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**Original article: Natural history of acute colonic
diverticular bleeding: prospective study in 133
consecutive patients**

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Faucheron

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Original article: Natural history of acute colonic diverticular bleeding: prospective study in 133 consecutive patients

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1
2 **Original article:** Natural history of acute colonic diverticular bleeding: prospective study in

3
4 133 consecutive patient 

Comment [UW1]: Title has been changed to answer comments from reviewers 2 & 3.

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8 **Short running title:** Colonic diverticular bleeding

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11 **Authors:** Gilles Poncet*, MD, PhD, Frederic Heluwaert†, MD, David Voirin*, MD, Bruno
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44 Endoscopy; Surgery
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SUMMARY

Comment [UW2]: Specific percentages have been avoided in the Summary (reviewer 1)

Background: Bleeding recurrence rate after spontaneous haemostasis of colonic diverticular haemorrhage varies in the literature, and a small minority of patients will require endoscopic, radiological or surgical intervention.

Aim: To study the natural history of colonic diverticular bleeding in consecutive patients.

Comment [UW3]: Background and aim of the study have been slightly changed, as we agree with the remarks from reviewers 2 & 3: the work is aimed at studying the natural history of acute diverticular bleeding rather than to support or refute colectomy as a primary treatment

Methods: We prospectively studied consecutive patients admitted for colonic diverticular bleeding from 1997 to 2005. Data on age, gender, 30-day mortality, therapeutic modality for bleeding management, and subsequent rebleeding were collected.

Results: One hundred and thirty three patients (mean age 75.7 years) were recruited. Bleeding stopped spontaneously in 123 patients (92.4%). A more interventional approach was necessary in 10 patients. Thirty-day mortality rate for first bleeding was 2.25%. Out of the 123 patients managed conservatively and submitted to an average follow-up of 47.5 months, 17 (13.8%) presented at least one recurrent diverticular bleeding. Spontaneous haemostasis was obtained in all recurrent cases except one, who died. The estimated bleeding recurrence rate was 3.8% at one year, 6.9% at 5 years and 9.8% at 10 years.

Conclusions: The low estimated rebleeding rate and the fact that rebleeding can be treated conservatively in most cases suggest that aggressive approach is not justified.

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INTRODUCTION

Colonic diverticular disease is common in Western countries, with a prevalence increasing from less than 10% in adults under 40 to about 60% in those over 80.¹ The disease remains asymptomatic in 80% of affected individuals, while the rest develops complications. The most frequent complication is diverticulitis with the risks of abscess formation, fistulation, perforation and obstruction.² The second complication is acute diverticular bleeding, affecting 3% to 15% of individuals with diverticular disease.³⁻⁶ Diverticular haemorrhage usually stops spontaneously in 70 to 90% of cases.⁷⁻⁹ The rate of rebleeding after one episode is between 20 to 38%, hence aggressive search for bleeding site and elective colectomy being sometimes proposed.^{8,10-12} This study was performed to provide the latest and most accurate answers to the following questions: *i*) what proportion of bleeding in patients with colonic diverticular stop spontaneously, *ii*) what is the 30-day mortality rate after the first episode of bleeding, *iii*) what proportion of patients bleed again and what is the outcome?

PATIENTS AND METHODS

Patients

We prospectively recruited consecutive patients who came to our institution with colonic diverticular bleeding from January 1997 to August 2005, among 1145 patients admitted for acute lower gastrointestinal (GI) bleeding in our GI bleeding intensive care unit and prospectively evaluated. All these patients had a systematic colonoscopy on entry as part of a protocol in our intensive care unit for lower GI bleeding. Diagnosis of diverticulosis as the source of haemorrhage was established according to the criteria proposed by Zuckerman¹³ and Jensen.³ These included evident endoscopic stigmata such as active bleeding, visible vessel and adherent clot, and presumptive findings such as presence of fresh blood within one or more colonic segments and diverticular erosions. Evidence of diverticular bleeding was also

Comment [UW4]: This is the only point from the reviewers comments we did not change, as the study is a true prospective one (first minor comment from reviewer 3). We develop our arguments in the separate sheet and slightly changed the text in that section, trying to be more convincing...

confirmed in some cases and for therapeutic objectives by helical CT angiography (n=4) or selective mesenteric arteriography (n=7) showing vascular extravasation within the colonic segment with diverticulosis at endoscopic examination.

