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ORIGINAL ARTICLE

Antibiotic treatment for uncomplicated and mild complicated diverticulitis: outpatient treatment for everyone

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Abstract
Purpose Antibiotic treatment is the treatment of choice for uncomplicated diverticulitis (uD) and can be performed for mild complicated diverticulitis (mcD). In several cases, outpatient treatment (OT) can be undertaken. This study assessed the 1-month failure rate of OT for uD/mcD compared to inpatient treatment (IT), and identified predictive factors for treatment failure.
Methods All consecutive patients (2006–2012) diagnosed with uD/mcD by CT scan were retrospectively analyzed. Acute uD was defined as absence of the following: abscess, fistula, extraluminal contrast, pneumoperitoneum, and need for immediate percutaneous drainage/surgery. Acute mcD was defined as complicated diverticulitis with abscess <4 cm or pneumoperitoneum <2 cm. All patients received antibiotherapy. Treatment failure was defined as (re)hospitalization the first month after treatment onset or need of drainage/surgery during hospitalization. All patients were contacted using a standardized questionnaire.
Results Out of 540 uD/mcD, IT was offered to 369 patients (68%) and OT to 171 patients (32%). The IT group had higher median age, more women, higher median Charlson Index, more severe median Ambrosetti score, longer median time in the emergency room, and higher median CRP. Response rates to the questionnaire were 56% (IT) vs. 62% (OT), $p = 0.18$. Failure rates were 32% in IT vs. 10% in OT group, $p < 0.01$. Among the uD/mcD patients, admission/CT time between midnight and 6 AM, Ambrosetti score of 4, and free air around the colon were risk factors for failure.
Conclusions Outpatient treatment for uncomplicated/mild complicated diverticulitis is feasible and safe. Prognostic factors of failure necessitating closer follow-up were admission/CT time, Ambrosetti score of 4, and free air around the colon.

Keywords Diverticulitis · Outpatient treatment · Treatment failure · Antibiotics

Introduction

Approximately 20% of patients with diverticular disease will present at least one episode of acute diverticulitis [1–4]. Recently, the treatment of diverticulitis has evolved to become more conservative even without antibiotics [5] and less invasive with percutaneous drainage or laparoscopic lavage [6]. Indications for emergency surgery are now restricted to gross purulent or fecal peritoneal contamination, septic shock, or failure of conservative treatment [7]. In addition, the majority of patients present with uncomplicated diverticulitis (uD), i.e., without complications such as abscess, bleeding, fistula, stenosis, or perforation with free air [8]. Patients with small abscess or low free air (mild complicated diverticulitis, mcD) can also be treated with antibiotics according to recent studies [8]. Several studies showed that outpatient treatment (OT) of uD and mcD was feasible and safe [9–11]. It has also been shown that OT was cost-beneficial and cost-effective inducing important savings for the hospital and the general health care system [10, 12, 13].

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However, decision for OT with antibiotherapy is often made subjectively by the doctor and depends on various not well-defined factors such as general health condition of the patient, ability to tolerate oral medication (no nausea or vomiting), absence of diarrhea, or support at home. For daily clinical practice, only few studies have investigated predictive factors of OT failure for uD [9, 14].

The aim of the present study was to assess the 1-month failure rate of antibiotic OT for uD and mcD compared to antibiotic inpatient treatment (IT), and to define predictive factors of treatment failure.

Material and methods

Patients, inclusion and exclusion criteria

All patients with uD and mcD presenting to the emergency room (ER) of the Lausanne University Hospital (CHUV) from January 2006 to December 2012 were retrospectively analyzed. Inclusion criteria were patients >18 years old and CT-based diagnosis of uD, i.e., diverticulitis without complication, or mcD. Complications of acute diverticulitis were defined in our study as extraluminal extravasation of contrast product on CT, pneumoperitoneum, presence of fistula, intra-abdominal or pericolic abscess, bleeding, or stenosis. Acute mcD was defined as patients with complicated diverticulitis with pneumoperitoneum <2 cm under the diaphragm or intra-abdominal/pericolic abscess <4 cm. Patients requiring an immediate (at admission) percutaneous drainage or surgery were excluded from the analysis. The number of prior diverticulitis episodes was not an exclusion criterion.

