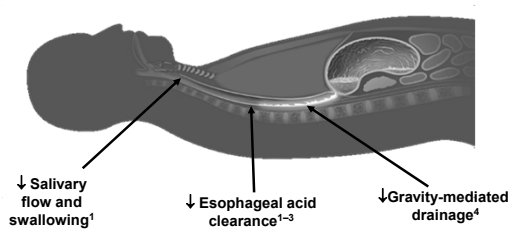
Case Study #1: Why am I always tired?

- 66 year old man c/o daytime sleepiness
- Recently retired
- PMHx: Hypertension, hypercholesterolemia
- Current meds: Hydrochlorothiazide, pravastatin
- PE: 6'0'' / 212 lbs - **BMI 28.7** BP: 140/90 mm Hg
- Impression: Sleep apnea or other sleep disorders
- Plan:
  - Reduce caffeine intake
  - Increase daytime activity
  - Sleep log (including spouse report)

Case Study: Return Visit at 3 Weeks

- Adopted lifestyle modifications
- Still very sleepy during the day
- Sleep log
  - No snoring/choking/apnoeic episodes
  - **Frequent nighttime cough (spouse aware, patient not)**
  - Some morning **hoarseness**
- Further questioning
  - Occasional **epigastric discomfort**
  - Previous **self-medication with antacids**
- Diagnosis: GERD (nighttime reflux)

Supine Position/Sleep Diminish Protective Barriers Against GE Reflux



[1]Orr W, et al. *Gastroenterology.* 1984;86:814–819. [2]Orr W, et al. *Am J Gastroenterol.* 2000;95:37–42. [3]Orr W, et al. *Am J Gastroenterol.* 1994;89:509–512. [4]Kjellén G, Tibbling L. *Scand J Gastroenterol.* 1978;13:283–288.

Nighttime reflux increases risk for GERD complications

Esophageal Disease Progression

- Erosive esophagitis[1]
- Complicated erosive esophagitis[2]
  - Ulceration
  - Strictures
  - Barrett's esophagus
- Adenocarcinoma[3]

Atypical Complications

- Respiratory disturbances[4]

Other Symptoms

- Sleep deprivation[4]

[1]Orr WC, et al. *Am J Gastroenterol.* 1994;89:509–512. [2]Robertson D, et al. *Gut.* 1987;28:1484–1488. [3]Lagergren J, et al. *N Engl J Med.* 1999;340:825–831. [4]Gislason T, et al. *Chest.* 2002;121:158–163.

Nighttime GERD Implicated in Sleep Disturbances

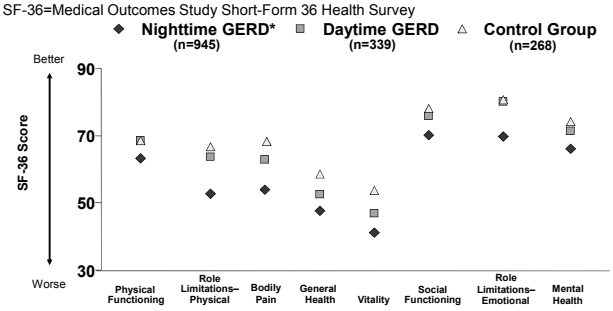
Symptom	Controls: No Nighttime Reflux (n=2,096)	Nighttime Reflux (n=101)
Nighttime symptoms (%)		
Snoring (≥3 nights/wk)	5	16*
Reported apnea (≥1 night/wk)	1	5†
Nightmares (≥1 night/wk)	4	17*
Daytime symptoms (%)		
Daytime sleepiness (≥3 days/wk)	14	30*
Involuntary falling asleep (≥1 day/wk)	4	8‡

*P<0.001; †P<0.01; ‡P<0.05

Adapted from Gislason T, et al. *Chest.* 2002;121:158–163.

Nighttime GERD is associated with an even lower Health Status than daytime GERD

SF-36=Medical Outcomes Study Short-Form 36 Health Survey



*P<0.001 vs. control group for all scales except "Physical Functioning." P<0.001 vs. daytime GERD for all scales.

