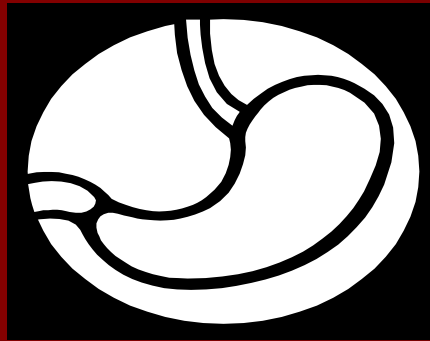


Less Common Causes of Esophagitis and Esophageal Injury and Esophageal Anatomic Anomalies

September 16, 2009



Lauren Briley, M.D.

University of Louisville

Department of Gastroenterology/Hepatology

Esophageal Ulcers

Causes of Esophageal Ulcerations

- Gastroesophageal reflux disease
- Infectious agents: CMV, HSV, HIV, *Candida*
- Inflammatory disorders - Crohn's disease, Behçet's, Vasculitis
- Irradiation
- Ischemia
- Pill-induced
- Graft-versus-host disease
- Caustic substance ingestion
- Post-sclerotherapy
- Post-esophageal variceal band ligation
- Dermatologic diseases: Epidermolysis bullosa dystrophica, Pemphigus vulgaris
- Idiopathic

Topics

- Pill induced esophagitis
- Chemotherapy related esophagitis
- Radiation esophagitis
- Post sclerotherapy ulceration
- Infectious esophagitis (immunocompetant vs. immunocompromised)
- Caustic injuries
- Miscellaneous Esophageal Abnormalities

Pill-Induced Esophagitis



Pill-Induced Esophagitis

Mechanism

- Injury is related to prolonged mucosal contact with a caustic agent
- 4 known mechanisms of pill induced injury:
 - production of a caustic acidic solution (e.g., ascorbic acid and ferrous sulfate)
 - production of a caustic alkaline solution (e.g., alendronate)
 - creation of a hyperosmolar solution in contact with esophageal mucosa (e.g., potassium chloride)
 - direct drug toxicity to the esophageal mucosa (e.g., tetracycline)

Pill-Induced Esophagitis

Risk Factors

- Risk factors for injury include advanced age, swallowing position, fluid intake, and pill size
- Studies have shown that left atrial enlargement, esophageal stricture, or esophageal dysmotility also increases the risk of pill injury
- Swallowing position may be the most important as pills can stay in the esophagus for up to 90 minutes when taken in supine position without sufficient fluid

1 DDSEP Version 5.0 Chapter 1, p. 22

2 Whitney B, Croxon R: Dysphagia caused by cardiac enlargement. *Clin Radiol* 1972; 23:147.

3 Mason SJ, O'Meara TF: Drug-induced esophagitis. *J Clin Gastroenterol* 1981; 3:115.

4 Walta DC, Giddens JD, Johnson LF: Localized proximal esophagitis secondary to ascorbic acid ingestion and esophageal motor disorder. *Gastroenterology* 1976; 70:766.

Pill-Induced Esophagitis

Symptoms

- Typically presents with chest pain – usually accentuated by inspiration
- Odynophagia may be present even to minimal liquids
- GERD-like symptoms also common

Pill-Induced Esophagitis

- Most common location of injury is at the aortic arch and the distal esophagus, but the injury can occur at any level
- Injury ranges from discrete pinpoint ulcers to circumferential ulceration spanning several centimeters



Pill-Induced Esophagitis Causes

Common drugs associated with esophageal injury¹

- Antibiotics: doxycycline, tetracycline, and derivatives (most common cause)₂; clindamycin; erythromycin; penicillin
- NSAIDs and ASA
- KCL
- Ascorbic acid
- Ferrous sulfate
- Quinidine
- Theophylline
- Antiretroviral drugs
- Bisphosphonates, especially alendronate (stricture formation in 1/3)₃

¹ DDSEP Version 5.0 Chapter 1, p. 22

² Feldman: Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 8th ed., 2006.

³ Kikendall JW: *Pill-induced esophageal injury*. In: Castell DO, Richter JE, ed. *The Esophagus*, 4th ed.. Philadelphia: Lippincott Williams & Wilkins; 2004:572.

Pill-Induced Esophagitis

Treatment

- Treatment is withdrawal of the offending agent if possible
- If offending agent must be continued, patient should take pill with 8 oz liquid and remain upright for at least 30 minutes after ingestion
- Viscous lidocaine for symptom control, rarely narcotics
- Symptom resolution and mucosal healing occur within days to weeks

Medication Related Esophagitis

Chemotherapy related

- May cause severe odynophagia due to oropharyngeal mucositis, which can also involve the esophageal mucosa
- Esophageal damage is unusual in the absence of oral changes
- Mucositis is usually self-limited, but some have damage that persists for weeks to months
- Chemotherapy given months after thoracic irradiation to the esophagus, particularly doxorubicin, may cause a "recall" esophagitis

Medication Related Esophagitis

Chemotherapy related

- Causative Chemotherapeutic Agents
 - Dactinomycin
 - Bleomycin
 - Cytarabine
 - Daunorubicin
 - 5-fluorouracil
 - Methotrexate
 - Vincristine

Feldman: Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 8th ed., 2006.

Radiation Esophagitis



Radiation Esophagitis

- Occurs after chest radiation at doses that exceed 30 Gy
- Levels higher than 60 Gy can lead to severe esophagitis and ulceration which can progress to hemorrhage, perforation and fistula
- Concomitant cytotoxic chemotherapy can potentiate injury (i.e. doxorubicin)

Radiation Esophagitis

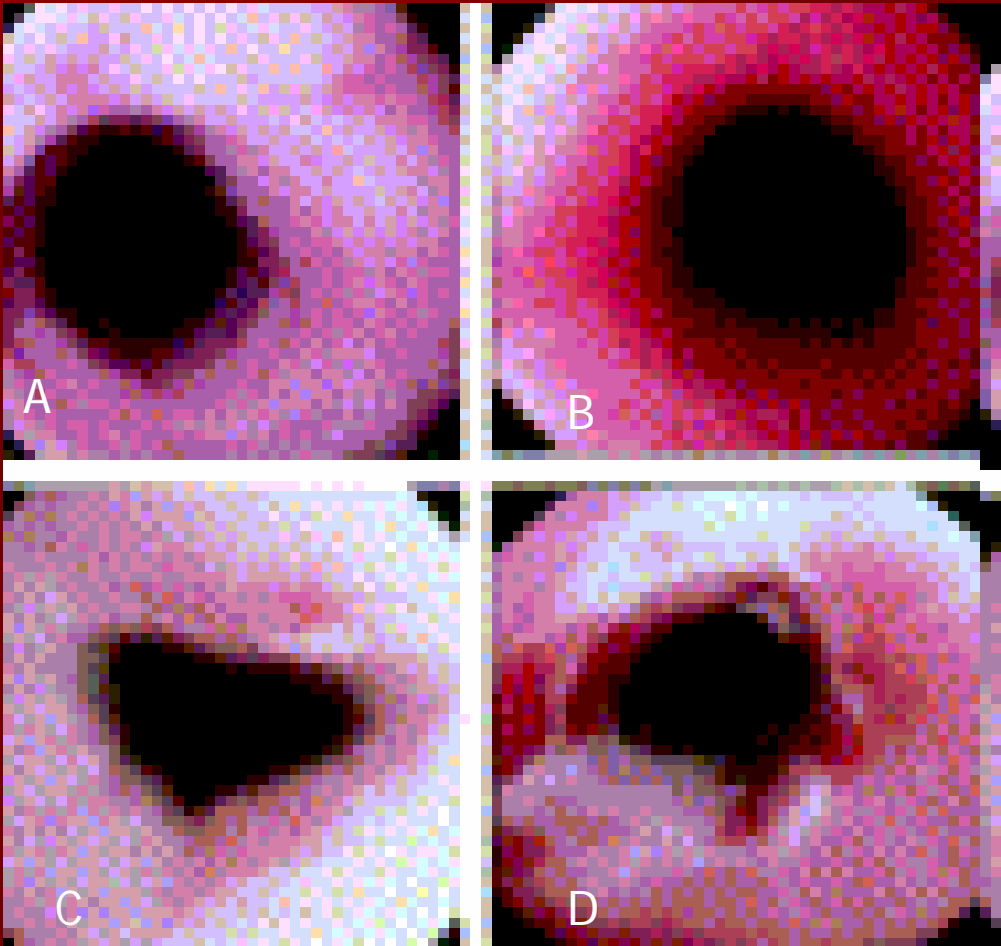
- Symptoms include substernal chest pain, dysphagia and odynophagia
- Acute symptoms begin after 2-3 weeks of conventional thoracic radiation
- Early inflammation can lead to dehydration and weight loss that may cause treatment interruption
- Late reactions involve fibrosis, which can lead to stricture
- Serious complications such as perforation or fistula formation can occur

Goldman: Cecil Medicine, 23rd ed., 2007.

