Esophagitis: Causes Other Than Reflux

60

Mike Thomson

Inflammatory processes in the pediatric esophagus have received a disproportionately small amount of attention until recently, when appreciation of their pathophysiology and concordant clinical importance has been highlighted. This increase in interest and exposure is probably a phenomenon secondary to a number of important factors, which include improved diagnostic yield from relatively recent technical advances in areas such as infant and pediatric endoscopy; advances in fields such as mucosal immunology, allowing for the realization that etiopathologic mechanisms for esophagitis are more complex than simple luminal chemical damage; and a shift in clinical opinion recognizing esophageal pathology as a major cause of nonspecific ubiquitous symptoms such as infant colic, feeding disorders, and recurrent abdominal pain among others. A state of knowledge such as this has made pediatric esophagitis, until recently, a relatively underdeveloped area of research and clinical understanding, but this is rapidly changing [1].

It is now clear, therefore, that esophagitis in infants and children has many responsible etiologic pathways that may have complex interactions and hence requires equally complex diagnostic and therapeutic strategies. Such causative factors are now known to include cow's milk protein (CMP) intolerance or allergy, pH-dependent and pH-independent gastroesophageal reflux (GER), dysmotility of various causes, and infective, traumatic, and iatrogenic causes, among others. Hence, the term "esophagitis" can be used to describe chemical, infectious, inflammatory, ischemic, immunologic, and degenerative abnormalities [2]. Nevertheless, there remains a minor degree of controversy regarding the definition and significance of esophagitis, as assessed by the standard diagnostic techniques, including endoscopy and biopsy [3, 4]. This chapter attempts to describe basic etiologies other than reflux-related esophagitis and does not deal with eosinophilic esophagitis which is dealt with in subsequent chapters.

Etiology and Pathophysiology

The etiologies of esophagitis in infancy and childhood can usefully be divided into the following groups:

1. Chemical:
   (a) Owing to refluxed contents from the stomach and duodenum such as gastric acid, pepsin, bile, and trypsin
   (b) Owing to swallowed substances, either intended such as medications or accidental caustic ingestion such as dishwasher liquid

M. Thomson
Centre for Paediatric Gastroenterology, Sheffield Children's Hospital NHS Foundation Trust, Sheffield S10 2TH, UK
e-mail: Mike.Thomson@sch.nhs.uk

H. Till et al. (eds.), *Esophageal and Gastric Disorders in Infancy and Childhood*,
DOI 10.1007/978-3-642-11202-7_60

2. Immunologic: owing to specific responses to specific antigens such as CMP or multiple food intolerance or allergy
3. Infective: associated with organisms as diverse as *Helicobacter pylori* (with associated reflux), *Candida*, cryptosporidiosis, herpes simplex, and *Cytomegalovirus* (CMV)
4. Traumatic: secondary to intraluminal trauma (e.g., long-term nasogastric tube) or irradiation (e.g., as part of bone marrow transplant conditioning)
5. Systemic disease manifestation: associated with conditions such as Crohn's disease and chronic granulomatous disease
6. Miscellaneous: such as that associated with passive smoking or that occurring in fictitious or induced illness (Munchausen syndrome by proxy)
7. Idiopathic: eosinophilic esophagitis

The etiopathologic role of each of these situations can therefore be usefully discussed under each heading, bearing in mind that an individual child or infant may, of course, have more than one factor contributing to the esophageal insult at any one time (e.g., GER and cow's milk-associated esophagitis).

Chemical

Chemical esophagitis owing to swallowed substances.

Ingested materials are usually household or garden substances and are usually markedly alkaline; the common one was dishwasher fluid, often with a pH of 9 or above. However, fortunately, in most countries, this has been replaced with powder, which is less easy to swallow, and even individually wrapped tablets of powder. Acute perforation, mediastinitis, and subsequent esophageal stricture have frequently been seen. The possibility of non-accidental injury should not be forgotten in this context. It is notable that the rate of subsequent stricture formation is high, and more recently, a potentially effective post-dilation topical application of an anti-fibrotic, mitomycin C, has shown promise in preventing restenosis and long-term repeated stricture dilation [5].

Restenosis post-dilation of strictures due to many variable pathologies has now been successfully prevented by the use of this substance applied topically at endoscopy – the only pathology which may be refractory to its effect is in epidermolysis bullosa [6] (Fig. 60.1).

Many medications have been associated with esophageal damage and symptoms of esophagitis, and these include tetracyclines (not recommended under the age of 12 years, of course), drugs used in acne therapy, and nonsteroidal anti-inflammatory drugs [7–10].

