

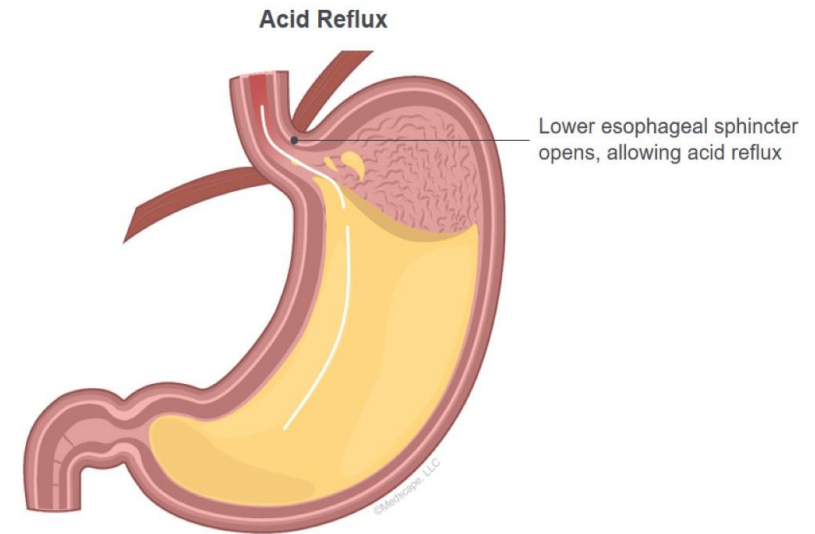
GASTRO-OESOPHAGEAL REFLUX DISEASE & RELATED REFLUX DISORDERS

Dr Jessica Wing

Wits Donald Gordon Medical Centre and Charlotte Maxeke
Johannesburg Academic Hospital

LAYOUT

- Definitions and epidemiology
- Risk Factors
- Clinical features and associations
- Pathophysiology and implications of management
- Diagnosis
- Complications
- Management
- Refractory GORD



DEFINITIONS AND EPIDEMIOLOGY

Definitions:

- Montreal: reflux of stomach contents into the oesophagus causing troublesome symptoms &/or complications
- **Lyon consensus: conclusive evidence** of reflux-related pathology on endoscopy &/or abnormal reflux on pH monitoring in the presence of compatible symptoms

Epidemiology

- Pooled prevalence from global population-based studies on GERD is +/- 13%
- Prevalence highest in South Asia and South-East Europe
- No prevalence data from Africa
- Accounts for +/- 110 000 admissions annually in USA hospitals

RISK FACTORS

Genetic

- Familial clustering of GORD and Barrett's oesophagus have been reported
- Case-controlled twin studies in Sweden & the USA suggest genetic liability for GORD to be 30%-40%
- May be related to a smooth muscle disorder associated with hiatal hernia, reduced LES pressure and impaired motility

Environmental

- Tobacco and alcohol consumption have a weak association with GERD symptoms
- Tobacco is a risk factor for erosive oesophagitis and adenocarcinoma



CLINICAL FEATURES

Oesophageal

- Typical symptoms:
 - **Heartburn or oesophageal chest pain, 2 or more days a week**
 - **Regurgitation “perception of effortless flow of gastric content in the mouth”**
- Waterbrash
- Odynophagia
- Dysphagia

Extra-oesophageal

- Asthma, chronic cough, aspiration pneumonia, bronchiectasis, interstitial pulmonary fibrosis, chronic bronchitis
- Sleep disorders, obstructive sleep apnoea
- Posterior laryngitis

ASSOCIATIONS

- Pregnancy (1st trimester)
- Systemic Scleroderma
- Zollinger Ellison syndrome
- Prolonged nasogastric tube intubation
- Post Heller's myotomy or per-oral-endoscopic myotomy
- Post bariatric surgery

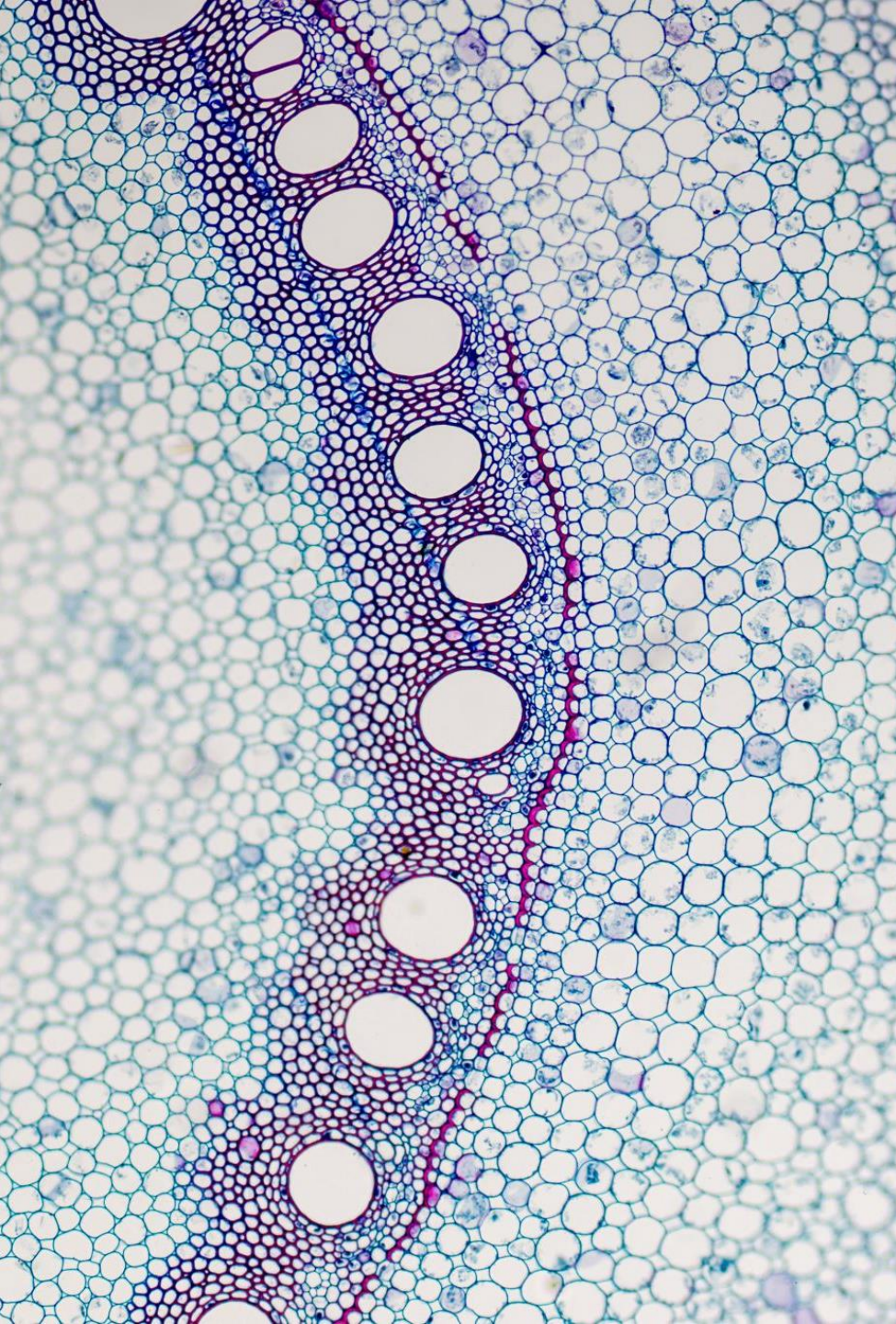
DIFFERENTIAL DIAGNOSIS

Oesophageal

- Zenker's diverticulum
- Eosinophilic oesophagitis
- Achalasia

Extra-oesophageal

- Gastroparesis
- Cholelithiasis
- Peptic ulcer disease
- Functional dyspepsia (disorders of the gut-brain interactions)
- Angina pectoris



PATHOGENESIS

- Imbalance between **oesophageal defensive** factors:
 1. Anti-reflux barrier
 2. Oesophageal clearance
 3. Tissue resistance
- **Aggressive factors** refluxing from the stomach:
 1. Gastric acidity
 2. Gastric volume
 3. Duodenal content



GASTRO-
OESOPHAGEAL
ANTI-REFLUX
BARRIER

1. Intrinsic lower oesophageal sphincter (LES) and its intra-abdominal location
 2. Diaphragmatic crura and phreno-oesophageal ligaments
 3. Acute angle of His
- Determines the **volume and frequency** of gastric oesophageal reflux

ANTI-REFLUX BARRIER

4 mechanisms which are considered a failure of the anti-reflux barrier

1. Decreased basal LES pressure
2. Transient LES relaxations
3. Swallow-associated LES relaxations
4. Hiatal hernia

TRANSIENT LES RELAXATIONS (TLESRS)

