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ORIGINAL ARTICLE

Prospective randomized trial comparing short-term antibiotic therapy versus standard therapy for acute uncomplicated sigmoid diverticulitis

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Abstract
Purpose To date, the standard therapy used for acute episodes of uncomplicated sigmoid diverticulitis has been a 7–10-day antibiotic treatment regimen. Thanks to the development of highly potent, broad-spectrum antibiotics such as ertapenem, the question arises as to whether the duration of treatment of acute uncomplicated sigmoid diverticulitis can be reduced by using highly effective antibiotics.
Methods To compare the efficacy of short-term therapy (4 days) versus standard therapy (7 days) for uncomplicated sigmoid diverticulitis, a prospective randomized multicenter trial was conducted. Patients were randomized to treatment groups after 4 days. Both patient groups were monitored until discharge and were followed up after 4–6 weeks and 52 months. The results were standardized and statistically evaluated.
Results Between 16 December 2004 and 15 November 2007, 123 patients from 11 hospitals were enrolled in the study. Seventeen patients dropped out. In the remaining 106 cases, no significant differences were discerned between the two groups in terms of the basic data, apart from the mean number of diverticulitis episodes (short term 1.28±0.64 versus standard 1.64±1.07, $p=0.037$). The mean hospital stay was 8.8 days, with significant differences seen between short-term and standard therapy (7.8±2.8 versus 9.7±3.2 days; $p=0.002$). After 4 days, treatment was classified as having proved successful in 98.0% of cases and after 7 days in 98.2% of cases. An overall success rate of 95.1% (94.0% versus 96.2%, n.s.) was recorded after 1 month.
Conclusion The results obtained with short-term ertapenem therapy (4 days) showed that this was as effective as standard therapy (7 days) for treatment of uncomplicated sigmoid diverticulitis.

Keywords Sigmoid diverticulitis · Conservative treatment · Antibiotic therapy · Ertapenem · Prospective randomized trial

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Introduction

Colonic diverticulosis is one of the diseases most commonly seen in the western world, affecting 50% of persons over the age of 70 years. Twenty-five percent of patients with colonic diverticulosis go on to develop diverticulitis or diverticular disease. Of the patients with diverticulitis, some 10% to 25% suffer significant complications. Complicated sigmoid diverticulitis is defined as diverticulitis with the formation of a treatment-resistant diverticular tumor, abscess, fistula, stenosis, bleeding, and/or perforation [1, 2]. In general, complicated diverticulitis is treated surgically and will not be further elaborated on in this paper (Fig. 1).

Uncomplicated acute sigmoid diverticulitis is treated conservatively. The decision to hospitalize a patient for diverticulitis depends on the patient's clinical status. Hospitalization is indicated if the patient is unable to tolerate oral food intake or has pain severe enough to require narcotic analgesia. A 7- to 10-day antibiotic regimen with a broad-spectrum antibiotic is recommended, with additional measures to combat anaerobes as well as parenteral nutrition in inpatients. Improvement of symptoms should be expected within 2–4 days. If conservative treatment fails after 2–4 days, it may be necessary to search for diverticulitis complications [3, 4].

The initial conservative treatment for uncomplicated sigmoid diverticulitis is successful in between 70% and 100% of cases [5–8].

In recent years, combinations of metronidazole and quinolones or third generation cephalosporins or betalactam antibiotics with betalactamase inhibitor have become the agents of choice for nonoperative intravenous therapy [3].

Treatment of bacterial infections in clinical practice is often complicated by antibiotic resistance. Prolonged therapy offers no benefit and increases the risk of resistance development. Successful treatment requires a "hit hard and hit fast" approach with an antibiotic that provides coverage of the relevant microorganisms. [9]. Furthermore, monotherapy is preferred to combination therapy and is possible for most infections. In addition to cost savings, monotherapy results in fewer medication errors and in fewer missed doses and drug interactions [10]. The development of novel antibiotic groups, such as the carbapenems, has opened up new possibilities for intravenous treatment of acute intra-abdominal infections. Myriad studies have shown that ertapenem was as effective as other therapeutic regimens [11, 12]. Furthermore, the results of short-term therapy for intra-abdominal infections are on a par with those obtained with standard therapy [13].

