Rates of Duodenal Biopsy During Upper Endoscopy Differ Widely Between Providers

Implications for Diagnosis of Celiac Disease

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Goal: The goal of this study is to determine factors associated with performance of duodenal biopsy during upper endoscopy.

Background: Celiac disease (CD) prevalence approaches 1% in the United States and Europe, yet CD remains underdiagnosed, in part because of low rates of duodenal biopsy during upper endoscopy. We aimed to identify patient and provider factors associated with performance of duodenal biopsy during upper endoscopy.

Study: In our hospital-based endoscopy suite, we identified all patients not previously diagnosed with CD who underwent upper endoscopy during a 5-year period for one of the following indications: abdominal pain/dyspepsia, gastroesophageal reflux (GERD), anemia/iron deficiency, diarrhea, and weight loss. We employed univariate and multivariate analysis to determine the association between clinical factors and the performance of duodenal biopsy.

Results: Of 8572 patients included in the study, 4863 (57%) underwent duodenal biopsy. Of those who underwent duodenal biopsy, 24 (0.49%) were found to have CD. On multivariate analysis, age, gender, indication, gross endoscopic appearance, physician affiliation with a celiac disease center, and absence of a participating trainee were all significantly associated with the performance of duodenal biopsy. There was wide variability among providers, with duodenal biopsy rates ranging from 27% to 91% during these procedures.

Conclusions: A duodenal biopsy is more likely to be performed in younger patients, females, and for key indications such as weight loss, diarrhea, and anemia. Providers varied widely in the performance of duodenal biopsy. Further study is warranted to better understand the decision to perform duodenal biopsy and to determine the optimal scenarios for its performance.

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Celiac disease (CD) is a chronic autoimmune enteropathy triggered by the ingestion of gluten in genetically susceptible individuals. The prevalence of CD is nearly 1% in the United States,[1,2] yet the disease remains under-diagnosed. In the United States, the majority of patients with CD have not been identified as such.[2–5] Untreated CD is associated with a number of long-term complications, including increased risk of malignancy and overall mortality.[4] Efforts are therefore warranted to better understand the factors contributing to under-diagnosis.[6]

The diagnosis of CD is made by upper endoscopy with duodenal biopsy.[7–9] Multiple biopsies are advocated because of the patchy nature of villous atrophy within the duodenum.[10] Although the rates of duodenal biopsy during upper endoscopy appear to be increasing over time,[11] published series from the last 15 years suggest that the majority of patients undergoing endoscopy for symptoms consistent with CD still may not have a duodenal biopsy performed during the procedure.[11,12] To date there have been a few reports addressing potential clinical, demographic, and provider-specific factors contributing to the under-performance of duodenal biopsy in the United States[11,13–15] but overall there remains a paucity of data exploring the decision to perform duodenal biopsy.

We aimed to determine the rate of duodenal biopsy during upper endoscopy for indications compatible with CD at a single academic center, as well as to analyze the clinical and demographic factors contributing to the performance of duodenal biopsy. We also aimed to explore variability among providers in the performance of duodenal biopsy, and some of the provider-specific factors that may contribute to the wide variability in practice patterns.

MATERIALS AND METHODS

We queried the endoscopy database to identify all adult ($\geq$18 y) patients who underwent upper endoscopy at Columbia University Medical Center, an urban tertiary care institution, between January 1, 2007, and December 31, 2011. We included all cases with at least one of the following indications: abdominal pain or dyspepsia, gastroesophageal reflux disease (GERD), anemia or iron deficiency, diarrhea, and weight loss. Other indications that could potentially fall within one of these accepted indications (eg, follow-up of gastritis/esophagitis, malabsorption, bloating, nausea and vomiting) were included and grouped as "other." If a patient

had more than one of the accepted indications listed for a single procedure, multiple indications were recorded for that procedure but included as separate indications within the multivariable analysis. Procedures performed for known or suspected CD as listed in the procedure indication (n = 646) were excluded. Urgent procedures for indications such as gastrointestinal bleeding or food impaction were excluded as well. If a patient underwent > 1 upper endoscopy during the study period, only the first examination was included for analysis.

In addition to the procedure indication, a number of demographic, clinical, procedural, and provider-specific covariates were recorded. These variables included patient age and gender, time of day of the procedure, year of procedure, gross endoscopic appearance of the duodenum (normal vs. abnormal), provider experience (years in practice), presence of a gastroenterology fellow during the procedure, and whether or not the attending provider was affiliated with the CD Center within our medical center. The primary outcome measure was the performance of duodenal biopsy during the procedure. A secondary outcome measure was whether or not the duodenal biopsy resulted in a new diagnosis of CD.