- Most common mechanism for reflux in patients with healthy sphincter pressures & in 50%-80 % of patients with GERD
- Occur independently of swallowing and are not accompanied by peristalsis
- Persist >10 seconds
- Diaphragmatic crura are inhibited during tLESRs
- Dominant stimulus is stretch of the proximal stomach by gas or food
- Other varying stimuli: dietary fat, stress, stimulation of the pharynx
- Reduced by: Anti-cholinergic drugs, GABA-agonists, 5-hydroxytryptamine antagonists, somatostatin, morphine, CCK-I receptor antagonists



SWALLOW-
INDUCED LES
RELAXATIONS

- 5%-10% of reflux episodes
- Uncommon mechanism:
 - Crural contraction
 - Short (5-10 seconds)
 - Prevented by oncoming peristalsis
- **Defective or incomplete peristalsis**
- More common when associated with a hiatus hernia

HYPOTENSIVE LES

- **Strain induced**
 - Relatively hypotensive LES is overcome by an abrupt increase in intra-abdominal pressure (e.g. coughing or bending)
- **Free reflux**
 - Characterized by a decrease in oesophageal pH without a change in intra-gastric pressure
 - LES pressure <5mmHg
 - Uncommon: end-stage systemic sclerosis or after myotomy for achalasia
 - Severe oesophagitis

MODULATORS OF LES PRESSURE

TABLE 46.1 Modulators of Lower Esophageal Sphincter Pressure

	Increase LES Pressure	Decrease LES Pressure
Hormones/ peptides	Gastrin	CCK
	Motilin	Secretin
	Substance P	Somatostatin
		Vasoactive intestinal peptide
Neural agents	α -Adrenergic agonists	α -Adrenergic antagonists
	β -Adrenergic antagonists	β -Adrenergic agonists
	Cholinergic agonists	Cholinergic antagonists
Foods and nutrients	Protein	Chocolate
		Fat
		Peppermint
Other factors	Antacids	Barbiturates
	Baclofen	Calcium channel blockers
	Cisapride	Diazepam
	Domperidone	Dopamine
	Histamine	Meperidine
	Metoclopramide	Morphine
	Prostaglandin F _{2α}	Prostaglandins E ₂ and I ₂
		Serotonin
	Theophylline	

HIATAL HERNIA

Hiatal hernia occurs in 54%-94% of patients with reflux oesophagitis

Non-reducible and large (>3cm)

Displaces LES proximally away from the crura

Reduces LES basal pressure

Shortens length of the high-pressure zone

Eliminates the increase in LES pressure during straining

Increase in tLESRs

Increased compliance of the OGJ

Persistent vestibule for the gastric “acid pocket” and re-refluxate impairing oesophageal clearance

IMPLICATIONS FOR MANAGEMENT

Gastro-oesophageal antireflux barrier

Anatomical and functional composition of the oesophagogastric junction

Decreased LES pressure⁵⁶

Prokinetics such as prucalopride can be used if LES pressure is very low

TLESRs⁵⁶

In postprandial belch-related reflux associated with TLESRs, baclofen can reduce the rate of TLESRs; treatment of prandial aerophagia with diet changes and sitting in an upright position during meals is an alternative

Swallow-associated LES relaxations⁴⁵

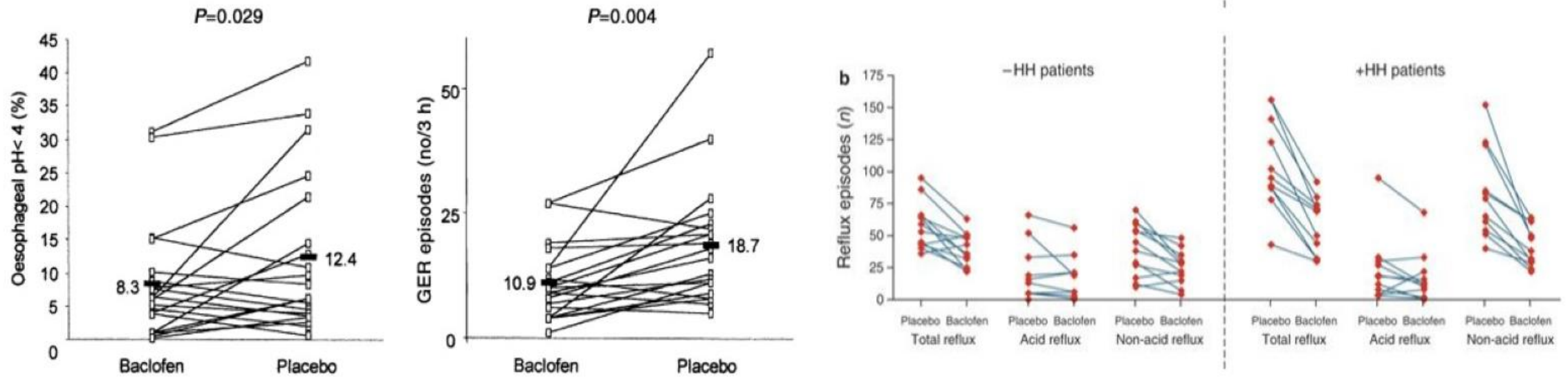
Most frequent in patients with hiatal hernia

Hiatal hernia⁵⁴

Diagnosis can occur during endoscopy, barium swallow or high-resolution manometry, which provides the most precise diagnosis

When a hiatal hernia is considered the main pathophysiological mechanism of reflux in a patient with reflux symptoms and pathological reflux monitoring, surgical treatment seems to be the best alternative, particularly when the hiatal hernia is larger than 3 cm

Baclofen*, a GABA β receptor agonist, reduces the number of TLESRs and reflux episodes



Baclofen is an option as an adjunct to PPI but has side effects that can be limiting

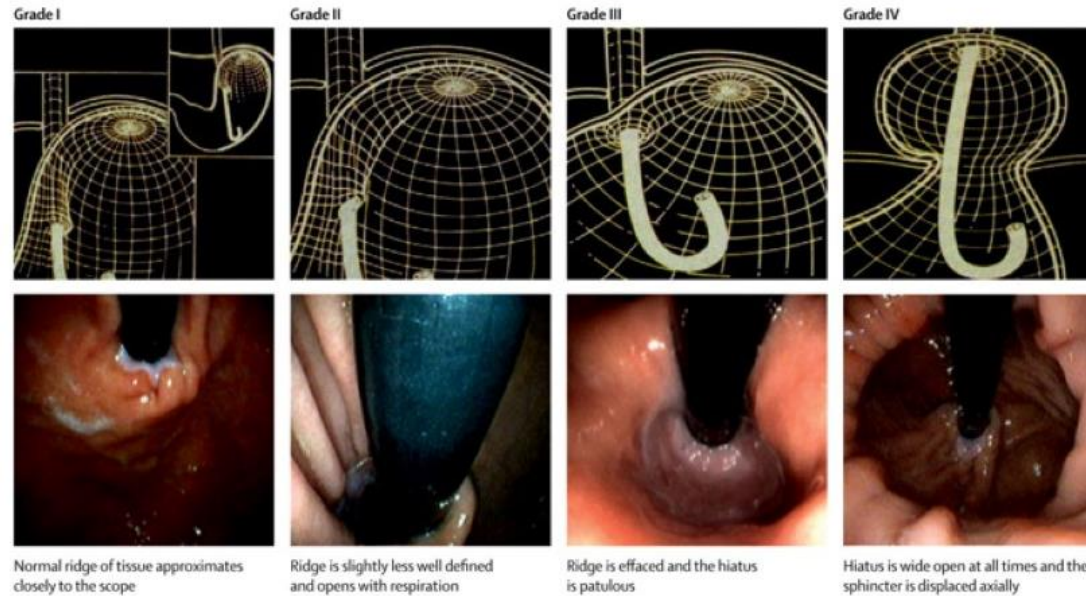
*Used off-label for GERD.

GABA β , gamma-aminobutyric acid beta; HH, hiatal hernia; TLESR, transient lower esophageal sphincter relaxation.

1. Van Herwaarden MA, et al. Aliment Pharmacol Ther. 2002;16:1655-1662; 2. Beaumont H, et al. Am J Gastroenterol. 2009;104:1764-1771.

