

# Efficacy and Safety of Nonantibiotic Outpatient Treatment in Mild Acute Diverticulitis (DINAMO-study)

## A Multicentre, Randomised, Open-label, Noninferiority Trial

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**Objective:** Mild AD can be treated safely and effectively on an outpatient basis without antibiotics.

**Summary of Background Data:** In recent years, it has shown no benefit of antibiotics in the treatment of uncomplicated AD in hospitalized patients. Also, outpatient treatment of uncomplicated AD has been shown to be safe and effective.

**Methods:** A Prospective, multicentre, open-label, noninferiority, randomized controlled trial, in 15 hospitals of patients consulting the emergency department with symptoms compatible with AD.

The Participants were patients with mild AD diagnosed by Computed Tomography meeting the inclusion criteria were randomly assigned to control arm (ATB-Group): classical treatment (875/125 mg/8h amoxicillin/clavulanic acid apart from anti-inflammatory and symptomatic treatment) or experimental arm (Non-ATB-Group): experimental treatment (antiinflammatory and symptomatic treatment). Clinical controls were performed at 2, 7, 30, and 90 days.

The primary endpoint was hospital admission. Secondary endpoints included number of emergency department revisits, pain control and emergency surgery in the different arms.

**Results:** Four hundred and eighty patients meeting the inclusion criteria were randomly assigned to Non-ATB-Group (n = 242) or ATB-Group (n = 238). Hospitalization rates were: ATB-Group 14/238 (5.8%) and Non-ATB-Group 8/242 (3.3%) [mean difference 2.58%, 95% confidence interval (CI) 6.32 to -1.17], confirming noninferiority margin. Revisits: ATB-Group 16/238 (6.7%) and Non-ATB-Group 17/242 (7%) (mean difference -0.3, 95% CI 4.22 to -4.83). Poor pain control at 2 days follow up: ATB-Group 13/230 (5.7%), Non-ATB-Group 5/221 (2.3%) (mean difference 3.39, 95% CI 6.96 to -0.18).

**Conclusions:** Nonantibiotic outpatient treatment of mild AD is safe and effective and is not inferior to current standard treatment.

**Trial registration:** ClinicalTrials.gov (NCT02785549); EU Clinical Trials Register (2016-001596-75)

**Keywords:** mild acute diverticulitis, nonantibiotic in acute diverticulitis, outpatient in acute diverticulitis

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Incidence of diverticular disease is increasing: approximately 30% of the population older than 45 years and 60% of those over 85 years have diverticula. Approximately 10%–25% of these patients will suffer an episode of acute diverticulitis (AD) at some point in their lifetime.<sup>1</sup> AD is 1 of the most prevalent reasons for consultation to EDs in Western countries.<sup>2</sup> However, 75% of these episodes do not present complications and most will have achieved good outcomes with conservative treatment.<sup>3</sup>

Since its initial description, the treatment of AD has not been based on a solid scientific grounding; it has consisted of hospital admission and antibiotics, assuming an infectious etiology.<sup>3</sup> In recent years, 2 randomized controlled trials have shown no benefit of antibiotics in the treatment of uncomplicated AD in hospitalized patients.<sup>4,5</sup> These studies found no significant differences with regard to time to recovery, complications, recurrences and need for surgery between groups with or without antibiotic treatment, and also suggested that antibiotics could be omitted in patients with a first episode of uncomplicated AD. Similarly, many systematic reviews and meta-analyses support the nonantibiotic treatment of uncomplicated AD,<sup>6,7</sup> and in fact this approach is included in the Guidelines of the American Society of Colon and Rectal Surgeons.<sup>8</sup>

Outpatient treatment of uncomplicated AD has been shown to be safe and effective.<sup>9</sup> No differences have been reported with regard to treatment failure, and the overall health care cost per episode is lower in outpatient group.

The main objective of the study was to establish whether patients treated with or without antibiotics on an outpatient basis would present differences in terms of admission rates. The secondary objectives were to analyse differences with regard to (1) ED revisits (and the reasons for revisit); (2) pain control at various time points; and (3) complication rates.

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A noninferiority design was chosen for the study on the assumption that the new non-antibiotic outpatient treatment regime would not be inferior to the standard treatment with antibiotics and hospital admission.

## METHODS

### Study Design

The DINAMO-study is a multicentre, prospective, open-label, noninferiority, randomized controlled trial<sup>10</sup> with an intention-to-treat approach and parallel assignment, and with the participation of 15 colorectal surgery units at acute-care secondary and tertiary hospitals throughout Catalonia (Spain). All the institutions belong to the Spanish Public Health System.

The trial was conducted in accordance with the Declaration of Helsinki, seventh revision,<sup>11</sup> the SPIRIT 2013 Standard Protocol Items for Clinical Trials<sup>12</sup> and the Spanish laws and regulations for biomedical research. Authorization was obtained from the Spanish Agency for Medicines and Medical Devices (*Agencia Española del Medicamento y Productos Sanitarios*, AEMPS).

