Gastro-esophageal reflux: Burning news?

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Introduction
Symptoms (prevalence)
Diagnosis
Treatment
Conclusions
NASPGHAN-ESPGHAN Guidelines for Evaluation and Treatment of Gastro-Esophageal Reflux in Infants and Children

Y. Vandenplas, C. Rudolph, G. Liptak, M. Lynette, C. Di Lorenzo, E. Hassall,
J. Sondheimer, M. Thomson, A. Staiano, G. Veereman, T. Wenzl

*J Pediatr Gastroenterol Nutr 2009;49:498-547*

Gastroesophageal reflux: management guidance for the pediatrician.

Lightdale JR, Gremse DA; Section on Gastroenterology, Hepatology, and Nutrition.

*Pediatrics. 2013 May;131(5):e1684-95*

This clinical report endorses the rigorously developed, well-referenced North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines and likewise emphasizes important concepts for the general pediatrician.

The overall results of our survey show that the majority of pediatricians are unaware of 2009 NASPGHAN-ESPGHAN guidelines and often prescribe PPIs despite a lack of efficacy for the symptoms being treated.

The over diagnosis of GERD places undue burden on both families and national health systems which has not been impacted by the publication of international guidelines.
Parents who received a GERD diagnosis were interested in medicating their infant, even when they were told that the medications are likely ineffective. However, parents not given a disease label were interested in medication only when medication effectiveness was not discussed (and hence likely assumed).

**Labeling an otherwise healthy infant as having a "disease" increased parents' interest in medicating their infant when they were told that medications are ineffective.**

These findings suggest that use of disease labels may promote overtreatment by causing people to believe that ineffective medications are both useful and necessary.
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A global evidence-based consensus on the definition of GERD in the pediatric population

GERD in pediatric patients is present when reflux of gastric contents is the cause of troublesome symptoms and/or complications

**Symptoms purported to be due to GERD**
- Infant or younger child (0–9 years), or older without cognitive ability to reliably report symptoms

**Symptomatic syndromes**
- Older child or adolescent with cognitive ability to reliably report symptoms

**Syndromes with esophageal injury**
- Typical reflux syndrome
- Reflux esophagitis
- Reflux stricture
- Barret’s esophagus
- Adenocarcinoma

**Definite associations**
- Sandifer’s syndrome
- Dental erosion

**Possible associations**
- Bronchopulmonary
  - Asthma
  - Pulmonary fibrosis
  - Bronchopulmonary dysplasia
- Laryngotracheal pharyngeal
  - Chronic cough
  - Chronic laryngitis
  - Hoarseness
  - Pharyngitis
- Rhinological and otological
  - Sinusitis
  - Serous otitis media
  - Infants
    - Pathological apnea
    - Bradycardia
    - Apparent life-threatening events

*Where other causes have been ruled out (e.g., food allergy, especially in infants)
GERD and tooth erosion: a cross-sectional observational study.
Farahmand F. Gut Liver 2013;7:278-81

112 children (3 - 12 years old)
Dental erosions in 53 /54 (98.1%) GERD patients
11/ 58 (19.0%) controls (p<0.0001)

In GERD patients,
the posterior occlusal surfaces of milk teeth were more affected (p<0.0001).

There was no correlation between GERD and the affected surfaces in permanent teeth,
nor in the patterns or erosion grades (localized or general).
In both groups, milk teeth had more erosions than permanent teeth,
but the difference was not statistically significant.
Total and abdominal **obesity** are risk factors for GER symptoms in children.

*Quitadamo P. JPGN 2012;55:72-5*

153 healthy children. The reflux symptomatic score resulted significantly higher in obese than in normal-weight children and in children with waist circumference >90th percentile compared with those with waist circumference <75th percentile.

- Total and abdominal obesity are risk factors for the development of GERD symptoms in children.
- The risk of GERD symptoms rises progressively with the increase in both body mass index and waist circumference, even in normal-weight children.
The “typical reflux syndrome…”

A. Does not exist in children

B. Cannot be diagnosed before the age of 8 years

C. Unconsolable crying in infants is the “infant manifestation” of the typical reflux syndrome
The “typical reflux syndrome…”

A. Does not exist in children
B. Cannot be diagnosed before the age of 8 years
C. Unconsolable crying in infants is the “infant manifestation” of the typical reflux syndrome
‘Typical Reflux Syndrome’ cannot be diagnosed in infants and children who lack the cognitive ability to reliably report symptoms.

Children < 8 (… up to 11) years old cannot report symptoms in a reliable / reproducible way
GERD in children and adolescents in primary care (1)

GERD cases during 2000-2005 (The Health Improvement Network (THIN))
UK primary care database via a computer search for diagnostic codes for GERD, followed by manual review of the patient records.

1700 children with a first diagnosis of GERD during 2000-05

Incidence GERD 0.84 / 1000 person-years

Incidence ↓ with age
from 1.48/1000 person-years among 1-year-old children
until the age of 12 years,
whereupon it ↑ to a maximum at 16-17 years of
2.26/1000 person-years for girls
1.75/1000 person-years for boys. ....
In addition to typical GERD symptoms (epigastric pain, heartburn, reflux, regurgitation), 21.2% of children reported nausea or vomiting.

Children with neurological disorders were at increased risk of a GERD diagnosis.

Hiatus hernia and congenital esophageal disorders were also associated with a diagnosis of GERD.

Children and adolescents using antiepileptics, oral/inhaled steroids, beta-agonists and paracetamol had an increased risk of a GERD diagnosis.
Follow-up of a cohort of children and adolescents with GERD who were free of reflux esophagitis at initial diagnosis.

The Health Improvement Network UK primary care database (which includes data on more than 2 million patients) to identify individuals aged 1-17 years with a first diagnosis of GER or heartburn in the period 2000-2005, via a computerized search followed by a manual review of the patient records.