Outcome measures and questionnaire

Patients' characteristics, symptoms, laboratory tests, treatment data, and orientation after diagnosis (home, hospital, transfer to another hospital) were recorded and retrospectively reviewed. Comorbidities of the patients were scored using the Charlson Comorbidity Index [15]. Severity of uD and mcD was graded by the CT scan-based classification of Ambrosetti, where diverticulitis was subdivided into moderate (1 = localized colic wall thickening >5 mm, 2 = pericolic fat infiltration) and severe (3 = abscess, 4 = extraluminal air or contrast) [16]. Treatment failure was defined as reappearance of symptoms and (re)hospitalization during the month following the start of antibiotic treatment, or need of drainage/surgery during primary hospitalization (inpatient group). Recurrence was defined as new symptoms appearing more than 1 month after initial treatment. All included patients were contacted using a standardized questionnaire to assess treatment failure. The questionnaires to the patients were sent in 2014. In case of non response, patients were sent the questionnaire one more time. The questionnaire asked if the patient had to be hospitalized for diverticulitis the month following the initial treatment, if he had to be operated during that hospitalization, if he had new symptoms more than 1 month after treatment, if he had a control colonoscopy (recommended for all patients >50 years of age and if >5 years from last colonoscopy), and if he underwent elective colon surgery during follow-up. Incomplete or unclear returned questionnaires were completed by contacting the general practitioner and/or the patient when needed.

Outpatient and inpatient treatments

All patients with uD and mcD received antibiotics independently of the treatment type (OT or IT).

All cases of diverticulitis diagnosed in the ER were presented to the surgeon on call or to the responsible ER senior physician. The decision of undertaking an OT was decided case by case by the surgeon or the ER physician. The elements motivating the decision were the patient's ability to tolerate oral medication, pain control with oral medications, and presence of support at home. In case of OT, one single shot of intravenous (IV) antibiotics was given in the ER, and then a course of oral antibiotics was ordered for a period of 10 days based on our institutional guidelines.

If the patient was hospitalized, IV antibiotics and IV fluids were started immediately. Antibiotics were switched to oral form when the pain was controlled by non-opioid analgesics (e.g., paracetamol or metamizole) and when the patient was able to tolerate oral medication. There was no alimentary restriction during the hospitalization. Patients were discharged once antibiotics were given orally and pain controlled with oral analgesics.

Statistical analysis

Comparisons between groups for continuous variables were done by using a Mann-Whitney U test or a t test depending on the variable distribution and the variance homogeneity. Fisher's exact test was used for discrete variables. GraphPad Prism© 5 for Mac OS X (GraphPad Software Inc.) was used for calculation and analysis. A p value <0.05 was considered to be statistically significant.

The study protocol was granted approval by the local Ethics Committee (protocol number: 255/13100613).

Results

Patient demographics and treatment characteristics

During the study period, 540 patients with uD and mcD were collected (Fig. 1). Among these 540 patients, 68% (369)

