Medical and Endoscopic Management of Esophageal Disease

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**MEDICAL THERAPY OF GERD**

### Chronic Therapy

**GERD often requires maintenance therapy to prevent relapse**

- Long term therapy is better with PPIs than H2 blockers in patients with erosive esophagitis


- Long term omeprazole therapy is efficacious and safe

Gastroenterology 2001; 121: 1095-1100

Loxiglumide

Atropine

**Decreases TLESR stimulated by gastric distension**

**Not clinically appropriate**

### Transient Lower Esophageal Sphincter Relaxation (TLESR)

**Dominant mechanism of gastroesophageal reflux**

**TLESR vasovagal reflux caused by gastric distension**

**Activation of the mechanoreceptors in the subcardiac region of the stomach**

### Nocturnal Gastric Acid Breakthrough

- Bacosan may reduce frequency of both acid and nonacid reflux, *Cont. 2002; 13: 907, 1999*

- Confusion
- Dizziness or Lightheadedness
- Drowsiness
- Nausea
- Unusual Weakness, especially muscle weakness
- Abdominal or stomach pain
- Trembling

### Medication Influencing TLESR

- Atropine and Morphine decrease frequency of TLESR
  - Not clinically appropriate

Pascual R et al Effect of morphine on gastroesophageal reflux and transient lower esophageal sphincter relaxation. Gastroenterology 112: 400-406

Wital RW et al Effect of atropine on the frequency of reflux and increased lower esophageal sphincter relaxation in normal subjects. Gastroenterology 104: 1947-1950

- **Lodigainide**
  - Cholecystokinin A antagonist
  - Decreases TLESR stimulated by gastric distension


**MEDICAL THERAPY OF GERD**

### Maintenance Therapy in Erosive Esophagitis (CONT.)

**SAFETY**

- No significant changes in mucosal histology in those individuals with and without histologic atrophy


- No carcinoids or gastric cancer

Gastric mucosal atrophy may be more common with HP infection

- 50% of patients may be able to switched to H2 blockers


### Nocturnal Gastric Acid Breakthrough

- End point of no symptoms more difficult to achieve than esophageal healing
- on demand therapy appears to be adequate

Babban KI et al. Symptomatic gastro-esophageal reflux disease: Double blind controlled study of intermittent treatment with omeprazole or ranitidine. The European Study Group. BMJ 1992; 292:


**MEDICAL THERAPY OF GERD**

### Maintenance Therapy in Nonerosive GERD

Less responsive to therapy than erosive esophagitis

- on demand therapy appears to be adequate

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**Predictors of Response to PPI Therapy in Patients with GERD: the Influence of Co-Morbid IBS and Psychological Disease**

85 GERD patients completed study, all treated with rabeprazole (Aciphex 20 mg per day)

- All patients completed the following indexes:
  - Digestive Health Symptom Index (DHSI), Reflux Disease Questionnaire, QOLRAD, IBS (psychological assessment)
  - IBS (irritable bowel syndrome): 3 Manning criteria on DHSI; psychological distress as BSI > 63

**Results**

- 31% of patients had IBS
- 38% of patients had psychological distress
- GERD patients with IBS: more severe total GERD symptoms, heartburn and Regurgitation (p < 0.05). All GERD patients improved with therapy, but those with IBS Less
- GERD patients with Psychiatric Distress: the baseline symptoms were the same but response to therapy is less (p < 0.05)

**Conclusions**

- Co-morbid conditions make symptoms worse and blunt response
- In refractory case be certain that more invasive therapy is justified!!

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**MEDICAL THERAPY OF GERD**

**Medication Influencing TLESR (CONT.)**

- N-monomethyl-L-arginine
  - Nitric oxide (NO) synthase inhibitor
  - Decreases TLESR stimulated by gastric distension
  - Decreases TLESR in humans
  - Central and peripheral mechanism


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**Summary**

- Genetic predictors and lifestyle changes have less impact than medications
- PPI’s are the basis of most therapeutic regimens
- Chronic maintenance is safe
- The prokinetic agent tegaserod may have a future role
- Blocking lower esophageal sphincter relaxation appears to be important
- The ideal surgical candidate is one with:
  - typical reflux who responds completely to medical management, yet desires surgical therapy
  - patients with nocturnal regurgitation accompanied by pulmonary complications

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**ESOPHAGEAL STENTS**

**Esophageal Stent**

- Used for decades to palliate dysphagia in esophageal carcinoma
- Non-expandable stents with dilation to insert it
- Patients with esophageal carcinoma, stent insertion may be followed by improved dilation and esophageal stents. Gastroint Endosc Clin North Am 1994; 4: 851-862
- Preferred therapy for tracheoesophageal fistulas secondary to esophageal cancer