Standardized protocol

We collected data on age, gender, symptoms on inclusion, anti-inflammatory drug intake [non steroidal anti-inflammatory drugs (NSAID) and steroids], anti-coagulants and anti-platelets medication (including aspirin) and delay between the first intake of these medications and the bleeding episode. We also recorded initial haemoglobin level measured on admission, lowest haemoglobin level observed during hospitalization, discharge haemoglobin level, admission platelet level, admission prothrombin level, number of packed red cell units transfused, length of hospital stay, and 30-day mortality. Therapeutic modality for the bleeding management was reported. In our GI bleeding intensive care unit standardized protocol, anti-coagulants were systematically stopped, antagonized by prothrombin complex, and replaced by heparin; NSAID were systematically discontinued; anti-platelets were stopped each time it was possible, depending on the patient's cardiac condition systematic cardiologist advice requested in emergency) and bleeding severity.

Prospective evaluation including data on subsequent bleeding was obtained by means of patients' examination including interview at regular intervals.

Statistics

Data were expressed as mean (range). Chi-square test was used to compare data. A p value of less than 0.05 was considered as significant. Recurrence rate was calculated using the Kaplan-Meier method.

RESULTS

Patients' demographics

Comment [UW5]: This paragraph has been created to answer remarks from reviewers 1 & 3

Comment [UW6]: VKA was replaced by anti-coagulant throughout the manuscript, to be more uniform and as it is the more usual term (answer to reviewer 1)

Comment [UW7]: The brand name 'Kaskadil' has been deleted as requested by reviewer 3 in his minor comments. This is also an answer to the fourth comment from reviewer 1

Comment [UW8]: This is the policy we use in the protocol that is ongoing in the GI bleeding intensive care unit (answer to reviewers 1)

Comment [UW9]: We added subheadings in this section as requested by reviewer 2



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2 During the study period, 133 consecutive patients (73 men) with a mean age of 75.7 years
3
4 (range 48-97) presenting with 157 diverticular bleeding episodes, were recruited. Women
5
6 were significantly younger than men (72.3 vs. 79.9 years, $p < 0.05$). Thirty four patients
7
8 (25.6%) presented with a systolic blood pressure below 80 mm Hg on admission, seven of
9
10 whom had lost consciousness. No patient had abdominal pain or fever. Biological data are
11
12 shown in table 1.

13 **Immediate outcome**

Comment [UW10]: See UW 8

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15 A  of 74 patients (55.6%) required blood transfusion, with a mean of 3.8 units of packed
16
17 red blood cells units per transfused patient (range 1-14) because of severe anaemia. Sixty two
18
19 patients received blood transfusion during the first episode and 12 during the second episode
20
21 of bleeding. The average length of stay in the GI bleeding unit was 9.2 days (range 3-38).
22
23 Although bleeding had spontaneously stopped, 3 patients (aged 71, 88, and 89 years) died
24
25 during the first 30 days (mortality rate of 2.25% for the first bleeding) from multiple organ
26
27 failure in the first patient, stroke in the second and both terminal respiratory and neurologic
28
29 diseases in the third patient.

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31 Out of the 133 patients, the first bleeding stopped spontaneously in 123 (92.4%).

