Title:
Diverticulitis in immunodeficient patients: our experience in the management of high-risk patients

Authors:
Javier Serrano González, José Luis Lucena de la Poza, Laura Román García de León, Jesús Gabriel García Schiever, Neda Farhangmehr Setayeshi, Pablo Calvo Espino, Arsenio Sánchez Movilla, Victor Sánchez Turrión

DOI: 10.17235/reed.2019.6281/2019
Link: PubMed (Epub ahead of print)

Please cite this article as:

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Diverticulitis in immunodeficient patients: our experience in the management of high-risk patients

Javier Serrano González¹, José Luis Lucena de la Poza¹, Laura Román García de León¹, Jesús Gabriel García Schiever², Neda Farhangmehr Setayeshi³, Pablo Calvo Espino², Arsenio Sánchez Movilla¹ and Víctor Sánchez Turrión¹


*This study was partially presented in the XXX National Surgery Congress, Madrid, 2014.

Received: 21/3/2019
Accepted: 4/7/2019
Correspondence: Javier Serrano González. General Surgery and Digestive Diseases Service. Hospital Universitario Puerta de Hierro Majadahonda. C/ Manuel de Falla, 1. 28222 Majadahonda, Madrid. Spain
e-mail: javierserranogdr@gmail.com

ABSTRACT
Introduction: acute diverticulitis is a very prevalent disease. The need for a more aggressive management in immunodeficient patients has not been established. We present the results of our unit with immunodeficient patients diagnosed with acute diverticulitis and their follow-up.

Objectives: to assess the possibility that a conservative management in this group is as valid as in the immunocompetent population.
Methods: a retrospective analysis study was performed in our hospital. Forty immunodeficient patients (transplant, corticoid treatment, dialysis, oncologic, HIV patients) diagnosed with acute diverticulitis were analyzed. The patients were managed with a surgical or non-surgical treatment according to their status on admission. The main analyzed items were the severity of the acute episode and the need for surgical treatment compared to the cause of immunodeficiency. Other studied variables included follow-up results and recurrences.

Results: thirty-two of the 40 patients studied received a non-surgical treatment during the acute episode, eight required emergency surgery (seven had a Hartmann procedure and one underwent a colon resection and anastomosis). Transplant patients and those between 40 and 50 years old proved to be higher risk groups. Three patients subsequently required elective surgery due to complications. Twenty-four patients had uneventful recoveries.

Conclusions: the frequency of complicated acute diverticulitis is higher in immunodeficient patients than that of the general population. Non-surgical treatment seems to be as safe as in immunocompetent patients. Younger and transplanted patients were higher risk groups for severe acute diverticulitis that required a more aggressive management initially.

Keywords: Diverticulitis. Colon. Immunodeficiency.

INTRODUCTION
Diverticular disease is defined as the presence of diverticula or pseudodiverticula in the colonic wall. In Western countries, it is mostly located in the sigmoid colon followed by the descending colon. The prevalence is influenced by life habits, especially high-fat, high-protein and low-fiber diets. This has also been observed in Asian countries, where customs are becoming more similar to those of Western countries during the last few decades (1,2). Up to 80% of the population over 70 years old have diverticula (3,4) and around 25% of these cases will develop at least one episode of acute diverticulitis (AD) during their lifetime (5).
Patients with conditions that compromise their immunological competence are more and more common in our daily practice as oncologic patients, chronic kidney disease (CKD) under dialysis and transplant patients, among others. Several studies describe a more aggressive evolution of recurrent episodes of AD in immunodeficient patients (ID) (6,7), with a higher ratio of complicated disease than immunocompetent patients (IC). They require a more active management of the disease due to the risk of more aggressive episodes, and elective surgical treatment is indicated after the first episode of non-complicated AD (8-10).

The goal of this study was to analyze the results of the ID patients treated in our hospital for AD, and to design the best care strategy for these cases.

MATERIALS AND METHODS
An observational retrospective and descriptive study was performed of ID patients diagnosed with AD, treated in a tertiary hospital between 2008 and 2016. This study was approved by the Ethics Committee for Clinical Research in our hospital. Immunodeficient patients were considered as those with chronic corticoid treatment, solid organ transplant, hematologic neoplasm, solid organ tumor, chronic kidney disease under dialysis and those with HIV infection. The patients included in the study were diagnosed with AD after a clinical and analytical evaluation and an abdominopelvic computed tomography (CT) scan (11,12). ID patients admitted with a diagnosis of AD but without available data for a proper analysis were excluded from the study.