Based on the findings of these studies, we conducted a prospective randomized multicenter trial to investigate the efficacy of short-term therapy (4 days) with ertapenem for uncomplicated sigmoid diverticulitis compared with 7-day standard therapy, as described above.

Patients and methods

Study design

The study carried out was a prospective, randomized, open-labeled multicenter clinical trial to investigate treatment of acute sigmoid diverticulitis with ertapenem (NIH Reg.-Nr.

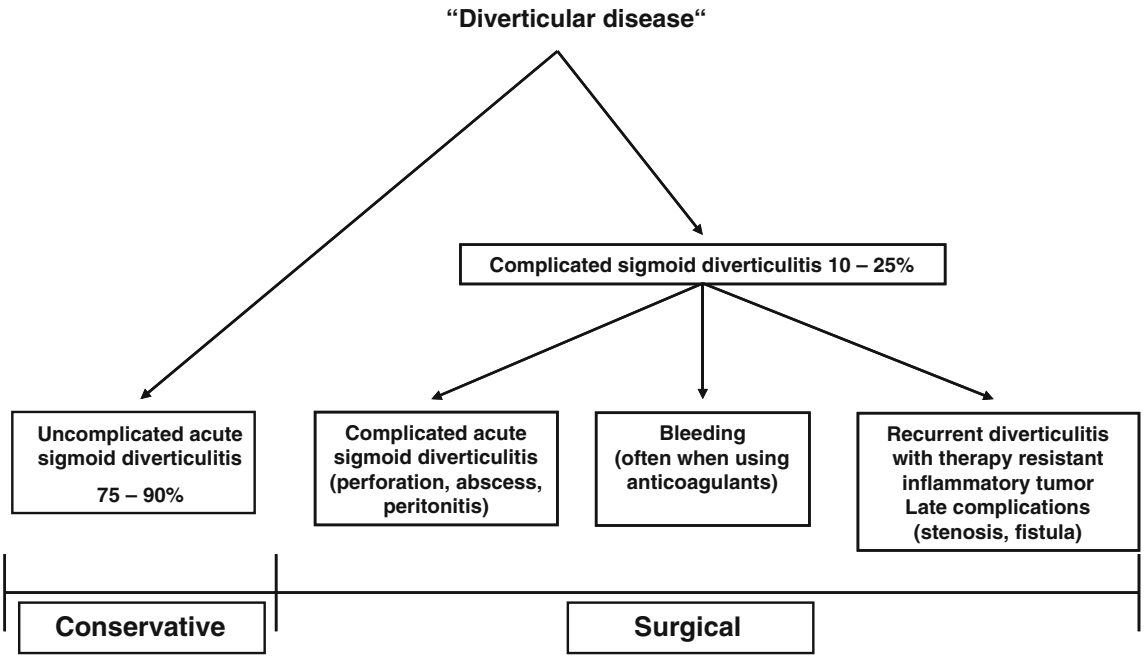

Fig. 1 Staging and treatment of "diverticular disease," sigmoid diverticulitis

NCT00097734). The aim of the study was to elucidate whether short-term therapy (4 days) with ertapenem is as effective as standard therapy (7 days), which is still recommended in the literature [3, 4]. This trial was approved by the ethics committees of each federal state of the various hospitals. The target study group comprised male and female patients between the age of 18 and 75 years admitted to hospital because of a diagnostically confirmed acute episode of sigmoid diverticulitis and the necessity of an inpatient treatment with parenteral nutrition [3, 4]. The inclusion and exclusion criteria are summarized in Table 1. After giving their informed consent, patients were enrolled in the study and were diagnosed and treated accordingly.

If treatment had proved successful, randomization was conducted on day4, via the study center, with antibiotic therapy being then either terminated or continued for a further 3 days. Day4 of therapy was chosen for randomization because experience has shown that in uncomplicated sigmoid diverticulitis, symptomatic improvement should be seen between days2 and 4. If a patient is not free of symptoms at day4 despite adequate treatment, based on the literature [3, 4], a complicated form of diverticulitis must be assumed, and the patient must therefore be evaluated as a dropout as per the trial protocol.

