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Abstract

Background: A recurrent episode of diverticulitis is a new distinct episode of acute inflammation after a period of complete remission of symptoms. Outdated literature suggested a high recurrence rate (>40%) and a worse clinical presentation with less chance of conservative treatment. More recent studies showed a more benign course with no need toward an aggressive policy of treatment. ***Methods:*** We report data from revised literature and from our study: a 4-year multicenter retrospective and prospective database analysis of 743 patients hospitalized for acute diverticulitis (AD) treated medically or surgically and then followed for a minimum of 9 years. ***Results:*** The literature showed a recurrence rate of 25–35% at 5 years of follow-up, with a reduced risk of severe complications (i.e. perforations), a risk of subsequent emergency surgery of 2–14% and a risk of stoma and related death of 0–2.7%. Several risk factors of recurrence have been advocated: family history, abscess, severe CT stage, comorbidities (renal failure, collagen vascular disease) and nonsteroidal anti-inflammatory drugs. Young age is still a matter of debate. These studies have different limitations: retrospective, lack of definition of AD, small number of patients, long recruiting time, short follow-up, study population or hospital-system based. In our study of 320 followed-up, medically treated patients, 61% were asymptomatic and 22% complained of chronic symptoms: the 12-year actuarial risk of recurrence, emergency surgery, stoma and death was 21.2, 8.3, 1 and 0%, respectively. Recurrence was related to very young age (<40 years) and more than 3 previous episodes of AD. ***Conclusion:*** This study confirms the benign course of diverticulitis treated conservatively, with a low long-term risk of serious complications and death, and does not support an aggressive surgical policy to prevent them.

Key Words

- Diverticulitis
- Risk of recurrence
- Subsequent surgery

Definition

Recurrent diverticulitis is defined as a new episode of acute diverticulitis (AD) assessed by clinical and radiological findings after complete remission of symptoms related to a well-documented previous episode of AD. The time interval claimed necessary to distinguish between the two episodes varies among authors, ranging between 1 [1], 2 [2,3] and 3 months [4].

Clinical Presentation

Similarly to the first attack, recurrent sigmoid diverticulitis generally presents with abdominal pain typically located in the left lower quadrant associated with a variable degree of peritoneal irritation. Local and general symptoms can worsen to generalized peritonitis and sepsis. The decision regarding whether to hospitalize a patient with diverticulitis depends upon several factors, including the severity of presentation, the ability to tolerate oral intake, the presence of comorbid diseases, and the available support system. Patients selected for outpatient management should be reliable and understand the indications for seeking immediate medical attention. These include an increase in fever or abdominal pain or the inability to consume adequate fluids. As a general rule, the elderly, immunosuppressed, those with significant comorbidities, and those with high fever or significant leukocytosis should be hospitalized.

Sometimes clinical manifestation of sigmoid diverticulitis is difficult to be interpreted especially in patients with a concurrent history suggestive for irritable bowel syndrome. Efforts should be made to avoid misdiagnosis that could lead to unnecessary surgery. Egger et al. [5] have showed that, despite technically successful surgery for diverticular disease, up to 25% of patients suffered persistent symptoms, including painful constipation, painful abdominal distension, abdominal cramps, and frequent painful diarrhea, at least partially due to an overlap with irritable bowel syndrome. Atypical clinical presentations include smoldering diverticulitis and segmental colitis associated with diverticulosis (SCAD). The former is diagnosed in a subgroup of patients with chronic left lower quadrant abdominal pain, occasional alteration of bowel habits, without fever or leukocytosis, that never develop AD for which surgery is curative in most of the cases. In a series of 930 patients who underwent sigmoid resection for diverticular disease, 47 (5%) had symptoms consistent with smoldering diverticular disease: all had chronic left lower quadrant pain for more 6 months (mean 93 months) and some also had an alteration in bowel habits or rectal bleeding. Acute or chronic inflammatory changes were present in 76% of resected specimens. Complete resolution of symptoms occurred in 77%, with 88% becoming pain free [6]. SCAD is a nonspecific localized inflammatory process; its pathogenesis and relationship with inflammatory bowel disease are still unclear. It most frequently affects middle-aged or elderly patients and is responsive to 5-aminosalcylate therapy [7].

Imaging and Diagnosis

In the absence of specific hematologic tests, imaging covers a crucial role in diagnosis and staging of AD.

