      - Stenosis

**Antibiotic therapy of diverticular disease (G. Latella, L’Aquila)**
The role of probiotics remains unclear
According to A. Gionchetti (Bologna), the role of probiotics in the treatment of diverticular disease remains unclear. Probiotic activity has been ascribed to different bacteria, he explained (figure 21). To date, however, there is only one study that reports an improvement in symptoms in patients with non-complicated diverticular disease after treatment with E. coli Nissle.

Mesalazine in addition to antibiotics
The data are more convincing with regard to mesalazine, according to V. Gross (Amberg), reporting on the possible therapeutic value of this agent as an adjunct to treatment with antibiotics. The rationale for a trial of 5-aminosalicylic acid relates to the broad anti-inflammatory activity of this agent, which is already in use for treatment of inflammatory bowel diseases.

Organisms associated with probiotic activity (A. Gionchetti, Bologna)
In addition, mesalazine inhibits reactive oxygen metabolites, with which intestinal bacteria interact, thus potentially modifying bacterial activity. The aminosalicylates also inhibit key enzymes in prostaglandin, leukotriene and thromboxane synthesis as well as of certain pro-inflammatory cytokines (figure 22).

**Fig. 22**

- Prostaglandin synthesis
- Leukotriene synthesis
- Thromboxane synthesis
- PAF synthesis
- Cytokines (IL-1, TNF)
- Reactive oxygen species
- Intestinal bacteria – colonic epithelium

**Long-term improvement in abdominal complaints**

The positive effects of these mechanisms on diverticular disease are shown, V. Gross said, by the data reports by Trespi et al. in a study of 166 patients with acute, non-complicated diverticular disease reporting mild to moderate symptoms. Patients reported significant improvement in abdominal symptoms during an eight-week course of mesalazine that followed antibiotic therapy. These positive effects even persisted over a follow-up period of four years (figures 23 and 24). Microscopic hemorrhages were also less common in patients treated with mesalazine.

**Fig. 23**

Trespi et al.: Further inflammatory recurrences. Kaplan-Meier actuarial estimate

<table>
<thead>
<tr>
<th>Months</th>
<th>CO</th>
<th>5-ASA</th>
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<td>48</td>
<td>10</td>
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</table>

**Inflammatory recurrences (V. Gross, Amberg)**
More patients remain complaint-free

The advantage of adding mesalazine in patients receiving antibiotics has also been shown in a study by Tursi et al. In this study, 218 patients with recurrent acute diverticulitis and at least two disease flares during the previous 12 months received rifaximine, either alone or in combination with mesalazine at a dose of 800 mg three times a day for seven days each month. The addition of mesalazine resulted in significantly more patients being complaint-free (figure 25). The difference between the two strategies in favor of the combined regimen became apparent after only three months.

After a year, 86% of patients on the combined therapy were complaint-free, compared with only 49% of those receiving antibiotics alone. According to V. Gross, two further studies document the significant therapeutic effects of mesalazine in diverticular disease, both in terms of improvement in symptoms and prophylaxis of recurrent inflammatory flares.
Be careful with analgesics and especially with NSAIDs

Because diverticular disease is often associated with pain, it is justified in the opinion of H. Mönnikes (Berlin) to inquire about the effects of analgesics and spasmolytics. To date, however, there are no controlled studies addressing this question. It is important to note that spasmolytics generally weaken muscular contraction and this effect may be responsible for some relief of pain. Care is important regarding the use of analgesics, especially NSAIDs, since these agents increase the risk of gastrointestinal bleeding and perforation.
Surgery: Can you kill two birds with one stone?
Special problems are associated with the surgical therapy of diverticular disease when the surgeon is confronted with intra-abdominal comorbidity, such as, for example, gallstones, colonic polyps, or adhesions and scar tissue from earlier operations. Such problems may make sigmoid resection much more difficult. On the other hand, as U. Roblick (Lübeck) asserted, this may be an opportunity to kill two birds with one stone, if both a sigmoid resection and cholecystectomy or lysis of adhesions can be done during a single surgical session.

Even if the absence of concomitant problems, the operation should only be performed by an experienced surgeon, since the danger of postoperative complications is not negligible, J. Jeekel (Rotterdam) said. Incisional hernias are the most common complication, occurring in 10–20% of patients.

