Asthma, GERD and Laryngeal Pharyngeal Reflux (LPR)

Richard F. Lockey, M.D.
Division of Allergy and Immunology
Department of Internal Medicine
University of South Florida
College of Medicine
and
James A. Haley Veterans’ Medical Center
Tampa, Florida
Outline

1. Definition and Description
2. Symptoms
3. Prevalence and Impact
4. Pathogenesis
5. Complications
6. Diagnosis
7. GERD and Upper Airway Disorders
8. GERD and Asthma
9. Management
Outline

1. Definition and Description
2. Symptoms
3. Prevalence and Impact
4. Pathogenesis
5. Complications
6. Diagnosis
7. GERD and Upper Airway Disorders
8. GERD and Asthma
9. Management
Definitions

• GER: backflow of stomach contents into the esophagus, usually acidic
• GERD: abnormal GER
  – DeMeester score with pH probe
  – Dobhan criteria for proximal GERD
  – May result in inflammation of esophagus
• LPR: laryngopharyngeal reflux
Definition of GERD – Genval Workshop

• “The term GERD should be used to include all individuals who are exposed to the risk of physical complications from gastroesophageal reflux, or who experience clinically significant impairment of health-related well-being (quality of life) due to reflux-related symptoms, after adequate reassurance of the benign nature of their symptoms”

Heartburn

- Heartburn is the most common manifestation of GERD
- The word ‘heartburn’ is often misinterpreted by patients\(^1\)
- Description of heartburn as “a burning feeling rising from the stomach or lower chest up towards the neck” can help patients to recognize this symptom\(^1\)
- When heartburn is the main or only symptom experienced by a patient, it is strongly suggestive of the presence of GERD\(^2\)

\(^1\)Carlsson et al. Scand J Gastroenterol 1998
\(^2\)Klauser et al. Lancet 1990
Typical symptoms of GERD other than heartburn

- Regurgitation (GER) = an effortless return of gastric contents into the esophagus and frequently into the mouth; often confused with vomiting

- Dysphagia = difficulty swallowing

Younes and Johnson. Gastroenterol Clin North Am 1999
• Laryngopharyngeal Reflux: a form of gastroesophageal reflux disease that produces prominent symptoms and signs in the pharynx and larynx characterized by acute, chronic, and intermittent laryngitis and pharyngitis.

http://www.medilexicon.com/medicaldictionary.php

December 1, 2010
1. Definition and Description
2. Symptoms
3. Prevalence and Impact
4. Pathogenesis
5. Complications
6. Diagnosis
7. GERD and Upper Airway Disorders
8. GERD and Asthma
9. Management
Atypical symptoms of GERD

- Throat clearing
- Globus
- Laryngospasm
- Dental erosion

- Chest pain
- Hoarseness
- Chronic cough
- Sore throat
- Wheezing

\(^1\) Mujica et al. Postgrad Med 1999
\(^2\) DeVault et al. Am J Gastroenterol 1999
Symptom patterns in GERD

- Reflux-related symptoms occur predominantly after meals
- Reflux-related symptoms are often triggered by
  - unusually large meals
  - fatty, spicy, or acidic foods
  - bending, stooping, or lying down
  - lifting, straining, or other strenuous activities
- The frequency of reflux-related symptoms varies widely

Johnsson et al. Gullet 1992
Distribution of GERD symptoms over 24 hours

Number of episodes of reflux symptoms/hour (mean x $10^2$)

Time of day

Breakfast  | Lunch  | Dinner

6 am  | 9 am  | 12 noon  | 3 pm  | 6 pm  | 9 pm  | 12 midnight  | 3 am  | 6 am

Johnsson et al. Gullet 1992

n = 105
Outline

1. Definition and Description
2. Symptoms
3. Prevalence and Impact
4. Pathogenesis
5. Complications
6. Diagnosis
7. GERD and Upper Airway Disorders
8. GERD and Asthma
9. Management
Prevalence of GERD worldwide

- **Italy**: 8% Heartburn, 10% Regurgitation (n = 999)
- **Japan**: 10% Heartburn, 4% Regurgitation (n = 500)
- **Scandinavia**: 14% Heartburn, 10% Regurgitation (n = 1010)
- **Canada**: 17% Heartburn, 11% Regurgitation (n = 1036)
- **United States**: 22% Heartburn, 18% Regurgitation (n = 1020)

Stanghellini. Scand J Gastroenterol 1999
Age-adjusted prevalence of GERD symptoms: the DIGEST study

The proportion of respondents experiencing symptoms increased significantly with age ($P<0.001$).

N=5581

Includes all respondents from US, Canada, European countries, and Japan.

Stanghellini. Scand J Gastroenterol 1999
Frequency of heartburn

- Daily: 21.5%
- 1/week: 11.3%
- >1/week: 24.4%
- >1/month: 16.5%
- 1/month: 11.5%
- <1/month: 13.8%

Oliveria et al. Arch Intern Med 1999
Severity of GERD symptoms does not correlate with severity of disease

Levine et al. Am J Gastroenterol 1999
Approximately half of all patients with reflux symptoms have erosive esophagitis.

Patients presenting with reflux symptoms (n = 97)

- Erosive esophagitis: 46%
- No erosive esophagitis: 42%
- Barrett’s esophagus: 12%

Winters et al. Gastroenterology 1987
Symptoms are not reliably predictive of mucosal damage

- Patients with and without erosive esophagitis are similar with respect to symptom severity\(^1\)
- Patients with and without erosive esophagitis are similar with respect to symptom frequency\(^1\)
- Patients with different grades of erosive esophagitis are similar with respect to symptom severity\(^2\)

\(^1\)Smout. Aliment Pharmacol Ther 1997
\(^2\)Lundell et al. Gut 1999
Outline

1. Definition and Description
2. Symptoms
3. Prevalence and Impact
4. Pathogenesis
5. Complications
6. Diagnosis
7. GERD and Upper Airway Disorders
8. GERD and Asthma
9. Management
Pathogenesis of GERD – overview

• GERD results from exposure of the esophageal mucosa to refluxed gastric contents

• In most patients with GERD, exposure of the esophagus to refluxate is greater than normal

• In a minority of patients, exposure is within normal limits; in these patients, GERD may be due to decreased mucosal resistance to refluxate

\(^1\) DeVault et al. Am J Gastroenterol 1999  
\(^2\) Dent et al. Gut 1998  
\(^3\) Shi et al. Gut 1995
Defective esophageal clearance

- Ineffective peristalsis
- Reduced salivary secretion
- Reduced secretion from esophageal submucosal glands
LES ‘dysfunction’

- Inappropriate and prolonged transient relaxations
- Reduction in basal LES pressure/tone
Hiatal hernia

- May trap a reservoir of gastric contents above the diaphragm, increasing reflux
- May compromise LES function
Increased intra-abdominal pressure

- Pregnancy
- Obesity
- Bending
- Straining
- Coughing
- Tight clothes
Delayed gastric emptying

- May result in an increase in the volume of gastric contents available for reflux into the esophagus
- Exact role in GERD remains to be clarified
Causes of increased exposure of the esophagus to gastric refluxate

- Defective esophageal clearance
- Hiatal hernia
- Lower esophageal sphincter (LES) 'dysfunction'
- Delayed gastric emptying
- Increased intra-abdominal pressure
Medications that may aggravate GERD symptoms by damaging the esophageal mucosa

- Tetracycline
- Quinidine
- Potassium chloride tablets
- Iron salts
- Aspirin and other NSAIDs
- Bisphosphonates
Medications that may aggravate GERD symptoms by impairing LES function

- **β-adrenergic agonists**
- **Theophylline**
- **Anticholinergics**
- **Tricyclic antidepressants**
- **Progesterone**
- **α-adrenergic antagonists**
- **Diazepam**
- **Calcium channel blockers**
Outline

1. Definition and Description
2. Symptoms
3. Prevalence and Impact
4. Pathogenesis
5. Complications
6. Diagnosis
7. GERD and Upper Airway Disorders
8. GERD and Asthma
9. Management
Complications of GERD

• Esophageal
  – Barrett’s esophagus
  – adenocarcinoma
  – stricture
  – ulceration
  – bleeding

• Extra-esophageal
  – asthma
  – reflux laryngitis
  – vocal cord ulcers
  – subglottic stenosis
  – tracheal stenosis
Outline

1. Definition and Description
2. Symptoms
3. Prevalence and Impact
4. Pathogenesis
5. Complications
6. Diagnosis
7. GERD and Upper Airway Disorders
8. GERD and Asthma
9. Management
Diagnostic methods in GERD

