

## Endoscopic Evaluation of Gastro-Esophageal Reflux Disease

David Armstrong<sup>a</sup>

Division of Gastroenterology, McMaster University Medical Centre, Hamilton, Ontario, Canada

*Endoscopy is, currently, the initial investigation of choice for the investigation of gastroesophageal reflux disease (GERD) in clinical practice and clinical research. Erosion severity is predictive of a patient's response to therapy and of the likelihood of relapse after therapy. It is, therefore, important to grade the severity of erosive reflux esophagitis, particularly in the context of clinical trials.*

*The Savary-Miller endoscopic classification system is used widely but usage and interpretation are very variable. The "MUSE" (metaplasia [M], ulceration [U], stricturing [S] and erosions [E]) classification provides clear definitions of the relevant endoscopic features, and it is based on a standardized report form, which allows the endoscopist to make a clear record of esophagitis severity. Recent studies confirm that endoscopists can identify erosions or mucosal breaks, ulcers, strictures, and metaplasia reproducibly. The "L.A." (Los Angeles) classification describes four grades of esophagitis severity (A to D), based on the extent of esophageal lesions known as "mucosal breaks," but it does not record the presence or severity of other GERD lesions. Thus, for patients with "complicated" reflux disease, the "MUSE" classification offers a more comprehensive description of esophagitis severity.*

*Endoscopy is not universally applicable: 40 to 60 percent of patients with typical reflux symptoms do not have esophageal erosions and are now considered to have "endoscopy negative reflux disease" (ENRD). Thus, endoscopy is not the final arbiter as to a diagnosis of reflux disease, and it is not, therefore, a necessary prerequisite to therapy. Endoscopy is indicated at first presentation for patients with alarm symptoms referable to the upper gastrointestinal tract. It has also been proposed that all patients with chronic GERD should have a "once-in-a-lifetime" endoscopy; in the absence of Barrett's esophagus or other complications, no follow-up is required unless the patient's symptoms change significantly. A surveillance program with multiple biopsies should be instituted if there is evidence of Barrett's esophagus. Endoscopic evaluation should document the presence and extent of esophageal erosions using the L.A. or MUSE classification systems; complications should also be documented and may be recorded using the MUSE classification. Non-erosive changes such as erythema may be ignored on the basis of present evidence, and there are no clear data to support the use of endoscopic biopsies for the diagnosis of GERD.*

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<sup>a</sup> To whom all correspondence should be addressed: David Armstrong, Division of Gastroenterology, Room HSC-4W8, McMaster University Medical Centre, 1200 Main Street West, Hamilton, Ontario, L8N 3Z5. Tel.: 905-521-2100, Ext. 76404; Fax: 905-521-5072; E-mail: armstro@fhs.csu.mcmaster.ca.

<sup>b</sup> Abbreviations: GERD, gastroesophageal reflux disease; ENRD, endoscopy negative reflux disease; M, metaplasia; U, ulceration; S, stricturing; E, erosions.

## INTRODUCTION

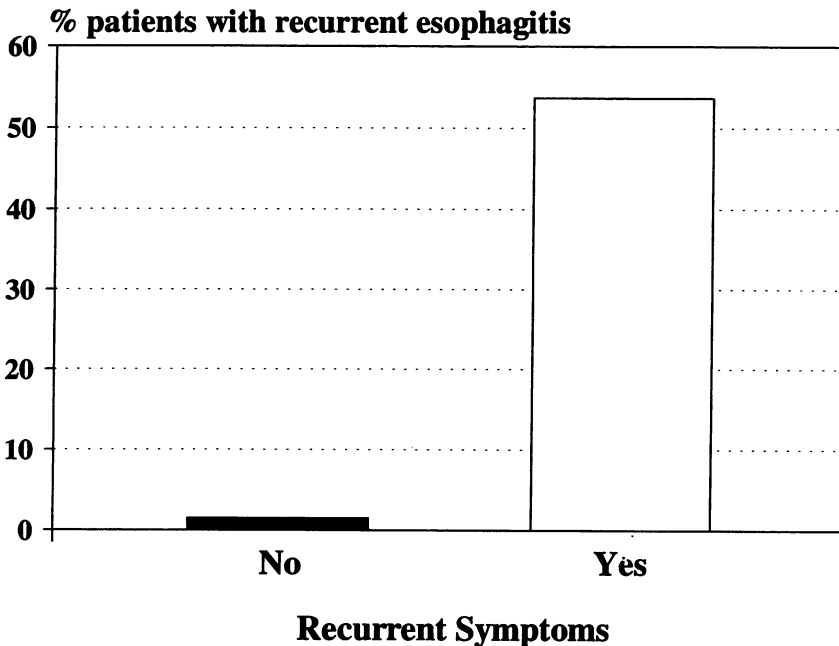
For many years, esophageal erosions have been considered the *sine qua non* of reflux esophagitis and, hence, of gastroesophageal reflux disease (GERD)<sup>b</sup>. At one end of the spectrum, lesions such as ulceration, stricture formation, and Barrett's esophagus are recognized to be more severe manifestations or complications of GERD, whereas "minor" changes such as erythema, edema, and friability are considered to be markers of minor esophageal damage.

