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Acute uncomplicated diverticulitis: key points for early management. A single-centre retrospective study

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Abstract. – OBJECTIVE: Acute uncomplicated diverticulitis is an important clinical condition usually managed in clinical practice with antibiotic therapies and hospitalization in ward. In this setting, recent papers and guidelines suggest to limit the use of antibiotics in selected cases and encourage an early discharge in low-risk patients. The purpose of this retrospective study is to identify serological inflammatory markers and CT findings of acute uncomplicated diverticulitis (AUD) at the onset of the disease and the correlation with the need for in-patient or out-patient management.

PATIENTS AND METHODS: It was used a database drawn from the collection of the patients admitted to our Emergency Room from January 2016 to 2019 and undergoing urgent abdominal CT-scan for suspicious of acute diverticulitis. For each patient we considered biochemical and radiological parameters at the onset of the disease and if patients were managed as in-patients (hospitalization in ward) or as out-patient (early discharged or after observation in Short Stay Unit).

RESULTS: Among patients with early diagnosis of AUD, 108 (65%) were hospitalized in ward with mean time of in-stay of 6.94 days, while only 58 (35%) patients with same diagnosis were managed as out-patient and early discharged from emergency room or after observation in short stay unit with a mean time of in-stay significantly shorter (3.39 days, *p*-value 0.0007). Higher levels of C reactive protein and the length of colon involved considered as percentage (%) in comparison with the entire colon were significantly related to the need for hospitalization (*p*-value 0.03).

CONCLUSIONS: Biochemical parameters and a more advanced radiological evaluation, as the length (%) of colon involved, could allow a stratification of patients with diagnosis of AUD at the admission and help physicians in the early management.

Key Words:
Diverticular disease, Antibiotic therapy, Personalized medicine.

Introduction

Diverticular disease (DD) is a clinical entity of common observation, including a huge variety of clinical conditions from the asymptomatic presence of diverticula to severe complicated diverticulitis[1]. Acute diverticulitis (AD) is the most common clinical complication of DD[2] and is represented by an acute episode of lower abdominal pain (left-sided in western countries) often associated with change in bowel movements, fever, leukocytosis, and increase of inflammatory markers[3,4]. Diverticulitis is highly prevalent, affecting 20% to 60% of the population[5,6] and its incidence has increased over time involving also younger patients[7-9]. In Europe, abdominal ultrasound is frequently used as first radiological approach and identifies diverticulitis with 94% of accuracy, but it is operator-dependent, with a poor assessment in obese patients and in patients with abdominal pain because of probe's compres-

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sion. CT imaging is the gold standard for the diagnosis, staging, and management of acute diverticulitis. It allows the direct visualization of the colonic wall, the perivisceral adipose tissue, and adjacent structures, reaching accuracy superior to 90% due to high levels of sensitivity and specificity, respectively 94% and 99%[10]. Diverticulitis is usually divided in uncomplicated or complicated, based on the presence of abscess, fistula, stricture or perforation. About 12% of patients with acute diverticulitis will develop complications[7] and 4%-10% of patients will have an ongoing diverticulitis despite antibiotic treatment[11]. The watershed between acute uncomplicated disease and mild complicated, however, is not well defined. The most used classification is represented by the modified Hinchey's Classification which includes uncomplicated diverticulitis in stage 0 and Ia[2,12,13], even if some authors still consider microperforation (Hinchey's stage Ia) as a disease's complication[14]. The mainstay of treatment for patients with acute uncomplicated diverticulitis (AUD) has been antibiotics until now, but the emerging concept that could be primarily an inflammatory rather than an infection associated disease[15] has questioned the role of antibiotics in AUD. A recent randomized control trial indicates that antibiotics in AUD do not hasten recovery or prevent subsequent surgery or complications[11]. In addition, both European and American Guidelines recommend the use of antibiotics in selected patients[16,17], such as in presence of immunosuppression or significant comorbidities[3,4,18]. While, on the other hand, in immunocompetent individuals symptomatic treatment should be used. Moreover, patients with diagnosis of AUD could be safely managed as out-patient or discharged after short observation in brief observation unit (BOU), with a success rate of treatment of approximately 95%[19,20]. The purpose of this retrospective mono-centric study conducted in a university hospital with an annual attendance at the Emergency Department (ED) of about 75000 patients (more than 87% adults) is to identify serological inflammatory markers and CT findings of AUD related to the need for in-patient or out-patient management in order to triage and stratify patients at the onset of disease.