- History
- Rhinoscopy
- Endoscopy
- Empiric therapy
- pH monitoring
- Radiology
History

- History-taking is the primary diagnostic tool for GERD
- Typical GERD can usually be diagnosed on the basis of history alone
Outline

1. Definition and Description
2. Symptoms
3. Prevalence and Impact
4. Pathogenesis
5. Complications
6. Diagnosis
7. GERD and Upper Airway Disorders
8. GERD and Asthma
9. Management
GERD and Chronic Rhinosinusitis

• Upper respiratory symptoms frequent among subjects with symptomatic GERD Dx’d by esophageal study

• GERD associated with chronic rhinosinusitis in children and adults

DiBaise et al. *Ann Int Med* 1998;1291078-83
GERD and Upper Airway Disorders
Factors Associated with GERD

• Lifestyle issues
  – EtOH, cigarette smoking
• Obesity
• Medications
  – Beta agonists, theophylline, first generation antihistamines
• Food
  – High fat diet
GERD and Upper Airway Disorders

Theodoropoulos DS, Ledford DK, Lockey RF et al. *Am J Respir Crit Care Med* 2001;164:72-76
GERD and Upper Airway Disorders
Pathophysiology

• Direct irritation by acid
• Neurogenic reflex (increased vagal tone)
• Neurogenic inflammation
• Visceral sensitivity
GERD and Upper Airway Disorders
Pathophysiology

Increased cholinergic tone mediated via vagus nerve (not limited to the nasal airway)

Visceral sensitivity via vagus nerve

Neurogenic inflammation via vagus nerve and neuropeptides (not limited to hypopharynx)

Stimulation of afferent fibers by refluxate

Vagus nerve

Gastroesophageal reflux

Stomach
GERD and Upper Airway Disorders
Pathophysiology

Theodoropoulos DS, Ledford DK, Lockey RF et al. *Am J Respir Crit Care Med* 2001;164:72-76
GERD and Upper Airway Disorders
Pathophysiology

Odds Ratio of GERD

<table>
<thead>
<tr>
<th>URS Score</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 4</td>
<td>1.5</td>
</tr>
<tr>
<td>= 8</td>
<td>3.8</td>
</tr>
<tr>
<td>= 11</td>
<td>6.8</td>
</tr>
</tbody>
</table>

Theodoropoulos DS, Ledford DK, Lockey RF et al. *Am J Respir Crit Care Med* 2001;164:72-76
GERD and Upper Airway Disorders
Pathophysiology

Upper Airway Symptoms Related to GER or GERD

• Throat clearing
• Voice change
• Hoarseness
• Cough
• Post nasal drip
• Nasal congestion

Theodoropoulos DS, Ledford DK, Lockey RF et al. Am J Respir Crit Care Med 2001;164:72-76
GERD and Upper Airway Disorders

Pathophysiology

Upper Airway Symptoms Possibly Related to GER or GERD

- Rhinorrhea
- Sneezing
- Sinusitis
- Sinus Headache
- Ear ache/fullness
- Otitis media with effusion
- Serous otitis media
- Upper airway itching

Theodoropoulos DS, Ledford DK, Lockey RF et al. *Am J Respir Crit Care Med* 2001;164:72-76
GERD and Upper Airway Disorders
Pathophysiology

Theodoropoulos DS, Ledford DK, Lockey RF et al. *Am J Respir Crit Care Med* 2001;164:72-76

[Diagram showing percentages of various conditions in different areas (Laryngeal, Nasal, Sinus, Pharyngeal, Aural) with statistical significance levels (p=0.001, p=0.02).]
GERD and Upper Airway Disorders

Normal

Larynx with GERD

From www.voiceproblem.org
GERD and Upper Airway Disorders

Belafsky Score for Diagnosis of LPR
(0-4 score for each component)
7 or more is diagnostic of LPR

- Subglottic edema
- Diffuse edema
- Ventricular obliteration
- Granuloma
- Vocal fold edema
- Posterior commissure hypertrophy
Outline

1. Definition and Description
2. Symptoms
3. Prevalence and Impact
4. Pathogenesis
5. Complications
6. Diagnosis
7. GERD and Upper Airway Disorders
8. GERD and Asthma
9. Management
GERD and Asthma

• William Osler noted “… attacks may be due to direct irritation of the bronchial mucosa or … indirectly, too, by reflex influences from the stomach…”.

• Up to 80% of patients with asthma have GERD.

Risk factors for exacerbation of difficult-to-treat asthma

136 subjects

- 39 had 3 severe exacerbations/yr
- 29 had 1 severe exacerbation/yr

Conclusions

1) Odds ratio (OR) associated with 3 exacerbations
   a) severe sinus disease, OR 3.7
   b) GERD, OR 4.9
   c) URIs, OR 6.9
   d) Psychological dysfunction, OR 10.8
   e) Obstructive sleep apnea, OR 3.4

2) All patients with frequent exacerbations had 1/5 while 52% had 3/5

Effects of 24 weeks of lansoprazole on asthma in patients with GERD symptoms

Multicenter, DB, randomized, placebo-controlled trial of 206 subjects with moderate-to-severe asthma with reflux symptoms given lansoprazole, 30 mg bid vs. placebo.

Conclusion

Did not improve symptoms by:

a) Assessment by:
   1) participant
   2) investigator

b) Pulmonary function studies

c) Decrease in albuterol use

But did:

a) Decrease asthma exacerbation

b) Improve quality of life.

Randomized DBPC Study of 770 Subjects with GERD and Asthma

- Randomized to receive esomeprazole 40 mg or P 2x QD for 16 wk
- No statistical difference in morning PEF overall
- Patients with nocturnal symptoms (NOC) improved AM PEF 8.7-L/min (p =0.03) and PM 10.2-L/min (p=0.012) over placebo
- 304 subjects on LABA improved both AM (12.2-L/min, p= 0.017) and PM (11.1-L/min, p =0.024) PEF, if they had GERD and NOC
- Conclusion: esomeprazole improves PEF in patients with asthma and GERD and NOC

- Kiljander TO et al. Am J Respir Crit Care Med 2006;173:1091
Cochrane Data Base Review of GERD Treatment for Asthma in Adults and Children (2006)

• 12 randomized controlled trials of Rx for GERD in adults and children
• 2 independent reviewers
• Interventions included proton pump inhibitors (6), H$_2$ receptor antagonists (5), surgery and conservative management (1)
• Temporal relationship in 4 trials found between asthma and GERD
• Anti-reflux Rx did not consistently improve lung function, asthma symptoms, nocturnal asthma and medication use
• Conclusion: No overall improvement but subgroups may gain benefit
Outline

1. Definition and Description
2. Symptoms
3. Prevalence and Impact
4. Pathogenesis
5. Complications
6. Diagnosis
7. GERD and Upper Airway Disorders
8. GERD and Asthma
9. Management
GERD and Asthma and Upper Airway Disorders

Treatment

• Empiric acid suppression
  – Proton pump inhibitors
  – H2 blockers
• Lifestyle changes
  – Diet
  – Weight loss
  – Cigarette smoking
  – EtOH
  – Elevation head of bed
• Modification of Rxs which aggravate GER
• Increase dose of PPIs after 6-8 weeks
• Confirmatory testing or GI consultation
Life-style modifications

Stop smoking
- Reduce weight
- Elevate head of bed

Modification

Avoid reflux-promoting agents e.g., alcohol, coffee; some foods
- not evidence-based

Eat small meals, no late meals, reduce fat

Consider alternatives to reflux-promoting drugs e.g., theophylline, anticholinergics
Thank you!
Treatment Data on the Use of Proton-Pump Inhibitors and Histamine$_2$-Receptor Antagonists (H$_2$-Blockers)*

- Healing of esophagitis
  - Proton-pump inhibitor
    - Superior to placebo (83% vs. 18%) at 8 wk; NNTB, 1.7
    - Superior to H$_2$-blocker (83% vs. 18%); relative risk, 0.51
    - Superior to H$_2$-blocker (84% vs. 52%); relative risk, 0.51
    - Significant Dose-response effect at 4 wk
      - Low dose vs. standard dose once daily: NNTB, 10
      - Standard dose vs. high dose once daily: NNTB, 25

* Relative risk refers to the probability of treatment failure in the active-treatment group. NNTB denotes number of patients needed to treat to benefit one patient.