32
33 In ten patients, a more aggressive approach was mandatory because of the severity of the
34
35 bleeding with no spontaneous haemostasis. The criteria for this aggressive approach were a
36
37 persistent bleeding with hemodynamic instability despite transfusion of 3 or more packed red
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39 cells units, interruption of medication if present and if possible in terms of cardiovascular
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41 indication, treatment with prothrombin complex and/or fresh frozen plasma if needed, and
42
43 standard resuscitation manoeuvres. Three patients were treated endoscopically (epinephrine
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45 injection in 3, clipping in 2), and was operated in an emergency (Hartmann's procedure)

Comment [UW11]: Answer to
comment from reviewer 2

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47 because of failure to obtain haemostasis by injection of diluted epinephrine and clipping. Four
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49 other patients were treated by arteriography followed by immediate superselective



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2 embolization leading to a secondary Hartmann's procedure for ischemic lesions in one.
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4 Lastly, 3 other patients required emergency surgery: the site of diverticular bleeding was
5
6 confirmed by angiography in 1 and helical CT scan in 1, and both patients underwent left
7
8 colectomy with primary anastomosis; the last one was treated by a non restorative subtotal
9
10 colectomy for non-identified site of the rebleeding diverticula.

11 Further follow-up

Comment [UW12]: See UW 8

12
13  Examining the 5 patients who had surgery during the first hospital stay, the 3 patients who
14
15 died and 2 patients who were lost to follow up, 123 patients were submitted to a median
16
17 follow-up of 47.5 months (range 5-136). Interestingly, one patient who required an
18
19 emergency left colectomy was readmitted for a rebleeding diverticulosis 14 months later and
20
21 was followed by simple surveillance.

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23
24 Among the 123 patients who were managed conservatively, 17 (13.8%) presented at least one
25
26 recurrent diverticular bleeding within 38 months in average (range 2-136).

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28 Among the 12 patients with only one rebleeding, 3 received blood transfusion of respectively
29
30 2, 4, and 6 units of packed red blood cells. One patient had a successful endoscopic
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32 haemostasis (clip). The other 11 patients were followed conservatively and had spontaneous
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34 haemostasis. No risk factor for rebleeding was identified in this series (Table 2).

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36 Four patients had two diverticular bleeding recurrences during the follow-up and two patients
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38 among them received respectively 2 and 3 units of red blood cells for the first recurrent
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40 episode and 3 patients received respectively 3, 3 and 5 units of red blood cells for the second
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42 bleeding episode. A spontaneous haemostasis was obtained in all cases. An 87-year old
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44 patient from that group died from multiple organ failure during hospitalization for the second
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46 bleeding recurrence.

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2 One patient presented with 3 diverticular rebleeding episodes required a blood transfusion (10
3 units) during the first one and none for the following. Each time, haemostasis occurred
4 spontaneously.
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8 The estimated bleeding recurrence rate from colonic diverticula (Kaplan Meier method) was
9
10 3.8% at one year, 6.9% at 5 years and 9.8% at 10 years in this series. One patient among the
11
12 17 (5.8%) presenting with a colonic diverticular rebleeding died.
13

14 15 16 **DISCUSSION**

17
18 Diverticular disease of the colon is the fifth most important gastrointestinal disease in terms
19 of direct and indirect health care costs in western countries.¹⁴ The colonic origin of lower GI
20 haemorrhage, in order of decreasing incidence, is diverticulosis, inflammatory bowel disease,
21 colonic neoplasia, infectious and ischemic colitis, benign anorectal disease, and arteriovenous
22 malformations.¹⁵ Positive diagnosis of bleeding diverticulosis has evolved during the last
23 decade with the development of new technologies such as CT helical angiography and
24 selective mesenteric angiography when the colonoscopy is not feasible, contra-indicated,
25 incomplete or non contributive.^{15,16} Management has also evolved with the advent of
26 interventional endoscopy (bipolar coagulation, epinephrine injection, clip placement)^{11,15,17,18}
27 and angiographic treatment (intra-arterial infusion of vasopressin, transarterial
28 embolization).¹⁹⁻²² In the 10 patients treated on this last series and whose massive diverticular
29 bleeding did not stop spontaneously, we could foresee haemostasis endoscopically in 2 and
30 superselective embolization in 4.
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44 Diverticular bleeding is caused by the rupture of small arteries, explaining the frequency of
45 sudden haemorrhage associated with low blood pressure at admission, as observed in more
46 than 25% of patients in this series. NSAIDs and high dose aspirin are responsible for early
47 bleeding (one week after first medication intake).²³ Anti-coagulants, low dose aspirin,
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clopidogrel and steroids seem to be associated with late bleeding (one year after first medication intake).

