



## Natural history of acute diverticulitis

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### Introduction

Diverticulosis is common in Western industrialized countries, has a similar prevalence in both sexes, and increases with age<sup>1</sup>. Although most patients remain asymptomatic throughout life, up to a quarter will experience acute diverticulitis (AD).<sup>2</sup>

While there are some clear indications for emergent/urgent surgery in acute diverticulitis<sup>2,3</sup>, the indications for elective prophylactic colectomy following an acute episode of acute diverticulitis are less clear.

In 1995 the American Society of Colon and Rectal Surgeons (ASCRS) guidelines recommended elective colectomy after a second episode of AD to prevent further recurrence and to reduce the operative risk associated with an emergency operation.<sup>4</sup> These guidelines, confirmed at the end of the 1990<sup>5</sup>, by others important Scientific Society<sup>5,6</sup>, were based upon only two studies about natural history of diverticulitis<sup>7,8</sup> presenting several bias: few recruited patients, retrospective and wide range of follow up and

unclear diagnosis of diverticulitis with a risk of overlapping with irritable bowel syndrome.<sup>9</sup>

Subsequent follow-up<sup>10,11</sup> and modelled analysis studies<sup>12-15</sup> questioned this management showing a substantial reduction in the estimated risk of recurrent AD and emergency surgery with related necessity of stoma or death.

In 2006 the ASCRS modified its previous statement, suggesting a more cautious approach to elective surgery with case-by-case evaluation, as the ideal treatment was still a matter of debate because the long-term history of patients treated for AD was unclear.<sup>16</sup>

The aim of this paper is to summarize the recent literature regarding course of patients treated nonoperatively for AD focusing on risk of recurrence, severe complications and related death and to analyze possible factors affecting the natural history of AD.

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### Risk of Recurrence

Outdated literature from the 1960s suggested a high recurrence rate (>40%) and a worse clinical presentation after each subsequent attack with less chance of conservative treatment.<sup>7</sup>

More recent studies showed a milder course of the disease. This is related mainly to an improved diagnosis of AD and recurrence with TC confirmation and to the routine introduction of dietary recommendations, the larger use of

antibiotics and a more meticulous monitoring of the clinical course. Considering retrospective, modelled analyzed and rare prospective studies reported in the last decade, with a minimum follow-up of 5 years, the incidence of recurrence is extremely variable ranging between 2 and 48% (medium 25.8%) although a clear tendency toward reduction of incidence in well designed and larger studies is confirmed (Table 1).

Author, year	Total	MT	Type	Mean f- u	Recurrence	Em. Surg	Stoma	Death
Chautems, 2002 <sup>18</sup>	118	118	P	9.5 y	37 (31%)	0	0	0
Broderick-Villa, 2005 <sup>12</sup>	3165	2551	MA	8.9 y	314 (13.3%)	NR	NR	NR
Anaya, 2005 <sup>13</sup>	25058	20136	MA	1-14 y	3828 (19%)	NR	NR	NR
Salem, 2007 <sup>19</sup>	163	163	P	5 y	2 (1.7%)	0	0	0
Shaikh, 2007 <sup>20</sup>	232	191	P	1-15 y	NR	9 (4.7%)	NR	1 (0.5%)
Eglinton, 2010 <sup>21</sup>	502	320	R	9 y	75 (23.4%)	10 (3%)	NR	0
Frileux, 2010 <sup>22</sup>	222	128	R	5-12 y	55 (43%)	7 (5.5%)	5 (3.9%)	1 (0.8%)
Klarenbeek, 2010 <sup>23</sup>	291	111	R	9-19 y	88 (48%)	NR	NR	NR
Hall, 2011 <sup>24</sup>	954	672	R	5 y	242 (36%)	27 (3.9%)	NR	NR
Binda, 2012 <sup>25</sup>	1043	320	P	10.7 y	55 (17.2%)	22 (6.9%)	3 (0.9%)	0

Table 1: MT=Medical Treated; P=Prospective; MA=Modelled Analysis; R=Retrospective; NR=Not Reported

Over the years a definition of the interval of time in which most recurrences occur has been debated with no agreement. While some concluded that first 2-year after the initial AD is the higher risk period<sup>21,26</sup> others that a 5-year period is more appropriate<sup>7,27</sup>.

In our experience, after a mean follow up of 10.7 years, 60,9% were asymptomatic, 21,9% presented recurrent symptoms and the 12 years actuarial cumulative risk of recurrence is 21.2%, homogeneously distributed over the entire observation time.<sup>25</sup>

## Risk of severe complications, emergency surgery and death

The risk of severe complications with related risk of emergency surgery, stoma formation and death is the main matter of concern and should drive studies and subsequent policy of treatment.