Treatment Data on the Use of Proton-Pump Inhibitors and Histamine$_2$-Receptor Antagonists (H$_2$-Blockers)*

- Healing of esophagitis  (cont’d)

  H$_2$-blocker

  Superior to placebo (41% vs. 20%) at 6 wk;
  NNTB, 5

  No significant dose-response effect (standard dose vs. high dose twice daily)

* Relative risk refers to the probability of treatment failure in the active-treatment group. NNTB denotes number of patients needed to treat to benefit one patient.

Treatment Data on the Use of Proton-Pump Inhibitors and Histamine$_2$-Receptor Antagonists (H$_2$-Blockers)*

- Resolution of heartburn†

Esophagitis
- Proton-pump inhibitor superior to placebo (56% vs. 8%) at 4 wk; NNTB 2 to 3
- Proton-pump inhibitor superior to H$_2$ blocker (77% vs. 48%) at 4 to 12 wk
- H$_2$-blocker superior to placebo (56% vs. 45%) at 12 wk
- No significant dose-response effect for proton-pump inhibitor at 4 wk
  - Low dose vs. standard dose once daily: 75% vs. 79%
  - Standard dose vs. high dose once daily: 73% vs. 76%

* Relative risk refers to the probability of treatment failure in the active-treatment group.
NNTB denotes number of patients needed to treat to benefit one patient.
† Resolution of heartburn is generally defined as no symptoms for 7 days.
Treatment Data on the Use of Proton-Pump Inhibitors and Histamine\textsubscript{2}-Receptor Antagonists (H\textsubscript{2}-Blockers)*

- Resolution of heartburn\textsuperscript{†} (cont’d)

Patients without known esophagitis

Proton-pump inhibitor superior to placebo (36.7\% vs. 9.5\%); NNTB, 3 to 4

Proton-pump inhibitor superior to H\textsubscript{2}-blocker (61\% vs. 40\%); NNTB, 5

H\textsubscript{2}-blocker superior to placebo (relative risk, 0.77; 95\% CI, 0.60 to 0.99)

No significant dose-response effect for H\textsubscript{2}-blocker at 8 wk%

Standard dose vs. high dose twice daily: 45.8\% vs. 44.8\%

*Relative risk refers to the probability of treatment failure in the active-treatment group. NNTB denotes number of patients needed to treat to benefit one patient.

\textsuperscript{†}Resolution of heartburn is generally defined as no symptoms for 7 days.

Treatment Data on the Use of Proton-Pump Inhibitors and Histamine$_2$-Receptor Antagonists (H$_2$-Blockers)*

- Maintenance therapy‡
  Remission of esophagitis
    Proton-pump inhibitor superior to placebo (93% vs. 29%)
    Low dose of proton-pump inhibitor sufficient in 35 to 95% of patients

- Remission of heartburn
  Acceptable symptom control with low-dose, intermittent therapy with proton-pump inhibitor in 83 to 92% of patients without esophagitis

*Relative risk refers to the probability of treatment failure in the active-treatment group.
NNTB denotes number of patients needed to treat to benefit one patient
‡The duration of maintenance therapy was 6 to 12 months
Consultation for GERD

1. Typical reflux
   a. If surgery contemplated, gastroenterology consult indicated
   b. If patient not responding to therapy
   c. If patient has any suspected complication (stricture, carcinoma, Barrett’s esophagus)
   d. Promotility therapy
Summary
GERD: Therapeutic approaches

- Life-style modifications
- Antacids and alginate
- Surgery
- H$_2$RA
- PPI
GERD and Upper Airway Disorders

Treatment

Algorithm for Treatment of Upper Airway Symptoms Associated with GERD

Initial Assessment
(Clinical profile, absence of other explanations of symptoms)

Empiric Therapeutic Trial
(Lifestyle, Diet, Change medications, PPI)

4 - 6 weeks of treatment

- Symptoms resolve diagnosis confirmed
  - Titrate and discontinue PPI over 2-6 months

- Symptoms improve
  - Maintain treatment for 4-6 wks and reassess

- Symptoms unchanged or minimally improved
  - Nasolaryngoscopy, if not done
GERD – two main categories

• GERD with erosive esophagitis

• GERD without erosive esophagitis = NERD (non-erosive reflux disease)
Patients experiencing daily heartburn at baseline and after 4 weeks of treatment

Venables et al. Scand J Gastroenterol 1997

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Baseline</th>
<th>After 4 weeks of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI</td>
<td>49%</td>
<td>8%</td>
</tr>
<tr>
<td>H₂RA</td>
<td></td>
<td>19%</td>
</tr>
</tbody>
</table>
The prevalence of GERD is widely underestimated

- Only a minority of patients with symptoms of GERD seek medical help\(^1\)
- Patients with symptoms of GERD are often misdiagnosed\(^2\)

\(^1\)A Gallup survey on heartburn across America. 1988
\(^2\)Jones et al. Gut 1990
What is the role of lifestyle factors in GERD?

• Contrary to commonly held opinion, lifestyle factors are not a dominant element in the pathogenesis of erosive esophagitis\(^1\)

• More research is needed to determine the role of lifestyle factors in endoscopy-negative reflux disease\(^1\)

• Lifestyle factors that may contribute to GERD include:
  – smoking
  – certain foods and drinks
  – certain medications

\(^1\)Dent et al. Gut 1998
Dietary factors that may aggravate GERD symptoms

- Caffeinated products
- Peppermint
- Fatty foods
- Chocolate

- Spicy foods
- Citrus fruits and juices
- Tomato-based products
- Alcohol
Helicobacter pylori in GERD

- Infection with *H pylori* may cause a variety of gastric diseases

- In the context of GERD, however, there is controversy regarding symptom improvement after therapy to eradicate *H pylori*
Radiology

• Now considered to be of very limited practical value in the diagnosis of GERD\(^1\)
• May be helpful in the detection of subtle strictures and hiatal hernias in patients with dysphagia
• May be helpful in identifying pathologies unrelated to GERD

\(^1\text{Dent et al. Gut 1998}\)
A. Therapy for Mild GERD

1. Mild or PRN GERD
   a. Life-style changes

Saco LS et al. Gastroenterology 1982;82:1369-73
B. Therapy for Mild to Moderate GERD (cont’d)

1. Histamine type-2 receptor antagonists (H$_2$RAs) standard of care
d. They can be used interchangeably
e. OTC H$_2$RAs are particularly useful before heavy meal or exercise or activity that potentiates reflux
f. Famotidine 10 mg taken before evening meal demonstrated to prevent reflux and restore sleep in patients awaked by GERD(1)

B. Therapy for Mild to Moderate GERD  (cont’d)

1. Histamine type-2 receptor antagonists
   g. Antacids provide more rapid response
   h. The peak potency of OTC H$_2$RAs and antacids are similar but H$_2$RAs last up to 10 hours
### Characteristics of the Proton Pump Inhibitors (PPIs)

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Esomeprazole</th>
<th>Lansoprazole</th>
<th>Omeprazole</th>
<th>Pantoprazole</th>
<th>Rabeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trade Name (Mfr.)</strong></td>
<td>Nexium (AstraZeneca)</td>
<td>Prevacid (TAP)</td>
<td>Prilosec (AstraZeneca)</td>
<td>Protonix (Wyeth)</td>
<td>Aciphex (Eisai, Janssen)</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hyper-sensitivity to the drug or another benzimidazole PPI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most common adverse events</td>
<td>Headache (4%) Diarrhea (4%) Abdominal pain (2%)</td>
<td>Diarrhea (4%) Abdominal pain (2%)</td>
<td>Headache (7%) Diarrhea (3%)</td>
<td>Headache (6%) Diarrhea (4%) Flatulence (2%)</td>
<td>Headache (2%)</td>
</tr>
</tbody>
</table>

