Incidence and Risk Factors for Gallstones in Patients with Inflammatory Bowel Disease: A Large Case-Control Study

Fabrizio Parente,[1] Luca Pastore,[2] Stefano Bargiggia,[1] Claudia Cucino,[2] Salvatore Greco,[2] Mirko Molteni,[2] Sandro Ardizzone,[2] Gabriele Bianchi Porro,[2] Gianluca M. Sampietro,[3] Riccardo Giorgi,[4] Roberto Moretti,[5] and Silvano Gallus[6]

The risk for gallstones (GD) in inflammatory bowel diseases and the factors responsible for this complication have not been well established. We studied the incidence of GD in a cohort of Crohn's disease (CD) and ulcerative colitis (UC) patients and investigated the related risk factors. A case-controlled study was carried out. The study population included 634 inflammatory bowel disease (IBD) patients (429 CD, 205 UC) and 634 age-matched, sex-matched, and body mass index (BMI)-matched controls free of GD at enrollment, who were followed for a mean of 7.2 years (range, 5-11 years).The incidence of GD was calculated by dividing the number of events per person-years of follow-up. Multivariate analysis was used to discriminate among the impact of different variables on the risk of developing GD. The incidence rates of GD were 14.35/1,000 persons/year in CD as compared with 7.75 in matched controls ($P = 0.012$) and 7.48/1000 persons/year in UC patients as compared with 6.06 in matched-controls ($P = 0.38$). Ileo-colonic CD location (OR, 2.14), disease duration >15years (OR, 4.26), >3 clinical recurrences (OR, 8.07), ileal resection >30 cm (OR, 7.03), >3 hospitalizations (OR, 20.7), multiple TPN treatments (OR, 8.07), and long hospital stay (OR, 24.8) were significantly related to GD in CD patients. *Conclusion:* Only CD patients have a significantly higher risk of developing GD than well-matched hospital controls. Site of disease at diagnosis, lifetime surgery, extent of ileal resections, number of clinical recurrences, TPN, and the frequency and duration of hospitalizations are independently associated with GD. (HEPATOLOGY 2007;45:1267-1274.)

The relationship between inflammatory bowel disease (IBD) and gallstones has been recognized since the late 1960s.[1] In particular, the occurrence of gallstone disease (GD) in patients with Crohn's disease (CD) has been investigated in several studies,[2-12] with prevalence rates ranging from 13% to 34%. Unfortunately, many of the aforementioned studies included selected CD patients (such as only those undergoing surgical resection or with disease confined to the terminal ileum), which may explain the great differences of prevalence between series, and others enrolled only limited number of patients, thus limiting the precision of estimates. In addition, only four of the aforementioned studies have been case controlled;[1,4,7,10] however, two of those were not age-matched or sex-matched and comprised only a small series of patients.[4,7] Because many risk factors for gallstones in CD patients may be similar to those in the general population [i.e., age, sex, and body mass index (BMI)], the exact relative risk of developing GD for a CD patient compared with a sex-matched, age-matched, and BMI-matched IBD-free control has not yet been determined well.

Even the pathogenesis of GD in CD remains to be elucidated. A cholesterol-supersaturated bile due to a

Abbreviations: BMI, body mass index; CD, Crohn's disease; GD, gallstones; IBD, inflammatory bowel disease; TPN, total parenteral nutrition; UC, ulcerative colitis; US, ultrasound.

From the [1]Gastrointestinal Unit, A. Manzoni Hospital, Lecco, Italy; the [2]Gastroenterology Unit, [3]Division of General Surgery, and [4]Liver and Infectious Disease Unit, L. Sacco University Hospital, Milan, Italy; the [5]Epidemiology Unit, Community Health Care Center, Lecco; and the [6]Section of Medical Epidemiology, Mario Negri Pharmacological Institute, Milan, Italy.

Received July 13, 2006; accepted November 27, 2006.

Presented at the Annual Meeting of the British Society of Gastroenterology (Birmingham 20-23 March 2006) and published in abstract form in Gut 2006; 55(suppl II):A74.

Address reprint requests to F. Parente, M.D., Gastrointestinal Unit, A. Manzoni Hospital, Via dell'Eremo 9/11, 23900 Lecco, Italy. E-mail: f.parente@ospedale.lecco.it; fax: (39) 0341-489966.

Published online in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/hep.21537

Potential conflict of interest: Nothing to report.

reduced absorption of bile acids in individuals with disease of the terminal ileum or after ileal resection has been adopted for a long time as the most likely biological explanation for the increased prevalence of GD among CD patients.[2,4,13] However, the recent demonstrations that CD patients with ileal resection have a normal or low saturation of bile[14,15] and that there is no clear relationship between extension of surgical resection and GD[10] indicates that other factors related to surgery (e.g., prolonged hospitalization) may play a major role in GD formation.