Reviewing literature data published in the last 10 years, the risk of severe complication for complicated recurrent episode of AD is low with a rate of emergent surgery ranging from 0 to 6.9%, risk of stoma formation ranging from 0 to 3.9%, and rate of related death inferior to 1%. (table 1).

A recent nationwide study by Ricciardi<sup>28</sup> based on 685,390 hospital discharges for sigmoid diverticulitis from 1991 to 2005, showed that the proportion of patients who underwent surgery for uncomplicated diverticulitis significantly decreased from 17.9 to 13.7%.

Throughout the study period, the percentage of patients with free perforation from AD did not vary despite an increasing ratio of hospital discharges for diverticulitis from 5.1 to 7.6 cases per 1,000 inpatients.

Although based on retrospective administrative data, this study confirms that a less aggressive strategy is not associated with an increase in complicated diverticulitis at recurrence and confirm previous results that after recovering from an episode of diverticulitis the risk of an individual to require an urgent Hartmann's procedure is 1 in 2,000 patients/years of follow-up<sup>9</sup>.

In our experience, the 12 years actuarial cumulative risk of emergency surgery is 8.3%, while risk of stoma is less than 1% with no related mortality<sup>25</sup>

## Risk factors

Several studies analyzed possible predictors for recurrent or complicated AD to identify the small part of patients with a previous AD may benefit from an elective resection. Main risk factors taken into account were previous episode of AD, age, degree of diverticulitis at CT scan, chronic use of drugs, comorbidities and familiarity

*Number of previous attacks.* The number of attacks of diverticulitis has been used as an indication for elective surgery based on the assumption that the risk of recurrence increases with each episode of AD and that recurrent AD less responds to medical treatment<sup>7,8</sup>.

Previous guidelines have recommended elective colectomy after two attacks<sup>4,6</sup>; Richards<sup>15</sup> after a third episode, whereas Salem<sup>14</sup> after a fourth attack. More recent literature<sup>21</sup> support the proposal that the number of attacks of diverticulitis alone should not be used as an indication for surgery.

Moreover for several years pertinent literature claimed that at each further episode there were less chances of response to medical treatment and an increasing risk of severe complications as high as 60% with a doubling of the mortality rate.<sup>4</sup>

More recently many studies have questioned these indications primarily because the majority of patients experiences an acute severe complication at their first presentation of diverticular disease and AD is not a good predictor for the development of further complications such as perforation, fistula or abscess<sup>29</sup>. In a recent study on 2950 patients with complicated diverticulitis, most patients (2133 (72.3%)) had suffered no prior episodes of AD; increasing episodes of AD were associated with an increased risk of developing a fistula, but there was no clear relationship with stricture or perforation/abscess.<sup>30</sup> Consequently, surgery at admission is less frequent among patients who present with a recurrence and no appreciable differences in operative complications, morbidity or mortality rates.<sup>31</sup>

A recent meta-analysis on the risk factors for free perforation due to sigmoid diverticulitis shows that the risk decreases with the number of previous episodes: from 25% during the first episode to 12.7% during the second, 5.8% the third and 0.9% the fifth ( $p = 0.001$ ).<sup>32</sup>

It has been suggested that previous attacks of AD may actually protect against free perforation through adhesion of the omentum or the small bowel to the site of perforation.<sup>29</sup>

In our experience although history of at least three episodes of AD were associated with an increased risk of AD recurrence, 88% of patients with free perforation were at their first episode of AD.<sup>25</sup>

In conclusion the most recent guidelines published by the Standards Committee of the American Society of Colon and Rectal Surgeons which state: "The number of attacks of diverticulitis is not an overriding factor in defining the appropriateness of surgery"<sup>16</sup>.

*Age.* Although hospital admission for AD is increasing in younger patients (lower than 45 years old)<sup>33</sup>, it is still controversial whether young age represents an independent risk factor of AD recurrence. It has been reported that younger patients are more prone to recurrent disease and more frequently require surgery for complicated diverticulitis<sup>34-37</sup>, supporting the recommendation of elective surgery after their first episode of uncomplicated diverticulitis<sup>4,6</sup>.

The previously mentioned large register study of Anaya<sup>13</sup> found that younger patients (<50 years) had greater risk of recurrence than older patients (27 % vs. 17 %,  $p < 0.001$ ) and more often underwent emergency resection or colostomy at relapse (7.5 % vs. 5 %,  $p < 0.001$ ). But even in a population under age 50 it would be necessary to operate 13 individuals to avoid one acute resection and/or colostomy. Furthermore mortality by emergency surgery in younger patients (< 50 years) was only 0.2 % as opposed to 3.4 % in older patients ( $p < 0.001$ ).

More recently Faria<sup>38</sup> confirmed that recurrent diverticulitis was significantly more frequent in younger patients (<50 years) with a shorter mean time to recurrence, but none required emergent surgery, coming to the conclusion that diverticulitis management should be based on the severity of the disease rather than on the age of the patient.