Bradley, J, Movsas, Benjamin. Radiation esophagitis: Predictive factors and preventive strategies. Seminars in Radiation Oncology. Oct 2004;280-286.

Radiation Esophagitis

Grading System: Kuwahata's Score



A Normal Mucosa

B Mucosa
w/Erythema

C Mucosa
w/Erosions

D Mucosa
w/Ulceration

Post-sclerotherapy Induced Esophageal Ulceration



Post-sclerotherapy ulceration

- 2 types of complications:
 - Gross structural injury
 - Alteration in esophageal motility

Post-sclerotherapy ulceration

- Sclerosant causes esophageal necrosis and ulceration – risk is proportional to number of injections and total dose sclerosant
- Small ulcers develop in almost all patients with large ulcerations in 50%
- Strictures occur in 15%; hematoma and perforation also possible
- Unusual complications with deep injection include pericarditis, esophageal-pleural fistula, tracheal compression from large hematoma

Post-sclerotherapy

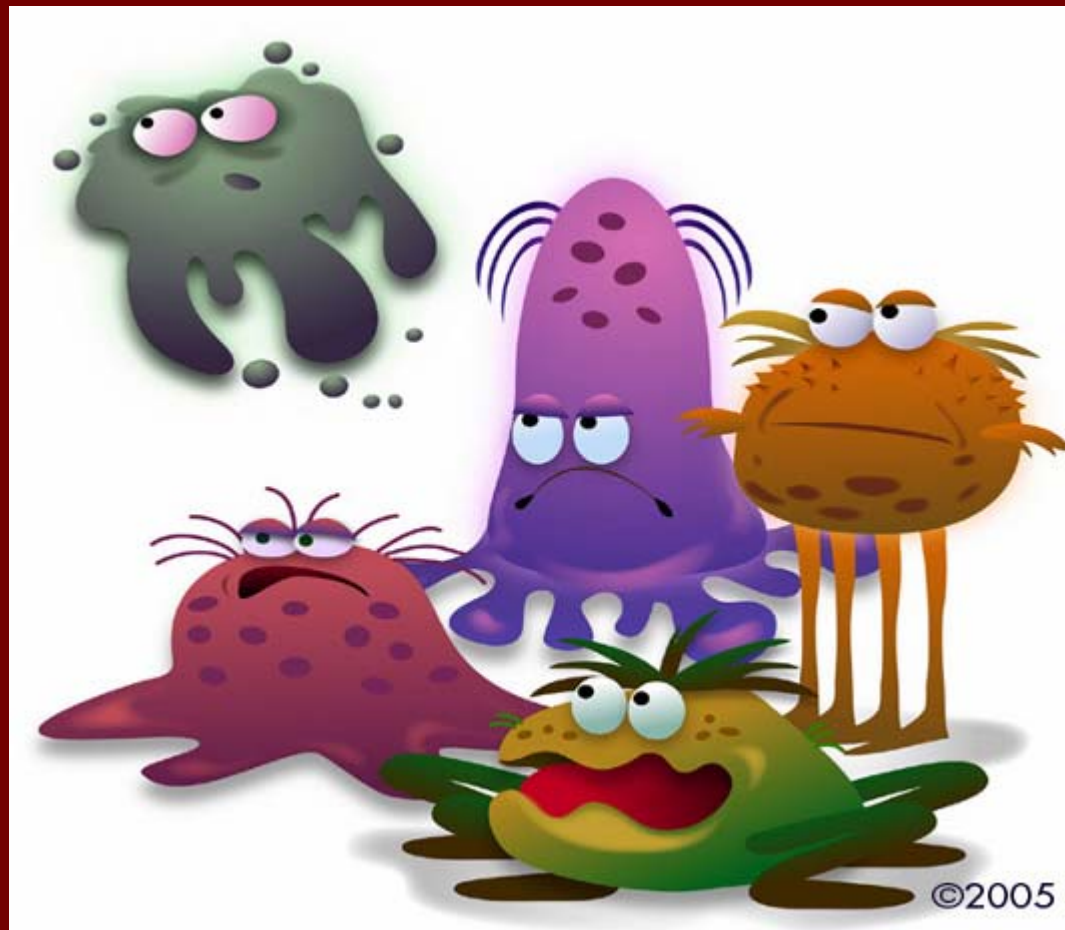
Dysmotility

- Altered motility may be due to wall injury or vagal dysfunction
- Studies have shown delayed esophageal transit time and decreased amplitude and coordination of contractions
- Increased acid reflux is often a consequence

Post-sclerotherapy ulceration

- Oral sulcrafate – only agent shown to be effective in healing ulcers and preventing strictures
- Acid suppressive therapy alone has not been shown to be effective

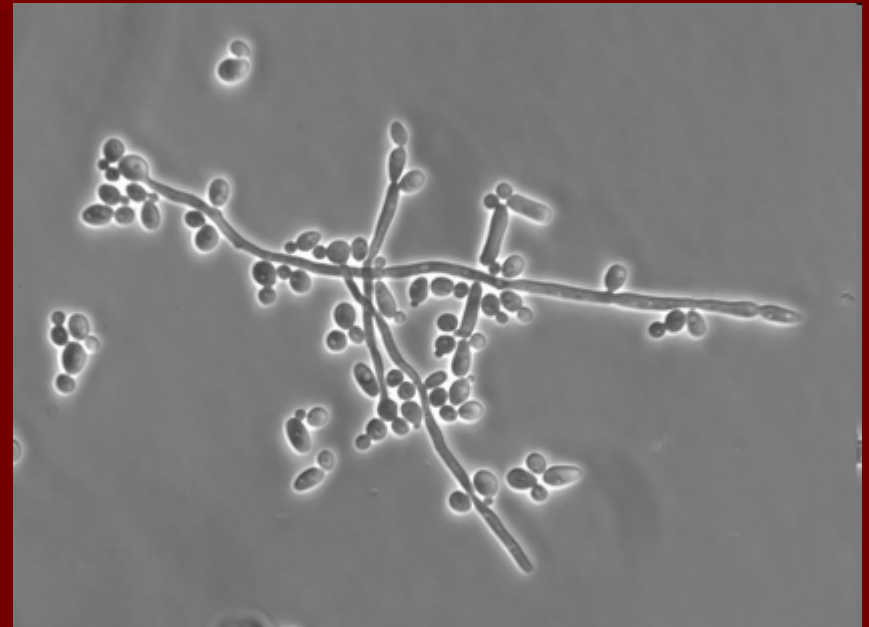
Infectious Esophagitis in the Immunocompetant



Infectious Esophagitis

Candida

- Most common infection in the immunocompetent host
- Candida colonization of the esophagus in healthy adults has a prevalence of approximately 20%
- May occur without underlying cause