Immunologic

Although it is now clear that multiple food antigens may induce esophagitis [11, 12], the most common precipitant is CMP. Standard endoscopic biopsy and histology do not reliably distinguish between primary reflux esophagitis and the emerging clinical entity of cow's milk-associated reflux esophagitis. This variant of cow's milk allergy appears to be a particularly common manifestation in infancy, with symptoms indistinguishable from primary GER but that settle on an exclusion diet [13]. Some dif-

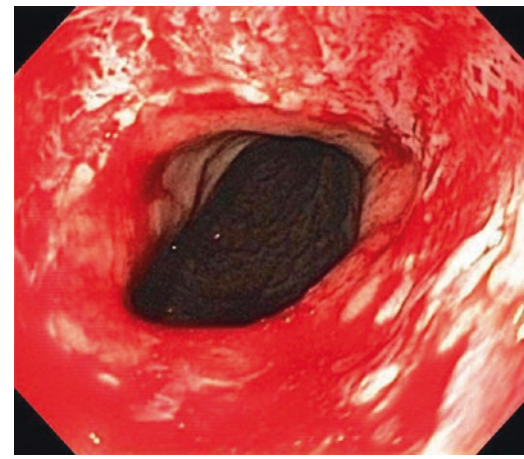

Fig. 60.1 Example of caustic injury to the esophagus

ferentiation from primary reflux has been suggested on the basis of an esophageal pH testing pattern and an α-lactoglobulin antibody response, although the former has not been substantiated by more than one center [13, 14]. There is recent evidence that this esophagitis is becoming a more common presentation of infant food allergy within the developed world and, in fact, may be induced by a variety of antigens in addition to cow's milk [11, 12]. Many affected infants have sensitized while exclusively breastfed, and a defect in oral tolerance for low doses has been postulated as the underlying cause [15, 16].

Esophageal mucosal eosinophilia has been described in both suspected cow's milk-associated [11] and primary reflux esophagitis (Fig. 60.2) [17], as well as in other conditions, such as idiopathic eosinophilic esophagitis (EE) [18]. A variety of immunohistochemical markers have been used to examine the esophageal mucosa, including eotaxin, a recently described eosinophil-specific chemokine (Fig. 60.3) [19], and markers of T-cell lineage and activation. Despite the mild histologic abnormality in CMP-associated esophagitis, an increased expression of eotaxin co-localized with activated T lymphocytes to the basal and papillary epithelium has been shown [20], distinguishing this from primary reflux esophagitis. The molecular basis of the eotaxin upregulation in cow's milk protein-sensitive enteropathy (CMPSE) is unknown. However, there is evidence from murine models of asthma that antigen-specific upregulation of eotaxin expression can be induced by T cells and blocked by anti-CD3 monoclonal antibodies. This suggests the possibility of a distinct mechanism in CMPSE, in which mucosal homing to the esophagus occurs of lymphocytes activated within the small intestine. This may explain the seemingly counterintuitive finding of the basal, as opposed to superficial, chemokine expression, and the common occurrence of mucosal eosinophilia in this condition. The esophageal motility disturbance of CMPSE-associated esophagitis is thus suggested to occur as a neurologic consequence of the inflammatory infiltration induced from lamina propria vessels into the epithelial compartment [21]. This proposed mechanism contrasts with the current concept of luminally induced inflammation found in primary reflux esophagitis and is consistent with the characteristic delayed onset and chronic nature of cow's milk-associated reflux esophagitis. It has also been suggested that increased numbers of mucosal mast cells allow a distinction to be made between allergy-induced and reflux-induced esophagitis [22]. Much work is required in this area and is ongoing.

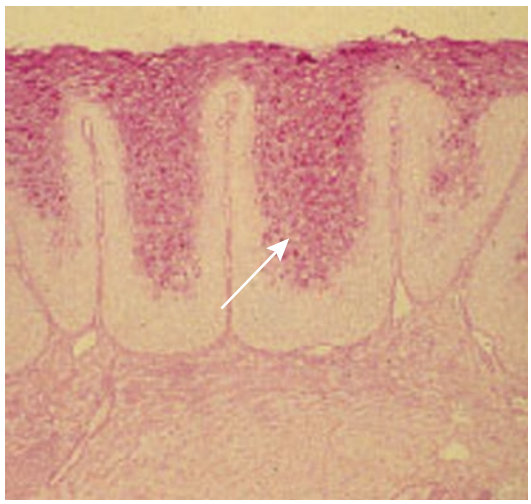

Fig. 60.2 Esophageal mucosal eosinophilia seen in cow's milk-associated and primary reflux esophagitis and primary eosinophilic esophagitis. (Eosinophils marked by *arrows*)