Patients were classified by the primary outcome measure of performance of duodenal biopsy, and univariate analysis across covariates was performed, using the global χ^2 test for categorical variables (eg, gender) and the Cochran-Armitage test for trend for ordered categorical variables (age, time of day, year of procedure, provider years in practice). The rate of duodenal biopsy was also calculated for each individual provider and providers were then compared using the χ^2 test. We performed multiple logistic regression analysis to evaluate the association between these variables and the performance of duodenal biopsy using odds ratios (OR) and corresponding 95% confidence intervals (CI). All variables in the univariate analysis were included in a single multivariate model, regardless of statistical significance in the univariate model. As a sensitivity analysis, the multivariable analysis was repeated after excluding the 4 physicians affiliated with the CD center. All reported *P*-values were 2-tailed with significance considered at $P < 0.05$. Statistical tests were performed using SAS version 9.3 (SAS institute, Cary, NC). The study (IRB-AAAJ7505) was approved by the Institutional Review Board of Columbia University Medical Center on April 16, 2012.

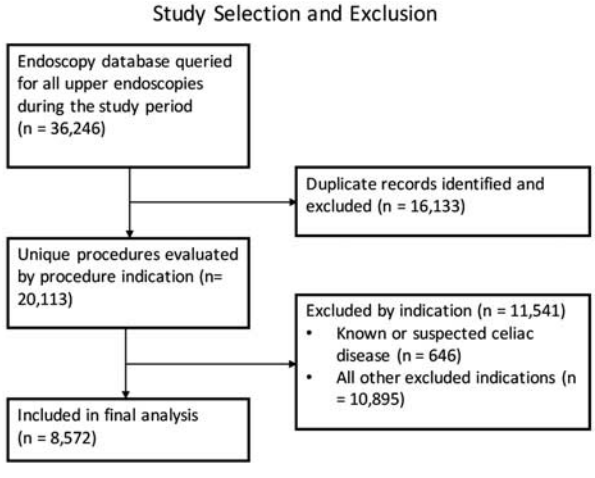

FIGURE 1. Study selection flowchart.

RESULTS

After exclusion of patients with known or suspected CD, repeat procedures, or acute indications including gastrointestinal bleeding or food impaction, a total of 8572 patients who underwent endoscopy by 51 providers met the inclusion criteria (Fig. 1). A majority of the patients undergoing endoscopy (63%) were female. There was wide variability in provider experience, ranging from 1 to 39 years in practice, and 1128 procedures (13%) were

TABLE 1. Variables Associated With the Performance of Duodenal Biopsy

Characteristics	Duodenal Biopsy Performed [n (%)]	P*
All	4863/8572 (57)	
Patient demographics		
Age		< 0.001
18-49	1798/2785 (65)	
50-69	1999/3769 (53)	
≥ 70	1066/2018 (53)	
Gender		< 0.001
Male	1600/3211 (50)	
Female	3263/5361 (61)	
Procedure		
Indication†		
Abdominal pain/dyspepsia	2847/4490 (63)	< 0.001
GERD	1729/3336 (52)	< 0.001
Anemia/iron deficiency	920/1524 (60)	0.002
Diarrhea	394/434 (91)	< 0.001
Weight loss	218/308 (71)	< 0.001
Other	239/479 (50)	0.002
Time of day		< 0.001
Before 9 AM	677/1415 (48)	
9:00-11:59 AM	1101/1900 (58)	
11:00 AM-12:59 PM	1110/1938 (57)	
1:00-2:59 PM	1159/1923 (60)	
3:00-4:59 PM	710/1189 (60)	
5 PM or after	106/207 (51)	
Year		0.014
2007	1118/1974 (57)	
2008	959/1681 (57)	
2009	954/1822 (52)	
2010	906/1611 (56)	
2011	926/1484 (62)	
Duodenum gross appearance		< 0.001
Normal	3919/7154 (55)	
Abnormal	944/1418 (67)	
Provider		
Years in practice‡		< 0.001
Quartile 1 (1-5)	673/982 (69)	
Quartile 2 (6-16)	913/1607 (57)	
Quartile 3 (17-22)	1356/2557 (53)	
Quartile 4 (23-39)	1821/3159 (58)	
Physician affiliated with celiac disease center		< 0.001
Yes	924/1128 (82)	
No	3939/7444 (53)	
Fellow participation		< 0.001
Yes	1149/2352 (49)	
No	3714/6220 (60)	

*P-values calculated using the χ^2, except for age, time of day, year, and provider years in practice, for which the Cochran-Armitage test was used.
†Some patients had multiple indications listed for a single procedure.
‡N < 8572 because only included providers with > 50 EGDs.