As far as concerns the risk of developing GD in patients with ulcerative colitis (UC), the findings reported so far are limited and contradictory. Lorusso et al. [7] and Jones et al.[16] have found that the prevalence of GD is higher in UC patients than in the general population. By contrast, 2 recent sonographic surveys of small UC populations have shown that these patients are not more frequently affected by GD in comparison with the general population.[12,17]

Therefore, the aims of this study were to evaluate the incidence of gallstones in a large series of patients with CD and UC over a maximum follow-up period of 11 years; to assess the relative risk of GD in CD and UC patients compared with a control population of similar age, sex, and weight; and to characterize the still undefined disease-related risk factors of this complication.

Patients and Methods

Setting. L. Sacco University Hospital is a 573-bed tertiary care academic hospital located in Western Milan. It is a national referral Centre for Inflammatory Bowel Disease (IBD), with the largest outpatient IBD clinic in the country and 3 consultant colorectal surgeons with specific interest in this field who perform all of the operations on IBD patients. All records (including demographic and clinical data, laboratory, x-ray, endoscopic, and surgical reports) of patients admitted to or seen as outpatients in our Centre, with a diagnosis of IBD, have been computerized since January 1, 1993 and are regularly updated.

Patients. From January 1993 to January 2000, all consecutive inpatients or outpatients with IBD attending our gastroenterology unit were screened for the inclusion in the current study. Eligible patients were those with an already confirmed diagnosis of CD or UC based on standard clinical, radiographic, endoscopic, and pathological criteria,[18,19] with no history of cholecystectomy nor already documented gallstone disease developed before or after IBD diagnosis. Exclusion criteria at enrollment were: age younger than 18 years, pregnancy or a diagnosis of cirrhosis based on previous liver biopsy or on clinical, biochemical, and ultrasonographic (US) findings. Primary sclerosing cholangitis was also considered a criterion of exclusion from the study. Written informed consent was obtained from all of the patients after having fully explained the purpose and the protocol of the study, which was approved by the Ethics Committee of L. Sacco University Hospital.

Abdominal US and Data Collected at Entry. All eligible patients, after an overnight fast, underwent basal sonography of the whole abdomen using a real-time US apparatus (Hitachi EUB 525 or Aloka Prosound 5500 SV, Tokyo, Japan) equipped with a convex 3.5-MHz and a linear 7.5-MHz transducer. All of the US examinations were performed by an experienced sonographer with specific and long-term training in abdominal US. Gallstone disease was defined as follows: the presence of echogenic structures with an acoustic shadow within a visible gallbladder lumen; one or more echogenic structures in the gallbladder without dorsal shadow, which by means of multiplanar visualization or attempted mobilization could be differentiated with certainty from a gallbladder septum, Heister's valve, or gallbladder polyps; a structure with significant echogenicity and dorsal shadow in the area of gallbladder, whose lumen was not definitely visualized.[20]

On study entry, the patient's database was updated if he or she was already under our care; otherwise a careful clinical history was taken, including all demographic data (age, sex, height, weight, site and duration of disease, type and number of previous surgeries, total length of previous bowel resections). Disease activity (CD activity index and UC activity index[21]) was also determined at entry. The criteria for admission to the study also required that patients had adequate medical records of clinical, anatomical, and therapeutic characteristics of disease, and had had a recent colonoscopy (or barium enema) and barium enteroclysis for disease restaging (within the last 6 months).

Data Management and Categorization of Risk Factors. The enrolled patients were divided into three age groups: younger than 40 years, 41 to 49 years, and 50 years and older. For evaluation of obesity, the patients were divided into four groups on the basis of their BMI (calculated as weight in kilograms divided by square of height in meters): less than 22, 22 to 24.9, 25 to 29.9, and 30 kg/m^2 or greater. The classification of CD localization at the time of diagnosis was categorized into four major groups: ileal disease only, ileocolonic disease, colonic disease only, and upper GI disease. The presence or the absence of fistulae were also taken into consideration. Patients with UC were divided into three subgroups: patients with rectosigmoid disease, patients with disease in-

volvement up to the left colic flexure, and those with disease extending beyond the splenic flexure. Pharmacological treatments at entry were categorized into four classes: no treatment, immunosuppressive drugs (azathioprine, infliximab, methotrexate), steroids, and mesalazine. Similarly, during follow-up, the long-term use of immunosuppressant agents as well as the number of treatments with medium- to high-dose steroids were registered. The types of intestinal resection(s) were classified into three groups: ileal resection, ileocecal resection/right-sided hemicolectomy, and colectomy. To study the impact of ileal resection on GD development, resection of the ileum was further categorized into two length classes: 1 to 30 cm and greater than 30 cm. In addition, nonoperated patients constituted one group. Clinical relapse was defined as the reappearance of symptoms related to CD or UC, variably associated with radiological, endoscopic, and laboratory findings, with a CD activity index greater than 200 or UC activity index greater than 2, considered severe enough to require treatment with a systemic steroid at medium-high dose; the number of total clinical relapses (before entry + during follow-up) was categorized as none, 1 to 2, or 3 or more. The number of total hospitalizations (before study entry + during the follow-up) was also categorized as fewer than 2, 2, and 3 or more. To evaluate the effect of hospitalization length on GD development, the total number of days in hospital was calculated and expressed as follows: less than 20 days, 20 to 39 days, and 40 or more days. Finally, the number of total parenteral nutrition (TPN) treatments during follow-up were categorized as none, 1, or 2 or more.