However, since the introduction of histamine H<sub>2</sub>-receptor antagonists, the resolution of erosive esophagitis has been the most common primary outcome measure used for therapeutic trials in GERD. Patients with more severe lesions, or complications of GERD, are rarely enrolled in therapeutic trials, while patients with minor endoscopic changes may be









enrolled, but their results are often excluded from the final analysis.

## DIAGNOSIS OF EROSIVE REFLUX ESOPHAGITIS

Erosive esophagitis is now considered, by many, to be synonymous with GERD, and the diagnosis of GERD is often, therefore, predicated on the observation of esophageal erosions. Of the diagnostic techniques available for investigating GERD, upper gastrointestinal radiology has low sensitivity and specificity for the detection of erosions and Barrett's esophagus, although it is somewhat better for the diagnosis of ulceration or stricturing. Esophageal acid exposure, quantified by ambulatory pH monitoring, correlates well with the degree of esophageal damage, but this technique cannot be used to diagnose erosive



**Figure 1. Recurrence of erosive esophagitis is rare in the absence of recurrent reflux symptoms [6].**

		Metaplasia	Ulcer	Stricture	Erosions
Severity	0 Absent	M <sub>0</sub> <input type="checkbox"/> absent	U <sub>0</sub> <input type="checkbox"/> absent	S <sub>0</sub> <input type="checkbox"/> absent	E <sub>0</sub> <input type="checkbox"/> absent
	1 Mild	M <sub>1</sub> <input type="checkbox"/>  "fingers" +/- "islands"	U <sub>1</sub> <input type="checkbox"/>  1 discrete ulcer	S <sub>1</sub> <input type="checkbox"/>  > 9 mm (standard endoscope passes)	E <sub>1</sub> <input type="checkbox"/>  only on peaks of folds
	2 Severe	M <sub>2</sub> <input type="checkbox"/>  circumferential	U <sub>2</sub> <input type="checkbox"/>  ≥ 2 discrete or confluent ulcers	S <sub>2</sub> <input type="checkbox"/>  ≤ 9 mm (standard endoscope does not pass)	E <sub>2</sub> <input type="checkbox"/>  confluent: on & between folds
		Hiatus Hernia      Yes <input type="checkbox"/> No <input type="checkbox"/>			

**Figure 2. A pictorial representation of the “MUSE” classification system, which can be used as the basis for an endoscopic report form. Metaplasia, Ulceration, Stricture formation and Erosions (M.U.S.E.) are assessed and graded independently according to their degree of severity (0: absent, 1: mild, 2: severe). For each lesion type, the appropriate box is ticked and, if relevant, the extent of a lesion such as columnar metaplasia may be marked with reference to the diaphragmatic hiatus. Examples of some MUSE classifications and the corresponding endoscopic appearances are: M<sub>2</sub>U<sub>0</sub>S<sub>1</sub>E<sub>2</sub>: active (with erosions) peptic stricture with a diameter greater than 9 mm, situated at the upper pole of a circumferential area of columnar metaplasia; M<sub>2</sub>U<sub>2</sub>S<sub>0</sub>E<sub>0</sub>: large, confluent ulcers associated with a circumferential area of columnar metaplasia; M<sub>0</sub>U<sub>0</sub>S<sub>0</sub>E<sub>1</sub>: erosions affecting only one fold. (Courtesy of Ref. [12]).**

esophagitis per se, and it certainly cannot be used to document resolution of erosive esophagitis. Upper gastrointestinal endoscopy has, therefore, become the predominant diagnostic modality for GERD in clinical and research practice.

