Colonoscopy with polypectomy is associated with a low rate of complications in patients with cirrhosis

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Background and study aims: Cirrhotic patients are at a theoretically increased risk of bleeding. The safety of polypectomy in cirrhosis is poorly defined.

Patients and methods: We performed a retrospective review of patients with cirrhosis who underwent colonoscopic polypectomy at a tertiary-care hospital. Patient characteristics and polyp data were collected. Development of complications including immediate bleeding, delayed bleeding, hospitalization, blood transfusion, perforation, and death were recorded to 30-day follow-up. Clinical characteristics between bleeders and non-bleeders were compared, and predictors of bleeding were determined.

Results: A total of 307 colonoscopies with 638 polypectomies were identified. Immediate bleeding occurred in 7.5% (95% CI 4.6%–10.4%) and delayed bleeding occurred in 0.3% (95% CI 0.0%–0.9%) of colonoscopies. All cases of immediate bleeding were controlled endoscopically and none resulted in serious complication. The rate of hospitalization was 0.7% (95% CI 0.0%–1.6%) and repeat colonoscopy 0.3% (95% CI 0.0%–0.9%); no cases of perforation, blood transfusion, or death occurred. Lower platelet count, higher INR, presence of ascites, and presence of esophageal varices were associated with increased risk of bleeding. Use of electrocautery was associated with a lower risk of immediate bleeding. There was no significant difference between bleeding and non-bleeding polyps with regard to size, morphology, and histology.

Conclusions: Colonoscopy with polypectomy appears safe in patients with cirrhosis. There is a low risk of major complications. The risk of immediate bleeding appears higher than an average risk population; however, most bleeding is self-limited or can be controlled endoscopically. Bleeding tends to occur with more advanced liver disease. Both the sequelae of portal hypertension and coagulation abnormalities are predictive of bleeding.

Introduction

To date, the most attention has been paid to the safety of upper endoscopic procedures in cirrhosis, as most life-threatening gastrointestinal bleeding events occur in the upper gastrointestinal tract. However, with earlier recognition, improvements in supportive care, novel treatments against the viral hepatitides, and improved access to liver transplantation, the survival of compensated cirrhotics is now estimated at more than 12 years [1,2] Given this life expectancy, more patients with early or compensated cirrhosis may be candidates for colonoscopy for colorectal cancer screening and surveillance [3,4]. Colonoscopy is also required as part of liver transplant evaluation to exclude the presence of colorectal cancer. With more patients living with cirrhosis, the question of safety of colonoscopy in cirrhosis increasingly confronts both the referring clinician and the endoscopist. There is a relative paucity of data to address this question. A review of the indexed literature over the last decade shows two series on the topic, both from South Korea, each with a relatively limited number of cirrhotic patients [5,6]. Data from the United States, where colonoscopy is the preferred method for colorectal cancer screening and surveillance and whose population of cirrhotic patient may differ from the cirrhotic populations of East Asia, are limited. Cirrhosis is a state of coagulopathy and of altered hemodynamics secondary to portal hypertension, both of which may predispose a patient to hemorrhage [7,8]. While a higher risk of polypectomy associated hemorrhage and other procedural complications may be expected, this risk has not been well defined. In this single-center retrospective series, we attempt to further characterize the

risk of immediate post-polypectomy bleeding (IPPB), delayed post-polypectomy bleeding (DPPB), need for hospitalization, need for blood transfusion, need for repeat colonoscopy, perforation, and death in patients with cirrhosis undergoing colonoscopic polypectomy.

Patients and methods

Our study was conducted with institutional review board approval (Stanford University, protocol ID 20122) at a tertiary-care United States Department of Veterans Affairs (VA) hospital. The VA healthcare system is the largest integrated healthcare system in the United States, and operates an enterprise-wide comprehensive electronic healthcare record system. The charts of all patients with the *International Classification of Diseases, Ninth revision* (ICD-9) codes for cirrhosis of any etiology (571, 571.2, 571.5) who received care at our medical center were identified. Among these patients, those who had undergone outpatient colonoscopy with at least 1 polypectomy between January 1, 2008 and June 30, 2014 were identified. Patients with a history of inflammatory bowel disease or liver transplant were excluded.