- Integrity of the Anti-Reflux Barrier

- Hill grade (GE flap valve)
- Axial length of hiatal hernia



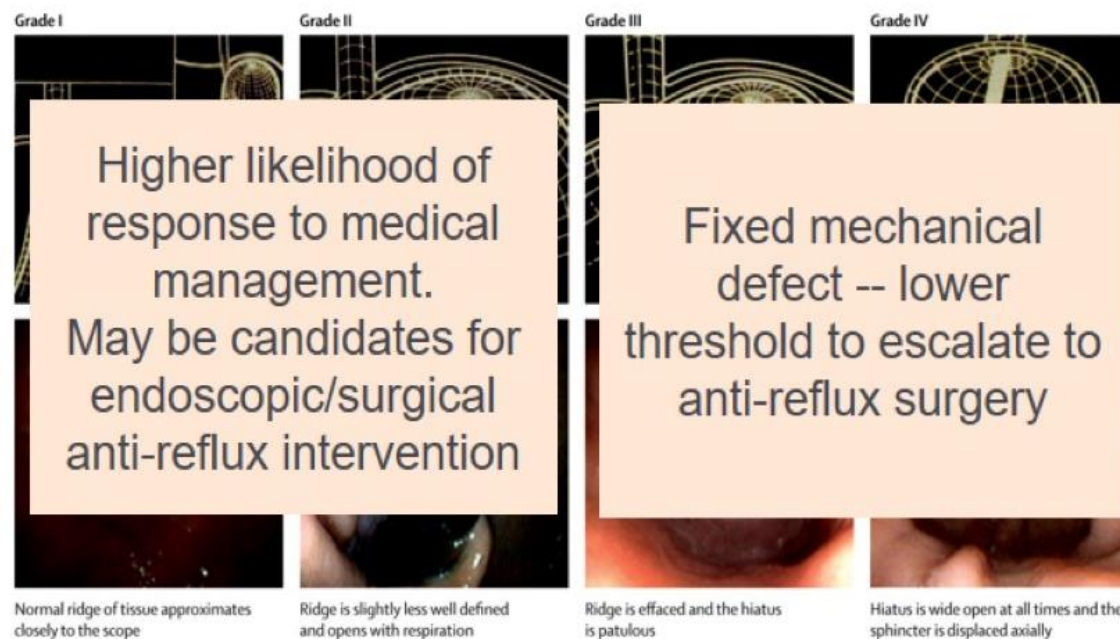
GE, gastroesophageal.

Hill LD, et al. J Clin Gastroenterol. 1999;28:194-197.

These materials are provided to you solely as an educational resource for your personal use. Any commercial use or distribution of these materials or any portion thereof is strictly prohibited.

- Integrity of the Anti-Reflux Barrier

- Hill grade (GE flap valve)
- Axial length of hiatal hernia



GE, gastroesophageal.

Hill LD, et al. J Clin Gastroenterol. 1999;28:194-197.

OESOPHAGEAL CLEARANCE

- Determines the **duration of acid exposure** to the oesophageal mucosa and the **severity of mucosal damage**
- Volume clearance (bolus clearance)
 - Peristaltic dysfunction: failed or weak contractions (<30mmHg)
- Salivary and oesophageal gland base titration
 - Neutralizes the residual acid after peristaltic contractions
 - Stimulated by acid in the proximal oesophagus (20 cm above the LES)

IMPLICATIONS FOR MANAGEMENT

Oesophageal clearance after reflux

Oesophageal peristalsis and volume clearance^{85,87}

Evaluation of oesophageal motility in patients with reflux symptoms is useful to identify severe oesophageal hypomotility

Currently, there is not a safe and efficient prokinetic for oesophageal hypomotility

When an oesophageal hypomotility disorder is diagnosed, assessing muscle reserve through the multiple rapid swallow test is clinically relevant; the absence of adequate peristaltic wave after the multiple rapid swallow test is more often associated with post-surgical dysphagia

To record all the medications that the patients consume, especially in the older population; anticholinergics, antidepressant and opioids can significantly affect oesophageal motility

Surgical or endoscopic treatment strategy, based on status of oesophageal motility, remains controversial

Swallowed saliva and chemical clearance^{88,89}

After refluxed stomach contents are cleared by peristalsis, the lower oesophageal mucosa remains acidic; saliva, containing bicarbonate, helps to neutralize acid and promote mucosal healing

Reduced salivation owing to ageing, medications and conditions such as chronic dry mouth can lead to prolonged acid clearance times, particularly during sleep

We suggest enquiring about symptoms of xerostomia, especially in the elderly population

PSPW⁹⁰

An abnormal PSPW index during pH-impedance monitoring can be useful for diagnosis of GERD in patients with inconclusive diagnosis

TISSUE RESISTANCE

- **Pre-epithelial factors**
 - Oesophageal secretion of prostaglandin E2 and glycoconjugate (mucin) may play a role
- **Epithelial factors**
 - Na^+/H^+ and $\text{Cl}^-/\text{HCO}_3^-$ transmembrane protein exchange channels maintain intracellular pH
 - Tight junctions
 - Dilated intracellular spaces (noted in erosive and non-erosive disease)
- **Post-epithelial factors:**
 - Oesophageal blood flow transporting nutrients, O_2 and HCO_3^- and removing H^+ and CO_2 increases in response to luminal acid

TISSUE RESISTANCE

- **NERD**
 - 70% of patients with GERD
 - Specific microscopic alterations of the mucosa (integrity of the tight apical intercellular junctions)
 - Histology: E-Cadherin cleavage > increased permeability > dilated intercellular spaces
 - Superficial sensory nerves expressing TRPV1 activated by H⁺ ions
- **ERD**
 - Histology: basal cell hyperplasia
 - Traditional “acid burn theory” challenged
 - Refluxate indirectly stimulates T-cell infiltration into the submucosa and via chemotaxis of inflammatory cells , cell death is mediated
 - Deeper sensory nerves

IMPLICATIONS FOR MANAGEMENT

Oesophageal mucosa

NERD 85	NERD is diagnosed when there is pathological acid exposure and a normal endoscopy performed 'off' PPIs
ERD ¹⁰⁶	Mild oesophagitis (LA Classification grades A and B) should be managed with standard PPI dosing and does not require further endoscopic controls Severe oesophagitis (LA Classification grades C and D) requires PPIs bid for 8 weeks and further endoscopic control



GASTRIC FACTORS

- Acid pocket : area at and just below the OGJ which escapes the buffering effect of meals
- Chronic short-segment acid reflux episodes
- *H. pylori* gastritis of the corpus (cagA + strains) can be protective:
 - Gastric atrophy and less acid secretion
 - Production of ammonia by the bacteria and increased gastric alkaline secretion
- *H. pylori* gastritis of the antrum increases gastrin production thereby increasing the risk of GERD

GASTRIC FACTORS: MOTILITY

- Delayed or abnormal fundal accommodation of the proximal stomach
- Prolonged post-prandial fundal relaxation or delay in the recovery tonic tone
- Poor correlation between oesophageal acid exposure and delayed gastric emptying but it is noted in 40% of patients with GORD
- Delayed gastric emptying may be in factor contributing proximal extent of reflux rather than total acid exposure
- Women and diabetics are more likely to have gastroparesis and secondary reflux

IMPLICATIONS FOR MANAGEMENT

Pathophysiological mechanism		Management implications
Gastric and biliopancreatic factors		
Composition and distribution of gastric contents	Postprandial acid and bile pockets ⁶	Capping the acid pocket with alginates can reduce acid and bile reflux
	<i>Helicobacter pylori</i> , gastric acid secretion and GERD ¹²	<i>Helicobacter pylori</i> is associated with a lower prevalence of reflux; however, it should be eradicated because it is strongly linked to gastric adenocarcinoma
Gastric motility	Gastric accommodation and gastric emptying ^{17,18}	Delayed gastric emptying should be managed with diet modification and prokinetics; these patients might have increased postprandial reflux with proximal extent and risk of extra-oesophageal reflux
	Bariatric surgical procedures and GERD ³⁰	Patients with GERD and obesity should focus on weight loss by either diet or bariatric surgery

REFLUXATE

- **Acidic (pH<4)**
 - Perception of heartburn & regurgitation is increased with greater, prolonged and more proximal exposure of acid to oesophageal mucosa
 - Mucosal damage especially if bile acids present
- **Weakly acidic (pH 4-6) or non-acidic (pH>6)**
 - Do not cause mucosal damage but are implicated in chronic cough and regurgitation
- **Gas refluxate**
 - Supra-gastric
 - Gastric (tLESRs)



REFLUXATE

- **Bile reflux**
 - More severe oesophageal mucosal damage
 - Increase mucosal permeability and dilatation of the intercellular spaces and H^+ ion absorption
 - Induce reactive O^2 species
 - Association with Barrett's oesophagus and erosive oesophagitis with an increased expression of IL-2; IL-8, TNF and COX2

IMPLICATIONS FOR MANAGEMENT

Refluxate

Chemical and gas/
liquid composition
of the refluxate

Acid reflux^{78,81}

PPIs should be adjusted to the reflux pattern, that is, twice daily in the presence of supine acid reflux; new potassium-competitive acid blocker medication to reduce acid secretion can be considered
Owing to the day-to-day variability in oesophageal acid exposure and symptoms, prolonged wireless pH monitoring can identify patients with difficult diagnosis of GERD and provide a guideline for PPI management⁷⁸

Bile reflux⁸²

Bile reflux has a major role in the pathogenesis of severe GERD; new bile acid sequestrants are under investigation