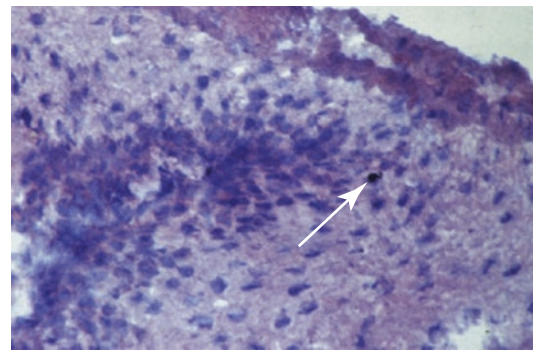

Fig. 60.3 Eotaxin, a recently described eosinophil-specific chemokine. (Darker staining area marked by an *arrow)*

Infective

The majority of infective esophagitis that occurs is in the immunocompromised child and is due to such agents as herpes simplex, CMV, *Candida*, and others. Mucosal damage owing to physical or chemical causes may predispose the patient to opportunistic infection. Oral herpes or *Candida* may offer some clue to etiology, and the older child will often complain of odynophagia or dysphagia. Diagnosis may be made on endoscopy with biopsy, but brushings may offer a greater diagnostic yield.

Viral esophagitis is usually due to herpes simplex, CMV, and, occasionally, *Varicella zoster* [23–25]. Herpes simplex esophagitis can occur in those with normal immune function [26], but is more often seen in those who are immunocompromised. In one series, 10% of the liver or kidney transplant recipients had herpes or CMV esophagitis [27], and it is also commonly seen in pediatric human immunodeficiency virus (HIV) infection [28]. The use of prophylactic acyclovir/ganciclovir is conjectural but may be of some benefit.

The diagnosis of herpes esophagitis is often difficult because the characteristic nuclear inclusions and multinucleate giant cells may not be seen in endoscopic biopsies; however, a prominent mononuclear cell infiltrate is described as characteristic (Fig. 60.4) [29]. It may be that the esophagus is particularly vulnerable in the GI tract owing to affinity of the herpes virus for stratified epithelium. Typically, roundish distinct disseminated lesions with yellowish borders are seen and have been termed "volcano ulcers" (Fig. 60.5) [30] although early in the presentation, vesicles may be noted. Although the inflammation can resolve spontaneously in the immunocompetent, in those with poor immune function, acyclovir and a high index of suspicion are recommended [30]. Resistance to acyclovir has been described, in which case, foscarnet is the agent of choice [31]. CMV esophagitis is confirmed by basophilic nuclear inclusions on biopsy of the edge of the ulcers, which are similar in appearance to herpetic ones. CMV is predominantly found in immunocompromised individuals, and treatment is with ganciclovir or foscarnet [25]. Hemorrhage, fistulae, and esophageal perforation in adults with viral esophagitis are described [32, 33]. Acute HIV infection can also cause esophagitis [34].

Candida, the most common infectious cause of esophagitis, has the classic appearance of white plaques on the mucosa, which cannot be washed or brushed off, unlike food or milk residue, and which often extends up to the upper

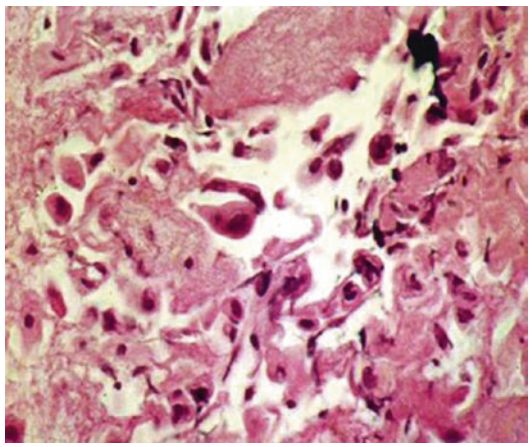

Fig. 60.4 Herpes esophagitis with nuclear inclusions, multinucleate giant cells, and a prominent mononuclear cell infiltrate

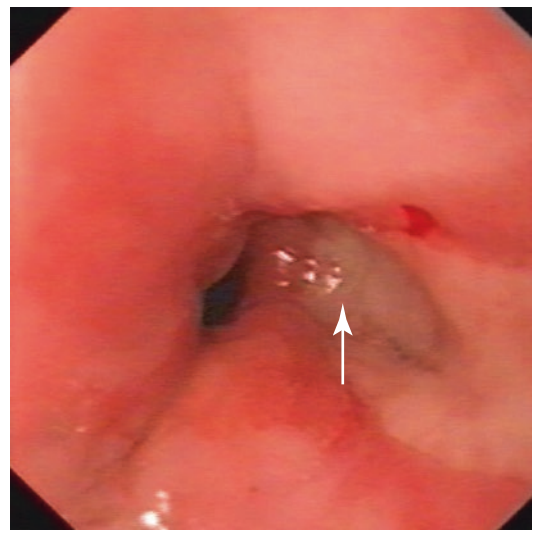

Fig. 60.5 Macroscopic appearances of herpes esophagitis. Roundish distinct disseminated lesions with yellowish borders are seen and have been termed "volcano ulcers" (*arrow*)