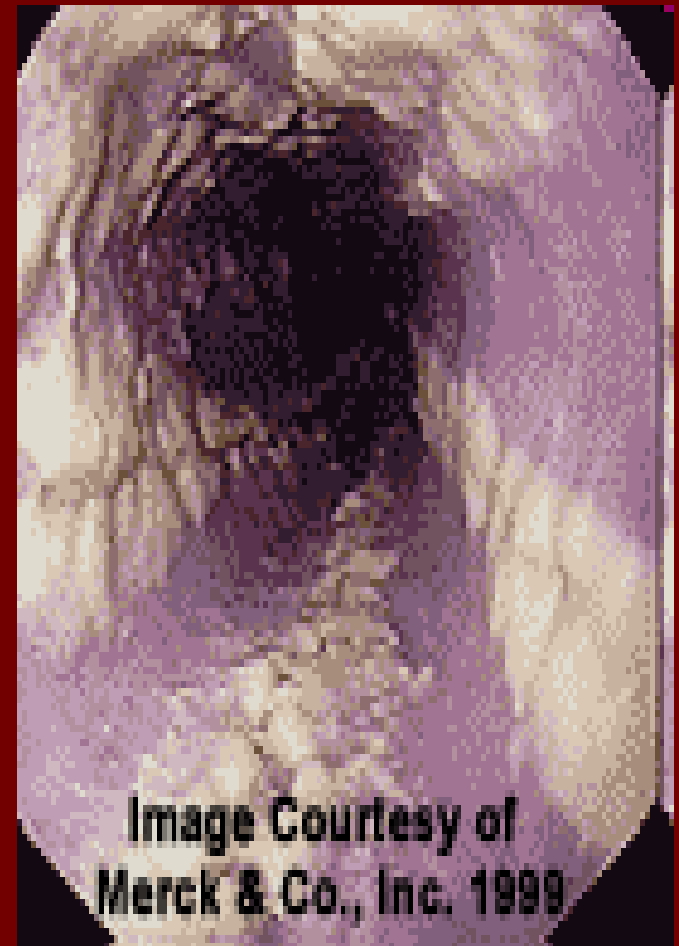


Infectious Esophagitis

Candida

- Risk Factors in Immunocompetant Host
 - Conditions that predispose to stasis in the esophagus i.e. achalasia, scleroderma
 - Topical (inhaled) steroids can also predispose
 - Alcoholism
 - Diabetes Mellitus
 - Advanced Age
 - Adrenal Insufficiency

Feldman: Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 8th ed., 2006



Infectious Esophagitis

Candida

- Characteristic adherent white pseudomembranes or plaques on endoscopy
- Diagnosis made by brushings or cytology showing inflammation, hyphae, and budding yeast
- Treatment is typically 14-21 days of oral fluconazole

Infectious Esophagitis

Herpes Simplex Virus

- Rare in the immunocompetant host
- Caused by primary infection or reactivation of latent virus in the distribution of the vagus, superior cervical or laryngeal nerve
- Oropharyngeal lesions found in only 20%
- Presents with severe odynophagia, heartburn and fever

Infectious Esophagitis

Herpes Simplex Virus

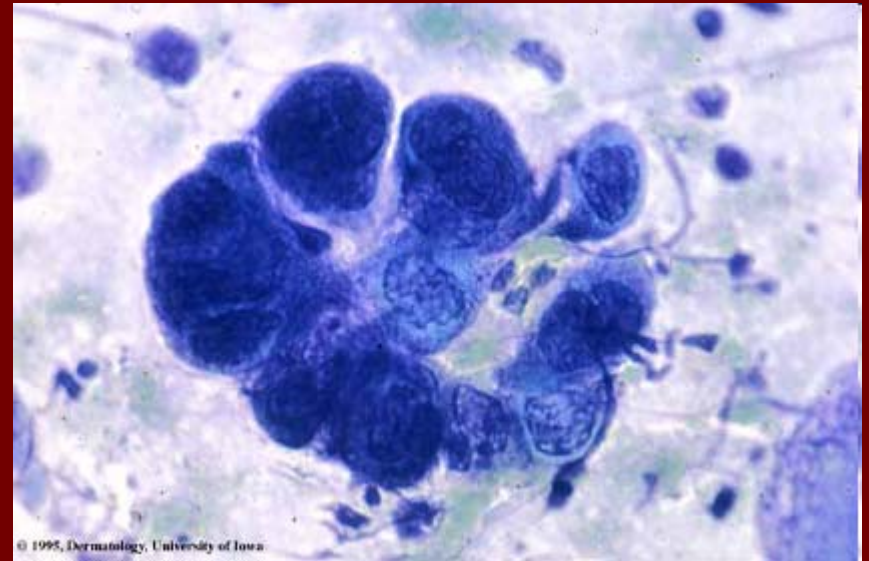
- Endoscopic appearance: friability, ulceration, and exudates typically in the distal esophagus
- Early lesions are round 1-3 mm vesicles which slough to form circumscribed ulcers with raised edges



Infectious Esophagitis

Herpes Simplex Virus

- Histologic findings: multinucleated giant cells, ballooning degeneration, and ground glass intranuclear Cowdry type A inclusion bodies
- Viral cultures from esophageal tissue are more sensitive than routine histology or cytology for diagnosis



© 1995, Dermatology, University of Iowa

Infectious Esophagitis

Herpes Simplex Virus

- Most cases are self limited and correspond to the length of associated nasolabial disease if present
- Treatment is oral acyclovir/valacyclovir
- Rarely, IV acyclovir with severe odynophagia

Infectious Esophagitis

HPV

- Esophageal infections are typically asymptomatic
- Lesions usually in mid to distal esophagus
- Lesions vary: Erythematous macules, white plaques, nodules, or exuberant frond-like lesions

Infectious Esophagitis

HPV

- Histology shows koilocytosis (atypical ringed nucleus), giant cells
- Treatment not usually necessary
- Although HPV is a known precursor to squamous cell carcinoma of the cervix, studies have been inconsistent in linking HPV to esophageal squamous cell carcinoma

Infectious Esophagitis

Trypanosoma Cruzi

- Chagas disease – parasite induced progressive destruction of mesenchymal tissue and nerve ganglion cells
- Endemic in South America
- Causes abnormalities of the heart, gallbladder, intestine, and esophagus

Infectious Esophagitis

Trypanosoma Cruzi

- Manifestations may appear 10-30 years after initial infestation
- Symptoms include dysphagia, cough, chest pain, and regurgitation
- Manometry is identical to achalasia except LES pressure is lower

Infectious Esophagitis

Trypanosoma Cruzi

- Mechanism involves development of anti-muscarinic receptor antibodies in response to infection
- May be responsive to nitrates, balloon dilation, or myectomy
- Patients with long standing stasis due to Chagas often have esophageal squamous hyperplasia and are at increased risk for esophageal cancer

Infectious Esophagitis

Mycobacterium Tuberculosis

- Esophageal manifestations almost always due to direct extension from mediastinal structures
- There are documented cases of primary esophageal TB
- Presents with dysphagia accompanied by weight loss, cough, chest pain and fever

Infectious Esophagitis

Mycobacterium Tuberculosis

- Endoscopic findings: shallow ulcers, heaped-up neoplastic appearing lesions, and extrinsic compression of the esophagus due to mediastinal lymphadenopathy
- Diagnosis made by sending biopsy/brushing for acid fast stain, PCR, and mycobacterial culture

Esophageal Infections in the Immunocompromised



Infectious Esophagitis

Immunocompromised Host

- Esophageal candidiasis most common cause of dysphagia and odynophagia in patients with HIV/AIDS
- A therapeutic trial of antifungal is indicated in most cases prior to further workup due to the frequency of candidal infections