The trial protocol, patient information and informed consent documents were approved by the ethics committees of all participating trial centres in accordance with the Royal Decree 1090/2015 of 4th December. The trial was registered at the ClinicalTrials.gov database (ID: NCT02785549) and the EU Clinical Trials Register database (EudraCT number: 2016-001596-75). The study protocol has been published previously by our team.<sup>10</sup>

### Participants

Inclusion criteria: age between 18 and 80 years (inclusive), modified Neff 0 AD on abdominal CT scan, no AD episode in the last 3 months, no antibiotic treatment for any reason in the last 2 weeks, no significant comorbidities, immunocompetence, patient's written informed consent, adequate cognitive capacity, adequate family support, good symptom control at the ED and maximum 1 of the following:  $T \geq 38^{\circ}\text{C}$ ,  $T < 36^{\circ}\text{C}$ ,  $L > 12,000/\mu\text{L}$ ,  $L < 4000/\mu\text{L}$ ,  $\text{HR} > 90$  bpm,  $\text{RR} > 20$  rpm,  $\text{CPR} > 15$  mg/dL.

Exclusion criteria: women in pregnancy or breastfeeding, age  $< 18$  years or  $> 80$  years, allergy to any of the study drugs, modified Neff grade I or upper AD, AD episode in the last 3 months, inflammatory bowel disease, antibiotic treatment for any reason in the last 2 weeks, presence of significant comorbidities, immunodepression, absence of patient's written informed consent, inadequate cognitive capacity, inadequate family support, poor symptom control at the ED ( $\text{VAS} \geq 5$ ) and/or systemic inflammatory response syndrome.

*Significant comorbidities* were defined as diabetes mellitus with organic involvement (retinopathy, angiopathy, nephropathy), emergency assistance for a cardiogenic event in the last 3 months (acute myocardial infarction, angina, heart failure), decompensation of chronic liver disease in the last 3 months ( $\text{Child} \geq \text{B}$ ) and end-stage renal disease. Immunocompetence was defined as the absence, and immunodepression as the presence, of any of the following: active neoplastic disease, hematologic malignancy, human immunodeficiency virus with low  $\text{CD4}^{+}$  count (AIDS), long term corticosteroid treatment, immunosuppressant therapy, transplant, splenectomy and genetic immunodeficiency.

"Adequate cognitive capacity" was defined as the ability to read and understand the description of the study and to provide signed informed consent. "Family support" was defined as "adequate" when the patient had someone able to take care of him/her and provide help as necessary.

The diagnosis of AD was performed by abdominal tomography (CT) and the modified Neff classification (mNeff)<sup>13</sup> was applied.<sup>14,15</sup> All eligible patients who were not included in the study

were registered and the reasons for their nonparticipation stated in accordance with the Consolidated Standards for Reporting Trials statement for noninferiority and equivalence randomized trials.<sup>16</sup>

### Randomization and Masking

Patients visiting the ED with clinical features compatible with AD underwent a blood test and an abdominal CT scan. Once the diagnosis of mild AD was confirmed (grade 0 mNeff), patients meeting the inclusion criteria were invited to take part in the study. On agreeing to participate, they provided written consent by signing a standardized informed consent document and were randomized to 1 of the 2 study arms in a 1:1 allocation ratio. The patients were randomized after successful symptom control in the ED. The study was open-label and no masking of patients or surgeons was performed. At the design stage we considered the possibility of carrying out a single blind antibiotic vs placebo trial, but we decided against this option because of the study's multicentre design.

### Procedures

In the Experimental arm (Non-ATB-Group), patients were given anti-inflammatory and symptomatic treatment with 600 mg/8 h ibuprofen alternating with 1 g/8 h acetaminophen. In the Control arm (ATB-Group) patients were treated with 875/125 mg/8 h amoxicillin/clavulanic acid apart from the same anti-inflammatory (NSAIDS) and symptomatic treatment.

Medical treatment was initiated in the ED. The route of administration was EV in the ED, and oral at discharge. Patients were discharged with medical treatment and diet recommendations when they achieved good symptomatic control in the ED. If no good symptomatic control was achieved after a maximum of 24 hours of observation in the ED, patients were admitted for EV treatment and therefore did not enter the study. The duration of medical treatment (with or without antibiotics) was 7 days.

### Outcomes

The 2 groups underwent the same clinical controls at 2, 7, 30, and 90 days after the episode, conducted by surgeons of the coloproctology unit. At each control, an overall assessment was made through a physical examination, the clinical evolution was monitored and adherence to the treatment was checked. The degree of pain was recorded at each control on a visual analogue scale (VAS, 0–10). If clinical worsening or poor symptomatic control was detected at any time, the patient was referred to the ED. Patients also consulted the ED if, at their own discretion and based on the information received, they presented any alarm symptoms (temperature  $> 38^{\circ}\text{C}$  or poor symptomatic control).

In the event of a revisit to the ED, an abdominal CT scan and a blood test were repeated. The same follow-up (FU) was maintained. The algorithm protocol recommended by the investigators for selecting the most appropriate treatment in the event of a revisit was described in the study protocol.<sup>10</sup>

### Sample Size

Based on the results of a previous study by our group, the sample size was calculated taking hospital admission as the main factor.<sup>14</sup> A noninferiority margin of 7% ( $\Delta$ ) for both the ATB-Group and the Non-ATB-Group on the basis of our previous study of outpatient treatment of AD, in which we obtained a success rate of 93%.<sup>14</sup> Using 80% power and a 1-sided significance level of 0.025. With an estimated patient loss of 10%, we concluded that a sample size of 230 patients per arm was required for the study.

