

Selective non-antibiotic treatment in sigmoid diverticulitis: is it time to change the traditional approach?

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Abstract

Background A growing body of knowledge is calling into question the use of antibiotics in acute diverticulitis (AD). Moreover, recent studies provide evidence regarding the security of treating patients with AD as outpatients. The aim of this study was to evaluate a restrictive antibiotic outpatient protocol for the treatment of mild-to-moderate episodes of AD.

Methods All patients with symptoms of AD presenting to our emergency department were assigned a modified Neff stage. Patients with mild AD received outpatient treatment without antibiotics. Patients with mild AD and comorbidities were admitted to receive the same treatment. Patients with moderate AD were admitted for 48 h and were then managed as outpatients until they had completed 10 days of antibiotic treatment.

Results Between April 2013 and November 2014, we attended 110 patients with a diagnosis of AD, 77 of whom we included in the study: 45 patients with mild AD and 32 with moderate AD. Of the patients with mild AD, 88.8 % successfully completed the non-antibiotic, non-admission treatment regime and 95.5 % benefited from a non-antibiotic regime, whether as outpatients or inpatients. A total of 88 % of patients with mild AD and 87.5 % of patients with moderate AD who met the inclusion criteria completed treatment as outpatients without incident. No major

complications (abscess, emergency surgery) or deaths were recorded.

Conclusions Outpatient treatment without antibiotics for patients with mild AD is safe and effective. Patients with moderate AD can be safely treated with antibiotics in a mixed regime as inpatients and outpatients.

Keywords Acute diverticulitis · Outpatient · Non-antibiotic · Sigmoid

Introduction

Acute sigmoid diverticulitis is a major health problem in Western countries and a common reason for consultation in surgical emergency departments. Prevalence of diverticulosis in individuals over 80 years of age is estimated to be 70 %. A low-fibre diet is thought to be one of the risk factors for this condition [1].

Traditionally, mild and moderate episodes of acute diverticulitis (AD) are treated in-hospital with broad-spectrum antibiotics, nil by mouth and bed rest. However, this practice is largely based on theories and expert opinions dating back to the mid-twentieth century.

Recent studies suggest that AD could be safely treated in an outpatient regime with no increase in either morbidity or mortality [2]. Traditional pathologic mechanisms are being questioned and replaced by more scientifically grounded hypotheses that strongly postulate an inflammatory origin. Local pro-inflammatory cytokines, microbiota shifts, disturbed neurological intestinal signalling due to alterations in colonic neuropeptides and abnormal colonic motility are all being proposed as potential etiologic factors [3–6].

Recent publications, therefore, call into question the benefits of antibiotic treatment for episodes of AD,

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especially for mild episodes [7]. Furthermore, recent international guidelines endorse this stance in their recommendations [8, 9].

Due to the growing scientific support for this new trend, we decided to change our treatment protocol for patients with AD, carefully selecting patients who would likely benefit from admission with antibiotic treatment or from non-antibiotic treatment as outpatients.

Our objective was to test the effectiveness and safety of a new treatment protocol for AD. Treatment of patients with mild AD included a non-antibiotic and non-admission regime in selected cases. Patients with moderate AD were managed with a short hospital stay and antibiotics.

Materials and methods

The study was conducted from April 2013 to November 2014 in our 400-bed university hospital, with a catchment population of 264,021 inhabitants. The treatment protocol was approved by the hospital research ethics committee. A prospective descriptive analysis of the outcome was performed.

All patients seen in the emergency department with clinical signs of AD (left iliac fossa abdominal pain, peritoneal irritation signs and/or leucocytosis) were included in the study. These patients underwent an abdominal computed tomography (CT) scan to confirm the diagnosis and grade the disease according to severity using the modified Neff (mNeff) classification [10] (Table 1; Fig. 1).

Written informed consent was obtained from all patients included in the study.