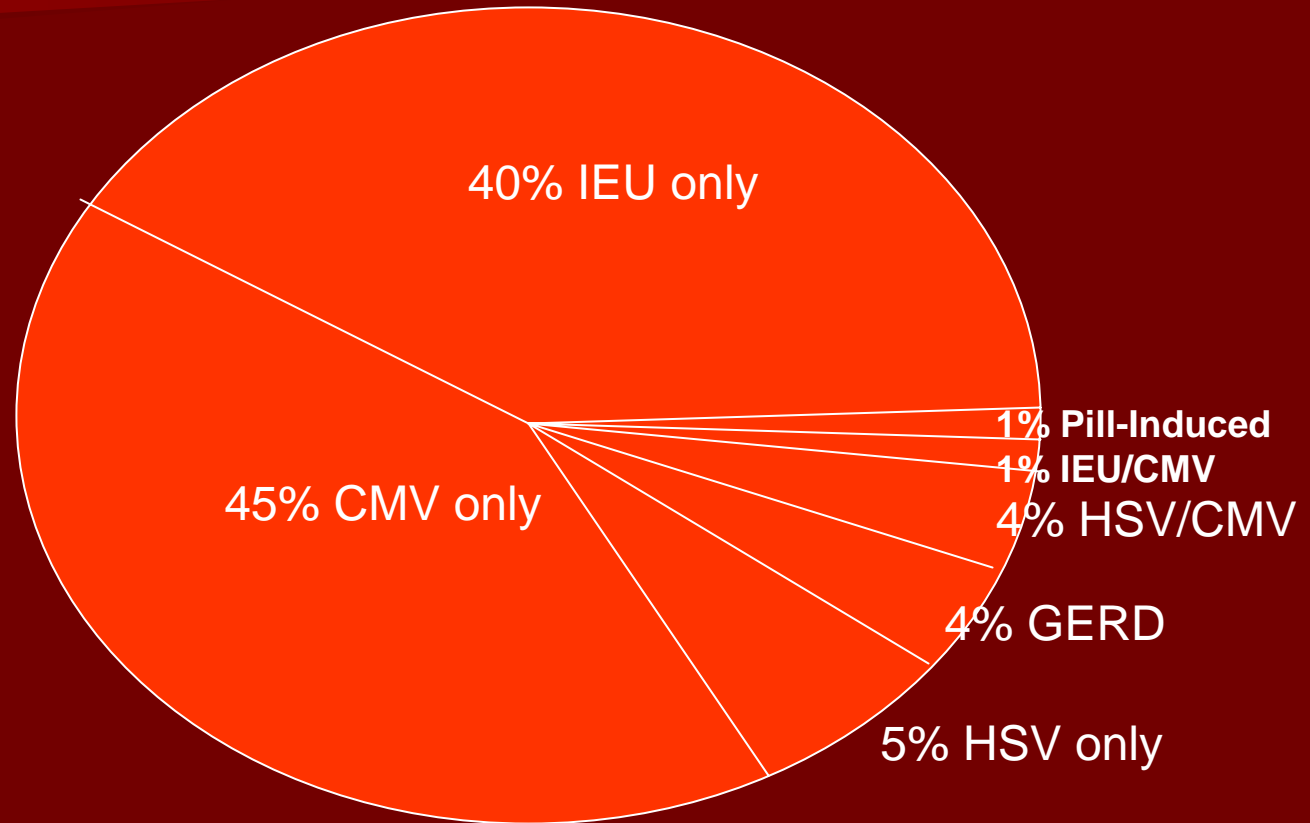
Infectious Esophagitis

Immunocompromised Host

- Prospective cohort study looked at 100 patients with HIV and esophageal ulcer
- Causes of ulcers determined from clinical, endoscopic, and pathologic findings
- CMV was the most common cause (45%)

Wilcox, CM, Schwartz, DA, Clark, WS. Esophageal ulceration in human immunodeficiency virus infection: causes, response to therapy, and long-term outcome. *Annals of Int Med* 1995; 123 (2): 143-149.

Etiology of Ulceration in 100 HIV + patients



CMV Esophagitis

- Odynophagia is the predominant presenting symptom
- Endoscopic findings may range from frank ulceration to segmental erosions
- Ulcerations are typically large, solitary, shallow lesions with clearly defined margins

CMV Esophagitis

- Diagnosis made by presence of histologic finding of intranuclear inclusions using immunohistochemical staining
- Deep biopsies are needed for diagnosis as the virus does not infect the squamous cell epithelium

Wilcox, C., Diehl, D., Cello, J., et al. Cytomegalovirus Esophagitis in Patients with AIDS: A Clinical, Endoscopic and Pathologic Correlation. *Annals of Internal Medicine*. Oct 1990:589-593.

Theise ND, Rotterdam H, Dieterich D. Cytomegalovirus esophagitis in AIDS: diagnosis by endoscopic biopsy. *American Journal of Gastroenterology*. 86(9):1123-6, 1991 Sep.

Infectious Esophagitis

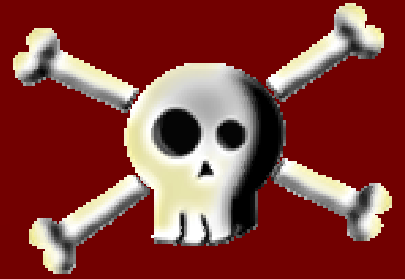
Immunocompromised Host

Idiopathic Esophageal Ulcers (IEU)

- Observed in later stages of HIV with $CD4 < 100$
- Case reports in post-renal/liver transplant patients
- May be single or multiple; usually distal esophagus
- By definition, all diagnostic studies are negative (biopsy, brushings, cx, etc)
- Treatment includes steroids and thalidomide

S Sor, MS Levine, TE Kowalski, et al. *Giant ulcers of the esophagus in patients with human immunodeficiency virus: clinical, radiographic, and pathologic findings.* Radiology, Vol 194, 447-451.

Mayo Clinic Board Review, 2nd edition



Caustic Ingestions



Caustic Ingestions

- Severity depends on:
 - Type of ingested substance
 - Amount, concentration and whether agent was solid or liquid
 - Duration of contact with the mucosa

Goldman, LP, Weigart, JM. Corrosive substance ingestion: A review. Am J Gastroenterol 1984; 79:85.
Wasserman, RL, Ginsburg, CM. Caustic substance injuries. J Pediatr 1985; 107:169.

