

## What are the risks of recurrence and complications following acute uncomplicated diverticulitis? Results of a long-term follow-up

Quais os riscos de recidiva e complicações após um episódio de diverticulite aguda não complicada? Resultados a longo-prazo

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### RESUMO

**Introdução e objetivos:** O tratamento de episódios recorrentes de diverticulite aguda não complicada (AUD) e a respetiva seleção para cirurgia eletiva são muito controversos. Propusemo-nos a avaliar o risco de recidiva de AUD e a determinar fatores associados à recidiva complicada e necessidade de cirurgia urgente.

**Métodos:** Efetuámos um estudo retrospectivo, de 311 doentes que recuperaram dum primeiro episódio de AUD, num Centro de referência terciário entre 2001 e 2014.

**Resultados:** Dos 311 doentes que recuperaram do episódio inicial de AUD, 85 (27,3%) recidivaram, maioritariamente no primeiro ano. Na análise multivariada, a obesidade ( $p = 0,038$ ) e idade inferior a 50 ( $p = 0,043$ ) estiveram associadas a maior risco de recidiva. Apenas 4,5% dos doentes desenvolveram doença complicada e os seus fatores preditivos foram Índice de Charlson ajustado à idade ( $ACCI \geq 3$  ( $p = 0,045$ ), imunossupressão ( $p = 0,064$ ) e proteína C-reativa (PCR)  $> 120$  mg/l no episódio inicial ( $p = 0,024$ ). A perfuração ocorreu com maior frequência nos que tiveram apenas um ou dois episódios de AUD ( $p = 0,210$ ).

**Conclusões:** A recidiva ocorre maioritariamente no primeiro ano, sendo mais frequente nos jovens e obesos. A recidiva complicada é pouco frequente e ocorre principalmente na primeira e segunda recidivas.  $ACCI \geq 3$ , imunossupressão e  $PCR \geq 120$  mg/l no primeiro episódio podem ser preditivos de doença complicada e devem ser considerados na ponderação para cirurgia eletiva.

### ABSTRACT

**Objectives:** To assess the risk of recurrence of acute uncomplicated diverticulitis (AUD) and determine factors associated with complicated recurrence and need of emergency surgery. **Background:** The main controversy in AUD is in the treatment of recurrent episodes and appropriate selection for elective resection.

**Methods:** This was a retrospective cohort study of 311 patients after recovery from the first episode of AUD in a tertiary referral Center between 2001 and 2014.

**Results:** Of 311 patients that recovered from the initial episode of AUD, 85 (27.3%) recurred and mainly in the first year. In multivariate analysis, obesity ( $p = 0,038$ ) and age under 50 ( $p = 0,043$ ) were associated with recurrence. Only 4.5% of the patients developed complicated disease and the predictive factors were age-adjusted Charlson index ( $ACCI \geq 3$  ( $p = 0,045$ ), immunosuppression ( $p = 0,064$ ) and C-reactive protein over 120 mg/l during the first episode ( $p = 0,024$ ). Individuals who had only one or two episodes of AUD were at a higher risk for perforation ( $p = 0,210$ ).

**Conclusions:** Recurrence occurs mostly in the first year and more frequently in young and obese patients. Complicated recurrence is uncommon and mainly at first or second recurrences.  $ACCI \geq 3$ , immunosuppression and  $CPR \geq 120$ mg/l at first episode can be predictors of complicated disease and should be considered before recommending elective surgery.

### INTRODUCTION

Acute diverticulitis (AD) is a common disease with increasing incidence, high morbidity and socio-economic costs.<sup>1-3</sup> It occurs in 4-20% of patients with diverticulosis, mainly with uncomplicated disease and 13-36% recur.<sup>1,4-6</sup> Elective surgery has played an important role in the definitive treatment of AD, although the indications have changed dramatically in the last decade.<sup>1,3-7</sup>

Historically, elective surgery was recommended after a second episode of acute uncomplicated diverticulitis (AUD) and for young patients after a solitary episode in order to prevent complicated diverticulitis (ACD) and the possible need for emergency surgery.<sup>8-13</sup> Since 2006, The American Society of Colon and Rectal Surgeons strongly advise that this decision should be individualized, based on reports of low rates of subsequent