third of the esophagus (Fig. 60.6) [35]. Oral *Candida* is not predictive of esophageal involvement except in the immunocompromised host, but even in these children, extensive esophageal involvement is seen in the absence of oral candidiasis [36]. Mucositis and a white cell count less than 0.5×10^6/L predispose patients with leukemia to candidal esophagitis [37]. Steroid use (even poor technique with inhaled steroids for asthma) or acquired or congenital immunocompromise may be etiologic and may have the appearance of white focal lesions on the esophageal surface (Fig. 60.7). This appearance may be difficult to distinguish from eosinophilic esophagitis. Apart from the macroscopic appearances, diagnosis is confirmed by the presence of hyphae in biopsies (Fig. 60.8). Culture is not helpful because coexistent oral *Candida* can confuse the assessment. Complications include fistulae, perforation, painless stricture formation, esophageal dysmotility, transient achalasia [38], and systemic candidiasis. A 2–6 week course of oral nystatin can be effective in those with normal immune function, but it is more convenient to give fluconazole. Fluconazole or liposomal amphotericin is required, and both are effective in the immunocompromised child. Esophageal resection and diversion for necrotizing candidal esophagitis have been successful in a 10-year-old [39].

Eradication of *H. pylori* in adults has been associated with increased acid production and hence more noxious gastroesophageal refluxate. However, there does not seem to be any increased incidence of esophagitis in the presence of, or following, the eradication of *H. pylori* in children [40]. Because *H. pylori* affects gastric epithelium, it is not surprising that it has been identified in Barrett epithelium in a child, in whom symptoms

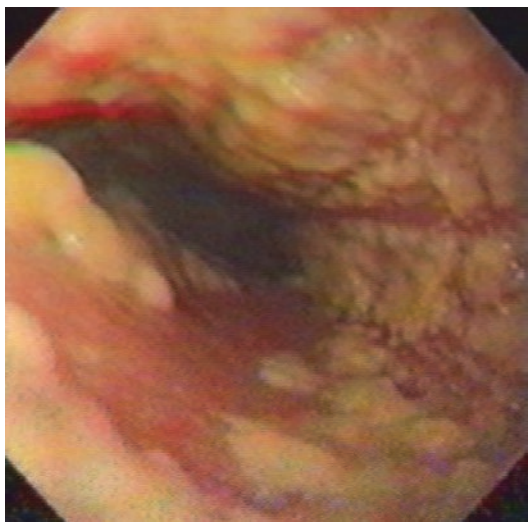

Fig. 60.6 Candidal esophagitis has the classic appearance of white plaques on the mucosa that cannot be washed or brushed off

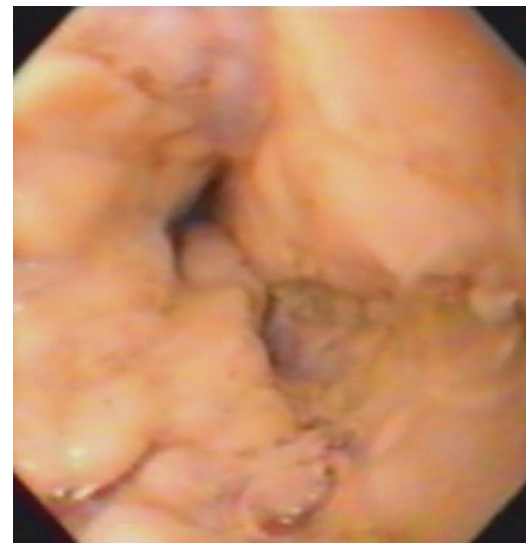

Fig. 60.7 Candidal esophagitis may have the appearance of white focal lesions on the esophagus, which may be difficult to distinguish from allergic esophagitis

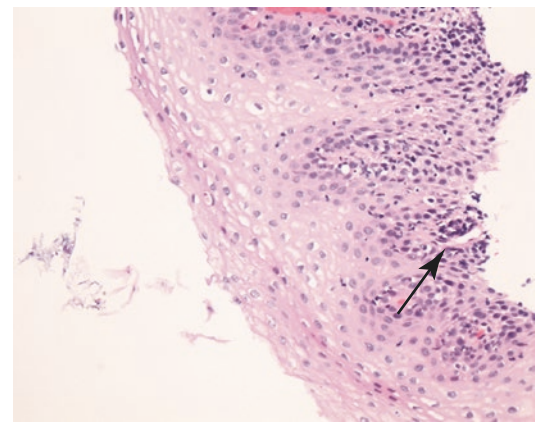

Fig. 60.8 Candidal hyphae (*arrows*)

resolved only with addition of amoxicillin to anti-reflux therapy [41]. Primary bacterial esophagitis is described in immunocompromised patients and may be successfully treated with long-term ciprofloxacin, metronidazole, or penicillin – or a combination dependent on bacteria and sensitivity [42].