Gas reflux^{70,71}

A significant proportion of patients with GERD have reflux related to belching; in some patients, this is secondary to aerophagia during meals followed by postprandial gastric belching; and in other patients, reflux is related to supragastric belching
Many of these patients are refractory to PPI treatment: for aerophagia and gastric belching, dietary habits and baclofen can be used; for supragastric belching, cognitive behavioural therapy is recommended

PERCEPTION OF OESOPHAGEAL SYMPTOMS

- **Psychoneuroimmune modulation**
 - Psychological stress
 - Sleep deprivation
 - Hypersensitivity of oesophageal nerves via dilated intercellular spaces
- **Hypervigilance**
 - Autonomic system arousal
 - Refractory GORD

IMPLICATIONS FOR MANAGEMENT

Oesophageal symptoms perception

Central and peripheral neural modulation¹²⁰

In patients with oesophageal hypersensitivity, there is a central abnormal modulation and a peripheral mucosal neuroimmune alteration

In oesophageal hypersensitivity, the pain modulators and a topical mucosal protection can reduce the symptoms

Hypervigilance¹²³⁻¹²⁵

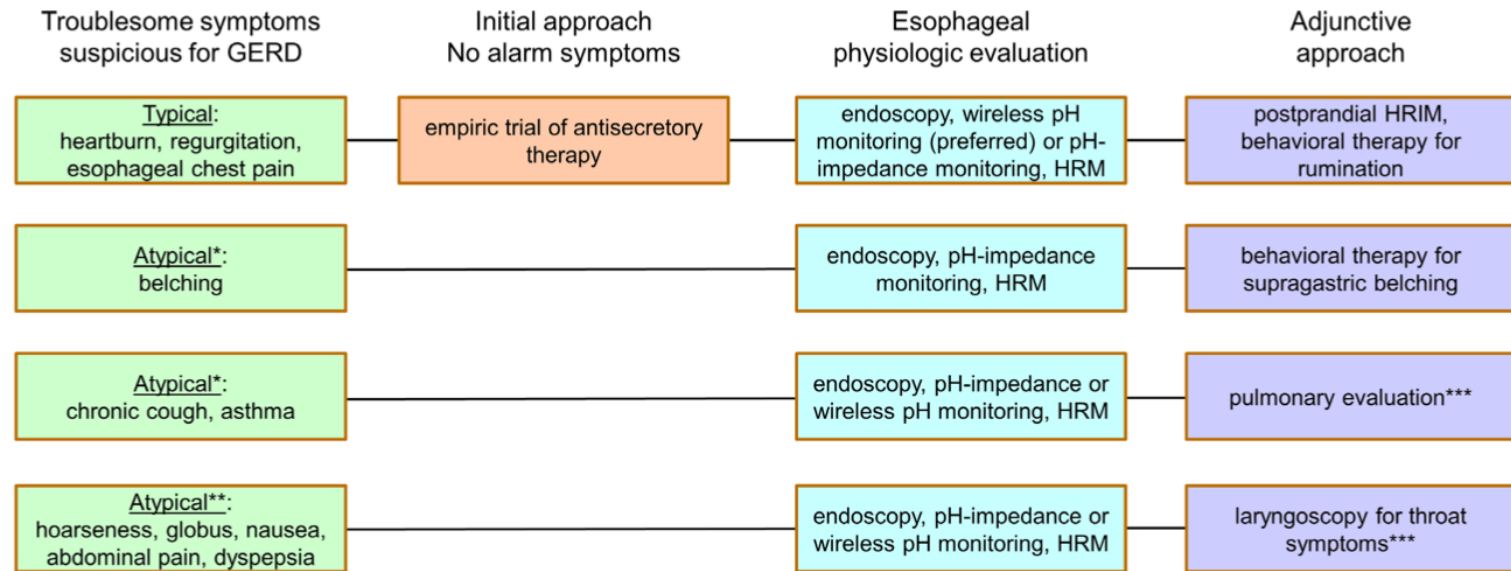
Hypervigilance in patients with oesophageal symptoms and psychological management of hypervigilance are useful



OBESITY

- As BMI increases the prevalence GERD symptoms and oesophagitis increases
- For every unit of BMI increase, the time whereby distal oesophageal pH is <4 , increases by 0.35%
- Increased intragastric pressure overwhelms the anti-reflux barrier
- Increased prevalence in hiatal hernia
- Low LES pressure (visceral fat secretes IL-6 & TNF-alpha)
- High-calorie meals are associated with delayed gastric emptying, increased frequency in tLESRs and fundic distension
- Hormonal changes predispose to GERD-related complications such as oesophageal cancer
- Sleeve gastrectomy is associated with increased GORD symptoms and oesophagitis as well as prevalence of Barret's oesophagus

DIAGNOSIS



* likelihood of GERD is lower than with typical symptoms, testing is performed to identify or rule out a reflux basis for symptoms

** likelihood of GERD is very low, upfront testing is typically not recommended except to rule out a reflux basis for symptoms

***adjunctive approaches may precede esophageal evaluation to rule out primary pulmonary and laryngeal disorders

ENDOSCOPY

LA grades: B,C,D oesophagitis

Biopsy proven Barrett's oesophagus

Presence of a peptic stricture

In unproven GERD, endoscopy should be performed in 2-4 weeks after discontinuation of anti-secretory therapy

LA grade B or higher, recurrent peptic stricture while on optimized anti-secretory therapy are indicative of refractory GERD

Los Angeles Classification System for Esophagitis

Los Angeles Grade A



One or more mucosal breaks no longer than 5 mm, not bridging the tops of mucosal folds

Los Angeles Grade B



One or more mucosal breaks longer than 5 mm, not bridging the tops of mucosal folds

Los Angeles Grade C



One or more mucosal breaks bridging the tops of mucosal folds involving < 75% of the circumference

Los Angeles Grade D



One or more mucosal breaks bridging the tops of mucosal folds involving > 75% of the circumference

Images courtesy of Esophageal Center, Northwestern University.

Lundell LR, et al. Gut. 1999;45:172-180; Armstrong D, et al. Gastroenterology. 1996;111:85-92.



Erosive esophagitis



Esophageal stricture
with chronic erosive
esophagitis



Barrett esophagus



Esophageal
adenocarcinoma with
Barrett esophagus

EE, erosive esophagitis.

Kahrilas PJ. N Engl J Med. 2008;359:1700-1707.

AMBULATORY REFLUX MONITORING

- Prolonged wireless pH monitoring off anti-secretory therapy provides highest diagnostic yield with a study duration of 96 hours
- Determines dominant physiological vs pathological acid exposure time (AET)
- Not widely available nor feasible , catheter-based pH monitoring remains a viable alternative
- AET <4% on all days with negative reflux-symptom association excludes GERD
- AET >6% for 2 days > is diagnostic of GERD, requiring treatment
- AET<4% with positive reflux-symptom association meets criteria for reflux hypersensitivity
- AET between 4-6% (borderline) is considered inconclusive and further testing and clinical context is needed

AMBULATORY PH-IMPEDANCE MONITORING

- Diagnostic value in unproven GERD when off anti-secretory therapy & typical reflux symptoms are associated with excessive belching, rumination is suspected and when pulmonary symptoms are being evaluated
- More reflux detected due to higher sensitivity of the impedance component independent of pH
- Expert interpretation required to overcome inaccurate automated analysis
- Shifts the diagnosis from functional heartburn to reflux hypersensitivity
- Gold standard for diagnosing supra-gastric belching

AMBULATORY PH-IMPEDANCE MONITORING

- Valuable in patients with proven GERD on a PPI with persisting symptoms
- Aid in decision-making regarding escalation of management beyond pharmacotherapy
- Total AET >6% is diagnostic of pathological GERD
- Total reflux episodes of <40/day is adjunctive evidence for absence of GERD while >80/day is adjunctive evidence for GERD
- Total reflux episodes 40-80/day off a PPI is inconclusive evidence for GERD
- Baseline Impedance <1500 ohms is adjunctive evidence for GERD while >2500 ohms is against GERD

OESOPHAGEAL MANOMETRY

- Typically, not indicated in the evaluation of uncomplicated GERD
- Useful in:
 - Accurately locating the LES when placing the pH impedance catheter
 - Detect “markers” of gerd: compromised oesophageal peristaltic function, abnormal OGJ morphology and barrier function
 - Evaluation for refractory symptoms or GERD
 - Documenting adequate peristalsis
 - Excluding achalasia and scleroderma
 - Recommended before anti-reflux surgery

COMPLICATIONS

GERD-related non-cancer deaths are rare (0.46 per 100,000 persons)

