Esophageal Dysphagia
Pathophysiologic Aspect and Treatment

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Anatomy of the Esophagus

Comprised of a body (18-25 cm) and two sphincters

UES

LES
Phases of Swallowing

Preparatory
• Oral
  (Volition/Cognition?)
• Pharyngeal
  (Non volition & Reflexive)

Bolus transit
• Airway protection
  (Non volitional)

• Esophageal
  (Non volitional)
ANATOMY OF ESOPHAGUS

- Esophagus length is 8-10 cm at birth, doubles in the first 2-3 yr of life, and is 18-25 cm in the adult.

**Layers**
- Mucosa
  - Epithelium (stratified squamous except at GE junction, which is columnar)
  - Lamina propria
  - Muscularis mucosae
- Submucosa
- Muscularis propria (Two Layers)
- Adventitia

Image excerpt from https://healthjade.com/what-is-the-esophagus/
Anatomy of the Esophagus

- **Muscularis propria (inner circular and outer longitudinal muscles)**
  - Proximal third predominantly striated muscle
  - Distal two-thirds predominantly smooth
- Anatomic condition for Zenker and Killian Jamison diverticula above and below the cricopharyngeous muscle
Esophageal Neuromuscular Arrangement

- Myenteric Plexus
- Sub-mucosal plexus
- Longitudinal muscle
- Circular muscle
- Esophageal plexus

ES
Anatomy and Development of Esophagus

- Spans three pressure compartments: cervical, thoracic, and abdominal
- Upper esophagus is derived from brachial arches 4, 5, and 6, but derivation of the lower is not known
- Beginning at 4 months, ciliated epithelium starts to be replaced by squamous epithelium
- Esophageal peristalsis: first trimester
- Gastroesophageal reflux: can occur in second trimester
Parasympathetic and Sympathetic Innervation of the Esophagus

Kuo B & Urma D. GI Motility online (May 2006) | doi:10.1038/gimo6
Upper Esophageal Sphincter and Upper Esophageal Musculature
Lower Esophageal Sphincter and Lower Esophageal Musculature

Gastroesophageal Mucosal Junction and Muscular Arrangement at the Lower Esophagus

Kuo B & Urma D. GI Motility online (May 2006) | doi:10.1038/gimo6
Diaphragmatic Crura and Esophageal Opening Viewed from Below (a) and as Viewed from Above (b). The Esophageal Opening is Created by a Loop of Right Crux of the Diaphragm.
EMBRYOLOGY OF THE ESOPHAGUS

- Develops from the post-pharyngeal foregut
- Can be distinguished from the stomach in 4wk old embryo
- Trachea begins to bud just anterior to the developing esophagus
- Disturbance of this stage can result in tracheoesophageal fistula
Esophageal Functions

• Motor function
  – Peristalsis/swallowing, bolus transport
    • Swallowing can be seen in utero as early as 16-20 wk
    • Sucking and swallowing are not fully coordinated before 34 wk
  – Belching, vomiting

• Sensory function
  – Sensation, pain, heartburn, pressure
  – Airway protection, reflex mechanism
Proposed Model of Oropharynx and Esophageal Deglutitive Control

- DSG contains the generator neurons involved in triggering, shaping, and timing the sequential or rhythmic swallowing pattern.

- VSG contains the switching neurons distribute swallowing drive to various pools of motoneurons involved in swallowing.

- Esophageal circuit may involve a DSG, a VSG, and the motor or preganglionic nuclei.
Inhibitory and Excitatory Innervation in Swallowing/Peristalsis

a: Swallowing network chain of neurons with excitatory (black triangles) and inhibitory (black dots) connections, and sensory feedback (broken lines).

b: The central pattern generator may be subdivided in an oropharyngeal and an esophageal network. Esophageal net is first inhibited by oropharyngeal net (black dot). This primary inhibition is followed by an excitatory action (black triangle), rendering possible the successive activation of esophageal neurons.
Esophageal Peristalsis

- **Striated muscle**: depends on central mechanisms, involving sequential activation of vagal lower motor neurons in the vagal nucleus ambiguous.

Mashimo H & Goyal R. GI Motility online (May 2006) | doi:10.1038/gimo3
Esophageal Peristalsis

- **Smooth muscle**: depends on both central and peripheral mechanisms.
  - **Central mechanism**: involves patterned activation of preganglionic neurons in dorsal motor nucleus of the vagus that project onto inhibitory and excitatory neurons in myenteric plexus.
Esophageal Motor Function
Peristalsis

- **Striated muscle**: depends on central mechanisms, involving sequential activation of vagal lower motor neurons in the vagal nucleus ambiguus.