In the context of managing erosive esophagitis, endoscopy has significant advantages: it can be used to document the presence and extent of esophageal erosions as well the presence of ulceration, stricturing, and Barrett’s esophagus or columnar metaplasia. It must be supplemented by biopsy for the diagnosis of

metaplasia and the potential sequelae of dysplasia and neoplasia; endoscopic biopsy, with or without brushings, also facilitates the diagnosis of other infective esophagitides and malignancies. However, although changes such as elongation of the stromal papillae [1], a neutrophil infiltrate, an eosinophil infiltrate [2, 3] and “balloon” cells [4] have all been described in association with gastroesophageal reflux disease, the sensitivity, and specificity of these findings for the diagnosis of GERD have not been defined, and the role of histology, therefore, remains undefined.

In general, the complications of GERD are relatively infrequent, and the most frequent identifiable lesion remains the esophageal erosion or “*touche peptique*” described by Savary [5]. For patients with erosive esophagitis, the recurrence of symptoms after therapy correlates well with the recurrence of esophageal erosions (Figure 1) [6]. Neither the extent nor the severity of erosions correlates directly with symptom severity in an individual patient; however, erosion severity is predictive of a patient’s probable response to therapy and also of the likelihood of relapse after cessation of therapy, unlike the presence of minor, non-erosive changes [7, 8]. It is, therefore, important to grade the severity of erosive reflux esophagitis, particularly in the context of clinical trials.

### ENDOSCOPIC GRADING OF ESOPHAGITIS SEVERITY

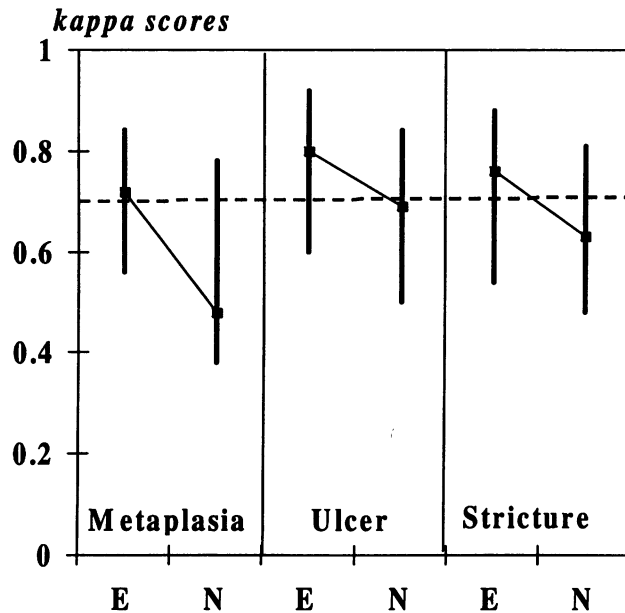
The most widely used classification system is that described first by Savary & Miller, in which disease severity is graded according to the extent of esophageal erosions [9]. The Savary-Miller classification recognizes also that complications of GERD are important but, in both versions described by the authors [9, 10], they are grouped together as high-grade esophagi-

tis (Grade 4 or Grade 5), regardless of whether or not there are concomitant erosions. In consequence, it is very difficult to use the Savary-Miller classification to document the healing of erosive esophagitis in patients with complicated disease. The recognition that metaplasia (M), ulceration (U), stricturing (S) and erosions (E) can occur independently of each other led to the formulation of the “MUSE” classification; in this case, the classification of erosion severity ( $E_0$  to  $E_2$ ) is based on the Savary-Miller classification, but it is supplemented by independent gradings of severity for ulcers ( $U_0$  to  $U_2$ ), strictures ( $S_0$  to  $S_2$ ) and metaplasia ( $M_0$  to  $M_2$ ) (Figure 2). This classification provides clear definitions of the different endoscopic features of GERD and is based on a pictorial report form, which allows the endoscopist to make a clear record of esophagitis severity [11, 12].

