GERD/GORD and the Role of Stomach Acid

Metabolic Medical Institute

Module IV

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Disclosures

- Disclosure of Financial Relationships
  - None
- Off-Label Usage
  - None

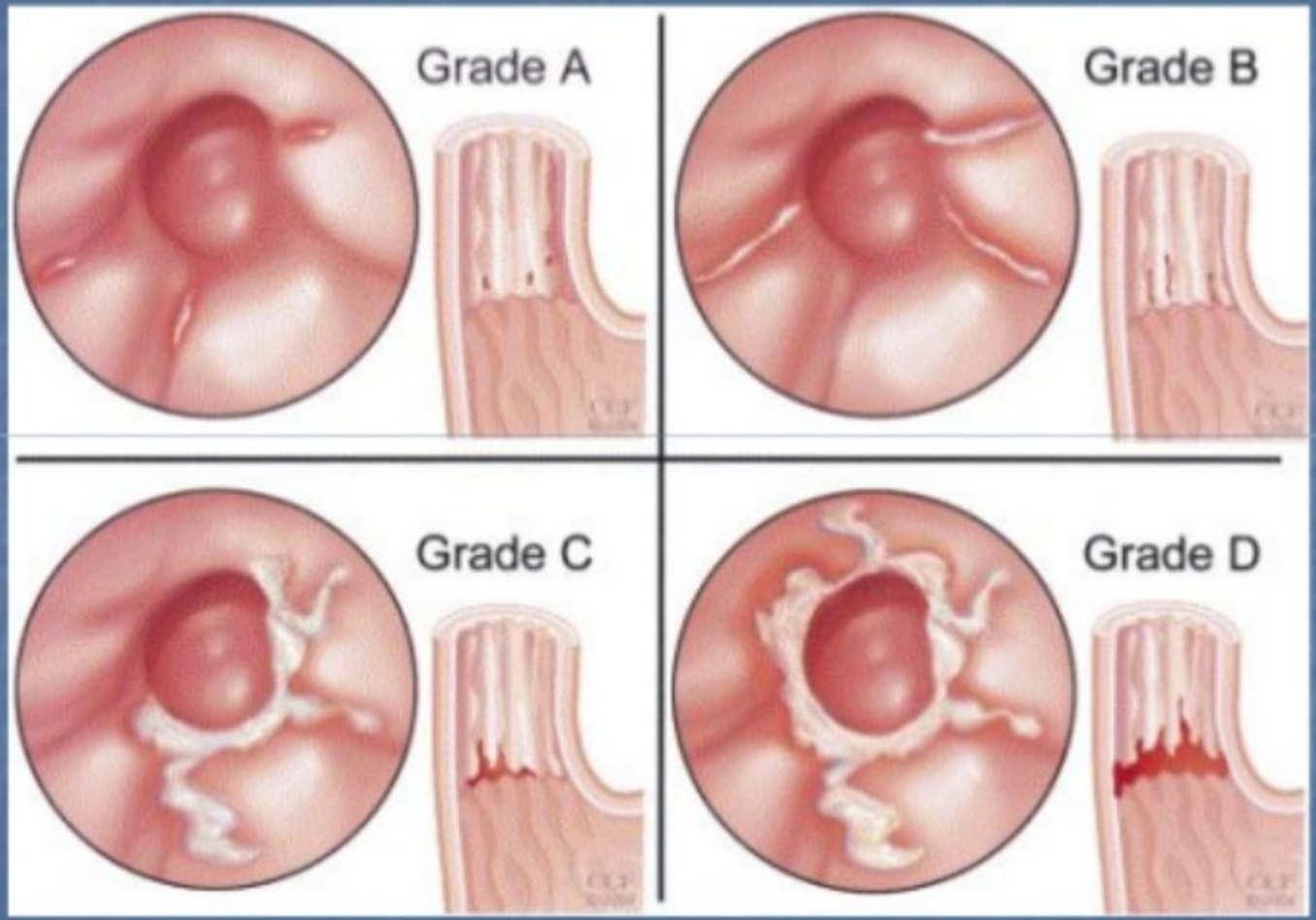
GERD Basics

- Reflux of gastric contents into the esophagus is normal physiology.
- Gastroesophageal reflux disease is defined as reflux leading to symptoms, esophageal mucosal injury, or both.
- There need not be esophageal lesions (erosions, ulceration, intestinal metaplasia) in order to diagnose GERD.
- The majority of patients with GERD show no abnormalities on upper endoscopy (NERD).

