Abstract. - While the treatment of complicated diverticular disease (DD) is standardized, the approach to the symptomatic DD and prevention of relapsing complicated DD is still debated. An open question is whether nonabsorbable antibiotics may reduce the incidence of major complications of DD.

We wanted to retrospectively analyze the prevalence of this disease in a large population of patients undergoing colonoscopy in our center in the last 10 years. Patients with symptomatic or complicated DD were treated with rifaximin 1,200 mg/die for 10-12 days during the acute phase in addition to the appropriate systemic antibiotics, followed by a prophylactic regimen with 800 mg/die for 7 days every month. The patients were followed up to December 2003, and the incidence of new complications and the relapses of symptomatology were determined.

A total of 11,344 patients were screened. Of them, 2,287 showed an anatomical diverticulosis, and 408 had a diagnosis of complicated DD. The results indicate that the prevalence of DD – either in the uncomplicated or complicated form – in our area (Abruzzo, Italy) is identical to that of European countries, whose diet is characterized by a low amount of fiber and a high content of calories and refined sugars.

Along a period of 10 years, a relapsing symptomatology of DD was observed in 112 patients treated with rifaximin (4.89%), while new complications of the DD were observed in 27 patients (1.18%). The comparison of these data with those of larger published series suggests a possible role of rifaximin in the prevention of DD main complications.

Key Words: Diverticulosis, Colonoscopy, Rifaximin, Glucomannan.
ing anaerobes. It is unabsorbed after oral administration, and it has been successfully used in the treatment of portal systemic encephalopathy, infectious diarrhea, and surgical prophylaxis, showing negligible side effects6.

Recently, it has become evident that cyclic administrations of rifaximin reduce the symptomatology in uncomplicated symptomatic DD. Tursi et al.7 have shown that rifaximin (800 mg/day) significantly reduces the symptoms in patients with recurrent attacks of acute diverticulitis of colon, while in patients with uncomplicated DD receiving glucomannan for one year, the addition of rifaximin (800 mg/day) has been shown to increase the percentage of asymptomatic patients to 56.5% compared to 29.2% of patients treated with glucomannan alone8. Thus, the use of non-absorbable antibiotics – such as rifaximin – in uncomplicated symptomatic DD has been recommended9.

A still unanswered question is, however, whether rifaximin may also reduce the incidence of major complications. Latella et al.8 have reported that the main complications of DD occurred in 1.34% of patients treated with glucomannan plus rifaximin and, in 3.22% of those treated with glucomannan alone. A longer-term follow-up (2 years) would be needed to confirm whether rifaximin may have a role in preventing major complications of DD.

In our study, we wanted to retrospectively analyze the prevalence of DD in a large population of patients who required us for care of their colonic disturbances. Moreover, since it is common practice of our Department to prescribe a repeated cyclic administration of rifaximin in all the patients with uncomplicated symptomatic DD, we tried to get more information from this survey on the potential of rifaximin to prevent the relapse of symptomatic DD and its complications.

**Materials and Methods**

The standard protocol of our Department for the management of patients with symptomatic uncomplicated DD is a treatment with a non-absorbable antibiotic, such as rifaximin (Normix® – Alfa Wassermann), administered at the dose of 1,200 mg/die for 10-12 days during the acute phase of a painful DD, followed by a regimen of 800 mg/die for one week every month. The drug is administered as 200-mg tablets, two to three times daily at 12- to 8-h interval.

In presence of a complicated DD with acute diverticulitis, we normally treated outpatients with a clear liquid diet and a broad-spectrum oral antibiotic with activity against anaerobes and gram-negative bacteria (in particular, *Escherichia coli* and *Bacteroides fragilis*); when the patient is become asymptomatic, a treatment with rifaximin 800 mg/die for one week every month is recommended. Also in this case, the drug is administered as 200-mg tablets, two times daily at a 12-interval.

In both the cases, a control colonoscopy is performed at least once every year, to check the condition of the colon. Medical examination and laboratory tests are also performed at these times, and the occurrence of complications and possible side effects is checked. Patients are then invited to return for a control visit whenever they believe it necessary.

Recurrence of symptomatic diverticulitis or appearance of complicated DD are evaluated on the basis of clinical (recurrence or new appearance of abdominal pain and/or disorders in bowel habits, fever) and endoscopic (inflamed mucosa and/or presence of stenosis associated with diverticula of the colon) findings.