Patients and Methods

To the aim of the study, from January 2017 to 2019, all consecutive patients admitted to ED of Fondazione Policlinico Universitario A. Gemelli, Rome, Italy, IRCCS, undergoing urgent abdominal CT-scan with diagnosis of AD, were included in the study. For each patient we considered biochemical and radiological parameters at the onset of the disease and if patients were managed as in-patients (hospitalization in ward) or as out-patient (early discharged or managed in BOU). According to the policy of our Hospital all patients at the admission to the ED gave their written informed consent to assess their medical records. Patients did not receive any grant for their participation in the study. The study protocol was approved by our local Ethics Committee.

Clinical and Biochemical Parameters

Laboratory exams at the onset of AD included: C reactive protein (mg/L), procalcitonine (ng/mL), creatinine (mg/dL), fibrinogen (mg/dL), and white blood cells (x10^9/L) levels. For each patient we evaluated baseline demographic characteristics and collected the hospitalization mean time, in ward or in short stay unit, type of nutrition and therapy adopted. All clinical and demographic data were collected from the hospital computerized clinical records (GIPSE®).

CT Technique and Image Analysis

Considering the role of CT-scan in this setting, an advanced analysis was performed on the radiological evaluation of these patients, according to most recent literature[21]. CT images were performed by expert radiologists (post-fellowship experience ranging from 10 to 30 years) with 64-slice multidetector computed tomography (GE Lightspeed VCT, GE Optima CT660, GE Revolution Evo), with 1.25 mm acquisition thickness and first generation Adaptive Statistical Iterative Reconstruction (ASIR) algorithm. Technical values of kV and mAs were modulated referring to abdominal circumference in order to optimize the images quality and reduce the radiation dose. Images acquisition was performed in craniocaudally scan direction and by the administration of iodinated intravenous contrast agent except for patients with reduced kidney function (defined by a Glomerular Filtration Rate (GFR) <30) or with history of allergy to two drugs or contrast agents; in these cases, CT-scans were performed only for basal condition.

In particular, the acquisition of images 70-80 s after the administration of contrast agent (portal phase) allowed the contrast-enhancement of the colon wall and the extension of the inflammation in the extracolic tissues.

After the acquisition, images were revised with post-processing technologies as "multiplanar reformatting" (MPR), "maximum intensity projection" (MIP) and "volume rendering" (VR).

For each patient we evaluated five parameters, represented in Figure 1 and described below:

a) Colonic segment involved, considering the subdivision of the whole colon in proximal or ascending colon, from the ileo-cecal valve until the hepatic flexure; transverse colon until the splenic flexure; descending colon; descending-sigmoidal junction; sigmoidal colon and finally recto-sigmoid junction.

b) Thickness of inflamed colonic wall (cm), measured on images acquired on the axial plane. In the specific involved tract, we used electronic caliper measurements by tracing a longitudinal centerline and the second line perpendicular the first one. In case of visible lumen, the measure was performed as distance from the serosal-to-mucosal surface, including folds and teniae of the colon; in case of the lumen was not clearly identified, we evaluated the serosa-to-serosa distance and divided in half.

c) Length of involved colon, expressed as linear measure (cm), more precisely as percentage respect to the whole colon. A specific post-processing 2D and 3D software (Vue PACS Carestream) was experimentally exerted in these images to identify the tubular structure of the colon and measure the different tracts manually. The software allowed the creation of a virtual image and the measurement of the length of the colon despite the fact that it is a tubular viscera with a flexuous course, often curved and with some convoluted traits.

d) Diverticula density, defined as number of diverticula distributed along the colon, obtained by an electronic indicator on axial images. According to Dickerson (Dickerson 2017) we adopted the same severity scale including minimal (few diverticula, with more than 5 cm of distance between