Options for GERD imaging and related diagnostics

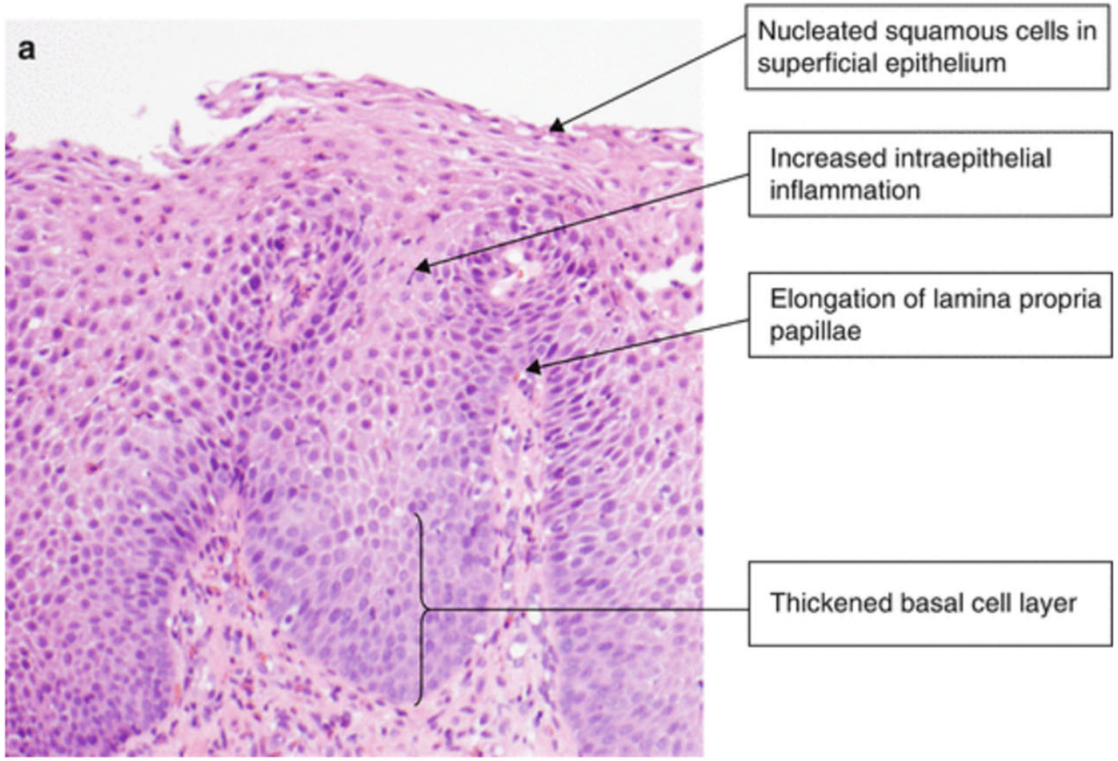
- EGD
  - Differentiates erosive from non-erosive reflux
- Esophageal manometry
  - Measures pressure of contractions
- 24 hour pH impedence testing
  - Indicates whether or not reflux is occurring
  - Measures duration and pH of the reflux since stimuli other than acid can evoke typical reflux symptoms
  - Measures degree of correlation between patient symptoms and reflux events
- Gastric emptying study
  - Measures residual test meal in stomach hourly for 4 hours

LA Classification of Esophagitis



From Nayar DS et al. Gastrointest Endosc 2004;60:253-7.

Histopathology of reflux esophagitis



May have increased scattered eosinophils, PMNs

Basal zone hyperplasia

Lamina propria papillae may extend into the upper 1/3 of the epithelium

GERD clinical manifestations

GERD – clinical picture

- typical symptoms :
  - heartburn (pyrosis)
    - painful retrosternal burning or pressure sensation
    - may be angina-like in quality
    - functional heartburn occurs when sx are present without evidence of reflux
  - regurgitation
    - Rising of gastric contents into the upper throat or mouth

GERD – extra-esophageal s/sx

- hoarseness
- cough
- asthma
- pharyngitis
- erosion of dental enamel
- sinusitis
- pulmonary fibrosis
- tonsillar hypertrophy
- recurrent otitis media
- sleep disturbances or apnea

Laryngopharyngeal reflux (LPR)

- LPR is a unique form of reflux with the only symptoms being in the larynx or pharynx

In laryngopharyngeal reflux (LPR) the patient feels no heartburn, but has sx in the larynx and /or pharynx

- Chronic throat clearing
- Chronic cough
- Chronic sore throat
- Halitosis
- Globus sensation
- Recurrent aspiration pneumonia
- Dysphagia
  - Esophageal webs
- Hoarseness – dysphonia
- Airway obstruction
  - glottic stenosis
  - laryngospasm