Independent of the occurrence of postoperative complications, there is no guarantee that the patient will be complaint-free after sigmoid resection, B. Egger (Berne) said. About one in four patients will continue to have complaints following the procedure, although these are usually mild. Recurrence of diverticulitis, however, is comparatively low at 2%, B. Egger said.

Take advantage of the possibilities for secondary prevention
In any case, every effort should be made to institute secondary preventive measures as prophylaxis against renewed diverticulitis flares. In the opinion of W.H. Aldoori (Mississauga), this is possible if patients can be motivated to take a diet high in fiber but low in red meat. “We know that the relative risk for developing diverticular disease can in general be reduced,” W.H. Aldoori said (figure 26). There is also a very pronounced relationship between physical activity and diverticular disease: the more exercise, the fewer the disease flares (figure 27).
A careful individualized benefit-to-risk analysis is important

Both in this area and with regard to the optimum management of diverticular disease in general many questions remain open and there is a dearth of controlled studies to validate the individual measures. Even the recommendation formulated in the European and American guidelines to refer a patient for sigmoid resection following the second disease flare is not evidence-based, D. Meyer (Würzburg) warned in his review of the results of the symposium.

In his opinion, one should be careful to avoid generalized recommendations and perform a careful benefit-to-risk analysis in each patient. Management options should be discussed with the patient and selected in relation to the severity of the disease and the respective risks of the planned procedures.

**Relative risk of diverticular disease (W.H. Aldoori, Mississauga)**
### Relative risk of diverticular disease by physical activity, non-vigorous, and vigorous activity levels (W.H. Aldoori, Mississauga)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total physical activity (median of total MET)</strong>&lt;sup&gt;5&lt;/sup&gt;</td>
<td>1  0.9</td>
<td>2  4.8</td>
</tr>
<tr>
<td><strong>RR&lt;sup&gt;1&lt;/sup&gt; (95% CI)</strong></td>
<td>1.0 (0.67–1.18)</td>
<td>2.0 67 (0.49–0.91)</td>
</tr>
<tr>
<td><strong>Multivariate RR&lt;sup&gt;2&lt;/sup&gt; (95% CI)</strong></td>
<td>1.0 (0.68–1.21)</td>
<td>2.0 71 (0.52–0.97)</td>
</tr>
<tr>
<td>Non-vigorous activity (median of total MET)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>1  0.1</td>
<td>2  1.4</td>
</tr>
<tr>
<td><strong>RR&lt;sup&gt;1&lt;/sup&gt; (95% CI)</strong></td>
<td>1.0 (0.83–1.55)</td>
<td>2.0 78 (0.56–1.10)</td>
</tr>
<tr>
<td><strong>Multivariate RR&lt;sup&gt;2&lt;/sup&gt; (95% CI)</strong></td>
<td>1.0 (0.84–1.58)</td>
<td>2.0 79 (0.56–1.12)</td>
</tr>
<tr>
<td>Vigorous activity (median of total MET)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>1  0</td>
<td>2  3.5</td>
</tr>
<tr>
<td><strong>RR&lt;sup&gt;1&lt;/sup&gt; (95% CI)</strong></td>
<td>1.0 (0.57–0.97)</td>
<td>2.0 79 (0.61–1.03)</td>
</tr>
<tr>
<td><strong>Multivariate RR&lt;sup&gt;2&lt;/sup&gt; (95% CI)</strong></td>
<td>1.0 (0.60–1.02)</td>
<td>2.0 88 (0.67–1.15)</td>
</tr>
</tbody>
</table>

1 Relative risk (adjusted for age).
2 Adjusted for age, energy-adjusted dietary fiber and total fat.
3 Includes flight of stairs climbed, walking or hiking outdoors (including walking at golf).
4 Includes running (≤ 10 minutes/mile), jogging (≥ 10 minutes/mile), lap swimming, tennis, squash or racquetball, callisthenics or rowing, bicycling (including stationary machines).
5 Total MET (maximal exercise test) = sum of the average time/week spent in each activity x MET-value of each activity.

### MET-value calculation

\[
\text{MET-value} = \frac{\text{calorie need/kg bw/hour during activity}}{\text{caloric need/kg bw/hour at rest}}
\]
How important is “broad-spectrum” anti-inflammatory therapy?