Hemorrhagic oesophagitis

Ulcer perforation and rupture

Aspiration pneumonia

Oesophageal strictures

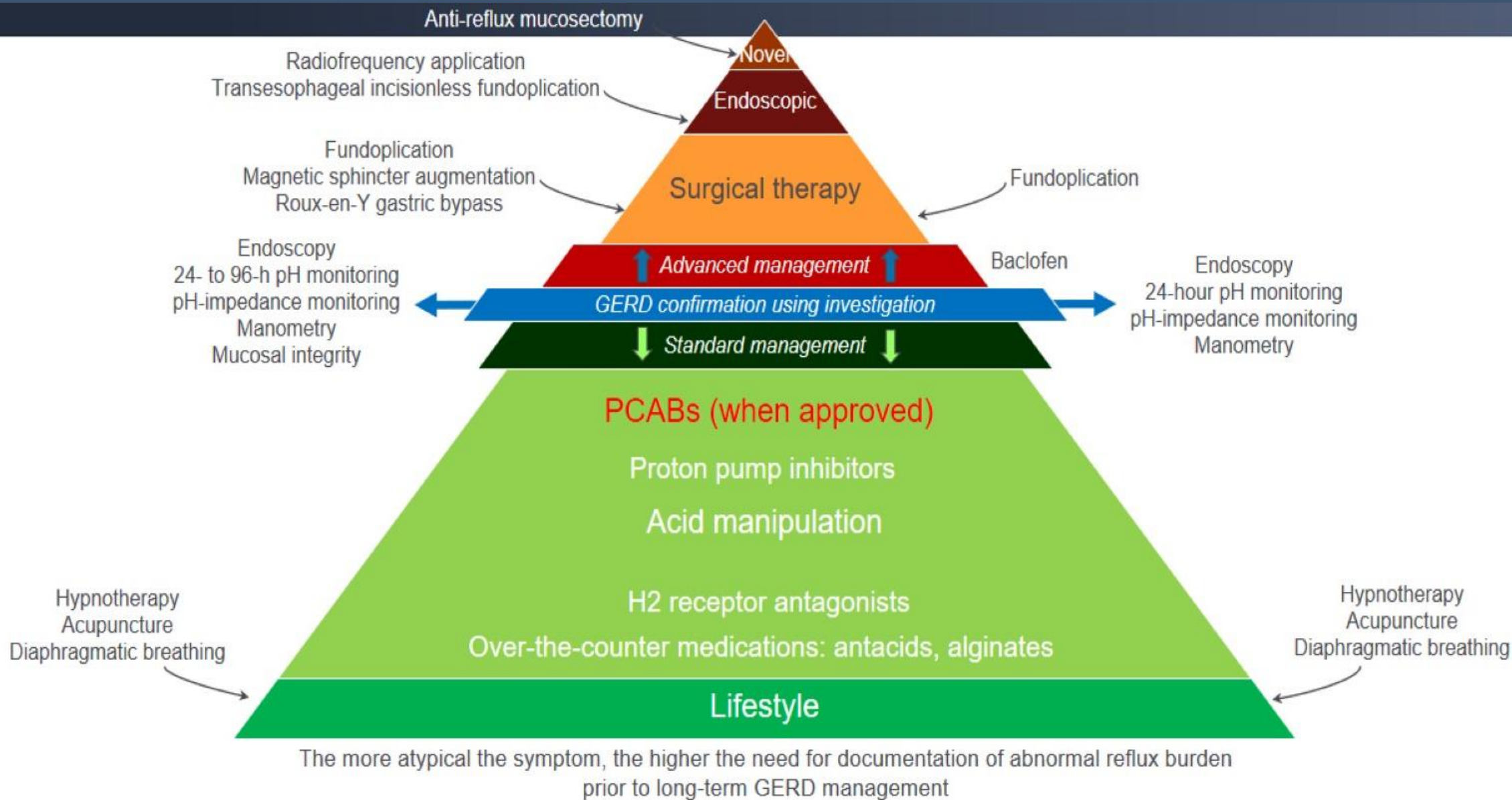
Barrett's oesophagus

OESOPHAGEAL STRICTURES

- 7%-23% of untreated reflux oesophagitis
- Commonly in older men with chronic NSAID use
- Smooth -walled, tapered circumferential narrowing in the distal oesophagus (1-8cm long)
- Complex: ranging from reversible inflammation to irreversible fibrosis
- **Treatment**
- Oesophageal lumen < 13mm dilatation needed
- Short & simple strictures: > blind dilatation with mercury filled dilators of increasing sizes (Hurst or Maloney)
- Longer and more complicated strictures: bougienage over a guidewire using hollow-centered or balloon dilators
- Maintenance PPI therapy
- Recalcitrant strictures: self-expanding plastic stents or intralesional steroid injections

BARRETT OESOPHAGUS

- Complication of GERD and risk factor for oesophageal adenocarcinoma
- Metaplasia of the stratified squamous cells of the distal oesophagus to columnar cells
- Treatment involves optimizing PPI and if dysplasia is present then endoscopic ablative therapy is considered



Modified from Rogers BD, et al. Indian J Gastroenterol. 2019;38:371-377; Zerbib F, et al. Neurogastroenterol Motil. 2021;33:e14075; Katz PO, et al. Am J Gastroenterol. 2022;117:27-56.

These materials are provided to you solely as an educational resource for your personal use. Any commercial use or distribution of these materials or any portion thereof is strictly prohibited.

MANAGEMENT

- **Lifestyle modification**
- Case-controlled studies: elevation of the head, left lateral decubitus position and weight loss were associated with improvement in GERD
- **Pharmacotherapy**
- Over-the-counter medications (Antacids)
 - Rapid onset and relief of heartburn but require frequent use
 - In a met-analysis Gaviscon provided better symptomatic relief than placebo (absolute benefit 26%; NNT 4)
 - Do not address or heal oesophagitis



MANAGEMENT

- **Prokinetics**
- Bethanechol (cholinergic agonist), metoclopramide (dopamine antagonist); cisperide (serotonin 5HT4 receptor agonist)
- Macrolides
- Increase LES pressure, gastric emptying and oesophageal clearance
- Effectiveness decreases with disease severity
- No effect on tLESRs
- Unreliable in healing oesophagitis
- Limited by side effects



MANAGEMENT

- **GABA agonists**
- Baclofen (5 to 20 mg po tds)
- Decreases tLESRs, acid and duodenal reflux significantly
- Improves GERD symptoms in patients for 4 weeks to several months
- Major limiting factor is tolerability
 - Nausea, vomiting, pre-syncope, drowsiness
- Lesogaberan, arbaclofen and placarbil have improved tolerability
- Abandoned due to limited clinical efficacy

MANAGEMENT

- **Histamine 2 Receptor Antagonists (H2RAs)**
- Cimetidine, ranitidine, famotidine, nizatidine
- More effective in controlling nocturnal than meal-stimulated acid secretion
- Met-analysis found that the overall oesophagitis healing rates rarely exceeded 60% after a 12 -week period
- Valuable to add for patients with nocturnal acid breakthrough on a PPI
- Tolerance develops
- Very safe side effect profile