⇒ 1242 individuals with an incident diagnosis of GERD but no record of esophagitis.

This cohort was followed-up to detect new diagnoses of esophageal complications and extra-esophageal conditions.

⇒ During a mean follow-up period of almost 4 years, 40 children and adolescents had a confirmed new diagnosis of reflux esophagitis (incidence: 10.9/1000 person-years).

No cases of Barrett's esophagus, esophageal stricture or esophageal ulcer.

Individuals with GERD had double the risk of an extra-esophageal condition such as asthma, pneumonia, cough or chest pain compared with children and adolescents with no diagnosis of GERD.
Pediatric GERD and acid-related conditions (ARC): trends in incidence of diagnosis and acid suppression therapy


- Between 2000 and 2005, annual incidence of GERD/ARC diagnosis among infants (age ≤1 year) more than tripled (from 3.4 to 12.3%) and increased by 30% to 50% in other age groups.
- Patients diagnosed by GI specialists (9.2%) were more likely to be treated with PPIs compared to patients diagnosed by primary care physician (PCP).
  - PPI-initiated patients doubled 1999 31.5% 2005 62.6% when compared with H²RA-initiated patients associated with 30% less discontinuation 90% less therapy switching in 1st month higher comorbidity burden pre-treatment total HCU costs when diagnosed
Prevalence and management of GERD in children and adolescents: a nationwide cross-sectional observational study.(1)


Nationwide prevalence GERD in French children and adolescents
404 GP & 180 paediatricians (P): register of all children and adolescents
(\(n = 10,394\), 0-17 yrs, mean \(3.8 \pm 5.6\) years; 5143 by GP and 5251 by P)
who presented over two 3-day periods (14-16 and 26-28 May 2008).

For all children who, in the physician's opinion,
showed symptoms of GOR,
a 24-item questionnaire covering the history
and management of GOR was completed.

Children with symptoms that impaired their daily lives were defined
as having GERD, the remainder as having physiological GER.
15.1% showed GER symptoms.

Extrapolation to French population:
- prevalence GER 10.3% -- GERD 6.2%

There was a significantly (p < 0.05) greater use of volume reduction or milk thickeners and dorsal positioning among infants with GERD versus physiological GER.

Significantly (p < 0.05) more infants and children with GERD received pharmacological therapy.
- PPI increased with age and was significantly (p < 0.05) higher among those with GERD.
Prevalence and management of GERD in children and adolescents: a nationwide cross-sectional observational study.(3)


### Prevalence of GER in France according to age

<table>
<thead>
<tr>
<th>Extrapolation to French population</th>
<th>0-23 month</th>
<th>2-11 year</th>
<th>12-17 year</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>24.4%</td>
<td>7.2%</td>
<td>10.7%</td>
<td></td>
<td>10.3%</td>
</tr>
</tbody>
</table>

### GER symptoms

<table>
<thead>
<tr>
<th>Mean duration (month)</th>
<th>0-23 month</th>
<th>2-11 year</th>
<th>12-17 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.4</td>
<td>20.9</td>
<td>21.8</td>
<td></td>
</tr>
</tbody>
</table>

#### Typical symptoms

- **Regurgitations**
  - 85% \(^\text{BC}\)
  - 36%
  - 33%

- **Vomiting**
  - 26% \(^\text{C}\)
  - 32% \(^\text{C}\)
  - 13%

- **Crying**
  - 45% \(^\text{BC}\)
  - -
  - -

- **Heartburn**
  - -
  - 37% \(^\text{A}\)
  - 86% \(^\text{AB}\)

#### Atypical symptoms

- **Feeding difficulties, anorexia**
  - 42% \(^\text{BC}\)
  - -
  - -

- **Failure to thrive**
  - 6% \(^\text{BC}\)
  - -
  - -

- **Postural defects**
  - 8% \(^\text{BC}\)
  - -
  - -

- **Stridor**
  - 10% \(^\text{BC}\)
  - 4% \(^\text{C}\)
  - <1%

- **Chronic cough**
  - 6% \(^\text{BC}\)
  - 68% \(^\text{AC}\)
  - 33% \(^\text{A}\)

- **Laryngitis, otitis**
  - -
  - 35% \(^\text{AC}\)
  - 12% \(^\text{A}\)

- **Asthma**
  - -
  - 24% \(^\text{AC}\)
  - 15% \(^\text{A}\)

- **Sinusitis**
  - -
  - 2% \(^\text{AC}\)
  - 6% \(^\text{A}\)

* The superscript letter signifies that the column value is significantly different (P<0.05) to the value of the presented column.
Prevalence and management of GERD in children and adolescents: a nationwide cross-sectional observational study. (4)


Overall prevalence GER
In children 0 à 17 years
10.3% (1,4 million)

Prevalence GER-Disease
In children 0 à 17 years
6.2% (840,000)
Introduction
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Ambulatory oesophageal pH monitoring: a comparison between antimony, ISFET, and glass pH electrodes.

Hemmink GJ. Eur J Gastroenterol Hepatol. 2010;22:572-7

During in-vivo experiments, significant differences were found in acid exposure times derived from

- antimony: 4.0 +/- 0.8%
- ISFET: 5.7 +/- 1.1%
- glass pH electrodes: 9.0 +/- 1.7%
Impedance Scale

Low Conductivity = High impedance

High Conductivity = Low impedance
Outcomes of endoscopy and novel pH-impedance parameters in children: is there a correlation?

van der Pol RJ JPGN 2013;56:196-200

26 children & 14 infants (26.5 months (2 months-16.2 years).

13 (32.5%) reflux esophagitis (RE)

negative association RI / MII baselines (P = 0.009)
SAP and RE (P = 0.039, odds ratio 1.018).