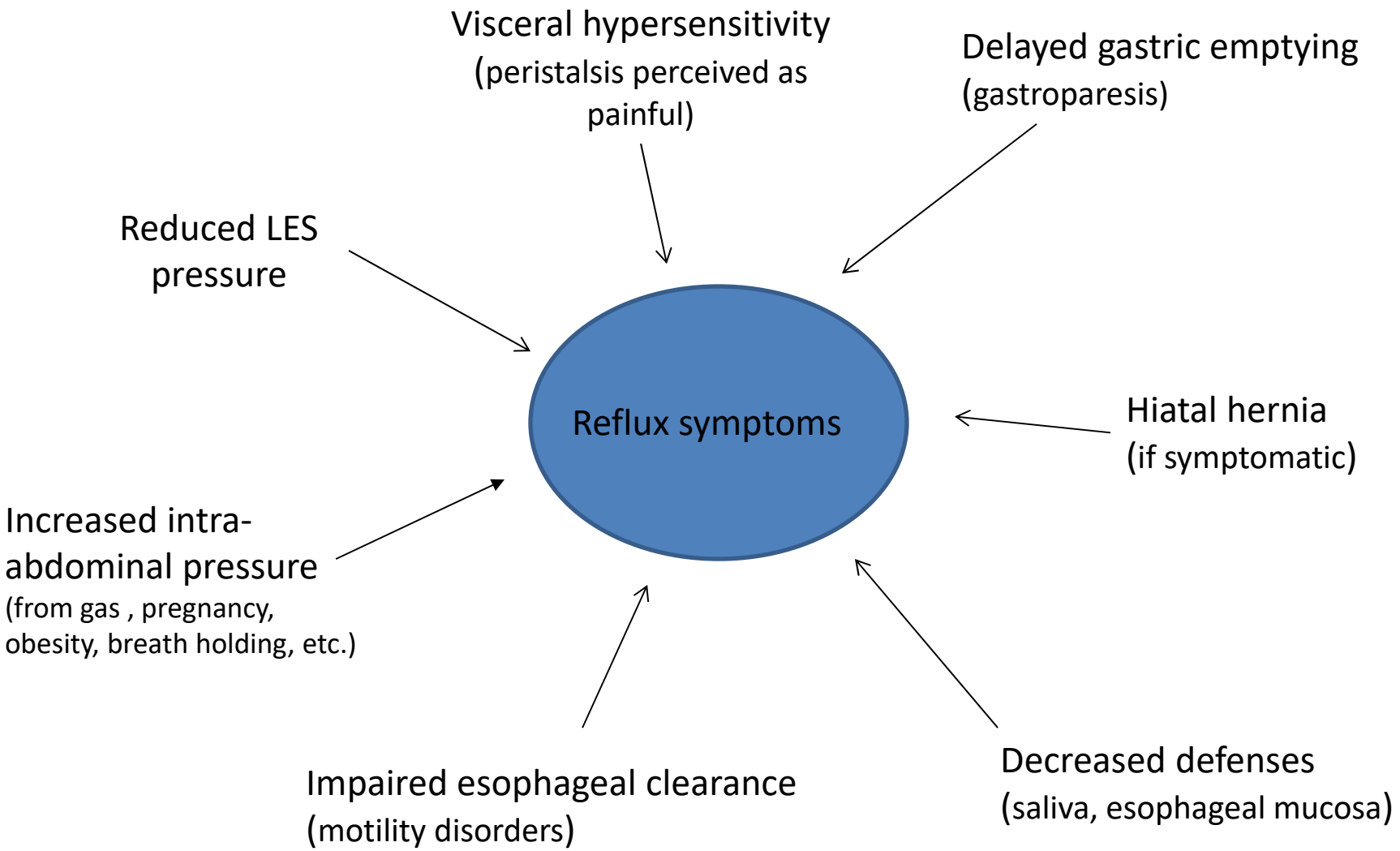
LPR and lingual tonsil thickness

- CTs of adults with LPR showed the mean lingual tonsil thickness to be 3.5 times greater than controls ($P<0.001$.)

Friedman M et al, Measurements of adult lingual tonsil tissue in health and disease. Otolaryngol Head Neck Surg 2010 Apr;142(4):520-5

Pathophysiology of GERD

Physiological factors which may cause reflux symptoms



Transient lower esophageal sphincter relaxations (TLESRs)

- Reflux can occur when increases in intra-abdominal pressure overpower a hypotensive LES
- Even more common is for reflux to occur during TLESRs
  - These are triggered by gastric distension and serve to enable gas to vent from the stomach.
  - TLESRs last for about 20 seconds - significantly longer than the typical primary peristaltic wave (swallow-induced relaxation)