Inflammatory processes play a significant role in diverticular disease. The role of anti-inflammatory therapy, given this background, and why mesalazine, a mainstay in the management of inflammatory bowel diseases, can be a good therapy option for diverticula are explained by V. Gross (Amberg) in an interview.

Professor Gross, are there parallels and similarities between diverticular disease and inflammatory bowel diseases?

Gross: The pathogenesis of diverticular disease is less well-understood than that of inflammatory bowel diseases. Evidence from pathology, however, shows that patients with symptomatic diverticular disease often exhibit microscopic inflammation of the mucosa in the vicinity of diverticula. In some cases, there may even be extensive inflammation, which is then termed segmental colitis. Whether this inflammation is the actual focus of the diverticular disease remains unclear. There is also evidence that the disease may be based on a disorder of the enteral nervous system, which may, in turn, be caused by an inflammatory process. As in inflammatory bowel disease, it would appear therefore to make sense to employ broad anti-inflammatory substances after an acute disease flare to prevent the development of recurrent diverticular disease.

What are the options for conservative therapy?

Gross: When discussing the conservative treatment of diverticular disease, one must differentiate between the treatment of the acute diverticulitis flare and prophylactic therapy, which is geared primarily at the prevention of complications. With regard to the prophylaxis of complications, patients should always be advised to take a high-fiber diet in order to prevent high pressure conditions in the bowel. In an acute disease flare, strict avoidance of oral intake and the administration of antibiotics are obligatory because the cause of acute diverticulitis is always bacterial. Diagnosis is based on physical examination and laboratory studies, as well as on imaging methods, such as ultrasound or, preferably, CT. It is important that the clinical situation improves under conservative therapy within a few days, with the patient becoming essentially complaint-free within a week’s time. If this does not happen, this suggests a complicated disease course with the danger of perforation. In such cases, the patient must always be referred for surgical intervention.
One broad anti-inflammatory drug is mesalazine, which is also standard therapy for ulcerative colitis. What should one expect from this agent in diverticular disease?

Gross: There are only a few studies of mesalazine in diverticular disease. The principle of such therapy, however, makes sense and is based on the idea of using the anti-inflammatory action of this agent to prevent recurrence of diverticulitis and the development of symptomatic diverticular disease. Studies have examined the effects of mesalazine in the post-acute situation and have shown that patients receiving mesalazine after resolution of the acute phase had fewer complaints and less frequently developed recurrent diverticulitis even over a follow-up period of four years. Another study in patients with acute diverticulitis used mesalazine for one year as interval therapy in combination with an antibiotic, in this case the poorly absorbed rifaximine, which is not currently licensed in Germany. The drugs were taken for one week each month. The group that received mesalazine in addition to the antibiotic experienced fewer cases of recurrent disease. In general, however, the only available data comes from randomized open studies, so that a final evaluation of these effects is not yet possible. I consider the use of mesalazine to be a therapeutic principle that appears to be certainly plausible in the treatment of diverticular disease and which has already been used by some colleagues in their own practices with good results. It would be helpful for the effects of mesalazine to be verified in a double-blind study, especially since the safety and tolerability of this medication are very good, as is known from the very extensive experience in patients with inflammatory bowel diseases.

Professor Gross, thank you very much for this interview.
Moderators, Speakers and Scientific Organizers

Prof. Dr. L.M.A. Akkermans
Academisch Ziekenhuis Utrecht de Uithof
Dept. of Experimental Surgery
G. 04.228
Box 85500
NL-3508 GA Utrecht
The Netherlands

Prof. Dr. M. Anthuber
Allgemeinchirurgie
Klinikum Augsburg
Stenglinstr. 2
D-86156 Augsburg
Germany

Prof. Dr. S. Bar-Meir
Chaim Sheba Medical Center
Department of Gastroenterology
2 Sheba Road
IL-52 621 Tel Hashomer
Israel

Prof. Dr. R. Cohen
St. Mark’s Hospital
Department of Surgery
Level 5x
Watford Road
Harrow HA1 3UJ, UK

PD Dr. B. Egger
Inselspital
Klinik für Viszerale und Transplantationschirurgie
CH-3010 Bern
Switzerland