performed by a physician affiliated with the CD center. The gross endoscopic appearance of the duodenum was normal in 83% of procedures. Among those patients with abnormal endoscopic findings (17%), duodenal biopsy was more common when there were gross findings suggestive of CD, such as atrophic or flattened mucosa (90% biopsy rate), scalloping (88%), or nodular mucosa (86%), compared with 67% among patients with abnormal findings overall. Among the 33% of patients with abnormal findings which did not trigger a duodenal biopsy, the most common abnormal findings were angioectasia, deformity/diverticulum, erythema/erosion, or ulcer (data not shown). A gastroenterology fellow participated in 27% of cases. Of the 8572 patients undergoing endoscopy, 4863 (57%) had a duodenal biopsy during the procedure. Of those who underwent duodenal biopsy 24 patients were ultimately found to have a histologic diagnosis of CD (0.49% of those biopsied). Among these patients ultimately found to have histology compatible with CD, 52% were in the youngest age group (18 to 49 y, compared with 32% in this age group for the entire study), 65% were female, and 61% were found to have a normal appearing duodenum at endoscopy. The procedural indications for the patients found to have CD were dyspepsia (52%, similar to overall study group), anemia (17%), diarrhea (26%), GERD (22%), weight loss (4%), and nausea/vomiting (9%, data not shown).

Basic characteristics and univariate predictors of duodenal biopsy are presented in Table 1. Biopsy was more often performed among younger patients (65% of patients aged 18 to 49 y compared with 53% of patients ≥ 50; $P < 0.001$) and women (61% vs. 50% of men; $P < 0.001$). Among the various procedure indications, duodenal biopsy was performed most commonly for diarrhea (91%) and weight loss (71%; $P < 0.001$ for both), while it was performed for only 60% of procedures done for anemia or iron deficiency ($P = 0.002$). Among providers who performed at least 50 endoscopies in this data set (n = 25), duodenal biopsy rates were highest among the least experienced providers (69% for quartile 1; $P < 0.001$) and among physicians affiliated with the institution's CD center (n = 4), with duodenal biopsy in 82% of their cases (Fig. 3). There was wide variability in duodenal biopsy rates among providers, ranging from 27% to 91% of all endoscopies performed by each provider (Figs. 2, 3).

On multivariate analysis (Table 2), age, gender, indication, gross endoscopic appearance, CD center affiliation, and fellow participation all showed a statistically significant association with the performance of duodenal biopsy. Women were more likely to undergo biopsy (OR, 1.57; 95% CI, 1.42-1.73), whereas older patients were less likely to be biopsied (OR, 0.67; 95% CI, 0.60-0.75 for age 50 to 69; OR, 0.56; 95% CI, 0.49-0.64 for age 70 or older; both compared with age 18 to 59). The procedure indication most strongly associated with performance of duodenal biopsy was diarrhea (OR, 4.41; 95% CI, 3.12-6.25 compared with abdominal pain/dyspepsia).

Overall there was no clear association between time of day, year of procedure, or provider years in practice and the