Patients with radiological features of mild AD (mNeff 0) who met the inclusion criteria for outpatient treatment (Table 2) were managed as outpatients after good symptom control and oral tolerance were ensured. They were advised to keep to a liquid diet for 2 days and prescribed non-steroidal anti-inflammatory drugs (NSAIDs) (1 g/8 h paracetamol alternating with 600 mg/8 h ibuprofen and 20 mg/24 h omeprazole). No antibiotics were prescribed. The patients were reviewed in the surgical outpatients clinic 48 h after emergency department consultation.

Patients with radiological features of mild AD who did not meet criteria for outpatient treatment were admitted for intravenous (IV) symptomatic treatment with paracetamol 1 g/8 h alternating with dexketoprofen 50 mg/8 h until symptoms and blood test parameters improved. No antibiotics were prescribed. On discharge, the patients were prescribed 1 g/8 h paracetamol alternating with 600 mg/8 h ibuprofen and 20 mg/24 h omeprazole. All patients were on this treatment for 7 days. Subsequently, symptomatic treatment was administered on demand, for no longer than 14 days, and supervised during follow-up.

Table 1 Modified Neff classification

Stage 0	Uncomplicated diverticulitis. Thickening of the wall, increased density of the pericolic fat
Stage Ia	Locally complicated diverticulitis. Localized pneumoperitoneum in the form of air bubbles
Stage Ib	Locally complicated diverticulitis. Abscess <4 cm diameter
Stage II	Complicated diverticulitis. Pelvic abscess >4 cm diameter
Stage III	Complicated diverticulitis. Distant abscess
Stage IV	Complicated diverticulitis. Abundant pneumoperitoneum and/or intrabdominal free liquid

Source: Neff and van Sonnenberg [10]

Patients with radiological features of moderate AD (mNeff Ia-Ib) who met the inclusion criteria for outpatient treatment were admitted for 48 h and received symptomatic treatment with 1 g/8 h paracetamol alternating with 600 mg/8 h ibuprofen and three doses of IV antibiotic therapy with ertapenem (the first dose administered in the emergency department and the other two in the ward). Patients experiencing no discomfort and able to tolerate liquids were discharged to complete a further 7 days of ertapenem treatment as outpatients in a day-hospital unit. They were also prescribed 1 g/8 h paracetamol alternating with 600 mg/8 h ibuprofen and told to keep to a low-residue diet at home. One week after discharge they came to a follow-up visit with an abdominal CT scan and blood test results and underwent a physical examination.

On discharge, all patients received a low-fibre dietary recommendations sheet, were informed of emergency department reconsultation criteria (temperature, poor symptom control, lack of oral tolerance) and were followed up at the outpatients unit at 7 and 30 days and 6 months after the initial consultation. After the acute phase, when good symptom control was attained, a high-fibre diet was recommended [11].

We performed a new CT scan and a blood test on all patients who returned to the emergency department. If either radiological progression or increased leucocytosis was noted, antibiotic treatment was prescribed. If not, the patient was admitted without antibiotics and given IV pain medications, assuming that the reason for consultation was poor symptom control.

Fibrocolonoscopy was selectively performed in patients over 50 years old, no sooner than 2 months after the AD episode, to confirm the diagnosis and/or to detect concomitant pathologies [12].

Patients with radiological features of severe AD (mNeff II, III, IV) and ineligible patients with moderate AD were excluded from the protocol. They were admitted, kept to nil by mouth and given IV symptomatic treatment (1 g/8 h paracetamol alternating with 50 mg/8 h dexketoprofen)