Protective mechanisms in the esophagus

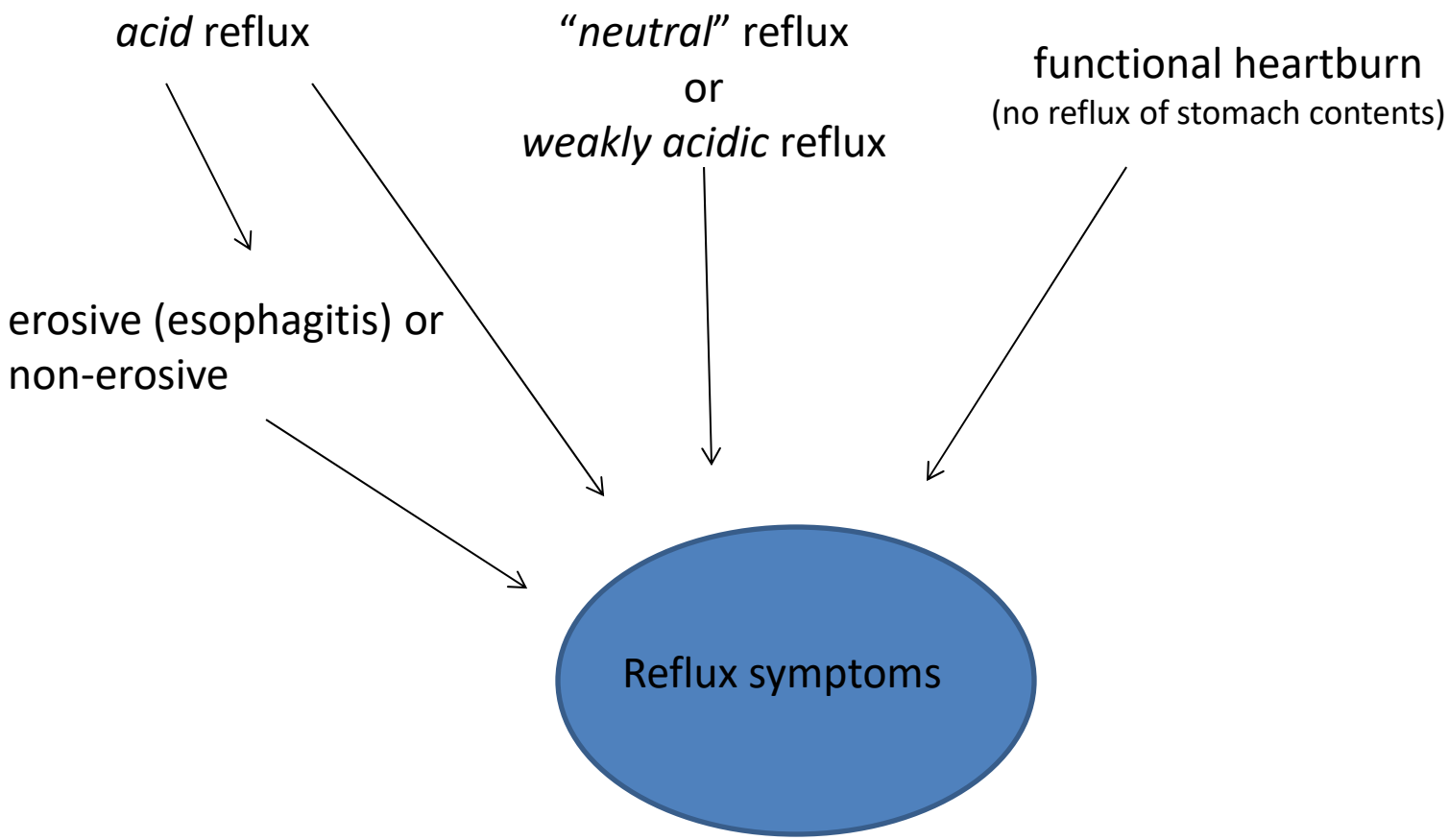
- Submucosal glands secrete mucin and bicarbonate
- LES tone prevents reflux
- Secondary peristalsis and swallowed saliva help clear and neutralize any refluxed acid

Factors increasing intra-abdominal pressure

- Obesity (visceral adiposity)
- Pregnancy
- Delayed gastric emptying/gastroparesis
- Increased gastric volume
- Constipation/bearing down (breath holding during exertion)
- SIBO

In GERD there is always too much acid, right?

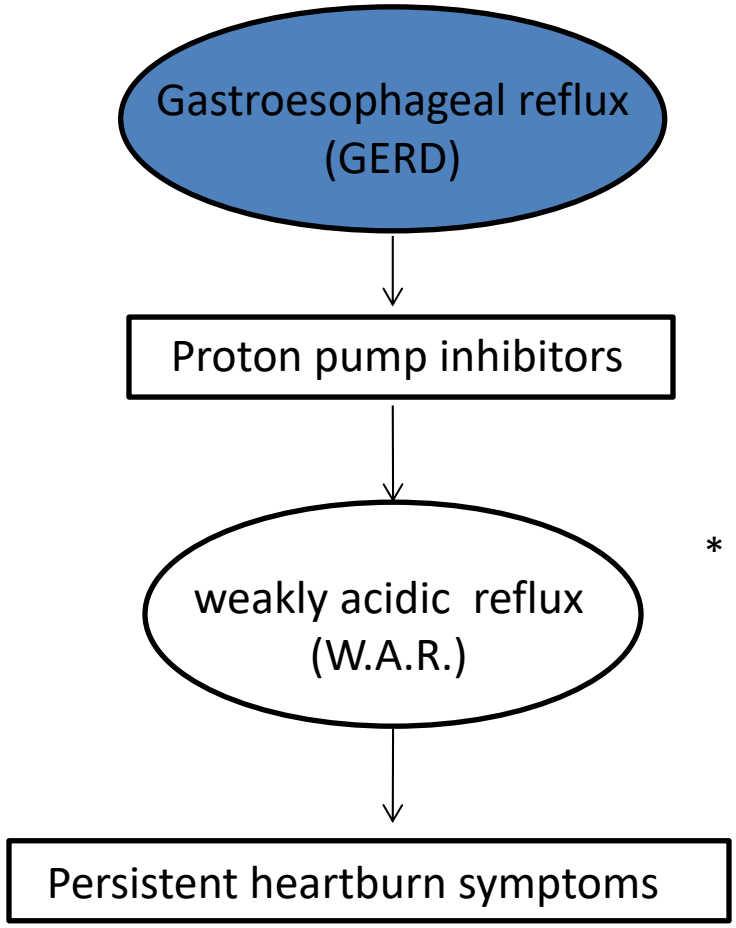
Not all reflux symptoms are due to excess acid