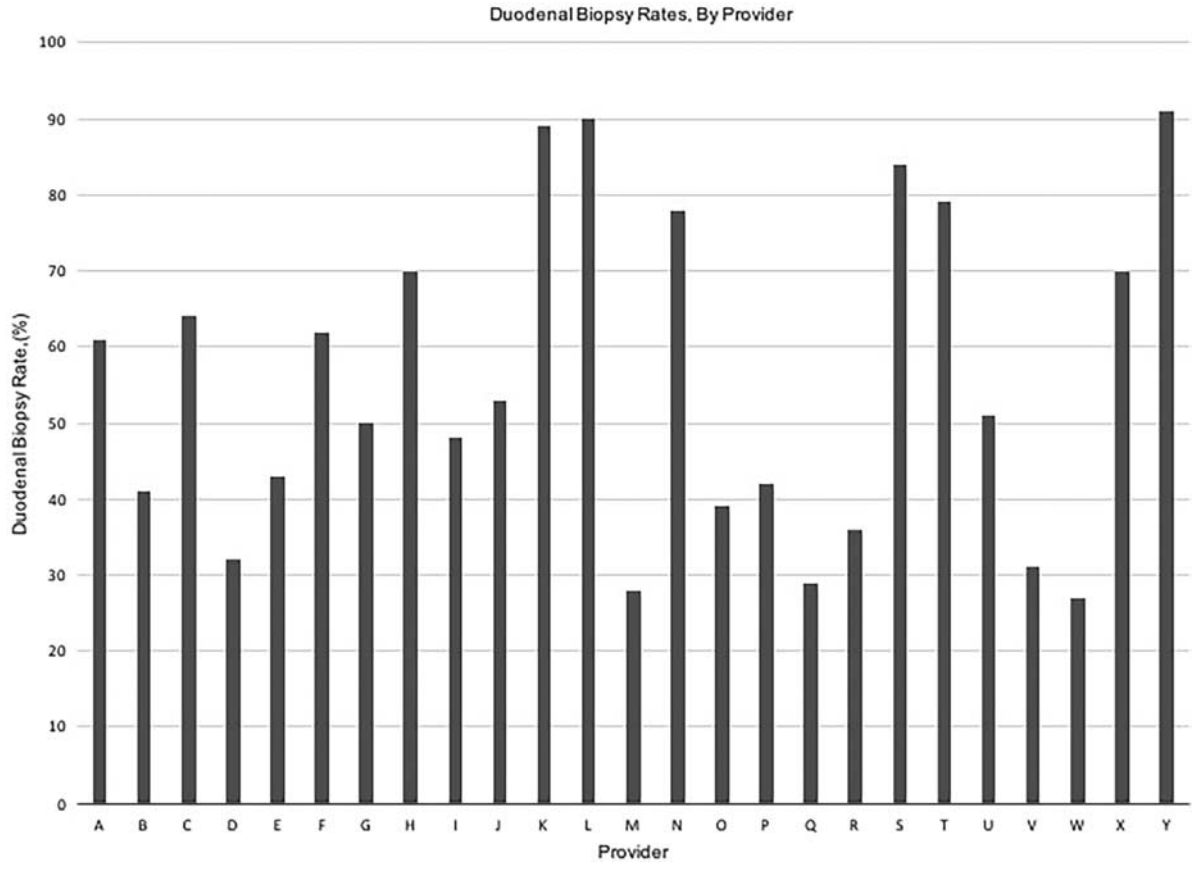

FIGURE 2. Variation in duodenal biopsy rates, listed by provider.

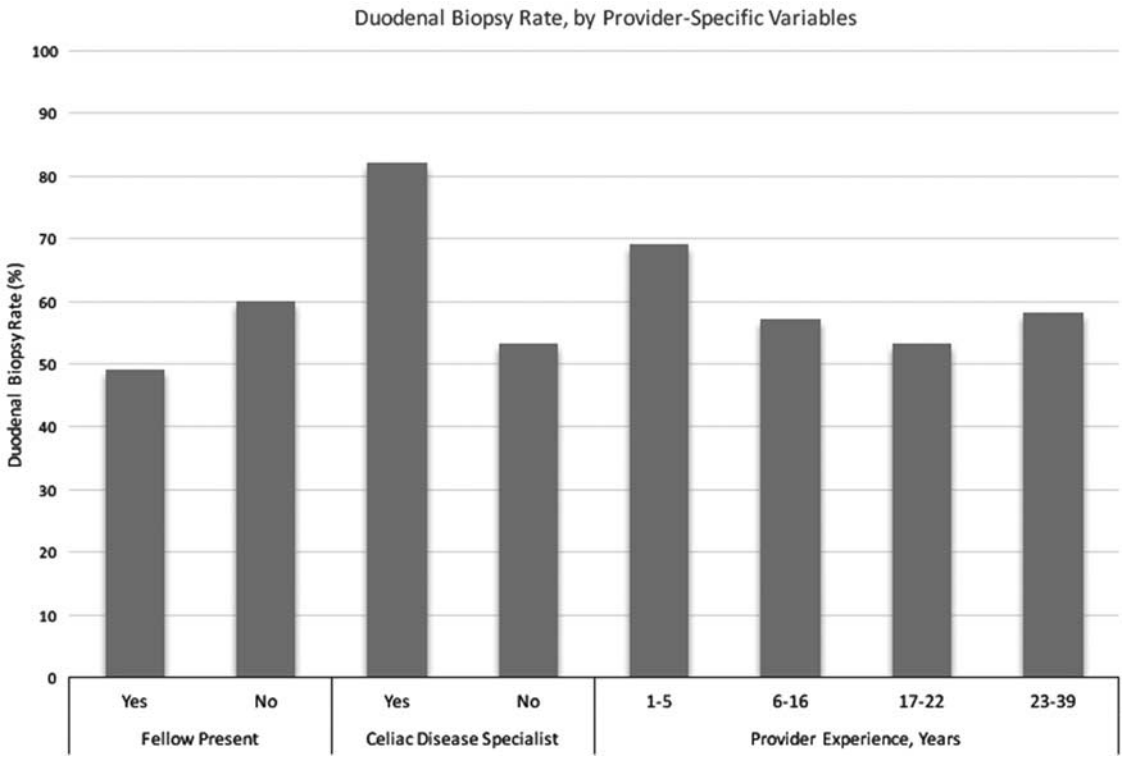

FIGURE 3. Variation in duodenal biopsy rates across provider-specific variables.