Clinical characteristics including age, gender, etiology of cirrhosis, and indication for colonoscopy were recorded. Presence of clinical sequelae of liver disease were recorded, including history or presence of esophageal varices (EV), history or presence of ascites (graded as none, mild, or moderate-to-severe), history or presence of hepatic encephalopathy (HE), and history or presence of hepatocellular carcinoma (HCC). For the purposes of this study, EV was defined as varices of any size or grade found on esophagogastroduodenoscopy within 36 months preceding or 24 months following colonoscopy, or the use of non-selective β-blocker for the indication of variceal prophylaxis at the time of colonoscopy. Moderate-to-severe ascites was defined as either refractory ascites per the American Association for the Study of Liver Diseases guidelines (fluid overload which is unresponsive to sodium-restricted diet and high-dose diuretic treatment, or recurring rapidly after therapeutic paracentesis), or the presence of moderate to large volume ascites on either ultrasonography or computed tomography within 24 months preceding or following colonoscopy [9]. All other ascites was defined as mild ascites. HE was defined as any history of HE decompensating event recorded by a VA provider, or the use of lactulose or rifaximin at time of colonoscopy. History of HCC was defined as any history of HCC recorded by a VA provider, or any previous treatment directed against HCC.

Laboratory values indicating degree of liver disease were recorded at time of colonoscopy, including total bilirubin, albumin, creatinine, platelet count, and international normalized ratio (INR). Model for end-stage liver disease (MELD) score and Child-Pugh score were calculated for each patient. Use of antiplatelet agents (e.g. aspirin, clopidogrel) and oral anticoagulants (both warfarin and target-specific oral anticoagulants) were recorded. The standard protocol for our endoscopy unit is for patients to discontinue warfarin for 5 days prior to colonoscopy, to discontinue direct target-specific oral anticoagulants 2 days prior to colonoscopy, to discontinue clopidogrel 5 days prior to colonoscopy, and to continue antiplatelet agents through colonoscopy. For each polypectomy performed, polyp-specific data were recorded, including polyp size, morphology (either diminutive, flat, sessile, or pedunculated), method of removal (cold biopsy, cold snare, hot biopsy, hot snare, endoscopic mucosal resection with submucosal injection and electrocautery [EMR]), and histology (adenomatous or non-adenomatous). The type of current was not standardized in this study, but blended current is typically used at our institution.

Each polypectomy was reviewed for occurrence of IPPB. Using the conventions of Kim *et al*, IPPB was defined as bleeding that continued for over 30 seconds from the polypectomy site, and classified as either oozing IPPB, or spurting IPPB [10] DPPB was defined by any episode of bleeding per rectum in the 30 days following colonoscopy for which the patient sought medical attention. Any occurrence of hospitalization, blood transfusion, repeat colonoscopy, perforation or death was recorded in the 30 days following colonoscopy. The primary endpoint of this study was defined as the incidence of hemorrhage following colonoscopic polypectomy; secondary endpoints were defined as incidence of hospitalization, blood transfusion, repeat colonoscopy, perforation, and death in the follow-up period.

Follow up data were obtained from routine post-procedure phone calls on the weekday following the procedure, gastroenterology clinic follow-up notes, liver clinic follow-up notes, general medicine clinic visits, hospitalization at the Palo Alto VA, and for patients hospitalized at other facilities standardized communication with the VA transfer center. Patients were excluded if no follow-up data within 30 days of colonoscopy were available.

Statistical methods

Patient characteristics between bleeders and non-bleeders as well as polyp characteristics between bleeding and non-bleeding polyps were compared using the Student *t* test for normally distributed continuous variables and the chi-squared test for categorical variables using STATA (version 13; StataCorp, College Station, TX). All *P* values were two-sided, and a $P \le 0.05$ was considered statistically significant.

For each patient and polyp characteristic that was found to be statistically different between bleeding and non-bleeding groups, receiver operating characteristic curves were defined as a predictor of bleeding. For continuous variables, the point of maximal inflection was used as a cutoff value to dichotomize into categorical variables. Univariate and multivariate regression analysis was then performed on these variables.