Patients were monitored until the end of their hospital stay, also in the event of their dropping out because of side effects or lack of clinical response (ineffectiveness). After discharge, further follow-up examinations were conducted 4–6 weeks as well as 52 weeks after completion of treatment to clarify issues relating to chronic problems, recurrences, or conductance of surgical treatment (Fig. 2). All data were recorded using structured registrations forms.

The primary endpoints were a clinically successful treatment outcome, recurrence rate, and surgical rate. A clinically successful treatment outcome was defined as compliance with at least four of the following criteria: absence of fever (≤38°C), absence of any signs of peritonitis or abdominal complaints, absence of leukocytosis (≤10,000 µl) as well as obviation of the need for additional antimicrobial treatment or surgical intervention. Secondary endpoints were trends in laboratory parameters after initiation of treatment, duration of hospital stay, duration of parenteral nutrition, frequency of surgical intervention, and repeat procedures as well as frequency of the need for intensive care.

Materials

Ertapenem (INVANZ®, Merck&Co., Inc., Whitehouse Station, NJ 08889, USA) is a 1-ß-carbapenem, available as an intravenous broad-spectrum antibiotic for treatment of severe and complicated intra-abdominal infections. It only needs to be administered once (1 g) daily, thanks to its

Table 1 Summary of inclusion and exclusion criteria for the trial

Inclusion criteria
Male or female patients aged between ≥18 and ≤75 years
Manifestation of at least two of the following symptoms of acute attacks of sigmoid diverticulitis
Fever (body temperature >38°C, sublingual)
Abdominal resistance
Increased leukocytes (leukocytes >10,000/µl)
Elevated CRP (≥20 and ≥ 2 mg/dl)
Detection of sigmoid diverticulitis using contrast medium
CT evidence/ultrasonography evidence of thickening of the wall of sigmoid colon
Conservative therapy possible, independently of previous clinical history
Exclusion criteria
Study medication or other betalactam antibiotics are contraindicated, e.g., patients with advanced renal insufficiency or patients requiring hemodialysis
Patients with hypersensitivity to betalactam antibiotics
Use of antibiotic treatment within the previous 2 weeks before enrolment in the trial
Patients with incurable hematological/oncological diseases
Patients taking immunosuppressants
Existing complications of sigmoid diverticulitis requiring emergency surgery
Women who are pregnant, breastfeeding, or who could become pregnant during the study
Participation in another clinical trial or use of another study medication during the previous 4 weeks before enrolment in the study or during the trial

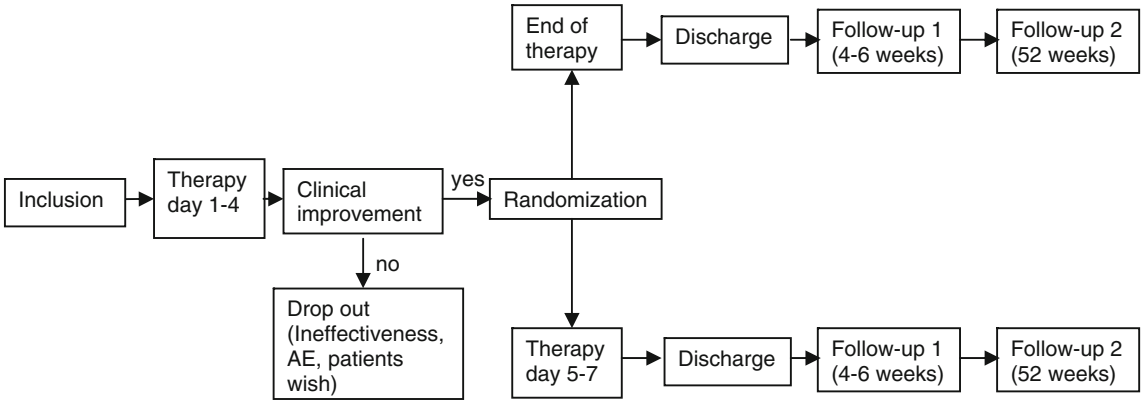

Fig. 2 Study flowchart: following enrolment in the study, 4-day therapy is first initiated with ertapenem; after investigating the success of treatment, patients are randomized to short- (4 days) or long-term therapy (7 days). Both groups continue to be monitored until discharged. Clinical examination is then conducted after 4–6 weeks and 52 months

pharmacokinetic profile. This dose must be halved for patients with creatinine clearance of less than 31 ml/min/1.73 m^2.

