Esophagitis and Barrett Esophagus: Unifying the Definitions and Diagnostic Approaches, With Special Reference to Esophageal Atresia

Eric Hassall

C hildren with Barrett esophagus (BE) usually have had severe chronic gastroesophageal reflux disease (GERD), which began in their first year of life (1). Certain disorders predispose children to the most severe and chronic GERD, and therefore to BE. These include congenital esophageal abnormalities such as esophageal atresia (EA) or congenital diaphragmatic hernia; significant neuromotor impairment such as cerebral palsy or syndromes (eg, Cornelia de Lange syndrome, Down syndrome); and those with chronic lung diseases such as cystic fibrosis (2,3). Children without these disorders but with hiatal hernia or with obesity or a strong family history of GERD or BE or adenocarcinoma also have a higher prevalence of BE (3,4). These groups of children are more likely to require long-term treatment for healing and maintenance (5,6).

Regardless of the underlying cause of GERD, the absence of uniformity of definitions of esophagitis and BE has made for difficulties in diagnosis and in design and interpretation of clinical studies. The goal of this study was to explain the new definitions and their importance in EA and propose a standardized timeline and manner for endoscopic evaluation. In this study, ''EA'' is used to denote atresia with or without fistula. The terms ''cardia-type mucosa'' and ''cardiac mucosa'' are used synonymously.

ESOPHAGITIS

Definition and Diagnosis

For the diagnosis of reflux esophagitis, visible mucosal breaks, that is, erosions of the esophagus, are the endoscopic sign of greatest interobserver reliability, when the erosions are at least in the distal esophagus (7). The clinical context is key because, for example, distal erosions are also seen in bulimia and other causes of recurrent vomiting. However, erosive reflux disease is less common than nonerosive reflux disease in adults, and even less so in children. For this reason, for more than 20 years, pediatric endoscopists have relied on a combination of histologic findings as diagnostic of reflux esophagitis, namely hyperplasia of the basal cell layer and the papillae, eosinophils, and more recently spongiosis (dilated intercellular spaces). These are reactive changes,

often absent even in erosive esophagitis, present in healthy volunteers, and occurring notably in eosinophilic esophagitis and other esophageal disorders. For these reasons, the recent consensus statements in pediatric GERD confirm that there are insufficient data recommending histology to diagnose or exclude the diagnosis of reflux esophagitis in children; and that the primary reason to take esophageal biopsies is to diagnose or exclude other conditions, such as esophageal metaplasia, eosinophilic esophagitis, Crohn esophagitis, and infections (8,9).

As in adults, reflux esophagitis in pediatrics (7) is defined endoscopically by visible breaks of the distal esophageal mucosa (8,9). In other words, it is not diagnosed by erythema, loss or increase of vascular pattern, ''inflammation,'' or ''edema'' (neither is an endoscopic finding)—all of which are subjective terms, within the range of normal, with no diagnostic correlate.

BARRETT ESOPHAGUS

The importance of BE is 2-fold: it is a marker for the presence of severe GERD and it has malignant potential. The diagnosis, therefore, has consequences for long-term follow-up and longevity. Because cancer only rarely occurs in the pediatric age group (10), that issue is discussed elsewhere (7,11). The issues in pediatrics largely pertain to accuracy of diagnosis, which has important implications for life or health insurance and for endoscopic surveillance.

Pathogenesis

Chronic, severe GERD damages the squamous mucosa of the tubular esophagus, exposing pluripotent stem cells in basal layers and ducts of esophageal glands to refluxed gastric juice, which in turn results in a change in cellular gene expression, resulting in columnar metaplasia. The actual progenitor cell is unknown (12).

Definition

A full history of BE is given elsewhere (12), but from the mid-1980s, the prevailing view was that the sine qua non for the diagnosis of BE was the presence on biopsy of intestinal metaplasia (IM), that is, goblet cells containing acid mucin (staining with Alcian blue at pH 2.5) (13). This is referred to as ''Barrett metaplasia'' or ''specialized metaplasia'' or variations on this. This was based on evidence that only IM in the esophagus was premalignant.