PPI THERAPY

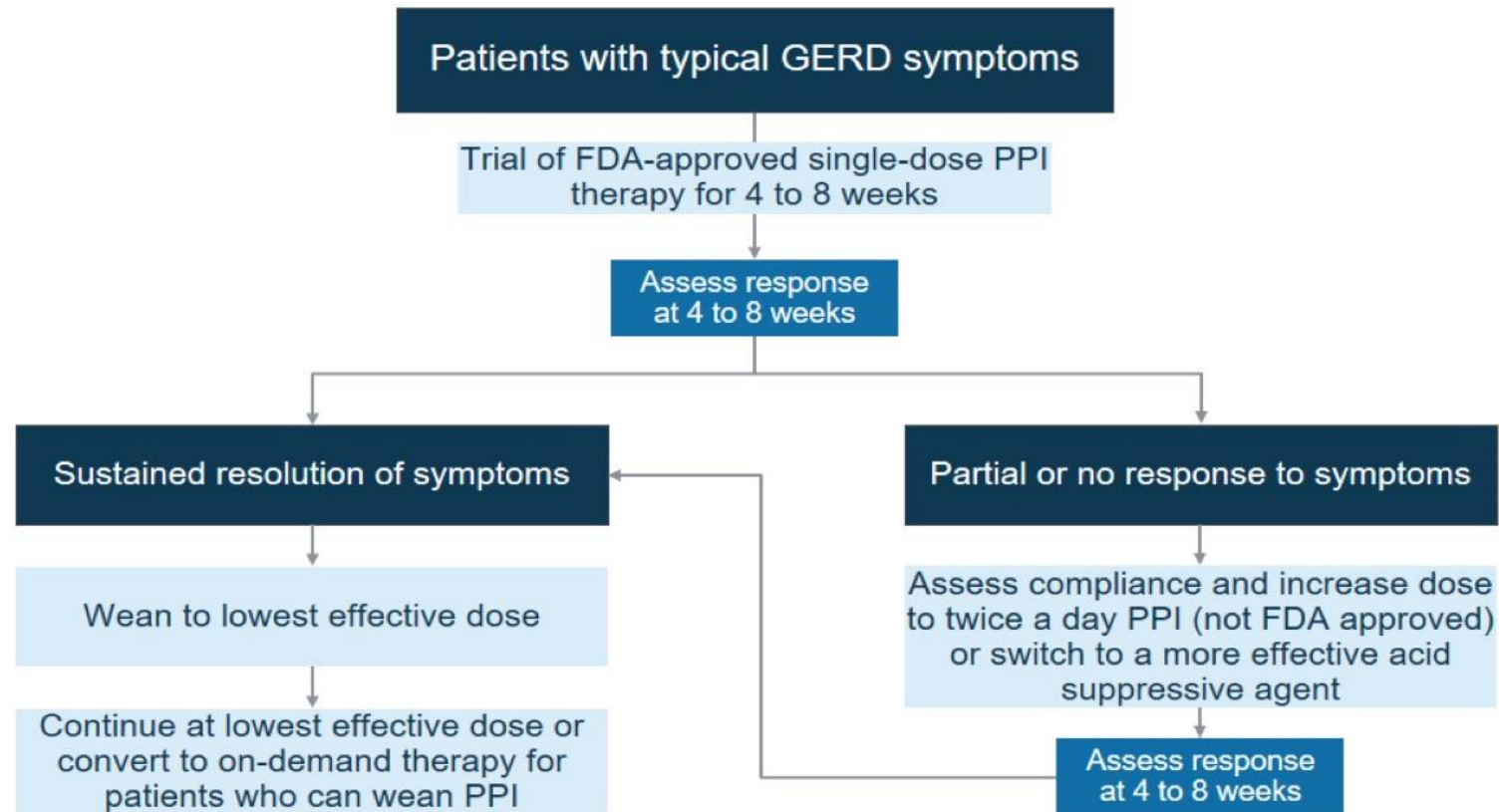
- PPIs treat the number of acid reflux episodes but not the proximal extent of the episodes nor the total amount
- Robust in treating heartburn usually within 1-2 weeks but not in treating regurgitation
- Superior in maintaining intragastric pH of >4 for 10-14 hours as compared to 6-8 hours with H2RAs
- Cochrane meta-analysis showed PPIs are superior to H2RAs and placebo in NERD and in undiagnosed reflux symptoms in primary care
- ERD: Large meta-analysis showed complete healing of even severe oesophagitis after 8 weeks of PPIs use in >80% of patients, compared to 51% with H2RAs and 28% with placebo



PPI THERAPY

- PPIs more efficacious than H2RAs in maintaining remission of oesophagitis over a 6–12-month period
- After oesophagitis is healed, recurrence occurs >80% patients with severe oesophagitis within 6 months after therapy had been stopped
- Open-compassionate use data from Australia and Netherlands support indefinite PPI therapy for patients with severe GERD
- All maintained remission for up to 11 years
 - Relapses rare
 - Strictures did not occur
 - Barrett's oesophagus did not progress

2022 AGA CLINICAL PRACTICE UPDATE FOR PPI THERAPY



POSITION PPI USE FOR SUCCESS

PPIs are acid-labile molecules

PPIs are not constructed the same

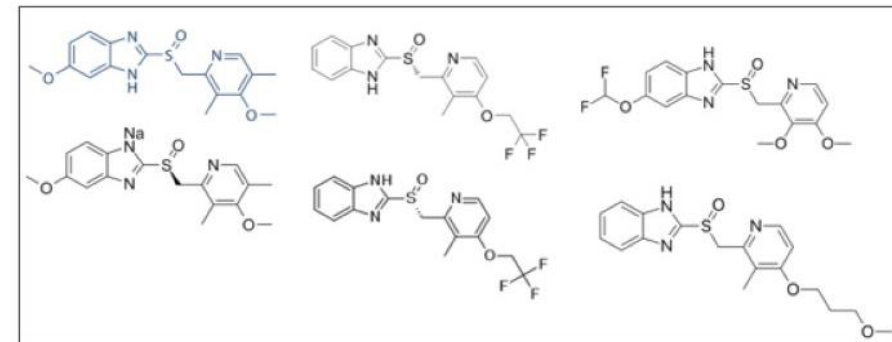
- Varying levels of intragastric pH control
- Varying levels of metabolism through CYP2C19

Before-meal dosing (before breakfast/dinner)

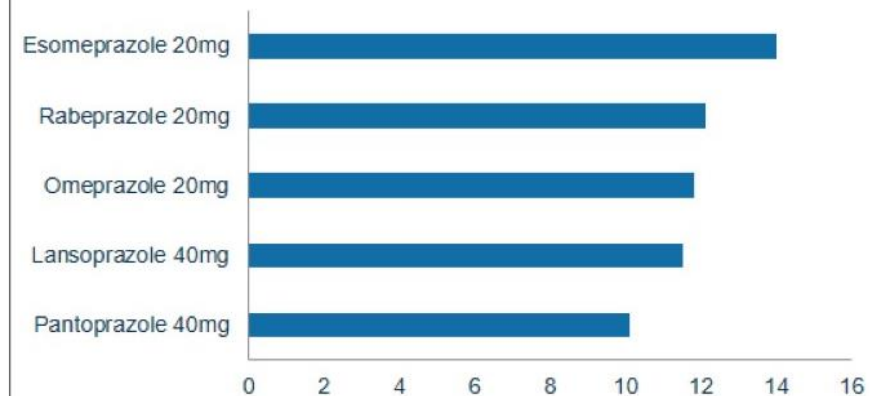
Multiple PPI switches are not recommended

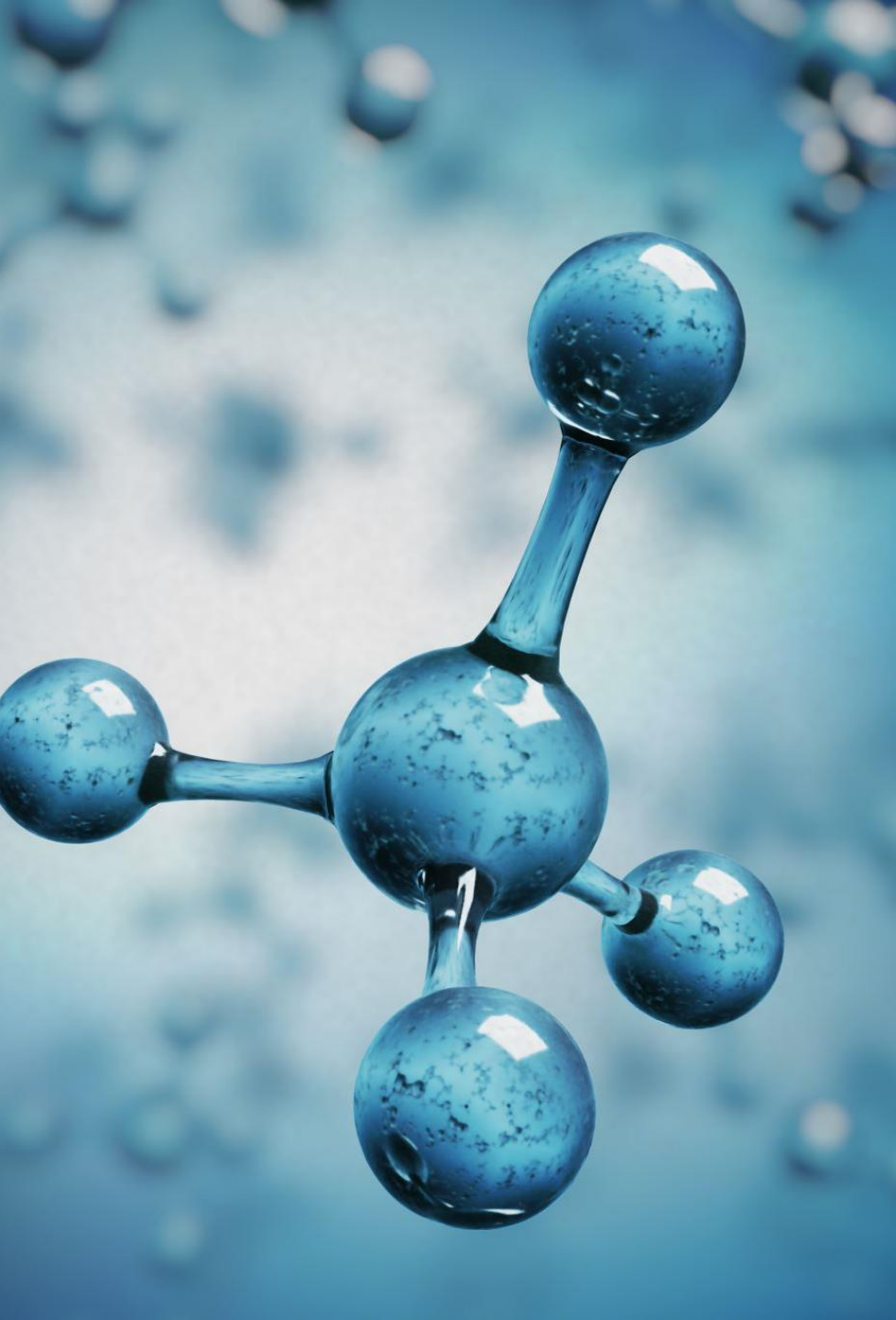
If switching, consider one with:

- Greater intragastric pH suppression
- Less metabolism via CYP2C19



Intragastric pH Control





WHY DO WE NEED A NEW TREATMENT OPTIONS ?