Statistical evaluation

Statistical evaluation was carried out with SPSS 14.0, with significance levels set at a p value <0.5. The t test was used for comparison of mean values, and Pearson's chi-square test for comparison of frequencies. For small values, Fisher´s exact test was used additionally.

Results

Patient population

Between 16 December 2004 and 15 November 2007, 123 patients from 11 hospitals were enrolled in the study. One hospital contributed 44 patients, one 23 patients, one 12 patients, one nine patients, two six patients, three five patients, and two four patients. The trial was completed on 12 December 2008, on carrying out the last follow-up examination.

The mean age of patients at admission was 59.5 years; 5.7% of patients were less than 40 years, and 53 patients were older than 65 years (43.1%); 47% of patients were female and 53% were male. The mean body mass index (BMI) was 27.9 kg/m^2; 25.4% of patients were obese (≥30 kg/m^2). After dropout of 17 patients, 50 patients were assigned to the short-term treatment group and 56 to the standard treatment group (Table 2). The only significant differences discerned between the two groups related to the mean number of episodes (short term 1.28±0.64 versus standard 1.64±1.07, p=0.037), attributable to the random distribution of the greater number of episodes seen in the 7-day treatment group.

Clinical severity and diagnostic findings, however, did not show any significant differences.

Table 2 Demographic data of patients randomized in the study

	Basic data for enrolled patients (n=106)			
	Total	4-day therapy	7-day therapy	Significance
Average age (years)	59.4±12.1 (26–82)	60.6±12.2	58.5±11.9	n.s.
Sex				
Female	48 (45.3%)	23 (46.0%)	25 (44.6%)	n.s.
Male	58 (54.7%)	27 (54.0%)	31 (55.4%)	n.s.
BMI (kg/m^2)	27.9 (17.3–41.4)	27.8	27.9	n.s.
Number of episodes (Ø)	1.47±0.9	1.28±0.7	1.64±1.1	p=0.037
1	72 (67.9%)	39 (78.0%)	33 (58.9%)	
2	26 (24.5%)	10 (20.0%)	16 (28.6%)	
3	4 (3.8%)	0 (0%)	4 (7.1%)	
4	2 (1.9%)	0 (0%)	2 (3.6%)	
5	1 (0.9%)	1 (2.0%)	0 (0%)	
7	1 (0.9%)	0 (0%)	1 (1.8%)	

Table 3 Breakdown of causes for dropping out of the study

	Dropout		
	No.	Percentage of dropout (n=17)	Percentage of primary enrolled patients (n=123)
Different antibiotic therapy before (Clont)	1	5.9	0.8
Upon patient's request	4	23.5	3.2
Allergic reaction	1	5.9	0.8
Pseudomembranous colitis	1	5.9	0.8
False diagnosis (Adnexitis, Endomyometritis)	1	5.9	0.8
Complicated diverticulitis	3	17.6	2.4
Randomization not possible because of persistent symptoms	6	35.0	4.8
Total	17	100	13.8

While a greater number of episodes were seen in patients over 65 years (up to 7), the proportion of initial events was somewhat higher than among younger patients 70.5% (31/44) versus 66.1% (41/62).

History and clinical findings

At the time of admission, apart from lower left abdominal pain, patients suffered from the following complaints: absence of bowel movement seen in 45.3% of cases (48/106) and inability to expel air (30.2%, 32/106), the most common complaints; followed by nausea and diarrhea, in 22.6% (24/106) and in 25.5% (27/106) of cases; and finally frequent micturition and dysuria, seen in 15.1% (16/106) and 13% of cases (14/106). Vomiting was noted in 6.6% (7/106) of patients. Clinical examination showed abdominal resistance in 85.7% of cases (90/106) and a palpable cylindrical mass in the lower left abdomen in 60.0% (63/106). The mean temperature was 37.3°C (37.3°C versus 37.3°C, n.s.; 35.6–39.8°C), leukocytosis was 12.9 tsd/µl (12.8 versus 12.9, n.s.; 5.0–23.0 tsd/µl), mean cross-reactive protein (CRP) values were 40.9 mg/dl (26.1 versus 54.62; p=0.042; 1–703 mg/dl).