Controls. The control group comprised 18-year-old to 66-year-old individuals randomly selected from patients with functional disorders of the upper or lower GI tract attending our outpatient dyspepsia or irritable bowel syndrome clinic. Eligible controls were individuals identified as having symptoms diagnostic of dyspepsia according to the Rome I criteria[22] or meeting Manning criteria for irritable bowel syndrome[23] and without evidence of any chronic systemic illness. Exclusion criteria were: history of GD or cholecystectomy, evidence of GD at basal abdominal US, age younger than 18 years, pregnancy, or a diagnosis of liver disease (see previous discussion). Each GD-free IBD patient enrolled was matched by age (±5 years), sex, and BMI class to one GD-free control.

Follow-up. Patients and controls were followed with periodic visits including liver US and biochemistry (only for IBD patients) every 12 months. If any problem developed between the scheduled visits—clinical recurrences, operations, and so forth—both IBD patients and controls were asked to contact the medical staff to be clinically evaluated. Patients and controls who failed to attend the follow-up visit and abdominal US within 12 weeks of the scheduled date were considered as protocol violations and excluded from the data analysis.

The study was closed on February 1, 2005, when the last patient included had a minimum follow-up of 5 years.

End-Points Definition.

1. Incidence of gallstones: development of gallstone disease of any degree (uncomplicated or complicated, asymptomatic or symptomatic) in patients and controls without GD at first abdominal US
2. Risk of developing GD in IBD patients: the risk of developing new GD in patients with CD and UC as compared with age-, sex-, and BMI-matched controls.
3. Relationship between demographic-/disease-related risk factors and GD: the impact of age, sex, BMI, disease localization at diagnosis, duration of disease, pharmacological treatment, type and extension of intestinal resection(s), total number of clinical recurrences, number of TPN treatments, total number of hospitalizations, and length of hospital staying on the development of GD.

Statistical Analysis. Distribution of the individual characteristics was evaluated by simple descriptive statistics.

The incidence rate of GD in IBD patients and controls was calculated by dividing the patients with new gallstones (numerator) with the persons-time-at-risk (denominator) for each sample, and 95% confidence intervals were calculated on each rate, and normal (Z) test and P value was performed. A P value less than 0.05 was considered statistically significant.

A multivariate analysis was performed using logistic regression analysis (with GD as the dependent variable) and a backward procedure. Factors with more than two classes of variable were considered using dummy variables, thus allowing a comparison between the classes with a higher prevalence of GD and the lowest frequency reference class. The goodness of fit was checked by means of the Hosmer-Lemeshow test and the analysis of residuals. Prevalence and odds ratios were calculated with their 95% confidence intervals.

Results

Clinical Results. Nine hundred thirty-seven IBD patients were screened in the study period. Two hundred eighty patients were not eligible for the study (116 had a diagnosis of indeterminate colitis, 97 had had previous cholecystectomy or an already documented gallbladder disease, 29 were younger than 18 years old, 22 had no adequate medical records of their disease or recent anatomical disease restaging, and 16 had serious liver diseases such as cirrhosis or sclerosing cholangitis). Of the 657

Table 1. Demographic and Clinical Characteristics of IBD Patients, Who Correctly Completed the Study, at Enrollment

Parameter	Crohn's Disease n = 415	Ulcerative Colitis n = 185
Males/Females	223/192	104/81
Age (mean ± SD)	34.7 ± 11.8	38.7 ± 12.8
BMI (mean, range)	22.7, 15-35	23.4, 16-38
Disease duration, years (mean ± SD)	4.9 ± 5.6	5.2 ± 5.4
Site of disease at diagnosis (CD)		
Ileum	152	
Ileum and colon	210	
Colon only	46	
Upper GI	7	
Site of disease at diagnosis (UC)		
Rectosigmoid only		32
Left-sided colitis		43
Pancolitis		110
Disease activity at entry (CDAI >150 for CD and DAI >2 for UC patients)		
Yes	74	83
No	341	102
Previous bowel surgery		
Yes	163	3
No	233	182

eligible patients, 23 refused to undergo systematic US and laboratory follow-up because of personal or geographic problems (e.g., resident abroad) and were therefore excluded.