In our experience<sup>25</sup> patients younger than 40 years had a threefold increased risk of recurrent AD compared with those aged 40 years or more.

In conclusion patients younger than 40 years, although having an increased risk of AD recurrence, seem not show a higher risk of subsequent emergency surgery during follow-up, as previously suggested.

### *CT Degree of Diverticulitis*

Based on Ambrosetti's classification<sup>39</sup>, the degree of diverticulitis on CT is predictive of long-term outcome. After successful medical

treatment of the acute episode, patients with severe diverticulitis on the CT (defined by wall thickening accompanied by abscess, extraluminal air or extraluminal contrast) had a statistically greater incidence of secondary bad outcome than patients with moderate (defined by wall thickening of  $\geq 5$  mm and signs of inflammation of pericolic fat) diverticulitis (36 vs. 17%)<sup>40</sup>. Hall<sup>24</sup> in a retrospective study on 672 patients followed up for 5 years after a first episode of AD and based on CT scan observed in a multivariate analysis as leftsided AD, a length of 15 cm of involved colon and a retroperitoneal abscess were predictors for recurrence.

### *Drugs*

Immunosuppressive therapy (including steroids) and nonsteroidal anti-inflammatory drugs (NSAIDs), have previously been identified as risk factors for complicated sigmoid diverticulitis and its severity.<sup>29,41</sup>

In a recent systematic review on twenty-five studies about the clinical course of diverticular disease in immunosuppressed patients and patients on chronic corticosteroid therapy, Authors concluded that these patients have a rate of acute diverticulitis and associated mortality (23% in surgically and 56% in medically treated patients) higher than the baseline population<sup>42</sup>.

About NSAIDs, cohort study on 47,210 US men showed that aspirin had a hazard ratio of 1.25 for diverticulitis, whereas NSAIDs regular users had a hazard ratio of 1.72.<sup>43</sup>

Wilson<sup>44</sup> in a prospective study found that NSAIDs intake during the previous days was reported in 34% of 92 patients admitted to hospital for AD.

Other investigations have examined the potential benefit of different drugs in the treatment of uncomplicated diverticular disease for modifying its natural history.

Uncontrolled studies found that mesalazine with or without rifaximin decreases recurrent episodes of diverticulitis and prevents main complications.<sup>45,46</sup>

In the same setting, the role of probiotic therapy through the correction of the possible action of altered peridiverticular microflora are

suggested, but studies enrolled small sample size without a placebo arm.<sup>47,48</sup>

In a study on 120 patients with perforated colonic diverticular disease<sup>49</sup>, calcium channel blockers showed a protective action. If confirmed, they could be the ideal prophylaxis in patients with more than 2 episodes of AD and in old patients affected by diverticular disease and with a recent diagnosis of mild or moderate hypertension.

### *Familiarity*

This hypothetical risk factor is analyzed only in the study by Hall<sup>24</sup>; it shows, in a multivariate analysis, that familiar history of AD is related to recurrence but it is difficult to differentiated genetic predisposition (genetic tissue defects as Marfan, Ehlers-Danlos, Williams-Buren syndrome)

from environmental factors (diet, fiber) and further study must be addressed to clarify this issue.

### *Comorbidities*

In an American cohort analysis, immunocompromised patients (organ transplant recipient, patients receiving chemotherapy or taking immunosuppressive therapy, having chronic renal failure, diabetes or collagen-vascular diseases) had a significant fivefold greater risk (36 vs. 7%) of a perforation in recurrent episodes of diverticulitis.<sup>50</sup>

According to others Authors these patients may benefit from early elective resection after a conservatively treated episode of diverticulitis.<sup>23,4</sup>

In a more recent study<sup>51</sup>, instead, patients with immunosuppression had a significant higher mortality rate than non-immunosuppressed patients, but only during their first episode of AD. After this first episode there is more risk of dying from other diseases than from complications of diverticulitis.

They concluded that "after successful medical treatment of acute diverticulitis, patients with immunosuppression need not be advised to have an elective sigmoidectomy".

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## Conclusion

Considering that the majority of patients experiences an acute severe complication at their first presentation of diverticular disease, most of patients remained asymptomatic after medical treatment, few patients developed

recurrent diverticulitis and finally the risk of further emergent surgery was low, and the risk of diverticular disease-related death was almost zero, this lecture does not support an

aggressive surgical policy in patients medically treated for an acute episode of diverticulitis. Although published in 2006<sup>16</sup>, guidelines by the Standards Committee of the American Society of Colon and Rectal Surgeons about elective resection after an AD are still current: "Decision should be made on a case by case basis" influenced by different factors including

age, frequency and severity of attacks and persistence of symptoms affecting quality of life, comorbidities and use of immunosuppressive therapy or NSAIDs. Any recommendation for routine elective resection following AD should await results of randomized studies

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