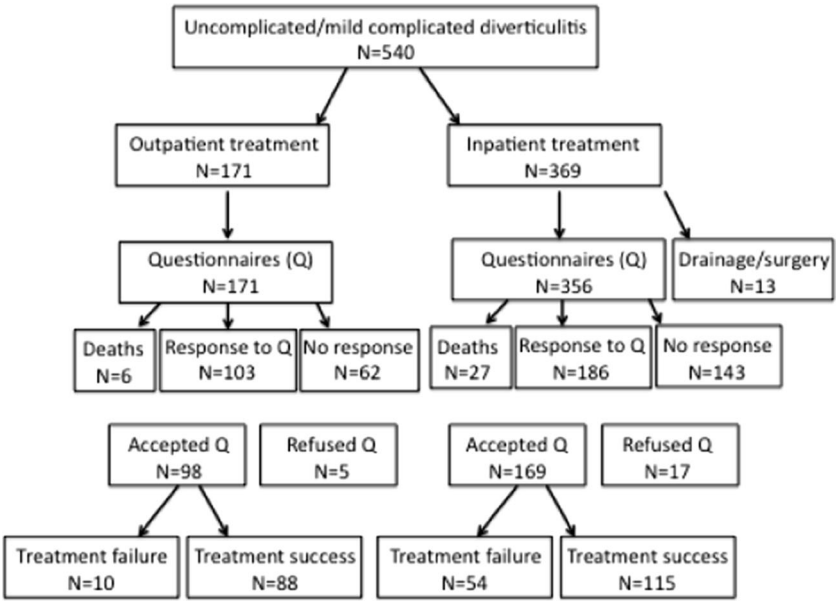

Fig. 1 Flowchart of the study patients

underwent IT and 32% (171) OT. For the IT group, the median length of stay was 4 days (IQR, 3–5). The number of first uD and mcD episodes was 263 (71%) and 123 (72%) in the IT and OT groups, respectively ($p = 0.92$). The percentage of OT increased over time (2006: 12/92 = 13%, 2012: 40/104 = 38%, $p < 0.001$). Overall, the IT group had a higher median age compared to the OT group ($p < 0.001$), comprised more women ($p = 0.003$), had a higher median Charlson Index ($p < 0.001$), comprised a higher number of high Ambrosetti scores ($p < 0.001$), had a longer median stay in the ER ($p < 0.001$), and had a higher median CRP ($p < 0.001$). Demographics were otherwise similar between the two groups (Table 1). Moreover, the two groups of patients treated from 2006 to 2008 and from 2009 to 2012 (corresponding to half of the study period) had no statistical difference in demographics and disease presentation, in parallel to the increased percentage of OT over the years.

Treatment outcomes

Twenty-seven patients in the IT group and 6 in the OT group were dead (unrelated to diverticulitis) at the time of questionnaire sending in 2014. The response rates of alive patients to the questionnaires were 56% (186/329) in the IT and 62% (103/165) in the OT ($p = 0.25$). There were no demographic differences between responders and non-responders (data not shown). Among the patients who responded and accepted the study (Qgroup: 267 patients, 22 refusals), 32% (54/169) mentioned a hospitalization for the same abdominal pain during the month after treatment in the IT group compared to 10% (10/98) in the OT group ($p < 0.001$). Between these latter two groups, there were no statistical differences in demographics, laboratory results, episode number, and antibiotherapy length. Among the Qgroup, 30/169 (18%) had an elective operation in the IT group and 14/98 (13%) in the OT group ($p = 0.50$). The median follow-up in the Qgroup was 59.5 and 46.5 months for the IT and OT groups, respectively ($p = 0.04$). Recurrences during the follow-up (new symptoms appearing more than 1 month after initial treatment) were 40/98 (41%) in the OT group and 70/169 (41%) in the IT group ($p = 1$).

Treatment failure

Treatment failure necessitating drainage or surgery during the hospitalization (not at admission, but during primary stay due to deterioration) occurred in 13 patients (4%; 5 women; 8 operations and 5 percutaneous drainages) in the IT group. There were no significant demographic differences between these 13 patients and the 356 other patients who had an IT (data not shown). Extraluminal air was associated with higher rate of IT failure ($p = 0.02$), and uD/mcD episode >2 was associated with higher rate of OT failure ($p = 0.02$). Colonoscopy between 4 and 12 weeks after the acute episode was performed in 199 patients (70 in the OT group, 129 in the IT group). The results of IT and OT are summarized in Table 2.

Risk factors for treatment failure

There was no difference in gender ($p = 0.89$) and age ($p = 0.89$) between failures and successful treatments. There were more treatment failures when admission time and CT time were between midnight and 6 AM ($p = 0.008$ and $p = 0.007$, respectively), but no difference regarding the trimester (season) of admission date. There was also no difference between the two groups concerning the time spent in the

Table 1 Patient demographics in the outpatient treatment group (OT) and in the inpatient treatment group (IT)