performance of duodenal biopsy. However, procedures during 2011, the most recent year in our data set, were associated with increased odds of duodenal biopsy compared with procedures from 2007 (OR, 1.21; 95% CI, 1.04-1.41). As for provider experience, although the second quartile (6 to 16 y in practice) was significantly associated with duodenal biopsy (OR, 1.29; 95% CI, 1.07-1.57), there was no discernable overall trend between years in practice and duodenal biopsy. The presence of a fellow during the case was negatively associated with duodenal biopsy (OR, 0.50; 95% CI, 0.44-0.56).

When we repeated the multivariable analysis after the exclusion of the 4 physicians affiliated with the CD center (n = 1395 procedures), there was no significant change in either the statistical significance or the effect size of the variables found to be associated with performance of duodenal biopsy on the original analysis (Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/JCG/A371).

DISCUSSION

Among 8572 patients undergoing endoscopy for indications compatible with CD, we found a number of factors that may influence the decision to perform small bowel biopsy, including age and gender, procedure indication, and provider expertise. Most notably, we also found extremely wide variability among providers in the frequency with which they perform duodenal biopsy.

To our knowledge, this is the largest series to date from a single institution examining individual practice patterns specific to the performance of duodenal biopsy during upper endoscopy. Our results are consistent with prior reports showing an association between patient age and gender and the performance of duodenal biopsy.[12,13,15] We found patients 50 years and older less likely to undergo duodenal biopsy compared with patients under 50 years old, and women more likely than men, with biopsies in 61% of women compared with 50% of men in our study ($P < 0.001$). Although CD was once thought to be a disease that presents in childhood, most diagnoses in the United States occur between ages 30 and 60, and new diagnoses can occur well into the older adult years.[16] There seems to be a similar misconception that CD is more common among women than men. Women in the United States are more likely to be diagnosed with CD,[17] despite equivalent seroprevalence between men and women.[1,3,4] As such, the lower rates of duodenal biopsy among men and older patients in our series and others may reflect missed opportunity to increase the low diagnosis rate of CD.

We also found a strong association between procedural indication and the performance of duodenal biopsy, with diarrhea, anemia, and weight loss most likely to result in a biopsy. Although the protean manifestations of CD are increasingly well recognized,[18] our results suggest that many providers still consider duodenal biopsy only in the presence of classical malabsorptive findings such as diarrhea and weight loss. Perhaps more surprising, however, was the finding that up to 9% of patients in our study with diarrhea and 40% of the patients with iron deficiency or anemia did not undergo duodenal biopsy, when these are well established indications supported by major society guidelines,[19,20] whereas the utility of duodenal biopsy for indications such as GERD or dyspepsia is uncertain. Heartburn has been reported to be a clinical manifestation of CD that may respond to the gluten-free diet.[21] Our group recently conducted a cost-effectiveness analysis for duodenal biopsy

TABLE 2. Multiple Logistic Regression Model Identifying Variables Associated With the Performance of Duodenal Biopsy

Characteristics	Odds Ratio	95% CI	*P*
Age			
18-49	Ref	—	—
50-69	0.67	0.60-0.75	< 0.001
≥ 70	0.56	0.49-0.64	< 0.001
Gender			
Male	Ref	—	—
Female	1.57	1.42-1.73	< 0.001
Indication			
Abdominal pain/dyspepsia	Ref	—	—
GERD	0.42	0.38-0.47	< 0.001
Anemia/iron deficiency	1.33	1.16-1.53	< 0.001
Diarrhea	4.41	3.12-6.25	< 0.001
Weight loss	1.17	0.80-1.71	0.41
Other	0.35	0.25-0.47	< 0.001
Time of day			
Before 9 AM	Ref	—	—
9:00-11:59 AM	1.34	1.15-1.56	< 0.001
11:00 AM-12:59 PM	1.27	1.09-1.48	0.002
1:00-2:59 PM	1.50	1.29-1.75	< 0.001
3:00-4:59 PM	1.47	1.24-1.75	< 0.001
5 PM or after	1.08	0.79-1.49	0.63
Year			
2007	Ref	—	—
2008	1.12	0.97-1.29	0.13
2009	0.79	0.68-0.91	0.001
2010	0.90	0.78-1.05	0.18
2011	1.21	1.04-1.41	0.02
Gross appearance			
Normal	Ref	—	—
Abnormal	1.69	1.48-1.93	< 0.001
Provider years in practice			
Quartile 1 (1-5 y)	Ref	—	—
Quartile 2 (6-16 y)	1.29	1.07-1.57	0.01
Quartile 3 (17-22 y)	0.87	0.72-1.04	0.12
Quartile 4 (23-39 y)	1.02	0.85-1.22	0.81
Physician affiliated with celiac disease center			
Yes	3.5	2.95-4.15	< 0.001
No	Ref	—	—
Fellow participation			
Yes	0.50	0.44-0.56	< 0.001
No	Ref	—	—