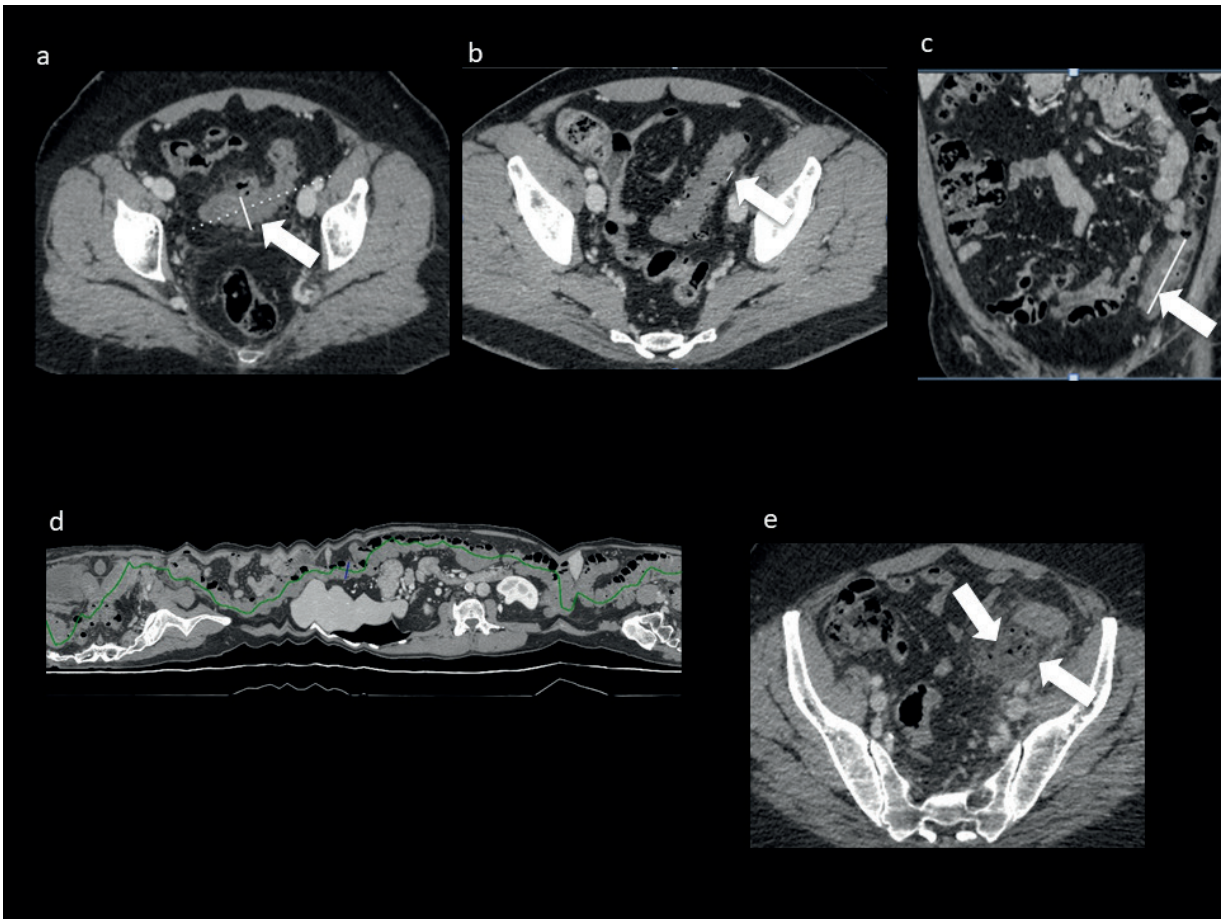

Figure 1. The five CT-scan parameters considered for each patient: a) Colonic segment involved, b) Thickness of inflamed colonic wall, c) Length of involved colon, d) Diverticula density and e) Presence of microperforation.

each other), mild (diverticula distanced from 1 to 5 cm), moderate (each diverticulum is next to another for less than 1 cm), and severe (several diverticula so close together that they cannot be distinguished from one another).

e) Presence of microperforation defined as extra colonic lumen microscopic bubbles sometimes associated with small fluid collections.