Recently this concept has undergone reconsideration. Although goblet cell metaplasia is believed to represent the endpoint of a GERD-induced chronic mucosal injury, at least in benign mucosa (14–16), reports in adults (17) and children (18) have shown that esophageal metaplasia can occur in the form of cardia-type columnar metaplasia without goblet cells.

Histochemical and genetic studies on cardia-type mucosa in biopsy and resected specimens show that the background nongoblet epithelium in BE is biologically intestinalized and exhibits several molecular abnormalities similar to the goblet cell–containing epithelium (19). Retrospective and outcome studies suggest a well-defined risk of neoplasia in patients with esophageal columnar metaplasia but without goblet cells (20). In addition, the mucosa of Barrett metaplasia is a mosaic of different columnar epithelia, and IM can be missed by sampling error at endoscopy. Lastly, it is possible that acid suppression may prevent or decrease goblet cell metaplasia (18).

For these reasons, recent consensus studies on adults and children include cardia-type epithelium in the definition of Barrett esophagus (8,9). The term ''endoscopically suspected esophageal metaplasia'' (ESEM) is recommended to describe endoscopic findings suggestive of BE that await histologic confirmation. When biopsies from ESEM show columnar epithelium, the diagnosis is Barrett esophagus, and the presence or absence of IM stated (7–9).

Diagnosis

Accurate diagnosis of BE begins with identification and documentation of the key endoscopic landmarks of the gastroesophageal junction—Z-line, lower esophageal sphincter zone, diaphragmatic pinchcock, and the top of the gastric folds. This is the basic ''process of care'' criterion for accurate diagnosis of BE (21). Documentation of esophagogastric landmarks together with multiple biopsies is necessary to characterize ''endoscopically suspected esophageal metaplasia.''

Landmarks are not always easily identifiable, especially in the operated esophagus (eg, repaired EA) or when hiatal hernia is present. Hiatal hernia is highly prevalent in adults with severe GERD, as it is in 40% of children with severe chronic GERD (6) and in almost all patients with long-segment BE (1,22).

Marked inflammation or pus may also make landmark identification difficult. In this circumstance, endoscopy should be repeated after 12 weeks or so of high-dose PPI treatment. This heals the esophagus and removes the ''exudative camouflage,'' after which the landmarks can be identified.

The suspected abnormal segment should be photographed to document the landmarks and the extent of the metaplastic segment recorded by a standardized method, both for the patient's chart and for subsequent review by the endoscopist and/or colleagues (8,9).

Another caveat regarding the nature of the columnar lining on biopsy is the risk of sampling error; that is, focal areas of goblet cell metaplasia can be missed, either by inadequate tissue sampling or because of failure to stain the biopsies with Alcian blue at pH 2.5 (21). The purpose of taking multiple closely spaced biopsies is to most accurately characterize the mucosa as purely gastric columnar, that is, cardia-type, or as columnar with IM, and to detect the presence of dysplasia. Biopsies containing oxyntic mucosa are likely to represent hiatal hernia as the source and are not considered metaplastic, although a mix of cardiac and oxyntic mucosa is often present in the most distal part of the metaplastic segment, with a mosaic of cardiac- and intestinal-type being more proximal (7,13,18,23,24).

Four-quadrant biopsies every 1 cm for circumferential metaplastic segments is advised (7). This should include several biopsies at and immediately distal to the cephalad-displaced Z-line, as the highest yield of goblet cell metaplasia is proximal, in both children (18,24) and adults (13,23).

Prevalence

Although the prevalence of BE is much lower in children than in adults, columnar metaplasia with goblet cells (IM) occurs in some 5% of children with severe chronic GERD from all causes, and in another 5% without IM (6). Under the new definition, 10% of patients in this series had BE.

REFLUX DISEASE AND BARRETT IN EA

Importance

Although esophageal continuity is reestablished surgically in EA, the repaired esophagus has never functioned in utero as a single coordinated motor peristaltic unit. Therefore, dysmotility and poor clearance of refluxate are often present. Hiatal hernia may be created surgically in the process of esophageal anastomosis. Patients with EA and severe chronic GERD often ''get used to'' their symptoms, which may become relatively ''silent.'' These days, most patients with EA have normal longevity, which means they are more likely to develop complications of GERD. Most symptoms and complications are treatable.