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ACD (13-23%) or need for emergency operation (<6%).<sup>1,3,5,12,14</sup> Moreover, the results of elective surgery are imperfect, with an overall morbidity of 7.6% to 19.6% and persistent symptoms in 25% of the patients, even in the laparoscopic era.<sup>4,6,12</sup>

There has been a shift to a more conservative management of AD, but we still must balance the risks and benefits of elective surgery for AUD in each patient. The ideal treatment of recurrent AUD and appropriate selection of these patients to elective surgery remains one of the most controversial issues.<sup>1,4,6,12</sup> The aim of this study was to assess the risk of recurrence of AUD and determine factors associated with complicated recurrence and need of emergency surgery.

## METHODS

We performed a retrospective study of patients admitted between January 2001 and December 2014 for AUD in a tertiary referral center for a population of 728,663 inhabitants.<sup>15</sup> Inclusion was based on clinical diagnosis supported by radiological evidence (ultrasound and/or computed tomography). Exclusion criteria were insufficient data, previous episode, right colon diverticulitis and chronic sequelae or other complications (bleeding, stenosis / obstruction, fistula and suspected neoplasia).

Subsequent ACD was defined as acute inflamed diverticula causing abscess or perforation.<sup>16</sup> The severity of ACD was classified according to the modified Hinchey Classification by Sher et al.: pericolic abscesses (stage I), distant abscesses amenable for percutaneous drainage (stage IIa), complex abscesses associated with a possible fistula (stage IIb), generalized purulent peritonitis (stage III) and fecal peritonitis (stage IV).<sup>17</sup>

The age-adjusted Charlson index (ACCI) was used to assess comorbidity.<sup>18</sup> The ACCI assigns one point each for history of myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disorder, peptic ulcer disease, mild liver disease, and diabetes mellitus (DM) without complications; two points are assigned for hemiplegia, moderate to severe renal disease, DM with complications, tumour without metastases, leukaemia, lymphoma, and myeloma; three points are assigned for moderate

or severe liver disease; and six points are assigned for metastatic solid tumour or acquired immunodeficiency syndrome. One additional point is assigned per decade of age over 49 years.<sup>18</sup>

For this study, the 311 patients that recovered from the initial episode of AUD were separated into two groups for analysis and statistical comparison: non-recurrent and recurrent groups. The recurrent group was further divided in uncomplicated and complicated recurrent groups. The demographic characteristics, baseline clinical parameters, and outcomes of patients in these groups were summarized and compared statistically.

The primary endpoint was recurrence of AUD following complete resolution of the initial episode. Successful medical treatment of AUD with oral or intravenous antibiotic was defined as the resolution of symptoms at the Hospital discharge.

Secondary endpoints were severity of the recurrent episode (uncomplicated versus complicated) and need for emergency surgery. We also evaluated possible predictive risk factors for recurrence and complicated disease.

IBM® SPSS Statistics version 22 was used for all the statistical calculations. Pearson's  $\chi^2$  test and Fisher exact test for  $n < 20$  was used for categorical variables. T test was used for continuous variables with normal distribution while Mann-Whitney was used for continuous variables without normal distribution. Multivariate analysis was performed by logistic regression modeling. Independent variables that reached significance by univariate analysis were compared with the dependent variables of recurrence and complicated disease. Results have been presented as p values, odds ratios with 95% confidence intervals and mean  $\pm$  standard deviation (SD).  $p < 0.05$  was considered statistically significant.

## RESULTS

Patient characteristics are summarized in Table 1. After a mean follow-up of 21 months, the overall recurrence rate was 27.3%. Of the 311 patients that recovered from the initial episode, 226 (72.7%) haven't other episodes of diverticulitis (non-recurrent group) and 85 (27.3%) were readmitted with recurrence (recurrent group). Half of the recurrences occurred in the first 11 months.

