

What is new in esophageal injury (infection, drug-induced, caustic, stricture, perforation)?

Fabio Pace^a, Spinello Antinori^b and Alessandro Repici^c

^aGastroenterology Unit, ^bInfectious Disease Unit, Department of Clinical Sciences "L. Sacco" and ^cGastroenterology Unit, IRCSS Hospital "Humanitas", Milan, Italy

Correspondence to Fabio Pace, MD, Gastroenterology Unit, Department of Clinical Sciences "L. Sacco", 20157 Milan, Italy
Tel: +39 02 39042943; fax: +39 02 39042337;
e-mail: fabio.pace@unimi.it

Current Opinion in Gastroenterology 2009, 25:372–379

Purpose of review

We will focus separately on infectious, drug-induced and caustic injury of the esophagus and their possible complications such as stricture and perforation.

Recent findings

There has been a decrease in opportunistic esophageal infection in HIV-positive patients, in particular candidiasis, which remains an important cause of inpatient charges, length of stay and total hospital costs, and new antifungal therapy are currently explored. As far as drug-induced esophageal injury is concerned, more than 1000 cases of all cases due to nearly 100 different medications have been described during the last 10 years. However, the estimated case frequency is probably much higher and the related literature is of low quality, as cases are reported selectively and stimulated by clustering of cases, newly implicated pills or unusual complications. Finally, in the field of caustic ingestion-related injury, there has been greater understanding of geographical differences in prevalence and more frequently involved substances, choice of optimal timing for endoscopy, relationship between symptoms and severity of lesions and appropriate role of steroids and other therapies, such as the topical application of mytomicin C.

Summary

This update covers the most relevant papers published on the three areas of interest during the last year.

Keywords

caustic ingestion, drug-induced esophagitis, esophagitis in HIV infection, infectious esophagitis

Curr Opin Gastroenterol 25:372–379
© 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins
0267-1379

Introduction

During the last year, the number of papers and the quality of the papers dealing with the subject of the paper has been relatively low, being predominantly based on case reports.

In the present review, we will focus separately on infectious, drug-induced and caustic injuries of the esophagus and their possible complications such as stricture and perforation.

Infectious esophagitis

Infectious esophagitis mainly due to viruses or fungi are commonly observed among immunocompromised patients, a growing population reflecting medical progress in several settings (e.g. management of patients with cancer and autoimmune diseases, increase in solid-organ transplant and hematopoietic stem cell transplantation). A 32% annual decline in the incidence of esophageal candidiasis was nicely documented in a multicenter study

population of almost 10000 HIV-infected patients recruited from Europe, Israel and Argentina [1,2]; concomitantly, the proportion of patients taking antifungal therapy during the study period declined from 18 to 2%.

However, opportunistic infections still occur in HIV-infected patients in western countries, despite the availability of potent antiretroviral drugs, mainly as a consequence of late presenter HIV infection or failing of antiretroviral regimens due to emergence of drug resistance [3]. Esophageal candidiasis occurred within 1 year after starting highly active antiretroviral therapy (HAART) in 3.4% of 1185 patients enrolled in the TREAT Asia observational database [4]. A similar incidence [3.3%; 95% confidence interval (CI) 1.9–5.9] was reported among adult patients diagnosed with AIDS in New York City during the year 2000, with candidiasis ranking fourth among the AIDS-defining illness [5]. In a retrospective multicohort study conducted in Europe and Canada in 760 patients presenting with AIDS at the time of HIV diagnosis, candida esophagitis accounted for 12.4% of all diagnoses [6]. Among 79 HIV-seropositive

patients who underwent upper endoscopy for gastrointestinal complaints, esophageal candidiasis was observed in 37%, followed by ulcers (24.7%) and esophagitis (11%) [7]. Using PCR, it was shown that cytomegalovirus (CMV) was the most frequently identified pathogen (31%) that caused esophageal ulcer, followed by HPV (20%) and HSV (10.3%); however, HIV was identified in 65.5% of all ulcers, but its role as a direct cause remains to be elucidated. The role of anidulafungin in the treatment of azole-refractory oropharyngeal and esophageal candidiasis was evaluated in a phase 2 open-label study [8]. Overall, 19 patients, of whom 12 had esophageal candidiasis, were treated with intravenous anidulafungin (100 mg loading dose followed by 50 mg daily for a maximum of 21 days). Patients had suffered a median of 5.5 episodes and had been previously treated with a variety of antifungal drugs including amphotericin B, voriconazole and caspofungin. Endoscopic success was observed in 92 and 50% of patients, respectively, at the end of therapy and at follow-up. All the three available echinocandins (caspofungin, anidulafungin and micafungin) have received regulatory approval in the US and European Union for the treatment of esophageal candidiasis [9*].