Other opportunistic organisms causing esophagitis, such as *Cryptosporidium* and *Acremonium*, have been reported [43, 44].

Traumatic

Trauma causing esophageal pathology could, of course, be accidental, intentional, or iatrogenic. The presence of a nasogastric tube may be associated with abrasive esophagitis, and it has been postulated that the severe esophagitis found in newborn infants in one study, in the absence of other etiologic factors, may have been secondary to enthusiastic upper GI suction at birth [45]. Of particular note was the severity of the esophagitis in the face of relatively minimal symptomatology, such as feeding refusal. Radiation-induced esophageal strictures are described in children receiving mediastinal irradiation (usually greater than 4,000 cGy) and doxorubicin, occurring between 1 and 10 years post-therapy [46]. Radiation-associated esophagitis following bone marrow transplant conditioning is known to occur in the subsequent 1–2 weeks but is usually amenable to medical therapy.

Systemic Disease Manifestation

GER occurs more commonly in diverse conditions such as cystic fibrosis, severe combined immunodeficiency, cerebral palsy, raised intracranial pressure, celiac disease, and conditions associated with impaired gastric emptying [47, 48]. Certain diseases are, however, associated with esophagitis, which is not via the pathogenetic pathway of reflux. Crohn's disease is a prime example, and Crohn's lesions in the esophagus are usually distinct rounded ulcers, although diffuse disease may also occur (Fig. 60.9). Endoscopic examination with biopsy of the upper GI tract should be part of the diagnostic workup of a child with suspected Crohn's disease [49]. Relapse of the disease may be associated with recurrence of esophageal manifestations [50]. Type 1b glycogen storage disease may present with similar phenotype to Crohn's disease, and severe esophageal involvement has been noted in childhood in this condition [51]. Inflammation and stricturing of the esophagus can occur in chronic granulomatous disease and can involve most of its length, making balloon dilation difficult [52]. Scleroderma and vasculitic conditions such as polyarteritis nodosa have significant esophageal pathology in adults but are very rare in pediatric populations. Graft-versus-host disease may present in the esophagus although this is less likely than other GI areas such as the stomach and rectum. Epidermolysis bullosa is a debilitating disease that may also involve the esophagus, as are other dermatological conditions which affect the esophagus such as lichen sclerosus et atrophicus.

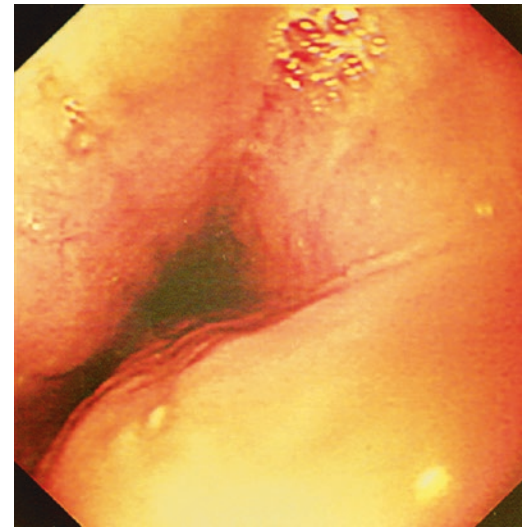

Fig. 60.9 Distinct round ulcers of Crohn's esophagitis

Miscellaneous

Passive smoking has a strong association with esophagitis in childhood. The reasons behind this are not completely understood, but nicotine is

known to relax the LES and may decrease mucosal blood flow. The nicotine levels in swallowed saliva may directly injure the esophagus or render it more susceptible to injury from acid exposure. Also, free radicals present in tobacco smoke may reduce antioxidant defenses [53].

Fictitious or induced illness (Munchausen syndrome by proxy) can be at the root of esophagitis in children, but this is usually due to the deliberate introduction into the esophagus by the perpetrator of caustic or irritative substances [54].

Idiopathic: Eosinophilic

Eosinophilic esophagitis (EE) is the subject of a subsequent chapter.

Management and Prognosis

Management of esophagitis must, of course, be dictated by its etiology, which further underlines the vital nature of obtaining an accurate diagnosis based on upper endoscopy and histologic assessment.

Because the vast majority of cases of esophagitis in infants and children will be due to GER, then treatment of GER and treatment of GER-related esophagitis will be very closely linked. Treatment of GER is also dealt with in other chapters. Other specific treatments for specific pathologies are also dealt with.