Adapted from Farup C, et al. *Arch Intern Med.* 2001;161:45–52.

Identifying Nighttime Reflux

- Symptom(s) when recumbent vs. upright
- Nocturnal symptoms:
  - heartburn, regurgitation
  - chronic cough/hoarseness, throat clearing
  - difficulty breathing, wheezing
- Sleep disturbance:
  - not falling asleep
  - not staying asleep
  - not waking refreshed
- Severe or difficult to control symptoms

Case study #2: **A tickle in the throat**

- 63 year old woman
- Occasional mild heartburn
- Cough for >3 months
- ENT reports reflux laryngitis
  - Rx PPI 40mg daily
- After 1 month no change in symptoms
- EGD is normal
  - PPI increased to 40 mg bid
- After another month no change in symptoms

Atypical Presentations of GERD

Esophageal chest pain

Pulmonary

- Asthma
- Apnea
- Bronchitis
- Atelectasis
- Aspiration pneumonia
- Pulmonary fibrosis

ENT

- Hoarseness
- Vocal cord granulomas
- Cough
- Laryngeal cancer
- Halitosis
- Dental enamel loss

GERD-induced cough / hoarseness

- Direct acid/peptic laryngeal irritation
  - Often at night
  - May have severe acid reflux
  - Typical GERD symptoms/esophagitis may be absent
- Potent & prolonged acid antisecretory therapy needed to heal (therapeutic trial)
- Recurs when anti-reflux therapy stopped

Reflux laryngitis: Specificity of laryngoscopic diagnosis?

- 66% of subjects with laryngitis were suspected of having GERD
- However, only 25% of these had an abnormal 24 hour pH study
- Response to PPI (30 mg bid ac for 8 weeks) was substantially higher in those with an abnormal pH study - 67% vs 11% (p=0.02).

Aliment Pharmacol Ther. 2007 Feb 1;25(3):287-95.

Indications for esophageal pH study

- GERD symptoms unresponsive to therapy
  - To confirm acid reflux – discontinue Rx
  - To evaluate treatment efficacy – continue Rx
- Atypical symptoms (after trial of PPI)
  - Chest pain
  - Cough, hoarseness
  - Asthma
- Prior to anti-reflux surgery

AGA position Statement, Gastroenterology 1996

Diagnosing reflux laryngitis

- Typical reflux symptoms present = GERD
- Clinical response of laryngeal symptoms to therapy with PPI?
  - prolonged (6-12 weeks)
  - high dose (e.g. 40 mg bid ac)
- Special studies:
  - 24 hour intra-esophageal pH study
  - Esophageal Multichannel Intraluminal Impedance
    - Can detect neutral pH reflux

Case study: **A tickle in the throat**

- Occasional heartburn resolved on PPI
- Cough persisted
- Saw ENT specialist in follow up
  He advised more aggressive GERD therapy
- Patient anxious to be rid of cough and is willing to "try anything" including surgery
- Esophageal MII-pH study normal (on PPI)
- Plan:
  - Seek other causes for cough (ENT & Pulmonary)
  - Rx antitussive

Case study #3: **An unusual case of esophagitis**

- 34 year old woman
- ER with food stuck in esophagus x 3 hours
- Multiple prior episodes (since age 19 years)
- Tolerates endoscopy poorly
  - told "esopghagus congenitally narrow"
  - suffers marked post-procedure chest pain
  - pediatric scope always required

Eosinophilic (allergic) esophagitis

- Rising incidence (1/100,000 in 1985 vs 105/100,000 in 2007)
- Children & in adults
- Associated with:
  - Allergies
  - Mild peripheral eosinophilia
  - Eosinophilic gastroenteritis
- Clinical features:
  - Early onset
  - Males > females
  - **Dysphagia & food bolus impaction**
  - Heartburn
  - Esophageal mucosal tears & perforation at EGD
  - **Misdiagnosed as congenital esophageal rings or as GERD**