### Statistical Analysis

The primary endpoint was analysed by both intention-to treat and per protocol analysis, because all randomized patients received

treatment. The description of the factors and the statistical analysis were performed using the Statistical Package for the Social Sciences program (SPSS Inc., Chicago, IL) version 26.

The quantitative variables were described using values of means and standard deviation when the distribution was considered normal (Kolmogorov-Smirnov test), otherwise using the values of the median and interquartile range (IQR). The categorical variables are described in absolute numbers and in percentages.

The univariate statistical analysis of the quantitative variables, with independent groups, was performed using the Student *t* test if its application conditions were fulfilled; otherwise, the Mann-Whitney *U* test was applied. For categorical variables, the Pearson  $\chi^2$  test was used. The results of the statistical tests are shown with a 95% confidence interval (CI) whenever possible. Statistical significance was set at a *P* value below 0.05.

We determined a 95% CI of the difference for the primary endpoint (one-sided 5%  $\alpha$  level). Thus, noninferiority was concluded if the lower bound of this interval was below the noninferiority limit ( $\Delta=7\%$ ).

The revisit to ED factor was analyzed with the Kaplan-Meier estimation method and the log-rank test.

## RESULTS

### Participant Flow and Recruitment

From November 2016 to January 2020, 849 patients diagnosed with mild AD (grade 0 mNeff)<sup>13</sup> were seen at the ED of the hospitals participating in the study. Four hundred and eighty patients with AD meeting the inclusion criteria were randomly assigned to the Non-ATB-Group (*n* = 242) or the ATB-Group (*n* = 238) (Fig. 1). In baseline characteristics of patients, no statistically significant differences were found between groups, except between CRP values, but they were not clinically relevant (Table 1).

### Main Objective: Admission to Hospital

Revisits to the ED resulted in 22/480 (4.6%) admissions: 14/238 (5.8%) in ATB-Group and 8/242 (3.3%) in Non-ATB-Group, with a 2.58% difference (95% CI 6.32 to -1.17), (*p* = 0.19). Non-ATB-Group showed noninferiority when compared to ATB-Group, with  $\Delta < 7\%$  (Fig. 2A). Most of the admissions were based on the study protocol recommendations upon revisit. However, the final decision regarding admission was taken by the physician.

All patients who revisited the ED underwent an abdominal CT scan (Fig. 1). In the ATB-Group, from the 14 patients admitted to hospitalization, 78.6% (11/14) had mNeff grade 0 AD and 21.4% (3/14) grade Ib. In the Non-ATB-Group, from the 8 patients admitted to hospitalization, 87.5% (7/8) had mNeff grade 0 AD and 12.5% (1/8) grade Ia.

In the ATB-Group, the same antibiotic, amoxicillin/clavulanic acid, was maintained in 57.1% (8/14) although in the other 42.8% (6/14) the antibiotic spectrum was widened. In Non-ATB-Group, all admitted patients were treated with amoxicillin/clavulanic acid. Median duration of the admission was 5 days in the ATB-Group (IQR 3 days) and 2.5 days in the Non-ATB-Group (IQR 3 days) (*P* = 0.002), a statistically significant difference. None of the patients in either group required emergency surgery.

### Secondary Objectives

#### Revisit

During the study period, 447 patients did not return to the ED. However, 40/480 (8.3%) revisits were recorded corresponding to 33 patients: 16/238 (6.72%) in the ATB-Group and 17/242 (7.02%) in the Non-ATB-Group (mean difference -0.3, 95% CI 4.22 to -4.83). A

total of 29 patients revisited ED once (14 ATB-Group and 15 Non-ATB-Group), 2 patients revisited twice (both Non-ATB-Group), one ATB-Group patient revisited 3 times and another ATB-Group patient revisited 4 times. Fig. 2B shows the number of patients who revisited the ED referred by the physician in each of the clinical controls and the patients who were subsequently admitted to hospital. Fig. 3 displays the revisits to the ED and measures taken. In the ATB-Group, 21 revisits were recorded corresponding to 16 patients and in the Non-ATB-Group, 19 revisits corresponding to 17 patients. In 11/19 (57.9%) there was no worsening of the complementary tests and patients could be kept under the same treatment (that is, NSAIDs on an outpatient basis).

We found no statistically significant differences between groups in any of the factors studied in patients who revisited the ED (Table 2). Interestingly, there were more admissions to hospital in the ATB-Group (14/21, 66.6%) than in the Non-ATB-Group (8/19, 42.1%). A therapeutic change (either starting antibiotic treatment or broadening the spectrum) was needed in 6 out of 21 (28.5%) ATB-Group patients and in 8 out of 19 (42.1%) Non-ATB-Group patients, although the differences were not statistically significant. The median time to revisit was 17 days in the ATB-Group (95% CI: 0 to 36.4) and 13 days in the Non-ATB-Group (95% CI: 4.5 to 25.5), with no statistically significant differences in the log-rank test (*P* = 0.82) (Fig. 4).