Prevalence of BE in EA

There have been several reports of BE in esophageal atresia in children (3,25–28) and adults (29,30) and reports of adenocarcinoma or squamous carcinoma (31–35). However, reliable prevalence data have been hard to come by because of small numbers, lack of uniform diagnostic definitions and approaches, lack of adherence to process of care criteria for diagnosis (21), and difficulties with long-term case acquisition and endoscopic follow-up. It is recognized that many patients with EA found to have severe esophagitis and metaplasia at endoscopy have few or no symptoms (29,30,36,37), so screening only symptomatic patients will miss these changes. Even the largest long-term studies with consistency of approaches (37,38) are beset by some of these problems.

In 1 large study from Australia (38), patients age >20 years in a joint pediatric-adult clinic were studied. Up to 1982, 485 infants had undergone surgery for EA at the Children's Hospital, Melbourne. Of these, 28 were unable to be contacted or had died; 288 were contacted, and 132 attended the clinic from 2000 to 2003. Only symptomatic patients offered endoscopy prospectively; 62 underwent esophagogastroduodenoscopy or had it within the last 5 years. Reflux esophagitis was diagnosed in 58%, and BE diagnosed on the basis of tongues extending >5 mm proximal to gastric folds, plus IM on biopsy. The authors suspected BE in 16, of whom 7 had IM, that is, 11%. This is 1 of the best studies published with a standardized protocol of landmark identification; but of the large cohort, endoscopic information was obtained in only 62 of 485 subjects. This likely represents a marked underdiagnosis of BE for reasons of acquisition (only symptomatic patients were endoscoped) and exclusion of metaplasia other than intestinal.

Management of BE

Management of BE is not the focus of this study, and therefore is addressed only in brief. The treatment of nondysplastic BE, whether in EA or not, is the same as the treatment of GERD. The presence of BE does not mandate fundoplication (11). The decision to perform fundoplication is driven by the same indications as GERD, for example, failure of optimized medical treatment, poor compliance, evidence of pulmonary aspiration, and damage. One difference is that, although most cases of GERD can and should be treated with only once-daily proton pump inhibitor (PPI), more aggressive medical management—that is, high-dose twice-daily treatment with PPI, monitored against esophageal pH study—is indicated in cases of BE. There is evidence that high-dose PPI or other medications may slow the development of dysplasia (39) or

reduce the risk of esophageal adenocarcinoma; (40) but there is no evidence that surgery does any better than medical treatment in accomplishing either of these goals (41,42).

Endoscopic Evaluation in EA

The purposes of performing endoscopy in EA are to diagnose the cause of symptoms, to determine whether metaplasia is present and what type it is, and to rule out dysplasia. Barium contrast, pH studies, and esophageal dilatation all have their roles, but are not discussed here. Symptomatic patients should undergo investigation regardless of age.

It is recognized that symptoms or their absence is not predictive of the presence of erosive esophagitis or Barrett metaplasia (29,30,36,37). The timeline from no dysplasia to high-grade dysplasia, when it does occur, appears to be at least 3 to 5 years (43). The youngest patient with adenocarcinoma of the esophagus documented in the literature is 10 years old (10).

Given these observations, it seems logical to screen all patients with EA at the age of 10 years or so, regardless of symptoms. If they are already taking acid-suppressive drugs, the initial procedure should be performed on treatment. Process of care criteria should be followed—landmarks documented in centimeters from the teeth and photographed, step-wise 4-quadrant large forceps biopsies taken, their origins relative to landmarks documented, and staining of biopsies with Alcian blue pH 2.5 performed. If erosive esophagitis is present or landmarks are unclear, endoscopy should be repeated after 3 to 4 months of high-dose PPI. For BE with or without IM, repeat endoscopy is recommended to be performed only in 3 to 5 years, unless new symptoms develop. For BE with dysplasia, the same management options apply as for adults (11).

