Barrett's Esophagus: Are We Making any Progress?

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Disclosures
Consultant: Ironwood Pharmaceuticals

58 year-old man with 20 years of heartburn that has recently increased in frequency and intensity.

How did GERD damage this esophagus?

Traditional Concept
Reflex Esophagitis Is a Caustic, Chemical Injury

58 year-old man with 20 years of heartburn that has recently increased in frequency and intensity.

How did GERD damage this esophagus?

58 year-old man with 20 years of heartburn that has recently increased in frequency and intensity.

How did GERD damage this esophagus?

Rat Model for GERD: Esophago-Duodenostomy

Resulted in severe, ulcerative reflux esophagitis in weeks

Sham-Operated Control

Postoperative Day 3
Submucosal Lymphocyte Infiltration
Inflammation did not start in the mucosa
Mucosa intact
Lymphocyte
Lymphocyte
First inflammatory cells were lymphocytes, not granulocytes

Postoperative Week 3
Basal Cell and Papillary Hyperplasia
Surface Cells Intact
Papillary Hyperplasia
Basal cell and papillary hyperplasia not due to death of surface cells

Cultures of Esophageal Squamous Cells Exposed to Acid and Bile Salts Secrete IL-8 (a Pro-Inflammatory Cytokine)

Reflux Esophagitis: A Cytokine-Mediated Injury
Reflux induces epithelial cells to secrete pro-inflammatory cytokines, which attract lymphocytes first, induce basal cell proliferation
Inflammatory cells mediate epithelial injury, not acid directly

Does Reflux Esophagitis in Humans Develop as a Cytokine-Mediated Injury Rather than a Caustic Chemical Injury?
- Patients typically have months to years of GERD symptoms before seeking medical attention.
  - Early histologic changes of reflux esophagitis not evaluated prospectively
- Severe reflux esophagitis healed by PPIs returns within 6-12 months of stopping PPIs.
  - Might induce acute reflux esophagitis by temporarily interrupting PPIs in patients with severe GERD?

Study of Acute Reflux Esophagitis in Humans
- 12 patients with severe (Los Angeles grade C) reflux esophagitis healed with PPI therapy
  - 11 men, 1 woman
  - Mean age 58 years (SD 13.1 years)
- Stopped PPIs for 2 weeks to induce acute reflux esophagitis
  - Endoscopy at 1 and 2 weeks after stopping PPIs

Esophageal Acid Exposure Increases Dramatically When PPIs are Stopped

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Baseline (on PPIs) Esophagitis Grade</th>
<th>Week 1 (off PPIs) Esophagitis Grade</th>
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Development of Endoscopic Reflux Esophagitis After Interruption of PPI Therapy

Baseline On PPIs

Baseline
On PPIs

1 Week
Off PPIs

Endoscopic Reflux Esophagitis Development


Development of Endoscopic Reflux Esophagitis After Interruption of PPI Therapy


Baseline On PPIs

Baseline
On PPIs

1 Week
Off PPIs

Epithelium

Basal Cell Hyperplasia

Papillary Hyperplasia

Lamina Propria

CD3 Immunostaining (T Lymphocytes)
Conclusions of Acute GERD Study

- Reflux esophagitis healed by PPIs returns within 2 weeks of stopping PPIs.
- Acute reflux esophagitis is characterized by T-lymphocyte infiltration of esophageal mucosa.
  - Neutrophils and eosinophils not prominent components
- Findings refute traditional concept that reflux esophagitis is a caustic chemical injury
- Findings support new concept that refluxed material does not kill esophageal squamous cells directly, but stimulates them to secrete cytokines that attract inflammatory cells that cause tissue damage


Barrett’s Esophagus

The condition in which a metaplastic columnar epithelium that predisposes to cancer development replaces the stratified squamous epithelium that normally lines the distal esophagus

Affects 5.6% of adult Americans


Barrett’s Metaplasia

Esophageal Adenocarcinoma

U.S. Incidence of Esophageal Adenocarcinoma Has Been Rising


Estimates of Cancer Risk for Individual Patients with Non-Dysplastic Barrett’s Have Been Falling

- 1990s Estimate: 1% per year
  1 in 100 patients per year
- 2000s Estimate: 0.5% per year
  1 in 200 patients per year
- 2017 Estimate: 0.1%-0.3% per year
  ~1 in 400 patients per year

ACG Clinical Guideline on Endoscopic Screening for Barrett’s Esophagus

- Not recommended for general population or for women
- Screening may be considered in men with chronic (>5 years) and/or frequent (≥weekly) GERD symptoms (heartburn, acid regurgitation) and ≥2 risk factors
  – Age ≥50 years
  – White race
  – Central obesity
  – History of smoking
  – Confirmed history of Barrett’s esophagus or esophageal adenocarcinoma in 1st relative
- In women, screening may be considered in individual cases as determined by the presence of multiple risk factors

Recommendations for Endoscopic Surveillance of Non-Dysplastic Barrett’s Esophagus

- AGA, ASGE, ACG
  Surveillance every 3 to 5 years

Why Should Proton Pump Inhibitors (PPIs) Prevent Cancer in Barrett’s Esophagus?
- Acid reflux causes reflux esophagitis (chronic inflammation)
  PPIs heal reflux esophagitis
- Acid causes DNA double-strand breaks in Barrett’s epithelial cells (potentially carcinogenic)
  PPIs decrease esophageal exposure to this carcinogen
- Acid promotes proliferation in Barrett’s metaplasia
  PPIs might prevent proliferation
- Acid stimulates esophageal secretion of pro-inflammatory and pro-proliferative cytokines
  Acid suppression may prevent cytokine secretion

PPIs Are Potentially Cancer-Protective.