In an interesting study, Tong *et al.* [10] evaluated the impact of esophageal candidiasis on US hospital inpatient charges, length of stay (LOS) and total hospital costs; using data extracted from the 2005 National Inpatient sample, they identified 45 727 patients with esophageal candidiasis. Median LOS was 7 days and total hospital charge was \$25 649; however, 78% of esophageal candidiasis patients were assigned to non-HIV-related disease related groups (DRGs), which increased the LOS (8.4 vs. 6.1; $P < 0.01$) and the total hospital charge (35 704 vs. 23 874; $P < 0.01$) in this category of patients. A review of the literature on acute viral infections in patients with systemic lupus erythematosus showed that gastrointestinal complaints were the most frequently diagnosed (31% of cases), with esophagitis ranking third after hepatitis and colitis and was mainly caused by HSV [11]. On the contrary, CMV and *Candida* were responsible for 8.8% of infectious esophagitis observed in 34 ABO-incompatible and positive cross-match renal-transplant recipients who received rituximab, a monoclonal chimeric human-murine anti-CD20 antibody, as a part of antirejection therapy [12]. Rituximab depletes the B-cell compartment by inducing cellular apoptosis and despite being licensed for the treatment of CD20-positive non-Hodgkin lymphoma is increasingly employed in recipients of solid-organ transplantation [13].

A severe case of cytomegalovirus esophagitis presenting as acute esophageal necrosis ('black esophagus') has been described in renal-transplant recipients with primary CMV infection [14]; the patient was treated successfully

with a 6-week antiviral therapy (intravenous ganciclovir followed by oral valganciclovir) associated with tapering immunosuppressive drugs. Acute esophageal necrosis is a rare entity characterized by a dark pigmentation of the esophagus (usually the distal part) associated with mucosal necrosis at histology examination. It has been associated with several different conditions (broad-spectrum antibiotics, herpetic infections, underlying malignancy, Stevens–Johnson syndrome, hyperglycemia, severe vomiting after excess alcohol consumption). A case of chronic Chagas disease characterized by progressive dysphagia was diagnosed in a Venezuelan woman settled in Italy since 1995; she was treated endoscopically with botulinum toxin associated with allopurinol with resolution of symptomatology [15]. That case report concerns the challenge of globalization and highlights the need to consider unusual cause of infective esophageal disease also in western countries. Immigration from Latin America to Europe, North America and Australia has risen steadily in the last few years with an estimated 2–4% patients coming from endemic areas chronically infected with *Trypanosoma cruzi* [16]. American trypanosomiasis or Chagas disease caused by *T. cruzi* is endemic in Latin America and during its chronic phase, a digestive form affecting esophagus and colon may develop. Patients with megaesophagus show clinical and manometric findings similar to those observed in idiopathic achalasia. Two recently published studies evaluated the role of interstitial cells of Cajal (ICCs) and immune response in the pathogenesis of chagasic megaesophagus [17,18]; in the first one, de Lima *et al.* [17] showed that ICCs were significantly reduced in the longitudinal and circular muscle layers and myenteric plexus of patients with chagasic esophagus compared with those in patients with nonchagasic esophageal disease. Ribeiro *et al.* [18] found a higher production of IFN- γ and IL-4 in culture supernatant of PBMC of patients with the digestive form of Chagas disease compared with those with the indeterminate form. As IL-4 is able to inhibit the microbicidal effect of macrophages, the authors suggest that it might be implicated in the escape mechanisms of the parasite. The different treatment approach of achalasia associated with Chagas disease in Brazil was reviewed by Herbella *et al.* [19], who reported on pros and cons of endoscopic (dilatation, injection of botulinum toxin) and surgical (Heller's myotomy, cardioplasty, vagotomy, Roux-en-Y-gastrectomy, esophagectomy) treatments.

Some light on the pathogenesis of idiopathic achalasia was shed by the elegant study by Facco *et al.* [20*], who investigated the T-cell receptor (TCR) repertoire of T lymphocytes infiltrating the lower esophageal sphincter (LES) of 59 patients with idiopathic achalasia and 38 controls (cadaveric multiorgan donors). They found that achalasia patients had higher lymphocytic infiltrate than controls and were mainly represented by CD3+CD8+ T

lymphocytes with a skewed TCR repertoire; moreover, these lymphocytes from LES of achalasia patients specifically responded *in vitro* to exposure to HSV-1 antigens, thus suggesting an immune-mediated inflammatory disease in which a latent infection leads to self-destruction of esophageal neurons in genetically susceptible patients [21]. These findings are extremely interesting and might contribute to the better understanding of other gastrointestinal motility disorders.