Nowadays, computerized tomography (CT) has become the optimal method of investigation and is considered the most reliable diagnostic tool for any abdominal pain suspected for AD. Due to the possibility of combination with endoluminal contrast enema, it has replaced the use of standard radiology by gastrografin enema. First reports are dated in the early 1990s, but it was only at the end of the 1990s that the technique had a wide diffusion in emergency settings. CT helps to establish differential diagnosis with urologic and gynecologic disease and it can provide additional information to separate moderate from severe AD. This way it can predict the chance of medical treatment failure, which is as high as 26% for severe diverticulitis versus 4% for the moderate clinical pictures [8,9].

Although more operator-dependent than CT, ultrasonography has been proposed as an equivalent diagnostic tool in regard to diagnosis or exclusion of AD [10]. Recent studies have confirmed its reliability so that its use has been suggested in all settings where a CT scan is not available [11,12].

Risk of Recurrence

Incidence and Time Interval

Outdated literature from the 1960s suggested a high recurrence rate (>40%) and a worse clinical presentation with less chance of conservative treatment. More recent studies showed a milder course of the disease. This might be related to the routine introduction of dietary recommendations, the larger use of antibiotics and a more meticulous monitoring of the clinical course. Considering cohort and modeled analyzed 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 43% although a clear tendency toward reduction of incidence is confirmed [13,14,15,16] (table 1).

Study	Total n	Follow-up (mean or range), years	Type	Medically treated, n	Recurrence n (%)	Emergent surgery n (%)	Stoma n (%)	Death n (%)
Chautems et al. [21], 2002	118	9.5	P	118	37 (31)	0	0	0
Broderick-Villa et al. [13], 2005	3,165	8.9	MA	2,551	314 (13.3)	N/A	N/A	N/A
Anaya and Flum [14], 2005	25,058	1–14	MA	20,136	3,828 (19)	N/A	N/A	N/A
Salem et al. [15], 2004	163	5	P	163	2 (1.7)	0	0	0
Shaikh and Krukowski [57], 2007	232	1–15	P	191	N/A	9 (4.7)	N/A	1 (0.5)
Eglinton et al. [17], 2010	502	9	R	320	75 (23.4)	10 (3)	N/A	0
Frileux et al. [56], 2010	222	5–12	R	128	55 (43)	7 (5.5)	5 (3.9)	1 (0.8)
Hall et al. [1], 2011	954	5	R	672	242 (36)	27 (3.9)	N/A	N/A
Binda et al. [3], 2012	1,043	10.7	P	320	55 (17.2)	22 (6.9)	3 (0.9)	0

P = Prospective; MA = modelled analysis; R = retrospective; N/A = not applicable.

Table 1. Risk of recurrence, emergent surgery, stoma and related death for recurrent AD reported in the literature in the last 10 years

Over the years a definition of the interval of time in which most recurrences occur has been debated with no agreement. While some concluded, according to their experience, that a 2-year interval is a sufficient range of time [17,18] others believe that a 5-year interval is more appropriate [19,20].

Risk Factors

Age

It is still controversial whether young age, generally defined as lower than 50 years, 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, supporting the recommendation of elective surgery after their first episode of uncomplicated diverticulitis [21,22,23,24,25]. In a recent study, no differences in the rate of successful conservative treatment were observed between patients at the first episode and those with recurrence with regard to age, suggesting that age is not a predictive factor of poor outcome [26]. Faria et al. [27] reported 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. A retrospective review found that only 1 of 196 medically managed patients <50 years old suffered from frank perforation during a median follow-up period of 5 years [28].
Similarly, the cut-off age (40 or 50 years) to identify patients at increased risk of relapse, because of an early age at onset of the disease, is also controversial. Some studies [24,25] evidenced that patients younger than 40 years of age had a significantly increased risk of AD recurrence. If confirmed in larger series, this finding can be relevant in view of the growing number of very young patients undergoing emergency surgery for AD in recent years [29]. However, patients younger

than 40 years, although having an increased risk of AD recurrence, did not show a higher risk of subsequent emergency surgery during follow-up, as previously suggested [21,24,25].

After Surgery

Patients who are treated operatively are usually cured, with the development of new diverticulitis in the remaining colon occurring in only 15% [30], and a need for further surgery in 2–11% [30,31]. However, up to 27% of these patients may describe abdominal pain postoperatively in the same location; these persistent symptoms may be explained by coexistent irritable bowel syndrome rather than recurrent diverticulitis. In a historical report by the Mayo Clinic, in a group of 501 patients followed up after bowel resection for diverticular disease, the rates of AD recurrence and emergency surgery were 10.4 and 3%, respectively [32]. Other series reported postsurgical AD recurrence rates between 1 and 10% and re-operation rates from 0 to 3% [33,34].