### Follow-Up, Pain Control and Recovery

At the end of the study period, there were 22/238 (9.2%) losses to FU in the ATB-Group group and 19/242 (7.9%) in the Non-ATB-Group group (Fig. 2C). The analysis made of remaining patients showed no statistically significant differences between groups in terms of clinical evolution, pain control and consultation to ED recommended by a physician. At 30-day FU, 212/216 ATB-Group patients (98.1%) and 218/223 Non-ATB-Group patients (97.7%) presented good clinical evolution and were able to eat a normal diet.

Patients in the ATB-Group showed a higher degree of pain at the 2-day clinical control, 13/230 (5.7%), Non-ATB-Group 5/221 (2.3%) (mean difference 3.39, 95% CI 6.96 to -0.18). Patients in the Non-ATB-Group recorded higher pain scores at later controls: the differences were not statistically significant (Fig. 2D).

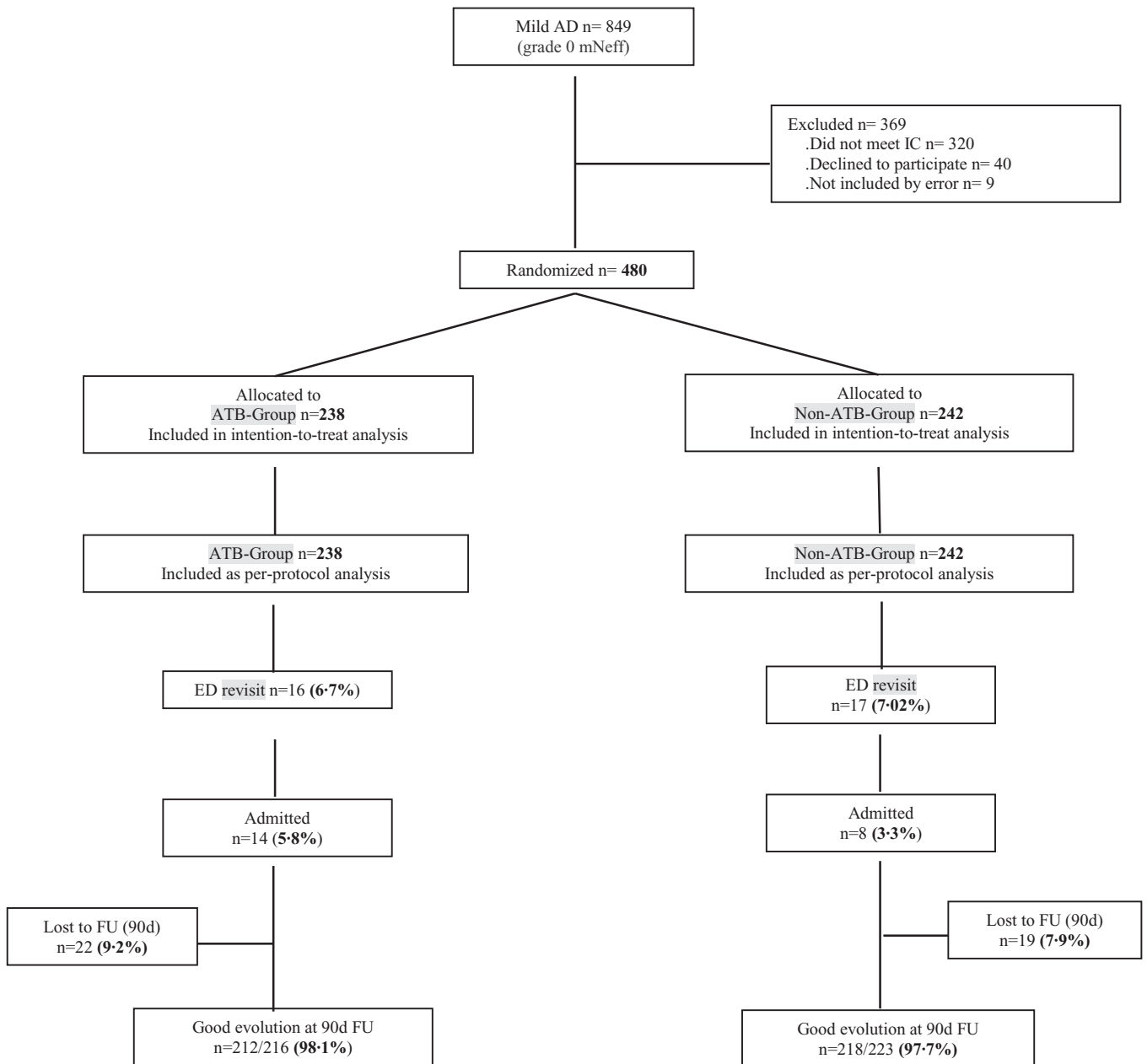
### Complications

No patients in either group needed emergency surgery during the study period.

## DISCUSSION

Diverticular disease has a high prevalence, especially in the western world, and between 15% and 20% of the population with diverticulosis present complicated AD.<sup>1</sup> Three-quarters of cases of AD are mild.<sup>2</sup> The gold standard test for AD, in addition to the medical history and physical examination, is CT,<sup>3</sup> which allows differential diagnosis and optimal classification. In our study we used the Neff classification, modified by the incorporation of substage Ia to characterize AD with localized pneumoperitoneum.<sup>13</sup> This classification allows us to differentiate between the initial stages of AD and to establish the appropriate treatment at each stage.