*Events equal or higher than placebo*

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Esomeprazole</th>
<th>Lansoprazole</th>
<th>Omeprazole</th>
<th>Pantoprazole</th>
<th>Rabeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy Category</td>
<td>B</td>
<td>B</td>
<td>C</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Pediatric use (minimum age for which use is indicated)</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Primarily via CYP2C19</td>
<td>Primarily via CYP3A and CYP2C19</td>
<td>Primarily via CYP2C19 and CYP3A4; undergoes extensive presystemic metabolism</td>
<td>Primarily via CYP2C19 and CYP3A4</td>
<td>Primarily via CYP3A and CYP2C19</td>
</tr>
</tbody>
</table>

a Events equal or higher than placebo

### Characteristics of the (PPIs)

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Esomeprazole</th>
<th>Lansoprazole</th>
<th>Omeprazole</th>
<th>Pantoprazole</th>
<th>Rabeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trade Name (Mfr.)</strong></td>
<td>Nexium (AstraZeneca)</td>
<td>Prevacid (TAP)</td>
<td>Prilosec (AstraZeneca)</td>
<td>Protonix (Wyeth)</td>
<td>Aciphex (Eisai, Janssen)</td>
</tr>
<tr>
<td><strong>Drug interactions with:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzo-diazepines that are metabolized by oxidation (eg, diazepam, triazolam)</td>
<td>Clearance of diazepam is reduced 45%</td>
<td>Interaction not likely</td>
<td>Clearance of benzo-diazepine is Reduced</td>
<td>Interaction not likely</td>
<td>Interaction not likely</td>
</tr>
<tr>
<td>Cilostazol</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Plasma concentration of cilostazol may be increased</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Concentration of cyclosporine may be increased</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Esomeprazole</th>
<th>Lansoprazole</th>
<th>Omeprazole</th>
<th>Pantoprazole</th>
<th>Rabeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade Name (Mfr.)</td>
<td><strong>Nexium</strong> (AstraZeneca)</td>
<td><strong>Prevacid</strong> (TAP)</td>
<td><strong>Prilosec</strong> (AstraZeneca)</td>
<td><strong>Protonix</strong> (Wyeth)</td>
<td><strong>Aciphex</strong> (Eisai, Janssen)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Not reported</td>
<td>Not reported</td>
<td>AUC of digoxin may be increased</td>
<td>Not reported</td>
<td>AUC of digoxin is increased 19%</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Absorption and activity of itraconazole may be reduced</td>
<td>Absorption and activity of itraconazole may be reduced</td>
<td>Bioavailability of itraconazole is reduced</td>
<td>Absorption and activity of itraconazole may be reduced</td>
<td>Absorption and activity of itraconazole may be reduced</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Absorption and activity of ketoconazole may be reduced</td>
<td>Absorption and activity of ketoconazole may be reduced</td>
<td>Absorption and activity of ketoconazole may be reduced</td>
<td>Absorption and activity of ketoconazole may be reduced</td>
<td>Bioavailability of ketoconazole is reduced 30%</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Interaction not likely</td>
<td>Interaction not likely</td>
<td>Clearance of phenytoin is reduced</td>
<td>Interaction not likely</td>
<td>Interaction not likely</td>
</tr>
</tbody>
</table>

# Characteristics of the PPIs

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Esomeprazole</th>
<th>Lansoprazole</th>
<th>Omeprazole</th>
<th>Pantoprazole</th>
<th>Rabeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade Name (Mfr.)</td>
<td><strong>Nexium</strong> (AstraZeneca)</td>
<td><strong>Prevacid</strong> (TAP)</td>
<td><strong>Prilosec</strong> (AstraZeneca)</td>
<td><strong>Protonix</strong> (Wyeth)</td>
<td><strong>Aciphex</strong> (Eisai, Janssen)</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>Should administer at least 30 minutes before sucralfate</td>
<td>Bioavailability of lansoprazole is reduced 17%; should administer at least 30 minutes before sucralfate</td>
<td>Bioavailability of omeprazole is reduced 16%; should administer at least 30 minutes before sucralfate</td>
<td>Should administer at least 30 minutes before sucralfate</td>
<td>Should administer at least 30 minutes before sucralfate</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Interaction not likely</td>
<td>Clearance of theophylline is increased 10%</td>
<td>Interaction not likely</td>
<td>Interaction not likely</td>
<td>Interaction not likely</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Interaction not likely</td>
<td>Interaction not likely</td>
<td>Clearance of warfarin is reduced</td>
<td>Interaction not likely</td>
<td>Interaction not likely</td>
</tr>
</tbody>
</table>

## Characteristics of the (PPIs)

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Esomeprazole</th>
<th>Lansoprazole</th>
<th>Omeprazole</th>
<th>Pantoprazole</th>
<th>Rabeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration with food</td>
<td>Should be administered at least 1 hour before a meal</td>
<td>Should be administered before eating</td>
<td>Should be administered before eating</td>
<td>May be administered without regard to food</td>
<td>Has not been evaluated; should be administered after the morning meal in the treatment of duodenal ulcer</td>
</tr>
<tr>
<td>Recommended dosage adjustments precautions in special populations</td>
<td>Do not exceed a dosage of 20 mg once a day in patients with severe hepatic impairment</td>
<td>Dosage reduction should be considered in patients with severe hepatic impairment</td>
<td>Dosage reduction should be considered in patients with hepatic impairment and in Asian patients</td>
<td>Caution must be exercised in patients with severe hepatic impairment</td>
<td>Caution must be exercised in patients with severe hepatic impairment</td>
</tr>
</tbody>
</table>

## Characteristics of the (PPIs)

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Esomeprazole</th>
<th>Lansoprazole</th>
<th>Omeprazole</th>
<th>Pantoprazole</th>
<th>Rabeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trade Name (Mfr.)</strong></td>
<td>Nexium (AstraZeneca)</td>
<td><strong>Prevacid</strong> (TAP)</td>
<td><strong>Prilosec</strong> (AstraZeneca)</td>
<td><strong>Protonix</strong> (Wyeth)</td>
<td>Aciphex (Eisai, Janssen)</td>
</tr>
<tr>
<td><strong>Products</strong></td>
<td>Delayed-release capsules containing enteric-coated pellets: 20 mg, 40 mg</td>
<td>Delayed-release capsules containing enteric-coated granules: 15 mg, 30 mg Unit-dose packets containing enteric-coated granules for delayed-release oral suspension: 15 mg, 30 mg</td>
<td>Delayed-release capsules containing enteric-coated granules: 10 mg, 20 mg, 40 mg</td>
<td>Delayed-release enteric-coated tablets: 20 mg, 40 mg (following reconstitution and dilution, administered by intravenous infusion over a period of approximately 15 minutes)</td>
<td>Delayed-release enteric-coated tablets: 20 mg</td>
</tr>
</tbody>
</table>

### Characteristics (contd.)

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Esomeprazole</th>
<th>Lansoprazole</th>
<th>Omeprazole</th>
<th>Pantoprazole</th>
<th>Rabeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade Name (Mfr.)</td>
<td>Nexium (AstraZeneca)</td>
<td>Prevacid (TAP)</td>
<td>Prilosec (AstraZeneca)</td>
<td>Protonix (Wyeth)</td>
<td>Aciphex (Eisai, Janssen)</td>
</tr>
<tr>
<td>Capsules or tablets should not be opened/split, chewed, or crushed</td>
<td>Yes(^b)</td>
<td>Yes(^c)</td>
<td>Yes</td>
<td>Yes(^d)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

\(^b\) Contents can be mixed with applesauce without chewing.

\(^c\) Contents can be sprinkled on applesauce, etc., or mixed in juice. Oral suspension used in 2 tbsp. water, stirred and swallowed immediately. With nasogastric tube, capsule can be mixed in 40 ml of juice.

\(^d\) Injection formulation administered IV.

E. Promotility Therapy for GERD

1. Cisapride (Propulsid®) and metoclopramide (Reglan®). Cisapride removed from market.
   a. These have efficacy similar to standard-dose H₂RAs
   b. Metoclopramide has been associated with drowsiness, irritability, extra-pyramidal effects (1)

E. Promotility Therapy for GERD (cont’d)

1. Cisapride and metoclopramide
   c. Cisapride provides symptomatic relief and healing of esophagitis with results comparable to cimetidine 400 mg q.i.d. or ranitidine 150 mg b.i.d. and superior to placebo

Lepoutre L et al. Digestion 1990;45:109-14
E. Promotility Therapy for GERD (cont’d)

1. Cisapride and metoclopramide
   d. Combined therapy (cimetidine and either metoclopramide, 10 mg q.i.d. or cisapride, 10 mg q.i.d.) cause improved healing of esophagitis compared with cimetidine alone

E. Promotility Therapy for GERD (cont’d)

1. Cisapride and metoclopramide

   e. Cisapride may be an effective maintenance therapy for GERD

Blum AL et al. Dig Dis Sci 1993;38:551-60
E. Promotility Therapy for GERD (cont’d)

1. Cisapride and metoclopramide
   f. Combination of cisapride and ranitidine superior to ranitidine alone but inferior to omeprazole alone

E. Promotility Therapy for GERD (cont’d)

1. Cisapride and metoclopramide
   g. Fatal dysrhythmias associated with the combination of cisapride and medications metabolized by cytochrome P-450 (antifungal agents and some antimicrobials)

Chan-Tompkins NH et al. Clin Infect Dis 1997;24:1285
E. Promotility Therapy for GERD (cont’d)

1. Cisapride and metoclopramide
   h. PPIs provide greater control of acid reflux with minimal risk and no cardiac rhythm disturbances
A. Therapy for Mild GERD (con’t)

1. Mild or PRN GERD
   b. Antacids and over-the-counter acid suppressants

Comment: Alginic acid more effective than placebo (Gaviscon®)

A. Therapy for Mild GERD (cont’d)

1. Mild or PRN GERD
   
c. Combined antacid/alginate acid therapy may be superior to antacids alone

A. Therapy for Mild GERD (cont’d)

1. Mild or PRN GERD

d. Efficacy proven in approximately 20% of patients using these OTC agents

Lieberman DA. Arch Intern Med 1987;147:717-20
Gauchos and Cowboys

- Courage is being scared to death – but saddling up anyway.