- **Smooth muscle**: depends on both central and peripheral mechanisms.
  - **Central mechanism**: involves patterned activation of preganglionic neurons in dorsal motor nucleus of the vagus that project onto inhibitory and excitatory neurons in myenteric plexus.
Smooth Muscle Esophageal peristalsis

• Peripheral mechanisms involve:
  – regional differences in the inhibitory and excitatory intramural nerves
  – intrinsic properties of the muscle

• Intramural inhibitory nerves:
  – release nitric oxide (NO) and vasoactive intestinal peptide (VIP)

• Intramural excitatory nerves:
  – release acetylcholine and substance P
Normal Esophageal Motor Function
Liquid Barium Swallow
Abnormal Esophageal Motor Function
Roast Beef swallow
Normal Esophageal Motor Function
Water Swallow Manometry
Normal Manometric Recording of Esophageal Peristaltic Contraction
Five Pressure Zones from Pharynx to Stomach
Five Pressure Zones from Pharynx to Stomach
Normal Esophageal Peristalsis

• Sequential contraction of circular and longitudinal muscles

• Preceded by deglutitive inhibition

• Swallow-induced peristalsis: primary peristalsis

Peristalsis induced by esophageal distention: secondary peristalsis
## Characteristics of Esophageal Peristalsis

<table>
<thead>
<tr>
<th></th>
<th>Velocity (cm/sec)</th>
<th>Duration (sec)</th>
<th>Amplitude (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal</td>
<td>3</td>
<td>1.75-2</td>
<td>50-110</td>
</tr>
<tr>
<td>Middle</td>
<td>5</td>
<td>~1.7</td>
<td>35-140</td>
</tr>
<tr>
<td>Distal</td>
<td>2.5-9</td>
<td>2-7</td>
<td>70-140</td>
</tr>
</tbody>
</table>

Bolus size, viscosity, temperature, patient position, intra-esophageal and pharyngeal events influence these parameters.

Primary Peristalsis as Recorded by an Intraluminal Manometry Catheter
Diagrammatic Representation of Deglutitive Inhibition
Schematic Representation of Esophageal Contractions.

Paterson W. GI Motility online (May 2006) | doi:10.1038/gimo6
Electrical Stimulation of Intrinsic Nerves in Circular Smooth Muscle Strips
Example of Esophageal Body distension-contraction
Esophageal Body distension-contraction plots

Ravinder K. Mittal, Kazumasa Muta, Melissa Ledgerwood-Lee, Ali Zifan
Am J Physiol Gastrointest Liver Physiol. 2020
Factors Involved in Esophageal Pre-peristalsis Distension

- Muscle relaxation due to neural inhibition
- Physical properties of the muscle tissue
  - Muscle thickness
  - Presence or absence of inflammation
- Properties of the bolus
  - Bolus volume and velocity
  - Bolus consistency/viscosity
  - Position/effect of gravity
- Effect of intra-thoracic pressure
Lower Esophageal Sphincteric mechanisms

- Include two sphincters:
  - Smooth muscle lower esophageal sphincter (LES)
    - maintains tonic contraction by myogenic and neurogenic mechanisms
  - Striated muscle diaphragmatic sphincter

- The two sphincters maintain tonic closure
- Both sphincter relax during swallowing and TLESR
- LES relaxation is a vagally mediated inhibition and involves nitric oxide and VIP as a neurotransmitter.
Lower Esophageal Sphincter Pressure

- LES pressure at any given time is the interplay of three elements; a vagally mediated inhibition that involves nitric oxide and VIP, an excitatory cholinergic (ACH) contraction and the LES myogenic tone.
Aerodigestive Tract and Esophagus Are Richly Connected by Reflexes

- Laryngeal Reflexes
  - UES +
  - Larynx +
  - Cough
  - Esophagus

- Pharyngeal Reflexes
  - Larynx +
  - Swallow +
  - UES +
  - Esophagus
  - LES -
  - Fundus

- Esophageal Reflexes
  - Larynx +
  - UES +
  - Esophagus +
  - LES -
  - Fundus
Esophago-glottal Closure Reflex

An Example of Glottal Closure Response to Esophageal Air and balloon Distension

Weakens with Age

Esophago-UES Contractile Reflex

Weakens with:
- age
- SERD/LPR

Airway Protective Reflexes

Examples of Normal UES Response to Ultra Low Intensity Fluid Stimulation and the effect of age

Ling Mei, R, Shaker, et al. Gastroenterology, 2018
Esophageal primary sensory fibers are carried in the vagus and the spinal nerves.