The primary endpoint of our study was to define the correlation between early biochemical and radiological features at the onset of AUD (Hinchey stage 0-Ia) and its management (in-patient *vs.* out-patient).

The secondary endpoints were to verify the correlation between microperforation (Hinchey stage Ia) and the need for hospitalization and mean time of in-stay; then, to define the correlation between antibiotic therapy and need for hospitalization and mean hospitalization time.

Statistical Analysis

A descriptive statistical analysis was performed using absolute and relative frequencies, mean and standard deviation (SD), when appropriate, for demographic and clinical characteristics of surveyed patients and clinical outcome parameter. Statistically significant differences in clinical outcome parameter, between hospitalized and non-hospitalized patient, were tested through *t*-test, Wilcoxon rank-sum (Mann-Whitney test), Chi-square test, as applicable. Association between length of stay and other continuous variables was tested using Spearman correlation. Multi-variate analysis was performed to evaluate the impact of independent variables in predicting length of stay. The statistical significance level was set at $p< 0.05$ and all the analyses were carried out by using software "Stata IC 13 for Mac" (Stata Corp., Lakeway, TX, USA).

Results

Summary of the Cohort Study

This retrospective study included 269 patients (M:F 133:136) admitted to the ED of our hospital between January 2016 and 2019 with diagnosis of AD. Among them, 103 patients had a diagnosis of complicated acute diverticulitis (51 cases underwent emergency surgery, 52 were treated conservatively and then sent to elective surgery in a deferred time), while 166 had a diagnosis of AUD (Figure 2). Antibiotic therapy was used in all patients as first choice, mainly including ciprofloxacin and metronidazole, administered alone (2.41% ciprofloxacin and 1.20% metronidazole) or in combination (46.39%), or piperacillin-tazobactam (18.67%). Other therapies as steroids, mesalazine, and probiotics were not regularly used in our cohort (3.6% of the population). Restriction of oral intake and intravenous fluids were adopted in all patients surveyed.

Predictors for In-Patient or Out-Patient Management

Among patients with diagnosis of AUD, 108 (65%) were hospitalized in ward with mean time of in-stay of 6.94 days, while only 58 (35%) patients with same diagnosis were managed as out-patient and discharged early from ED or after observation in BOU with a mean time of in-stay significantly shorter (3.39 days, *p*-value 0.0007). All patients were discharged in good clinical conditions, without complications (Figure 1).

Considering AUD patients (Table I) males were 79 (47.59%) and females 87 (52.41%), with no significant differences (p=0.827) in gender composition between in-patient and out-patient management. No significant correlations were found for mean age (61.44±15 years, p=0.2895) between out-patient (59.52±11.03 years) and in-patient management (62.20±15.75 years). Also the presence of fever, defined as body temperature > 38°C at the admission to ED, seemed to be not significantly (p=0.359) related to different management of AUD patients.

Therefore, we analyzed biochemical and radiologic parameters at the onset of AUD and their possible correlation with the in-patient or out-patient management.

Among inflammatory markers, C reactive protein was significantly related to the need for hospitalization (*p*-value 0.0387), while procalcitonin, fibrinogen, leukocytosis, creatinine, seemed to not show a significant correlation (Table II).

The most common radiologic signs of AUD as measure of colonic segments involved, thickness wall and diverticular density were not significantly related to the need for hospitalization. Instead, a new, easy-to-find, radiologic parameter, not currently used in clinical practice, as the length of colon involved considered as percentage (%) of the entire colon, was significantly related to the need for hospitalization (*p*-value 0.0304). Interestingly, a significant correlation was also found between microperforation and length (%) of colon involved (*p*-value 0.01) and all patients with signs of microperforation at CT scan were treated as in-patient (Table II) with a significantly higher mean time of hospitalization (*p*-value 0.0018).