MII baseline values not predictive for conventional pH-MII parameters reflux esophagitis

Manual analysis / automated calculation MII baselines: good correlation Distal MII baselines < proximal esophagus (P = 0.049)
Esophageal impedance baseline in age-dependent
Salvatore S. JPN (in press)
Esophageal impedance is age dependent
Salvatore S. JPGN (in press)
Comparison of UGI contrast studies and pH/impedance tests for the diagnosis of childhood GER.


retrospective, compared UGI studies pH/impedance tests.

GER UGIS: 116 / 579 children (20%)
66 also underwent a pH/impedance test

Using pH/impedance tests as the reference for GER,
UGIS sensitivity of 42.8%
negative predictive value of 24%

No significant correlation (P > 0.05) between the reflux index and the number of reflux episodes in the pH/impedance tests and height of reflux in the UGI study
1. Questionnaires
   ⇒ 1st to do, but…. limitations
2. Radiology
   ⇒ anatomy
3. Scintigraphy
4. Ultrasound
5. Endoscopy (+ biopsy)
   ⇒ ? Esophagitis
6. Manometry
7. pH metry
   ⇒ ? acid GER-D in extra-esophageal symptoms
8. Impedance-metry
   ⇒ ? acid & non-acid GER-disease
9. Therapeutic trial
   ⇒ no data
Cough and GER…

A. There is evidence that cough may induces GER
B. There is evidence that reflux may induce cough
C. There is evidence that PPI decrease cough
D. In patients with CF, mainly acid reflux is increased
Cough and GER…

A. There is evidence that cough may induce GER
B. There is evidence that reflux may induce cough
C. There is evidence that PPI decrease cough
D. In patients with CF, mainly acid reflux is increased
## Symptoms with associated reflux events

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Pts No.</th>
<th>Symptoms No.(median)</th>
<th>GER related No.(%)</th>
<th>AR related No.(%)</th>
<th>WAR related No. (%)</th>
<th>AlkR related No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crying</td>
<td>88</td>
<td>872 (8)</td>
<td>395 (45)</td>
<td>174 (44)</td>
<td>215 (54)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>48</td>
<td>229 (3)</td>
<td>196 (86)</td>
<td>80 (41)</td>
<td>103 (52)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Cough</td>
<td>102</td>
<td>975 (7)</td>
<td>510 (52)</td>
<td>243 (48)</td>
<td>247 (48)</td>
<td>20 (4)</td>
</tr>
<tr>
<td>Others</td>
<td>13</td>
<td>64 (3)</td>
<td>29 (45)</td>
<td>16 (55)</td>
<td>13 (45)</td>
<td>0</td>
</tr>
<tr>
<td>All</td>
<td>126</td>
<td>2172 (6)</td>
<td>1136 (52)</td>
<td>516 (45)</td>
<td>581 (51)</td>
<td>39 (3)</td>
</tr>
</tbody>
</table>

*Esophageal impedance in children: symptom-based results*

*S. Salvatore J Pediatr 2010;157:949-54*
Reflux episodes in relation with the 3 age groups and the 3 predominant symptoms.

<table>
<thead>
<tr>
<th>ITEM</th>
<th>CRYING</th>
<th>COUGH</th>
<th>VOMITING</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-6mo</td>
<td>6-12mo</td>
<td>&gt;12mo</td>
</tr>
<tr>
<td>No. patients</td>
<td>37</td>
<td>30</td>
<td>21</td>
</tr>
<tr>
<td>No. events</td>
<td>456</td>
<td>279</td>
<td>137</td>
</tr>
<tr>
<td>Median</td>
<td>11</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>GER related (%)</td>
<td>44</td>
<td>44</td>
<td>50</td>
</tr>
<tr>
<td>AR associated (%)</td>
<td>36</td>
<td>57</td>
<td>43</td>
</tr>
<tr>
<td>WAR associated (%)</td>
<td>62</td>
<td>42</td>
<td>54</td>
</tr>
<tr>
<td>AlkR associated (%)</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>
Cow's milk challenge increases weakly acidic reflux in children with CMA and GERD.

*Borrelli O. J Pediatr 2012;161:476-481*

### Table II. Reflux characteristics during AAF and CM administration

<table>
<thead>
<tr>
<th></th>
<th>AAF period</th>
<th>CM period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of reflux episodes</td>
<td>65 (39-87.5)</td>
<td>105 (58-127.5)*</td>
</tr>
<tr>
<td>Chemical composition of refluxate</td>
<td>[median (25th to 75th)]</td>
<td>[median (25th to 75th)]</td>
</tr>
<tr>
<td>Acid episodes</td>
<td>31 (9.5-44)</td>
<td>34 (14-41)</td>
</tr>
<tr>
<td>Weakly acidic episodes</td>
<td>19 (13-26.5)</td>
<td>53 (38.5-60.5)*</td>
</tr>
<tr>
<td>Weakly alkaline episodes</td>
<td>5 (3.5-10)</td>
<td>10 (2.5-15)</td>
</tr>
<tr>
<td>pH-only reflux episodes</td>
<td>9 (7-16)</td>
<td>11 (5.5-15)</td>
</tr>
<tr>
<td>Reflux composition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liquid</td>
<td>71%</td>
<td>78%</td>
</tr>
<tr>
<td>Mixed</td>
<td>27%</td>
<td>21%</td>
</tr>
<tr>
<td>Gas</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Esophageal acid exposure time (mean ± SD)</td>
<td>3.4 ± 2.6</td>
<td>3.6 ± 2.7</td>
</tr>
<tr>
<td>Number of long-lasting episodes (&gt;5 min) [median (25th to 75th)]</td>
<td>3 (1-3)</td>
<td>2 (1.5-2.5)</td>
</tr>
</tbody>
</table>

*P < .001 by Wilcoxon signed rank test.

Related to allergy? Or faster gastric emptying AAF?
The relationship between GER and cough in children with chronic unexplained cough using combined impedance-pH-manometry recordings.


