NERD: A four letter word?
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  • Boston Children’s Hospital Translational Research Program.

Goals
• What is NERD?
• How do you diagnose it?
• How do you treat it?
• What are the outcomes of NERD?
What is NERD? The old definition...

- No erosions visualized endoscopically
- An abnormal amount of acid reflux by pH probe
- Classic reflux symptoms of heartburn

Does the definition need revision because...

- Most scopes are performed on PPI so erosions healed by the time of scope (i.e. Are we converting erosive patients into non-erosive?)
- pH-MII has uncovered the importance of both acid and nonacid reflux
- Most pediatric patients don’t complain of heartburn
- Many pediatric patients don’t want 24 hour probe testing
- Pediatric gastroenterologists rely on histologic evidence, not just visual evidence

Things to remember about reflux testing

- Abnormal amount of reflux
- Abnormal % time pH<4
- Abnormal number of reflux events (total, acid or nonacid)
- High correlation between reflux events and symptoms
- Symptom index (SI: % of symptoms associated with reflux)
- Symptom sensitivity index (SSI: % of reflux events associated with symptoms)
- Symptom association probability (SAP: Statistical likelihood that symptoms and reflux are not associated by chance using a Fisher’s exact test)
New Definitions

<table>
<thead>
<tr>
<th></th>
<th>Typical Symptoms</th>
<th>Endoscopically</th>
<th>Abnormal amount of acid reflux</th>
<th>Symptom association with acid or non-acid reflux</th>
</tr>
</thead>
<tbody>
<tr>
<td>NERD</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Hypersensitive Esophagus</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional Heartburn</td>
<td>+</td>
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</tbody>
</table>

Should hypersensitive esophagus be considered NERD? Functional heartburn?

NERD/Hypersensitive Esophagus

Functional heartburn

![Graphs showing esophageal function and reflux](image-url)
**Manometry in NERD patients**

Riboli et al Clin Gastro Hep 2014

Table 2: TLESRs and Reflux Episodes During TLESRs, in Patients and Healthy Volunteers

<table>
<thead>
<tr>
<th></th>
<th>NERD patients</th>
<th>Healthy volunteers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean TLESR: Mean reflux during TLESRs</td>
<td>11.7 ± 2.1</td>
<td>12.7 ± 2.4</td>
</tr>
<tr>
<td></td>
<td>5.2 ± 2.8</td>
<td>6.5 ± 2.1</td>
</tr>
</tbody>
</table>

**NERD patients feel symptoms similarly to erosive reflux disease (ERD) patients**

Weijenborg et al AJP-Gastrointest Liver Physiol 2014

Regional sensitivity of the esophagus in NERD patients

Emerenziani et al NGM 2009

<table>
<thead>
<tr>
<th></th>
<th>NERD pH ≤ 4</th>
<th>NERD pH &gt; 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid reflux (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 cm above LOS</td>
<td>14 ± 2</td>
<td>10 ± 5</td>
</tr>
<tr>
<td>15 cm above LOS</td>
<td>17 ± 6</td>
<td>16 ± 7</td>
</tr>
<tr>
<td>20 cm above LOS</td>
<td>20 ± 5</td>
<td>30 ± 15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>NERD pH ≤ 4</th>
<th>NERD pH &gt; 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 cm above LOS</td>
<td>8 ± 2</td>
<td>7 ± 4</td>
</tr>
<tr>
<td>15 cm above LOS</td>
<td>16 ± 7</td>
<td>22 ± 9</td>
</tr>
<tr>
<td>20 cm above LOS</td>
<td>23 ± 12</td>
<td>33 ± 9</td>
</tr>
</tbody>
</table>

Table 1: Proportion (%) of symptomatic events according to the acidity at each esophageal site.
Visceral hypersensitivity throughout the esophagus
Thous et al APT 2008

NERD Algorithm
Savarino et al. Nat Reviews Gastro 2013
Adults suggest functional heartburn is not NERD
NERD by definition needs some abnormal reflux testing, not just symptoms

Incidence of subtypes
Savarino Nat Med Rev 2013
Incidence of functional heartburn and hypersensitive esophagus
Fong Kuen et al Clinical Gastro Hepatol 2015

54% of patients do not have a diagnosis that responds to PPI therapy

Frequency of Subtypes in Pediatrics
Borelli et al NGM 2012

Can we diagnose NERD by:

 • Symptoms
 • Proton pump inhibitor trial
 • Endoscopy
 • Impedance
Can you tell based on history who has which diagnosis?
Kowdziel et al APT 2013

What about other symptoms besides heartburn?
Savino et al J Prac Gastroenterol 2009

Can you tell based on history who has which diagnosis?
Lee et al Archives Dis Child 2010
Prevalence of GER Symptoms in Children

PPI Trial

Patients with ERD and NERD respond symptomatically to PPIs at the same rate
Bytzer et al 2012

Table 3. Response to PPI, Defined as the Absence of the Most Bothersome Symptom During the Last 3 Days of Treatment, in GORD Patients With and Without Know Erosions and in NongORD Patients

<table>
<thead>
<tr>
<th></th>
<th>GORD</th>
<th>No erosions</th>
<th>NongORD</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients n = 298</td>
<td>57% (6/137)</td>
<td>49% (142/288)</td>
<td>30% (92/304)</td>
</tr>
<tr>
<td>Patients with erosions n = 258</td>
<td>59% (15/25)</td>
<td>59% (132/222)</td>
<td>29% (73/254)</td>
</tr>
<tr>
<td>Patients without erosions n = 220</td>
<td>57% (12/21)</td>
<td>49% (138/282)</td>
<td>29% (72/256)</td>
</tr>
<tr>
<td>Patients without symptoms specific for GORD n = 168</td>
<td>90% (15/17)</td>
<td>94% (157/165)</td>
<td>29% (23/81)</td>
</tr>
</tbody>
</table>

NOTE: Symptoms typical for GORD were defined as heartburn, regurgitation, dysphagia, or central chest pain as the most bothersome symptom. *p < .05, **p < .01, vs nonGORD (Fisher exact test).
PPI trial cannot differential patients with and without GERD symptoms

Bytzer et al 2012

Response of Symptoms to PPI

• Eliminated/Omitted as part of the NERD definition because:
  • PPI effect may be placebo
  • PPI dose may not have been adequate for symptom relief
  • Patients with a positive symptom association with nonacid reflux (hypersensitive esophagus to nonacid reflux) won't respond to PPIs but still have NERD

Baseline Impedance Values
Can I get by just using baseline impedance values?