Diverticular bleeding usually stops spontaneously in 70 to 90% of cases.^{7-9,15} In the present series, bleeding ceased spontaneously in 92.4% of cases, which is slightly higher than the previously published rates. The reason for this is probably due to multiple factors; the first one might be the highly specialization of the GI bleeding intensive care unit in which the team was used to manage such conditions, avoiding unnecessary, too early therapeutic endoscopy, arteriography or surgery; the second reason is that anti-coagulants, anti-platelets or NSAID medications were discontinued in the majority of cases whenever possible; the third reason is that gastroenterologists and surgeons from the same team carefully followed patients together, in order not to miss the time of surgery, when needed.

Thirty day mortality rate in this series is 2.25% (3 patients out of 133) for the first diverticular bleeding and 5.8% (1 patient out of 17) for the subsequent bleeding episodes. In all of these cases, haemostasis was spontaneously obtained by medical management and deaths occurred because of severe underlying conditions, in patients older than the others in the same series. Mortality rates in the literature vary from 0³ to 40%.²⁴ These wide variations are due to many reasons, such as time of publication, method of treatment used, association with other conditions, severity of the disease, or selection of patients. In a recent national population study, 30-day mortality following diverticular disease hospital admission was 5.1% and 1-year mortality was 14.5%.²⁵ Increasing age, comorbidity and emergency admission as for diverticular bleeding were independent predictors of mortality.²⁵ For instance, it has been proven that mortality increases significantly when patients receive more than 10 units of blood,²² or when patients require emergency total colectomy for non localized colonic diverticular bleeding by a non specialized surgeon. In a collected series of patients with surgery for bleeding diverticulosis, reviewed by Bender *et al.*,²⁶ there was a cumulative

1 mortality rate of 22.6% in all series from 1972 to 1990. Interestingly, the mean age of the
2 patients in our series (75.7 years) is far higher than those usually published in the literature, so
3 that a mortality rate of 2.25% might seem not too high.
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8 The rebleeding rate in this series is 13.8% (17 patients out of 123 stopped bleeding after
9 conservative management) within a mean time of 47.5 months. This rate compares favourably
10 with most of the rates published in the literature. In 1994, McGuire stated that “the rebleeding
11 rate after one episode was usually said to be 20%, a rate that might have been diluted by
12 inclusion of other diagnoses”.⁸ Twenty eight of the 73 patients (38.4%) from his series rebled
13 at a mean follow-up of 4.3 years, 6 of whom required an emergency surgery and 22 stopped
14 spontaneously.⁸ Longstreth¹⁰ and later on Hoedema *et al.*²² reported rebleeding rates of 25
15 to 30%. The difference between these studies and our work might be the length of follow-up,
16 which is a little shorter in our series (47.5 months). Another explanation might be the patients
17 lost on follow-up; if we assume that the 2 patients who never came to their follow-up in our
18 series might have rebled, the percentage would have been 15.2% (19 patients out of 125),
19 which is closer to the published  of 20 to 38%. But the most obvious cause is probably
20 the aggressive approach we had concerning the first bleeding: endoscopic haemostasis in 3
21 patients, embolization in 4, and medication discontinuation in the majority of patients being
22 on anti-coagulants, anti-platelets or NSAIDs; Jensen *et al.* reported a bleeding recurrence rate
23 of 0% when the 10 patients of their series underwent endoscopic treatment (epinephrine
24 injection, bipolar coagulation, or both), instead of a recurrence rate of 52.9% in the 17
25 patients who only had simple surveillance after colonoscopy.³ The authors concluded that
26 colonoscopic treatment of such patients may prevent recurrent bleeding and decrease the need
27 for surgery. In the study of Bloomfeld, although the haemostatic procedures were similar to
28 the previous study, results were less encouraging: among 13 patients with active diverticular
29 bleeding endoscopically managed, 5 and 3 respectively presented an early or a late recurrence
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Comment [UW13]: The word
'admit' has been replaced by 'assume'.
Thanks to reviewer 3.