Diseases associated with hypochlorhydria

- DM - Fifteen to 20% of type 1 diabetic patients exhibit parietal cell antibodies (PCA), which are associated with autoimmune gastritis, hypochlorhydria, iron deficiency and pernicious anemia. (De Block CEM, 2002)
- Chronic autoimmune atrophic gastritis (Massironi S, 2019)
- Childhood asthma (Ghezzi M, 2011)
- Hypo/hyperthyroidism, Hashimoto's thyroiditis (Valdes SH, 2013)
- Rheumatoid arthritis -Chronic atrophic gastritis may be associated with hypergastrinemia and hypo- or achlorhydria (Ebert EC, 2011)
- SIBO (Quigley EMM, 2109)

Why heartburn can persist despite PPI use*



* Or because they did not have acid reflux, but rather functional heartburn or hypochlorhydria prior to PPI use

Non-acid reflux (weakly acid reflux)

- Non-acid reflux is significantly increased following the use of acid suppression therapies.

- This study cautions against the widespread use of acid suppression in patients with idiopathic pulmonary fibrosis given the potential role for non-acid reflux in its pathogenesis.

(Kilduff CE, 2014)

Emmanouela Tsoukali, 2010 PMC2912118

- The possible mechanisms by which persistent weakly acidic reflux might contribute to persistent symptoms in patients under PPI treatment may include:
  - esophageal distension by increased reflux volume
  - persistent impaired mucosal integrity (ie, dilation of intercellular spaces)
  - esophageal hypersensitivity to weakly acidic reflux events

Why Might PPIs Fail to Relieve Reflux Symptoms?

Failure of PPI therapy may be due to true refractory GERD, or other non-reflux diseases

Is there appropriate use of the drug ?

- lack of patient adherence to PPI therapy
- inadequate dosage of PPI)

Is there residual acid reflux due to inadequate acid suppression or rapid metabolism of PPI?

Is there "non-acid" reflux?

Is there delayed gastric emptying?

Failure of PPI therapy may be due to true refractory GERD, or other non-reflux diseases

- Is GERD a misdiagnosis?
- Causes of misdiagnosis of GERD are functional heartburn, achalasia, Candida esophagitis, eosinophilic esophagitis, etc.
- The diagnosis and treatment are specific to each of these causes of refractoriness to clinical therapy with PPI. Other conditions cause symptoms similar to GERD.

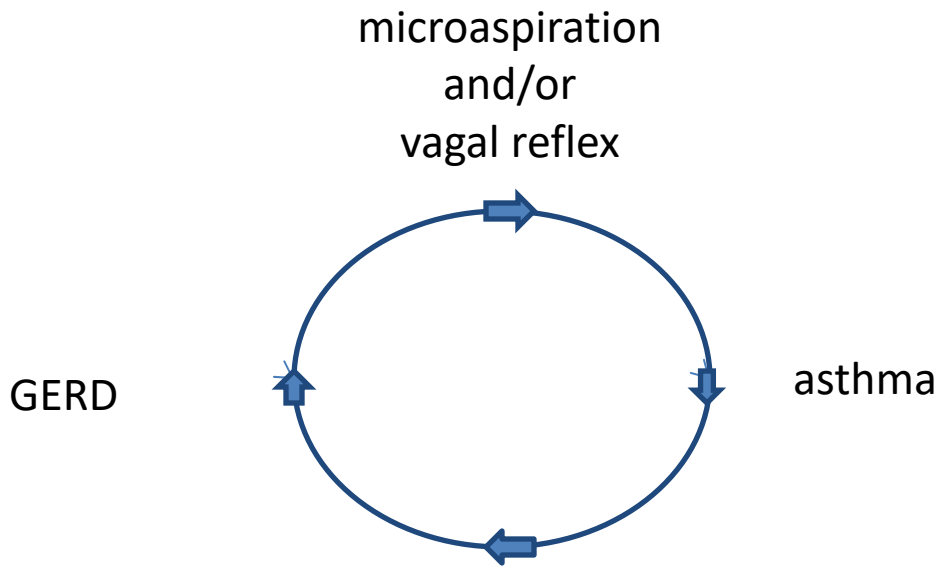
Azzam RS, 2018 PMID: 30304291

Asthma and GERD

- GERD can trigger asthma symptoms:
  - vagal reflex, by the presence of acid in the esophagus
  - microaspiration of gastric contents into the trachea.

- Conversely, asthma may cause GERD :
  - asthma alters intrathoracic pressure, thereby triggering the vagal reflex;
  - asthma drugs may change the LES pressure.

Pathophysiology of the asthma-GERD relationship



adapted from Cavalcanti de Albuquerque Patient J et al, 2011 and Harding SM et al, 2005

Pediatric Asthma and WAR

- Weakly acid reflux is frequently seen in school aged asthmatic children.