Most of the vagal afferent endings form two specialized structures:
- intraganglionic laminar endings (IGLEs)
- intramuscular arrays (IMAs)
Esophageal primary afferent fibers: muscle tension-sensitive mucosal mechano/chemosensitive tension/mucosal receptors

Muscle tension-sensitive fibers in the vagus nerve have low thresholds for response and serve in physiologic reflexes

Spinal afferent fibers may serve in nociception and encode noxious intensity of stimulus.
Different/Specialized Esophageal Sensory Field Effect on UES Motor Function

Aslam et al, Neurogastroenterology & Motility, 2003
## Deterioration of Esophageal Sensory Function

<table>
<thead>
<tr>
<th></th>
<th>aging</th>
<th>smoking</th>
<th>alcohol</th>
<th>GERD</th>
<th>Reflux laryngitis</th>
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<tbody>
<tr>
<td>Secondary peristalsis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Esophago-UES contractile reflex</td>
<td>-</td>
<td>-</td>
<td>NS</td>
<td>+/-</td>
<td>NS</td>
</tr>
<tr>
<td>Esophago-UES relaxation reflex</td>
<td>-</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Acid sensation</td>
<td>+</td>
<td>NS</td>
<td>NS</td>
<td>-</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS: Not Studied  
+ : Deterioration documented  
- : Deterioration not documented
| Etiologies of Esophageal Dysphagia |  |
|-----------------------------------|  |
| **Strictures:**                   | **Primary motor:** |
| Peptic                            | Achalasia          |
| Radiation                         | Esophagogastric junction outflow obstruction (EGJOO) |
| Caustic                           |  |
| Pill-induced                      |  |
| Rings                             |  |
| Webs                              |  |
| Plummer-Vinson syndrome           | Jackhammer esophagus |
| Ineffective esophageal body peristalsis | |
| **Inflammatory conditions:**      |  |
| Eosinophilic esophagitis          |  |
| Lymphocytic esophagitis           | Secondary motor: |
| Lichen planus                     |  |
| Bullous pemphigold                | Systemic sclerosis (scleroderma) |
|                                   | Polymyositis/Dermatomyositis |
|                                   | Chagas disease |
| **Iatrogenic:**                   |  |
| Post surgical (reflux therapy)    |  |
| Post endoscopic therapy for Barrett`s |
| **Esophageal malignancy**         |  |
| Benign tumors:                    |  |
| Leiomyoma                         |  |

Modified from Jacobs JW, in Castell’s ‘The Esophagus’ Sixth Edition. John Wiley & Sons Ltd. Chapter 1
Symptoms of Esophageal Dysphagia

- Motor disorders:
  
  Difficulty swallowing both Solid and Liquid

- Structural Disorders:
  
  Difficulty swallowing Solids
Idiopathic Achalasia
Achalasia/Dysphagia

- Fluid with each bite
- Chest gurgling
- Stretching or standing with eating
- Defective belch
- Nocturnal cough/choke
- Chest pain/heartburn
Achalasia Esophagus an Example of Esophageal Inhibitory Neural Dysfunction

- GEJ Outflow Obstruction
- Achalasia Type II
- Achalasia Type I
- Achalasia Type III

Idiopathic Achalasia
Effect of CCK and Amyl Nitrite in Achalasia Esophagus
# Current Available Treatments for Achalasia

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Durability</th>
<th>Procedural Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical therapy(^a)</td>
<td>On demand/</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>not durable</td>
<td></td>
</tr>
<tr>
<td>Botulinum toxin injection</td>
<td>6-12 mo(^54)</td>
<td>Performed in endoscopy laboratory Moderate sedation or monitored anesthesia care</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Procedure time &lt;30 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60 min observation</td>
</tr>
<tr>
<td>Pneumatic dilation</td>
<td>2-5y(^55,56)</td>
<td>Performed in endoscopy laboratory with fluoroscopy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate sedation or monitored anesthesia care</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Procedure time, 30 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-6 h observation</td>
</tr>
<tr>
<td>Surgical myotomy</td>
<td>5-10 y(^56)</td>
<td>Operating room                      General anesthesia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Procedure time, 90 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hospital stay, 1-2 d</td>
</tr>
<tr>
<td>Per-oral endoscopic myotomy</td>
<td>Unknown</td>
<td>Operating room or endoscopy laboratory General anesthesia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Procedure time, 90 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Requires overnight stay</td>
</tr>
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</table>

\(^a\) Oral calcium channel blockers, nifedipine, isosorbide dinitrate, or sildenafil.
Pneumatic Dilatation

• Provide immediate symptomatic relief, decrease in LES pressure, and increase in esophageal emptying

• Standard practice: graduated dilations from 30-40mm.