Both acid and WA GER may precede cough in children with unexplained cough, but cough does not induce GER. Objective cough recording improves symptom association analysis.
Role of GER in children with unexplained chronic cough (1)

45 children with chronic cough: 24-hour MII-pH
20 children with erosive reflux disease (ERD): controls.

24 children had
cough-related reflux (CRR) in 24/45
(19 no GI symptoms)
cough-unrelated reflux (CUR) in 21/45

CRR + ERD: ↑ AR, WAc, WAlk reflux
ERD: ↑ eso acid exposure & acid clearance time
than in CRR and CUR
In children with unexplained chronic cough, asymptomatic acid and nonacid GER is a potential etiologic factor. The increased acid exposure time and delayed acid clearance characteristic of ERD are absent in cough-related GER.
Nocturnal reflux in children and adolescents with persistent asthma and gastroesophageal reflux (1)

38 patients 10 years (range 5 - 15) with persistent asthma for at least 2 years
GI symptoms: regurgitation, heartburn, and abdominal pain

GER: considered positive RI > 5%
Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV(1)),
forced mid-expiratory flow rate (FEF(25-75%)), and FEV(1)/FVC ratio

GER prevalence was 47.3%.
RI supine 8.7% (3.2 to 23.6); upright 10.5% (5.2 to 15.0)
FEF(25-75%) was below the predicted value: 54.5% (39.4 to 96.9).
RI was not significantly correlated with FVC, FEV(1) and FEF(25-75%).
Nocturnal reflux in children and adolescents with **persistent asthma** and gastroesophageal reflux.

*Molle LD. J Asthma 2009;46:347-50*

A high prevalence of GER was found in children and adolescents with persistent asthma, equally distributed in the supine (nocturnal) and upright positions.

There was no correlation with pulmonary function test.
Impact of laryngopharyngeal (LPR) and GER on asthma control in children.

*Kilic M. Int J Pediatr Otorhinolaryngol 2013;77:341-5*

Prevalences of LPR and GER were 70% and 46% in asthmatic patients. The reflux symptom score and LPR disease index were not useful to predict LPR or GER.

*There was no association between asthma control status and LPR and GER.*

Vocal nodule seems to be a valuable sign to evaluate LPR in asthmatic children.

The frequency of LPR and GER are independent of asthma control, atopy and long acting beta agonist usage.
Clinical studies show that GERD is highly prevalent in children with asthma, with estimates as high as 80%, but nearly half of the children are asymptomatic. However, there is no conclusive evidence per se that asymptomatic GERD informs asthma control, and treatment of GERD in the few controlled trials available for review does not substantively improve asthma outcomes. In a recent large controlled clinical trial, treatment with a PPI was not only ineffective, but adverse effects were common, including an increased prevalence of symptomatic respiratory infections.

Current evidence does not support the routine use of anti-GERD medication in the treatment of poorly controlled asthma of childhood.
24 infants
N° nonacid GER (NAGER) / hour was > during sleep time than during daytime and awakening following sleep onset (median 0.27 vs 1.85 and 1.45, P<0.01). A total of 1204 (range 7-86 per infant) arousals in 24 infants was detected, 165 (13.7%) that followed GER episodes, and 43 (3.6%) that preceded GER episodes.
7 patients: positive SAP for arousals (5/7 exclusively because of NAGER)
9 patients: positive SAP for awakenings (4 because of NAGER, 4 because of AGER, and 1 NAGER acid GER.
Awaking: longer mean clearance time of AGER during sleep (165.5 vs 92.8 seconds, P=0.03).

**GER: frequent cause of interrupting sleep**

NAGER equally important as AGER to cause arousals and awakenings
Combined esophageal intraluminal impedance, pH and skin conductance monitoring to detect discomfort in GERD infants.

*Cresi F. PLoS One 2012;7:e43476*

12 infants (17-45 days) out of 194.38 hrs of adequate MII/pH and skin conductance monitoring, 584 reflux events were observed

- 35.78% were positive for stress,
- of which 16.27% were acid and 83.73% weakly acidic.

Significant association GER & discomfort (p<0.05) present in all infants

*Discomfort was significantly associated with reflux events and did not differ between weakly acidic and acid refluxes.*
Introduction
Symptoms (prevalence)
Diagnosis
Treatment
Conclusions
Inclusion:
ITT-population:
115 infants (mothers consulted because > 5 regurgitations/day)

3 day diary
Only 89/115 (77%) did regurgitate > 5 times/day !!!
The concept that infant irritability and sleep disturbances are manifestations of GER is largely extrapolated from adult descriptions of heartburn and sleep disturbances that improve with antacid therapy.

What is the evidence in infants?
Multicenter, DB, R, PC trial assessing the efficacy and safety of PPI lansoprazole in infants with symptoms of GER disease. 


Symptoms were tracked through daily diaries and weekly visits

**Efficacy:** > 50% reduction of feeding-related crying

216 infants screened, 162 randomized

<table>
<thead>
<tr>
<th></th>
<th>Lansoprazole</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder</td>
<td>44/81 (54%)</td>
<td>44/81 (54%)</td>
</tr>
</tbody>
</table>

No difference in any secondary measures or analyses of efficacy

<table>
<thead>
<tr>
<th></th>
<th>Lansoprazole</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1 AEs</td>
<td>62%</td>
<td>46% (P=.058)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower RTI (n)</td>
<td>10</td>
<td>2 (P=.032).</td>
</tr>
</tbody>
</table>
Efficacy and safety of once-daily esomeprazole for the treatment of GERD in neonatal patients.