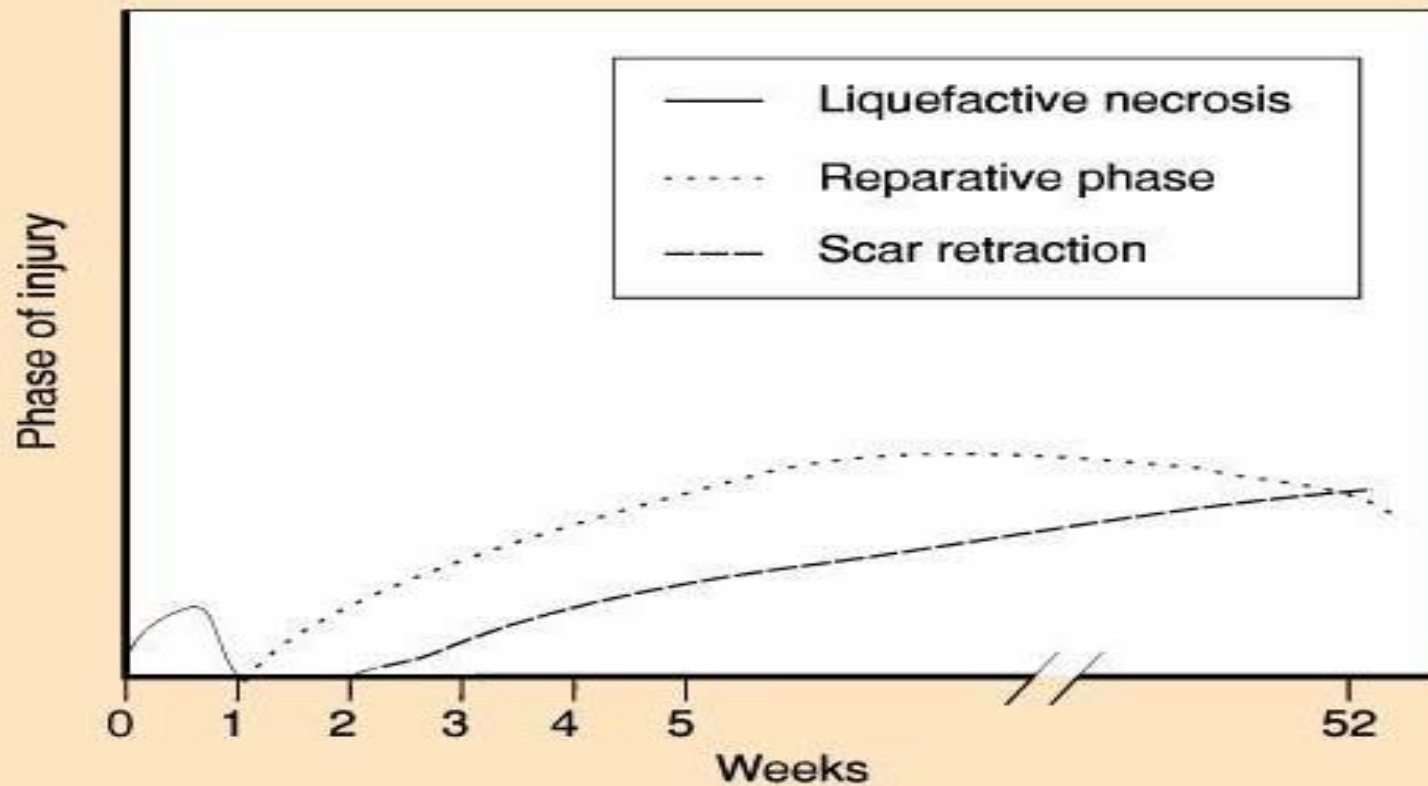
Caustic Ingestions

- Causes:
 - Accidental in children < 5 and intentional in adults/adolescents
 - Most common cause – strong alkali substances (KOH/NaOH) – found in drain cleaners, cleaning products, disc batteries
 - “Lye” Implies substances that contain KOH/NaOH
 - Highly concentrated acids are less common
 - Bleach ingestion frequently reported, but rarely causes esophageal injury

Caustic Ingestions

- Alkali substances – Esophageal injury more than stomach injury due to some neutralization by stomach acid
- Duodenal damage less common (30% vs. 100% esophagus/94% stomach)
- Causes liquefactive necrosis
- Injury extends rapidly (within seconds) through the mucosa and esophageal wall
- Extensive transmural injury more common with liquid substances – can cause perforation, mediastinitis, peritonitis and death

Pathogenesis of Alkali Ingestions



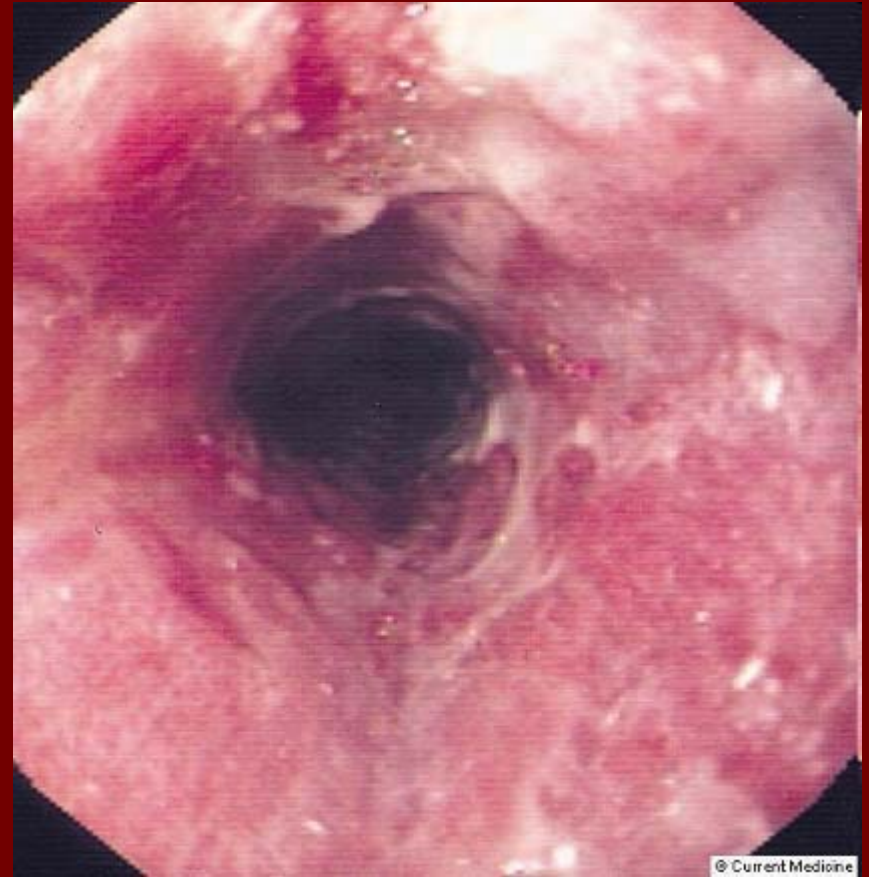
Caustic Ingestions

Pathophysiology - Acids

- Acidic substances – gastric injury because pass quickly into stomach
- Amount ingested is usually limited due to pain on mucosal contact
- Produces superficial coagulation necrosis, thrombosis mucosal vessels/tissue consolidation, protective eschar
- Antrum receives the most injury due to pylorospasm and poor emptying

Caustic Injuries - Staging

- Used to predict clinical outcome
- Based on study of 81 patients with corrosive ingestion



Caustic Injuries - Staging

- Grade 1/2A – good prognosis, low acute morbidity and subsequent stricture
- Grade 2B/3A – 70-100% develop stricture
- Grade 3B – 65% early mortality; most required esophageal resection

Grade	Endoscopic mucosal appearance
0	Normal
1	Mucosal edema and hyperemia
2A	Superficial ulcers, bleeding, exudates
2B	Deep focal or circumferential ulcers
3A	Focal necrosis
3B	Extensive necrosis

Zargar, SA, Kochhar, R, Mehta, SK. The role of fiberoptic endoscopy in the management of corrosive ingestion and modified endoscopic classification of burns. *Gastrointest Endosc* 1991; 37:165.