Why Might PPIs Promote Cancer in Barrett’s Esophagus?

- Acid promotes proliferation in Barrett’s metaplasia
  PPIs might prevent proliferation
- Acid suppression may prevent cytokine secretion

PPIs Are Potentially Cancer-Promoting.

Recent, Large Case-Control Studies on Risk of Developing HGD or EAC in Barrett’s Patients on PPIs

- PPIs increase the risk of neoplasia? Confounding by Indication?
- PPI use is not associated with a significant decrease in the incidence of esophageal adenocarcinoma.

Arguments Favoring Antireflux Surgery Over PPIs for Cancer Prevention in Barrett’s Esophagus

- PPIs target acid exclusively, but acid is not the only harmful agent in refluxed gastric juice.
  - Refluxed bile salts might contribute to carcinogenesis.
- Antireflux surgery can prevent reflux of all gastric material
- Some small, observational studies suggest that surgically-treated Barrett’s patients develop less dysplasia and cancer.
Antireflux Surgery *Might* Protect Against Cancer in Barrett’s Esophagus Better than Medical Therapy.

- Potential advantage is small
- Not clear that this small, potential advantage justifies the risks of antireflux surgery

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**ACG Clinical Guideline on Treatment of GERD in Barrett’s Esophagus**

- Patients with Barrett’s esophagus should receive once-daily PPI therapy.
  - Routine use of twice-daily dosing is not recommended unless necessitated because of poor control of symptoms or esophagitis.
- Antireflux surgery should not be pursued in patients with Barrett’s esophagus as an antineoplastic measure.
  - However, this surgery should be considered in those with incomplete control of reflux symptoms on optimized medical therapy.

*Am J Gastroenterol 2016;111:30.*

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**Accurate T Staging **Crucial** to Determine if Curative Endoscopic Therapy Feasible**

- High Grade Dysplasia, Intramucosal Carcinoma
  - Lymph node metastases in 1%-2%
  - Curative endoscopic therapy feasible
- Submucosal invasion
  - Lymph node metastases in >10%
  - Failure rate for endoscopic therapy unacceptable
- Endoscopic mucosal resection (EMR) the best procedure for T staging

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**Endoscopic therapy is appropriate for neoplasms confined to the mucosa.**

*Drawing courtesy of Tom Rice*

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**EMR is as much a staging procedure as it is a therapeutic procedure.**

If EMR shows submucosal invasion, then endoscopic therapy is not advised.
Radiofrequency Ablation (RFA)

Randomized, Sham-Controlled Trial of Radiofrequency Ablation for Dysplasia in Barrett’s

Randomized Trial of RFA vs. Surveillance for Low-Grade Dysplasia (LGD) in Barrett’s Esophagus

- 136 patients with LGD confirmed by expert pathologist
  - Randomized to RFA (68 pts.) or surveillance (68 pts.)
  - Progression to high-grade dysplasia or cancer at 3 years

Endoscopic Eradication Therapy for Mucosal Neoplasia (Low-Grade or High-Grade Dysplasia, Intramucosal Carcinoma) in Barrett’s Esophagus

- EMR of mucosal irregularities for staging and therapy
  - “Endoscopists who plan to practice endoscopic ablative procedures should additionally offer EMR.”

- Radiofrequency ablation of remaining Barrett’s metaplasia to minimize metachronous neoplasia


Phoa KN. JAMA 2014;311:1209.
Surveillance Endoscopy after Endoscopic Eradication Therapy for High-Grade Dysplasia

- Recurrence rates are substantial

Recurrent HGD/IMC

<table>
<thead>
<tr>
<th>Follow-Up Months</th>
<th>Recurrence of Neoplasia after Complete Eradication of IM</th>
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- After RFA, intestinal metaplasia recurs in ~10% per year.


ACG Clinical Guideline on Management of Barrett’s Esophagus after Endoscopic Therapy

- Following endoscopic therapy with complete elimination of intestinal metaplasia (CEIM), endoscopic surveillance should be continued to detect recurrent metaplasia/dysplasia.

- Endoscopic surveillance following CEIM...
  - For patients with HGD or IMC: Q 3 months year 1, Q 6 months year 2, and annually thereafter.
  - For patients with LGD: Q 6 months year 1, and annually thereafter.

Am J Gastroenterol 2016;111:30.

RFA for Non-Dysplastic Barrett’s Esophagus?

- Generally requires several endoscopies for complete eradication
- Complication rate low, but not trivial
- Substantial rate of recurrence of metaplasia
- Efficacy in preventing cancer not established
- Does not eliminate need for surveillance

Chronic GERD symptoms and ≥1 risk factor(s) for adenocarcinoma (Age>50, male, white, hiatal hernia, obesity, intra-abdominal body fat, smoking)

No more screening

Barrett’s esophagus

No dysplasia

Surveillance endoscopy every 3-5 yrs

Low-grade dysplasia

High-grade dysplasia or intramucosal Ca

Have diagnosis confirmed by expert pathologist

Endoscopic eradication or surveillance endoscopy every 6-12 months

Endoscopic eradication


• Knowledge is knowing a tomato is a fruit.

• Wisdom is knowing not to put it in fruit salad.