- El coraje tiene miedo a morir, pero sigamos cabalgando

--- John Wayne
(1907 – 1979)
• Asthma Clinic Research Center – network of academic asthma research centers – constituted and funded by the American Lung Association (ALA)

• Purpose: conduct clinical trials in asthma relevant to practical questions about treatment
Acid Reflux in Children with Asthma

- **Hypothesis**: children (6-17 yo) with symptomatic asthma have improved asthma control with medical treatment of esophageal reflux using proton-pump inhibitor (PPI), lansoprazole, compared to placebo-treated children.

- **General Goal**: enroll children with poor asthma control whom asthma physicians might consider evaluating for GERD or treatment with a PPI

- **Eligible children may be identified by**: screening at participating centers, existing patient registries, advertisements, or referrals.

- **USF Division Allergy/Immunology**: 4 enrolled patients – 2 have randomized to study medication. Recruitment until 2011.
GERD is a common and significant problem

Lockey et al. Gastroenterology 1997

Prevalence (%) vs Age (years)

- Males
- Females

Any episode of GERD symptoms
At least weekly episodes of GERD symptoms

Prevalence (%) range:
- 0 to 80

Age ranges:
- 25 - 34
- 35 - 44
- 45 - 54
- 55 - 64
- 65 - 74

Lockey et al. Gastroenterology 1997
Multi-Center DBPC of 207 Patients with GERD Symptoms and Moderate to Severe Asthma

• Lansoprazole 30 mg BID or placebo BID for 24 weeks
• Asthma symptoms, albuterol use, PEF, FEV1, FVC, and investigator-assessed asthma Sx at 24 wks did not improve
• The asthma quality-of-life with standardized activities improved (p=0.025)
• Exacerbations (p=0.17) and oral corticosteroid-treated exacerbations (p=0.016) improved
• Conclusions: In adult patients with moderate to severe asthma, lansoprazole BID reduced asthma exacerbations and improved QOL, particularly in patients receiving more than one asthma-control medication

• Littner MR. Chest 2005;128;1128
C. Therapy for Moderate to Severe GERD (cont’d)

1. H₂RAs in divided doses are effective treatment in many patients with less severe GERD.

   e. H₂RAs at these doses still inferior to proton pump inhibitors (PPI) and more costly at high doses

Euler Ar et al. Am J Gastroenterol 1993;88:520-4
D. Proton Pump Inhibitors (PPIs) (cont’d)

2. Concerns about PPIs
   a. PPIs decrease gastric acid secretion (1)
   b. This leads to increased gastrin production from antral-G cells and increased serum gastrin levels (2 to 4 times basal) (2)
   c. Question whether or not these changes in serum gastrin may produce dangerous trophic effects on gastric mucosa

(1) Klinkenburg-Kriol EC et al. Gastroenterology 1990;99:621-8
(2) Jansen JB. Gastroenterology 1990;99:621-8
D. Proton Pump Inhibitors (PPIs) (cont’d)

2. Concerns about PPIs
   d. Omeprazole and lanzoprazole are approved for 1 yr of continuous usage
   e. No cases of gastric carcinoid tumor in patients receiving PPIs
   f. Atrophic gastritis not reported with long-term omeprazole
D. Proton Pump Inhibitors (PPIs) (cont’d)

2. Concerns about PPIs
   
g. Cobalamin absorption may be decreased with chronic PPI but no change in serum levels reported after 7 yr of therapy (1)
   
h. No evidence of bacterial overgrowth after long-term acid suppression (2)
   
i. Potential benefit of chronic PPI therapy outweighs risk in patients with chronic or complicated GERD

(2) Hutchinson S et al. Age Ageing 1997;26:87-9
- Esophagitis occurs when excessive reflux of acid and pepsin results in necrosis of surface layers of esophageal mucosa, causing erosions and ulcers. Impaired clearance of the refluxed gastric juice from the esophagus also contributes to damage in many patients. Whereas some gastroesophageal reflux is normal (and relates to the ability to belch), several factors may predispose patients to pathologic reflux, including hiatus hernia, lower esophageal sphincter hypotension, loss of esophageal peristaltic function, abdominal obesity, increased compliance of the hiatal canal, gastric hypersecretory states, delayed gastric emptying, and overeating. Often multiple risk factors are present.

The pyramid of diseases associated with GERD

- Erosive esophagitis
- Non-erosive reflux disease
- Chest pain
- ENT
- Asthma
- Misc

Prevalence of GERD

0% → Yes
100% → No

Need to investigate role of acid

Richter. Am J Gastroenterol 2000
Reflux disease questionnaire

• The patient grades the frequency and severity over the previous 4 weeks of
  – a burning feeling behind the breastbone
  – pain behind the breastbone
  – an acid taste in the mouth
  – unpleasant movement of material upwards from the stomach
When is history not enough?

- Additional diagnostic procedures are indicated if
  - the history is atypical and the diagnosis of GERD is uncertain
  - alarm symptoms are present
  - symptoms are frequent and long-standing
  - symptoms do not respond to therapy
  - continuous chronic therapy is needed
Alarm symptoms suggesting early work-up

- Dysphagia
- Bleeding
- Weight loss
- Choking, chronic cough, shortness of breath, or hoarseness
- Chest pain
Endoscopy

- Allows direct visualization of the esophageal mucosa and biopsy if necessary
- The technique of choice for determining the presence and severity of erosive esophagitis
- The only reliable method for the detection of Barrett’s esophagus

DeVault et al. Am J Gastroenterol 1999
pH monitoring

• Allows investigation of
  – the amount and timing of reflux
  – the correlation between reflux and symptoms
  – the effect of therapy on reflux

• In general, most useful in
  – endoscopy-negative patients
  – patients with chest pain or pulmonary/upper respiratory symptoms
  – patients with refractory symptoms

¹DeVault et al. Am J Gastroenterol 1999
Treatment of GERD

A. Therapy for Mild GERD
B. Therapy for Mild to Moderate GERD
C. Therapy for Moderate to Severe GERD
D. Proton Pump Inhibitors (PPIs)
E. Promotility Therapy for GERD
F. Maintenance Therapy for GERD
G. Surgical Therapy for GERD
H. Consultation for GERD
I. Barrett’s Esophagus
J. Refractory to Therapy
B. Therapy for Mild to Moderate GERD

1. Histamine type-2 receptor antagonists (H₂RAs) standard of care
   a. Four H₂RAs available by prescription
      1) Ranitidine (Zantac®), 150 or 300 mg
      2) Ninatizine (Axid®), 150 or 300 mg
      3) Famotidine (Pepsid AC®), 10 mg
      4) Cimetidine (Tagamet®), 300, 400 mg
   b. The doses OTC usually one-half of standard lowest prescription dose
   c. Doses shown to decrease gastric acid, particularly post-perennial
Treatment of GERD

A. Therapy for Mild GERD
B. Therapy for Mild to Moderate GERD
C. Therapy for Moderate to Severe GERD
D. Proton Pump Inhibitors (PPIs)
E. Promotility Therapy for GERD
F. Maintenance Therapy for GERD
G. Surgical Therapy for GERD
H. Consultation for GERD
I. Barrett’s Esophagus
J. Refractory to Therapy
Treatment of GERD

A. Therapy for Mild GERD
B. Therapy for Mild to Moderate GERD
C. Therapy for Moderate to Severe GERD
D. Proton Pump Inhibitors (PPIs)
E. Promotility Therapy for GERD
F. Maintenance Therapy for GERD
G. Surgical Therapy for GERD
H. Consultation for GERD
I. Barrett’s Esophagus
J. Refractory to Therapy
C. Therapy for Moderate to Severe GERD