The analyzed data included: age at the time of diagnosis, gender, severity of the disease (using the Modified Hinchey Classification), cause of immunodeficiency (13), risk factors for a poor outcome (RFPO) (diabetes mellitus, chronic kidney disease without dialysis, high blood pressure, smoking habit or dyslipidemia) (14-16), treatment (medical vs surgical), days of admission, need for surgical treatment during follow-up, complications during hospital stay and recurrences.

Medical treatment consisted of nil per os (NPO), intravenous fluids, wide spectrum antibiotics and intravenous analgesia (17). Antibiotic treatment for admitted patients was performed using intravenous piperacillin/tazobactam 4/0.5 g every six hours,
adjusting the dosage to kidney function when necessary. Tigecyclin + ciprofloxacin were used in patients with an allergy. This treatment continued for at least five days, followed by oral amoxicillin/clavulanic acid for another 5-7 days (ciprofloxacin + metronidazole in allergic patients). Emergency surgical treatment (EST) was performed in patients with generalized peritonitis (stages III and IV of the Hinchey Classification) or in the case of septic shock. Surgical procedures included the Hartmann procedure or resection via primary anastomosis; the decision was made by the responsible surgeon based on their experience, local contamination and the patient’s status and stability (18-20). Elective colonic resection was indicated in a few cases after conservative management of the acute episode, depending on the severity of the first episode and the appearance of subsequent relapses (21). After discharge, the patients underwent at least a six-month follow-up, with clinical, analytical and radiologic tests. A colonoscopy was also performed if this had not been performed during the five years prior to the first episode of AD.

**Statistical analysis**
Quantitative variables were expressed as absolute values and qualitative variables were expressed as absolute values and percentages. Statistical analysis was performed using the IBM® SPSS® Statistics 20 program. The Student’s t test was used to compare quantitative variables, assuming a \( p < 0.05 \) as statistically significant. Chi-squared test contingency tables were used to analyze qualitative variables. These tables are useful when analyzing the relationship between two categorical variables, on which only a nominal measurement can be made. Thus, it is possible to assess the existence of statistical significant differences between corrected typified residues (CTR). Residues are the differences between the observed and the expected frequencies in each box of the table; they are used to understand the association between the compared elements. CTR have a normal distribution, with a mean of 0 and a standard deviation of 1. With these tools and a confidence level of 0.95, statistical significant differences were found when studying the CTR and these differences were statistically significant when the residues where outside of the interval \((-1.96; 1.96)\). The positive or negative result of this residue shows the direct or inverse relationship between the categories.
RESULTS

During the study period, 578 patients were analyzed and all were admitted to our unit after being diagnosed with AD. Forty-six patients of these were analyzed and six were excluded due to insufficient data (Fig. 1). Of the 40 analyzed patients (6.9% of the total patients admitted with AD), 21 were male (52%) and 19 female (48%) with an average age of 63 years old, ranging from 43 to 85 years old.

Among the different causes for ID, the cohort was divided in 14 patients (35%) who had previously received a transplant: six had a kidney transplant (43% of all patients with a transplant), five bi-pulmonary (36%), two liver (14%) and one heart (7%); four patients (10%) had a chronic kidney disease with dialysis and six (15%) had hematologic neoplasms; two had acute myeloid leukemia (33%), one prolymphocytic leukemia (17%), one multiple myeloma, one B lymphoma and one T lymphoma; eight patients (20%) were actively receiving treatment for a solid tumor; six patients (15%) were receiving treatment with corticoids, including one with systemic erythematosus lupus, one with Sjögren’s syndrome, one for psoriatic arthropaty, two cases of rheumathoid arthritis and one case of polychondritis; and two patients (5%) had an active HIV infection.

Among the RFPO, ten patients had high blood pressure (25%), five were diabetic (12.5%), four were active smokers (10%), two were dyslipidemic (5%) and two had chronic kidney disease without dialysis (CKDWOD, 5%). Ten patients had no risk factors that could predict a poor outcome of the disease.