“Hospital admission” was considered as the main factor because it allowed us to assess the safety of outpatient care and the likelihood of treatment failure in mild AD. The delta margin was based on the results of our previous study, which achieved a success rate of 93% in the outpatient protocol for the treatment of uncomplicated AD.<sup>14</sup> The dose and duration of treatment in the 2 arms (ATB-Group: antibiotic and Non-ATB-Group: anti-inflammatory) were prescribed using the outpatient treatment protocols in the antibiotic group applied in previous studies.<sup>14,15</sup>



**FIGURE 1.** CONSORT diagram. AD, acute diverticulitis; d, days; ED, emergency department; FU, follow-up; IC, inclusion criteria; mNeff, modified Neff CT-scan classification.

Two randomized controlled trials have already reported non-antibiotic treatment of uncomplicated AD,<sup>4,5</sup> but neither was performed on an outpatient basis. With follow-up periods of 12 months, Daniels et al<sup>4</sup> and Chabok et al<sup>5</sup> demonstrated that antibiotic-free treatment does not worsen complications, cause recurrences, or delay complete recovery. As a result, in our study design we considered that a follow-up of more than 90 days was unnecessary to estimate the recovery time.

The results of our outpatient treatment regimen show that it is a safe and effective option. Sixteen out of 238 (6.72%) patients in the antibiotic group revisited the ED compared with 17/242 (7.02%) in the nonantibiotic group, and 14 out of 238 (5.8%) in the antibiotic

group required hospitalization, compared with 8 out of 242 (3.3%) in the nonantibiotic group; the differences were not statistically significant, and the 95% confidence intervals were far from the non-inferiority margin. These results are similar to those recorded in the DIVER study.<sup>10</sup> In that study, the primary endpoint was treatment failure, which was recorded in 4 out of 66 patients (6.1%) in the admitted group and in 3 out of 66 (4.5%) in the outpatient group ( $p = 0.619$ ). The overall number of admissions in our study was 22/480 (4.6%), similar to the rates in the DIVER study<sup>8</sup> (6.1%) and in our previous study (64/68, 6%).<sup>13</sup>

The 40 ED revisits (a rate of 8.3%) were distributed evenly between the 2 groups: 21 (8.8%) in the ATB-Group and 19 (7.8%) in

**TABLE 1.** Baseline Characteristics of Patients According to Study Group

	ATB-Group (n = 238)	Non-ATB-Group (n = 242)	P
Age (yr) / Median (IQR)	57 / (19)	59 / (18)	0.13*
Gender (male: female)	120:118	104:138	0.12^
Temperature (°C) / Median (IQR)	36.3/(0.7)	36.4 / (0.8)	0.63 <sup>†</sup>
Respiratory rate (rpm)/Median (IQR)	21/(0)	21 / (1)	0.07*
Heart rate (bpm)/ Median (IQR)	80/(16)	80 / (15)	0.31*
CRP (mg/dL)/ Median (IQR)	4.4/(5.5)	5.1 / (6.5)	0.01*
Leucocytosis (U/ $\mu$ L) /Mean (SD)	10,691/(2979)	10,822 / (3,023)	0.63*
Pain (VAS)/Median (IQR)	5/(3)	4 / (2)	0.07*

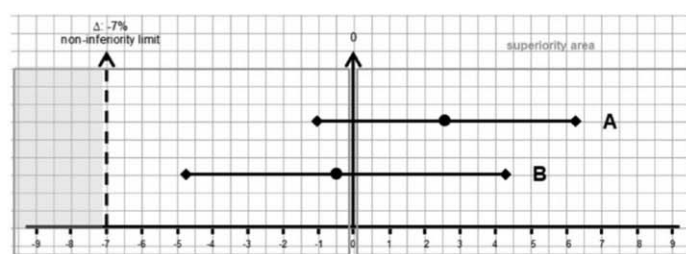
Figures shown are averages except for gender.

ATB-Group indicates control arm; CRP, C-reactive protein; IQR, interquartile range; Non-ATB-Group, experimental arm; SD, standard deviation; VAS, visual analogue scale.

\*Mann-Whitney U test.

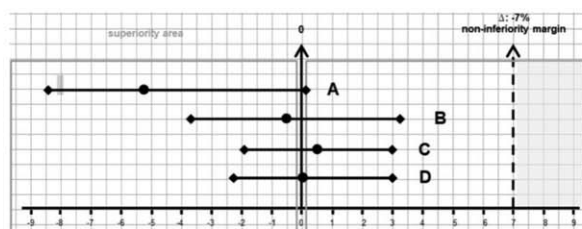
^Fisher exact test.

†T-Test.