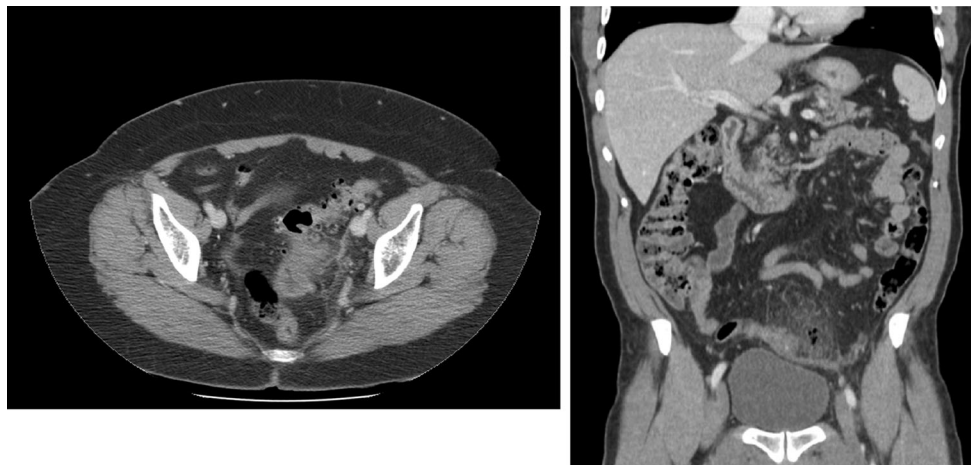


Fig. 1 *Left* abdominal computed tomography (CT) cut showing mNeff 0 acute diverticulitis (wall thickening and increased pericolic fat density); *right* abdominal CT cut showing mNeff Ia acute diverticulitis (locally increased pericolic fat density and air bubbles)

Table 2 Inclusion criteria for outpatient treatment of acute diverticulitis

Patient's written informed consent
Adequate family support
Age 18–80 years
No AD episode in the last 3 months
mNeff 0, Ia or Ib AD (abdominal computed tomography scan)
Immunocompetence (no corticosteroid therapy). No significant comorbidities (diabetes mellitus, renal insufficiency, morbid obesity)
Good oral tolerance
Good symptom control by oral medication
Maximum one of the following SIRS criteria (* $T > 38$ °C or < 36 °C, $L > 12,000$ or $< 4000/uL$, $HR > 90$ bpm, $RR > 20$ rpm) or $CRP > 15$ mg/dL

AD acute diverticulitis, SIRS systemic inflammatory response system, T temperature, L leucocytosis, HR heart rate, RR respiratory rate, CRP C-reactive protein

and antibiotic therapy (metronidazole 500 mg/8h plus gentamicin 240 mg/24 h or metronidazole 500 mg/8 h plus ceftriaxone 1 g/12 h) if presenting with renal insufficiency (according to our hospital's standard antibiotic therapy protocol for treatment of Gram-negative and anaerobic infections). The treatment algorithm is summarized in Fig. 2.

Results

Between April 2013 and November 2014, we attended 110 patients with a diagnosis of AD in our emergency department, 33 of whom were excluded in the initial recruitment stage: 10 patients with mild AD who, because they had received at least one dose of antibiotic in the emergency

department, could not join the non-antibiotic treatment arm; 11 patients with severe AD (mNeff II-IV); and 12 patients with moderate AD who, because they did not fulfil the inclusion criteria for outpatient treatment, were admitted under a standard antibiotic regime. Of the 77 remaining patients, 44 men and 33 women, mean age 57.2 years (range 29–80 years), 45 had mild AD and 32 had moderate AD (see Fig. 3).

Of the patients with mild AD, 80 % (36/45) received treatment without antibiotics in an outpatient regime. The remaining nine were admitted for treatment with NSAIDs without antibiotics. Of the 36 patients with mild AD included in the non-antibiotic and non-admission treatment arm, 88.8 % (32/36) successfully completed the outpatient treatment protocol without antibiotics, while four patients required deferred admission for poor symptom control. One of the four patients received antibiotic therapy (because of worsening leucocytosis) and three were treated with NSAIDs without antibiotics. One patient in this last group underwent elective laparoscopic sigmoidectomy 3 months after the episode of poor symptom control.

Of the nine patients with mild AD included in the non-antibiotic and admission treatment arm, three patients were subsequently readmitted. Two patients had poor symptom control and were treated with NSAIDs. Radiological progression was detected in one patient who was admitted with antibiotic therapy, with a good result. In both treatment arms, antibiotics on readmission were prescribed in case of radiological progression or worsening of biologic parameters.