In recent years, it has become clear that the profusion of classification systems has made it increasingly difficult to compare the results of different therapeutic trials in GERD. This prompted the formation of an International Working Group charged with developing a standardized endoscopic esophagitis classification system, which would be generally acceptable in clinical or research practice. In an initial step, the group identified endoscopic

**Table 1. Diagnostic agreement between expert endoscopists (*kappa* values) for the identification of “mucosal” breaks [13].**

“Mucosal break”		<i>kappa</i> value
Length (mm)	Exudate	
< 5 mm	No	0.49
< 5 mm	Yes	0.88
> 5 mm	No	0.29
> 5 mm	Yes	0.55
Affecting only one fold		0.84
Circumferential		0.59



**Figure 3.** *Kappa* scores for evaluation of endoscopic features of complicated reflux esophagitis by 29 experienced endoscopists (E) and 13 novices (N), based on reporting of endoscopic video recordings and slide material. A *kappa* score  $\geq 0.70$  (dashed, horizontal line) is considered to indicate good agreement between observers. With permission from Ref. [13].

features, associated with GERD, which could be recognized reproducibly by endoscopists. These studies, based on high-quality 35 mm slides and video recordings of esophageal endoscopies, indicate that endoscopists can identify reliably, erosions or mucosal breaks, particularly if they have an overlying exudate (Table 1) as well as ulcers, strictures and metaplasia (Figure 3). This study suggested also that experienced endoscopists could identify reliably, some of the minor changes (erythema, edema, friability) attributable to reflux [13]. In conjunction with this, the group formulated a new classification system — the “L.A.” classification (first presented at the 1992 World Congress of Gastroenterology in Los Angeles) — which described four grades of esophagitis severity (Grade A to Grade D) based on the extent of mucosal breaks. The term “mucosal break” was coined to

encompass erosions as well circumscribed areas of erythema since it was felt there were no clear criteria for distinguishing between a “denuded” erosion and an erosion covered by “slough” or an “exudate.” The term “mucosal break” is also intended to include ulcers since there are no defined criteria for determining when an erosion deepens sufficiently to become an ulcer. Validation studies with the current version of the L.A. classification system indicate that the higher grades of esophagitis are associated with lower healing rates and higher relapse rates. Since it is based on endoscopic features, which can be identified reproducibly by endoscopists, the L.A. classification has the potential to be a generally-accepted, standardized classification system for erosive esophagitis. However, the L.A. classification does not record the presence or severity of other GERD lesions, which are, themselves,

identified reliably by endoscopists; thus in clinical practice and in therapeutic trials that include patients with "complicated" reflux disease, the MUSE classification offers a more comprehensive description of esophagitis severity.

### LIMITATIONS OF ENDOSCOPY

Despite its importance in clinical and research practice, endoscopy is not, however, universally applicable. It is inappropriate for the diagnosis of hiatal herniation or esophageal dysmotility. More importantly, there is an increasing recognition of "endoscopy negative reflux disease" (ENRD): recent studies suggest that 40 to 60 percent of patients with typical reflux symptoms do not, in fact, have esophageal erosions [14, 15]. For some physicians, this represents proof final that these patients do not have GERD and, in some jurisdictions, that these patients do not merit therapy with proton pump inhibitors. Despite this, many such patients will have evidence of a temporal correlation between reflux episodes and symptoms during esophageal pH monitoring studies, and their symptoms will often be relieved by medical anti-reflux therapy [14, 15]. Thus, it is becoming clear that the clinical spectrum of GERD does include ENRD and that endoscopy is not, therefore, the final arbiter as to a diagnosis of reflux disease.

### ROLE OF ENDOSCOPY FOR EVALUATION OF GERD

What then is the place of endoscopy in clinical practice? Endoscopic confirmation of esophageal erosions is highly specific for a diagnosis of GERD, but it has low sensitivity, and there is, therefore, the danger that endoscopy alone will underestimate greatly the prevalence of GERD.