- In addition to asthma sx, recurrent lower respiratory tract infections are increased with WAR.

Ghezzi M, 2011 PMID: 21334184

More GERD Mechanisms

Dilated intercellular spaces (DIS)

- DIS is present on esophageal biopsy in virtually all GERD patients.

The pathophysiology is thought to be:

- repeated mucosal exposure to
  - refluxed acid
  - digestive enzymes
  - bile acids

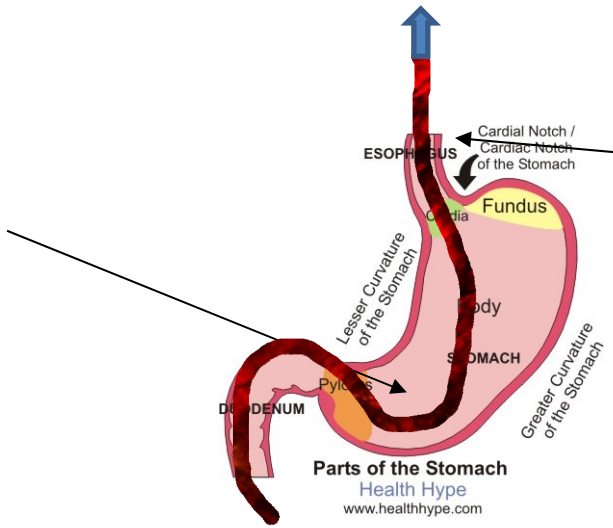
Dilated intercellular spaces (DIS)

- DIS is also present in
  - 30% of asymptomatic patients
  - esophageal candidiasis
  - food allergy
  - eosinophilic esophagitis
  - esophageal cancer

- DIS is “leaky esophagus syndrome”

Repeated exposure leads to DIS

refluxed digestive enzymes and bile



refluxed acid

Models of heartburn pathophysiology

- Dilated intercellular spaces may be responsible for:
  - enhanced perception of proximal acid reflux
  - Symptoms in NERD patients irrespective of esophageal acid exposure

GERD and distention

- Esophageal balloon distension in healthy subjects and patients with GERD may provoke typical heartburn symptoms.
- Regardless of the esophageal location of the balloon distension, some patients developed chest pain and others heartburn for the same balloon volumes.
- These data may suggest that motor events in the esophagus can be perceived as heartburn by a subset of patients

Apple vs Pear obesity and GERD

- Two meta-analyses show a positive association for body weight (BMI) and GERD.(Corley D, 2006 and Hampel H, 2005)

- Central adiposity (apple or orange fat) *leads to a 1.87 higher risk of developing erosive esophagitis compared to normal weight controls.* (Singh S, 2013)

- Increased hip circumference or gluteofemoral (pear-shaped) obesity *is inversely related to erosive esophagitis and Barrett's esophagus in addition to being protective for progression to T2DM and CVD*. (Rubenstein JH, 2013)

Drug induced GERD

- Major causes are
  - NSAIDS
  - Aspirin
  - bisphosphonates

Drug induced GERD

from http://www.mayoclinic.org/diseases-conditions/gerd/expert-answers/heartburn-gerd/faq-20058535

Medications and dietary supplements that can irritate the esophagus and cause heartburn :

- Antibiotics, such as tetracycline
- Bisphosphonates taken orally, such as alendronate (Fosamax), ibandronate (Boniva) and risedronate (Actonel)
- Iron supplements
- Quinidine
- Pain relievers, such as ibuprofen (Advil, Motrin IB, others) and aspirin
- Potassium supplements

- Medications and dietary supplements that can increase acid reflux and worsen GERD :

- **Anticholinergics** prescribed for overactive bladder and irritable bowel syndrome
- **Tricyclic antidepressants** (amitriptyline, doxepin, others)
- **Calcium channel blockers and nitrates**
- **Narcotics** (opioids), such as codeine, and those containing hydrocodone and acetaminophen (Lortab, Norco, Vicodin)
- **Progesterone**
- Quinidine
- Sedatives or tranquilizers, including **benzodiazepines**
- Theophylline

How effective are standard reflux medications in *children*?

A systematic review in JAMA pediatric found:

- "Evidence to support the efficacy and safety of H2RAs in infants and children is limited and of poor quality. Well-designed placebo-controlled trials are needed before thorough conclusions can be drawn."
- "H2RAs compared with proton pump inhibitors were not significantly different in any of the outcome measures."

(van der Pol R, 2014)

How effective is standard anti-reflux medication in adults with *NERD*?

- Over 40% do not respond to standard medical anti-reflux treatment.