1. H$_2$RAs in divided doses are effective treatment in many patients with less severe GERD. 
   a. 33 Randomized trials with more than 3,000 patients
   b. Symptomatic relief expected of 27% of placebo-treated and 60% of H$_2$RA-treated
   c. Esophagitis healed in 24% of placebo-treated and 50% of H$_2$RA-treated
   d. Higher doses and more frequent dosing of H$_2$RAs appear more effective
Treatment of GERD

A. Therapy for Mild GERD
B. Therapy for Mild to Moderate GERD
C. Therapy for Moderate to Severe GERD
D. Proton Pump Inhibitors (PPIs)
E. Promotility Therapy for GERD
F. Maintenance Therapy for GERD
G. Surgical Therapy for GERD
H. Consultation for GERD
I. Barrett’s Esophagus
J. Refractory to Therapy
D. Proton Pump Inhibitors (PPIs)

1. Symptomatic relief and esophagitis healed better with PPIs than H₂RAs
   a. Symptomatic relief in 27% of placebo-treated, 60% of H₂RA-treated, and 83% of PPI-treated patients
   b. Esophagitis healed in 24% of placebo-treated, 50% of H₂RA-treated and 78% of PPI-treated
   c. PPIs eliminate and heal esophagitis more frequently and rapidly than other agents
   d. Higher doses and more frequent doses of H₂RAs are more effective but inferior and more costly than PPIs
Treatment of GERD

A. Therapy for Mild GERD
B. Therapy for Mild to Moderate GERD
C. Therapy for Moderate to Severe GERD
D. Proton Pump Inhibitors (PPIs)
E. **Promotility Therapy for GERD**
F. Maintenance Therapy for GERD
G. Surgical Therapy for GERD
H. Consultation for GERD
I. Barrett’s Esophagus
J. Refractory to Therapy
Gastroenterology Consult
Treatment of GERD

A. Therapy for Mild GERD
B. Therapy for Mild to Moderate GERD
C. Therapy for Moderate to Severe GERD
D. Proton Pump Inhibitors (PPIs)
E. Promotility Therapy for GERD
F. Maintenance Therapy for GERD
G. Surgical Therapy for GERD
H. Consultation for GERD
I. Barrett’s Esophagus
J. Refractory to Therapy
F. Maintenance Therapy for GERD

1. GERD is a chronic condition and continuous therapy indicated to prevent complications of GERD (esophagitis, stricture, adenocarcinoma, etc.)
   a. Effective maintenance should control symptoms and prevent complications
   b. Adjustments in medications are necessary

Antonson CW et al. Gastroenterology 1990;98:A16
F. Maintenance Therapy for GERD (cont’d)

1. GERD is a chronic condition and continuous therapy indicated to prevent complications of GERD (esophagitis, stricture, adenocarcinoma, etc.)
   c. Full dose of H₂RA given once daily not effective therapy for GERD
   d. Reduced doses of PPIs have not been shown consistently to be effective for long-term therapy

Bank et al. Gastroenterology 1991;100:A29
F. Maintenance Therapy for GERD (cont’d)

1. GERD is a chronic condition and continuous therapy indicated to prevent complications of GERD (esophagitis, stricture, adenocarcinoma, etc.)

e. PPIs but not H₂RAs prevent recurrent strictures

Marks RD et al. Gastroenterology 1994;106:907-15
Treatment of GERD

A. Therapy for Mild GERD
B. Therapy for Mild to Moderate GERD
C. Therapy for Moderate to Severe GERD
D. Proton Pump Inhibitors (PPIs)
E. Promotility Therapy for GERD
F. Maintenance Therapy for GERD
G. Surgical Therapy for GERD
H. Consultation for GERD
I. Barrett’s Esophagus
J. Refractory to Therapy
G. Surgical Therapy for GERD

1. Antireflux surgery, performed by an experienced surgeon, is a maintenance option for patients with documented GERD.
   a. Two published studies show surgery more effective than medical therapy. (One study compared antacids and lifestyle changes over 36-months. Second study compared surgery versus ranitidine and metoclopramide.)

G. Surgical Therapy for GERD (cont’d)

1. Antireflux surgery, performed by an experienced surgeon, is a maintenance option for patients with documented GERD.

b. Randomized trial 310 patients initially controlled with omeprazole 40 mg per day found surgery to be slightly superior (maintenance of esophagitis healing and symptoms) to omeprazole 20 mg per day at the end of 3 yr period.

Lundell L et al. Gastroenterology 1998;114:A207
G. Surgical Therapy for GERD (cont’d)

1. Antireflux surgery, performed by an experienced surgeon, is a maintenance option for patients with documented GERD.

c. If dose is titrated to 40-60 mg per day of omeprazole medical and surgical treatments equal.
Treatment of GERD

A. Therapy for Mild GERD
B. Therapy for Mild to Moderate GERD
C. Therapy for Moderate to Severe GERD
D. Proton Pump Inhibitors (PPIs)
E. Promotility Therapy for GERD
F. Maintenance Therapy for GERD
G. Surgical Therapy for GERD
H. Consultation for GERD
I. Barrett’s Esophagus
J. Refractory to Therapy
Treatment of GERD

A. Therapy for Mild GERD
B. Therapy for Mild to Moderate GERD
C. Therapy for Moderate to Severe GERD
D. Proton Pump Inhibitors (PPIs)
E. Promotility Therapy for GERD
F. Maintenance Therapy for GERD
G. Surgical Therapy for GERD
H. Consultation for GERD
I. Barrett’s Esophagus
J. Refractory to Therapy
I. Barrett’s Esophagus

Gastroenterology consult
Treatment of GERD

A. Therapy for Mild GERD
B. Therapy for Mild to Moderate GERD
C. Therapy for Moderate to Severe GERD
D. Proton Pump Inhibitors (PPIs)
E. Promotility Therapy for GERD
F. Maintenance Therapy for GERD
G. Surgical Therapy for GERD
H. Consultation for GERD
I. Barrett’s Esophagus
J. Refractory to Therapy
J. Refractory to Therapy

1. Refractory to medical therapy is rare. The diagnosis should be confirmed before high dose acid suppression or antireflux surgery.
   a. This may involve pH study, endoscopic studies, manometric studies. Recent report of 2 patients who had refractory reflux (by pH study and symptoms) while taking omeprazole, who had better acid suppression with high-dose H$_2$-receptor therapy.

Leite LP et al. Am J Gastroenterol 195;90:1874-7
J. Refractory to Therapy (cont’d)

1. Refractory to medical therapy is rare. The diagnosis should be confirmed before high dose acid suppression or antireflux surgery.

b. Cases rare but emphasize need for individualizing therapy.

Primary reference is by DeVault KR, Am J Gastro 1999;94:1434-1442
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Reference</th>
<th>Population size</th>
<th>Study design</th>
<th>Method of data collection</th>
<th>Definition of reflux symptoms</th>
<th>Definition of extra-oesophageal symptom example</th>
<th>Prevalence of extra-oesophageal symptom in children with GERD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory symptoms</td>
<td>El-Serag et al. 12</td>
<td>1980 with GERD + 7980 controls</td>
<td>Association case-controlled study</td>
<td>Database</td>
<td>Physician diagnosis</td>
<td>13.2% vs. 6.8% of controls ($P &lt; 0.0001$)</td>
<td>6.3% vs. 2.3% of controls ($P &lt; 0.0001$)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Tolia et al. 20</td>
<td>173 with GERD + 169 controls</td>
<td>Association case-controlled study</td>
<td>Database</td>
<td>Physician diagnosis</td>
<td>11% vs. 0.1% of controls ($P &lt; 0.0001$)</td>
<td>20% vs. 31% of controls ($P &lt; 0.12$)</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>49% vs. 63% of controls ($P &lt; 0.01$)</td>
</tr>
<tr>
<td>ALTE</td>
<td>Khalaf et al. 25</td>
<td>42 with severe RI + 66 controls</td>
<td>Cross-sectional controlled study</td>
<td>Continuous recording of respiratory rate, heart rate, nasal air flow</td>
<td>Respiratory distress syndrome defined by clinical features and positive chest radiograph</td>
<td>62% vs. 36% of controls ($P = 0.02$)</td>
<td></td>
</tr>
<tr>
<td>General respiratory symptoms</td>
<td>El-Serag et al. 12</td>
<td>1980 with GERD + 7980 controls</td>
<td>Association case-controlled study</td>
<td>Database</td>
<td>Physician diagnosis</td>
<td></td>
<td>4.2% vs. 1.4% of controls ($P &lt; 0.0001$)</td>
</tr>
<tr>
<td>ENT symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.1% vs. 4.6% of controls ($P &lt; 0.0001$)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>Linnett et al. 28</td>
<td>52 with GERD + 52 healthy controls</td>
<td>Prospective controlled study</td>
<td>Dental examination/medical/dental records</td>
<td>WHO criteria for caries</td>
<td>14% had erosion vs. 10% of controls ($P &lt; 0.05$)</td>
<td></td>
</tr>
<tr>
<td>Otitis media</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dental symptoms</td>
<td>Ersin et al. 27</td>
<td>38 with GERD + 42 healthy controls</td>
<td>Cross-sectional controlled study</td>
<td>Questionnaire/dental exam</td>
<td>WHO criteria for caries with Eccles &amp; Jenkins index for erosion by GERD</td>
<td>76% had erosion vs. 10% of controls ($P &lt; 0.0001$)</td>
<td>37% had severe erosion vs. 1% of controls ($P &lt; 0.05$)</td>
</tr>
</tbody>
</table>