REFERENCES

1. Hassall E. Barrett's esophagus: new definitions and approaches in children. *J Pediatr Gastroenterol Nutr* 1993;16:345–64.
2. Snyder JD, Goldman H. Barrett's esophagus in children and young adults. Frequent association with mental retardation. *Dig Dis Sci* 1990;35:1185–9.
3. Hassall E. Co-morbidities in childhood Barrett's esophagus. *J Pediatr Gastroenterol Nutr* 1997;25:255–60.
4. Romero Y, Cameron AJ, Schaid DJ, et al. Barrett's esophagus: prevalence in symptomatic relatives. *Am J Gastroenterol* 2002;97:1127–32.
5. Hassall E. Outcomes of fundoplication: causes for concern, newer options. *Arch Dis Child* 2005;90:1047–52.
6. Hassall E, Kerr W, El-Serag HB. Characteristics of children receiving proton pump inhibitors continuously for up to 11 years duration. *J Pediatr* 2007;150:262–7.
7. Vakil N, van Zanten SV, Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006;101:1900–20.
8. Sherman P, Hassall E, Fagundes-Neto U, et al. A global evidence-based consensus on the definition of gastroesophageal reflux disease in children. *Am J Gastroenterol* 2009;104:1278–95.
9. Vandenplas Y, Rudolph CD, Di Lorenzo C, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2009;49:498–547.
10. Hassall E, Dimmick JE, Magee JF. Adenocarcinoma in childhood Barrett's esophagus: case documentation and the need for surveillance in children. *Am J Gastroenterol* 1993;88:282–8.
11. Sharma P. Clinical practice. Barrett's esophagus. *N Engl J Med* 2009; 361:2548–56.
12. Spechler SJ, Fitzgerald RC, Prasad GA, et al. History, molecular mechanisms, and endoscopic treatment of Barrett's esophagus. *Gastroenterology* 2010;138:854–69.
13. Weinstein WM, Ippoliti AF. The diagnosis of Barrett's esophagus: goblets, goblets, goblets. *Gastrointest Endosc* 1996;44:91–5.
14. Bremner CG, Lynch VP, Ellis FH Jr. Barrett's esophagus: congenital or acquired? An experimental study of esophageal mucosal regeneration in the dog. *Surgery* 1970;68:209–16.
15. Fitzgerald RC. Barrett's oesophagus and oesophageal adenocarcinoma: how does acid interfere with cell proliferation and differentiation? *Gut* 2005;54(Suppl 1):i21–6.
16. Gillen P, Keeling P, Byrne PJ, et al. Experimental columnar metaplasia in the canine oesophagus. *Br J Surg* 1988;75:113–5.
17. Peitz U, Vieth M, Pross M, et al. Cardia-type metaplasia arising in the remnant esophagus after cardia resection. *Gastrointest Endosc* 2004;59:810–7.
18. Hassall E. Cardia-type mucosa as an esophageal metaplastic condition in children: "Barrett's esophagus, intestinal metaplasia-negative." *J Pediatr Gastroenterol Nutr* 2008;47:102–6.
19. Liu W, Hahn H, Odze RD, et al. Metaplastic esophageal columnar epithelium without goblet cells shows DNA content abnormalities similar to goblet cell-containing epithelium. *Am J Gastroenterol* 2009;104:816–24.
20. Riddell RH, Odze RD. Definition of Barrett's esophagus: time for a rethink—is intestinal metaplasia dead? *Am J Gastroenterol* 2009;104: 2588–94.
21. Ofman JJ, Shaheen NJ, Desai AA, et al. The quality of care in Barrett's esophagus: endoscopist and pathologist practices. *Am J Gastroenterol* 2001;96:876–81.
22. Cameron AJ. Barrett's esophagus: prevalence and size of hiatal hernia. *Am J Gastroenterol* 1999;94:2054–9.
23. Chandrasoma PT, Der R, Dalton P, et al. Distribution and significance of epithelial types in columnar-lined esophagus. *Am J Surg Pathol* 2001; 25:1188–93.
24. Qualman SJ, Murray RD, McClung HJ, et al. Intestinal metaplasia is age related in Barrett's esophagus. *Arch Pathol Lab Med* 1990;114:1236–40.
25. Cheu HW, Grosfeld JL, Heifetz SA, et al. Persistence of Barrett's esophagus in children after antireflux surgery: influence on follow-up care. *J Pediatr Surg* 1992;27:260–4. discussion 265–6.
26. Cooper JE, Spitz L, Wilkins BM. Barrett's esophagus in children: a histologic and histochemical study of 11 cases. *J Pediatr Surg* 1987;22:191–6.
27. Lindahl H, Rintala R, Sariola H, et al. Cervical Barrett's esophagus: a common complication of gastric tube reconstruction. *J Pediatr Surg* 1990;25:446–8.
28. Othersen HB Jr, Ocampo RJ, Parker EF, et al. Barrett's esophagus in children. Diagnosis and management. *Ann Surg* 1993;217:676–80. discussion 680–1.
29. Krug E, Bergmeijer JH, Dees J, et al. Gastroesophageal reflux and Barrett's esophagus in adults born with esophageal atresia. *Am J Gastroenterol* 1999;94:2825–8.
30. Deurloo JA, Ekkelkamp S, Bartelsman JF, et al. Gastroesophageal reflux: prevalence in adults older than 28 years after correction of esophageal atresia. *Ann Surg* 2003;238:686–9.
31. Pultrum BB, Bijleveld CM, de Langen ZJ, JT P. Development of an adenocarcinoma of the esophagus 22 years after primary repair of a congenital atresia. *J Pediatr Surg* 2005;40:e1–e4.
32. Adzick NS, Fisher JH, Winter HS, et al. Esophageal adenocarcinoma 20 years after esophageal atresia repair. *J Pediatr Surg* 1989;24:741–4.
33. Alfaro L, Bermas H, Fenoglio M, et al. Are patients who have had a tracheoesophageal fistula repair during infancy at risk for esophageal adenocarcinoma during adulthood? *J Pediatr Surg* 2005;40:719–20.
34. Deurloo JA, van Lanschot JJ, Drillenburg P, et al. Esophageal squamous cell carcinoma 38 years after primary repair of esophageal atresia. *J Pediatr Surg* 2001;36:629–30.
35. LaQuaglia MP, Gray M, Schuster SR. Esophageal atresia and antethoracic skin tube esophageal conduits: squamous cell carcinoma in the conduit 44 years following surgery. *J Pediatr Surg* 1987;22:44–7.
36. Castilloux J, Bouron-Dal Soglio D, Faure C. Endoscopic assessment of children with esophageal atresia: lack of relationship of esophagitis and esophageal metaplasia to symptomatology. *Can J Gastroenterol* 2010;24:312–6.
37. Sistonen SJ, Koivusalo A, Nieminen U, et al. Esophageal morbidity and function in adults with repaired esophageal atresia with tracheoesophageal fistula: a population-based long-term follow-up. *Ann Surg* 2010; 251:1167–73.