Drug-induced esophageal injury

As already reported in the last year review, a great variety of medications have been reported to cause esophageal injury, with more than 1000 cases of pill-induced esophageal injury due to nearly 100 different medications described in the literature up to 1999 [22]. This is an impressive number, but is quite small compared with the estimated case frequency; cases are reported selectively in the literature because of clustering of cases, newly implicated pills or unusual complications. This selective reporting limits our ability to assess the epidemiology of this iatrogenic disease. Thus, pill-induced esophageal injury remains an overlooked entity; furthermore, no major contributions have been published in the past year.

The reader is referred to last year's report [23*] for the description of risk factors that predispose to pill-induced esophageal injury as well as its diagnosis and clinical features.

Specific medications causing esophageal injury

In this section, we will focus on specific medications causing esophageal injury.

Alendronate

Oral intake of alendronate and other nitrogen-containing class of bisphosphonates drugs has been associated, in postmarketing studies but not in placebo-controlled clinical trials, with upper gastrointestinal intolerance and esophageal injury, including ulceration, stricture and perforation. This has led to intake instructions and development of novel protection formulations [24], as well as intravenous formulations, that are potentially less injurious for the gastrointestinal tract. Endoscopic studies have identified differences among aminobisphosphonates (etidronate, alendronate, risendronate and ibandronate) in their potential for injury which is thought to arise due to toxicity from the medication itself and nonspecific irritation secondary to contact between the pill and the esophageal mucosa, similar to other cases of 'pill esophagitis'. Previous studies have shown that the histologic abnormalities associated with alendronate-induced esophagitis are aspecific, with the presence of inflammatory exudate and inflamed granulation tissue [25]. A recent histopathologic study described one case

of an elderly woman who presented with alendronate-induced esophagitis. The histopathologic changes that make this case unique are the large, 'bizarre' squamous epithelial cells and scattered dyskariotic cells, two findings not well described in previous reports [26]. These unique features add to the histologic spectrum of alendronate-induced esophageal injury and shall help in differentiating this type of esophagitis from those with other causes.

Antibiotics

Doxycycline-induced esophageal injury is mostly found in young persons with no history of esophageal dysfunction and has generally a benign course. A recent report first described the case of a 16-year-old white girl who, while taking 100 mg doxycycline capsules twice a day for acne vulgaris for 3 months, developed heartburn, mid-sternal pain and dysphagia; an upper endoscopy revealed multiple circumferential deep ulcerations surrounding fragile, irregular, hyperemic and hypertrophic mucosa at the level of the mid-esophagus and concomitantly in the distal part of the esophagus extensive ulcerations, mimicking esophageal cancer [27]. Because doxycycline is frequently prescribed in the clinical practice of periodontics, it is important for dentists to be aware of this potential drug reaction. It seems, however, that this particular adverse drug effect is unrecognized by many dentists and other healthcare professionals [28].

NSAIDs

Despite the fact that NSAIDs have been proposed for chemoprevention of adenocarcinoma progression in Barrett's esophagus [29] and the observation that frequent use of aspirin and NSAIDs is associated with reduced occurrence of esophageal cancers, particularly among those with frequent symptoms of gastroesophageal reflux [30], these drugs have been found, in a study conducted on a large French population, to increase the risk of GERD symptoms by approximately 60% [31]. Information on the mechanism through which NSAIDs may cause GERD is limited, although data from one pH-metry study conducted with ibuprofen suggest that this drug may significantly increase the duration of acid reflux compared with both baseline and placebo treatment [32]. A recent case report has provided anecdotic evidence that OTC ibuprofen capsule ingestion can be associated with esophageal perforation, as this happened to a previously well, 18-year-old man presenting with sudden onset of severe, retrosternal pain, dysphagia and odynophagia [33].

Although it has traditionally been assumed that selective COX-2 inhibitors should offer a more favorable gastrointestinal toxicity profile than nonselective agents, recent data indicate that there is little clinically significant difference between the incidence of upper gastrointestinal symptoms with the two classes of drugs [34].

Others

Aluminum phosphide is a pesticide whose ingestion leads to lethal systemic poisoning with 80–90% mortality. Survivors have taken either a very small amount or the tablet had been exposed to air, rendering it less toxic, but often causing severe esophageal injuries. A recent paper has examined the presentation and treatment of 11 cases of esophageal injury due to this compound [35]. In this series, 10 patients had esophageal stricture and one had tracheoesophageal fistula with stricture. Endoscopic bougie dilatation was sufficient in seven patients and surgical intervention was required in the four who underwent definitive repair through gastric tube or feeding jejunostomy with a second-stage repair planned in two. There was no mortality but significant morbidity. Authors of this article claim that mortality and morbidity could be prevented by withdrawing this pesticide from the market, making its sale difficult, or modifying the packaging.