Six hundred thirty-four IBD patients (429 with CD and 205 with UC) fulfilled all inclusion criteria and were enrolled in the study. The median follow-up time was 7.2 years (5-11 years). During the study, 34 of the 634 patients enrolled were lost after the first consultation or before completing the minimum period of follow-up; therefore, 600 patients (415 with CD and 185 with UC) were included in the final analysis. The main demographic characteristics of the enrolled patients who correctly completed the study in the two groups are shown in Table 1. Demographic and disease-related characteristics of IBD patients excluded from the study did not significantly differ from those of enrolled patients

Incidence of Gallstone Disease. We documented 54 new cases of GD during 4,725 person-years of follow up in IBD patients as compared with 31 cases during 4,489 person-years of follow-up in matched controls.

The incidence rate of GD in CD patients was 14.35 [95% CI 10.01-18.69]/1000 persons/year as compared with 7.75 [95% CI 4.51-10.99]/1000 persons/year in matched controls ($P = 0.012$). The incidence rate of GD in UC patients was 7.48 [95% CI, 3.41-11.55]/1000 persons/year as compared with 6.06 [95% CI, 2.30-9.81]/1000 persons/year in matched-controls ($P = 0.38$).

Among the 54 CD patients developing new GD, 10 underwent cholecystectomy for symptomatic disease or complications (2 had emergency laparotomy for acute cholecystitis), whereas 2 patients had cholecystectomy during the course of laparotomy for intestinal or colonic resections; in particular, the rate of cholecystectomy for symptomatic stones were 21.9% (9/41) and 15.3% (2/13) among CD and UC patients, respectively; by contrast, the rate of cholecystectomy among the 31 matched controls developing new GD was 6.4% (2/31).

Risk Factors for Developing GD. The estimated risk of GD for CD and UC patients after adjustment for age, sex, and BMI was 2.09 (95% CI, 1.20-3.64) and 1.33 (95% CI, 0.56-3.16), respectively, compared with CD- and UC-free controls (Table 2).From the backward stepwise selection analyses, age, anatomical site of disease, BMI, duration of disease, lifetime surgery (yes/no), extent of ileal resection, number of hospitalizations, number of TPN treatments, total number of days in hospital, and number of clinical recurrences reached significance in patients with CD and were therefore included in the multivariate model. Among the candidate risk factors for GD, ileocolonic site of CD (OR. 2.14; 95% CI, 1.02-4.52), disease duration longer than 15 years (OR, 4.26; 95% IC, 1.64-11.1), more than three clinical recurrences (OR, 8.07; 95% CI, 1.03-63.3), more than three high-dose steroid treatments (OR, 2.23; 95% CI, 1.07-4.62), ileal resection greater than 30 cm (OR, 7.03; 95% CI, 2.56-19.3), two or more TPN treatments (OR, 8.07; 95% CI, 1.03-63.3), more than three hospitalizations (OR, 20.7; 95% CI, 4.73-90.5), and total number of days in hospital more than 40 (OR, 24.8; 95% CI, 7.14-86.3) strongly increased the risk of developing GD in CD patients. Sex, body mass index, and type of pharmacological treatment at entry had no significant influence on the probability of developing GD; nor did long-term immunosuppressive

Table 2. Distribution of 415 Patients with Crohn's Disease and 415 Controls Matched for Age, Sex, and BMI Class and 185 Patients with Ulcerative Colitis and Matched Controls According to the Prevalence of Gallstone Disease

Disease	Cases with IBD N	Cases with IBD (%)	Controls N	Controls (%)	OR* (95% CI)
Crohn's disease					
Gallstones (NO)	374	(90.1)	394	(94.9)	1†
Gallstones (YES)	41	(9.9)	21	(5.1)	**2.09 (1.20–3.64)**
Ulcerative colitis					
Gallstones (NO)	172	(93.0)	175	(94.6)	1†
Gallstones (YES)	13	(7.0)	10	(5.4)	1.33 (0.56–3.16)

NOTE. Results are given as odds ratios (OR) and correspondent 95% confidence intervals (95% CI).

*Estimated by unconditional logistic regression model after adjustment for age, sex, and BMI.

†Reference category is "No Gallstones."

therapy during follow-up (Table 3). By contrast, in patients with UC a clear numerical trend toward a higher frequency of GD in association with longer disease duration, number of hospital admissions, and longer hospital staying was seen, although none of these factors reached statistical significance (Table 4).