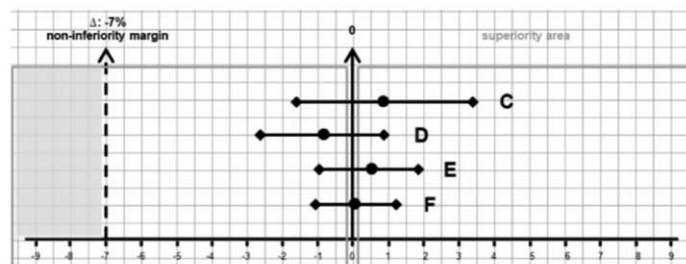
90-days FU	ATB-Group (%)	Non-ATB-Group (%)	P	CI 95% ( ATB-Group (%) – Non-ATB-Group (%) )
(A) Admission	14/238 (5.8%)	8/242 (3.3%)	0.19	2.58 (6.32 to -1.17)
(B) ED revisit	16/238 (6.7%)	17/242 (7%)	1	-0.3 (4.22 to -4.83)

**A**



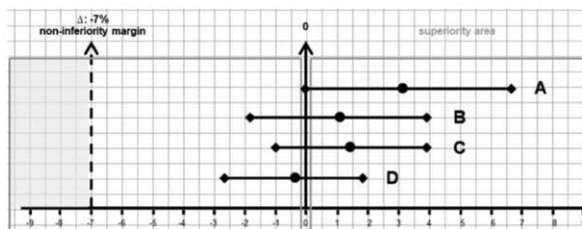
N=480	FU-losses		P	Remaining cases		Good clinical evolution		P	CI 95% (ATB-Group (%) – Non-ATB-Group (%) )
	ATB-Group (%)	Non-ATB-Group (%)		ATB-Group (%)	Non-ATB-Group (%)	ATB-Group (%)	Non-ATB-Group (%)		
(A) 3-days FU	8 (3.4%)	21 (8.7%)	0.02	230	221	221 (95.9%)	212 (95.9%)	0.79	-4.19 (0.22 to -8.6)
(B) 7-days FU	30 (12.6%)	23 (9.5%)	0.31	208	219	201 (96.6%)	212 (96.8%)	1	-0.17 (3.2 to -3.6)
(C) 30-days FU	13 (5.5%)	18 (7.4%)	0.46	225	224	220 (97.8%)	217 (96.9%)	0.58	0.9 (3.0 to -2.1)
(D) 90-days FU	22 (9.2%)	19 (7.9%)	0.63	216	223	212 (98.1%)	218 (97.7%)	1	0.4 (3.04 to -2.3)

**C**



ED revisit referred by surgeon	ATB-Group (%)	Non-ATB-Group (%)	P	CI 95% (ATB-Group (%) – Non-ATB-Group (%) )
(C) 2-days FU	6/230 (2.6%)	4/221 (1.8%)	0.75	0.8 (3.51 to -1.91)
(D) 7-days FU	1/208 (0.5)	3/219 (1.4%)	0.62	-0.89 (0.91 to -2.69)
(E) 30-days FU	2/225 (0.9%)	1/224 (0.4%)	1	0.44 (1.95 to -1.06)
(F) 90-days FU	1/216 (0.2%)	1/223 (0.2%)	1	0.01 (1.27 to -1.25)