Comorbidities

Although it is not clear if immunocompromised patients (organ transplant recipient, patients receiving chemotherapy or taking immunosuppressive therapy) have a higher risk of AD, studies support that they are more likely to have a complicated diverticulitis with perforation or abscess formation [34].
Moreover, risk factor analysis showed that those patients using immunosuppression 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. Therefore, these patients may benefit from early elective resection after a conservatively treated episode of diverticulitis [35,36].

Degree of Diverticulitis

Based on Ambrosetti's classification, 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 had a statistically greater incidence of secondary bad outcome than patients with moderate diverticulitis (36 vs. 17%) [9,37]. Hall et al. [1] 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 left-sided AD, a length of >5 cm of involved colon and a retroperitoneal abscess were predictors for recurrence.

Family History

Only one study [1] shows that a family history of AD is related to recurrence after an initial episode of AD calculated in a multivariate analysis. 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.

Drug

Drugs which certainly have a role in favoring diverticulitis including recurrence are nonsteroidal anti-inflammatory drugs (NSAIDs) and immunosuppressors including steroids.
NSAIDs including aspirin are associated with an increased risk of diverticulitis. A cohort study on 47,210 US men showed that aspirin had an hazard ratio of 1.25 for diverticulitis, whereas NSAIDs regular users had a hazard ratio of 1.72 [38].
Wilson et al. [39] in a prospective study found that NSAIDs intake during the previous days was reported in 34% of 92 patients admitted to hospital for AD.

Immunosuppression and especially intake of steroids have previously been identified as risk factors for complicated sigmoid diverticulitis and its severity [36,40]. Histopathological studies have demonstrated that inflammation mediated by activated macrophages might represent the cellular link between steroid use and complicated diverticulitis [41].
Some investigations have examined the potential benefit of anti-inflammatory drugs such as 5-ASA +/– rifaximin in the treatment of uncomplicated diverticular disease for modifying its natural history. Uncontrolled studies found that mesalazine decreases recurrent episodes of diverticulitis and prevents main complications [42,43]. 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 [44,45].
In a study on 120 patients with perforated colonic diverticular disease [46], 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.

Risk of Severe Complications

Following successful conservative therapy for a first attack of diverticulitis, approximately one-third of patients will remain asymptomatic, one-third will have episodic abdominal cramps without frank diverticulitis, and one-third will proceed to a second attack of diverticulitis [1,18,47,48,49]. For several years pertinent literature claimed that after 2 attacks of uncomplicated diverticulitis, at each further episode there was progressively a higher probability of recurrent attacks with less chances of response to medical treatment and an increasing risk of complicated diverticulitis as high as 60% with a doubling of the mortality rate. These data have been the foundation for recommending an operation after a second attack [33,47].
More recently many studies have questioned these indications primarily because the majority of patients experiences an acute 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 [15,19,50,51]. Furthermore, recurrent episodes of uncomplicated diverticulitis do not lead to failure of a conservative treatment or to an increased risk for poor outcomes if they develop complicated diverticulitis [51,52,53]. Consequently, surgery at admission is less frequent among patients who present with a recurrence [53]. No appreciable differences in operative complications, morbidity or mortality rates were reported in recent literature [51,52]. Considering the site of recurrence, a recent study by Gervaz et al. [2] shows that recurrence after an uncomplicated episode of AD in 35% of cases affects a different segment of colon than the previous episode.
Perforation is commonest during the first episode of AD and it occurs more often in patients with 1 or 2 prior attacks compared with patients with multiple episodes of diverticulitis. A recent meta-analysis on the risk factors for free perforation due to sigmoid diverticulitis [54] 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 ($p < 0.001$). 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 [51]. A recent nationwide study by Ricciardi et al. [55] 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 [55]. In fact, 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 [32].
In conclusion, reviewing literature data published in the last 10 years (table 1), the risk of severe complication for complicated recurrent episode of AD is low with a rate of emergent surgery ranging from 0 [15,21] to 5.5% [56], risk of stoma formation ranging from 0 [15] to 3.9% [56], and rate of related death ranging from 0 [17,21] to 0.5% [57].