Infective causes of esophagitis in pediatrics require specific therapies. Viral esophagitis is usually due to herpes simplex, CMV, and, occasionally, *Varicella zoster* [23–25]. Although the inflammation can resolve spontaneously in the immunocompetent, in those with poor immune function, acyclovir and a high index of suspicion are recommended [30]. The use of prophylactic acyclovir is conjectural but may be of some benefit posttransplant. Resistance to acyclovir has been described, in which case, foscarnet is the agent of choice [31]. CMV esophagitis is predominantly found in immunocompromised individuals, and treatment is with ganciclovir or foscarnet [25]. Hemorrhage, fistulae, and esophageal perforation in adults with viral esophagitis have been described [32, 33].

Acute HIV infection can also cause esophagitis, and antiretroviral regimens are needed [34].

Candida is the most common infectious cause of esophagitis. A 2- to 6-week course of oral nystatin can be effective in those with normal immune function, but it is more convenient to give fluconazole. Fluconazole and liposomal amphotericin are both effective and are necessary in the immunocompromised child.

Eradication of *H. pylori* is not likely to improve coexistent esophagitis, and, indeed, in adults, eradication has been associated with increased acid production and hence more noxious gastroesophageal refluxate. However, there does not seem to be any increased incidence of esophagitis in the presence of or following the eradication of *H. pylori* in children [40]. Primary bacterial esophagitis is described in immunocompromised patients and requires appropriate antibiotics dictated by sensitivity testing [42]. Other opportunistic organisms causing esophagitis, such as *Cryptosporidium* and *Acremonium*, have been reported and require appropriate therapy [43, 44].

Treatment of caustic esophagitis is initially conservative, with barium swallow at 4–6 weeks post-ingestion, endoscopic assessment, and, if necessary, stricture dilation. The place of steroids in stricture prevention is controversial and not routine in many centers. Recently, the use of an anti-fibrotic, mitomycin C, applied topically to the mucosa post-stricture dilation has been used successfully in patients who have required multiple stricture dilations, with prevention of restenosis (Fig. 60.1) [5]. Antibiotic therapy for mediastinitis and judicious use of surgery may be employed.

Older children whose esophageal stratified epithelium is exposed to long-term acid may, as with adults, develop gastric metaplasia, eponymously termed Barrett's esophagus [55–57]. This increases the lifelong risk for esophageal adenocarcinoma approximately 30- to 40-fold. Debate surrounds the relative merits and success rates of anti-reflux surgery or long-

term proton pump inhibitor use, and this is dealt with in greater detail elsewhere in the book.

Prognostication in infant and childhood esophagitis is wholly dependent on etiology, however, fortunately, the most common causes, reflux and allergy, are relatively self-limiting, with a natural improvement and recovery by 18 months to 2 years in the vast majority. This is dealt with in greater detail at the beginning of the section on treatment. It is the responsibility of the pediatrician to prevent avoidable complications such as peptic strictures occurring during the period of vulnerability until such an age has been reached. A low threshold for diagnosis and intervention is therefore sensible in this population.

Treatment of EE is dealt with in detail in a seperate chapter.

In summary, pediatric esophagitis is no longer regarded as a unidimensional reflux-related condition, and the main reason cited by the recent conjoint ESPGHAN-NASPGHAN working group on reflux and esophagitis for endoscopic assessment in this group of patients is diagnostic differentiation of reflux esophagitis from other conditions such as eosinophilic esophagitis and other inflammatory and infective etiologies [58]. The developments in physiologically appropriate tools such as impedance and the rapid rise in comprehension of issues such as neurohumoral interactions controlling esophageal function, combined with the recent apparent explosion in incidence of new esophageal diseases in children – for example, eosinophilic esophagitis – suggest that the study and clinical care of children with esophageal inflammatory disorders are likely to be of expanding interest to the pediatric gastroenterology community as each year goes by.