According to the results of the CT scan performed for every patient in the Emergency Ward, 26 cases (65%) developed a non-complicated AD (Hinchey stage Ia); three patients (7.5%) were classified as stage Ib, four patients (10%) as stage II, two patients (5%) had a stage III and five cases (12.5%) had a stage IV AD. One of the cases was diagnosed with a right AD (patient with a kidney transplant, stage Ia) and the rest were diagnosed with AD of the descending or sigmoid colon. All received treatment in our hospital except one, who refused to be admitted.

Of all the patients in our study, 32 (80%) initially received conservative treatment and eight (20%) required EST (six had undergone a previous transplant and two were
oncologic patients). Resection of the affected colonic segment with a colostomy was performed in all cases, except for one case in which a resection and primary anastomosis was performed. With regard to the severity of the AD cases that required EST, one patient (12%) was a stage II, two were stage III (25%) and five patients (63%) were classified as a stage IV. All patients diagnosed with a stage III or stage IV AD were treated with EST (Table 1).

Three of the patients who initially received a non-surgical management (NSM) with antibiotics underwent surgical treatment during the first year of follow-up after the acute episode. Sigmoidectomy and primary anastomosis were performed in two cases, one with CKD and a stage II AD with persistent rectorrhagia after the acute episode, and the other patient underwent chronic corticoid treatment and had persistent subocclusive episodes after the initial episode was resolved. Another patient with stage II AD and lymphoma underwent a Hartmann’s procedure.

The average time of admission was 14.5 ± 20 days (4-115), with a median stay of eight days. Treatment with antibiotics was continued for an average of 17.3 ± 11.1 days (7-68), with a median of 14.5 days. Twenty-four of the patients (60% of the total) had an uneventful hospital stay. Among the patients who received NSM, the complications registered were one respiratory infection (2.5%), five patients (12.5%) relapsed at least once after being discharged (there were no complicated AD in any of the readmitted patients) and one patient died (2.5%) (this patient had acute myeloid leukemia and was admitted with a stage Ia AD). Among those who received EST, complications included one paralytic ileus (2.5%), one surgical wound infection (2.5%), one intra-abdominal abscess that required percutaneous drainage (2.5%) and one patient who required a second surgery (2.5%) due to a dehiscence of the primary anastomosis. In the second group, one patient (2.5%) who had a pulmonary adenocarcinoma with brain metastases and underwent a Hartmann’s procedure died.

**Age and gender**

Of the patients who required an EST, 50% were male and 50% were female. The average age of the patients with EST was 54 years old; the average age in the NSM group was 65 years old (p = 0.013). When the patients were divided into age groups
(Fig. 2), the group aged 40-50 years was found to have a higher risk of being diagnosed with stage II (CTR = 3.3) and stage IV (CTR = 2) AD, and a lower tendency of having stage la disease (CTR = -3.3). Furthermore, there were significant differences in this age group regarding surgical treatment, as EST was more frequently required than NSM (CTR = 2.4). In addition, eleven out of the 12 cases (91%) older than 70 years of age were diagnosed of with stage la AD (CTR = 2.3).

**Cause of immunodeficiency**

Patients with hematologic neoplasms, chronic corticoid treatment and CKD had higher rates of stage la AD (100%, 83% and 75%, respectively). Meanwhile, the percentage of patients with a previous transplant diagnosed with stage la non-complicated AD was 43% (CTR = -2.2). These patients had a higher risk of being diagnosed with stage IV AD (80% of all patients with stage IV AD, CTR = 2.3) (Fig. 3). Regarding the need for an EST, six patients (75%) had undergone a transplant, which amounted to 43% of the patients in this group (CTR = 2.7). There were no statistically significant differences with regard to the relationship between the transplanted organ and the severity of the disease or the treatment received.

**Risk factors for poor outcome of AD**

There was a significant association in the CKDWOD group that favored EST (CTR = 2.9). Both patients with this condition (100%) received an EST.

**Recurrences**

There were no statistically significant differences in any of the analyzed subgroups (p = 0.4).

**DISCUSSION**

According to previous studies, ID patients tend to have a more aggressive first episode of AD, with higher mortality rates compared to IC patients (22). In our study, the percentage of complicated AD was 35%, which is higher than the rate described in the scientific literature for IC patients (12% according to the study of Fung et al. and 25%
as reported by Weizman et al.) (23,24). Patients with previous solid organ transplants have a higher risk of a complicated AD and for the requirement of EST. A correlation was observed between the younger age groups and a more severe presentation. The opposite was also observed between more moderate presentations and the older age groups.