Mycophenolate mofetil (MMF) is a commonly used immunosuppressive drug used in the management of transplant recipients. Although gastrointestinal toxicity is a known complication of MMF, the literature describing the pathologic features of MMF in the gastrointestinal tract is sparse. A recent study has characterized the pathologic features of MMF toxicity in both the upper and lower gastrointestinal tracts, correlating it with clinical and endoscopic findings [36]. Seventy-five gastrointestinal biopsies (nine esophageal, 15 gastric, 16 duodenal, five ileal, 30 colonic) from 46 transplant recipients from 2002 to 2006 were obtained and assessed for multiple histologic features. Interestingly, among other gastrointestinal pathologies, only MMF-treated patients showed ulcerative esophagitis (five of seven cases) [36].

Homeopathic pills may prove to be injurious for the esophageal mucosa; a recent case report has described an esophageal mucosa ulcer occurring in a healthy 35-year-old woman who had no previous history of esophageal disorders and received homeopathic medication [37]. This case shows that pill entrapment can occur even in the esophagus of healthy young individuals and that esophageal ulcer can be triggered by substances generally thought devoid of any potentially mucosal aggressive effect.

Caustic ingestion-related injuries of the esophagus

Caustic injury to the aerodigestive tract remains a significant medical and social concern despite various efforts to minimize the hazards of caustic household products.

Agents with pH less than 2 or those with pH higher than 12 are extremely corrosive. Acutely, caustic damage to the gastrointestinal tract ranges from mild to extensive. In

severe cases, organ perforation leading to death is possible. Long-term complications resulting from caustic ingestion include stricture formation and development of esophageal carcinoma. The extent of tissue destruction depends on the type of agent, its physical properties, concentration, duration of contact and amount of substance ingested.

In the United States, a decline in the incidence of caustic injuries has been noted with an estimated incidence of 5000 to 15 000 cases per year [38]. However, an increase has been reported in other countries such as Turkey and India [38,39]. Alkaline material accounts for most cases of caustic ingestion in the developed world, whereas acid ingestion appears to be more common in developing countries, like India, where hydrochloric acid and sulfuric acid are easily accessible [38,39].

The gold-standard method to safely assess the depth, extent of injury and appropriate therapeutic regimen is still esophagogastroduodenoscopy. Appropriate timing of endoscopy is still under debate and several authors have investigated whether or not urgent endoscopy should be performed. A group in Detroit has retrospectively examined their experience with 95 consecutive adult patients admitted over a 28-year period to an urban emergency hospital for ingestion of caustic material [40]. More than one-third of the patients had grade II moderate injury (25 patients) or deep grade III injury (13 patients). The ingestion of strong acid or strong alkali often produced deep grade III changes, whereas bleach, detergent, ammonia or other substances usually caused grade I injury. Operative interventions were required for 11 patients with grade III injury and six patients with grade II injury. Endoscopic grading was very accurate in predicting the onset of complications including late esophageal stricture. There were no complications due to endoscopy and the authors suggest that upper gastrointestinal endoscopy after caustic ingestion should be performed early to define the extent of injury and guide appropriate therapy.

Another group retrospectively evaluated the role of a six-point EGD classification system of injury (Zagar's modified endoscopic classification) in predicting outcomes in 273 adult patients diagnosed with caustic agent ingestion [41]. All patients underwent UGI within 24 h and were followed for at least 6 months. Stricture was the most common complication ($n=66$, 24.18%), followed by aspiration pneumonia ($n=31$, 11.36%) and respiratory failure ($n=21$, 7.69%). Compared with patients with grade IIIa mucosal injury, those with grade IIIb mucosal injuries were at a greater risk of prolonged hospital stay, ICU admission and gastrointestinal and systemic complications. According to their results, the authors conclude that EGD should be performed within 12–24 h and

the mucosal damage categorized according to a six-point scale to correctly predict immediate and long-term complications and to guide appropriate therapy.

Several investigators have attempted to correlate symptoms with injury severity and outcome following caustic ingestion in order to determine which patients should undergo EGD after corrosive ingestion. An interesting multicenter observational Italian study has investigated the correlation between symptoms and severity of esophageal injury in 167 children who presented with caustic substance ingestion [42]. Signs and symptoms were divided into minor (oral and/or oropharyngeal lesions and vomiting) and major (dyspnea, dysphagia, drooling and hematemesis). An endoscopy was performed in all patients within 12–24 h of the substance being ingested. The results demonstrated that the incidence of patients with third-degree lesions but without any early symptoms and/or signs is very low [odds ratio (OR) 0.13; 95% CI 0.02–0.62; $P=0.002$], and therefore an upper endoscopy could be avoided in patients presenting with mild symptoms. The conclusion of this observational study was that the risk of severe damage increases proportionally with the number of signs and symptoms, and an endoscopy is mandatory only in symptomatic patients. A retrospective analysis of all patients admitted to an otolaryngology unit because of caustic injury has shown that roughly 50% of patients with grade II injury at upper endoscopy will subsequently develop strictures requiring multiple dilations [38]. More importantly, this retrospective series have demonstrated that oral injury is not always a useful marker of significant distal injury, as six patients (12%) had evidence of esophageal injury without oral injury.