■ TABLE 1  
**Patients characteristics and clinical outcomes**

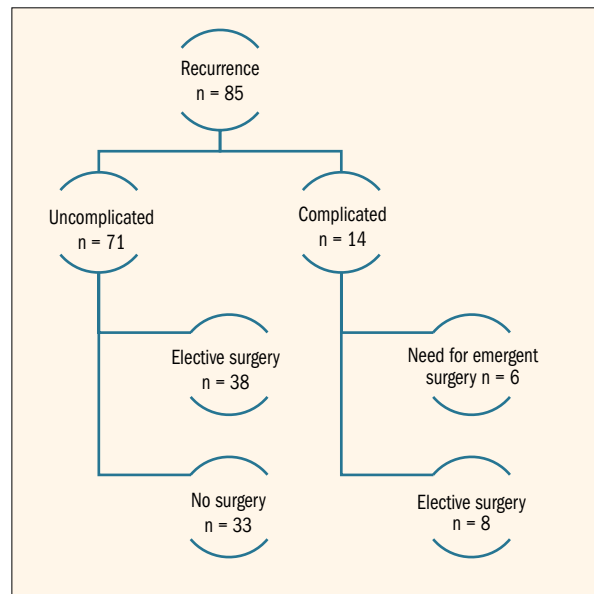
	Patient characteristics, n=311
Age, years < 50 years	61.6 ± 13.6 31 (10)
Sex, men	154 (49.5)
ACCI ≥ 3	2.5 ± 1.8 171 (45)
Imunosupression	14 (4.5)
Obesity	17 (5.5)
Leucocyte count (×10 <sup>9</sup> /l)	1.2 ± 4.2
C-reactive protein (mg/l)	81.1 ± 76.6
Hospital stay, days	5.7 ± 2.8
	<b>Clinical outcomes</b>
Recurrence	85 (27.3)
Re-recurrence	24 (7.7)
Complicated recurrence	14 (4.5)
Need for emergency surgery	6 (1.9)
Elective surgery	46 (14.8)
Mortality	4 (1.3)

Values are median± standard deviation or n (%); ACCI, age-adjusted Charlson index.

The re-recurrence rate was 7.7% (24 patients) in a median time of 3.5 months. We also verified that only 14 patients (4.5%) developed complicated disease and 6 needed emergency surgery (1.9%) - see Figure 1 and Table 1.

### 1 . Recurrent vs non-recurrent group

In multivariate analysis only age under 50 and obesity were significantly related with recurrence (Table 2). The odds for obese were 2.9 (95% CI 1.1-7.9; p=0,038) and for younger patients were



**FIGURE 1:** Flowchart of the management of recurrence after recovery of index episode of uncomplicated diverticulitis.

1.9 (95% CI 1.0-3.6; p=0.043).

### 2. Recurrent complicated vs recurrent uncomplicated group.

The recurrence was uncomplicated in 71 (83.5%) and complicated in the other 14 patients (16.5%) - See Figure 1. The median time for uncomplicated recurrence was 12 months whereas for complicated recurrence was 5 months. The patient characteristics are shown at Table 3.

Of the 71 individuals with uncomplicated recurrence, 33 (46.5%) weren't operated, and 38 (53.5%) were submitted to elective surgery without mortality: 29 (76.3%) after the second episode, seven (18.4%) after the third episode and two (5.3%) following the fourth episode.

In the group of 14 patients who developed complicated recurrence, 8 have complicated at the first recurrence, mainly with free perforation, and 3 complicated at the second recurrence after a median time of 5 and 2 months, respectively. There was need for emergency surgery in 6 patients (5 with Hinchey 3 and 1 with Hinchey 2B) and the remaining 6 patients (Hinchey 1 and 2A) were submitted to elective surgery after successful medical treatment. Hinchey 3 patients were managed with Hartmann's operation with subsequent stoma reversal. The mortality rate of the complicated recurrent group was 14.3%: one