- PPIs are vulnerable to degradation by gastric acid (enteric coating protects them from acid but delays their absorption)
- PPIs are prodrugs and must be activated by gastric acid to covalently bind to proton pumps
- Only affect actively secreting parietal cells
 - Fasting: only 5% of proton pumps are actively secreting
 - With meals: 60%-70% of proton pumps actively secreting
- Short plasma half life (2-3hours)
 - Stomach actively generates new pumps (25% in 24 hours)
 - Repeated dosing required
- Variability with metabolism by CYP2C19

LONG-TERM PPI USE CONTROVERSIES

Risk of Cancer	Risk of Infections	Absorption/ Metabolism Vitamins and Minerals	Effects on Other Drugs	Miscellaneous Adverse Effects
<ul style="list-style-type: none"> Gastric cancer after <i>Helicobacter pylori</i> treatment 	<ul style="list-style-type: none"> Enteric infections Pneumonia <i>Clostridioides difficile</i> SBP in cirrhotic patients COVID-19 	<ul style="list-style-type: none"> B12, iron, calcium Hypomagnesemia Bone fracture 	<ul style="list-style-type: none"> Clopidogrel 	<ul style="list-style-type: none"> Interstitial nephritis Renal disease Colitis Celiac disease Myocardial infarction Stroke Dementia Early death

SBP, spontaneous bacterial peritonitis.
Vaezi M, et al. *Gastroenterology*. 2017;153:35-48; Moayyedi P, et al. *Gastroenterology*. 2019;157:682-691.e2.

These materials are provided to you solely as an educational resource for your personal use. Any commercial use or distribution of these materials or any portion thereof is strictly prohibited.

LONG-TERM PPI USE CONTROVERSIES

Risk of Cancer	Risk of Infections	Absorption/ Metabolism	Effects on Other Drugs	Miscellaneous Adverse Effects
<ul style="list-style-type: none"> Gastric cancer after <i>Helicobacter pylori</i> treatment 	<p>Most identified by weak associations in observational studies that cannot establish cause and effect</p> <ul style="list-style-type: none"> Enteric <i>Clostridioides</i> peritonitis <p>High-quality study established modest but significant association of PPIs only with enteric infections</p> <p>Cannot exclude the possibility that PPIs might confer a small increase in risk of developing these AEs</p> <p>Most GI specialists agree that the well-established benefits of PPIs far outweigh their theoretical risks</p>	<ul style="list-style-type: none"> B12, iron, anemia 	<ul style="list-style-type: none"> Clopidogrel 	<ul style="list-style-type: none"> Interstitial nephritis Renal disease Colitis Celiac disease Myocardial infarction Stroke Dementia Early death

AE, adverse event; SBP, spontaneous bacterial peritonitis.
 Vaezi M, et al. Gastroenterology. 2017;153:35-48; Moayyedi P, et al. Gastroenterology. 2019;157:682-691.e2.

POTASSIUM-COMPETITIVE ACID BLOCKERS (PCABS)



- Acid stable
- Do not require enteric coating



- Active drugs
- Not prodrugs like PPIs



- Inhibit H⁺,K⁺-ATPase
- Bind ionically to H⁺,K⁺-ATPase
- Bind active and inactive proton pumps
- No need to time dose around meals



- Not metabolized primarily by CYP2C19

PIPELINE OF PCABS

Drug	Approval Status ^[1]
Vonoprazan	<ul style="list-style-type: none"> Approved in the United States for <i>Helicobacter pylori</i> infection as part of dual or triple therapy with antibiotics^[2,3] Approved in Japan for EE, GERD, GU, DU, and <i>H pylori</i> infection Approved in Philippines, Singapore, Thailand, Argentina, Peru, South Korea, Taiwan, Malaysia, Ecuador, China, Indonesia, Brazil, and Mexico for various acid-related disorders Under FDA review for treatment of erosive GERD^[3] Phase 3 trial completed for NERD
Tegoprazan	<ul style="list-style-type: none"> Approved in South Korea for EE, NERD, GU, and <i>H pylori</i> infection Phase 3 trials initiated for GERD/NERD
Fexuprazan	<ul style="list-style-type: none"> Approved in South Korea for EE Additional clinical trials ongoing in the United States/Canada in EE
Revaprazan	<ul style="list-style-type: none"> Approved in South Korea and India for "gastritis," GU, and DU

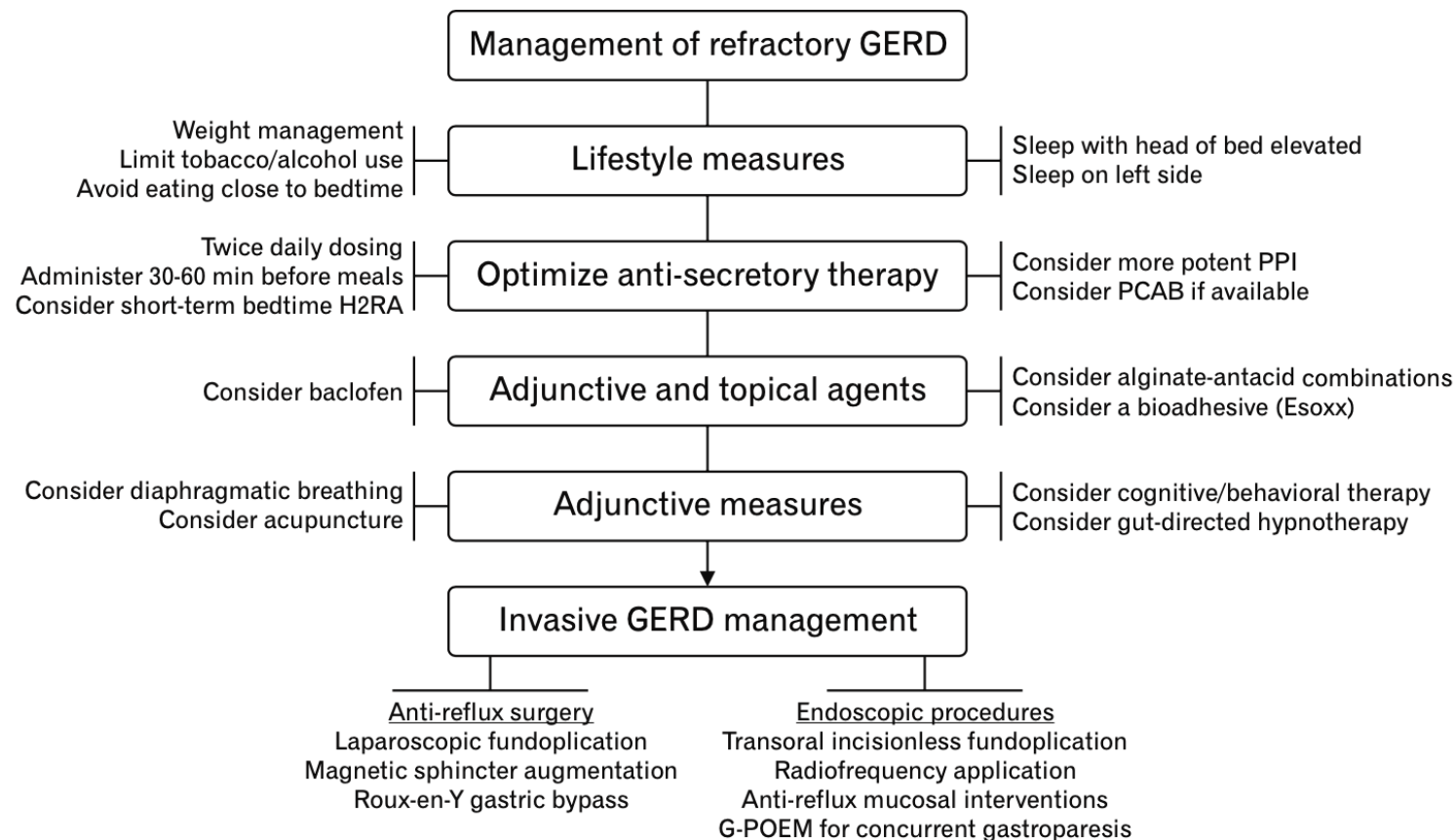
DU, duodenal ulcer; FDA, US Food and Drug Administration; GU, gastric ulcer; NERD, non-erosive reflux disease; PCAB, potassium-competitive acid blocker.
 1. Abdel-Aziz Y, et al. Aliment Pharm Ther. 2021;53:794-809; 2. Vonoprazan [PI]. Approved 2022. Revised August 2023; 3. <https://www.medscape.com/viewarticle/988325> Accessed September 15, 2023.
 These materials are provided to you solely as an educational resource for your personal use. Any commercial use or distribution of these materials or any portion thereof is strictly prohibited.