The most concerning chronic complications after caustic ingestions include stricture formation and esophageal malignant transformation. As strictures may develop in 26–55% of patients who ingest caustic substances [43], early interventions are aimed at preventing or minimizing this complication. The most common, and perhaps the most controversial, treatment used to prevent stricture formation is parenteral corticosteroids. Corticosteroids are believed to attenuate inflammation, granulation and fibrous tissue formation. However, recent reports have tempered the initial enthusiasm regarding the use of steroids in patients who ingested caustic substances [44].

A systematic analysis of 50 years of human data has been conducted to re-evaluate the usefulness of steroids in grade II injury [45]. Through a Medline search, the authors have identified human reports including cases with endoscopically documented grade II burns and at least 10 days of steroid therapy or no steroids. Pooled data were evaluated by χ^2 -test with α level set at 0.05. Among a total of 328 patients, 30 of 244 patients who received

steroids and 16 of 84 patients who did not receive steroids developed strictures, respectively. This difference was not statistically significant and despite the fact that the heterogeneity of the data prevented formal meta-analysis, the authors concluded that the existing data fail to support the use of steroids also in patients with caustic-induced grade II esophageal burns.

In the case of extensive esophagogastric necrosis, emergency esophagogastric resection is required to avoid the extension of corrosive lesions to adjacent organs and death.

In the absence of pharyngeal strictures, the therapeutic approach relies on retrosternal coloplasty, and the cervical anastomosis is performed between the colon and the healthy cervical esophagus.

When esophageal strictures are associated with pharyngeal strictures, surgical treatment is more challenging because reconstruction at this level interferes with the mechanisms of deglutition and respiration. Several techniques have been described for the treatment of this condition, but none is accepted as the gold standard. The postoperative course and late functional outcomes after colopharyngoplasty were retrospectively evaluated in one of the largest reported experience including a group of 58 consecutive patients [46]. In this series, operative mortality was 2%; postoperative complications required reoperation in 16 patients (28%), whereas long-term success of colopharyngoplasty was eventually obtained in 31 patients (67%). Logistic regression analysis of the surgical data showed that advanced age, a previous history of psychiatric disease and early reoperation had an adverse impact on the long-term outcome.

Once strictures are formed, patients often require endoscopic balloon dilatation or bougienage for relief of dysphagia and control of other associated symptoms such as aspiration and malnutrition. Unfortunately, caustic strictures are more resistant to endoscopic dilation as compared with strictures due to other causes such as reflux or anastomotic strictures [47^{*}]. There is no clear consensus concerning the best endoscopic treatment of benign refractory esophageal strictures due to caustic ingestion [48,49]. Different procedures are currently used: frequent multiple dilations, retrievable metal and plastic self-expanding stent, nasogastric intubation, PEG placement and surgery.

There are several controversial issues regarding the available data on the management of benign esophageal strictures secondary to caustic strictures which do not allow us to draw a final conclusion on the therapeutic option. Most studies include patients with different cause of stricture and do not provide a uniform dysphagia

scoring system. Similarly, the definitions of technical and clinical success have varied among studies precluding an accurate comparison between patients across studies. Finally, in the majority of cases, authors do not provide information on stricture length or diameter at the time of stent placement nor give details regarding management of the disorder prior to stent placement and fail to report prior attempts to endoscopic therapy (dilatation, needle-knife techniques, steroid injection) and/or to acid suppressive therapy.

Fortunately, a definition of refractory and recurrent esophageal strictures has been proposed recently [50], thus leading to a more uniform evaluation of the patients and their strictures. According to this new description, a stricture is defined as an anatomic restriction because of luminal scarring or fibrosis that results in the clinical symptom of dysphagia, in the absence of endoscopic evidence of inflammation. This may occur as the result of either an inability to successfully dilate the anatomic stenosis to a diameter of 14 mm over five sessions at 2 weekly intervals (refractory) or as a result of inability to maintain a satisfactory luminal diameter for 4 weeks once the target diameter of 14 mm has been achieved (recurrent). Stent migration is one of the major problems associated with the use of metal and plastic stent for benign esophageal strictures. An Italian group has recently described a new technique to fix a suspended esophageal silicone prosthesis to the neck in benign esophageal strictures, thus limiting the risk of migration of the expandable metallic or plastic stents [51]. Although this solution cannot be considered optimal because of patient complaints, it may result in a valid alternative as rescue therapy for patients in whom the risk of stent migration is high because of stricture position or morphology.