■ TABLE 2

**Demographics and other possible risk factors by recurrence**

	Non-recurrent group, n (%) n=226	Recurrent group, n (%) n=85	p value
<b>Demographics</b>			
Age, y; mean±SD	63.5 ± 13.7	56.5 ± 12.1	0.000
< 50, y	31 (13.7%)	21 (24.7%)	0.021
ACCI	2.7 ± 1.9	2.1 ± 1.7	0.008
< 3	114 (50.4%)	57 (67.1%)	0.009
<b>Other possible risk factors</b>			
Immunosuppression	10 (4,4)	4 (4,7)	0.915
Corticosteroid use	10 (4,4)	4 (4,7)	0.915
CRD	10 (4,4)	3 (1,2)	0.725
Diabetes	32(14,2)	9 (10,5)	0.407
Obesity	8 (3.5%)	9 (10.6%)	0.015
Leucocyte count ( $\times 10^9/l$ )	1.2 ± 0.4	1.2 ± 0.4	0.700
C-reactive protein (mg/l)	79.6 ± 77.5	86 ± 74.0	0.635

Values are median± standard deviation or n (%); ACCI, age-adjusted Charlson index; CRD, chronic renal disease; y, years.

patient with 87 years died before emergency surgery and another with 78 years died with septic shock after Hartmann's procedure.

### 3. Predictive factor for complicated disease

We compared the uncomplicated and complicated groups for possible predictive risk factors - See table 2. Most of the complications occurred at the second episode. We also identified, besides no statistical significance, that patients who had only one or two episodes of AUD were at a higher risk for perforation than patients with more than two episodes ( $p=0.210$ ). Age did not affect the likelihood of developing complicated disease ( $p=0.78$ ). The mean ACCI for complicated recurrence was higher than for the uncomplicated group ( $p=0.045$ ). A CRP over 120 mg/l during the first episode was associated with complicated recurrence (OR=5.1;  $p=0.024$ ). Multivariate analysis didn't identify any positive association

with complicated disease, perhaps by the small number of patients in this group.

### DISCUSSION

There aren't criteria to define and distinct recurrent and persistent diverticulitis. We defined successful medical treatment of AUD as the resolution of symptoms at the Hospital discharge and this could lead to inclusion of patients with persistent disease with raised CRP. Under this assumption, in the present study, the majority of patients of AUD followed a benign course with recurrence in 27.3% of the individuals, similar to recent studies that report it to be 13% to 36%.<sup>5,6</sup> Few studies provide data of re-recurrence, revealing it to be uncommon (<6%).<sup>6,19,20</sup> We identified a re-recurrence rate of 7.7%, which is slightly higher.

In multivariate analysis, obesity and age were statistically associated with recurrence. Recent

■ TABLE 3

**Demographics and other possible risk factors by complicated recurrence**

	Uncomplicated recurrence, n (%) n = 71	Complicated recurrence, n (%) n = 14	p value
<b>Demographics</b>			
Age, y	56.3 ± 11.1	57.4 ± 16.6	0.569
< 50, y	18 (25.4)	3 (21.4)	0.518
Sex, men	42 (59.2)	8 (57.1)	0.9
ACCI	1.9 ± 1.6	2.6 ± 1.5	0.045
ACCI > 3	15 (21.1)	5 (35.7)	0.518
<b>Other possible risk factors</b>			
Immunosuppression	2 (2.8)	2 (14.3)	0.125
Corticosteroid use	2 (2.8)	2 (14.3)	0.125
CRD	2 (2.8)	1 (7.1)	0.421
Diabetes	7 (9.9)	2 (14.3)	0.457
Obesity	8 (11.3)	1 (7.1)	0.543
Number of previous episodes	1.4 ± 0.7	1.9 ± 1.2	0.073
≤ 2 episodes	64 (90.1)	11 (78.6)	0.210
> 2 episodes	7 (9.9)	3 (21.4)	
Time for second episode	17.6 ± 19.4	13.8 ± 18.7	0.226
Time for third episode	9.7 ± 15.8	6.3 ± 11.2	0.406
Leucocyte count (×10 <sup>9</sup> /l)	1.2 ± 0.4	1.3 ± 0.4	0.237
CRP (mg/l) ≥ 120	74.8 ± 69.3 7 (9.9)	122.0 ± 80.6 5 (35.7)	0.043 0.024