Treatment of Eosinophilic Esophagitis

- **Proton pump inhibitor**
- **Topical steroid**
  - **e.g. SWALLOWED Fluticasone (220 mcg/puff, 2 bid)**
- **Identify food allergies and avoid the allergens**
- **Trial of an elimination diet**
- **Systemic steroid – rarely needed**
- **Esophageal dilatation - with caution**
- **Other: Cromolyn sodium, montelukast (10-100 mg/d), anti-IL-5 mAb, azathioprine**

Case study #3: **An unusual case of esophagitis**

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Case study #4: **Scoping out heartburn**

- 65 year old man
- > 15 years of heartburn
- Controlled on PPI 40 mg daily for 8 years
- Referred by PCP because:
  - Very concerned about longterm PPI use
  - Very concerned about esophageal cancer risk
- How would you advise him?

Indications for PPI use

Acute / brief:

Peptic ulcer healing
H. pylori eradication (with antimicrobials)

Chronic:

GERD (including maintenance therapy to control symptoms and prevent complications)
Patients at high risk for recurrent peptic ulceration (e.g. requiring NSAID)
Zollinger Ellison syndrome
Eosinophilic esophagitis

Which PPI to use and at which dose?

- Various PPIs show similar efficacy in clinical trials
  - However, idiosyncratic patient differences in efficacy/response may be apparent
- Dose variable depending on symptom severity and clinical response
- Metabolism varies due to common, genetically determined variations in the activity CYP2C19 (a cytochrome P450 family enzyme)
  - These variations may lead to either increased or reduced effects and so alter dose requirements.
  - Also carry potential for decreased clopidogrel activation

Safety of prolonged PPI therapy:

Used since 1980s with excellent safety profile

Less concerning:

- Malabsorption
  - Minimal or no clinical significance
    - Vitamin B12 malabsorption – ? annual testing
    - Iron malabsorption – ??? annual CBC
- Atrophic gastritis in *H pylori* infected on chronic PPI
  - Not sufficiently certain to warrant *H pylori* testing
- Hypergastrinemia and carcinoid tumors
  - Evident in rats but not in humans

Safety of prolonged PPI therapy:

Used since 1980s with excellent safety profile

- Enteric infections including C. difficile, Salmonella and Campylobacter
- Pneumonia (both hospital- & community-acquired)
- [illegible]g
- [illegible]
- [illegible]
- Chronic kidney disease
- Dementia

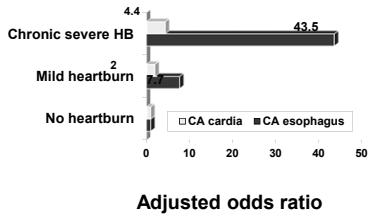
- Most of these reported associations are subject to potential confounding by other factors
- Overall very safe medications for chronic use **if indicated**

Safety of prolonged PPI therapy: general considerations

- Recommendation: Prescribe lowest dose and shortest regimen appropriate to the condition being treated.
- Rebound gastric acid hypersecretion may occur on discontinuing chronic PPI
  - Consider tapering if >6 months of treatment
    - – reduce dose by 50% per week to zero

Many patients return to PPI use within one year after stopping?
- GERD – 79% resumed
- Dyspepsia – 67% resumed
- Other - 42% resumed

GERD increases risk for Esophageal Adenocarcinoma
"Killer Heartburn!"
(Lagergren, NEJM, 1999)

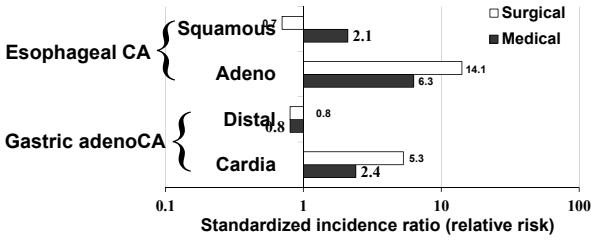


Cancer incidence in GERD

- Swedish inpatient register
- 66,965 patients with GERD
- 376,622 person years of follow up
- Cancer incidence in GERD (**0.04% per annum**):
  - Esophageal adenoCA: **22.4 per 100,000 person years**
  - Gastric cardia adenoCA: **21.8 per 100,000 person years**
  - Incidence **5 fold higher in men** *versus* women
- 11,077 patients with anti-reflux procedures