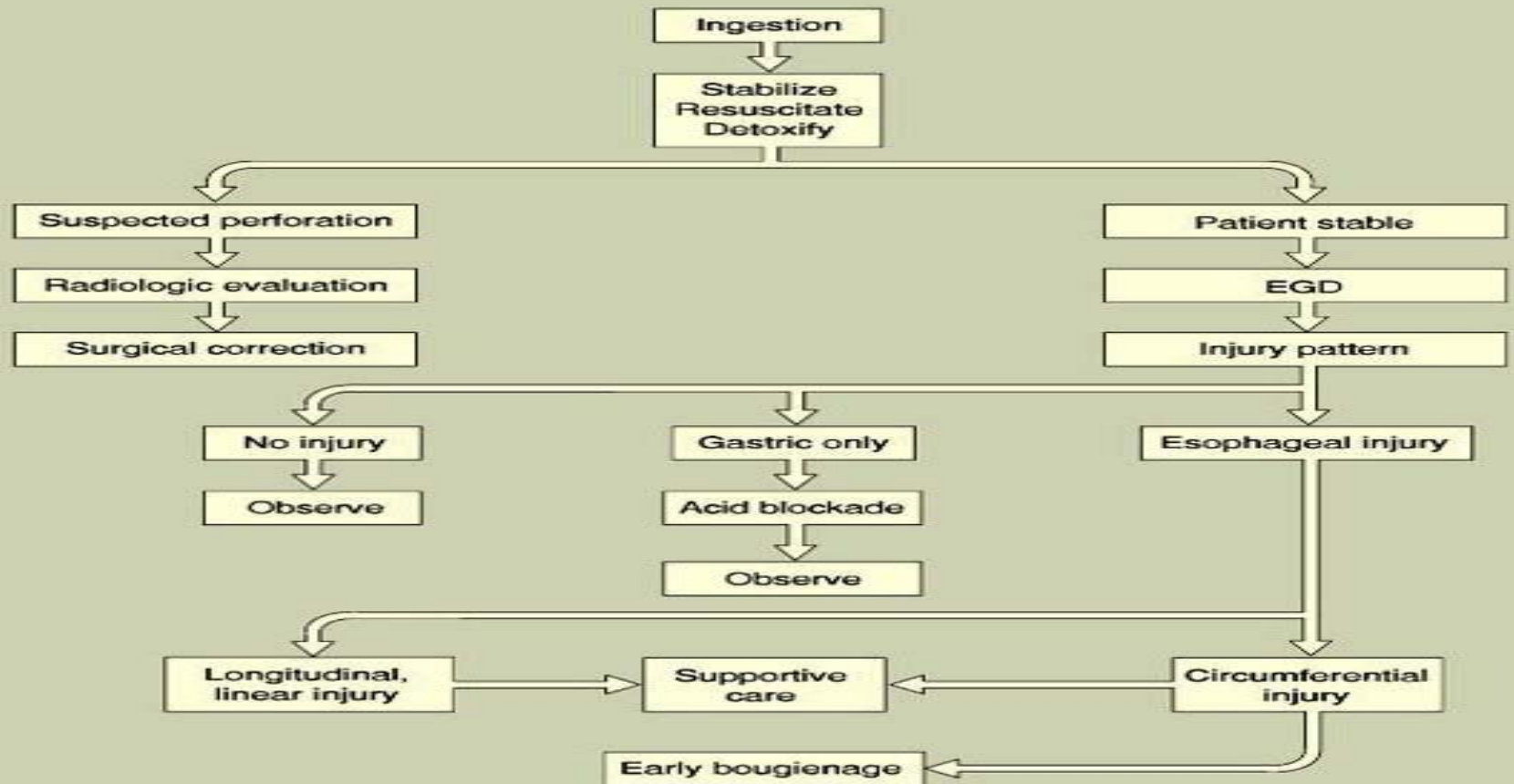
Caustic Ingestion

Management

- Grade 1/2A
 - No therapy; start on clear liquids and advance to regular diet in 24-48 hours
- Grade 2B/3
 - Initiate nasoenteric tube feeding after 24 hours
 - Oral liquids after 48 hours only if patient can swallow saliva
- Grade 3
 - Observe carefully for signs of perforation for at least 7 days post ingestion

Caustic Ingestion

Management Algorithm



Caustic Ingestion

Strictures

- Highest risk with Grade 2B/3 injury
- Dysphagia usually presents after about 2 months (can vary)
- Wait 3-6 weeks after injury to dilate
- Perforation occurs in approximately 0.5% and requires surgical repair in 70% perforations
- Goal is to dilate lumen to 15 mm/relieve dysphagia

Broor, SL, Raju, GS, Bore, PP, et al. Long-term results of endoscopic dilation for treatment of corrosive esophageal strictures. Gut 1993; 34: 1498.

Caustic Ingestion

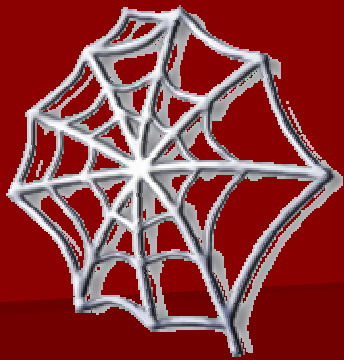
Development of esophageal cancer

- Risk of developing esophageal squamous cell carcinoma increases 1000-fold after lye ingestion
- One study (n=63), latency period 41 years (range 13-71 years)
- Nearly all had consumed an alkali

Esophagus

Miscellaneous

- Esophageal Webs
- Esophageal Rings
- Esophageal Diverticula



Esophageal Webs



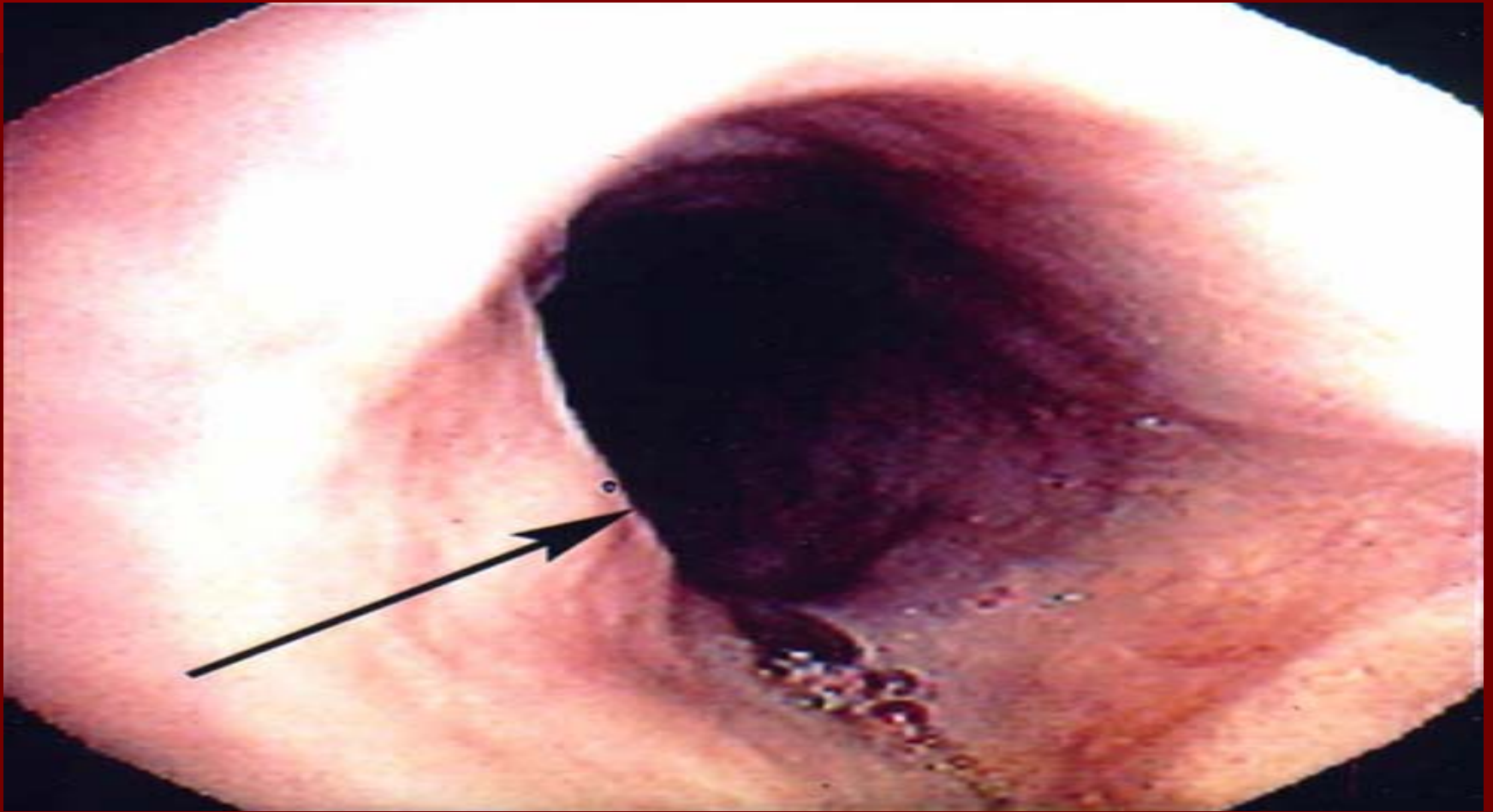
Esophageal Webs

- Thin protruding mucosal folds, lined by squamous epithelium
- Most common in the anterior cervical esophagus
- Easy to miss on endoscopy due to proximal location
- Pathogenesis unknown