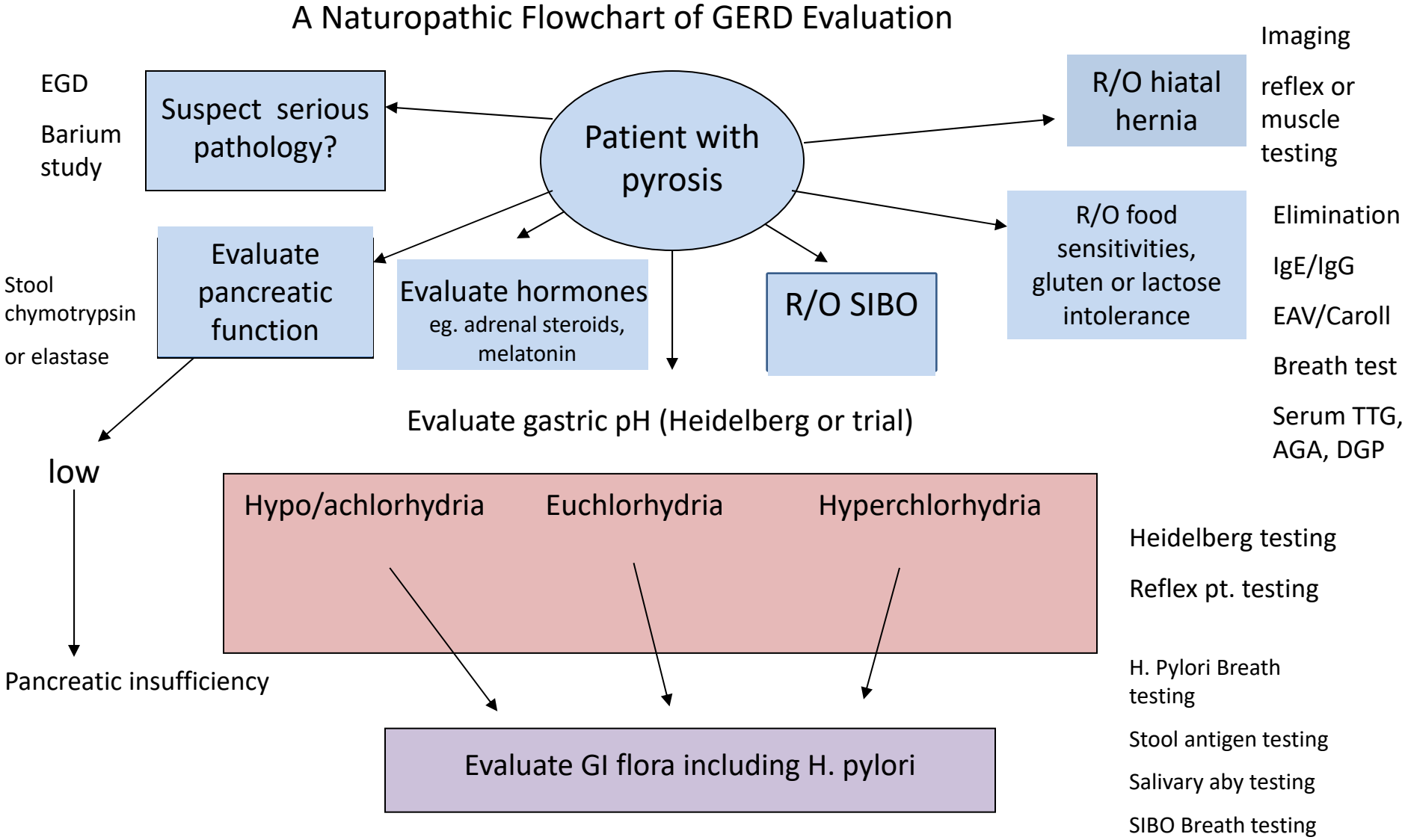
(Noar M, 2014)

- A meta-analysis of 17 RCTs including 6072 patients found that the rate of symptomatic relief of PPI in NERD was 51.4% (95%CI: 0.433-0.595, *P* = 0.000)

- The adverse event rate in PPI in NERD was 21.0% (95%CI: 0.152-0.208, *P* = 0.000)

(Ji-Xiang Zhang, 2013)

A Naturopathic Flowchart of GERD Evaluation



GERD

- Modalities

  Exacerbated by: CRAP

  – C
    - Coffee
    - Cigarettes
    - Chocolate

  – R
    - Refined carbohydrates and carbohydrates in general
    - Rx
    - Rapid eating

  – A
    - Acid foods
    - Alcohol
    - Allergic foods
    - Apple fat

  – P
    - Pop (soda)
    - Peppermint
    - Packin' in food qhs
    - Progesterone

Reworked From *No More Heartburn*, Sherry Rogers, MD

Heartburn combinations

- Aloe Vera Leaf Inner Fillet Extract
- Glutamine
- Glycine
- N-acetyl glucosamine
- Gamma oryzanol
- Deglycyrrhized Licorice Root
- d-Limonene
- Zinc Carnosine

- SIG: 1 rounded tsp in water BID ac or 1-2 caps ac

Lamson protocol

- To decrease irritative products of fermentation
  - Pancreatic enzymes with meals
  - Betaine HCl if indicated
- To improve tone of sphincters, mucosal health and GI motility
  - Phosphatidylcholine – 420 mg BID
  - If the above is not adequate, add Huperzine – 50 mg BID

Melatonin (CS Bang, et al, 2019)