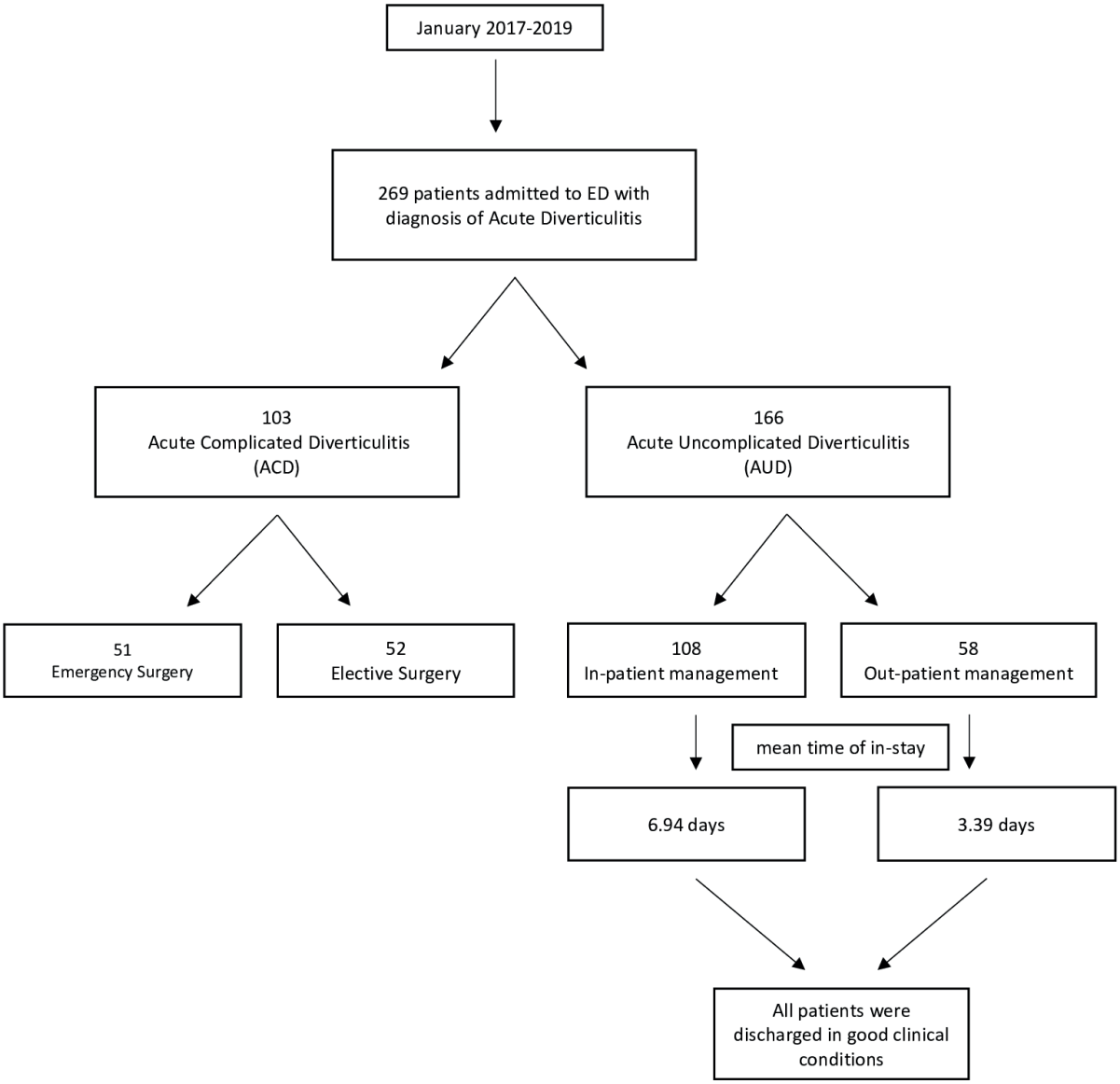

Figure 2. Flow chart of the study.

Regarding the time of in-stay, blood inflammatory markers seemed to be the only factors significantly related to the hospitalization time CRP, fibrinogen and procalcitonin are all significantly related to the time of in-stay (*p*-value respectively 0.0053, 0.0001, 0.0302; Table III).

All patients with AUD were treated with antibiotic therapy. Ciprofloxacin plus metronidazole (oral or intravenous) was the most represented combination treatment, reported in the 47% of the entire study population, and included patients with microperoforation.