Our Study

In order to gather information on the natural history of complicated colonic diverticular disease, a joint study group, the Italian Study Group on Complicated Diverticulosis (GISDIC) was formed in 1997 [3]. All consecutive patients with left-sided AD diagnosed clinically (abdominal pain, associated with leukocytosis ($>11 \times 10^9$) and/or fever >38°C) and confirmed by imaging (CT scan, ultrasonography, water-soluble contrast enema) either alone or in combination and/or by operative findings, entered the study.
To ensure expeditious collection of data from a suitable sample size of well documented patients, we recruited patients over a 4-year period (1996–1999); information on those admitted in 1996 and 1997 was retrospectively accrued from clinical records, while data on patients treated between 1998 and 1999 were entered into the database prospectively on hospital admission.
The primary endpoint was to assess the rate of recurrence of AD requiring hospitalization during the follow- up period. Additional endpoints were to assess the risks of emergency surgery, stoma and disease-related mortality during follow-up. The following data were collected: persistence or recurrence of chronic symptoms attributable to complicated diverticular disease, new episodes of AD, new hospital admissions for AD, type of treatment and outcome. Recurrence was defined as a new episode of AD requiring hospitalization that had occurred at least 2 months after complete resolution of the index episode that resulted in inclusion in the study. A standardized flow sheet was used to collect data on medical history, diagnostic work-up, type of treatment and follow-up to create a dedicated database.
Between January 1996 and December 1999, 1,046 patients were recruited; 303, for different reasons, did not meet the inclusion criteria. Of the remaining 743 eligible patients, 407 (54.8%) were registered retrospectively and 336 (45.2%) prospectively. Patient characteristics are shown in table 2. Of these, 126 (24%) reported at least one previous episode of AD and 76 (14.8%) had been previously hospitalized for the disease. There was no significant difference in any of the investigated characteristics between the retrospectively and the prospectively enrolled patients.

	Total n (%)	p value
Gender		
Male	320 (43.1)	
Female	423 (56.9)	0.92
Age		
<40 years	26 (3.5)	
40–49 years	67 (9.0)	
50–59 years	101 (13.6)	
60–69 years	167 (22.5)	
70–79 years	226 (30.4)	
≥80 years	156 (21.0)	0.15
Diagnosis of diverticular disease		
Disease previously unknown	228 (30.7)	
Year of enrolment	336 (45.2)	
1–5 years before enrolment	97 (13.1)	
>5 years before enrolment	82 (11.0)	0.21
Previous episodes of AD		
None	617 (83.1)	
1	79 (10.6)	
≥2	47 (6.3)	0.21
Previous hospital admissions due to AD		
None	667 (89.8)	
≥1	76 (10.2)	0.75
Severe co-morbidity		
Absent	311 (76.4)	
Present	96 (23.6)	0.48

Table 2. Characteristics of eligible patients admitted to hospital for acute left-sided diverticulitis between 1996 and 1999

Medical treatment (MT) was administered in 501 (67.4%) patients. In all, 242 (32.6%) patients underwent surgery (ST): of these 67 (28%) patients had Hinchey stage 3 or 4 disease.
Follow-up data were collected prospectively on 474 (64.8%) of 731 patients: 320 (64%) of 500 MT patients and 154 (66.7%) of 231 ST patients. The mean actuarial follow-up was 10.7 (95% CI 10.4–11.0) years.

Outcome

Table 3 summarizes the outcome of patients followed up according to their initial treatment. A significantly higher prevalence of persistent chronic symptoms (21.9 vs. 16.2%) was observed among the MT compared with the ST patients (p = 0.035).

	Total (n = 474/100%)	Initial treatment		Crude OR (95% CI)	p value
		MT (n = 320/100%)	ST (n = 154/100%)		
Asymptomatic	315 (66.6%)	195 (60.9%)	120 (77.9%)	1 ref.	
Recurrent symptoms	95 (20.0%)	70 (21.9%)	25 (16.2%)	1.72 (1.00–2.97)	0.047
Episodes of AD requiring hospital admission	64 (13.5%)	55 (17.2%)	9 (5.8%)	3.76 (1.79–7.89)	<0.0001
Emergent surgery[a]	24 (5.1%)	22 (6.9%)	2 (1.3%)	5.61 (1.30–24.17)	0.02
Stoma	3 (0.6%)	3 (0.9%)	0 (0.0%)	N/A	
Disease-related death	1 (0.2%)	0 (0.0%)	1 (0.6%)	N/A	

* Two patients had three hospital admissions.
[a] The risk of emergent surgery was calculated comparing the number of surgical events to the number of the remaining patients in the two patient groups.
N/A = Not applicable.