All 32 patients in the moderate AD group received mixed treatment. Of these patients, 87.5 % (28/32) completed the outpatient regime without incident. The remaining patients (two with mNeff Ia and two with mNeff Ib AD) were readmitted for poor symptom control. They all

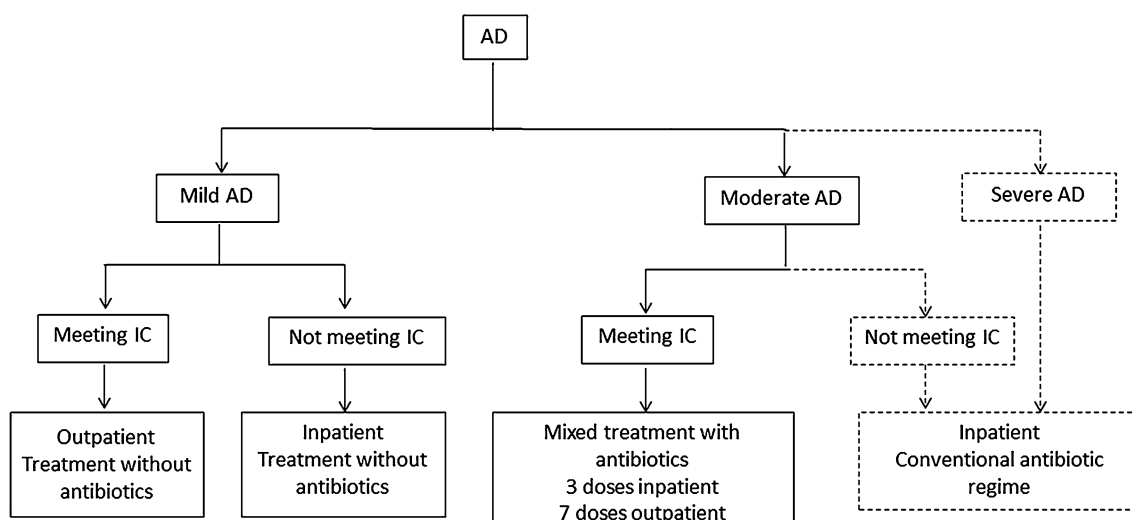


Fig. 2 Treatment algorithm (*AD* acute diverticulitis, *IC* inclusion criteria)