38. Taylor AC, Breen KJ, Auldist A, et al. Gastroesophageal reflux and related pathology in adults who were born with esophageal atresia: a long-term follow-up study. *Clin Gastroenterol Hepatol* 2007;5:702–6.

39. El-Serag HB, Aguirre TV, Davis S, et al. Proton pump inhibitors are associated with reduced incidence of dysplasia in Barrett's esophagus. *Am J Gastroenterol* 2004;99:1877–83.

40. Nguyen DM, Richardson P, El-Serag HB. Medications (NSAIDs, statins, proton pump inhibitors) and the risk of esophageal adenocarcinoma in patients with Barrett's esophagus. *Gastroenterology* 2010;138:2260–6.

41. Lundell L, Miettinen P, Myrvold HE, et al. Comparison of outcomes twelve years after antireflux surgery or omeprazole maintenance therapy for reflux esophagitis. *Clin Gastroenterol Hepatol* 2009;7:1292–8.

42. Spechler SJ. Surgery for gastroesophageal reflux disease: esophageal impedance to progress? *Clin Gastroenterol Hepatol* 2009;7:1264–5.

43. Reid BJ, Blount PL, Rubin CE, et al. Flow-cytometric and histological progression to malignancy in Barrett's esophagus: prospective endoscopic surveillance of a cohort. *Gastroenterology* 1992;102: 1212–9.