Table 3. Outcome of patients followed up according to the initial treatment

Recurrence

There were one or more hospital admissions for recurrent AD in 64 patients: 55 of 320 MT patients (17.2%) and 9 of 154 ST patients (5.8%) ($p < 0.0001$). The MT patients had an almost fourfold higher probability of hospital admission for recurrent AD (OR = 3.76; 95% CI 1.79–7.89; $p < 0.001$).
Among the MT patients, those younger than 40 years of age at entry and those with three or more previous episodes of AD showed a higher risk of recurrence (HR = 5.01, 95% CI 1.25–20.08; $p = 0.023$ and HR = 3.90, 95% CI 1.69–9.03; $p = 0.001$, respectively). Patients younger than 40 years of age were noted to have a threefold increased risk of recurrent AD compared with those aged 40 or more (HR = 3.32; 95% CI 1.15–9.55; $p = 0.026$).
The 12-year cumulative incidence of recurrent AD was 21.2% among the MT and 11.8% among the ST patients ($p = 0.001$). There was no difference in the incidence of episodes of recurrent AD among patients entered retrospectively or prospectively. The extent of proximal and distal resection did not influence the risk of recurrence among ST patients.
The study failed to show an interval of time in which most recurrences occur, such as the first 2 [17,50] or 5 years [19,20] as reported in other series, as they were distributed over the entire observation time.

Subsequent Surgery

During the follow-up period, an emergency surgical procedure was performed in 24 (5.3%) patients (21 colectomies with primary anastomosis and 3 Hartmann's procedures) and it was fivefold more frequent among the MT (22/320) than among the ST patients (2/154) (age- and gender-adjusted HR = 5.83; 95% CI 1.36–24.92; $p = 0.017$). The Hinchey stage was available for 23 of the 24 operated patients: Hinchey 0 in 1, Hinchey 1 in 17, and Hinchey 3 in 5. The frequency of Hinchey stage 3 and 4 disease did not substantially differ between patients operated on at initial observation (27.6%) and at recurrence after medical treatment (19.0%) [58,59,60]. Among the 21 MT patients, 4 (19%) presented with Hinchey 3 stage disease; 3 of which underwent a Hartmann's procedure, with a 0.9% (3/320) rate of stoma formation.
The 12-year cumulative incidence of subsequent emergency surgery was 8.3% among the MT patients and 1.9% among the ST patients ($p = 0.008$). No association was observed between the risk of emergency surgery and the investigated parameters (sex, age at entry, number of previous AD episodes and type of recruitment). One of the 24 operated patients died shortly after surgery because of sepsis (4.2% operative mortality rate). During the follow-up period, 10 patients underwent elective surgery for symptomatic diverticular disease: 8 (2.5%) of 320 MT and 2 (1.3%) of 154 ST patients ($p = 0.33$).
Four of the 154 ST patients required subsequent surgery: 3 for incisional hernia and 1 for adhesions.

Mortality

In all, 85 of 474 patients died during the follow-up period: 1 patient died postoperatively (see above); 38 died of cardiovascular disease, 15 of cancer, and 11 of other causes; the cause of death was classified as unrelated but not available for 20 patients. Of these 85 deaths, 61 (19.1%) occurred among 320 MT and 24 (15.6%) among 154 ST patients. The 12-year actuarial survival rate was 75.4 and 83.9%, respectively ($p = 0.64$). After adjustment for gender, age and type of treatment (MT or ST) at entry, the cumulative number of AD episodes and presence of co-morbidity, the only covariate significantly associated with the risk of death was increasing age ($p < 0.0001$).

Conclusions

Our long-term prospective follow-up study of patients hospitalized after an acute episode of diverticulitis shows that the vast majority of medically treated patients remains asymptomatic. Only a few patients develop recurrent diverticulitis. The risk of further surgery is very low, and the risk of diverticular disease-related death is nil. On the other hand, resective surgery after an episode of AD does not entirely protect patients against recurrence, although the observed risk was significantly lower when compared with medically treated patients. Therefore, we believe that preventive surgery is not justified if not in selected cases associated to recognized risk factors.

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