Borrelli et al. NGM 2012

Baseline impedance correlates with other reflux parameters

Borrelli et al. NGM 2012
Intercellular space

Can I get by just using...Light Microscopy? Electron microscopy?

EM and light microscopy give similar results and distances bigger in NERD
Riboč et al Dig Liv Dis 2009

ICS similar between NERD and ERD patients
Caviglia et al APT 2007
No difference in ISD in children with NERD versus ERD
Borrelli et al NGM 2012

<table>
<thead>
<tr>
<th>ISD (μm)</th>
<th>NERD (n = 10)</th>
<th>ERD (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean value ± SD (95% CI)</td>
<td>1.4 ± 0.3 (0.8-2.1)</td>
<td>1.4 ± 0.3 (0.8-2.1)</td>
</tr>
<tr>
<td>Mean of Minimum value ± SD (95% CI)</td>
<td>1.4 ± 0.3 (0.8-2.1)</td>
<td>1.7 ± 0.6 (1.3-3.1)</td>
</tr>
<tr>
<td>Mean of Minimum value of ISD ± SD (95% CI)</td>
<td>1.4 ± 0.3 (0.8-2.1)</td>
<td>1.5 ± 0.3 (0.8-2.1)</td>
</tr>
</tbody>
</table>

NERD: non erosive reflux disease; ERD, erosive reflux disease.

Differences cellular spaces on esophageal histology
Altaf et al JPGN 2014

The value of inflammation on histology?

Early microscopes
Microscopically, you cannot tell NERD from ERD
Kandulski et al APT 2013

Role of microscopic inflammation and NERD
Savarino et al J Gastro 2014

Can I differentiate patients based on Histology?

<table>
<thead>
<tr>
<th></th>
<th>NEOG</th>
<th>NEOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Age (mean, range)</td>
<td>52.2±16.9</td>
<td>64.1±23.9</td>
</tr>
<tr>
<td>BMI (mean, range)</td>
<td>22.4±4.7</td>
<td>24.8±4.1</td>
</tr>
<tr>
<td>Dyspepsia (yes/no)</td>
<td>7/4</td>
<td>7/4</td>
</tr>
<tr>
<td>Esophagitis (yes/no)</td>
<td>5/6</td>
<td>6/5</td>
</tr>
<tr>
<td>Erosions (yes/no)</td>
<td>4/7</td>
<td>5/6</td>
</tr>
<tr>
<td>Hiatal hernia (yes/no)</td>
<td>2/9</td>
<td>3/8</td>
</tr>
<tr>
<td>Male Gender</td>
<td>7/4</td>
<td>7/4</td>
</tr>
</tbody>
</table>

NERD: nonerosive reflux disease; ERD: erosive reflux disease; EAP, endoscopic appearance; P < 0.05 by Fisher’s exact test. According to Los Angeles classification. References to histology.

Borelli NGM 2012
Why do we care about the names?
Treatments are different
Savarino et al Nat Med Rev GI 2013

PPI response in NERD
Dean et al Clinical Gastro Hepatol 2004
**PPI response in the first week predicts longer term symptom relief in NERD patients**

Talley et al. APT 2006

Complete PPI response on days 5–7 provided an 85% probability of complete resolution of heartburn at 4 weeks.

If moderate to severe symptoms after 5–7 days of PPI, still a 22% probability of complete resolution of heartburn.

Resolution at 4 weeks

2–3 day PPI trial NOT adequate to predict long term PPI response.

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**NERD patients who respond to PPIs partially or completely after 8 weeks of therapy have a 100% success of symptom resolution longer term.**

If no response after 8 weeks, unlikely to respond with additional therapies.

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**NERD patients do as well after fundoplication as ERD patients**

SSRI for hypersensitive esophagus
Viazis et al Am J Gastro 2012

219 Patients recorded symptoms during the study day
Positive StI 105 (47.9%)
75 (71.4%) Hypersensitive esophagus
53 Patients Cilostatram 30 mg > 1
36 Patients Placebo > 1
26 Patients (61.5%) No symptoms
12 Patients (33.3%)
P=0.021

SSRI for functional heartburn
Ostovaneh et al NGM 2014

Proposal for PPI Non-Responders

Endoscopy
Erosions? Histologic evidence of esophagitis?

Yes
GERD EoE

No
Impedance off medication
Pathologic reflux?

Yes
NERD + symptom association

No
Hypersensitive Esophagus

Yes
No
Functional Heartburn
Summary

• The definitions of NERD are changing and definitions are critical for understanding response to therapies
• One of the main indications of pH-MII testing (off therapy) may be to differentiate NERD from functional heartburn
• Novel diagnostic tools such as measurement of intercellular spaces and baseline impedance values have not yet replaced endoscopy and pH-MII testing for diagnosis
• Pediatric trials of therapies for patients with NERD are critical

“Be nice to nerds. Chances are you'll end up working for one.” -Bill Gates