There were no significant differences between the esomeprazole and placebo groups in the percentage change from baseline in the total number of GERD-related signs and symptoms (-14.7% vs -14.1%, respectively). Mean change from baseline in total number of reflux episodes was not significantly different between esomeprazole and placebo (-7.43 vs -0.2, respectively); however, the percentage of time pH was <4.0 and the number of acidic reflux episodes >5 min in duration was significantly decreased with esomeprazole vs placebo (-10.7 vs 2.2 and -5.5 vs 1.0, respectively; P ≤ .0017). The number of patients with adverse events was similar between treatment groups.

**Signs and symptoms of GERD traditionally attributed to acidic reflux in neonates were not significantly altered by esomeprazole treatment.**

**Esomeprazole was well tolerated and reduced esophageal acid exposure and the number of acidic reflux events in neonates.**
PPI: side effects

- bacterial overgrowth (~ 30% !)
- community-acquired pneumonia (children, adults)
- gastroenteritis (children)
- clostridium difficile infection
- candidemia (preterms)
- necrotizing enterocolitis (preterms)
- parietal cell hyperpalsia / benign gastric polyps
- case reports: acute interstitial nephritis, acute hepatitis
- osteopenia, hip fractures
- ? Allergy
- ? Magnesium

*Chai G. Pediatrics 2012;130:23-31*

### TABLE 3
Top Drug Molecules Dispensed to the Pediatric Population From US Retail Pharmacies According to Patient Age in 2010

<table>
<thead>
<tr>
<th>Drug Molecule</th>
<th>0-23 Months (N = 31.6 million prescriptions)</th>
<th>2-11 Years (N = 134.2 million prescriptions)</th>
<th>12-17 Years (N = 96.6 million prescriptions)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Share, %</td>
<td>Share, %</td>
<td>Share, %</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>17.3</td>
<td>11.3</td>
<td>Methylenidate</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>6.1</td>
<td>5.8</td>
<td>Albuterol</td>
</tr>
<tr>
<td>Nystatin</td>
<td>5.9</td>
<td>5.8</td>
<td>Azithromycin</td>
</tr>
<tr>
<td>Albuterol</td>
<td>5.8</td>
<td>4.5</td>
<td>Amoxicillin</td>
</tr>
<tr>
<td>Cefdinir</td>
<td>4.9</td>
<td>3.9</td>
<td>Amphetamine/dextroamphetamine</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>4.2</td>
<td>2.9</td>
<td>Montelukast</td>
</tr>
<tr>
<td>Amoxicillin/Clavulanate</td>
<td>3.4</td>
<td>2.7</td>
<td>Norgestimate-ethinyl estradiol</td>
</tr>
<tr>
<td>Dextromethorphan/Phenylephrine/Chlorpheniramine</td>
<td>2.4</td>
<td>2.6</td>
<td>Lisdexametamine</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>2.2</td>
<td>1.9</td>
<td>Fluticasone</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>2.0</td>
<td>Amoxicillin/Clavulanate</td>
<td>Hydrocortisone bitartrate/apap</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>1.8</td>
<td>Amphetamine/dextroamphetamine</td>
<td>Ibuprofen</td>
</tr>
<tr>
<td>Multivitamins with fluoride</td>
<td>1.7</td>
<td>Multivitamins with fluoride</td>
<td>Amoxicillin/Clavulanate</td>
</tr>
<tr>
<td>Budesonide</td>
<td>1.6</td>
<td>Lisdexametamine</td>
<td>Sulfamethoxazole/trimethoprim</td>
</tr>
<tr>
<td>Lansoprazole*</td>
<td>1.8</td>
<td>Sodium fluoride</td>
<td>Doxycline hydrochloride</td>
</tr>
<tr>
<td>Cephalixin</td>
<td>1.5</td>
<td>Ibuprofen</td>
<td>Cephalixin</td>
</tr>
<tr>
<td>Mupirocin</td>
<td>1.4</td>
<td>Mometasone</td>
<td>Sertraline</td>
</tr>
<tr>
<td>Sulfamethoxazole/trimethoprim</td>
<td>1.3</td>
<td>Dexamethasone</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Polymyxin b sulfate/trim</td>
<td>1.0</td>
<td>Sulfamethoxazole/trimethoprim</td>
<td>Minocycline</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>1.0</td>
<td>Clonidine</td>
<td>Prednisone</td>
</tr>
<tr>
<td>Montelukast</td>
<td>0.9</td>
<td>Budesonide</td>
<td>Clindamycin phosphate/benzoyl peroxide</td>
</tr>
<tr>
<td></td>
<td>All others</td>
<td>All others</td>
<td>All others</td>
</tr>
<tr>
<td></td>
<td>32.0</td>
<td>41.8</td>
<td>57.5</td>
</tr>
</tbody>
</table>

Data include all formulations (e.g. oral tablet, oral syrups, topical cream). Source: VONA, 2002 through 2010; extracted March 2011.

* A total of 515,000 lansoprazole prescriptions (358,000 prescriptions in patients aged 0 to <1 year and 157,000 prescriptions in patients aged 1 to <2 years).
<table>
<thead>
<tr>
<th>Medication group (ATC 3)</th>
<th>DDD</th>
<th>% DDD (**)</th>
<th>N° patients</th>
<th>RIZIV (in 10⁶ €)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astma, inhalation (R03B)</td>
<td>4.242.010</td>
<td>45%</td>
<td>78.545</td>
<td>2,9</td>
</tr>
<tr>
<td>Sympathicomimetics inhalation (R03A)</td>
<td>983.727</td>
<td>11%</td>
<td>56.729</td>
<td>0,5</td>
</tr>
<tr>
<td>Betalactam-antibiotics, penicilline (J01C)</td>
<td>758.308</td>
<td>8%</td>
<td>94.809</td>
<td>0,8</td>
</tr>
<tr>
<td>PPI (A02B)</td>
<td>652.901</td>
<td>7%</td>
<td>14.484</td>
<td>0,3</td>
</tr>
<tr>
<td>Antimicrobials (S01A)</td>
<td>550.638</td>
<td>6%</td>
<td>27.292</td>
<td>0,1</td>
</tr>
</tbody>
</table>

2007: 120 663 births
2007: 14 484 infants treated with PPI/H2RA = 12%


- Alginates/antacids and prokinetics ↓ with age (p<0.05)
- PPI ↑ with age (p<0.05)
Omeprazole and asthma outcome in children with asthma and GER-disease: a randomised control trial.