REFRACTORY GERD

Definitions:

- Persistent symptoms while on optimized therapy in the context of proven GERD is referred to refractory symptoms
- Refractory GERD:
- LA B,C,D oesophagitis & recurrent stricture on endoscopy while on optimized therapy
- pH impedance: AET >4% and >80 reflux/day on an optimized antisecretory regimen

MANAGEMENT APPROACH TO REFRACTORY GERD



PCABS ARE AN OPTION FOR REFRACTORY GERD

GERD patients with...



Our patient:

Severe reflux esophagitis (LA-C or LA-D) who do not heal on optimized double dose PPI

Patients who are not good candidates for anti-reflux procedure due to comorbidities

Patients with motility issues: esophagus and gastric

Patients with documented abnormal acid exposure on double dose PPI therapy with reflux related symptoms

WHO ARE GOOD CANDIDATES FOR ANTI-REFLUX SURGERY?

GERD patients with...

Severe reflux esophagitis (LA-C or LA-D) who do not want to take PPIs indefinitely

Typical GERD symptoms who cannot be weaned off PPIs and do not want to take PPIs indefinitely

Troublesome regurgitation^[1]

PPI-refractory heartburn that clearly is reflux-related (supported by meticulous workup that includes reflux monitoring)^[2]

1. Bell R, et al. Gastrointest Endosc. 2019;89:14; 2. Spechler SJ, et al. N Engl J Med. 2019;381:1513.

SURGICAL OPTIONS

Anti-reflux surgery

- Nissen(360-degree) and Toupet (partial) fundoplication
- Increase basal LES pressure, decrease tLESRs and inhibits complete LES relaxation
- Comparable long-term efficacy to PPI therapy in multiple randomized trials & may be superior in terms of symptomatic relief in refractory GERD
- Long-term monitoring shows sustained relief for up to 17 years off PPI therapy

Complications

- Re-intervention for recurrent GERD & fundoplication failure
- Gas-bloat syndrome
- Dysphagia
- Post-operative obstructive symptoms

SURGICAL OPTIONS

Anti-reflux surgery

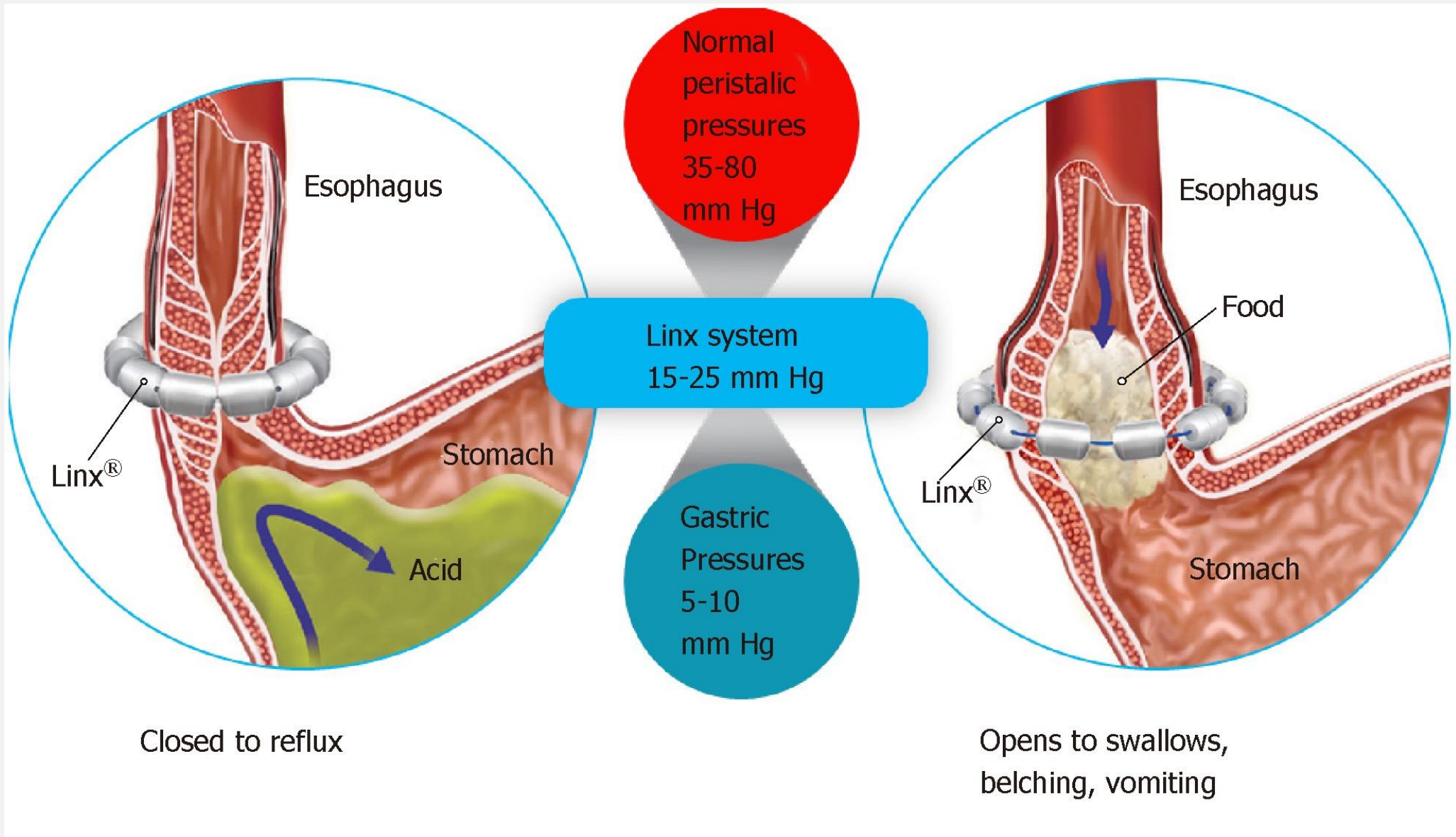
- Laparoscopic anti-reflux surgery
 - Post-operative PPI use is up to 43%
 - 17.7% risk of recurrence of GERD
- Roux-en-Y gastric bypass
 - Primary for refractory GERD
 - Failed fundoplication
 - Refractory GERD following sleeve gastrectomy

Complications

- Re-intervention for recurrent GERD & fundoplication failure
- Gas-bloat syndrome
- Dysphagia
- Post-operative obstructive symptoms

SURGICAL OPTIONS

- **Magnetic sphincter augmentation (MSA)**
- Bracelet of magnetencased in titanium is implanted around the OGJ
- 58% of patients normalize their AET within a year and 90% halve their PPI use
- >80 total reflux episodes on pre-operative pH impedance testing, predicts favourable outcomes post MSA
- Particularly favourable in patients with regurgitation-predominant symptoms
- Sustained improvement noted 5-years post-implantation
- Mild dysphagia with resolution (89% at 1 year & 96% at 3 years)



ENDOSCOPIC OPTIONS

Anti-reflux mucosectomy

- Creates scarring around the OGJ using crescentic or circumferential mucosal resection
- Observational studies: improvement in reflux-related quality of life has been demonstrated
- Anti-reflux band mucosectomy
- Anti-reflux mucosal ablation using argon plasma coagulation
- Pooled success rate of 73.8% reported over short-term follow up

Complications

- Post-procedure dysphagia requiring dilatation in 10%
- Perforation in 2.2%

ENDOSCOPIC OPTIONS

- **Transoral incisionless fundoplication (TIF)**
- Create a flap valve involving 180-270degrees of the circumference of the OGJ
- Plicates portion of proximal stomach
- Accentuate angle of His
- Long term effect is not established
- **G-POEM (gastric per-oral endoscopic myomectomy)**
- Subset of patients with refractory GERD and gastroparesis

REFERENCES

- Davis T, Gyawali P. 2024. Refractory gastroesophageal reflux disease: diagnosis and management. *Journal of Neurogastroenterology and Motility*. 30(1): 17-28
- Gyawali P, Yadlapti R, Fass R, Katzka D, et al. 2023. Updates to the modern diagnosis of GERD: Lyon consensus 2.0. *GUT*. 73:361-371
- Arguero J, Sifrim D. 2024. Pathophysiology of gastro-oesophageal reflux disease: implications for diagnosis and management. *Nature reviews Gastroenterology and Hepatology*.
- Richter J, Vaezi M. Gastroesophageal reflux disease. Ch 46. In: Sleisenger and Fordtran's *Gastrointestinal and Liver Disease* 11th edition, ed. By R Chung, D Rubin, C Wilcox. Philadelphia: Elsevier, 202, pp 670-690.