Diagnosis

Computed tomography (CT) was performed for 97.2% (103/106) of patients and ultrasonography in 49.1% (52/106) of cases. Wall thickening was noted in 97.1% (102/106) (98.0% (49/50) versus 96.6% (54/56), n.s.) and pericolic infiltrate in 40.6% (42/106) (32.0% (16/50) versus 48.2% (27/56); n.s.). However, there was no correlation between degree of severity and treatment course.

Dropout

In total, 17 patients dropped out in the course of the study. In six cases, patients could not be randomized after 4 days of treatment because of severe persistent symptoms. On the other hand in two cases in the 7-day group, treatment was terminated prematurely at the request of the patients who were now free of symptoms. Two patients did not want to be enrolled in the study any more. Three patients had, after all, complicated diverticulitis and had to be operated on. One of the patients had a false primary diagnosis and had to be treated for adnexitis/endomyometritis. An allergic reaction, possibly due to antibiotic administration, was noted in one case. In one case, pseudomembranous colitis occurred on the last day of the 7-day treatment regimen, after the patient had been largely free of any complaints and symptoms related to sigmoid diverticulitis (Table 3).

Side effects

Side effects were suspected in three cases (2.4%), but in no case could the symptoms be unequivocally attributed to antibiotic treatment. Severe side effects were not observed in any of the cases (Table 4).

Table 4 List of symptoms manifested and recorded as potential side effects

	Side effects manifested (or suspected)		
	Total	4-day therapy	7-day therapy
Adverse event (AE)	3 (2.4%)	3 (5.1%)	0 (0%)
Allergic reaction	1	1	0
Headache	2	2	0
Serious adverse event (SAE)	0 (0%)	0 (0%)	0 (0%)

Table 5 Course of clinical symptoms during and after short-term and standard therapy with ertapenem

	Progression of symptoms after therapy (n=106)			
	Before therapy (4/7days) (n=106)	On day 4 (4/7days) (n=106)	On day 8 (7days) (n=56)	1month (4/7days) (n=91)
No regular bowel movement	48 (45.3%)	26 (24.8%)	9 (16.1%)	4 (4.4%)
Inability to expel air	32 (30.2%)	22 (21.0%)	9 (16.1%)	0 (0%)
Diarrhea	24 (22.6%)	26 (24.5%)	7 (12.5%)	4 (4.4%)
Nausea	27 (25.5%)	0 (0%)	1 (1.7%)	1 (1.1%)
Vomiting	7 (6.6%)	0 (0%)	2 (3.5%)	0 (0%)
Dysuria	14 (13.2%)	2 (1.9%)	1 (1.7%)	1 (1.1%)
Frequent micturition	16 (15.1%)	5 (4.8%)	0 (0%)	1 (1.1%)
Abdominal tension	90 (85.7%)	4 (3.8%)	1 (1.7%)	4 (4.4%)
Palpable cylindrical mass	63 (60.0%)	29 (27.4%)	5 (8.9%)	8 (8.8%)

Hospital stay

The patients' mean hospital stay was 8.8 days (5–24 days) for all patients, with a significant difference being observed here between short-term and standard therapy groups (7.8± 2.8 versus 9.7±3.2 days; p=0.002). Intensive care was not necessary at all.

Treatment course

It was possible to bring about a marked reduction in the typical symptoms already after 4 days. No differences of note were observed between study days4 (4+7-day therapy) and 8 (7-day therapy).

There was virtually no evidence of specific symptoms after 1 month (Table 5).

Duration of parenteral nutrition

Whereas in the 4-day ertapenem treatment group, oral food intake on post-therapy (day5) did not prove to be a problem in 47/50 (94.0%) patients (versus 24.6% (13/56) in the standard group, p<0.001), parenteral nutrition was continued for 47 of 56 patients of the standard therapy group (83.9%). Problem-free food intake had been introduced by day8 of the hospital stay for 55 of 56 patients (98.2%).