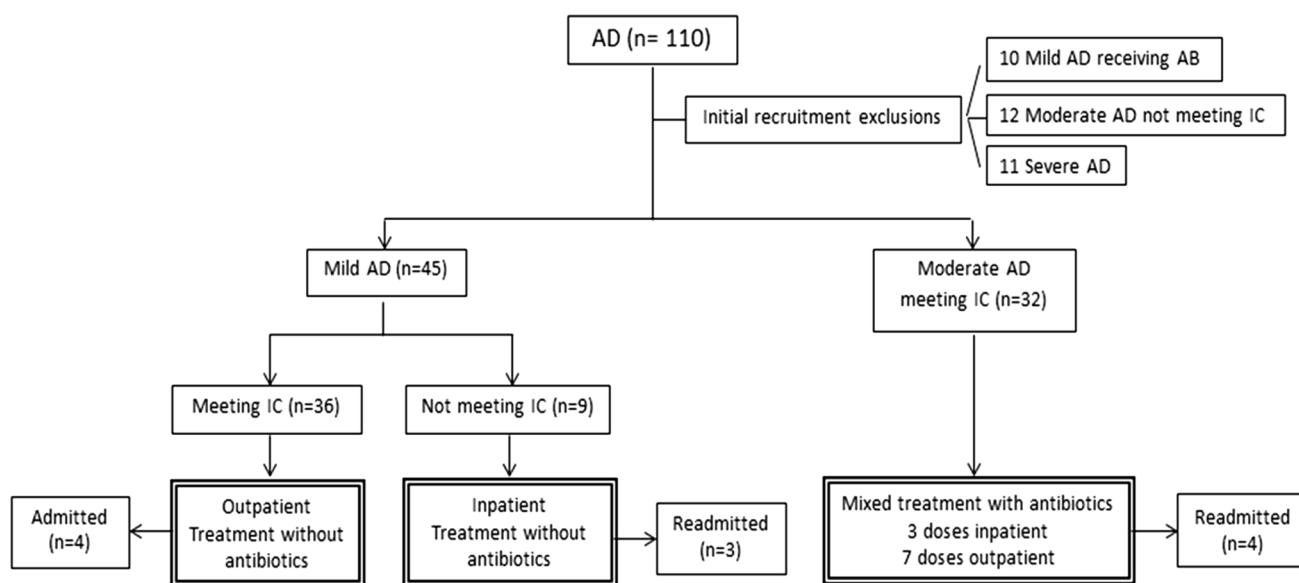


Fig. 3 Outcomes flowchart (*AD* acute diverticulitis, *IC* inclusion criteria, *AB* antibiotics)

were treated with conventional antibiotic therapy according to the hospital's protocol for treatment of Gram-negative and anaerobic infections). The control CT scan did not show radiological progression in any case.

Ninety-five and half per cent (43/45) of the patients with mild AD benefited from a non-antibiotic regime: 32 patients who successfully completed the outpatient treatment protocol without antibiotics, three patients of this group who required deferred admission for symptom control and were treated without antibiotics, six patients who did not meet the inclusion criteria for ambulatory treatment and who successfully completed the non-antibiotic and admission treatment and two patients of this group who

required readmission for symptom control and were treated without antibiotics.

Follow-up at a mean time of 6 months (range 3–12 months) revealed that 84 % (27/32) of mild and 83 % (19/23) of moderate AD patients were asymptomatic. No major complications (abscess, emergency surgery) or deaths were recorded.

Discussion

We report the safety of the treatment without antibiotics for selected patients with mild AD.

Our results show that a non-antibiotic outpatient regime could be feasible for a high percentage of patients with mild AD (mNeff 0). As for patients with moderate AD (mNeff Ia-Ib), these could benefit from antibiotic therapy in an outpatient regime. As far as we are aware, this study is one of the first on outpatient non-antibiotic treatment for mild AD [13].

Of the patients with mild AD who were included in the non-antibiotic non-admission arm, 88.8 % successfully completed the outpatient treatment protocol without antibiotics, with only a few requiring admission for poor symptom control and non-compliance with the protocol. Of patients with moderate AD, 87.5 % were successfully treated in an antibiotic outpatient regime, with only 12.5 % requiring admission and all of these responding well to antibiotic therapy. No patients required, urgent surgery or percutaneous drainage due to local complications.

Isacson et al. [13] also reported results of treatment without antibiotics in an outpatient regime of 155 patients with mild AD. Their study design and inclusion criteria are similar to ours, but their follow-up is shorter. Although their results are similar to ours, they report a lower failure rate, 2.6 %, for treatment without antibiotics. However, for those patients who failed non-antibiotic treatment, there is a 75 % complication rate (two perforations and one abscess out of four admitted patients).

Appropriate treatment of AD is a matter of ongoing debate. Conservative treatment included admission, antibiotics, nil by mouth and bed rest in most studies. Nowadays, patients with uncomplicated AD can be treated conservatively, without surgery, with a success rate of 93–100 % [14–17].

There is a large amount of conflicting, low-quality scientific evidence regarding current treatments for diverticular disease, largely based on theories and studies dating to the mid-twentieth century and expert opinion [18]. However, recent research has provided better insights into inflammatory mechanisms, shifting the emphasis from traditional mechanical theories (fecaliths obstructing a diverticular sac, prompting barotrauma, mucosal abrasion, inflammation and bacterial overgrowth) to pro-inflammatory local factors, microbiome shifts, visceral hypersensitivity and abnormal motility as potential etiologic factors, especially for chronic diverticular disease [3].