	OT *n* = 171	IT *n* = 369	*p* value
Age (years)	53 (44–64)	61 (50–72)	*<0.001*
Women/men	62/109	185/184	*0.003*
Charlson Index [15]	2 (1–3)	3 (2–4)	*<0.001*
Ambrosetti stage 1/2/3/4 [16]	9/149/7/6	9/250/43/67	*<0.001*
Number of 1st episode	123 (72%)	263 (71%)	0.918
Right colon	6 (4%)	25 (7%)	0.164
Alive/dead	165/6	342/27	0.086
Time spent in the ER[a] (min)	310 (237–396)	345 (273–437)	*<0.001*
Time between admission and CT (min)	173 (113–256)	171 (121–246)	0.935
Symptom duration (h)	48 (24–72)	48 (24–96)	0.615
Previous abdominal surgery	85 (50%)	213 (58%)	0.080
Mean arterial pressure (mmHg)[b]	99 (89–108)	100 (89–108)	0.747
Heart rate[b]	84 (74–92)	84 (73–93)	0.942
Temperature (°C)[b]	36.7 (36.2–37.2)	36.9 (36.5–37.5)	0.242
Leukocyte count (G/l)[b]	11 (8–13)	11 (9–13)	0.185
C-reactive protein level (mg/l)[b]	42 (20–73)	77 (37–133)	*<0.001*
Thrombocyte level (G/l)[b]	233 (202–274)	236 (197–275)	0.967
Creatinine level (μg/l)[b]	80 (68–89)	81 (69.5–96.5)	0.060

All values are median (interquartile range) or number (%). Significant *p* values appear in italics.

[a] Emergency room

[b] At admission

ER ($p = 0.91$). The median Charlson Index was similar. There were significantly more Ambrosetti grade 2 and fewer grade 4 in the group with no treatment failure. Free air around the colon was associated with a statistically significantly increased risk of failure ($p = 0.0004$) (Table 3).

Discussion

The present study showed that antibiotic OT of acute uD and mcD was feasible and safe with a low 1-month failure rate of 10% compared to 32% for antibiotic IT. Predictive factors of treatment failure for OT and IT were an ER admission time and a CT performed between midnight and 6 AM, an Ambrosetti score of 4, and the presence of free air around the colon.

The reason why an admission time and a CT between midnight and 6 AM were associated with an increased risk of treatment failure is not evident. It might be that patients are more reluctant to come to the ER during night meaning that those coming at night have a more severe disease. However, we included only uD and mcD, and all CT scans were reviewed by a senior radiologist in the morning. If the diverticulitis was not uncomplicated or mild complicated as defined above according to our criteria, patients were excluded from the study. It is also possible that a circadian variation can be implicated or that this finding resulted from an out-of-hour effect. Etzioni et al. found in a retrospective study that being a woman and having free fluid on the CT were risk factors for OT failure [9]. Similarly to the results of this study, age, laboratory results, or the Charlson Index were not prognostic factors of failure in our cohort. Of note, in their study

Table 2 Outcomes of responders ($n = 267$) by treatment group

	OT *n* = 98	IT *n* = 169	*p* value
Median follow-up (months)	46.5 (29–74)	59.5 (34–82)	*0.035*
Treatment failure	10 (10%)	54 (32%)	*<0.001*
If treatment failure, operation during hospital stay	3 (3%)	13 (8%)	0.701
Elective colic resection	14 (13%)	30 (18%)	0.497
Colonoscopy after episode	70 (71%)	129 (76%)	0.380

Significant *p* values appear in italics.

Table 3 Characteristics of patients with treatment failure and with no treatment failure

	Treatment failure $n = 64$	No treatment failure $n = 203$	p value
Women/men	31/33	96/107	0.887
Age (years)	60 (48.5–69.5)	58.9 (50.4–69)	0.887
Admission time			
00:00–6:00	13	11	*0.008*
6:01–12:00	21	78	0.460
12:01–18:00	16	65	0.350
18:01–23:59	14	49	0.866
Admission date			
1/1–31/3	12	31	0.559
1/4–30/6	17	58	0.874
1/7–30/9	24	62	0.357
1/10–31/12	11	52	0.181
CT time[a]			
00:00–6:00	14	18	*0.007*
6:01–12:00	10	29	0.686
12:01–18:00	24	92	0.378
18:01–23:59	12	58	0.186
Time spent in the ER[b] (min)	164.5 (113.8–233)	181.5 (99–254.8)	0.906
Charlson Index [15]	3 (1–4)	3 (2–4)	0.869
Episode number >2	55 (86%)	190 (94%)	0.067
Ambrosetti score [16]			*0.001*
1	3	6	0.451
2	38	163	*0.001*
3	6	17	0.801
4	17	17	*0.0004*
Free air on CT:			
- In the pericolic fat	8	15	1
- Around the colon	12	8	*0.0004*
Symptom length (hours)	48 (16.5–72)	48 (24–72)	0.153
Right/left colon	3/61	9/194	1
Mean arterial pressure (mmHg)[c]	97 (88–112)	100 (89–108)	0.752
Temperature (°C)[c]	36.8 (36.5–37.5)	36.8 (36.4–37.3)	0.321
Heart rate[c]	81 (70–90)	84 (74–92)	0.284
CRP level (mg/l)[c]	54 (29–113)	63 (32–116)	0.565
Leukocyte count (G/l)[c]	11.3 (9.1–13.5)	11.5 (9.5–13.5)	0.794
Thrombocyte level (G/l)[c]	238 (194–277)	237 (198–269)	0.856
Creatinine level (μg/l)[c]	77 (67–87)	80 (69–92)	0.233