Esophageal Webs

- Can be associated with iron deficiency, glossitis, spoon nails (Plummer-Vinson syndrome/Patterson Kelly syndrome)
- Can occur as extracutaneous manifestation of systemic disorder:
Epidermolysis bullosa, bullous pemphigoid, pemphigus vulgaris, Chronic GVHD

Upper Esophageal Web – Plummer Vinson Syndrome



Esophageal Webs

- True prevalence unknown – largely asymptomatic
- In large retrospective studies using barium contrast exam, 5-15% that reported dysphagia were found to have webs – although some may have been incidental finding

Webb WA, McDaniel L, Jones L. Endoscopic evaluation of dysphagia in two hundred and ninety-three patients with benign disease. *Surg Gynecol Obstet* 1984;158:152-6.

Esophageal Webs - Diagnosis

- Radiographic techniques more sensitive than endoscopy due to proximal location
- Barium swallow vs. videoradiography with lateral/AP views are the optimal studies

Esophageal Webs

- Treatment-
 - usually ruptured with endoscope
 - dilation sometimes necessary
 - rarely, refractory to standard dilation requiring endoscopic laser division or surgical resection

Esophageal Webs

Image taken from UTD, Courtesy of Jonathan Kruskal, MD, PhD.



Esophageal Rings



Esophageal Rings

- Schatski's Ring
 - thin mucosal structures at the GE junction
 - lined proximally by squamous and distally by columnar epithelium
- Muscular Ring
 - located within 2 cm of the z-line
 - more common in children
 - hypertrophy of the esophageal musculature
 - caliber changes during peristalsis

Schatski's Ring

- Accounts for 15-26% of esophageal dysphasia
- Almost always symptomatic when internal diameter is < 13 mm or 39 French and rarely symptomatic if > 20 mm

Wilcox CM, Alexander LN, Clark WS. Localization of an obstructing esophageal lesion. Is the patient accurate? *Dig Dis Sci.* 1995;40:2192.

Schatski's Ring

- Usually presents in one of two ways:
 1. Intermittent dysphagia for solids causing alteration of eating habits (i.e. small bites) +/- progressive over time
 2. "Steakhouse syndrome" – acute unexpected obstruction after swallowing large food bolus

Schatski's Ring

- Asymptomatic rings found in 6-14% routine barium studies
- Endoscopy less sensitive than barium esophagram for detection b/c lower esophagus has to be adequately insufflated
- The endoscopic detection rate is highest with apertures less than 13 mm.

Ott, DJ, Gelfand, DW, Lane TG, et al. Radiologic detection and spectrum of appearances of peptic esophageal strictures. *J Clin Gastroenterol* 1982; 4:11.

Detection of esophageal rings and strictures by radiography and endoscopy

Ott, DJ, Gelfand, DW, Lane TG, et al. Radiologic detection and spectrum of appearances of peptic esophageal strictures. *J Clin Gastroenterol* 1982; 4:11.

Aperture, mm	N	Radiographic detection, (%)	Endoscopic detection, (%)
<13	22	91	82
14-19	26	96	54
20-25	12	100	25
Total	60	95	58

Schatski's Ring - Treatment

- Treatment if symptomatic is bougie dilation to disrupt the ring
- Symptom recurrence is common
- 61 patients followed for 6 years – 63% had recurrent dysphagia
- Return of symptoms did not correlate with original size of the ring
- Best results achieved with single, large (> 50 French) Bougie

Schatski's Ring - Treatment

- Patients with recurrence can be safely redilated without increase in complication rate

Eckhardt VF, Kanzler G, Willems D. Single dilation of symptomatic Schatski rings: a prospective evaluation of its effectiveness. *Dig Dis Sci* 1992;37:577-82.

Esophageal Diverticula



Esophageal Diverticula

- Defined by their anatomic position
 - Zenker's (cervical) – near cricopharyngeus muscle
 - Midesophageal – middle third – usually at level of carina
 - Epiphrenic – distal, but proximal to LES

Zenker's Diverticula

- Most frequent type
- Found in 1.8 - 2.3% patients with dysphagia undergoing radiological exam

Ekkberg O, Wahlgren L. Dysfunction of pharyngeal swallowing. A cineradiographic investigation in 854 dysphagia patients. *Acta Radiol* 1985;26:389-395.

Zenker's Diverticula

- Prevalence estimated at 0.01 to 0.11% general population
- Most commonly presents in seventh to eighth decade of life
- Etiology controversial – spasm, neuromuscular incoordination, GERD have all been proposed

Watemberg S, Landau O, Avrahami R. Zenker's diverticulum: reappraisal. *Am J Gastroenterol* 1996;91:1494-8.

Ellis FH. Pharyngoesophageal (Zenker's) diverticulum. *Adv Surg* 1995;28:171-89.

Zenker's - Presentation

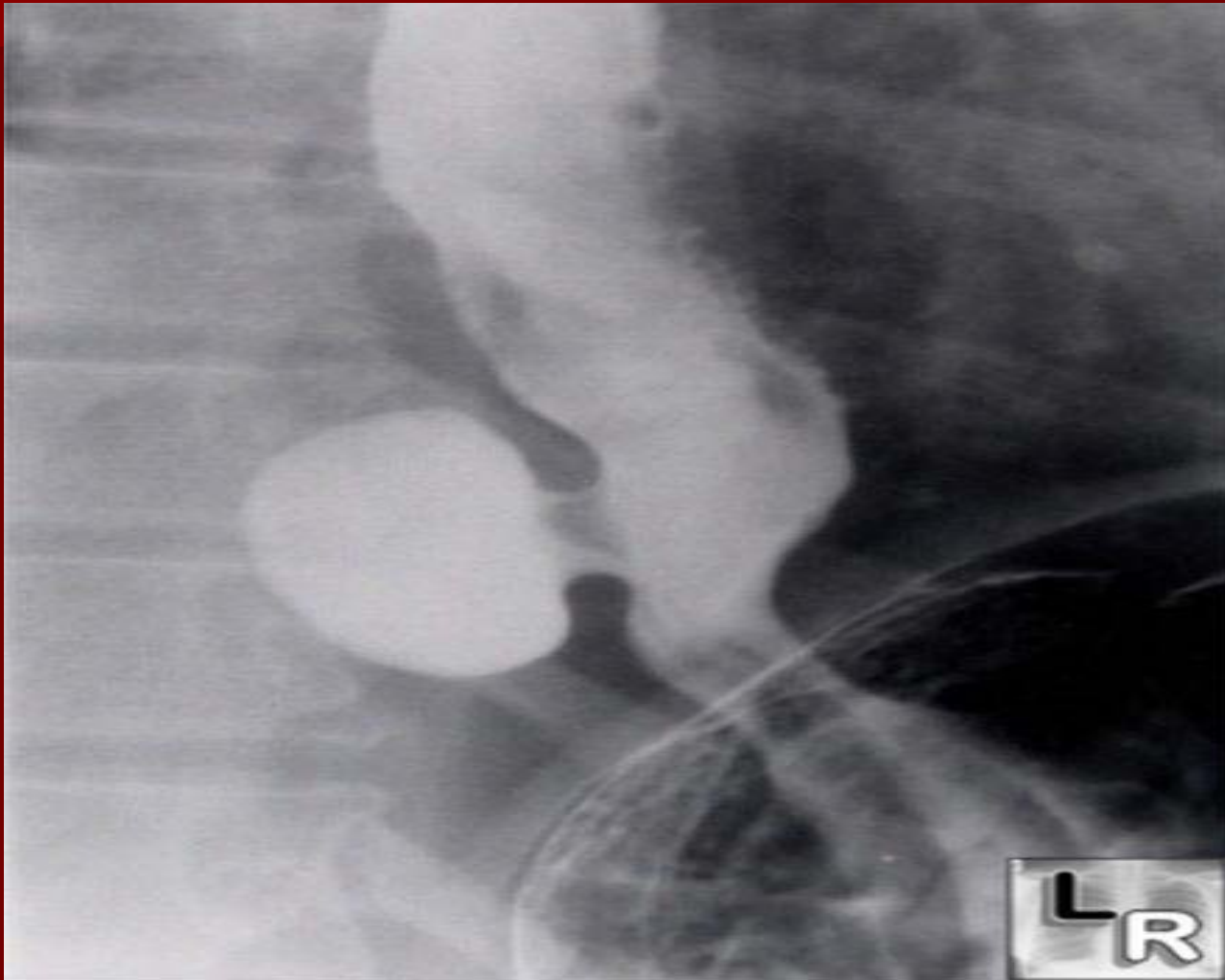
- Progressive upper esophageal dysphagia
- Late findings include regurgitation of undigested food, halitosis, aspiration, voice changes, and rarely neck mass
- Weight loss in one-third of symptomatic
- Aspiration pneumonia most common complication