*Stordal K. Arch Dis Child* 2005;90:956-60

38 children (7-16 years): asthma and symptoms suggesting GERD and 24 hr pH metry RI > 5%

**Table 3** Outcome measures in children with asthma and GORD treated with omeprazole and placebo

<table>
<thead>
<tr>
<th></th>
<th>Omeprazole (n=18)</th>
<th>Placebo (n=18)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom score</td>
<td>-1.28 (-2.65 to 0.1)</td>
<td>-1.28 (-3.27 to 0.72)</td>
<td>1.00</td>
</tr>
<tr>
<td>PAQLQ</td>
<td>-0.62 (-0.29 to -0.95)</td>
<td>-0.50 (-0.29 to -0.70)</td>
<td>0.51</td>
</tr>
<tr>
<td>FEV1% (mean, median)</td>
<td>-1.38 (0.33)</td>
<td>-2.01 (-0.50)</td>
<td>0.77</td>
</tr>
<tr>
<td>FEF25-75 (mean, median)</td>
<td>-0.07 (-0.05)</td>
<td>0.04 (0.05)</td>
<td>0.12</td>
</tr>
<tr>
<td>Rescue medication (mean, median)</td>
<td>-1.9 (0.0)</td>
<td>-1.9 (0.5)</td>
<td>0.89</td>
</tr>
<tr>
<td>ECP baseline</td>
<td>25.9 (14.3, 37.5)</td>
<td>20.2 (12.7 to 27.7)</td>
<td>0.89</td>
</tr>
<tr>
<td>ECP change</td>
<td>1.27 (-5.5 to 8.1)</td>
<td>1.39 (-4.3 to 7.1)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Values expressed as changes from baseline (week 0) to end of treatment (week 12) with 95% confidence intervals for mean (± 1.96 SEM) unless otherwise stated.

**NO effect**
Lansoprazole for children with poorly controlled asthma: a RCT (1)
Writing Committee for the American Lung Association Asthma Clinical Research Centers. JAMA.2012;307:373-81

Lansoprazole (n:149) 15 mg/d if weighing less than 30 kg
30 mg/d if weighing 30 kg or more
Placebo (n = 157).
Mean age was 11 years (SD, 3 years)

• Mean difference in change (lansoprazole minus placebo) in the Asthma Control Questionnaire score: 0.2 units (95% CI, 0.0-0.3 units).
• No statistically significant difference in the mean difference in change for the secondary outcomes of
  • forced expiratory volume in the first second (0.0 L; 95% CI, -0.1 to 0.1 L)
  • asthma-related quality of life (-0.1; 95% CI, -0.3 to 0.1)
  • rate of episodes of poor asthma control (RR 1.2; 95% CI, 0.9-1.5)
115 children with pH metries: prevalence of GER was 43%  
In the subgroup with a positive pH study,  
no treatment effect for lansoprazole vs placebo  
was observed for any asthma outcome.

Children treated with lansoprazole reported more respiratory infections  
(relative risk, 1.3 [95% CI, 1.1-1.6]).
Effect of proton pump inhibition on acid, weakly acid and weakly alkaline GER in children.

Higher rate of bronchoalveolar lavage culture positivity in children with nonacid reflux and respiratory disorders.

Rosen R. Pediatr. 2011;159:504-6

• ? children with chronic cough or wheezing and with more full-column, nonacid reflux have a higher likelihood of a positive BAL fluid culture
• 46 children with cough patients who had a positive culture had significantly more full-column, nonacid GER than those who had a negative culture

\( PPI \rightarrow ? \uparrow pos \text{ culture BAL} \)
Patients with asthma and heartburn should be treated for the heartburn.

Despite a high frequency of abnormal reflux studies in asthmatic patients, only a select group with nocturnal asthma symptoms, or with steroid dependent, difficult to control asthma may benefit from long term medical or surgical anti-reflux therapy.
Prenatal exposure to acid-suppressive drugs and the risk of childhood asthma: a population-based Danish cohort study
Andersen AB. Aliment Pharmacol Ther. 2012;35:1190-8

... 2238 (1.1%) children were prenatally exposed to PPIs and 24,506 (12.4%) children developed asthma during follow-up (median follow-up = 6.8 years).

The adjusted IRR of asthma associated with prenatal exposure to PPIs was 1.41 (95% CI: 1.27-1.56), compared with those unexposed.

The association did not vary by trimester of exposure

Prenatal exposure to H2RAs was associated with similar increase in risk. The aIRR for maternal PPI and H2RA use in the year after, but not during pregnancy was 1.32 (95% CI: 1.20-1.46) and 1.13 (0.93-1.36), respectively, compared with non-use during and in the year after pregnancy.
At present,
no single diagnostic test can prove or exclude
extraesophageal presentations of GERD
in pediatrics.
In many cases the clinician must make management decisions based on inconclusive diagnostic studies with no certainty regarding outcome.
Challenges in the diagnosis of GERD in infants and children.


Although evidence for a "relation" between GER and extra-esophageal symptoms is demonstrated, the "causality" between both is not proven.

MII measures non-acid or weakly acid reflux. However, as long as medical therapeutic options are limited to anti-acid medications, MII lacks therapeutic implications, and therefore clinical impact.
Prenatal exposure to acid-suppressive drugs and the risk of childhood asthma: a population-based Danish cohort study. (1)


In this cohort study, 197,060 singletons born between 1996 and 2008 in northern Denmark were followed until the end of 2009. Data were obtained through Danish medical registries.