Results

A total of 344 colonoscopies with polypectomies were identified. Of these, 35 did not have follow-up data recorded within 30 days of colonoscopy and were excluded, and 2 patients had undergone liver transplant and were excluded. A total of 307 colonoscopies with 638 polypectomies were therefore included for analysis. Baseline clinical characteristics of all cirrhotic patients are shown in **Table 1**. The average age of the patients was 60 ± 6 years, and the patients were predominantly male (98.4%). The majority of patients were early cirrhotics, with 85.7% Child-Pugh class A, 13.0% Child-Pugh class B, and 1.3% Child-Pugh class C. The mean MELD score was 9.6 ± 3.3. 28% had EV present (20.5% based on esophagogastroduodenoscopy, 7.5% based on use of non-selective β-blocker for prophylaxis), 24.1% had ascites (19.2% mild, and 4.9% moderate-to-severe), 7.8% had HE, and 10.1% had a history of HCC.

Incidence of complications

Twenty-three colonoscopies were complicated by IPPB (7.5%, 95% CI 4.6%-10.4%). Twenty-one IPPBs were oozing IPPBs, and 2 IPPBs were spurting IPPBs. All 23 IPPBs either ceased or were con-

Table 1 Baseline clinical characteristics of patients (n = 307).

Characteristic	Mean ± SD, or frequency
Age (years)	60.2 ± 5.8
Gender (male)	302 (98.4 %)
Bilirubin (mg/dL)	1.3 ± 0.8
Albumin (g/dL)	3.6 ± 2.0
Platelet count (K/μL)	140.6 ± 68.2
INR	1.2 ± 0.3
Creatinine (mg/dL)	1.0 ± 0.7
MELD	9.6 ± 3.3
Encephalopathy Present	24 (7.8 %)
Ascites	
None	233 (75.9 %)
Mild	59 (19.2 %)
Moderate-to-severe	15 (4.9 %)
Esophageal varices present	86 (28.0 %)
History of HCC	31 (10.1 %)
Child-Pugh Class	
A	263 (85.7 %)
B	40 (13.0 %)
C	4 (1.3 %)
Antiplatelet Use	71 (23.1 %)
Oral Anticoagulant Use	3 (1.0 %)

ALT, alanine aminotransferase; INR, international normalized ratio; MELD, model for end-stage liver disease; HCC, hepatocellular carcinoma.

trolled by the end of the colonoscopy. Twenty-one IPPBs were controlled with the application of a hemostatic clip, and 2 IPPBs ceased spontaneously. No IPPB resulted in hospital admission.

One colonoscopy was complicated by DPPB (0.3 %, 95 % CI 0.0 %–0.9 %), requiring repeat colonoscopy (0.3 %, 95 % CI 0.0 %–0.9 %). There were 2 episodes of hospitalization for any reason (0.7 %, 95 % CI 0.0 %–1.6 %), 1 for DPPB and 1 for abdominal pain. No colonoscopy resulted in blood transfusion, perforation, or death (**Table 2**).

Table 2 Rate of complications following colonoscopy with polypectomy (n = 307).

Complication	Frequency
Immediate post-polypectomy bleeding	23 (7.5 %)
Oozing	21 (6.8 %)
Spurting	2 (0.7 %)
Controlled by end of colonoscopy	23 of 23 (100 %)
Delayed post-polypectomy bleeding	1 (0.3 %)
Required hospitalization	2 (0.7 %)
Required repeat colonoscopy	1 (0.3 %)
Required blood transfusion	0 (0 %)
Resulted in perforation	0 (0 %)
Resulted in death	0 (0 %)

Characteristics of bleeders

Because bleeding was the primary endpoint, patients who developed bleeding were compared with patients who did not develop bleeding after colonoscopy. Bleeders (n = 24) and non-bleeders (n = 283) were significantly different in several clinical aspects (**Table 3**). Patients who bled had significantly lower platelet counts and higher INR than patients who did not bleed. Patients who bled had more sequelae of portal hypertension, including a higher incidence of EV and more severe ascites. Patients who bled also had overall more advanced liver disease as evidenced by the Child-Pugh class distribution compared to non-bleeders. There was no difference between bleeders and non-bleeders in age, gender, or etiology of cirrhosis. There was no difference between bleeders and non-bleeders in total bilirubin, creatinine, or MELD. There was no difference between bleeders and non-bleeders in rates of HE and HCC. There was no difference between bleeders and non-bleeders in use of anti-platelet agents, oral anti-coagulants, or diuretics.