ALTE, apparent life-threatening event; ENT, ear, nose and throat; GERD, gastro-oesophageal reflux disease; RI, reflux index (% of total time when pH < 4); WHO, World Health Organization.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Reference</th>
<th>Population Size</th>
<th>Definition of extra-oesophageal symptom</th>
<th>Prevalence of extra-oesophageal symptom in children with GERD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td></td>
<td></td>
<td></td>
<td>13.2% vs. 6.8% of controls (P &lt; 0.0001)</td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>Pneumonia</td>
<td>El-Serag et al.</td>
<td>Physician diagnosis</td>
<td>6.3% vs. 2.3% of controls (P &lt; 0.0001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1980 with GERD + 7980 controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td></td>
<td></td>
<td></td>
<td>1% vs. 0.1% of controls (P &lt; 0.0001)</td>
</tr>
</tbody>
</table>

ALTE, apparent life-threatening event; ENT, ear, nose and throat; GERD, gastro-oesophageal reflux disease; RI, reflux index (% of total time when pH < 4); WHO, World Health Organization

Adapted from Tolia V. *Aliment Pharmacol Ther* 2009;29(3):258-272
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Reference</th>
<th>Population Size</th>
<th>Definition of extra-oesophageal symptom</th>
<th>Prevalence of extra-oesophageal symptom in children with GERD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALTE</td>
<td>Tolia</td>
<td>173 with GERD+</td>
<td>Physician</td>
<td>20% vs. 31% of controls (P &lt; 0.12)</td>
</tr>
<tr>
<td>General respiratory symptoms</td>
<td>et al.</td>
<td>169 controls</td>
<td>diagnosis</td>
<td>49% vs. 63% of controls (P &lt; 0.01)</td>
</tr>
<tr>
<td>General respiratory symptoms</td>
<td>Khalaf et al.</td>
<td>42 with severe RI + 66 controls</td>
<td>Respiratory distress syndrome defined by clinical features and positive chest radiograph</td>
<td>62% vs. 36% of controls (P = 0.02)</td>
</tr>
</tbody>
</table>

Adapted from Tolia V. *Aliment Pharmacol Ther* 2009;29(3):258-272
## Prevalence of Extra-Oesophageal Symptoms in Children with GERD

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Reference</th>
<th>Population Size</th>
<th>Definition of extra-oesophageal symptom</th>
<th>Prevalence of extra-oesophageal symptom in children with GERD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinusitis</td>
<td>El-Serag</td>
<td>1980 with GERD +</td>
<td>Physician</td>
<td>4.2% vs. 1.4% of controls (P &lt; 0.0001)</td>
</tr>
<tr>
<td>Otitis media</td>
<td>et al.</td>
<td>7980 controls</td>
<td>diagnosis</td>
<td>2.1% vs. 4.6% of controls (P &lt; 0.0001)</td>
</tr>
<tr>
<td>Dental erosion</td>
<td>Linnett et al.</td>
<td>52 with GERD + 52 healthy controls</td>
<td>WHO criteria for caries</td>
<td>14% had erosion vs. 10% of controls (P &lt; 0.05)</td>
</tr>
</tbody>
</table>

Adapted from Tolia V. *Aliment Pharmacol Ther* 2009;29(3):258-272
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Reference</th>
<th>Population Size</th>
<th>Definition of extra-oesophageal symptom</th>
<th>Prevalence of extra-oesophageal symptom in children with GERD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental symptoms</td>
<td>Dental erosion</td>
<td>Ersin et al.</td>
<td>WHO criteria for caries Eccles &amp; Jenkins index for erosion by GERD</td>
<td>76% had erosion vs. 10% of controls (P &lt; 0.0001) 37% had severe erosion vs. 1% of controls (P &lt; 0.05)</td>
</tr>
</tbody>
</table>

Adapted from Tolia V.  *Aliment Pharmacol Ther* 2009;29(3):258-272
### Prevalence of GERD in children with extra-oesophageal symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Reference</th>
<th>Population size</th>
<th>Study design</th>
<th>Method of data collection</th>
<th>Definition of extra-oesophageal symptoms</th>
<th>Diagnosis of reflux symptom</th>
<th>Prevalence of GERD in-patients with extra-oesophageal symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>Stordal et al.</td>
<td>872 asthmatics</td>
<td>Cross-sectional controlled study</td>
<td>Questionnaire</td>
<td>GINA classification(^6)</td>
<td>GERD questionnaire(^{13})</td>
<td>19.7% of asthmatics had a positive GERD symptom score vs. 8.5% of controls (odds ratio, 2.6, (P &lt; 0.001))</td>
</tr>
<tr>
<td>Asthma</td>
<td>Barakat et al.</td>
<td>75 asthmatics</td>
<td>Cross-sectional controlled study</td>
<td>Medical history/examination</td>
<td>Physician diagnosis</td>
<td>Endoscopy/ultrasound</td>
<td>GI symptoms in 65% of those with asthma vs. 16% of controls ((P &lt; 0.001))</td>
</tr>
<tr>
<td>Asthma</td>
<td>Chopra et al.</td>
<td>80 asthmatics</td>
<td>Cross-sectional controlled study</td>
<td>Medical examination</td>
<td>(\geq 3) episodes of reversible bronchospasm that lessen after therapy</td>
<td>Presence of scintigraphic reflux on scintiscanning, vs. 0% of controls ((P &lt; 0.05))</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>Hughes et al.</td>
<td>9 asthmatics</td>
<td>Cross-sectional controlled study</td>
<td>Medical examination</td>
<td>ATS criteria for reversible obstructive airway disease</td>
<td>Oesophageal pH monitoring; reflux defined as a decrease in pH to &lt; 4 for at least 15 s</td>
<td></td>
</tr>
</tbody>
</table>

---

Tolia V, Vandenplas Y. Aliment Pharmacol Ther 2009;29(3):258–272
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Reference</th>
<th>Population size</th>
<th>Study design</th>
<th>Method of data collection</th>
<th>Definition of extra-oesophageal symptoms</th>
<th>Diagnosis of reflux symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>Dehley et al.¹⁵</td>
<td>296 asthmatics + 1510 controls</td>
<td>Population-based, cross-sectional controlled study</td>
<td>Questionnaire</td>
<td>Physician diagnosed or a positive response to selected questions on the ISAAC questionnaire⁶²,⁶³</td>
<td>Positive response to selected questionnaire questions</td>
</tr>
<tr>
<td>ALTE</td>
<td>Gorrotxategi et al.²¹</td>
<td>14 infants with ALTE + 10 controls</td>
<td>Cross-sectional controlled study</td>
<td>Medical examination</td>
<td>Defined using guidelines from NIH Consensus Development Conference on infant apnoea</td>
<td>24-h pH monitoring</td>
</tr>
<tr>
<td>ALTE</td>
<td>Kahn et al.²²</td>
<td>20 infants admitted for ALTE + 10 controls</td>
<td>Cross-sectional controlled study</td>
<td>Medical examination</td>
<td>Physician diagnosis</td>
<td>Oesophageal pH monitoring</td>
</tr>
<tr>
<td>ALTE</td>
<td>Kahn et al.²³</td>
<td>50 infants admitted for ALTE + 50 controls</td>
<td>Cross-sectional controlled study</td>
<td>Medical examination</td>
<td>Physician diagnosis</td>
<td>pH &lt; 4 for ≥30 sec</td>
</tr>
<tr>
<td>ALTE</td>
<td>Sacre and Vandenplas²⁴</td>
<td>62 infants with ALTE + 378 controls</td>
<td>Cross-sectional controlled study</td>
<td>Medical examination</td>
<td>Physician diagnosis</td>
<td>24-h pH monitoring</td>
</tr>
<tr>
<td>ENT symptoms</td>
<td>Contencin and Narcy²⁶</td>
<td>8 patients consulting for laryngotraehitis + 6 controls</td>
<td>Cross-sectional controlled study</td>
<td>Medical examination</td>
<td>Physician diagnosis</td>
<td>Dual-channel pH monitoring. Pathological gastro-oesophageal reflux defined as RI &gt; 5.2%</td>
</tr>
</tbody>
</table>