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2 up to 35 months, thus corresponding to a success rate of 38.4%.¹¹ Smoot *et al.* reported
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4 neither recurrence nor complication following endoscopic haemostasis carried out in 7
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6 patients actively bleeding from colonic diverticula (follow-up period not stated).²⁷ Finally,
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8 with the more recent review of Pilichos *et al.* presenting the results of all relevant studies and
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10 reports on this topic, one could write that out of 63 patients endoscopically treated, 6 (9.5%)
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12 presented an early relapse of bleeding and non method-related complication, although the
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14 follow-up period was only mentioned for 17 patients.¹⁷

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16 Once bleeding has recurred and ceased spontaneously, the rebleeding rate increases and is
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18 close to 50%, as reported by Breen *et al.*.²⁸ We observed a slightly lower rate of 29.4%, as 5
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20 patients out of 17 presented with more than one rebleeding. We also noticed that further
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22 bleeding recurrences were not especially more severe than the first recurrence, and that
23
24 spontaneous haemostasis could be obtained in all cases.

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26 The estimated bleeding recurrence rate from colonic diverticula in our series was 3.8% at one
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28 year, 6.9% at 5 years and 9.8% at 10 years, which is far lower than the previous rate published
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30 in the literature.^{8,10} An 87-year old patient died early from multiple organ failure after a
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32 second recurrence, giving a mortality rate for rebleeding of 5.8%. These data argue that there
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34 is no place for a preventive colonic resection after a spontaneous haemostasis of a colonic
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36 diverticula bleeding. Moreover, one of our patients operated in emergency for persisting
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38 haemorrhage later presented a recurrent diverticular bleeding.

41 **Conclusion**

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43 In this prospective study, the first colonic diverticular bleeding stopped spontaneously in
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45 92.4% of cases. In the remaining patients, haemostasis was obtained using endoscopic
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47 treatment, embolization, and/or surgery. Among the 123 patients with a mean follow-up of
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49 47.5 months, 13.8% presented with at least one bleeding recurrence, none of whom required
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surgery. The low estimated rebleeding rate of 9.8% at ten years, associated with the fact that rebleeding could be managed conservatively in this series argue for a non aggressive approach to prevent recurrence.

For Peer Review

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Table 1: Biological data of patients admitted for colonic diverticular bleeding

Biological variables	Mean (ranges)
Admission haemoglobin level (g/L)	115.18 (42-164)
Lowest haemoglobin level during hospital stay (g/L)	93.42 (42-147)
Discharge haemoglobin level (g/L)	105.98 (82-147)
Admission platelets level ($\times 10^3/\text{mm}^3$)	246.82 (102-837)
Admission Prothrombin level (%)	68.14 (9-100)

For Peer Review

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 **Table 1:** Comparison between rebleeding and non-rebleeding groups

Comment [UW14]: This table has been added to give answers to reviewers 2 and 3. In the same time, the figure and tables 1 and 2 from the previous version have been deleted

	Rebleeding group	Non-rebleeding group	p
Number of patients	17	113	
Sex ratio (males/females)	8/9	63/50	NS
Mean age (range)	74.1 (48-88)	75.3 (51-97)	NS
Patients with no medication (%)	3 (17.6)	15 (13.2)	NS