**References**


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**Disease**

- GERD: the influence of Co-Morbid IBS and Psychological Disease

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Esophageal Stent

- Retrospective Population-based study
  - All patients treated with esophageal stenting for malignant disease Swedish Registry 1997-2000
  - N: 1052 with esophageal or cardia cancer
    - 420 (38%): treated with stenting
      - 74 yo: median age
      - 7 days: median in-hospital stay
      - 100 days: median survival
  - N: 152/420 (38%): evaluated for complications
    - 41/152 (27%): complications of some type
    - 20/152 (13%): direct procedure related complications
    - 2/152: procedure related deaths (esophageal perforations)

Esophageal Stent (cont.)

- Non-expandable stents ("Celestin Tubes")
  - Difficult to insert
  - Always require dilation
  - Always require very heavy sedation or plexus block
  - High risk of perforation
  - Expanding Metal Stents:
    - Easy to place
    - Subject to tumor overgrow and ingrowth
    - Difficult to remove
- Plastic Stents
  - Difficult to place and remove
  - Less tumor ingrowth and overgrowth
ESOPHAGEAL STENT

**Esophageal Stent (cont.)**

- Ruptured esophagus (Boerhaave’s syndrome)
- Use of self-expanding stents
  - As a adjuvant to surgical repair with continued leakage
  - As a primary solution
- Stent type:
  - Ultraflex stent (Microvasive)
    - Does not expand forcefully
    - Knitted nitinol wire
    - Smooth ends
    - **Advantages**
      - Prevent ischemic complications
      - Safer stent removal


**Complications**

- Early Complications (17/40%): within 7 days
  - Perforation and death at time of dilation of the malignant stricture (2)
  - Stent migration (7)
  - Hemorrhage (7)
  - Stent displacement (4)
  - Food bolus impaction (1)
- Late Complications (25/60%): after 8 days
  - Tumor ingrowth or overgrowth and food impaction (14 required repeat intervention)
  - Leak (3)
  - Bowel perforation (1)

- Technical complications (4) (50%)
  - Stent migration (7)
  - Perforation and death at time of dilation of the malignant stricture (2)

- Survival not influenced by complications (except perforation) (p=0.32)

**Chest pain and pharyngeal discomfort:** >95% within two days

**Modified Ultraflex Stent**

- With a knitted nitinol wire
- Initially more radially strong


**Self Expanding Plastic Stents (SEPS)**

- Results:
  - Successful dilation in all groups at one week
  - Dysphagia improved in all groups at one week
  - Technical success 100%
  - Fewer reflux episodes in the new stent as compared to the Dosten or the open stent

- Conclusions:
  - Effective
  - Advantage: probably less ingrowth and removable


Esophageal Stent (cont.)

Complications:

- Perforation (4-8%)
  - Risk factors: previous surgery, radiation and angulated esophagus
  - Mortality: 8-15%

- Stent migration

Late:

- Tumor ingrowth or overgrowth
- Necrosis with chest pain and bleeding

Endoscopic Ablation of Barrett’s Esophagus

Barrett’s = Intestinal Metaplasia

- Metaplasia = change in cell-type
- Squamous to specialized intestinal cells
- First described by Norman Barrett in 1950
- Related to esophagus in 1953 (Allison/Johnson)
- Adaptive mechanism to injury

Barrett’s Esophagus is due to Chronic GERD

Conventional wisdom

- 18.6 million U.S. adults with daily GERD
  - Frank et al. Upper GI Symptoms in N. America. Digestive Disease Sciences 2000; 45(4)
- 12% Barrett’s prevalence in GERD population (2.0 M)

Growing incidence and prevalence

- 6.8% of persons over age 40 have Barrett’s (8.7 M)
- 25% of persons without GERD > age 50 have Barrett’s (20 M)

Normal Esophagus
Barrett’s Disease Evolution and Demographics

Barrett’s Classification and Management

- Non-dysplastic IM
  - Surveillance every 1-3 years
  - Attempt to detect progression at treatable stage
  - Not preventative

- LGD
  - Surveillance every 6-12 months
  - Attempt to detect progression at treatable stage
  - Not preventative

- HGD and CIS
  - Treated like adenocarcinoma
  - Standard of care is esophagectomy
  - PDT has been more recent option

Is Barrett’s Benign?