Midesophageal/Epiphrenic

- Prevalence unknown – each account for 15% of diverticula in most series
- Pathogenesis
 - thought to be due to dysmotility → high luminal pressure → outpouching at point of wall weakness (pulsion diverticula)

Kaye MD. Oesophageal motor dysfunction in patients with diverticula of the mid-thoracic oesophagus. *Thorax* 1974;29:666-71.

Epiphrenic Diverticulum



Midesophageal Diverticulum



Midesophageal/Epiphrenic

- Associated with nutcracker esophagus, hypertensive LES, DES, and achalasia
- Can develop above esophageal stricture

Kaye MD. Oesophageal motor dysfunction in patients with diverticula of the mid-thoracic oesophagus. *Thorax* 1974;29:666-71.

Debas HT, Payne SP, Cameron AJ, Carlson HC. Physiopathology of lower esophageal diverticulum and its implications for treatment. *Surg Gynecol Obstet* 1980;151:593-600.

Midesophageal/Epiphrenic

- Usually asymptomatic/incidental finding
- Can have same symptoms as symptomatic Zenker's
- Difficult to determine if symptoms due to diverticulum or underlying motility disorder

Diverticula - Diagnosis

- Contrast radiographic studies preferred method of diagnosis
- Barium swallow detects Zenker's pouches over 2 cm

Diverticula - Treatment

- Small, asymptomatic Zenker's - observation
- Large or symptomatic Zenker's – surgery (diverticulectomy with myotomy or diverticuloplexy with myotomy) vs. newer endoscopic techniques
- Midesophageal/epiphrenic – treat underlying disorder

Tobin, RW. Esophageal Rings, Webs, and Diverticula. *J Clin Gastro* 1998; 27(4): 285-295.

Esophageal Intramural Pseudodiverticulosis (EIPD)

- Numerous, small (1-3mm), flask-shaped outpouchings
- Most commonly appreciated on barium esophagram
- Almost always associated with mid- or upper esophageal stricture
- Diverticula are distal to stricture and not thought to be pulsion related

EIPD

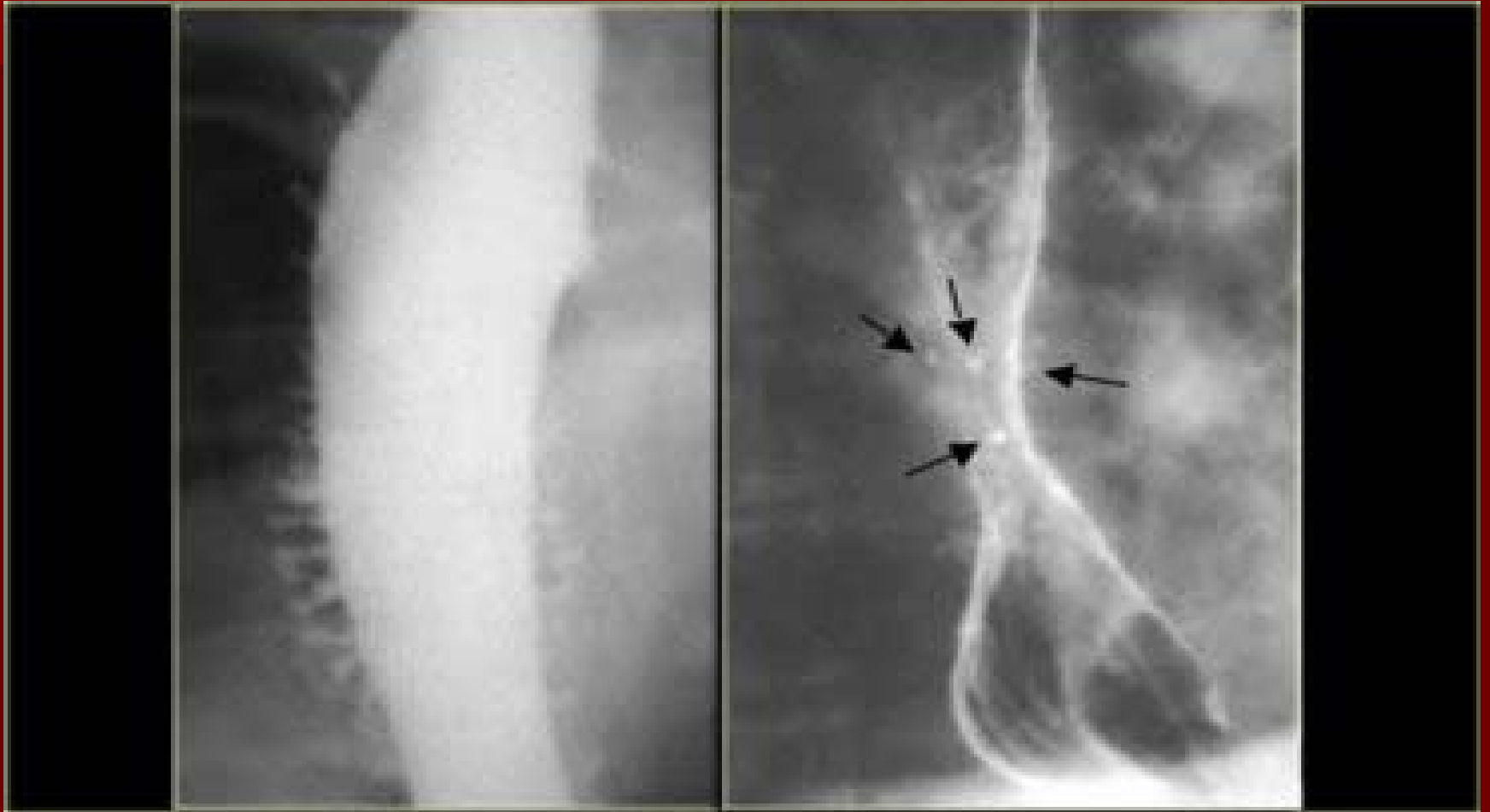
- Pathogenesis unclear
- One-third will have associated candida esophagitis
- Most common presentation is dysphagia, which is most likely due to the stricture

EIPD



Figure 1: Single-contrast esophagogram reveals moderate stricture in the upper esophagus. Multiple flask-shaped outpouchings are found in the esophageal wall. Tiny collections of barium are found outside the esophageal wall that do not communicate with the lumen (arrows). Some of the pseudodiverticula show thin interconnecting intramural tracks (star).

EIPD



EIPD Treatment

- Dilation of symptomatic strictures
- Medical treatment of GERD and Candida esophagitis



Questions?