ALTE, apparent life-threatening event; ATS, American Thoracic Society; ENT, ear, nose and throat; GERD, gastro-oesophageal reflux disease; GI, gastrointestinal; GINA, Global Initiative for Asthma; ISAAC, International Study of Asthma and Allergies in Childhood; NIH, National Institutes of Health; RI, reflux index.
## Prevalance of GERD in Children with Extra-Oesophageal Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Reference</th>
<th>Population size</th>
<th>Diagnosis of reflux symptom</th>
<th>Prevalence of GERD in patients with extra-oesophageal symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>Stordal et al.</td>
<td>872 asthmatics + 264 controls</td>
<td>GERD questionnaire</td>
<td>19.7% of asthmatics had a positive GERD symptom score vs. 8.5% of controls (odds ratio, 2.6, ( P &lt; 0.001 ))</td>
</tr>
</tbody>
</table>

ALTE, apparent life-threatening event; ATS, American Thoracic Society; ENT, ear, nose and throat; GERD, gastro-oesophageal reflux disease; GI, gastrointestinal; GINA, Global Initiative for Asthma; ISAAC, International Study of Asthma and Allergies in Childhood; NIH, National Institutes of Health; RI, reflux index

Adapted from Tolia V. *Aliment Pharmacol Ther* 2009;29(3):258-272
# Prevalance of GERD in Children with Extra-Oesophageal Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Reference</th>
<th>Population size</th>
<th>Diagnosis of reflux symptom</th>
<th>Prevalence of GERD in patients with extra-oesophageal symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory symptoms</td>
<td>Barakat et al.</td>
<td>75 asthmatics + 25 controls</td>
<td>Endoscopy / ultrasound</td>
<td>GI symptoms in 65% of those with asthma vs. 16% of controls (P &lt; 0.001)</td>
</tr>
</tbody>
</table>

Adapted from Tolia V. *Aliment Pharmacol Ther* 2009;29(3):258-272
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Reference</th>
<th>Population size</th>
<th>Diagnosis of reflux symptom</th>
<th>Prevalence of GERD in patients with extra-oesophageal symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>Chopra et al.</td>
<td>80 asthmatics + 10 controls</td>
<td>Presence of sciatica tracer in oesophagus in more than two frames</td>
<td>39% of asthmatics demonstrated reflux on scintiscanning vs. 0% of controls (P &lt; 0.05)</td>
</tr>
</tbody>
</table>

Adapted from Tolia V. *Aliment Pharmacol Ther* 2009;29(3):258-272
## Prevalance of GERD in Children with Extra-Oesophageal Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Reference</th>
<th>Population size</th>
<th>Diagnosis of reflux symptom</th>
<th>Prevalence of GERD in patients with extra-oesophageal symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>Hughes et al.</td>
<td>9 asthmatics + 7 controls</td>
<td>Oesophageal pH monitoring; reflux defined as a decrease in pH to &lt; 4 for at least 15 s</td>
<td>Gastro-oesophageal reflux occurred in 33% of asthmatics vs. 57% of controls. No significant difference between the two groups in number or duration of reflux episodes or % of time pH &lt; 4</td>
</tr>
</tbody>
</table>

Adapted from Tolia V. *Aliment Pharmacol Ther* 2009;29(3):258-272
## Prevalance of GERD in Children with Extra-Oesophageal Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Reference</th>
<th>Population size</th>
<th>Diagnosis of reflux symptom</th>
<th>Prevalence of GERD in patients with extra-oesophageal symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>Debley et al.</td>
<td>296 asthmatics + 1510 controls</td>
<td>Positive response to selected questionnaire questions</td>
<td>19.3% of adolescents with current asthma had GERD symptoms vs. 2.5% of adolescents without asthma (P &lt; 0.001)</td>
</tr>
</tbody>
</table>

Adapted from Tolia V. *Aliment Pharmacol Ther* 2009;29(3):258-272
## Prevalance of GERD in Children with Extra-Oesophageal Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Reference</th>
<th>Population size</th>
<th>Prevalence of GERD in patients with extra-oesophageal symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENT symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laryngotracheitis</td>
<td>Contencin and Narcy</td>
<td>8 patients consulting for laryngotracheitis + 6 controls</td>
<td>Dual-channel pH monitoring. Pathological gastro-oesophageal reflux defined as RI &gt; 5.2% 62.5% of patients had pathological gastro-oesophageal reflux vs. 16.6% of controls</td>
</tr>
</tbody>
</table>

Adapted from Tolia V. *Aliment Pharmacol Ther* 2009;29(3):258-272
<table>
<thead>
<tr>
<th>Reference</th>
<th>Population size</th>
<th>Study design</th>
<th>Definition of reflux symptoms</th>
<th>Definition of extra-oesophageal symptom</th>
<th>Drug and dosage</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khosho and Haydel&lt;sup&gt;29&lt;/sup&gt;</td>
<td>44</td>
<td>Investigator-blinded prospective trial</td>
<td>24-h pH monitoring pH &lt; 4 for &gt;5% of the time</td>
<td>Asthma ≥ 3 episodes per year despite optimal treatment</td>
<td>Group A: esomeprazole (40 mg/day)/metoclopramide&lt;br&gt;Group B: ranitidine (150 mg 3 times daily)&lt;br&gt;Group C: control (fundoplication)&lt;br&gt;All had previously had PPI/prokinetic for 1 year</td>
<td>Following 6 months' treatment, group B had significantly more exacerbations than groups A and C</td>
</tr>
<tr>
<td>Jordan et al.&lt;sup&gt;29&lt;/sup&gt;</td>
<td>34</td>
<td>Randomized placebo-controlled trial</td>
<td>Oesophageal 24-h pH monitoring</td>
<td>Physician diagnosis of persistent crying</td>
<td>4 weeks treatment with ranitidine (3 mg/kg, 3 times daily) plus cisapride (0.2 mg/kg, 4 times daily)</td>
<td>Anti-reflux medications were not superior to placebo in treating infants with persistent crying</td>
</tr>
<tr>
<td>Stordal et al.&lt;sup&gt;19&lt;/sup&gt;</td>
<td>38 with asthma</td>
<td>Randomized placebo-controlled trial</td>
<td>Questionnaire/RI ≥ 5 on 24-h pH monitoring</td>
<td>Physician-diagnosed asthma</td>
<td>Omeprazole 20 mg once daily or placebo for 12 weeks</td>
<td>Asthma symptoms scored by two questionnaires did not differ significantly between groups following treatment</td>
</tr>
</tbody>
</table>

PPI, proton pump inhibitor; RI, reflux index.
### Outcomes of GERD Drug Therapy on Extra-Oesophageal Symptoms

<table>
<thead>
<tr>
<th>Reference</th>
<th>Pop. size</th>
<th>Study design</th>
<th>Definition of extra-oesophageal symptom</th>
<th>Drug and dosage</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khosho and Haydel</td>
<td>44</td>
<td>Investigator-blinded prospective trial</td>
<td>Asthma ≥ 3 episodes per year despite optimal treatment</td>
<td>Group A: esomeprazole (40 mg/day) / metoclopramide, Group B: ranitidine (150 mg 3 times daily), Group C: control (fundoplication). All had previously had PPI / prokinetic for 1 year</td>
<td>Following 6 months treatment, group B had significantly more exacerbations than groups A and C</td>
</tr>
</tbody>
</table>

Adapted from Tolia V. *Aliment Pharmacol Ther* 2009;29(3):258-27
Outcomes of GERD Drug Therapy on Extra-Oesophageal Symptoms

<table>
<thead>
<tr>
<th>Reference</th>
<th>Pop. size</th>
<th>Study design</th>
<th>Definition of extra-oesophageal symptom</th>
<th>Drug and dosage</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stordal et al.</td>
<td>38 with asthma</td>
<td>Randomized placebo-controlled trial</td>
<td>Physician-diagnosed asthma</td>
<td>Omeprazole 20 mg once daily or placebo for 12 weeks</td>
<td>Asthma symptoms scored by two questionnaires did not differ significantly between groups following treatment</td>
</tr>
</tbody>
</table>

Adapted from Tolia V. *Aliment Pharmacol Ther* 2009;29(3):258-27