Discussion

Despite the existing knowledge of a causal relationship between IBD and gallstones, the true relative risk of this complication among IBD patients has not been well established; this could be mainly attributed to the lack of prospective well-controlled epidemiological and cohort studies as well as the inclusion, in many of the earlier studies, of selected patients not representative of the entire IBD population.[24] Indeed, for assessment of the genuine relative risk of GD in IBD, the inclusion of nonselected patients with mild to severe disease as well as the choice of a control population comprising subjects of similar age, sex, and geographical area is essential to minimize the influence of those demographic, environmental, and genetic factors that play an important role in GD formation.[25,26]

The current prospective cohort study is the first to be designed to investigate the incidence of gallstones in patients with CD and UC with no gallbladder disease at enrollment as well as the clinical pattern of newly diagnosed GD in this subset of patients as compared with CD- and UC-free hospital controls; we found that the incidence of GD in CD patients was significantly higher than that observed in a control population recruited in the same geographical area; by contrast, the incidence of GD in UC patients was significantly lower and quite comparable to that observed in sex-, age-, and BMI-matched UC-free controls. In particular, CD was associated with an approximately 2-fold relative risk (OR, 2.09; 95% CI, 1.20-3.64) of developing gallstones even after adjustment for age, sex, and BMI, which, together with genetic predisposition, constitute the well-known major risk factors for gallstones in the general population.[25,26] Our findings are in agreement with those reported in the only 2 case-controlled prevalence studies conducted so far by Lorusso et al. [7] and Lapidus et al.,[10] in which the relative risk for GD in CD were 3.6 and 1.8, respectively. The lack of excess risk of developing GD in UC patients (OR, 1.33; 95% CI, 0.56-3.16) agrees with the results of two recent sonographic surveys on smaller UC populations, showing that these patients are not more frequently affected by GD in comparison with the general population.[12,17]

As far as concerns the factors associated with the development of gallstones in IBD patients identified at logistic regression analysis, we confirmed that the risk of GD

Table 3. Distribution of 415 Patients with Crohn's Disease According to the Prevalence of Gallstone Disease and Selected Risk Factors

Parameter	Total of Subjects n	Patients With Gallstones n (%)	OR* (95% CI)
Sex			
Men	223	21 (9.4)	1.00†
Women	192	20 (10.4)	1.19 (0.61–2.30)
Age (years)			
<40	195	10 (5.1)	1.00†
41–49	118	10 (8.5)	1.59 (0.63–3.99)
≥50	102	21 (20.6)	**4.36 (1.93–9.85)**
BMI (kg/m^2)			
<22	144	9 (6.3)	1.00†
22–24.9	166	18 (10.8)	1.56 (0.66–3.66)
25–29.9	97	12 (12.4)	1.59 (0.61–4.12)
≥30	8	2 (25.0)	4.37 (0.71–26.7)
Duration of disease (years)			
<10	189	7 (3.7)	1.00†
10–15	105	11 (10.5)	**2.84 (1.05–7.72)**
≥15	121	23 (19.0)	**4.26 (1.64–11.1)**
Therapy at entry			
None	138	14 (10.1)	1.00†
AZA + antiTNF + MTX	70	8 (11.4)	1.07 (0.41–2.78)
BUD + STE	51	6 (11.8)	1.24 (0.43–3.57)
MES + SASP	150	12 (8.0)	0.70 (0.30–1.60)
AA	6	1 (16.7)	1.01 (0.10–9.94)
Number of hospitalizations			
<2	160	2 (1.3)	1.00†
2	131	13 (9.9)	**8.50 (1.86–38.8)**
≥3	124	26 (21.0)	**20.7 (4.73–90.5)**
Total days in hospital			
<20	182	3 (1.6)	1.00†
20–39	144	10 (6.9)	**4.55 (1.21–17.1)**
≥40	89	28 (31.5)	**24.8 (7.14–86.3)**
Number of relapses			
No	33	1 (3.0)	1.00†
1-2	232	13 (5.6)	2.47 (0.30–20.0)
≥3	150	27 (18.0)	**8.07 (1.03–63.3)**
Lifetime surgery			
No	183	7 (3.8)	1.00†
Yes	232	34 (14.7)	**4.00 (1.69–9.48)**
Site of disease at entry			
Ileum	155	10 (6.6)	1.00†
Ileum and colon	210	30 (14.3)	**2.37 (1.09–5.12)**
Colon only	46	0 (0.0)	0.00 (0.00–1.24)
Duodenum, jejunum	7	1 (14.3)	5.58 (0.56–56.1)
Ileal resection in cm			
No	184	7 (3.8)	1.00†
1–30	142	19 (13.4)	**3.69 (1.48–9.24)**
≥30	66	14 (21.2)	**7.03 (2.56–19.3)**
Colon only	23	1 (4.3)	0.90 (0.10–8.03)
Fistulizing disease			
No	351	32 (9.1)	1.00†
Yes	64	9 (14.1)	1.72 (0.76–3.92)
Long-term AZA/MTX			
No	247	20 (8.1)	1.00†
Yes	166	20 (12.0)	1.80 (0.91–3.56)
High-dose steroids (no. of rx)			
0–2	331	27 (8.2)	1.00†
≥3	80	14 (17.5)	**2.23 (1.07–4.62)**
TPN (No. of treatments)			
0	33	1 (3.0)	1.00†
1	232	13 (5.6)	2.47 (0.30–20.0)
≥2	150	27 (18.0)	**8.07 (1.03–63.3)**

NOTE. Results are given as odds ratios (OR) and correspondent 95% confidence intervals (95% CI).