An outcomes study has shown [16] that endoscopy leads to a significant change in therapy for patients with reflux symptoms, but the change was most marked in patients who had erosive esophagitis; it is not clear that the failure to alter therapy in patients with ENRD was appropriate. It has been argued that endoscopy is not necessary to make a diagnosis of GERD in a patient with typical symptoms unless there is a suspicion of serious underlying disease based on the patient's age or alarm symptoms such as weight loss, dysphagia, anemia or gastrointestinal blood loss. If reimbursement policies mandate a confirmed diagnosis of erosive esophagitis before effective antisecretory therapy can be started, endoscopy should be performed early, and, if possible, the patient should stop acid antisecretory or prokinetic therapy at least one to two weeks prior to endoscopy. If erosive esophagitis is confirmed, there seems to be no reason to repeat endoscopy simply to confirm healing since there is a good correlation between symptoms and the recurrence of erosions [6]. In the majority of patients, GERD is a chronic, relapsing condition, and the only indication for repeat endoscopy would be a significant change or worsening of the patient's symptoms.

For the present, the other major indication for endoscopy is the exclusion of Barrett's esophagus. There is continuing controversy over the advisability of surveillance follow-up for patients with Barrett's esophagus, but a cost-modeling study suggests that it is cost-effective, if the incidence of carcinoma in Barrett's exceeds 1 percent [17]; this provides support for current recommendations that endoscopic surveillance be conducted every two years in patients with confirmed Barrett's esophagus. The natural history of Barrett's esophagus is still unclear but data from Olmsted County [18] suggest that the area of involved mucosa does not progress significantly with time over follow-up

periods of three to eight years. Thus, on present evidence, it would seem reasonable to suppose that a patient who does not have Barrett's esophagus at the time of diagnosis is unlikely to develop metaplasia subsequently. This has led to the concept of a "once-in-a-lifetime" endoscopy for patients with GERD. Under this model, there would be no need to perform an endoscopy before embarking on therapy but one examination should be performed — during ongoing therapy — to exclude Barrett's and to minimize the likelihood of confusion between the histological changes of acute inflammation and those of metaplasia or dysplasia.

## CONCLUSION

In the long run, the role of endoscopy will change as more is learned about the natural history of symptomatic GERD and its relationship to erosive esophagitis, about the natural history of Barrett's esophagus and its progression to esophageal adenocarcinoma and about the importance of carditis and its relationship to the increasing incidence of adenocarcinoma of the cardia.

Endoscopic evaluation of a patient with reflux symptoms reassures the patient and the physician that no complications of GERD or other potentially serious condition has been overlooked. It also provides some indication as to the most appropriate therapy, the likelihood of response to therapy, and the likelihood of subsequent relapse. Against these advantages must be weighed the potential financial cost of the procedure to the patient and the health care system. Endoscopy is relatively costly, but the absolute cost varies considerably; complications from upper gastrointestinal endoscopy are very infrequent, but they have been recorded. The major disadvantage of endoscopy arises from the notion

that GERD is synonymous with erosive esophagitis; this may lead to a failure to diagnose GERD and, hence, to inappropriate or inadequate therapy for ENRD.

For the present, endoscopy is not a necessary prerequisite to therapy for typical reflux symptoms, but it is indicated at first presentation for patients with alarm symptoms referable to the upper gastrointestinal tract. Whenever it is performed, endoscopic evaluation should document the presence and extent of esophageal erosions using the L.A. or MUSE classification systems; the presence and extent of complications should also be documented and may be recorded using the MUSE classification. Non-erosive changes such as erythema may be ignored on the basis of present evidence and there are no clear data to support the acquisition of endoscopic biopsies for the diagnosis of GERD. However, a diagnosis of Barrett's esophagus must be confirmed histologically and endoscopic biopsies are, therefore, essential if the endoscopic appearances of the distal esophagus suggest the development of columnar metaplasia. An endoscopic surveillance program with multiple biopsies should be instituted if there is histological evidence of Barrett's esophagus, provided that the patient would be willing and able to undergo further therapy in the event that dysplastic or neoplastic lesions were identified. Endoscopic follow-up is not required for uncomplicated erosive reflux esophagitis or ENRD unless there has been a significant change in the patient's symptoms.

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