<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total</th>
<th>% risk in 4 yrs</th>
<th>% risk per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total IM Patients</td>
<td>618</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>New LGD</td>
<td>100</td>
<td>16.1%</td>
<td>4.1%</td>
</tr>
<tr>
<td>HGD</td>
<td>32</td>
<td>3.4%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Cancer</td>
<td>12</td>
<td>2.0%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

5.6% HGD/CA  1.4% HGD/CA
**One Outcome of Surveillance**

- Esophageal Adenocarcinoma
- Baseline Barrett’s Esophagus

**Ablation / Removal Tools**

- Photodynamic therapy
- HALO360 (most recent)
- Argon plasma (APC)
- MPEC (gold probe)
- KTP or Nd:YAG
- Cryotherapy
- Endo-Window (EES)
- Endoscopic mucosal resection (EMR)

**Mucosal Ablation**

**What is ablation?**

- Implies destruction and, ultimately, removal
- Mechanism…heating of tissue to the point of vaporization and/or coagulation
- Endpoint is irreversible cell injury and, ultimately, cell death

**“Ideal” Ablation Objectives**

- Per-oral endoscopic approach
- Remove all IM
- Circumferential ablation
- Quick
- Uniform reproducible ablation depth
- Target depth…muscularis mucosae
- No injury to submucosa or deeper structures
- Very low risk of complications
TREATMENT OBJECTIVES
- Muscularis mucosae
  (Ablation Target Depth)
- Submucosa with esophageal glands
- Muscularis propria

HALO360 ablation depth reduces the risk of strictures
EMR Depth

Ablation Technical Challenges
- Endoluminal target (<30 mm ID)
- Very dynamic target
- Distant from operator (>40 cm)
- Can’t use laparoscopy instrument paradigm (rigid instruments, angle of attack, feedback, great visualization)
- Unforgiving organ (thin wall, mediastinum)
- Thin, corrugated target epithelium

Thin Corrugated Target Epithelium

Endoluminal Target

Historically... Point and Shoot Inadequate
- Hand-held “Point and Shoot”
  Technically demanding to achieve proper effect
- Non-uniform ablation
- Uncontrolled power delivery
- Visual endpoint for completing session
- Anatomy of distal esophagus not considered, its not round
- Repeat therapy is the rule

Thermocoagulation modalities plus Proton Pump Inhibitor Compared
- Patients with Barrett’s esophagus 2-7 cm in length without cancer or dysplasia
  Randomized to pantoprazole (40mg twice per day) and
  - Argon plasma coagulation (APC) or
  - Multipolar electrocoagulation (MPEC)
- N: 235 patients screened
  - 52 patients randomized
    - Length of Barrett’s segment 3.1 cm in MPEC vs 4.0 cm in APC (p=0.03)
    - Mean treatment sessions 2.9 MPEC vs 3.8 APC (p=0.04) (intention to treat analysis) (p=0.249 adjusted for different length)
    - Endoscopic ablation achieved MPEC 88% vs APC 75%
    - Histologically achieved in 81% MPEC vs 65% APC
    - Treatment duration mean time 6 minutes MPEC vs 10 minutes APC (p=0.01)
THERMOCOAGULATION MODALITIES PLUS PROTON PUMP INHIBITOR COMPARED

- Complications
  - Upper abdominal pain 8% MPEC vs 13% APC (p=0.64)

- Conclusions
  - Tread in MPEC toward fewer sessions
  - Greater endoscopic and histologic ablation


Complications: Complications
- Photosensitivity (69%)
- Stricture formation (36%)


High-power Radiofrequency (RF) Ablation device (HALO 360)

- Esophageal Adenocarcinoma progression
  - PDT+PPI: 13%
  - PPI: 28% (p=0.006)

- 18 month follow-up:
  - 75% of PDT+PPI patients free of IM-HGD
  - 52% of PDT+PPI free of IM


Ablation Objectives Revisited
- Removal all IM
- Circumferential
- Don’t go deeper than muscularis mucosae
- Don’t require “point and shoot”
- Automate the process
- Quick
- Avoid strictures and buried glands

Photodynamic Therapy (PDT)
- N: 208 with IM-HGD
  - Randomized 2:1 PDT+PPI: PPI alone
  - PDT+PPI: 1 (96%), 2 (68%) or 3 (47%) treatment sessions
  - Photosensitizing agents and endoscopically delivered laser

Results at 24 months follow-up
  - PDT+PPI: 13%
  - PPI: 28% (p=0.006)


HALO360 System

- HALO360 Energy Generator
  - 2001 FDA clearance for treatment of Barrett’s esophagus.
  - HALO360 Ablation Catheter