Abbreviations: AZA, azathioprine; Anti-TNF, Anti-TNF antibodies; MTX, methotrexate; BUD, budesonide; STE, systemic steroids; MES, mesalazine; SASP, Salazopyrin; AA, antibiotics; TPN, total parenteral nutrition.

*Estimated by multiple unconditional logistic regression model after adjustment for age, sex, and BMI. †Reference category.

Table 4. Distribution of 185 Patients with Ulcerative Colitis According to the Prevalence of Gallstone Disease and Selected Risk Factors

Parameter	Total No. of Subjects n	Patients With Gallstones n (%)	OR* (95% CI)
Sex			
Men	104	6 (5.8)	1.00†
Women	81	7 (8.6)	1.79 (0.56–5.71)
Age (years)			
<40	49	1 (2.0)	1.00†
41–49	49	2 (4.1)	1.79 (0.15–21.1)
≥50	87	10 (11.5)	5.83 (0.69–49.2)
BMI (kg/m^2)			
<22	45	2 (4.4)	1.00
22–24.9	85	6 (7.1)	1.43 (0.27–7.74)
25–29.9	48	4 (8.3)	1.30 (0.21–7.99)
≥30	7	1 (14.3)	4.25 (0.29–62.3)
Duration of disease (years)			
<10	41	0 (0.0)	1.00†
10–15	53	3 (5.7)	
≥15	91	10 (11.0)	3.15 (0.81–12.3)
Therapy at entry			
None	155	12 (7.7)	1.00†
AZA + MTX	4	0 (0.0)	0.00 (0.00–12.4)
STE	1	0 (0.0)	0.00 (0.00–2.14)
MES + SASP	25	1 (4.0)	0.53 (0.06–4.46)
Number of hospitalizations			
<2	55	1 (1.8)	1.00†
2	51	1 (2.0)	1.07 (0.06–17.9)
≥3	79	11 (13.9)	6.96 (0.84–57.9)
Total days in hospital			
<20	61	2 (3.3)	1.00†
20–39	61	5 (8.2)	2.38 (0.43–13.3)
≥40	63	6 (9.5)	2.46 (0.46–13.3)
Number of relapses			
No	46	0 (0.0)	1.00†
1–2	97	11 (11.3)	
≥3	42	2 (4.8)	0.46 (0.09–2.25)
Lifetime surgery			
No	163	10 (6.1)	1.00†
Yes	22	3 (13.6)	2.95 (0.68–12.8)
Site of disease at entry			
Pancolitis	110	7 (6.4)	1.00†
Left-sided colitis	43	6 (14.0)	2.67 (0.77–9.29)
Proctosigmoiditis	32	0 (0.0)	0.00 (0.00–1.83)

NOTE. Results are given as odds ratios (OR) and correspondent 95% confidence intervals (95% CI).

*Estimated by multiple unconditional logistic regression model after adjustment for age, sex, and BMI.

†Reference category. Abbreviations: AZA, azathioprine; MTX, methotrexate; STE, systemic steroids; MES, mesalazine; SASP, Salazopyrin.

significantly increased with age; indeed, the frequency of GD in CD increased from 5% in the group of patients younger than 30 years to 21% in the 50 years of age and older group, carrying with the latter a fourfold risk of developing GD in comparison with the youngest (OR, 4.26; 95% CI, 1.64-11.1). A similar trend was observed in patients with UC, although it did not reach statistical significance because of the limited number of patients recruited, thus confirming that age represents a *per se* relevant risk factor for gallstones regardless of the type of IBD.

Unlike other studies,[11,17] our data indicate that disease duration is an important risk factor for GD in patients with CD; indeed, we showed that the frequency of GD approaches 20% after a duration of more than 15 years, and this subset of patients carries a fourfold risk of developing GD as compared with those with disease lasting less than 10 years. Even the location of CD was independently associated with GD: patients with ileocecal or ileocolonic involvement run a double risk of developing GD in comparison with patients with small bowel involvement only. This agrees with the studies of Kangas et al.[8] and Fraquelli et al.,[11] which documented the relevance of an ileocecal or ileocolonic CD localization in increasing the risk of GD.