In our experience, NSM with antibiotics, which was the treatment initially used in 80% of our patients, showed satisfactory results and surgical treatment due to poor progress was not required in any case. Twenty per cent required EST and Hartmann’s procedure was the safest technique (25) (88% of the cases with initial EST) in the context of severe intra-abdominal infection, patients with anastomosis dehiscence risk factors and, occasionally, in patients with septic shock that required vasoactive drugs during surgery. There were no cases of laparoscopic drainage and lavage. The percentage of patients that required surgery was higher than for IC patients who needed EST (20% vs 7-10%) (26-28). Among the RFPO for AD, the group with CKD without dialysis had a higher risk of EST, in spite of the small sample size. No other RFPO were found to be responsible for a higher risk of requiring initial EST, including DM.

There was a global mortality of 5% during the acute episode for IC patients, which is higher than in previously reported studies (29). The recurrence rate of 12.5% was similar to that described in the literature for IC patients (around 10% in the first year) (30). This percentage seems to be higher in patients with chronic corticoid treatment. There is still controversy in the literature regarding patient management after an acute episode has been resolved, with no clear guidelines to determine if elective surgical treatment is indicated and when (31,32). There is evidence that colonic resection and primary anastomosis is the preferred procedure when elective surgery is performed (33,34).

Our study has some limitations. First, this was a retrospective study with a limited number of patients and therefore, it is more difficult to obtain statistically significant differences. Thus, further studies with larger sample sizes are needed. Furthermore, this study was performed following the modified Hinchey classification for AD, although other more modern classifications could have been used such as those
proposed by Sartelli et al. (35) or Mora et al. (modified Neff classification) (36). Anyway, we believe our results are equivalent, considering uncomplicated AD Hinchey’s stage Ia (Sartelli’s “uncomplicated”, modified Neff’s “stage 0”). A higher proportion of complicated presentations would have required surgical treatment (Hinchey’s stages Ib-IV, Sartelli’s complicated stages 1-4 and modified Neff’s stages 1-4).

CONCLUSIONS
There are proportionally more complicated AD in ID patients than in the general population. However, NST seems to be as safe as in IC patients, with the same indications for surgical treatment in both groups. Recurrence rates are also similar, which we believe does not justify performing surgery outside the actual guidelines for the general population. Younger patients and those with a history of solid organ transplants are the main groups with a higher risk of developing more severe episodes that might require a more aggressive management when diagnosed.

REFERENCES
2. Loffeld RJ, Van Der Putten AB. Diverticular disease of the colon and concomitant abnormalities in patients undergoing endoscopic evaluation of the large bowel, Colorectal Dis 2002;4(3):189e192. DOI: 10.1046/j.1463-1318.2002.00328.x


Table 1. Comparison between medical treatment vs emergency surgical treatment

<table>
<thead>
<tr>
<th>Medical treatment</th>
<th>Emergency surgical treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 male</td>
<td>Sex</td>
</tr>
<tr>
<td>15 female</td>
<td></td>
</tr>
<tr>
<td>65 years old</td>
<td>Average age</td>
</tr>
<tr>
<td>11 days</td>
<td>Average time of admission</td>
</tr>
<tr>
<td>Hinchey</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Ia</td>
</tr>
<tr>
<td>3</td>
<td>Ib</td>
</tr>
<tr>
<td>3</td>
<td>II</td>
</tr>
<tr>
<td>0</td>
<td>III</td>
</tr>
<tr>
<td>0</td>
<td>IV</td>
</tr>
<tr>
<td>Cause for immunosuppression</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Transplant</td>
</tr>
<tr>
<td>6</td>
<td>Solid tumor</td>
</tr>
<tr>
<td>6</td>
<td>Corticoid therapy</td>
</tr>
<tr>
<td>6</td>
<td>Hematologic tumor</td>
</tr>
<tr>
<td>4</td>
<td>CKD</td>
</tr>
<tr>
<td>2</td>
<td>HIV</td>
</tr>
<tr>
<td>Patient’s progress</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>No complications</td>
</tr>
<tr>
<td>5</td>
<td>Recurrences</td>
</tr>
<tr>
<td>1</td>
<td>Deaths</td>
</tr>
</tbody>
</table>
Fig. 1. Management of the patients in our study.
Fig. 2. Emergency surgical treatment in the different age groups.
Fig. 3. Association between the cause of immunodeficiency and the severity of acute diverticulitis.