• Complications following dilation:
  - esophageal perforation, highest risk after 1st dilation
  - GERD
Pneumatic Dilatation

• Outcomes: 54 pts followed for 13.8 yrs.
  – Fewer younger patients (20%) remain in clinical remission 5 years after a single dilation than older patients (58%).
  – Repeated dilations result in less than 30% chance of remaining in remission for more than 5 years.

Pneumatic Dilatation

- Outcomes: 54 pts followed for 13.8 yrs.
  - Post-dilation pressure <10mm Hg is the most favorable prognostic variable
  - Young patients (<40) and patients who do not achieve a significant decrease in LES pressure after a single dilation are unlikely to achieve long-term clinical remission.

Comparison of Surgical Myotomy and Pneumatic Dilatation

– Cumulative risk of subsequent intervention after 1, 5, 10 years, respectively:

  • 36.8%, 56.2%, 63.5% pneumatic dilatation
  • 16.4%, 30.3%, 37.5% surgical myotomy (p<0.001)

– No significant difference between patients regarding use of anti-reflux medications following treatment using either modality

Lopushinski S et al. JAMA 2006;296(18):2227-2233
Comparison of Surgical Myotomy and Pneumatic Dilatation

- Recent findings of systematic review and meta-analysis
- Little difference in outcomes comparing Heller myotomy to pneumatic dilation
- Study of 2-year and 5-year remission
- Either treatment is a viable alternative for initial achalasia treatment

Adenocarcinoma of the Cardia

Presented as Pseudoachalasia
Esophageal Motor Function

• Affected by:
  – Position /Gravity
  – Bolus physical property (volume, consistency, etc)
  – Swallow interval
  – Intra-abdominal pressure/weight
  – Medication
Effect of Position/Gravity on Esophageal Peristalsis

Effect of Position/Gravity on Esophageal Peristalsis

Effect of bolus physical Property on Esophageal Symptoms and Peristalsis

Effect of bolus physical property on esophageal symptoms and peristalsis.

Jackhammer Esophagus / Diffuse Esophageal Spasm
Treatment of Esophageal Diffuse Spasm

- Pharmaco-therapy
  - Nitrates
  - Calcium channel blockers
  - Phosphodiesterase-5 Inhibitors (Sildenafil)
  - Peppermint oil
  - Hyoscine sulfate (Belladonna)
  - Tricyclic antidepressants
- Botulinum toxin injection
- POEM (Per oral Endoscopic Myotomy)
- Surgical myotomy
Increased Proximal esophageal contraction after induction of ineffective distal contraction by sildenafil in healthy volunteer.
Effect of PDE-5 Inhibitors on Distal Esophageal Peristaltic Amplitude - 1h post

- Baseline: 239
- Sildenafil: 134
- Vardenafil: 54
- Tadalafil: 51

Comparison of Manometric Features and Symptom Score at Pretreatment and with the Three PDE-5 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post-sildenafil</th>
<th>Post-vardenafil</th>
<th>Post-tadalafil</th>
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<tbody>
<tr>
<td>LESP</td>
<td>40</td>
<td>23</td>
<td>8.6</td>
<td>18.9</td>
</tr>
<tr>
<td>DEA</td>
<td>239</td>
<td>134</td>
<td>54</td>
<td>51</td>
</tr>
<tr>
<td>Symptom score</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

DEA: Distal Esophageal Amplitude in mmHg

Dysphagia with Odynophagia

Quinidine

Herpes Esophagitis

Doxycycline

Candidiasis
Dysphagia / Odynophagia (Pill-Induced Injury)
Iatrogenic Dysphagia

- Doxycycline
- Tetracycline
- KCL (delayed release)
- Quinidine
- Aspirin (NSAIDS)
- Ascorbic acid
- Fe^{++} sulfate
- Theophyline
An Example of Post Fundoplication (iatrogenic) Dysphagia
Eosinophilic Esophagitis (EOE)

A clinicopathological disease characterized by:

- Symptoms including but not restricted to food impaction and dysphagia in adults, and feeding intolerance and GERD symptoms in children;
- ≥ 15 eosinophils/HPF;
- Exclusion of other disorders associated with similar clinical, histological, or endoscopic features, especially GERD.