Asthma in offspring was defined as at least two prescriptions of both a β-agonist and an inhaled glucocorticoid and/or a hospital diagnosis of asthma during the follow-up.
Evolution

http://www.youtube.com/watch?v=5VzEMr4NhgE&feature=player_detailpage

http://www.youtube.com/watch?v=PvxTfgBszc8&feature=player_detailpage

Introduction  Symptoms  Prevalence  Diagnosis  Treatment  Conclusions
ESOPHAGEAL IMPEDANCE BASELINE IS AGE-DEPENDENT

Salvatore S. (in press)
ESOPHAGEAL IMPEDANCE BASELINE IS AGE-DEPENDENT

Salvatore S. (in press)
Detection of GER in children using combined MII and pH measurement: data from the German Pediatric Impedance Group.


Table I. Number of patients in the different subgroups with abnormal measurement data based on different pathological findings

<table>
<thead>
<tr>
<th></th>
<th>Patients with GI symptoms (n = 325)</th>
<th>Patients with pulmonary symptoms (n = 329)</th>
<th>Patients with neurologic symptoms (n = 46)</th>
<th>All patients (n = 700)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal measurements, n</td>
<td>114 (48 female, 66 male)</td>
<td>133 (57 female, 76 male)</td>
<td>23 (11 female, 12 male)</td>
<td>270 (116 female, 154 male)</td>
</tr>
<tr>
<td>Age, years, median (range)</td>
<td>6.5 (1 month-16 years)</td>
<td>2 (1 month-16 years)</td>
<td>0.5 (3 weeks-15 years)</td>
<td>2.8 (6 weeks-16 years)</td>
</tr>
<tr>
<td>Only pathological pH</td>
<td>26 (23%)</td>
<td>21 (16%)</td>
<td>2 (9%)</td>
<td>49 (18%)</td>
</tr>
<tr>
<td>Pathological MII and pH</td>
<td>55 (48%)</td>
<td>35 (26%)</td>
<td>11 (48%)</td>
<td>101 (37%)</td>
</tr>
<tr>
<td>Pathological MII</td>
<td>33 (29%)</td>
<td>77 (58%)</td>
<td>10 (43%)</td>
<td>120 (45%)</td>
</tr>
</tbody>
</table>
Pediatric GERD and acid-related conditions (ARC): trends in incidence of diagnosis and acid suppression therapy (1)


Cohorts of GERD/ARC children (age 0-18 years) were identified from a large US administrative claims database covering 1999-2005 using ICD-9 codes.

Comparison between various age and patient groups for incidence healthcare utilization (HCU) costs therapy discontinuation switching rates

....
GER is not associated with dental erosion in children.

Wild YK. Gastroenterology 2011;141:1605-11

cross-sectional study 59 children (9-17 y) with symptoms of GER
20 asymptomatic children (controls)

Controlling for age
dietary intake
oral hygiene,
there was no association between GER symptoms
and dental erosion by tooth location or affected surface.

Salivary flow did not correlate with GER symptoms or erosion.

Location-specific dental erosion is not associated with GER, salivary flow, or bacterial load.
Pediatric use of H2RA and PPI in Belgium (Inami/Riziv)
Daily Defined Dosis

<table>
<thead>
<tr>
<th>% Infants (0-1y) with Anti-Acid</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12,1</td>
<td>14,2</td>
<td><strong>15,5</strong></td>
<td>17,2</td>
<td>18,6</td>
</tr>
</tbody>
</table>
The natural course of gastro-oesophageal reflux.
*Salvatore S. Acta Paediatr. 2004;93:1063-9*

<table>
<thead>
<tr>
<th>Symptoms/signs</th>
<th>Infants</th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Regurgitation</td>
<td>+++++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Heartburn</td>
<td>?</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>?</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Chest pain</td>
<td>?</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>?</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Excessive crying/irritability</td>
<td>+++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Anaemia/melaena/haematemesis</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Food refusal/feeding disturbances/anorexia</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Abnormal posturing/Sandifer’s syndrome</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Persisting hiccups</td>
<td>++</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Dental erosions/water brush</td>
<td>?</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hoarseness/globus pharyngeus</td>
<td>?</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Persistent cough/aspiration pneumonia</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Wheezing/laryngitis/ear problems</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Laryngomalacia/stridor/croup</td>
<td>+</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Chronic asthma/sinusitis</td>
<td>-</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Laryngostenosis/vocal nodules problems</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>ALTE/SIDS/apnoea/desaturation</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>+</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Sleeping disturbances</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Impaired quality of life</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Stenosis</td>
<td>-</td>
<td>(+)</td>
<td>+</td>
</tr>
<tr>
<td>Barrett’s/oesophageal adenocarcinoma</td>
<td>-</td>
<td>(+)</td>
<td>+</td>
</tr>
</tbody>
</table>

+++ , very common; ++, common; +, possible; (+), rare; -, absent; ?, unknown.
Limitations:
- the use of an exploratory definition for GERD/ARC
- administrative claims data
- potential coding errors

⇒ The diagnosis of GERD/ARC incidence increased for children of all ages between 2000 and 2005.
Primare Care Physicians made the majority of diagnoses.
PPI initiations have surpassed H²RA initiations.
Characteristics of GER and potential risk of gastric content aspiration in children with cystic fibrosis.


Although WA-GER is uncommon, acid GER is prevalent in children with CF. It is a primary phenomenon and is not secondary to cough.

*One third of the children with CF have bile acids (BA) in saliva, which may indicate an increased risk for aspiration. However, the impact of salivary BA and potential aspiration on CF pulmonary disease needs further investigation.*
Efficacy and safety of Rabeprazole in children (1-11 years) with GERD: A Multicenter, Double-Blind, Parallel-Group Study.