In another study from Turkey, the long-term effects of placement of a home-made polytetrafluorethylene stent on esophageal remodeling has been investigated in 11 of 68 patients treated by a group of investigators through a 9-year period [52]. Results of this study are very promising, as, after a mean follow-up of 3.5 years (1–6 years), long-term relief of dysphagia was obtained in eight out of 11 patients who underwent placement of this home-made polytetrafluorethylene stent.

Topical application of mitomycin C has been recently described as a new treatment modality for patients with refractory strictures due to caustic ingestion [53,54].

The exact mechanism by which mitomycin C exerts an antifibroblast activity is still unknown, but it may be a result of the reduction of fibroblast proliferation and consequent reduction in the amount of fibrous scar formation. Local application of mitomycin C may be per-

formed by using different endoscopic techniques. In one of the first reported experience, the solution of mitomycin C (1 mg/ml) was applied locally for 2 min, using a rigid endoscope and a swap [55]. Alternatively, a cotton pledget held by endoscopic forceps and soaked in a 0.1 mg/ml solution of mitomycin C can be applied topically under direct vision, either using an overtube or front-loading the pledget in a standard cap used for band ligation of varices attached to the end of the endoscope, to prevent mitomycin C from touching the normal mucosa [56].

Again, in most of the reported cases, differences exist with regard to the most effective concentration, duration or frequency of application of mitomycin C.

Moreover, the important questions of the use of mitomycin in children and its theoretical risk of secondary long-term malignancy have not yet been addressed. Studies with larger groups of patients, long-term follow-up and probably a standardized technique of application are awaited before the use of this substance can be recommended as the first-line therapy for patients with benign esophageal strictures secondary to caustic ingestion.

Conclusion

In the case of esophageal injury of whatever cause, endoscopy remains the main diagnostic tool. Although opportunistic esophageal infection in HIV-positive patients seems to decline, it remains an important cause of inpatient charges, LOS and total hospital costs. Despite the huge number of different drugs reported to cause esophageal injury, the estimated case frequency is probably much higher, but unfortunately the quality of available literature is unsatisfactory and almost exclusively based on case reports of limited numbers.

Finally, in the field of caustic ingestion-related injury, there has been greater understanding of geographical differences in prevalence and more frequently involved substances, choice of optimal timing for endoscopy, relationship between symptoms and severity of lesions and appropriate role of steroids and other therapies.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 393).

- 1 Mocroft A, Oancea C, van Lunzen J, et al. Decline in esophageal candidiasis and use of antimycotics in European patients with HIV. *Am J Gastroenterol* 2005; 100:1446–1454.
- 2 Raufman JP. Declining gastrointestinal opportunistic infections in HIV-infected persons: a triumph of science and a challenge for our HAARTs and minds. *Am J Gastroenterol* 2005; 100:1455–1458.