during endoscopy for GERD and found that routine small bowel biopsy met the threshold for cost effectiveness at a celiac disease prevalence of 1.8%.[22] Another recent report from a large cohort in Olmsted County, MN, suggests that routine testing for CD among patients with functional gastrointestinal symptoms may not confer significant clinical benefit.[23] The optimal diagnostic strategy during upper endoscopy remains uncertain.

We examined a number of other procedure-specific and provider-specific factors with variable significance in their association with duodenal biopsy. There was not a clear trend in overall biopsy rates during our study period, although the year 2011 alone (the final year of the study) did show a statistically significant association with performance of duodenal biopsy compared with 2007 (OR, 1.21; 95% CI, 1.04-1.41), perhaps suggesting increasing biopsy rates over time. Other studies have suggested as well that duodenal biopsy rates in the United States do seem to be increasing over time. A 2004 analysis of a national endoscopy database reported duodenal biopsy rates of only 11% during procedures for indications of diarrhea, anemia, iron deficiency, or weight loss.[12] A later report from the same database showed an increase in duodenal biopsy over time, by 2009 occurring in 51% of procedures for the same indications.[15] By comparison, in 2011 the overall biopsy rate was 62% in our cohort.

Among our other procedural variables, we did not find time of day to be strongly associated with duodenal biopsy. Time of day has previously been examined as a potential factor influencing the quality of colonoscopy, with data to suggest that provider fatigue may have an effect on adenoma detection rate.[24] But in our study there was no clear association between time of day and duodenal biopsy. The multivariable model did suggest that duodenal biopsy was more common during standard business hours (9 AM to 5 PM, compared with before 9 AM) but this finding may reflect the inadvertent inclusion in our study of a small number of urgent cases performed early in the morning or late in the evening. Between the hours of 9 AM and 5 PM there was no clear trend toward a lower biopsy rate later in the day.

Surprisingly, we found the presence of a fellow to be negatively associated with the performance of duodenal biopsy. In the colonoscopy literature, at least one study reports improved procedure quality if a fellow is present.[25] It is possible that fellows were more likely to be present for urgent cases referred from the inpatient consult service, rather than the outpatient service, and thus by the nature of the procedure less likely to perform routine duodenal biopsies. Although we excluded patients whose procedures were performed for the indication of acute upper gastrointestinal bleeding, it is possible that some patients with that clinical condition were included and not documented as such in the indication field of the procedure note. Alternatively, fellows and their supervising gastroenterologists with heavy clinical demands may have been subjected to time pressures that led to lower rates of duodenal biopsy.

Among the attending physicians, we found great variability in the performance of duodenal biopsy, with biopsy rates during endoscopy ranging from 27% to 91% ($P < 0.001$; see Fig. 2). Not surprisingly, the 4 CD specialists were more likely to perform duodenal biopsies (82% of procedures, compared with 53% among all other providers, $P < 0.001$, see Fig. 3), but wide variability remained even if these providers were excluded. We initially hypothesized that provider experience (number of years in practice) may influence the decision to perform duodenal biopsy, with younger providers more likely to biopsy. The multivariable model suggests that there may be a trend in this direction—with quartile 2 (6 to 16 y in practice) statistically more likely to perform biopsy compared with quartile 1, whereas neither quartile 3 nor quartile 4 shows a statistically significant association—but overall there is not a clear linear trend across all 4 quartiles. Moreover, the possible trend favoring duodenal biopsy among the least experienced providers does not seem to hold when the 4 CD specialists were excluded (see supplementary table, Supplemental Digital Content 1, http://links.lww.com/JCG/A371). This discrepancy may be because of the fact that one of the CD specialists with a high rate of biopsy was in quartile 1, so when this provider was excluded in the sensitivity analysis, there was a greater difference in biopsy rates between the 1st and 4th quartiles of experience than was seen in the initial analysis. Still, with or without the CD specialists there was not a clear trend across all 4 quartiles of provider experience.

As noted above, there was one prior report suggesting decreased adherence to duodenal biopsy guidelines among higher-volume providers,[14] as well as one report of increased rates of duodenal biopsy at academic centers compared with

community sites.[12] In the colonoscopy literature there is evidence that provider experience and procedure volume are associated with improved cecal intubation rate[26] as well as fewer adverse events,[27] although adenoma detection rate may suffer with very high or very low procedure volumes.[28] Further study is indicated to explore more fully the provider factors leading to the performance of duodenal biopsy during upper endoscopy.