- HALO360 Sizing Balloon, Output cable, and Foot pedal not shown

High-power Radiofrequency (RF) Ablation device (HALO 360)

- Energy delivery in < 1 sec
- 3mm circumferentially
- Standardized energy density

Results
- Controls depth of ablation
- Enables uniform ablation
- Prevents strictures, buried glands, and perforations
- Eliminates point-and-shoot by providing an even target

Magnified Electrode

Balloon-based Electrodes

- Electrodes Clearly Spaced
- Energy delivery in < 1 sec
- 3mm circumferentially
- Standardized energy density

Results
- Controls depth of ablation
- Enables uniform ablation
- Prevents strictures, buried glands, and perforations
- Eliminates point-and-shoot by providing an even target
Irrigate
Measure Landmarks
Place Guidewire

Automated Sizing
Dilates and Calibrates Size

Baseline
Insertion of Electrode followed by Inflation

Result of 1 second ablation
Endoscopic Appearance

Baseline, 4 cm IM
Clean base after immediate slough (10 J/cm² twice)

 AIM-II
Baseline, 3 cm IM
Acute, 10 J/cm² twice
1 mo, no evidence of IM, no stricture
3 mo, no evidence of IM, no stricture

Clinical Trials using HALO³⁶⁰

Study Objectives
- Can we completely remove all Barrett’s (surface)
- How deep does the ablation extend (depth)
- What is the response rate (effectiveness)
- What is the adverse event profile
- How well tolerated is the procedure
- How can the device be improved to be easier to use, safer, and more effective

Control of Ablation Depth
Dosimetry Study to Validate Depth of Penetration

Immediate Effect of 10 J/cm²

Linear Response to Varying Energy Density
Ablation of intestinal metaplasia (IM) containing high-grade dysplasia (HGD) has been reported to be curative. A Prospective multicenter evaluation of a balloon-based ablation device for the ablation of non-dysplastic Barrett’s esophagus: One year results of the ablation of intestinal metaplasia (AIM-I) trial; AGA: S1691; Presented at DDW 2005

**Aim:** Successful ablation of Barrett’s esophagus with low grade dysplasia using a balloon-based ablation device: Preliminary results of the ablation of intestinal metaplasia with LGD (AIM-LGD) Trial; Gastrointestinal Endoscopy 2005; 61:AB143 Presented at DDW 2005

Ablation of circumferential segments with IMM-HGD using the HALO 360 system: Maximum ablation depth (histological layer) Complete ablation of IM and HGD

**Background:** Ablation of intestinal metaplasia (IM) containing high-grade dysplasia in patients undergoing esophagectomy

**Prior to esophagectomy:**
- Ablation of circumferential segments with IMM-HGD using the HALO 360 system
- Settings randomized to 10, 12 & 14 J/cm² and 2, 3 and 4 applications

**Following Esophagectomy: Ablations zones evaluated**
- Maximum ablation depth (histological layer)
- Complete ablation of IM and HGD

**Results:**
- Maximum ablation depth (histological layer)
- 10 treatment zones created
- no adverse events
- no evidence of transmural thermal effect

**Pathology:**
- Gross: sloughing mucosa

Histology: maximum ablation depth was lamina propria (LP) or muscularis mucosa (MM) Edema in submucosa at 14 J/cm². of highest energy level 9/10 ablation zones complete ablation of IM and HGD 1/10 viable IM-HGD at margin of zones (12 J/cm² x 2): incomplete overlap

**Clinical Results Summary**
- No buried glands
- No strictures
- AIM-I one year data: 67% complete response (CR)
- AIM-II 12 month data: 51% complete response (CR)
- Treatment to complete response is achievable

**Complete Response Post-ablation**

**Before**
- 62 y/o male with HGD

**~1 month post procedure**
- Complete Cure

**Histology:**
- Maximum ablation depth was lamina propria (LP) or muscularis mucosa (MM) Edema in submucosa at 14 J/cm². of highest energy level 9/10 ablation zones complete ablation of IM and HGD 1/10 viable IM-HGD at margin of zones (12 J/cm² x 2): incomplete overlap

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Conclusion

- Barrett’s is a common disease
- Barrett’s progresses to HGD/EAC (1.4%/pt/yr)
- Removal of IM may be comparable to removal of colon polyps in terms of cancer prevention and avoidance of esophagectomy
- Challenges in past (stricture and buried glands)
- New ablation technology
  - Controlled ablation depth for removing IM/dysplasia
  - Complete elimination possible without stricture formation or buried glands
  - Multi-center, randomized, sham-controlled trial prepared to start in Jan 2006 for LGD and HGD management