Among the group managed as out-patient, only 11% of them received antibiotics by oral administration, with a mean time of in-stay (1.5±1.224 days) significantly shorter (p=0.0000) compared to patients who started intravenous treatment (3.7±0.693 days), with no differences in terms of clinical outcome. A multi-variate analysis in this specific subgroup showed that the only independent variable predicting time of in-stay is the method of antibiotic administration (oral or intravenous).

Discussion

Our study cohort represents a large population of patients affected by acute diverticular disease,

Table I. Baseline characteristics of AUD patients at the admission in ED.

Patients with AUD	N= 166
Male/Female	79/87
Age (years) mean± SD	61 ± 15
Biochemical parameters mean± SD	
- C reactive protein (n.v. < 5.0 mg/l)	90.4 ± 76.6
- Procalcitonine (n.v. <0.5 ng/ml)	1.96 ± 7.1
- Creatinine (n.v. 0.50 - 1.00 mg/dl)	1 ± 0.5
- Fibrinogen (n.v. 200 - 400 mg/dl)	561.7± 172.6
- White blood cells (n.v. 4.00 - 10.00 x109/L)	11.56 ± 3.96
Fever (n of pts)	65 (39%)
CT findings	
- Right colon inflammation (n of pts)	4
- Thickness of inflamed colonic wall (mm) mean± sd	1.4±0.3
- Length of colon involved (%) mean	5.3
- Microperforation (n of pts)	17
- Diverticula density (n of pts)	
Minimal	7
Mild	16
Moderate	81
Severe	62

Legend: n.v. normal value, SD standard deviation.

which, as known, has multiple clinical features, probably linked to different underlying pathological mechanisms, still not completely understood. Binda et al[9] recently reported a large national analysis showing that admissions for acute diverticulitis increased in Italy between 2008 and 2015 and highlighted the importance of this condition in terms of need for hospitalization in ward and its huge impact on costs, not yet clearly evaluated in Italian papers and guidelines[22,23]. Deepening the need for hospitalization, need for hospitalization, some previous studies showed significant cut-off value for biochemical parameters of inflammation[24] predictive for the severity of the disease[25-29] and a recent interesting paper showed all significant CT findings predictive of colonic diverticulitis recurrence[21]. However, it remains difficult to have an accurate risk stratification of patients at the onset of the disease, according to serological and radiologic parameters, even if it could be extremely useful in every day clinical practice for the early management of these patients both in terms of need for hospitalization and therapies adopted. Notably, the primary objective of this retrospective analysis was to find a possible correlation between biochemical and CT findings with the need for hospitalization of uncomplicated diverticulitis, since as far as we know no study has yet performed such analysis before.

Our study attempted to provide data from an advanced third-level center, which could help the admitting physicians in the ED in the early management of patients with uncomplicated acute diverticulitis. In this setting, we found that the combination of high level of PCR and in-depth radiological evaluation in terms of length of colon involved calculated as percentage of the entire colon, are strongly related to the need for hospitalization in ward, while lower level of PCR and length of colon involved (%) could be related with out-patient management of these patients with no difference in terms of clinical outcome. Moreover, as reasonably expected, inflammatory markers as PCR, procalcitonin, and fibrinogen showed a significant correlation also with the time of hospitalization perhaps identifying the subgroup of those patients with an underlying mechanism of inflammation not yet completely understood and not present in all cases affected by AUD. Similarly, Sallinen et al[30] recently purposed a model for defining AD in five different stages of severity disease considering clinical, radiologic, and physiologic data as a classification to use in the everyday clinical practice. Despite this, in the field of AUD, neither predictive parameters of clinical outcomes nor clinical or radiological signs at the onset of disease that could help physicians in the "early" management of these patients, have been clarified.

Antibiotic therapy is also a critical point. The idea that AUD should be treated with antibiotic treatment is deeply rooted but it is in contrast

Table II. Association between biochemical and radiological parameters at the admission to ED and in-patient or out-patient management, tested through t-test, Wilcoxon rank-sum (Mann-Whitney) test and Chi-square test.