We have therefore performed a retrospective analysis on all the patients who underwent a colonoscopy at our Department of Endoscopic Surgery, for colonic disturbances. Within this population, we have identified the patients who showed diverticula of the colon (anatomical diverticulosis); most of them were asymptomatic, while others had a diagnosis of symptomatic or complicated DD.

Diagnosis of symptomatic uncomplicated DD was done in patients who presented with non-specific complaints – e.g., lower abdominal pain, usually left-sided, abdominal distension, and disturbances of the bowel habits. Such patients did not usually manifest signs of inflammation, such as pyrexia or neutrophilia, which could indicate diverticulitis. Pain was generally exacerbated by eating and
diminished with defecation or flatus, which suggested colonic wall tension due to raised intraluminal pressure.

Diagnosis of complicated DD was done in patients with diverticulitis; pain was intermittent or constant and was sometimes associated with a change in bowel habits. Complications of diverticulitis were considered an abscess with perforation of the diverticulum and localized phlegmon, a colovesicular fistula, a partial colonic obstruction during an episode of acute diverticulitis, and GI bleeding.

The case reports forms of the patients who had affected either by uncomplicated or complicated DD, and received a prophylactic treatment with rifaximin, were examined up to December 2003. The following events were recorded: (a) a relapse of uncomplicated DD; (b) either a relapse or the first appearance of complicated DD. The data were collected and analyzed by a SPSS software for Windows, in order to achieve information on the frequency of relapsing DD in patients treated with rifaximin.

### Results

Our survey indicate that between January 1994 and December 2003, a total of 11,344 patients underwent a colonoscopy in our center for different reasons. Of them, 2,287 showed the presence of colonic diverticula (anatomical diverticulosis); they were 1,211 males and 1,076 females, distributed in three age ranges (< 50 yrs: 27; 50-80 yrs: 1,795; > 80 yrs: 465). These patients represented the 20.16% of all the screened patients (Table I). Among the patients with diverticulosis, 1,772 patients (77.5%) showed an asymptomatic anatomical diverticulosis, while the remaining 515 patients (22.5%) reported non-specific abdominal complaints, such as lower abdominal pain of the left quadrant, abdominal distension, and disturbances of the bowel habits. These values are in agreement with those recently reported for DD in European and US populations, for asymptomatic (75-80%) and symptomatic (20-25%) of patients with anatomical diverticulosis.4,10-12

A subgroup of 408 patients reported a diagnosis of complicated DD (3.59% of all the screened patients, and 17.84% of those with DD). Also these values approached those reported by the few available prospective studies, which indicate a 25% incidence of complications among the patients with DD.3

The most frequent complications we observed in these patients, were inflammation (250 patients), followed by GI bleeding (135 patients) and stenosis (23 patients). Twenty-three patients with complicated diverticular-

### Table I. Overview of the results of a retrospective analysis on 11,344 screened patients at the Department of Endoscopic Surgery of L'Aquila (Italy), between 1994 and 2003. The number of patients with diagnosis of diverticular disease (DD) and with complicated DD at the early visit are reported, as well as patients requiring surgery for complicated DD. The results are expressed as absolute number of patients and percent on the total number of screened patients with diverticulosis.

<table>
<thead>
<tr>
<th>Age range</th>
<th>N° of screened patients</th>
<th>Patients with DD (N°/% of screened patients)</th>
<th>Patients with complicated DD (N°/% of screened patients)</th>
<th>Patients with complicated DD requiring surgery (N°/% of screened patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50 yrs</td>
<td>3,218</td>
<td>27 (0.84%)</td>
<td>1 (0.03%)</td>
<td>1 (0.03%)</td>
</tr>
<tr>
<td>50-80 yrs</td>
<td>6,709</td>
<td>1,795 (26.76%)</td>
<td>317 (4.72%)</td>
<td>198 (2.95%)</td>
</tr>
<tr>
<td>&gt; 80 yrs</td>
<td>1,417</td>
<td>465 (32.82%)</td>
<td>90 (6.35%)</td>
<td>51 (3.59%)</td>
</tr>
<tr>
<td>Total</td>
<td>11,344</td>
<td>2,287 (20.16%)</td>
<td>408 (3.59%)</td>
<td>250 (2.20%)</td>
</tr>
</tbody>
</table>

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tis required surgery (1.00% of all the patients with DD, and 0.20% of all the screened patients). The epidemiological studies report that about 1-2% of patients with DD require hospitalisation, and 0.5% require surgery3,13-14.