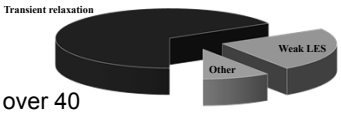
Ye et al, Gastro 2001:121:1286

Antireflux surgery does not reduce cancer risk in men with GERD



Ye et al, Gastro 2001:121:1286

LES dysfunction in GERD



> 50% of those over 40 years of age regularly experience heartburn

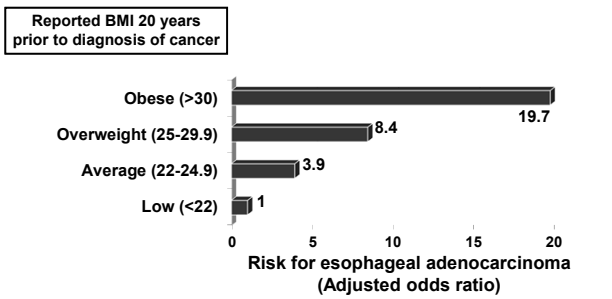
Impaired esophageal peristalsis
Delayed gastric emptying

"You're only as young as your weakest sphincter"

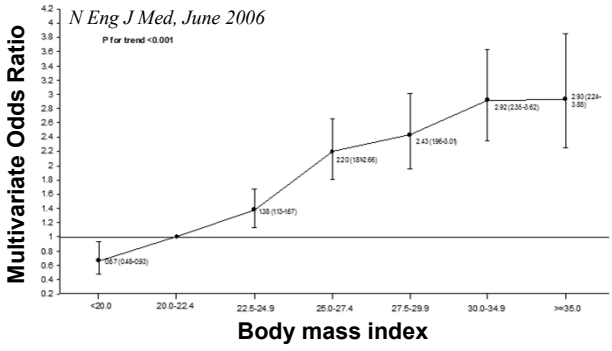
Lauren Harris, M.D. Boston University

Body Weight & Esophageal AdenoCA

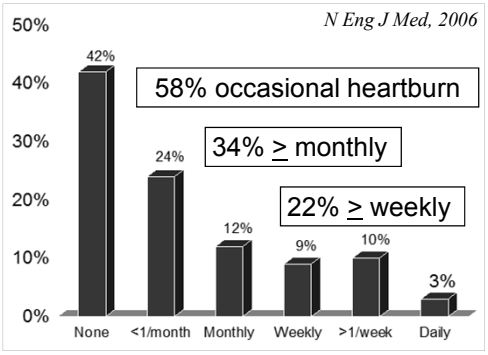
Lagergreen et al, Ann Int Med 1999



Association between BMI & Frequent (≥ weekly) GERD



Prevalence of Heartburn
(Nurses' Health Study)



Screening in GERD: A personal position statement

- Diagnose & treat GERD (with PPI as needed)
- Do **not** advocate routine screening for Barrett's in patients with GERD
- Await further evidence-based recommendations
- Encourage normal BMI
- Advocate colon cancer screening

Should we screen for Barrett's Esophagus in patients with chronic GERD?

As we know,
There are known knowns.
There are things we know we know.
We also know
There are known unknowns.
That is to say
We know there are some things
We do not know.
But there are also unknown unknowns,
The ones we don't know
We don't know.

—Feb. 12, 2002, Department of Defense news briefing

Should we screen for Barrett's esophagus in patients with chronic GERD?

Pro

- **GERD causes Barrett's & Barrett's leads to cancer**
- **Longstanding GERD indicates cancer risk esp. in white males**
- **Screening may identify early-stage, curable disease**
- **You get paid if you do**
- **You might be sued if you don't**

Con

- **Heartburn & BE are common**
- **Esophageal adenoCA is not common (0.04% pa in GERD)**
- **Heartburn is not a sensitive predictor of carcinoma risk (~40% have no history of GERD)**
- **The effectiveness of screening even in subjects with known long segment Barrett's is unproven**