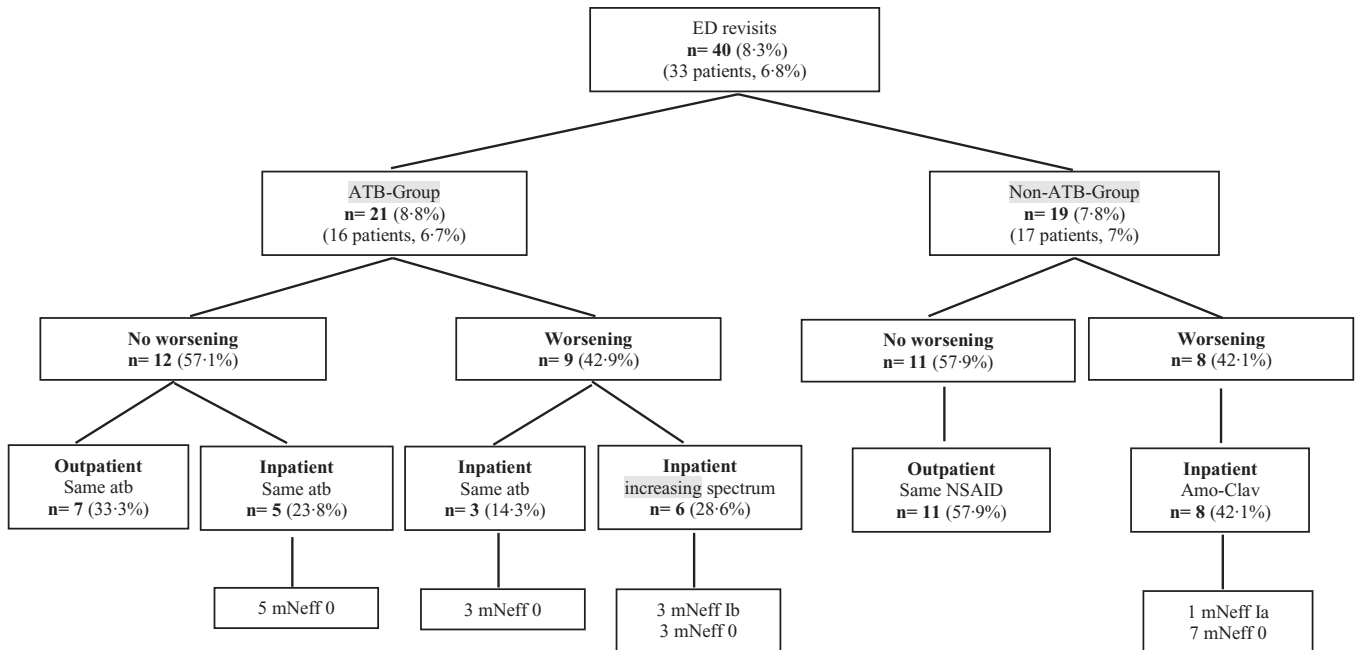
**B**



	ATB-Group (%)	Non-ATB-Group (%)	p	CI 95% (ATB-Group (%) – Non-ATB-Group (%) )
(A) 2-days FU	13/230 (5.7%)	5/221 (2.3%)	0.09	3.39 (6.96 to -0.18)
(B) 7-days FU	6/208 (2.9)	4/219 (1.8%)	0.53	1.06 (3.9 to -1.8)
(C) 30-days FU	6/225 (2.7%)	3/224 (1.3%)	0.34	1.3 (3.9 to -1.3)
(D) 90-days FU	3/216 (1.4%)	4/223 (1.8%)	1	-0.4 (1.9 to -2.7)

**D**

**FIGURE 2.** Differences in admission to hospital and revisit to Emergency Department (ED) between treatment arms Error bars indicate 2-sided 95% CIs. The dashed arrow at  $x = \Delta$  indicates the noninferiority margin. The bold arrow indicates the zero. The region to the left of  $x = \Delta$  indicates the zone of inferiority. Calculations are made considering Follow Up (FU)-losses at each time point. 2A. A- Patients admitted to hospital after revisit to ED during the 90-day FU period. B- Patients who revisited ED during the 90-day FU period. 2B. Patients referred to ED by the surgeon at each clinical control: C- 2-days, D- 7-days, E- 30-days, F- 90 days. ATB-Group, control arm; CI, confidence interval; ED, emergency department; FU, follow-up; Non-ATB-Group, experimental arm. 2C: Patients with good clinical outcome during follow-up. Error bars indicate 2-sided 95% CIs. The dashed arrow at  $x = \Delta$  indicates the noninferiority margin. The bold arrow indicates zero. The region to the right of  $x = \Delta$  indicates the zone of inferiority. Calculations are made considering FU-losses at each time point. Good clinical evolution was defined as good pain control, good oral tolerance to the diet (liquids, low-fibre or normal) and normal abdominal palpation. ATB-Group, control arm; CI, confidence interval; FU, follow-up; Non-ATB-Group, experimental arm. 2D: Patients with poor pain control in each treatment arm along the study period. Error bars indicate 2-sided 95% CIs. The dashed arrow at  $x = \Delta$  indicates the noninferiority margin. The bold arrow indicates the zero. The region to the left of  $x = \Delta$  indicates the zone of inferiority. Calculations are made considering FU-losses at each time point. Poor pain control was defined as VAS  $\geq$  5. ATB-Group, control arm; CI, confidence interval; ED, emergency department; FU, follow-up; Non-ATB-Group, experimental arm.



**FIGURE 3.** Revisits to the ED and attitude taken. During the study period there were 40 revisits to the ED in 33 patients: 29 patients revisited once, 2 patients revisited twice, 1 patient revisited 3 times and 1 patient revisited 4 times to the ED. 447 patients did not revisit ED. Amo-Clav, amoxicillin/clavulanic acid; atb, antibiotic; ED, emergency department; mNeff, modified Neff CT-scan classification; NSAID, non-steroidal anti-inflammatory drugs.

the Non-ATB-Group group. In all cases, analytical tests and control CT were performed to rule out worsening. Poor symptom control was recorded in 12/21 (57.1%) of the ATB-Group and in 11/19 (57.9%) of the Non-ATB-Group. In the Non-ATB-Group, the same antibiotic was maintained in all cases and was administered in-hospital on 5 occasions: all these cases in the Non-ATB-Group group were discharged again with anti-inflammatory treatment. Analytical or radiological worsening was detected in 9/21 (42.9%) of the ATB-Group and in 8/19 (42.1%) of the Non-ATB-Group. In the ATB-Group, all patients were admitted; in 3 cases the same treatment was maintained and in the other 6 it was changed to a more powerful antibiotic. In the Non-ATB-Group, all 8 cases were admitted and antibiotic treatment was started. Only 3 patients in the ATB-Group presented radiological deterioration to mNeff grade Ib, and 1 patient in the Non-ATB-Group

was seen to have progressed to mNeff grade Ia on the control CT at the consultation. None of the consultations required emergency surgery or any measures other than hospital admission or change of antibiotic treatment. So we can say that the action protocol described in the DINAMO study is safe and does not represent an increased risk.

None of the follow-up controls carried out at outpatient clinics reached the limit of noninferiority for patient referral (Fig. 2B). In addition, there were no differences between groups in terms of pain control in any of the controls up to 90 days, nor in relation to clinical evolution.