Values are median ± standard deviation or n (%); ACCI., age-adjusted Charlson index; CRD, chronic renal disease; y, years; CRP, C-reactive protein.

studies have reported an increasing incidence of AD in younger patients, ranging from 18% to 34%.<sup>21-23</sup> In our study 10% of the individuals were younger than 50 years and recurred twice the older patients, however this was not associated with more complications. Obesity, which has been steadily increasing in developed countries has been recognized as an important risk factor

for developing diverticulitis in several long term cohort studies.<sup>24</sup> A Swedish study showed that a BMI ≥30 kg/m<sup>2</sup> gave a RR of 4.4 of being hospitalized with symptomatic diverticular disease over a 28-year follow-up.<sup>25</sup>

Like reported in modern studies by Buchs<sup>7</sup>, Eglinton<sup>19</sup> and Hall *et al*<sup>26</sup>, in this study, complicated recurrence was uncommon (4.5%), however

53,5% of our patients with recurrent AUD were submitted to elective surgery, mainly before the adoption of current conservative guidelines.

In this study, 27.3% of the patients recurred, mainly in the first year and of these 16.5% had complicated disease that commonly emerged in the second episode (74.6%). The re-recurrence rate was low (7.7%) and free perforation occurred only in first and second recurrences. So, the majority of complicated disease (71.4%) occurred at the second episode.

We didn't find a statistical relation between the number of recurrences and complications, confirming recent works that suggests that multiple episodes of diverticulitis are not associated with increased mortality or increased risk of ACD.<sup>5, 27</sup> Recently, three studies reported ACD as being more common in the first or second episode of AD compared to those with more than two.<sup>27-29</sup> We also identified, besides no statistical significance, that patients who had only one or two episodes of AUD were at a higher risk for perforation than patients with more than two episodes (OR=2.5; 95% CI 0.56-11.13; p=0.210).

Comorbidities are generally predictive of more severe disease.<sup>30</sup> Lorimer et al. identified a Charlson score of 3 as being predictive of ACD.<sup>29</sup> In our work, the mean ACCI for complicated recurrence was 2.6 points, 0.7 points higher than for the uncomplicated group, (p=0.045). However, we didn't observe statistical significance for ACCI of 3, perhaps by the small number of patients in this group.

Patients with immunosuppression and CRD have a significantly greater risk of recurrent, complicated diverticulitis requiring emergency surgery.<sup>5</sup> In our study immunosuppression was only due to corticosteroid use and the odds for recurrence were of almost sixfold. However, this finding wasn't statistical significant due to the small number of patients (Pearson's  $\chi^2$  test of 0,064 and Fisher test for small n of 0,125). The odds for CRD patients were of 2.7 but with no statistical relevance, maybe for the same motive.

Recent evidence suggests that CRP is the most sensitive serological marker in AUD, and that a concentration above 150-200 mg/l may be correlated with perforation.<sup>28,30-33</sup> It was also proposed that a CRP level exceeding 50 mg/l should

be included in the diagnostic criteria for AD.<sup>34</sup> Surprisingly, in our study, a raised CRP (over 120 mg/l) during the first episode was associated with following complicated recurrence (OR=5.1; 95% CI 1.3-19.5; p=0.024). This is in agreement with Buchs et al. who reported that a raised serum level of CRP (over 240mg/l) during the first episode of AUD was associated with recurrence in the first six months.<sup>7</sup>

This study is limited by its retrospective nature. Future prospective research with extended patient follow-up evaluating the long-term consequences of non-operative treatment and comparing quality of life with those submitted to surgery may determine patients prone to recur who would benefit from prophylactic surgery after AUD.

## CONCLUSIONS

Our study has demonstrated that after an episode of AUD recurrence is common in the first year and more frequent in young and obese. We also found that the incidence of complicated recurrence is low and the majority presents at first or second recurrence in the first six months. Based on our data, ACCI $\geq$ 3, immunosuppression and high CPR at first episode can be predictors of complicated recurrence and should be considered before recommending elective surgery. ■

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