Furuta GT, et al. Gastroenterology. 2007;133:1342-1363
Eosinophilic Esophagitis Clinical Presentation

- Male gender preponderance (3:1)
- Diagnosed in the third or fourth decade of life.
- The most common presenting symptom in adults:
  - Dysphagia to solids (60%-90%).
  - Food impaction in 50% to 60%
  - 50% to 55% of patients presenting to ER with FI have EE
  - GERD (heartburn and regurgitation) 24%-50%
- Most patients who have EE (82%) have normal or negative pH studies
Different Terminology Referring to Eosinophilic Esophagitis

- Allergic Esophagitis
- Primary Eosinophilic Esophagitis
- Idiopathic Eosinophilic Esophagitis
- Corrugated Esophagus
- Ringed Esophagus
- Feline Esophagus
- Trachealized Esophagus
- Small-Caliber Esophagus
Eosinophilic Esophagitis
Endoscopic Features

- Proximal Esophageal strictures
- White papules (eosinophilic microabscess)
- Longitudinal lines or tear
- Felinization/corrugation
- Fixed or transient concentric ring
- Crepe paper appearance
- Loss of vascular pattern
- Small caliber
Eosinophilic Esophagitis Endoscopic Features
Association with allergens

- Majority of patients with EE have atopia (50-80%)
- History of atopy, includes: asthma, hay fever, atopic dermatitis, allergic rhinitis, food allergy (*shellfish, avacado, peanuts, honey, milk, soy, egg and wheat*)
- Strong familial pattern with higher prevalence in siblings
- Antigen exposure in the esophagus (food) may serve as trigger:
  - most patients have symptomatic improvement when food allergen identified and eliminated
Management Options for Eosinophilic Esophagitis

- Acid suppressive therapy
- Topical steroids
  - Oral Viscus Budesonide
  - Fluticasone inhaler to swallow
  - Leukotriene inhibitors (some respond)
- Systemic steroid
- Dilatation
- Diet elimination therapy
Dietary Treatment

- Food allergens contribute to EoE pathogenesis in children
  - Food antigen removal treats symptoms and underlying histopathology
- Specific elimination of foods most likely to cause EoE
  - (eggs, wheat, soy, cow’s milk protein, peanut, seafood)
  - This is done stepwise; 3 item, 5 item elimination diet
- Elemental/amino acid-based formula

A Conceptual Approach to Understanding Treatment Response in Eosinophilic Esophagitis

Therapeutic endpoints in eosinophilic esophagitis.
Disorders of the Proximal Esophagus

Can present with OPD symptoms

Proximal rings
- Plummer-Vinson Syndrome
- Eosinophilic Esophagitis

Proximal strictures
- Benign
- Malignant
Gastroesophageal Reflux Disease
GERD

Los Angeles classification for erosive esophagitis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>One (or more) mucosal break, ≤5 mm long, that does not extend between the tops of two mucosal folds</td>
</tr>
<tr>
<td>B</td>
<td>One (or more) mucosal break, &gt;5 mm long, that does not extend between the tops of two mucosal folds</td>
</tr>
<tr>
<td>C</td>
<td>One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but that involves &lt;75% of the circumference</td>
</tr>
<tr>
<td>D</td>
<td>One (or more) mucosal break that involves at least 75% of the esophageal circumference</td>
</tr>
</tbody>
</table>
Prague Classification of Barrett’s Esophagus
Progression in Barrett’s (PIB) Risk Score

PIB Risk Score

- Male Sex - 9 points
- Cigarette Smoking - 5 points
- BE length - 1 point / cm length
- Confirmed Low Grade Dysplasia - 11 points

PIB Risk Score

- High >20 points: Annual Risk progression 2.1%
- Intermediate 11-20 points: Annual Risk progression 0.73%
- Low 0-10 points: Annual Risk progression 0.13%

Potpourri of the Structural Causes of Esophageal Dysphagia
Thank You
GERD Symptom Duration and Probability of Barrett’s Esophagus