Characteristics of polyps

Analyzed at the polyp level, 37 polyps bled and 601 polyps did not bleed after removal (**Table 4**). Size, morphology, and histology were not statistically different between bleeding and non-

Table 3 Clinical characteristics of patients by bleeding status.

Characteristic	Non-bleeding (n = 283)	Bleeding (n = 24)	*P* value
Age (years)	60.14 ± 5.87	60.27 ± 5.07	0.92
Gender (male)	280 (98.25 %)	23 (100 %)	0.5
Bilirubin (mg/dL)	1.24 ± 0.82	1.44 ± 0.77	0.27
Albumin (g/dL)	3.66 ± 2.12	3.39 ± 0.54	0.55
Platelet count (K/μL)	143.13 ± 66.91	108.82 ± 49.06	**0.02**
INR	1.145 ± 0.23	1.27 ± 0.44	**0.03**
Creatinine (mg/dL)	1.00 ± 0.73	0.82 ± 0.3	0.23
MELD	9.56 ± 3.15	10.52 ± 4.36	0.17
Encephalopathy Present	21 (7.39 %)	3 (13.04 %)	0.33
Ascites			**< 0.01**
None	222 (78.17 %)	11 (47.83 %)	
Mild	52 (18.31 %)	7 (30.43 %)	
Moderate-to-severe	10 (3.52 %)	5 (27.74 %)	
Esophageal varices present	72 (25.35 %)	14 (60.87 %)	**< 0.01**
History of HCC	28 (9.86 %)	3 (13.04 %)	0.626
Child-Pugh Class			**< 0.01**
A	246 (86.62 %)	17 (73.91 %)	
B	36 (12.68 %)	4 (17.39 %)	
C	2 (0.70 %)	2 (8.70 %)	
Antiplatelet Use	64 (22.54 %)	7 (30.43 %)	0.387
Oral Anticoagulant Use	3 (1.06 %)	0 (0 %)	0.67

ALT, alanine aminotransferase; INR, international normalized ratio; MELD, model for end-stage liver disease; HCC, hepatocellular carcinoma.

Characteristic	Non-bleeding polyps (n = 601)	Bleeding polyps (n = 37)	*P* value
Size (mm)	5.60 ± 5.01	5.02 ± 4.99	0.49
Morphology			0.14
Diminutive	139 (23.1 %)	15 (41.7 %)	
Flat	71 (11.8 %)	4 (11.1 %)	
Pedunculated	34 (5.6 %)	2 (5.5 %)	
Sessile	351 (58.3 %)	15 (41.7 %)	
Other	7 (1.2 %)	0 (0 %)	
Histology			0.073
Non-adenomatous Polyp	180 (29.90 %	10 (27.78 %)	
Adenomatous polyps	422 (70.10 %)	26 (72.22 %)	
Removal Method			**< 0.01**
Cold biopsy	172 (28.5 %)	19 (52.8 %)	
Cold snare	183 (30.4 %)	13 (36.1 %)	
Hot biopsy	16 (2.7 %)	0 (0 %)	
Hot snare	112 (18.6 %)	2 (5.6 %)	
EMR	119 (19.8 %)	2 (5.6 %)	

Table 4 Characteristics of polyps by bleeding status.

EMR, endoscopic mucosal resection.

bleeding polyps. Polypectomies complicated by bleeding were more often performed with "cold" techniques (cold biopsy and cold snare), and less often performed with electrocautery (hot snare and EMR).

Predictors of bleeding

Table 5 demonstrates univariate and multivariate predictors of IPPB. On univariate analysis, a platelet count of greater than 150 (K/μL) predicted against bleeding (OR = 0.24, 95 % CI 0.08 – 0.80). Both mild and moderate-to-severe ascites predicted bleeding, though moderate-to-severe ascites was more strongly predictive (OR = 11.50, 95 % CI 2.97 – 44.52). Presence of EV predicted IPPB (OR = 4.92, 95 % CI 1.93 – 12.56). More advanced Child-Pugh score had a trend toward statistical significance, but did not reach statistical significance at the defined p-value. Use of hot snare (OR = 0.16, 95 % CI 0.04 – 0.66) and EMR (OR = 0.15, 95 % CI 0.03 – 0.72) predicted against bleeding. On multivariate analysis, moderate-to-severe ascites remained a predictor of immediate bleeding (OR = 2.82, 95 % CI 1.45 – 5.50). Conversely, use of hot snare (OR = 0.19, 95 % CI 0.04 – 0.83), and EMR (OR = 0.18, 95 % CI 0.04 – 0.87) remained significant predictors against immediate bleeding.