Another interesting finding of this study concerns the role of lifetime bowel surgery in the development of GD in CD; similar to results reported by others,[9-11] our data indicate that previous intestinal resections are significantly associated with GD; in addition, we documented a major role of the length of ileal resection in this matter: indeed, patients undergoing ileal resection longer than 30 cm run a sevenfold risk of developing GD in comparison with those not receiving ileal resection. The pivotal role of ileal resection in the CD-associated lithogenic process could be explained in many ways: (1) a decreased intestinal reabsorption of bile salts with subsequent excretion of supersaturated bile and formation of cholesterol gallstones. This mechanism has been accepted for a long time as the most important in CD-related gallstone formation[27]; however, recent animal and human data have shown that cholesterol supersaturation is a transient phenomenon after ileal resection and an increased channeling of cholesterol into *de novo* synthesis to compensate for increased intestinal loss of bile acids rapidly occur[28]; (2) a reduced gallbladder motility in patients with CD, which may facilitate GD formation in the presence of cholesterol supersaturation. In this regard, some evidence has been seen of an impaired fatty-meal–induced gallbladder motility in patients with ileal and ileocolonic disease,[29,30] and Annese and Vantrappen also demonstrated decreased gallbladder contractility in patients with inactive CD[31]; (3) a marked reduction in gallbladder emptying associated with fasting and total parenteral nutrition; a prolonged fasting state or the use of total parenteral nutrition both can induce biliary sludge due to reduced gallbladder emptying.[32] Because these factors are common in patients undergoing surgery for CD, the association between stones and intestinal resection may be attributed also to these perioperative defects in gallbladder motility. Periods of prolonged fasting, bowel rest, and TPN are also common in patients who have not been operated on, but who

are undergoing intensive medical therapy for clinical recurrence; this is the reason we investigated the role of hospitalization and TPN, as surrogates of the aforementioned conditions, on the development of GD. Our findings show that both the number of hospitalizations and the total length of hospital stays constitute relevant risk factors for gallstones in CD: indeed, patients with more than 3 hospitalizations and a total length of hospital stay greater than 40 days had almost a 20-fold risk of developing GD in comparison with those who had been hospitalized less frequently and for shorter periods. These data are robust enough to hypothesize that a combination of factors, partly related to CD *per se* (e.g., site of disease, ileal resection) but partly attributable to disease morbidity (e.g., hospitalizations, number of recurrences, number of TPN therapies), finally lead to gallstone formation in this population. Therefore, secondary prevention measures, including long-term prophylaxis with ursodeoxycholic acid or the stimulation of cholecystokinin secretion during total parenteral nutrition,[33] could be taken into consideration in the highest-risk subgroups (e.g., patients with extensive ileal resection and multiple hospitalizations). This is of particular importance if we consider that the risk of developing symptomatic gallstones seems to be quite high in patients with CD: in our series, indeed, nearly 22% of patients with gallstones and CD underwent cholecystectomy during follow-up for GD-related symptoms as compared with 15% of UC patients and 6% of CD- and UC-free controls.

In summary, this case-controlled study of patients with IBD concludes that patients with CD run a doubled risk of GD development compared with well-matched IBD-free hospital controls. By contrast, the risk of gallstone formation in patients with UC is significantly lower and similar to the control population. Age, site of CD at diagnosis, lifetime surgery, frequency of clinical recurrences, the extent of ileal resection but also the number of hospitalizations, the length of hospital stay, and a high number of TPN treatments are all independent variables associated with gallstones, the pathogenesis of which appears to be multifactorial. More than 20% of these newly developed gallstones in CD are symptomatic and require cholecystectomy, thus suggesting the opportunity of adopting prevention strategies in the future management of CD subgroups at higher risk of gallstones.