Most international guidelines recommend antibiotics for the treatment of diverticulitis [19, 20], even though there is no solid evidence that routine administration influences the course of uncomplicated AD [21]. Moreover, some recommendations are based on studies that simply compare different antibiotic regimes [17, 22]. Kellum et al. [23], for instance, found no difference in success rates for groups taking different types of antibiotics. As for the administration route, it has been suggested that most patients with

uncomplicated AD could be safely managed with oral antibiotics [16, 24]. Schug et al. [17] concluded that short-term antibiotic therapy was as effective as standard therapy for the treatment of uncomplicated AD. In recent years, the literature has reflected an ongoing interest in the usefulness of antibiotics in the treatment of AD. Hjern et al. [26] found no significant differences in outcomes in a retrospective case–control study that compared an antibiotic regime with a non-antibiotic regime. A recent large Swedish prospective open-label randomized multicentre study recruited 623 patients with CT-diagnosed uncomplicated AD [7] who were randomized to either an antibiotic or non-antibiotic regime. There were no significant differences in frequency of abscess, perforation or need for surgery after 1 year, indicating that antibiotics did not prevent complications in the short term. Meanwhile, still pending are results of the DIABOLO trial [27], a randomized controlled trial comparing the cost-effectiveness of a conservative strategy (admission and antibiotics) with a liberal treatment strategy (without antibiotics and with no strict requirement for admission) with respect to the primary endpoint which was time-to-full recovery.

Until more solid evidence is available, the latest guidelines state that antibiotics should not be routinely used to treat uncomplicated AD (grade of recommendation A), but reserved for cases of septicaemia, poor general condition, pregnancy and immunosuppression (grade of recommendation C [9, 28, 29]).

In our study, antibiotic treatment was administered only to patients with moderate AD and to a very limited number of patients with mild AD. We used ertapenem, as recommended in previously published protocols [30].

Several studies have demonstrated outpatient treatment to be highly effective for selected patients with AD, with success rates in recent series ranging from 94 to 97 % [2, 15, 31, 32]. Mizuki et al. [32] demonstrated that outpatient treatment of patients with mild or uncomplicated diverticulitis was safe. Alonso et al. [15] and Biondo et al. [2] concluded that outpatient treatment was safe and effective for selected patients with uncomplicated AD and resulted in important reductions in healthcare costs. A systematic review by Jackson et al. [33] concluded that an outpatient-based approach is justified in most cases of AD. However, the review included just one randomized controlled trial and both radiological and non-radiological selection criteria and management protocols varied significantly across studies.

In our study, we used the mNeff classification [10] to confirm the diagnosis of AD and grade AD according to severity. We are of the opinion that an abdominal CT scan should be performed on all patients with suspected diverticulitis in order to definitively confirm the diagnosis and obtain objective non-observer-dependent information.

Although ultrasound has good sensitivity and specificity for AD, our protocol required a diagnostic technique that would admit more accurate grading. We also believe that a CT scan and the mNeff classification enabled a better selection of patients who would successfully complete an outpatient regime [25].

Analgesia is an essential component of the treatment of patients with AD. We used a NSAID (ibuprofen) for pain control and symptom relief. We are aware that a number of studies link chronic NSAID treatment with complications like bleeding or perforation of diverticula [34–37]. Nevertheless, most of these studies did not describe the treatment duration or dosage, so there is no concrete evidence that NSAIDs have a negative impact on the course of an acute episode when used for a short period. Our experience with ibuprofen to treat AD showed that symptom control was good and there were no side effects.

In reference to dietary recommendations, during patients' hospital stay and at discharge, we recommend a low-fibre diet. Mizuki et al. [32] prescribed a liquid diet (without fibre) for several days to patients with acute uncomplicated diverticulitis with good results. There is a lack of high-quality medical literature concerning diet during the acute phase.

The present is a descriptive prospective study. Despite the design limitations, our results suggest that a non-antibiotic regime for patients with mild AD is safe and effective. Furthermore, this treatment can safely be administered on an outpatient basis with strict follow-up by specialized medical units. Apart from the therapeutic advantages, our protocol enhances hospital efficiency by reducing the number of admissions and saving on health-care expenditure.

Conclusions

A non-antibiotic regime for patients with mild AD appears to be safe and effective.

Patients with mild-to-moderate AD, would, nonetheless, benefit from the results of new randomized controlled trials to formulate more precise recommendations in future clinical guidelines.

Compliance with ethical standards

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

Ethical approval The treatment protocol was approved by the hospital research ethics committee. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national 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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