- 3 Battagay M, Fluckinger U, Hirschel B, Furrer HJ. Late presentation of HIV-infected individuals. *Antivir Ther* 2007; 12:841–851.
- 4 Zhou J, Paton NI, Ditangco R, on behalf of the TREAT Asia HIV Observational DataBase. AIDS-defining illness diagnosed with in 90 days after starting highly active antiretroviral therapy among patients from the TREAT Asia HIV observational database. *Intern J STD AIDS* 2007; 18:446–452.
- 5 Hanna DB, Gupta LS, Jones LE, *et al.* AIDS-defining opportunistic illnesses in the HAART era in New York City. *AIDS Care* 2007; 19:264–272.
- 6 Mussini C, Manzardo C, Johnson M, *et al.* Patients presenting with AIDS in the HAART era: a collaborative cohort analysis. *AIDS* 2008; 22:2461–2469.
- 7 Borges MC, Baima Colares JK, Malta Lima D, Fonseca BAL. Advantages and pitfalls of the polymerase chain reaction in the diagnosis of esophageal ulcers in AIDS patients. *Dig Dis Sci* 2008. [Epub ahead of print]
- 8 Vazquez JA, Schranz JA, Clark K, *et al.* A phase 2, open-label study of the safety and efficacy of intravenous anidulafungin as a treatment for azole-refractory mucosal candidiasis. *J Acquir Immune Defic Syndr* 2008; 48:304–309.
- 9 Sable CA, Strohmaier KM, Chodakewitz JA. Advances in antifungal therapy. • *Annu Rev Med* 2008; 59:361–379.
A well written review summarizing the results obtained with novel antifungal drugs in different clinical conditions including *Candida* esophagitis.
- 10 Tong KB, Murtagh KN, Lau C, Seifeldin R. The impact of esophageal candidiasis on hospital charges and costs across patients subgroups. *Curr Med Res Opin* 2008; 24:167–174.
- 11 Ramos-Casals M, Cuadrado MJ, Alba P, *et al.* Acute viral infections in patients with systemic lupus erythematosus. Description of 23 cases and review of the literature. *Medicine* 2008; 87:311–318.
- 12 Grim SA, Pham T, Thielke J, *et al.* Infectious complications associated with the use of rituximab for ABO-incompatible and positive cross-match renal transplant recipients. *Clin Transplant* 2007; 21:628–632.
- 13 Becker YT, Samaniego-Picota M, Sollinger HW. The emerging role of rituximab in organ transplantation. *Transpl Int* 2006; 19:621–628.
- 14 Trappe R, Pohl H, Forberger A, *et al.* Acute esophageal necrosis (black esophagus) in the renal transplant recipient: manifestation of primary cytomegalovirus infection. *Transpl Infect Dis* 2007; 9:42–45.
- 15 Niola P, Battaglia E, Casabianca A, *et al.* A case of Chagas' disease. *Dig Liver Dis* 2008; 40:906–907.
- 16 Schumis GA. Epidemiology of Chagas disease in nonendemic countries: the role of international migration. *Mem Inst Oswaldo Cruz* 2007; 102 (Suppl 1): 75–85.
- 17 de Lima MA, Cabrine-Santos M, Tavares MG, *et al.* Interstitial cells of Cajal in chagasis megaesophagus. *Ann Diagn Pathol* 2008; 12:271–274.
- 18 Ribeiro MB, Crema E, Rodrigues V Jr. Analysis of the cellular immune response in patients with the digestive and indeterminate forms of Chagas' disease. *Hum Immunol* 2008; 69:484–489.
- 19 Herbella FAM, Aquino JLB, Stefani-Nakano S, *et al.* Treatment of achalasia: lessons learned with Chagas' disease. *Dis Esophagus* 2008; 21:461–467.
- 20 Facco M, Brun P, Baesso I, *et al.* T cells in the myenteric plexus of achalasia patients show a skewed TCR repertoire and react to HSV-1 antigens. *Am J Gastroenterol* 2008; 103:1598–1609.
An interesting and well done study showing the role of HSV-1 as immune trigger of the inflammatory response leading to the neuronal damage observed in patients with idiopathic achalasia.
- 21 Boeckstaens GE. Achalasia: virus-induced euthanasia of neurons? *Am J Gastroenterol* 2008; 103:1610–1612.
- 22 Kikendall JW. Pill esophagitis. *J Clin Gastroenterol* 1999; 28:298–305.
- 23 Geagea A, Cellier C. Scope of drug-induced, infectious and allergic esophageal injury. *Curr Opin Gastroenterol* 2008; 24:496–501.
• The last year review on drug-induced, infectious and allergic esophageal injury. Comprehensive and useful.
- 24 Marshall J, Thabane M, James C. Randomized active and placebo-controlled endoscopy study of a novel protected formulation of oral alendronate. *Dig Dis Sci* 2006; 51:864–868.
- 25 Abraham SC, Cruz-Correa M, Lee LA, *et al.* Alendronate-associated esophageal injury: pathologic and endoscopic features. *Mod Pathol* 1999; 12:1152–1157.
- 26 Gómez V, Xiao SY. Alendronate-induced esophagitis in an elderly woman. *Int J Clin Exp Pathol* 2009; 2:200–203.
- 27 Tahan V, Sayrak H, Bayar N, *et al.* Doxycycline-induced ulceration mimicking esophageal cancer. *Cases J* 2008; 1:144.
- 28 Segelnick SL, Weinberg MA. Recognizing doxycycline-induced esophageal ulcers in dental practice: a case report and review. *J Am Dent Assoc* 2008; 139:581–585.
- 29 Hillman L. Management strategies for Barrett's esophagus. *J Gastroenterol Hepatol* 2007; 22:771–772.
- 30 Sadeghi S, Bain CJ, Pandeya N, *et al.* Australian Cancer Study. Aspirin, nonsteroidal anti-inflammatory drugs, and the risks of cancers of the esophagus. *Cancer Epidemiol Biomarkers Prev* 2008; 17:1169–1178.