The number of new diagnoses of celiac disease was relatively low in this study, 0.49% of patients who were biopsied, which is far lower than the 0.8% to 1% estimated seroprevalence in the United States.[1,4] This low prevalence of biopsy-confirmed CD within the cohort is not surprising; however, since all patients with known or suspected CD before endoscopy were excluded from the current study. Among those excluded were 646 patients who underwent EGD for suspected CD (eg, positive serologies or a symptomatic response to gluten) or follow-up of CD during our study period, resulting in 111 diagnoses of CD (17% of those biopsied). Thus, the actual prevalence of biopsy-confirmed CD at our center is likely significantly higher than was found in the current study among unselected patients undergoing endoscopy for common upper GI complaints. Prior studies from other centers with CD expertise would suggest a higher diagnostic yield for CD in unselected patients than was seen in our study, again likely as a result of our exclusion criteria. For example, Mooney et al[29] reported a 1.3% detection rate of CD for patients with GERD symptoms undergoing endoscopy, but there was no exclusion of patients with suspected CD in this study, and by protocol all patients underwent routine duodenal biopsy, compared with 57% in our study. Paradoxically, the low diagnostic yield in our study may be in part because of clinical suspicion and serologic testing for celiac disease among primary doctors and gastroenterologists at our center, with such patients then being excluded from the current study.

Our study has a number of limitations. The data were collected from a 5-year endoscopy experience at a single academic center with 4 CD specialists on faculty, raising questions of generalizability. The biopsy rate of 57% is likely higher than may be found in more typical settings, given the awareness that the CD specialists presumably bring to this institution. Certain data were not available in the endoscopy database, including patient race/ethnicity, socioeconomic status, and number of duodenal biopsy specimens submitted to pathology. Furthermore, although we were able to report on new cases of CD resulting from duodenal biopsies during the study, further pathologic data was not available through our query, so we were unable to report on other potentially relevant pathologic diagnoses. Serologic data were also not available, so we cannot report any potential concordance between histologic and serologic evidence of CD.

We attempted to include a wide range of procedural indications while excluding urgent procedures for acute presentations such as gastrointestinal hemorrhage or food impaction, but there likely were a small number of misclassified inpatient procedures that were included in this analysis. Conversely there may also have been procedures performed in line with our prespecified indications that were mislabeled and as such not included. We also attempted to exclude patients with known CD or positive serology, but serologic data were not available in our database, so cases of known or suspected CD were identified by the procedure indication listed by the endoscopist. Therefore, there may have been patients with known or suspected CD that was not documented in the procedure indication and could potentially bias the results toward overestimating rates of duodenal biopsy.

As noted in the Materials and methods section, we chose a priori in the study design to include all recorded variables in the multivariate analysis, even those which did not meet statistical significance in the univariate model. Although the sample size was relatively large, we recognize the risk of multiple comparisons contributing to the possibility of type 1 error because of the large number of variables in the multivariate analysis.

CONCLUSIONS

We found that the performance of duodenal biopsy during gastrointestinal endoscopy was dependent on variables including younger age, female gender, and procedure indication. Endoscopists varied widely in the performance of duodenal biopsy. Further study is warranted in order to better understand how providers decide whether or not to biopsy the duodenum, and to establish validated indications for biopsy among patients with common upper gastrointestinal symptoms.