Prof. Dr. S. Feuerbach
Röntgendiagnostik
Klinikum der Universität Regensburg
D-93042 Regensburg
Germany

Prof. Dr. A. Fingerhut
Centre Hospitalier Intercommunal
F-78303 Poissy
France

Prof. Dr. W.E. Fleig
Innere Medizin I
Martin-Luther-Universität Halle-Wittenberg
Ernst-Grube-Str. 40
D-06120 Halle
Germany

PD Dr. C. Folwaczny
Medizinische Poliklinik
Klinikum der Universität München-Innenstadt
Nussbaumstr. 20
D-80336 München
Germany

Dr. A. Forbes
St. Mark’s Hospital
Digestive Diseases Research Centre
Watford Road
Harrow HA1 3UJ, UK

Prof. Dr. C. Gasché
Universitätskliniken Wien
Klinik für Innere Medizin IV
Währinger Gürtel 18–20
A-1090 Wien
Austria

Prof. Dr. P. Gionchetti
Università di Bologna
Policlinico S. Orsola
Istituto di Clinica e Gastroenterologia
Via Massarenti 9
I-40138 Bologna
Italy

Prof. Dr. V. Gross
Klinikum St. Marien Amberg
Innere Medizin II
Mariahilfbergweg 7
D-92224 Amberg
Germany

Prof. Dr. N.Y. Haboubi
Trafford General Hospital
Surgical Pathology
Moorside Road, Davyhulme
Manchester M41 5SL, UK

PD Dr. J.C. Hoffmann
Medizinische Klinik I
Charité Universitätsmedizin
Campus Benjamin Franklin (CBF)
Hindenburgdamm 30
D-12203 Berlin
Germany

PD Dr. S. Hollerbach
Allgemeines Krankenhaus Celle
Gastroenterologie
Siemensplatz 4
D-29223 Celle
Germany

Prof. Dr. C. Hüscher
Ospedale San Giovanni
Department of Surgery
Via dell’Aamba Aradam, 9
I-00184 Rome
Italy
Prof. Dr. K.-W. Jauch  
Chirurgie  
Klinikum der Universität München-Großhadern  
Marchioninistr. 15  
D-81377 München  
Germany

Prof. Dr. D. Meyer  
Chirurgie  
Klinikum der Universität Würzburg  
Josef-Schneider-Str. 2  
D-97080 Würzburg  
Germany

Prof. Dr. J. Jeekel  
Erasmus Medical Center  
Department of Surgery  
Dr. Molewaterplein 40  
NL-3015 GD Rotterdam  
The Netherlands

Prof. Dr. R. Jones  
UMDS of Guy’s & St. Thomas Hospitals  
Department of General Practice  
Division of Primary Health Care  
80 Kennington Road  
London SE11 6SP, UK

Prof. Dr. H. Koop  
HELIOS Klinikum Berlin  
Klinikum Buch  
Innere Medizin II  
Hobrechtsfelder Chaussee 100  
D-13125 Berlin  
Germany

Prof. Dr. H.-J. Krammer  
II. Med. Universitätsklinik  
Universitätsklinikum Mannheim  
Theodor-Kutzer-Ufer 1–3  
D-68167 Mannheim  
Germany

PD Dr. M. Kreis  
Chirurgie  
Klinikum der Universität München-Großhadern  
Marchioninistr. 15  
D-81377 München  
Germany

Prof. Dr. W. Kruit  
Evang. Krankenhaus Kalk  
Innere Medizin  
Buchforststr. 2  
D-51103 Köln  
Germany

PD Dr. H. Mönnikes  
Hepatologie/Gastroenterologie  
Charité Universitätsmedizin  
Campus Virchow-Klinikum (CVK)  
Augustenburger Platz 1  
D-13353 Berlin  
Germany

Prof. Dr. J. Mössner  
Universitätsklinikum Leipzig  
Innere Medizin II  
Philipp-Rosenthal-Str. 27  
D-04103 Leipzig  
Germany

Prof. Dr. J.M. Müller  
Allgemein- und Visceralchirurgie  
Charité Universitätsmedizin  
Campus Charité Mitte  
Schumannstr. 20–21  
D-10117 Berlin  
Germany