- 31 Ruzsniowski P, Soufflet C, Barthelemy P. Nonsteroidal anti-inflammatory drug use as a risk factor for gastro-oesophageal reflux disease: an observational study. *Aliment Pharmacol Ther* 2008; 28:1134–1139.
- 32 Cryer B, Spechler SJ. Effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on acid reflux in patients with gastroesophageal reflux disease (GERD). *Gastroenterology* 2000; 4 (Suppl 2):A862.
- 33 Singh NP, Rizk JG. Oesophageal perforation following ingestion of over-the-counter ibuprofen capsules. *J Laryngol Otol* 2008; 122:864–866.
- 34 Scheiman JM. Unmet needs in nonsteroidal anti-inflammatory drug-induced upper gastrointestinal diseases. *Drugs* 2006; 66 (Suppl 1):15–21.
- 35 Darbari A, Tandon S, Chaudhary S, *et al.* Esophageal injuries due to aluminum phosphide tablet poisoning in India. *Asian Cardiovasc Thorac Ann* 2008; 16:298–300.
- 36 Parfitt JR, Jayakumar S, Driman DK. Mycophenolate mofetil-related gastrointestinal mucosal injury: variable injury patterns, including graft-versus-host disease-like changes. *Am J Surg Pathol* 2008; 329:1367–1372.
- 37 Corleto VD, D'Alonzo L, Zykaj E, *et al.* A case of oesophageal ulcer developed after taking homeopathic pill in a young woman. *World J Gastroenterol* 2007; 14:2132–2134.
- 38 Arévalo-Silva C, Eliashar R, Wohlgelemerter J, *et al.* Ingestion of caustic substances: a 15-year experience. *Laryngoscope* 2006; 116:1422–1426.
- 39 Riffat F, Cheng A. Pediatric caustic ingestion: 50 consecutive cases and a review of the literature. *Dis Esophagus* 2009; 22:89–94.
- 40 Tohda G, Sugawa C, Gayer C, *et al.* Clinical evaluation of caustic injury in the gastrointestinal tract in 95 adult patients in an urban medical center. *Surg Endosc* 2008; 22:1119–1125.
- 41 Cheng HT, Cheng CL, Lin CH, *et al.* Caustic ingestion in adults: the role of endoscopic classification in predicting outcome. *BMC Gastroenterol* 2008; 8:31.
- 42 Bertelli P, Falchetti D, Giuliani S, *et al.*, and the Caustic Ingestion Italian Study Group. Caustic ingestion in children: is endoscopy always indicated? The results of an Italian multicenter observational study. *Gastrointest Endosc* 2008; 68:434–439.
- 43 Salzman M, O'Malley RN. Updates on the evaluation and management of caustic exposures. *Emerg Med Clin N Am* 2007; 25:459–476.
- 44 Pelclová D, Navrátil T. Do corticosteroids prevent oesophageal stricture after corrosive ingestion? *Toxicol Rev* 2005; 24:125–129.
- 45 Fulton JA, Hoffman RS. Steroids in second degree caustic burns of the esophagus: a systematic pooled analysis of fifty years of human data: 1956–2006. *Clin Toxicol (Phila)* 2007; 45:402–408.
- 46 Chirica M, de Chaisemartin C, Goasguen N, *et al.* Colopharyngoplasty for the treatment of severe pharyngoesophageal caustic injuries: an audit of 58 patients. *Ann Surg* 2007; 246:721–727.
- 47 Dua KS, Vleggaar FP, Santharam R, *et al.* Removable self-expanding plastic esophageal stent as a continuous, nonpermanent dilator in treating refractory benign esophageal strictures: a prospective two-center study. *Am J Gastroenterol* 2008; 103:2988–2994.
• This is one of the largest prospective studies addressing the role of temporary self-expanding plastic stents placement in the treatment of refractory benign strictures including those secondary to caustic ingestion.
- 48 Ragunath K. Refractory benign esophageal strictures: extending the role of expandable stents. *Am J Gastroenterol* 2008; 103:2995–2996.
- 49 Holm AN, de la Mora Levy JG, Gostout CJ. Self-expanding plastic stents in treating benign esophageal conditions. *Gastrointest Endosc* 2008; 67:20–25.
- 50 Kochman ML, McClave SA, Boyce HW. The refractory and the recurrent esophageal stricture: a definition. *Gastrointest Endosc* 2005; 62:474–475.
- 51 Ancona E, Guido E, Cutrone C, *et al.* A new endoscopic technique for suspension of esophageal prosthesis for refractory caustic esophageal strictures. *Dis Esophagus* 2008; 21:262–265.
- 52 Atabek C, Surer I, Demirbag S, *et al.* Increasing tendency in caustic esophageal burns and long-term polytetrafluorethylene stenting in severe cases: 10 years experience. *J Pediatr Surg* 2007; 42:636–640.

- 53** Daher P, Riachy E, Georges B, *et al.* Topical application of mitomycin C in the treatment of esophageal and tracheobronchial stricture: a report of 2 cases. *J Pediatr Surg* 2007; 42:E9–E11.
- 54** Rosseneu S, Afzal N, Yerushalmi B, *et al.* Topical application of mitomycin-C in oesophageal strictures. *J Pediatr Gastroenterol Nutr* 2007; 44:336–341.
- 55** Uhlen S, Fayoux P, Vachin F, *et al.* Mitomycin C: an alternative conservative treatment for refractory esophageal stricture in children? *Endoscopy* 2006; 38:404–407.
- 56** Heran MK, Baird R, Blair GK, Skarsgard ED. Topical mitomycin-C for recalcitrant esophageal strictures: a novel endoscopic/fluoroscopic technique for safe endoluminal delivery. *J Pediatr Surg* 2008; 43:815–818.