All values are median (interquartile range) or number (%). Significant p values appear in italics.

[a] CT times were missing for 10 patients (4 in the failure group and 6 in the non failure group)

[b] Emergency room

[c] At admission

Etzioni et al. found a failure rate of 6%, in line with the 10% of failure that we observed in the OT group.

Patients with one of the above-mentioned risk factors for treatment failure should have a tighter outpatient follow-up. This follow-up can be undertaken with repetitive phone calls or with an early visit to their general practitioner [10]. Such institutional guidelines have been put in place since, and outcomes are now assessed prospectively.

For patients with uD and mcD who had IT, risk factors for early failure during the hospital stay could not be identified. However, early failure requiring drainage or surgery during the index hospitalization occurred in 4% of patients only.

Despite the fact that no clear institutional guidelines for IT or OT were available during the study period, the percentage of OT for uD and mcD increased with time from 13 to 38%. This observation corroborates the results of several articles that showed that OT was safe and feasible in case of uD and mcD [7, 9–11, 17]. In a multicentric randomized controlled trial, Chabok et al. have even demonstrated that antibiotics were not superior to symptomatic treatment in terms of complications, recurrence, and recovery time [5]. Based on these data and the low failure rate, OT without antibiotics could be proposed in more patients. In the present study, all patients received antibiotherapy for uD and mcD. Based on the results of the previously mentioned study [5] and the future results of an ongoing trial comparing antibiotics vs. no antibiotics [18], treatment is becoming more conservative. OT has several advantages. It allows decreasing the hospital costs normally induced by a hospitalization for uD and mcD, and it can reduce the overload of hospitalized patients [10, 12]. Another corollary of OT is the diminution of the risks of nosocomial infection [19]. Of note, our study did not assess the feasibility of OT without antibiotics as all patients received antibiotherapy in our protocol.

There is presently no clear consensus regarding the definition of uD. In the current literature, abscess <2 or <5 cm depending on the diverse guidelines is classified as uD or mcD [7, 8, 20–22]. Recently, the presence of free air >2 cm or retroperitoneal air was shown to be risk factors for conservative treatment failure [14]. In the present study, an abscess <4 cm was considered as mcD in light of recent literature. These patients were successfully treated as outpatients. However, the case number of this subgroup is too small for definitive recommendations.

Several limitations of this study need to be addressed. Firstly, due to its retrospective design it is possible that some patients or some data not mentioned in the charts were missed. Secondly, patients who were first treated by their general practitioner and then presented to the ER were also included. However, they were not considered as OT failure because their initial diagnosis was not based on CT scan. Thirdly, the survey could contain a potential recall bias. Finally, the outcomes of non-responders are not known. However, a response rate of 56 and 62% is not perfect but correct for an aged study population and is in line with the literature. Interpretations of the results should therefore be made with caution. Another strong point is that all diagnoses were based on systematic abdominal CT scans.

This study thus confirmed that OT is safe for uD and mcD with a low 1-month failure rate and a similar recurrence rate as IT. OT could be used more often without excess risk in all patients presenting with uD or mcD. ER admission and CT time, severity of uD/mcD, and presence of free air were identified as risk factors for treatment failure in this study. The next step would be to develop a score based on the risk factors for treatment failure to guide the follow-up and to validate it with a prospective population.

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Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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