Prof. Dr. D. Örtli  
Mittlere Strasse 91  
CH-4012 Basel  
Switzerland

Dr. M.Z. Panos  
Euroclinic  
9, Athanasiadou Street  
GR-11 521 Athens  
Greece

Prof. Dr. S. Post  
Klinikum Mannheim  
Chirurgie  
Theodor-Kutzer-Ufer 1–3  
D-68167 Mannheim  
Germany

Prof. Dr. A. Revhaug  
University Hospital of Tromsø  
Department of Surgery  
N-9038 Tromsø  
Norway

Dr. G. Latella  
Universita di L’Aquila  
Cattedra di Gastroenterologia  
Via S. Sisto 22 E  
I-67100 L’Aquila  
Italy

Prof. Dr. P. LAYER  
Israelitisches Krankenhaus in Hamburg  
Innere Medizin  
Orchideenstieg 14  
D-22297 Hamburg  
Germany

Prof. Dr. B. Lembcke  
St. Barbara-Hospital  
Innere Medizin  
Barbarastr. 1  
D-45964 Gladbeck  
Germany

Dr. J.O. Lindsay  
The Royal London Hospital  
Endoscopy Unit  
Whitechapel  
London E1 1BB, UK

Dr. M. Lukas  
Charles University  
First Faculty of Medicine  
V Medical Department  
U nemocnice 2  
CZ-128 08 Prague  
Czech Republic

Prof. Dr. P. Marteau  
Hôpital Européen  
Georges Pompidou  
Service d’Hépato-Gastroentérologie  
20, rue Leblanc  
F-75908 Paris  
France

Dr. J.O. Lindsay  
The Royal London Hospital  
Endoscopy Unit  
Whitechapel  
London E1 1BB, UK

Dr. M. Lukas  
Charles University  
First Faculty of Medicine  
V Medical Department  
U nemocnice 2  
CZ-128 08 Prague  
Czech Republic

Prof. Dr. P. Marteau  
Hôpital Européen  
Georges Pompidou  
Service d’Hépato-Gastroentérologie  
20, rue Leblanc  
F-75908 Paris  
France

PD Dr. D. Meyer  
Chirurgie  
Klinikum der Universität Würzburg  
Josef-Schneider-Str. 2  
D-97080 Würzburg  
Germany
Dr. Dr. U.J. Roblick
Universitätsklinikum
Schleswig-Holstein
Campus Lübeck
Chirurgie
Ratzeburger Allee 160
D-23562 Lübeck
Germany

Dr. S. Schanz
Evang. Krankenhaus Kalk
Innere Medizin
Buchforststr. 2
D-51103 Köln
Germany

Prof. Dr. J. Schölmerich
Klinik für Innere Medizin I
Klinikum der Universität Regensburg
D-93042 Regensburg
Germany

Prof. Dr. V. Schumpelick
Allgemeinchirurgie
Universitätsklinikum Aachen
Pauwelsstr. 30
D-52074 Aachen
Germany

Prof. Dr. N. Senninger
Allgemeine Chirurgie
Klinikum der Universität
Waldeyerstr. 1
D-48149 Münster
Germany

Prof. Dr. R. C. Spiller
University Hospital
Queen's Medical Centre
Division of Gastroenterology
C Floor, South Block
Nottingham NG7 2UH, UK

Prof. Dr. M. Starlinger
Allgemeine öffentliche Krankenanstalten
Chirurgische Abteilung
St. Veiter Str. 47
A-9026 Klagenfurt
Austria

PD Dr. T. Wedel
Anatomie
Universitätsklinikum
Schleswig-Holstein
Campus Lübeck
Ratzeburger Allee 160
D-23562 Lübeck
Germany

S.D. Wexner, M.D.
Professor of Medicine
Cleveland Clinic Florida
Department of Colorectal Surgery
2950 Cleveland Clinic Boulevard
Weston, FL 33331
USA

Prof. Dr. M. Zeitz
Medizinische Klinik I
Charité Universitätsmedizin
Campus Benjamin Franklin (CBF)
Hindenburgdamm 30
D-12203 Berlin
Germany

Prof. Dr. H. Zirngibl
Helios Klinikum Wuppertal
Chirurgie
Heusnerstr. 40
D-42283 Wuppertal
Germany
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