Discussion

Based on this series of 308 colonoscopies performed at a tertiary care VA hospital, colonoscopy with polypectomy appears to be safe in patients with cirrhosis, with a low risk of major complications. No colonoscopy in this series led to death, perforation, or blood transfusion, and the risks of DPPB (3 per 1,000), hospitalization (6.5 per 1,000), and repeat colonoscopy (3 per 1,000) were low. Using similar definitions, a large retrospective Canadian study of almost 100,000 outpatient colonoscopies performed between 2002 and 2003 revealed a pooled rate of bleeding requiring hospitalization within 30 days of colonoscopy at 1.64 per 1000 and rate of death at 0.074 per 1000 [11]. A large retrospec-

Table 5 Predictors of post-polypectomy bleeding

Predictor	Odds ratio	Standard error	Z score	95 % CI	*P* value
Univariate analysis					
INR > 1.5	2.23	1.45	1.23	0.62 – 8.01	0.22
Platelet count > 150 (K/μL)	0.24	0.15	–2.34	0.08 – 0.80	**0.02**
Ascites					
Mild	3.70	2.00	2.41	1.27 – 10.7	**0.02**
Moderate-to-severe	11.50	7.94	3.54	2.97 – 44.52	**< 0.01**
Esophageal varices	4.92	2.35	3.34	1.93 – 12.56	**< 0.01**
Child-Pugh class B or C	2.28	1.16	1.63	0.85 – 6.16	0.1
Endoscopic removal method					
Cold snare	0.64	0.28	–1.00	0.27 – 1.53	0.32
Hot snare	0.16	0.12	–2.53	0.04 – 0.66	**0.01**
EMR	0.15	0.12	–2.38	0.03 – 0.72	**0.02**
Multivariate analysis					
INR > 1.5	2.18	1.36	1.24	0.64 – 7.43	0.21
Platelet count > 150 (K/μL)	0.45	0.27	–1.33	0.14 – 1.46	0.18
Ascites (Moderate-to-severe)	2.82	0.96	3.06	1.45 – 5.50	**< 0.01**
Esophageal varices	2.58	1.33	1.83	0.94 – 7.10	0.07
Endoscopic removal method					
Cold snare	0.61	0.28	–1.09	0.25 – 1.48	0.28
Hot snare	0.19	0.14	–2.21	0.04 – 0.83	**0.03**
EMR	0.18	0.14	–2.14	0.04 – 0.87	**0.03**

INR, international normalized ratio; EMR, endoscopic mucosal resection.

tive study of over 2.3 million outpatient colonoscopies performed in the state of Florida performed at both ambulatory surgery centers and hospital outpatient departments between 1997 and 2004 revealed a 30-day hospitalization rate of 1.98 per 1000 and 30-day bleeding rate of 1.65 per 1000 [12]. These numbers are roughly in line with our observation in this cirrhotic cohort, suggesting that the risk of DPPB, hospitalization for any reason, repeat colonoscopy, and death is not significantly increased in cirrhotic patients compared to all other patients.

Based on our series there does appear to be an increased risk of immediate bleeding among cirrhotic patients undergoing polypectomy. IPPB complicated 7.5% of the colonoscopies in this series and 0.7% of the colonoscopies in this series were complicated by spurting IPPBs, which appears to be higher than the average risk population. As a measure for comparison of post-polypectomy bleeding rate within the VA system, our data can be compared to the results of the Veterans Affairs Cooperative Study Group 380 [13]. In this large, multicenter VA series of 1,680 asymptomatic patients between the ages of 50 and 75 undergoing colonoscopy with polypectomy, 6 patients developed immediate hemorrhage which required hospitalization (0.4%). Unfortunately, the rate of immediate hemorrhage not requiring hospitalization was not reported. Using definitions of IPPB similar to ours, Kim *et al.* found in 5,152 Korean patients undergoing 9,336 polypectomies a rate of IPPB of 4.2% of colonoscopies and 2.8% of polypectomies [10]. Notably, spurting IPPB complicated 0.1% of their colonoscopies. The increased risk of bleeding in our series was consistent with the studies of cirrhotic patients of Jeon *et al.* (3.0%) and Lee *et al.* (12.4%) [5, 6].