REFERENCES

1. Fasano A, Berti I, Gerarduzzi T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. *Arch Intern Med*. 2003;163:286–292.
2. Rubio-Tapia A, Ludvigsson JF, Brantner TL, et al. The prevalence of celiac disease in the United States. *Am J Gastroenterol*. 2012;107:1538–1544; quiz 1537, 1545.
3. Katz KD, Rashtak S, Lahr BD, et al. Screening for celiac disease in a North American population: sequential serology and gastrointestinal symptoms. *Am J Gastroenterol*. 2011;106:1333–1339.
4. Rubio-Tapia A, Kyle RA, Kaplan EL, et al. Increased prevalence and mortality in undiagnosed celiac disease. *Gastroenterology*. 2009;137:88–93.
5. Ludvigsson JF, Rubio-Tapia A, van Dyke CT, et al. Increasing incidence of celiac disease in a North American population. *Am J Gastroenterol*. 2013;108:818–824.
6. Lebwohl B, Bhagat G, Markoff S, et al. Prior endoscopy in patients with newly diagnosed celiac disease: a missed opportunity? *Dig Dis Sci*. 2013;58:1293–1298.
7. Pais WP, Duerksen DR, Pettigrew NM, et al. How many duodenal biopsy specimens are required to make a diagnosis of celiac disease? *Gastrointest Endosc*. 2008;67:1082–1087.
8. Rostom A, Murray JA, Kagnoff MF. American Gastroenterological Association (AGA) Institute technical review on the diagnosis and management of celiac disease. *Gastroenterology*. 2006;131:1981–2002.
9. Rubio-Tapia A, Hill ID, Kelly CP, et al. ACG clinical guidelines: diagnosis and management of celiac disease. *Am J Gastroenterol*. 2013;108:656–676; quiz 677.
10. Hopper AD, Cross SS, Sanders DS. Patchy villous atrophy in adult patients with suspected gluten-sensitive enteropathy: is a multiple duodenal biopsy strategy appropriate? *Endoscopy*. 2008;40:219–224.
11. Lebwohl B, Kapel RC, Neugut AI, et al. Adherence to biopsy guidelines increases celiac disease diagnosis. *Gastrointest Endosc*. 2011;74:103–109.
12. Harewood GC, Holub JL, Lieberman DA. Variation in small bowel biopsy performance among diverse endoscopy settings: results from a national endoscopic database. *Am J Gastroenterol*. 2004;99:1790–1794.
13. Dixit R, Lebwohl B, Ludvigsson JF, et al. Celiac disease is diagnosed less frequently in young adult males. *Dig Dis Sci*. 2014;59:1509–1512.

14. Lebwohl B, Genta RM, Kapel RC, et al. Procedure volume influences adherence to celiac disease guidelines. *Eur J Gastroenterol Hepatol*. 2013;25:1273–1278.
15. Lebwohl B, Tennyson CA, Holub JL, et al. Sex and racial disparities in duodenal biopsy to evaluate for celiac disease. *Gastrointest Endosc*. 2012;76:779–785.
16. Green PHR, Stavropoulos SN, Panagi SG, et al. Characteristics of adult celiac disease in the USA: results of a national survey. *Am J Gastroenterol*. 2001;96:126–131.
17. Murray JA, Van Dyke C, Plevak MF, et al. Trends in the identification and clinical features of celiac disease in a North American community, 1950-2001. *Clin Gastroenterol Hepatol*. 2003;1:19–27.
18. Reilly NR, Green PH. Epidemiology and clinical presentations of celiac disease. *Semin Immunopathol*. 2012;34:473–478.
19. Goddard AF, James MW, McIntyre AS, et al. Guidelines for the management of iron deficiency anaemia. *Gut*. 2011;60:1309–1316.
20. Fine KD, Schiller LR. AGA technical review on the evaluation and management of chronic diarrhea. *Gastroenterology*. 1999; 116:1464–1486.
21. Nachman F, Vazquez H, Gonzalez A, et al. Gastroesophageal reflux symptoms in patients with celiac disease and the effects of a gluten-free diet. *Clin Gastroenterol Hepatol*. 2011;9:214–219.
22. Yang JJ, Thanataveerat A, Green PH, et al. Cost effectiveness of routine duodenal biopsy analysis for celiac disease during endoscopy for gastroesophageal reflux. *Clin Gastroenterol Hepatol*. 2015;13:1437–1443.
23. Choung RS, Rubio-Tapia A, Lahr BD, et al. Evidence against routine testing of patients with functional gastrointestinal disorders for celiac disease: a population-based study. *Clin Gastroenterol Hepatol*. 2015;13:1937–1943.
24. Leffler DA, Kheraj R, Bhansali A, et al. Adenoma detection rates vary minimally with time of day and case rank: a prospective study of 2139 first screening colonoscopies. *Gastrointest Endosc*. 2012;75:554–560.
25. Rogart JN, Siddiqui UD, Jamidar PA, et al. Fellow involvement may increase adenoma detection rates during colonoscopy. *Am J Gastroenterol*. 2008;103:2841–2846.
26. Harewood GC. Relationship of colonoscopy completion rates and endoscopist features. *Dig Dis Sci*. 2005;50:47–51.
27. Chukmaitov AS, Menachemi N, Brown SL, et al. Is there a relationship between physician and facility volumes of ambulatory procedures and patient outcomes? *J Ambul Care Manage*. 2008; 31:354–369.
28. Ko CW, Dominitz JA, Green P, et al. Specialty differences in polyp detection, removal, and biopsy during colonoscopy. *Am J Med*. 2010;123:528–535.
29. Mooney PD, Evans KE, Kurien M, et al. Gastro-oesophageal reflux symptoms and coeliac disease: no role for routine duodenal biopsy. *Eur J Gastroenterol Hepatol*. 2015;27:692–697.