References

1. Heaton KW, Read AE. Gallstones in patients with disorders of the terminal ileum and disturbed bile salt metabolism. Br Med J 1969;3:494-496.
2. Cohen S, Kaplan MM, Norton RA, Patterson JF. Gallstones in inflammatory bowel disease. Am J Dig Dis 1974;19:109-112.
3. Hill GL, Mair WS, Goligher JC. Gallstones after ileostomy and ileal resection. Gut 1975;16:932-936.
4. Whorwell PJ, Hawkins R, Dewbury K, Wright R. Ultrasound survey of gallstones and other hepatobiliary disorders in patients with Crohn's disease. Dig Dis Sci 1984;29:930-933.
5. Bluth EI, Merritt CR, Sullivan MA, Kurchin A, Ray JE. Inflammatory bowel disease and cholelithiasis: the association in patients with an ileostomy. South Med J 1984;7:690-692.
6. Anderson H, Bosaeus I, Fasth S, Hellberg R, Hulten L. Cholelithiasis and urolithiasis in Crohn's disease. Scand J Gastroenterol 1987;22:253-256.
7. Lorusso D, Leo S, Mossa A, Misciagna G, Guerra V. Cholelithiasis in inflammatory bowel disease: a case-control study. Dis Colon Rectum 1990;33:791-794.
8. Kangas E, Lehmusto P, Matikainen M. Gallstones in Crohn's disease. Hepatogastroenterology 1990;37:83-84.
9. Hutchinson R, Tyrrel PM, Kumar D, Dunn JA, Li JK, Allan RN. Pathogenesis of gallstones in Crohn's disease: an alternative explanation. Gut 1994;35:94-97.
10. Lapidus A, Bangstad M, Astrom M, Muhrbeck O. The prevalence of gallstone disease in a defined cohort of patients with Crohn's disease. Am J Gastroenterol 1999;94:1261-1266.
11. Fraquelli M, Losco A, Visentin S, Cesana BM, Pometta R, Colli A, et al. Gallstone disease and related risk factors in patients with Crohn disease: analysis of 330 consecutive cases. Arch Intern Med 2001;161:2201-2204.
12. Bargiggia S, Maconi G, Elli M, Moltenic P, Ardizzone S, Parente F, et al. Sonographic prevalence of liver steatosis and biliary tract stones in patients with inflammatory bowel disease: study of 511 subjects at a single centre. J Clin Gastroenterol 2003;36:417-420.
13. Dowling RH, Bell GD, White J. Lithogenic bile in patients with ileal dysfunction. Gut 1972;13:415-420.
14. Lapidus A, Einarsson K. Effects of ileal resection on biliary lipids and bile acid composition in patients with Crohn's disease. Gut 1991;32:1488-1491.
15. Lapidus A, Einarsson C. Bile composition in in patients with ileal resection due to Crohn's disease. Inflamm Bowel Dis 1998;4:89-94.
16. Jones MR, Gregory D, Evans KT, Rhodes J. The prevalence of gallbladder disease in patients with ileostomy. Clin Radiol 1976;27:561-562.
17. Kratzer W, Haenle MM, Mason RA, von Tirpiz C, Kaechele V. Prevalence of cholelithiasis in patients with chronic inflammatory bowel disease. World J Gastroenterol 2005;11:6170-6175.
18. Malchow H, Ewe K, Brandes JW, Goebell H, Ehms H, Sommer H. European cooperative Crohn's disease study (ECCDS): results of drug treatment. Gastroenterology 1984;86:249-266.
19. Rubin PH, Present DH. Differential diagnosis of chronic ulcerative colitis and Crohn's disease of the colon: one, two, or many diseases? In: Kirsner JB, Shorter RG, eds. Inflammatory bowel disease. Baltimore: Williams & Wilkins, 1995, pp. 355-379.
20. Barbara L, Sama C, Morselli Labate AM, Taroni F, Rusticali AG, Festi D, et al. A population study on the prevalence of gallstone disease: the Sirmione study. HEPATOLOGY 1987;7:913-917.
21. Xiao Li F, Sutherland LR. Assessing disease activity and disease activity indices for inflammatory bowel disease. Curr Gastroenterol Rep 2002;4:490-496.
22. Talley NJ. Non-ulcer dyspepsia: myth and realities. Aliment Pharmacol Ther 1991;5:145-162.
23. Manning AP, Thompson WG, Heaton KW, Morris AF. Towards positive diagnosis of the irritable bowel syndrome. Br Med J 1978;2:653-654.
24. Afdhal NH. Crohn's and stones. Am J Gastroenterol 1999;94:1130-1132.
25. Rome Group for Epidemiology and Prevention of Cholelithiasis (GREPCO). Prevalence of gallstone disease in an Italian adult female population. Am J Epidemiol 1984;119:796-805.
26. Muhrbeck O, Ahlberg J. Prevalence of gallstone disease in a Swedish population. Scand J Gastroenterol 1995;30:1125-1128.
27. Ferezou J, Beau P, Parquet M, Champarnaud G, Lutton C, Matidchansky C. Cholesterol and bile acid byodynamics after total small bowel resection and bile diversion in humans. Gastroenterology 1993;104:1786-1795.

28. Lapidus A, Einarsson C. Bile composition in patients with ileal resection due to Crohn's disease. Inflamm Bowel Dis 1998;4:89-94.
29. Damiao AO, Sipahl AM, Vezozzo DP, Goncalves PL, Fukul P, Laudanna A. Gallbladder hypokinesis in Crohn's disease. Digestion 1997;58:458-463.
30. Murray FE, McNicholas M, Stack W, O'Donoghue DP. Impaired fatty-meal-stimulated gallbladder contractility in patients with Crohn's disease. Clin Sci 1992;83:689-693.
31. Annese V, Vantrappen G. Gallstones in Crohn's disease: another hypothesis. Gut 1994;35:1676.
32. Pitt HA, King W, Mann L, Roslyn JJ, Berquist WE, Ament ME, et al. Increased risk of cholelithiasis with prolonged total parenteral nutrition. Am J Surg 1983;145:106-112.
33. Guglielmi FW, Boggio-Bertinet D, Federico A, Forte GB, Guglielmi A, Loguercio C, et al. Total parenteral nutrition-related gastroenterological complications. Dig Liver Dis 2006;38:623-642.