Biochemical and Radiological Parameters	Hospitalized	Managed in ER	*p*-value
C reactive protein in mg/dl (mean± SD)	99.6±80.5	70.7±63.0	0.0387*
Procalcitonine (mean± SD) **	1.9±7.0	1.9±7.0	0.9839
Creatinine (mean± SD)	0.9±0.6	1.0±0.9	0.8833
Fibrinogen (mean± SD)	574.4±189.9	531.4±118.6	0.1719
White blood cells (mean± SD)	11.6±4.1	11.2±3.7	0.5828
Lenght of colon involved (mean percentage± SD)	5.5±2.2	4.7±1.8	0.0304*
Thickness of inflames colonic wall (mean± SD)	1.4±0.3	1.3±0.3	0.1478
Diverticula density (mean± SD)	3.3±0.8	3.1±1.1	0.4086
Presence of microperforation (percentage)***	14.4%	0.0%	0.006*
	Patient with microperforation	**Patient without microperforation**	
Hospitalization time in days (mean± SD)**	8.2±5.0	5.5±6.1	0.0018*

*significative *p*-value < 0.05. ** Wilcoxon rank-sum (Mann-Whitney) tested. ***Chi-square tested. Legend: SD standard deviation.

with the relevant problem of increasing antibiotic multi-resistance. Several studies faced with this innovative purpose to adopt a non-antibiotic treatment in these patients[31,32], but reliable studies are still not comprehensive and retrospective analyses represent most of the consistent data, also because there is a "poor" compliance to this alternative treatment, despite encouraging data and no evidence of increased risk of complications[33]. Antibiotic therapy in acute diverticulitis is a mainstay difficult to unhinge and our study has interestingly showed that in case of out-patient management, antibiotic therapy is the only significant parameter that has an impact on the time of in-stay. It is to be thought whether antibiotic therapy in these cases allows a rapid resolution or viceversa, it is limiting the discharge with alternative therapeutic approaches as anti-inflammatory agents[34-37] or gut microbiota modulators[38-40].

However, our study has several limitations. First, as a retrospective analysis, data extraction was limited and some bias can have indirectly influenced the principal endpoints. Second, it was difficult to assess the real impact of antibiotic therapy (mood and time of administration) and nutrition (stop of oral intake) since they are still widely used in case of diagnosis of AUD. Third, calprotectin values or microbiota data are missing because they are not available in an emergency setting, even if they should be considered in further prospective studies as possible predictive factors of severity. Finally, analysis of costs was not included in this study, but it is a crucial point needed to be explored. Further clinical trials are necessary not only to evaluate new possible strategies for the "early" management of these patients and its impact on costs, but also for assessing the role of new alternative therapies for a more targeted and personalized approach to patients.

Table III. Association between time of in-stay and the biochemical and radiological parameters tested through Spearman correlation.

Biochemical and Radiological Parameters	rho	p-value
C reactive protein (mg/dl)	0.42	0.0053*
Procalcitonine	0.57	0.0001*
Creatinine	0.15	0.3507
Fibrinogen	0.34	0.0302*
White blood cells	0.23	0.1496
Percentage of length of colon involved	0.27	0.0887
Thickness of inflames colonic wall	0.17	0.2985
Diverticula density	-0.04	0.7965

*significative *p*-value < 0.05.

Conclusions

The management of diverticular disease is changing, and it is possible that AUD, considered for many years for in-patient management, now evolves into a fast-resolution disease with out-patient management not requiring antibiotic therapy. To date, there are no data about clinical or radiological factors significantly related to this, even if it is a key point for finding the best early management both tailoring therapies and reducing inappropriate hospitalizations and costs. Our retrospective study showed that biochemical parameters and a more advanced radiological evaluation, as the length (%) of colon involved, could allow a detailed stratification of these patients at the admission. Further studies are needed to define cut-off values and precise role of blood inflammatory markers in the risk stratification of AUD patients and to validate the length of colon involved, expressed as percentage of the whole colon, as new, easy-to-find, radiological parameter that could help physicians in the early tailored management of patients with uncomplicated acute diverticulitis.

Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study was approved by the local Ethics Committee.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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