References

1. Thomson M. The pediatric esophagus comes of age. J Pediatr Gastroenterol Nutr. 2002;34:S40–5.
2. Vandenplas Y. Reflux esophagitis in infants and children: a report from the Working Group on Gastro-oesophageal Reflux Disease of the European Society of Paediatric Gastroenterology and Nutrition. J Pediatr Gastroenterol Nutr. 1994;18:413–22.
3. Hassall E. Macroscopic versus microscopic diagnosis of reflux esophagitis: erosions or eosinophils? J Pediatr Gastroenterol Nutr. 1996;22:321–5.
4. Vandenplas Y. Reflux esophagitis: biopsy or not? J Pediatr Gastroenterol Nutr. 1996;22:326–7.
5. Afsal N, Lloyd-Thomas A, Albert D, Thomson M. Treatment of oesophageal strictures in childhood. Lancet. 2002;359:1032.
6. Rosseneu S, Afzal N, Yerushalmi B, Ibaguen-Secchia E, Lewindon P, Cameron D, Mahler T, Schwatgen K, Kohler H, Lindley K, Thomson M. Topical application of mitomycin-C in oesophageal strictures. J Pediatr Gastroenterol Nutr. 2007;44(3):336–41.
7. Goldberg N, Ott M, Parker-Hartigan L. Medication-induced esophagitis. J Pediatr Health Care. 1996; 10:35–6.
8. Biller J, Flores A, Buie T, et al. Tetracycline-induced esophagitis in adolescent patients. J Pediatr. 1992;120:144–5.
9. Kato S, Komatsu K, Harada Y. Medication-induced esophagitis in children. Gastroenterol Jpn. 1990;25:485–8.
10. Holvoet J, Terriere L, Van Hee W, et al. Relation of upper gastrointestinal bleeding to non-steroidal anti-inflammatory drugs and aspirin: a case control study. Gut. 1991;32:730–4.
11. Kelly KJ, et al. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. Gastroenterology. 1995;109: 1503–12.
12. Hill DJ, Hosking CS. Emerging disease profiles in infants and young children with food allergy. Pediatr Allergy Immunol. 1997;8(10 Suppl):21–6.
13. Iacono G, et al. Gastroesophageal reflux and cow's milk allergy in infants: a prospective study. J Allergy Clin Immunol. 1996;97:822–7.
14. Cavataio F, et al. Clinical and pH-metric characteristics of gastro-oesophageal reflux secondary to cows' milk protein allergy. Arch Dis Child. 1996;75:51–6.
15. Murch S. Diabetes and cows' milk. Lancet. 1996;348:1656.
16. Walker-Smith JA, Murch SH. Gastrointestinal food allergy. In: Diseases of the small intestine in childhood. 4th ed. Oxford (UK): Isis Medical Media; 1999. pp. 205–34.
17. Winter HS, et al. Intraepithelial eosinophils: a new diagnostic criterion for reflux esophagitis. Gastroenterology. 1983;83:818–23.
18. Liacouras CA, et al. Primary eosinophilic esophagitis in children: successful treatment with oral corticosteroids. J Pediatr Gastroenterol Nutr. 1998;26: 380–5.
19. Garcia-Zepeda EA, et al. Human eotaxin is a specific chemoattractant for eosinophil cells and provides a new mechanism to explain tissue eosinophilia. Nat Med. 1996;2:449–56.
20. Butt A, Murch S, Ng C-L, et al. Upregulated eotaxin expression and T-cell infiltration in the basal and papillary epithelium in cow's milk associated reflux oesophagitis. Arch Dis Child. 2002;86:0–6.