The main limitation of the study is the significant number of patients excluded, due to the application of strict selection criteria. This high proportion is due to the fact that the patients were to be

**TABLE 2.** Characteristics of Patients who Revisited ED

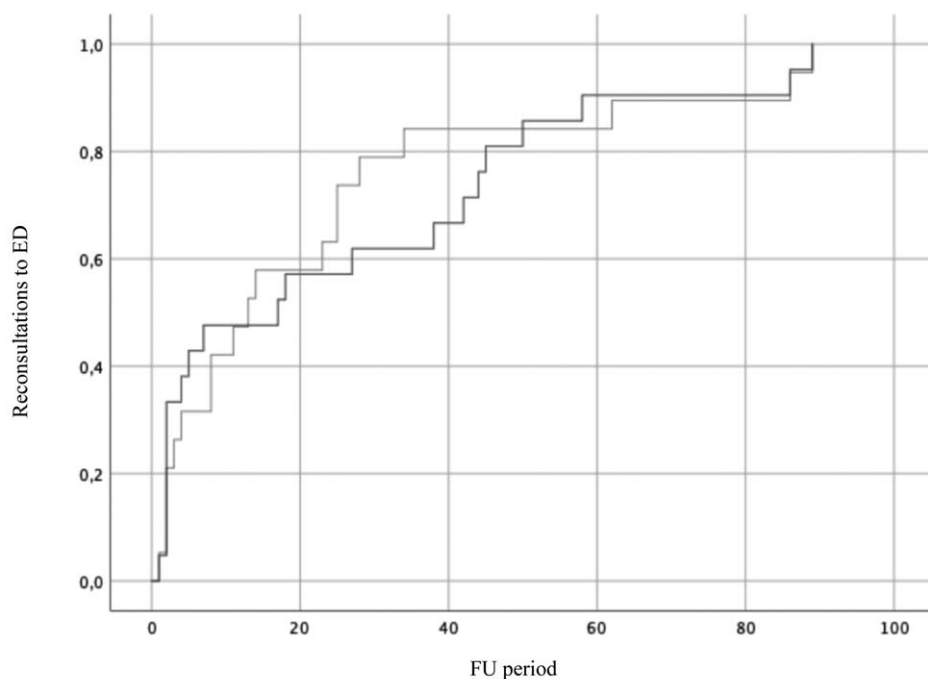
	ATB-Group (%) 21 (52.5)	Non-ATB-Group (%) 19 (47.5)	95% CI (CA (%) – EA (%))	P
Days to revisit / Median (IQR)	17 / (43)	13 / (25)	..	0.98
T <sup>o</sup> ≥ 38°C	1 (4.8)	2 (10.5)	-5.8 (10.8 to 22.3)	0.6
CRP ≥ 15 mg/dl	4 (19)	0	19 (35.9 to 2.3)	0.1
Leucocytosis ≥ 12000/μL	8 (38.1)	7 (36.8)	1.25 (31.3 to -28.8)	1
Higher VAS*	16 (76.2)	11 (57.9)	18.3 (47 to -10.4)	0.31
Admitted to hospital	14 (66.6)	8 (42.1)	20.3 (58.8 to -0.11)	0.11
Medical treatment upgrade†	6 (28.6)	8 (42.1)	-13 (15.9 to -43)	0.51

Calculations are based on 21 revisits in ATB-Group and 19 revisits in Non-ATB-Group.

\*Patients who had the same or more pain in the revisit to the ED compared with the initial ED evaluation.

†Initiating antibiotic in Non-ATB-Group or widening spectrum of antibiotic in ATB-Group.

ATB-Group indicates control arm; CI, confidence interval; CRP, C-reactive protein; ED, emergency department; IQR, interquartile range; Non-ATB-Group, Experimental arm; T<sup>o</sup>, temperature; VAS, visual analogue scale.



Days	0	5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90
Non-ATB-Group	0	6	8	11	11	14	15	16	16	16	16	16	16	17	17	17	17	17	19
ATB-Group	0	9	10	10	12	12	13	13	14	17	18	18	18	18	18	18	18	18	21

**FIGURE 4.** Kaplan-Meier cumulative incidence of revisits to the ED in each treatment arm over the study period. Red line: ATB-Group. Blue line: Non-ATB-Group. ATB-Group, control arm; ED, emergency department; FU, follow-up; Non-ATB-Group, experimental arm.

selected for outpatient treatment, and so, to ensure high levels of safety, restrictive criteria had to be applied. The DIABOLO study<sup>4</sup> also excluded a high number of patients: 323 of the 893 possible candidates (36.2%). In addition, since the physicians in the trial were involved in the decisions regarding hospital admission (the primary outcome factor) there may also have been some observer/selection bias. Another limitation has been the lack of use of placebo. However, the high complexity of its control, in a multicenter study, made us reject this procedure.

It is also true that some guidelines such as those of the American Society of Colon and Rectal Surgeons<sup>8</sup> already accept the non-use of antibiotics in the cases of healthy patients with uncomplicated diverticulitis. Some other studies<sup>16</sup> also administer outpatient treatment without antibiotics for AD. However, the research described here is the first prospective, multicentre, randomized study to attempt to demonstrate the noninferiority of outpatient nonantibiotic treatment of mild diverticulitis. We believe that our results can be extrapolated to populations of any kind and that episodes of uncomplicated AD can be treated on an outpatient basis and without antibiotics, provided that well-defined clinical and radiological criteria are applied.

In conclusion, the DINAMO study demonstrates that antibiotic-free outpatient treatment of mild AD is not inferior to standard antibiotic treatment in terms of hospital admission, revisit rates, or

subsequent recovery. There were no additional complications or serious adverse effects compared with the current standard treatment. Therefore, this is a safe and effective therapeutic approach that can be considered as routine practice, offering the economic advantages of outpatient care and the practical advantages of the avoidance of antibiotic treatment.

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