The results of the 10-year follow-up of the patients either with symptomatic or complicated DD are reported in Table II. All these patients received a cyclic monthly (7 days every month) administrations of rifaximin 800 mg/die for prophylactic purposes.

Along a period of 10 years, a relapsing symptomatology of DD was observed in 112 patients (4.89% of all the patients with anatomical or complicated DD), while new complications of DD (diverticulitis, GI bleeding, etc) were observed in 27 patients (1.18%). No case-control group is available for comparison, since for ethical reasons we have never left untreated patients with symptomatic DD.

### Discussion

The results coming from the first part of our study indicate that the prevalence of DD – either in the uncomplicated or complicated form – in the area (L’Aquila, Abruzzo, Italy) is practically identical to that of other European countries, whose diet is characterized by a low amount of fiber and a high content of calories and refined sugars.

More interestingly, in the second part of our retrospective 10-year survey of patients with DD who were routinely treated with cyclic administration of rifaximin, we have observed incidences of relapsing symptomatology (4.89%) and of new complications (1.18%) that appear to be lower than those reported in published epidemiological investigations.

For instance, in patients with symptomatic uncomplicated DD treated with a fiber only (glucomannan 4 g/day), Latella et al.8 have reported a 3.22% incidence of main complications of DD in a 12-month period, a value which seems to be higher than that we observed (1.18%) in a 10-year period. Moreover, Buttenschoen et al.15 reported that lower GI bleeding is observed in about 10-30% of old people with DD, while in a large series of hospital admissions diverticulitis was the most common complication of DD (51%)16.

Our data therefore encourage us to prospectively investigate in an ad hoc trial the potential of rifaximin for prophylaxis of complications in patients with uncomplicated DD. On the other hand, the use of rifaximin in uncomplicated DD is suggested by the observations that these patients show a low grade of mucosal inflammation that is provoked and maintained by changes in bacterial microflora17. This inflammation may evolve in major DD complications, thus providing a rationale for the use of rifaximin in the prevention of relapses and complication of DD.

<table>
<thead>
<tr>
<th>Age range</th>
<th>No of screened patients with anatomical or symptomatic DD</th>
<th>Patients with relapsing symptomatology (No/%)</th>
<th>Patients with relapsing complications (No/%)</th>
<th>Total n° of relapse (No/%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50 yrs</td>
<td>27</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>50-80 yrs</td>
<td>1,795</td>
<td>79 (4.40%)</td>
<td>19 (1.06%)</td>
<td>98 (5.46%)</td>
</tr>
<tr>
<td>&gt; 80 yrs</td>
<td>465</td>
<td>33 (7.09%)</td>
<td>8 (1.72%)</td>
<td>41 (8.82%)</td>
</tr>
<tr>
<td>Total</td>
<td>2,287</td>
<td>112 (4.89%)</td>
<td>27 (1.18%)</td>
<td>139 (6.08%)</td>
</tr>
</tbody>
</table>
Furthermore, rifaximin has been shown to improve the symptoms in uncomplicated DD, although the mechanism is still to be completely defined. One hypothesis is that rifaximin reduces the metabolic activity of the intestinal bacterial flora, reducing in particular the degradation of dietary fiber and the production of gas. The increase in fecal bulk with identical intake of dietary fiber seen after antimicrobial treatment is probably the result of an increased amount of nondegraded fiber in the feces, which because of their water-holding capacity bulks both the intracolonic content and the feces.

The reduction in fermentation of the fiber obtained by administering antibiotics also leads to a reduction in the production of gas (H₂, CO₂, CH₄) which may induce symptoms such as pain and bloating by the “air trapping” mechanism. Finally, antibiotics may also act by reducing bacterial overgrowth aided by the fecal stasis inside the diverticula, which may be responsible for diarrhea in DD.

A nitibiotics and rifaximin may, therefore, improve symptoms of uncomplicated DD and reduce the incidence of the main complications, by affecting fiber degradation, gas production, and bacterial overgrowth.

References