21. Collins SM. The immunomodulation of enteric neuromuscular function: implications for motility and inflammatory disorders. Gastroenterology. 1996;111: 1683–99.
22. Justinich C, et al. Mucosal mast cells distinguish allergic from gastroesophageal reflux-induced esophagitis. J Pediatr Gastroenterol Nutr. 1996;23:342–74.
23. Gill R, Gebhard R, Dozeman R, Sumner H. Shingles esophagitis: endoscopic diagnosis in two patients. Gastrointest Endosc. 1984;30:26–7.
24. Agha F, Lee H, Nostrant T. Herpetic esophagitis: a diagnostic challenge in immunocompromised patients. Am J Gastroenterol. 1986;81:246–53.
25. Parente F, Bianchi Porro G. Treatment of cytomegalovirus esophagitis in patients with acquired immunodeficiency syndrome: a randomized controlled study of foscarnet versus ganciclovir. The Italian Cytomegalovirus Study Group. Am J Gastroenterol. 1998;93:317–22.
26. Springer D, DaCosta L, Beck I. A syndrome of acute self-limiting ulcerative esophagitis in young adults probably due to herpes simplex virus. Dig Dis Sci. 1979;24:535–44.
27. Alexander J, et al. Infectious esophagitis following liver and renal transplant. Dig Dis Sci. 1988;33:1121–6.
28. Powell K. Guidelines for the care of children and adolescents with HIV infection. Approach to gastrointestinal manifestations in infants and children with HIV infection. J Pediatr. 1991;119(1 (Pt 2)):S34–40.
29. Greenson J, Beschorner W, Boitnott J, Yardley J. Prominent mononuclear cell infiltrate is characteristic of herpes esophagitis. Hum Pathol. 1991;22:541–9.
30. Becker K, Lubke H, Borchard F, Haussinger D. Inflammatory esophageal diseases caused by herpes simplex virus infections—overview and report of 15 personal cases. Z Gastroenterol. 1996;34:286–95.
31. Chatis P, Miller C, Schraeger L, Crumpacker C. Successful treatment with foscarnet of an acyclovir-resistant mucocutaneous infection with herpes simplex virus in a patient with acquired immunodeficiency syndrome. N Engl J Med. 1989;320:296–300.
32. Rattner H, Cooper D, Zaman M. Severe bleeding from herpes esophagitis. Am J Gastroenterol. 1985;80:523–5.
33. Cronstedt J, Bouchama A, Hainau B, et al. Spontaneous esophageal perforation in herpes simplex esophagitis. Am J Gastroenterol. 1992;87:124–7.
34. Rabeneck L, Popovic M, Gartner S. Acute HIV infection presenting with painful swallowing and esophageal ulcers. JAMA. 1990;263:2318–22.
35. Wigg A, Roberts-Thomson I. *Candida* oesophagitis. J Gastroenterol Hepatol. 1998;13:831.
36. Braegger C, Albisetti M, Nadal D. Extensive esophageal candidiasis in the absence of oral lesions in pediatric AIDS. J Pediatr Gastreonterol Nutr. 1995;21:104–6.
37. DeGregorio M, Lee W, Ries C. *Candida* infections in patients with acute leukemia: ineffectiveness of nystatin prophylaxis and relationship between oropharyngeal and systemic candidiasis. Cancer. 1982;50:2780–4.
38. Bode C, Schroten H, Koletzko S, et al. Transient achalasia-like esophageal dysmotility disorder after *Candida* esophagitis in a boy with chronic granulomatous disease. J Pediatr Gastroenterol Nutr. 1996;23:320–3.
39. Gaissert H, Breuer C, Weissburg A, Mermel L. Surgical management of necrotizing *Candida* esophagitis. Ann Thorac Surg. 1999;67:231–3.
40. Rosioru C, Glassman M, Halata M, Schwartz S. Esophagitis and *Helicobacter pylori* in children: incidence and therapeutic implications. Am J Gastroenterol. 1993;88:510–3.
41. De Giacomo C, Fiocca R, Villani L, et al. Barrett's ulcer and *Campylobacter*-like organisms infection in a child. J Pediatr Gastroenterol Nutr. 1988;7: 766–8.
42. Walsh T, Beltisos N, Hamilton S. Bacterial esophagitis in immunocompromised patients. Arch Intern Med. 1986;146:1345–8.
43. Kaslow P, et al. Esophageal cryptosporidiosis in a child with acquired immune deficiency syndrome. Gastroenterology. 1986;91:1301–3.
44. Mascarenhas M, McGowan K, Ruchelli E, et al. *Acremonium* infection of the esophagus. J Pediatr Gastroenterol Nutr. 1997;24:356–8.
45. Deneyer M, et al. Esophagitis of likely traumatic origin in newborns. J Pediatr Gastroenterol Nutr. 1992;15:81–4.
46. Mahboubi S, Silber J. Radiation-induced esophageal strictures in children with cancer. Eur Radiol. 1997;7:119–22.
47. Boeck A, Buckley R, Schiff R. Gastroesophageal reflux and severe combined immunodeficiency. J Allergy Clin Immunol. 1997;99:420–4.
48. Thomson M, Walker-Smith J. Dyspepsia in infants and children. Baillieres Clin Gastroenterol. 1998; 12:601–24.
49. Witte A, Veenendaal R, Van Hogezand R, et al. Crohn's disease of the upper gastrointestinal tract: the value of endoscopic examination. Scand J Gastroenterol. 1998;225:100–5.
50. D'Haens G, Rutgeerts P, Geboes K, Vantrappen G. The natural history of esophageal Crohn's disease: three patterns of evolution. Gastrointest Endosc. 1994;40:296–300.
51. Schulman H, Weizman Z, Barki Y, et al. Inflammatory bowel disease in glycogen storage disease type 1B. Pediatr Radiol. 1995;25 Suppl 1:S160–2.
52. Renner W, Johnson J, Lichtenstein J, Kirks D. Esophageal inflammation and stricture: complication of chronic granulomatous disease of childhood. Radiology. 1991;178:189–91.
53. Shabib S, Cutz E, Sherman P. Passive smoking is risk factor for esophagitis in children. J Pediatr. 1995;127:435–7.
54. Meadow R. Munchausen syndrome by proxy: the hinterland of child abuse. Lancet. 1977;ii:343–4.
55. Hassal E. Barrett's esophagus: new definitions and approaches in childhood. J Pediatr Gastroenterol Nutr. 1993;16:345–64.

56. Knuff T, Benjamin S, Worsham F, et al. Histologic evaluation of chronic gastroesophageal reflux an evaluation of biopsy methods and diagnostic criteria. Dig Dis Sci. 1984;29:194–201.
57. Leape L. Esophageal biopsy in the diagnosis of reflux esophagitis. J Pediatr Surg. 1981;16:379–84.
58. Vandenplas Y, Rudolph C, Di Lorenzo C, Hassall E, Liptak G, Mazur L, Sondheimer J, Staiano A, Thomson M, Veereman-Wauters G, Wenzl T. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of NASPGHAN and ESPGHAN. J Ped Gastroenterol Nutr. 2009;49(4):498–547.