Follow-up

After 1 month, it was possible to follow up on average 96.2% (102/106) of patients (46 (92.0%) versus 56 (100%), n.s.). After 1 year, the overall follow-up was 71.7% (76/106) (36 (72.0%) versus 40 (71.4%), n.s). In the long-term therapy group, two patients died after initial follow-up. While these had been asymptomatic on completion of treatment and at the time of initial follow-up, they had been classified as ASA III and IV already on inclusion in the study (severe cardiac disease) (Table 6).

Treatment success

After 4 days, as well as at the time of completion of the standard therapy, treatment was classified as successful in 98.1% (102/106) of cases. No significant differences were observed between the two treatment groups after this time. No significant differences were noted at either time between short-term and standard therapy (98.0% (49/50) versus 98.2% (55/56)).

The overall success rate observed after 1 month was 95.1% (97/102): 47/50 in the short-term (94.0%) versus 54/56 in the standard therapy group (96.4%) (n.s.).

After 1 year, an average of 7.9% (7/88) of patients had been administered an antibiotic once again. A recurrence of

Table. 6 Follow-up of the 106 randomized patients

	Follow-up (n=106 enrolled patients)			
	Total	4-day therapy (n=50)	7-day therapy (n=56)	Significance
Follow-up 1 (1 month)	91 (85.5%)	40 (80.0%)	51 (91.1%)	n.s.
Follow-up 2 (1 year)	76 (71.7%)	36 (72.0%)	40 (71.4%)	n.s.
Died	2 (1.9%)	0	2 (3.6%) (cardiac reason, ASA III/IV)	

Table 7 Treatment outcome during therapy and follow-up, considering the number of recurrences and surgical therapy in the course of the study

	Evaluation of treatment outcome			
	Total	4-day therapy	7-day therapy	Significance
4 days	104/106 (98.1%)	49/50 (98.0%)	55/56 (98.2%)	n.s.
8 days	104/106 (98.1%)	49/50 (98.0%)	55/56 (98.2%)	n.s.
1 month	97/102 (95.1%)	47/50 (94.0%)	54/56 (96.4%)	n.s.
Additional antibiotic therapy	7/88 (7.9%)	4/39 (10.3%)	3/49 (6.1%)	n.s.
Recurrence	8/88 (9.1%)	3/40 (7.5%)	5/48 (10.4%)	n.s.
Postinflammatory stenosis	2/88 (2.3%)	1/40 (2.5%)	1/48 (2.1%)	n.s.
Surgery performed elective	37/92 (40.2%)	16/43 (37.2%)	21/48 (42.9%)	n.s.
Early elective because of complications	2/92 (2.2%)	2/43 (4.6%)	0/48 (0%)	s.
Interenteric fistula	1/92 (1.1%)	1/43 (2.3%)	0/48 (0%)	
Abscess	1/92 (1.1%)	1/43 (2.3%)	0/48 (0%)	

sigmoid diverticulitis was seen in 9.1% (8/88) of cases. No significant differences were discerned between the groups.

By the second follow-up, an average of 42.4% (39/92) (41.8% (18/43) versus 42.9% (21/48); n.s.) of patients had undergone surgery; this was an elective procedure apart from for two cases in the short-term group therapy group. One patient was admitted with an abscess 3 weeks after short-term therapy. Retrospectively viewed, this patient still harbored non-specific symptoms after termination of treatment, and oral food intake was also delayed. The second patient was operated on after 8 weeks because of an interenteric fistula. Food intake had also proved difficult after treatment. The hospital stay was 15 and 13 days, respectively, and as such was markedly longer than the average hospitalization period (Table 7). In both of the cases, a wrong initial diagnosis has to be suspected because of the prolonged hospital course. Both patients belonged to the short-term therapy group.

Discussion

Antibiotic therapy for uncomplicated acute sigmoid diverticulitis must be effective against aerobic (*Escherichia coli*, *Proteus*, *Klebsiella*, and *Enterococcus*) and anaerobic (*Bacteroides*, *Clostridium*, *Bifidobacterium*, and *Peptostreptococcus*) bacteria. In general, this is assured by using a broad-spectrum antibiotic or combination therapy with metronidazole and quinolones or third generation cephalosporins or betalactam antibiotics with a betalactamase inhibitor [3]. The literature cites a treatment period between 5 [14] and 7–10 days [1, 3, 4, 15–18].