- In contrast to the sedative agents which suppresses normal acid clearance mechanisms triggered by arousal from sleep, melatonin generated by the enterochromaffin cells in the stomach and intestinal tract (including melatonin agonists) induces sleep through activation of melatonin receptors and has shown esophageal mucosal protective effect by minimizing contact with acid, bile, or pepsin reflux in animal studies (Konturek SJ, 2006 and Patrick L, 2011)
- Improvement of sleep quality by melatonin or melatonin receptor agonists is also expected as one of the mechanisms of alleviating symptoms of GERD by raising perception threshold for pain (Schey R, 2007)

My suggestions for a more detailed EGD

- Request:
  - An assessment of the LES tone
  - 4 random biopsies of D3 or D4 for celiac dx if the duodenum is grossly normal
  - A jejunal aspirate culture for bacteria
  - A gastric pH reading
  - Brush border enzyme assay from biopsy specimen
    - disaccharidases – lactase, sucrase, maltase, isomaltase

Gastroparesis

Gastroparesis

- Etiology
  - Insulin resistance
  - Gluten intolerance
  - Viral
  - Idiopathic
    - Autoimmune diseases
    - hypochlorhydria

Diseases associated with gastroparesis:

- Diabetes –
  - 55-75% of DM1 pts
  - 15-20% of DM2 pts
- Hypothyroidism
- SLE
- Scleroderma
- Parkinson's
- Stroke
- TBI

Gastroparesis

What other drugs can trigger gastroparesis?

- Tobacco
- Calcium channel blockers
- L-dopa
- Hyoscyamine
- Anticholinergics
- Opiates

Gastroparesis – clinical picture

- If a diabetic has any other form of neuropathy (decreased DTRs, numbness in toes) they will likely also experience delayed digestion

- Sx/signs of gastroparesis include:
  - heartburn
  - regurgitation into the throat
  - belching, early satiety
  - Nausea
  - Vomiting
  - epigastric cramping

Testing for gastroparesis

- Barium swallow
  - Gastric dilation
  - Delayed emptying of barium
  - Retained gastric debris (bezoars)
  - Retained gastric fluid
- R-R interval (Bernstein)
- Gastric emptying study (scintigraphy)

Scintigraphy: The Gold Standard

- An isotope-labelled solid test meal is eaten by the patient and the imaging is used to calculate the gastric emptying time.
- The test meal contains technetium-99 m [99Tcm] sulphur-colloid bound to egg. This is in the form of a sandwich, or added to scrambled eggs or a mashed potato.
- Premenopausal women have slower gastric emptying than men.

Evaluation of scintigraphy

- Following ingestion of the test meal, scintigraphy should be performed for at least 2 hours and accuracy is improved by extending the test out to 4 hours.
- The most accurate measurement of gastric emptying is residual content at 4 h, with >10% considered abnormal.

Treatments for gastroparesis

See handout for patients:

- Psychophysiology of digestion
- Diet
- Botanicals
- Acid/enzymes
- Exercises and physical modalities
- Prescription prokinetics

Diet

- Smaller, more frequent meals
- Reduced dietary fiber
- Reduced portions of fat
- Avoidance of red meat
- Reduced protein and fat in evening meals
- Smaller evening meals

Diet, cont.

- Adequate hydration
- Reduced alcohol consumption
- Avoidance of broccoli and cabbage
- Gluten-free diet or grain-free diet

Botanicals

- Aloe vera juice – 0.5 - 8 ounces 15-30 minutes ac
- Papain tablets - 3-5 cc
- Ginger (Zingiber officinalis) 500 mg cc

Organotherapy

- Nervinum vagum – 10 gtts BID for 3 weeks followed by a one week off . Do this each month for three months

Acid and enzymes

- Vinegar - 1-2 tsp in ¼ cup of water ac
- Herbal bitters -4-15 drops direct on tongue or diluted in water and swallowed ac
- Betaine HCl – 324-520 mg caps
  - 1 or more capsules cc
- Pancreatic enzymes (derived from Aspergillus) ac

Exercise and physical modalities

- Exercises:
  - If tolerated, contract and relax the abdominal muscles with a regular rhythm immediately after meals. Work up to 100 repetitions per meal.
  - If tolerated, flex and extend the abdomen twenty times after each meal.
  - Breath training
- Neurofeedback, peripheral biofeedback (ie heart rate variability)
- Bio-resonance therapy, pulsed electromagnetic field

Prokinetics

- Erythromycin (Compounded strength) – 50 mg ac or qhs or ¼ of a 250 mg tablet
  - (12-25 mg for children)

- Prucalopride (resolor) – 0.5 - 2 mg ac and/or qhs

- Iberogast – 20 gtts ac and/or 60 gtts qhs

Prevention of dysplasia and adenocarcinoma in Barrett's esophagus

- Treat the cause of ongoing GERD
- PPI's?
- Incr. fruits and vegetables
- Treat SIBO if present to prevent excess deconjugation of bile salts
- Use berry extract and/or retinoids
- Curcumin or other herbal COX-2 inhibitors
- Selenium
- Green tea catechins
- Ursodeoxycholic acid