We found that overall more advanced liver disease predicted bleeding. This may be both due to the coagulopathy of cirrhosis as well as the hemodynamic consequences of portal hypertension. Platelet count was significantly lower and INR was significantly higher in the bleeding cohort as compared to the non-bleeding cohort; moreover, a platelet count of greater than 150 (K/μL) predicted against bleeding. The rate and severity of ascites, and the rate of EV formation were significantly higher in the bleeding vs non-bleeding group. Moreover, EV and the presence of moderate-to-severe ascites were independent predictors of bleeding at the univariate level, suggesting a significant contribution of elevated portal pressures in explaining the increased risk of bleeding.

Despite the increased risk of immediate bleeding among our cirrhotic cohort, the majority of the bleeding was relatively mild, and importantly all cases of bleeding either spontaneously terminated or could be controlled endoscopically by the end of colonoscopy. This would suggest that the moderately increased risk of bleeding is safely manageable and should not preclude colonoscopy in early-stage cirrhosis. As cirrhosis becomes more advanced, the risk of bleeding increases and the expected benefit of cancer screening and surveillance decreases given decreased overall life-expectancy. Clinicians must weigh this balance carefully prior to performing polypectomy.

In our study, use of hot snare and EMR predicted lower risk of immediate bleeding. Similarly, Kim *et al.* found use of cold snare polypectomy resulted in a five-fold increased risk for IPPB relative to hot snare polypectomy [10]. There have been conflicting data about the timing of bleeding with different types of currents. In an earlier report, Van Gossom *et al.* reported IPPB to be more common with blended currents, and DPPB to be more common with pure coagulation current [14]. A recent analysis of 15,553 polypectomies however did not find an association between removal method and risk of DPPB [15]. Our institution used blended current. Despite the risk of immediate bleeding, we generally prefer using cold snare for polyps less than 1 cm because immediate bleeding is typically easily managed endoscopically and delayed cautery-related complications can potentially be avoided.

In our study, polyp characteristics such as size, morphology, and histology were not significantly associated with risk of bleeding. This is somewhat surprising given the previous literature showing that polyp size and morphology have been associated with bleeding [10, 16]. Also in our study the use of antiplatelet agents and oral anticoagulants were not significantly associated with risk of bleeding, though small sample size of patients taking oral anti-coagulants (1%) precludes rigorous analysis.

Instrumentation of the gastrointestinal tract can introduce bacteremia into the bloodstream. It is estimated that transient bacteremia can be detected following 4.4% of colonoscopies [17]. For average-risk patients, there is little risk associated with transient bacteremia; however in patients with cirrhosis and ascites, there have been case reports of bacterial peritonitis following colonoscopy [18, 19]. We did not observe any occurrences of peritonitis in this cohort, perhaps due to the rarity of this complication.

The study has several important limitations. First and foremost is the recognition that this is a series, and the results described are therefore descriptive and not controlled. With that in mind, it is important to note that many of the large colonoscopic studies widely referenced in the literature are also series in nature, and still provide useful descriptive data which can be compared and analyzed [10 – 13]. Another limitation is the single-center nature of the study. The cohort's high male gender composition (98.4%) and other characteristics of a VA population may not represent all patients with cirrhosis in the general population. It must also be recognized that the number of advanced cirrhotics in this series was relatively low (40 patients with Child-Pugh class B cirrhosis, and four patients with Child-Pugh class C cirrhosis). While our series was selected from a general outpatient cirrhotic cohort, the findings may not apply to a cohort of patients with more severe liver disease (such as patients undergoing liver transplant evaluation). Finally the experience of the operator, including fellows performing colonoscopy under the supervision of attending physicians, was not included in the analysis but the low bleeding rate made this issue less important.

Conclusions

With these limitations in mind, this study adds to the quite limited body of literature regarding the safety of colonoscopy in cirrhosis. As improvements in care lead to longer life expectancies for cirrhotic patients, colorectal cancer screening will become more important in the future. Additional prospective studies can and should be carried out to confirm the findings from this retrospective study.

Competing interests: None

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