From a microbiological viewpoint, preference should be given to bactericidal antibiotics over bacteriostatic agents, and monotherapy is better than combination therapy. Furthermore, the duration of antibiotic treatment should be kept as short as possible to avoid side effects, superinfections, and resistance development. The economic implications of the duration and frequency of antibiotic administration should also be taken into consideration [19, 20]. Whereas daily treatment with the combination drug tazobactam costs around 100 euros, the costs incurred for a daily single dose of ertapenem are around 68 euros.

Ertapenem is becoming increasingly more established as a broad-spectrum antibiotic for treatment of intra-abdominal infections. In several prospective randomized studies using other comparable combination therapies, it was possible to demonstrate that equally good clinical and laboratory results were obtained [11]. This antibiotic, which belongs to the carbapenem group, is endowed with many of the attributes outlined above. Another important aspect here is that only a single daily dose of the antibiotic is needed.

Premature resolution of the pathological clinical and laboratory parameters suggests that shorter treatment duration is advisable for uncomplicated acute sigmoid diverticulitis. This prospective randomized trial demonstrated that a shorter 4-day treatment period is just as effective as the standard treatment (98.0% versus 98.2% after 4 days or 98.0% versus 98.2% after 8 days or 94.0% versus 96.4% after 1 month; n.s.), which confirms the experience by other authors that symptoms should be improved after 2–4 days [3, 4]. Here there was no evidence that the number of previous episodes or age played any role. Only in exceptional cases was prolongation of antibiotic therapy beneficial.

The shorter duration of antibiotic therapy with patients' speedier convalescence also provides for earlier oral food intake, and thus for discontinuation of the recommended parenteral nutrition [3, 4]. It was possible to bring about a significant reduction in the average hospital stay for the 4-day therapy group (7.8 versus 9.7 days; $p=0.002$). Two patients from the standard group dropped out of the study after 4 days because their symptoms had resolved. No patient who responded to treatment required intensive care treatment.

Proof has been furnished that after this period of time, pathogens will have been eradicated [13]. There is also a greater likelihood of occurrence of pseudomembranous colitis and resistance development with longer treatment duration.

The only imbalance in this study is the significantly higher rate of previous episodes of sigmoid diverticulitis in the 7-day group (1.28 versus 1.64, $p=0.037$). Based on the literature [3–5, 11, 17, 18, 21, 22], this cannot be viewed as an important influence factor in follow-up. The follow-up data show occurrence of a new relapse in 9.1% of cases within 1 year without significant difference between the two groups (7.5% versus 10.4%). The documented recurrence rate after treatment in most retrospective studies is 10–30% [3]. Just under one third (32.1%) of the enrolled patients had already experienced one or several episodes of sigmoid diverticulitis. Within the first year, an elective sigmoid resection was carried out for 40.2% of patients. No differences were seen between the groups (37.2% versus 42.9%). Hence the elective resection rate is somewhat above the range of the initially documented recurrence rate and, no doubt, higher than the figures described in the literature for this short period of time [4, 18, 23–26].

In two cases, early resection had to be performed because of complications (abscess and interenteric fistula); both patients belonged to the short-therapy group. Convalescence was delayed for both patients during the first hospital stay, suggesting that here a more complex baseline situation can be assumed a priori. It is likely that short-term therapy counters masking of complications, thus helping to distinguish better between uncomplicated and complicated cases.

Conclusion

The present prospective randomized comparative study demonstrates that acute episodes of uncomplicated sigmoid diverticulitis can be treated with the broad-spectrum antibiotic ertapenem, from the carbapenems group, using a 4-day administration regimen and additional parenteral nutrition, with the same effectiveness as when using the hitherto recommended 7-day treatment. The same therapeutic successes are scored already after 4 days as seen in the 7-day group. Only rarely is any improvement in outcome observed after prolonged treatment. The most essential and significant difference is in the duration of the hospital stay, which for the 4-day therapy group was on average 2.4 days shorter than for the 7-day treatment group. Significant cost savings can thus be achieved with the 4-day therapy.

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Conflict of interest The authors declare that they have no conflict of interest.

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