Haddad I. JPGN 2013 (in press)

Overall, 81% (87 of 108) achieved endoscopic/histologic healing at week 12 with higher healing in the low-weight cohort (82% [5 mg dose], 94% [10 mg dose]) compared with high-weight cohort (76% [10 mg dose], 78% [20 mg dose]). There was a significant (P < 0.001) decrease in the mean Total GERD Symptoms and Severity score from 19.7 points (baseline) to 8.6 points (week 12) with 26% fewer children reporting GERD symptoms at week 12.

The average frequency of symptoms per child decreased from 7.7 (week 1) to 4.7 (week 12). The GERD Symptom Relief score showed that 71% children felt better, 81% were investigator-rated "Good to Excellent" on the Global Treatment Satisfaction scale; 77% were parent/caregiver-rated "Good to Excellent" on the Clinical Global Impressions Improvement scale.

Rabeprazole was effective and safe in 1-11 year old children with GERD.
Proton pump inhibitor use in pediatric patients less than 12 months of age
Chen IL. JPGN 2012;54:8-14.

Review by FDA
Prescription rate 2002-2009 in USA: x 11 !

efficacy (PPI-placebo)

4 randomized trials
- esomeprazole 0.69 (95% CI 0.35 – 1.35)
- lansoprazole 1.00
- pantoprazole 1.00
- omeprazole 3 doses (0.5, 1.0, 1.5 mg/kg/day): NS
Results: Of the 98 patients enrolled, 81 (82.7%) experienced symptom improvement determined by physician global assessment (PGA) during open-label esomeprazole treatment; 80 entered the double-blind phase. During this phase, discontinuation rates owing to symptom worsening were 48.8% (20/41) for placebo-treated versus 38.5% (15/39) for esomeprazole-treated patients (hazard ratio 0.69; \( P = 0.28 \)). Posthoc analysis of infants with symptomatic GERD (ie, no diagnostic procedure performed) revealed that time to discontinuation was significantly longer with esomeprazole than placebo (hazard ratio 0.24; \( P = 0.01 \)); the complementary subgroup difference was not significant (hazard ratio 1.39; \( P = 0.48 \)). Esomeprazole was well tolerated.
A total of 515 reflux episodes were recorded with MII/pH (acid: 181; weakly acid: 310; weakly alkaline: 24); 180 (35%) reached the highest impedance channel (hypo-pharynx); 74/180 (41%) were not related to a change in pH, according to the antimony electrode of the MII/pH catheter located at the upper esophageal sphincter. The OP monitoring measured 39 acid events; 17 (43.6%) were swallows according to MII, and 15 (38.5%) were not associated with MII or pH change. Only seven episodes were detected simultaneously with both techniques (1.3% for MII vs. 18% for OP; P = 0.0002). We found 49 pH-only refluxes at the pH sensor in the hypo-pharynx with MII/pH; only three (6.1%) correlated with OP reflux. Correlation in time between cough and reflux events was positive in 5/10 patients for MII (symptom index 5/10, symptom association probability 4/10), but in 0/10 patients according to OP pH metry.

CONCLUSION:
OP pH only detected fewer reflux episodes than MII pH; 35% of the OP

Twenty-three infants (16 preterm and 7 term infants) in hospital, who underwent monitoring, were studied retrospectively. GER indices and apnea-related symptoms were measured by both MII-pH and conventional pH based analysis.

RESULTS:
Of the total 998 GER episodes assessed by MII-pH monitoring, 407 (40.8%) were weakly acidic. A total of 1689 GER episodes were detected by pH based analysis and 270 (16%) were related to retrograde bolus movement. A total of 8 apnea-related symptoms were reported. Five patients had a positive symptom associated with MII-pH, 1 by both MII-pH and conventional pH, 1 only by conventional pH.

CONCLUSIONS:
Addition of MII-pH monitoring to conventional pH monitoring improves the diagnosis of symptom association analysis in preterm infants and neonates with apnea-related symptoms. Conventional pH monitoring is still important in the era of impedance monitoring.
We retrospectively reviewed charts from patients who underwent MII-pH.

119 MII-pH studies (63 met inclusion criteria)
main indication: cough.
6 children had pathological GER based on DeMeester score.
Using impedance criteria, 10/63 patients abnormal evaluation
(mean reflux episodes 107).

7 (15.2%) association between symptom and reflux event.
No association was demonstrated between
the extraesophageal signs and symptoms
297 MII-pH tracings were analysed. Endoscopic and histological esophagitis were detected in 30% and 29% patients, respectively. Median IB z-score was significantly decreased both in proximal (p=0.02) and distal (p=0.006) esophagus in patients with endoscopic (but not histological) esophagitis. Patients with more severe esophagitis showed the lowest baseline z-score. Bolus exposure index and the number of reflux episodes were the variables that were significantly associated with the IB z-score.

IB z-score is significantly ↓ in endoscopic esophagitis. Severity of esophagitis, bolus exposure index and number of reflux episodes are factors influencing IB.
Effect of proton pump inhibition on acid, weakly acid and weakly alkaline GER in children.


14 (67%) patients reported clinically relevant symptom improvement after 2 months of PPIs intake. At the first endoscopy, 8 (38%) patients had macroscopic signs of reflux esophagitis; after two months of therapy, 6/8 (75%) patients had a complete mucosal recovery. There was a significant reduction in the total percentage of mean acid reflux time (from 13.1% to 3.8%), and the De Meester score dropped to normal (from 46.4 to 13.1).

**PPI**

- Mean number of acid reflux ↓ significantly from 48 to 15 / 24 hours,
- Mean number of weakly acid reflux ↑ from 26 to 64 / 24 hours.

**PPI do not affect the total number of reflux episodes.**

**PPI decrease the acidity of refluxate.**

Mostly of patients with typical reflux symptoms report symptom improvement