

## NERD: A four letter word?

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  - NASPGHAN/Astra Diseases of the Upper Tract
  - Boston Children's Hospital Translational Research Program.

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### Goals

- What is NERD?
- How do you diagnose it?
- How do you treat it?
- What are the outcomes of NERD?



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What is NERD? The old definition...

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

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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

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### 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)

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## New Definitions

	Typical Symptoms	Erosions Endoscopically	Abnormal amount of acid reflux	+ Symptom association with acid or
Should hypersensitive esophagus be considered NERD? Functional heartburn?				
NERD	+		+	+/-
Hypersensitive Esophagus	+			+
Functional Heartburn	+			

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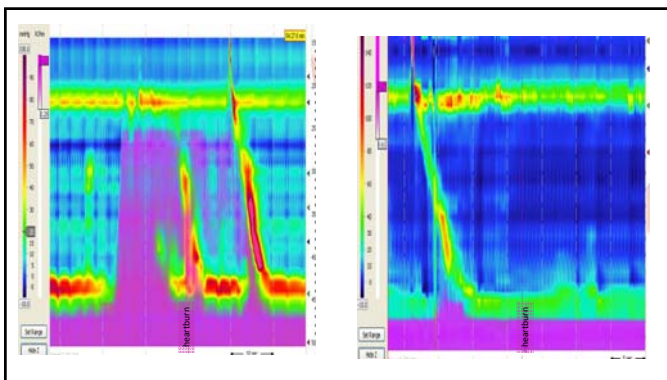
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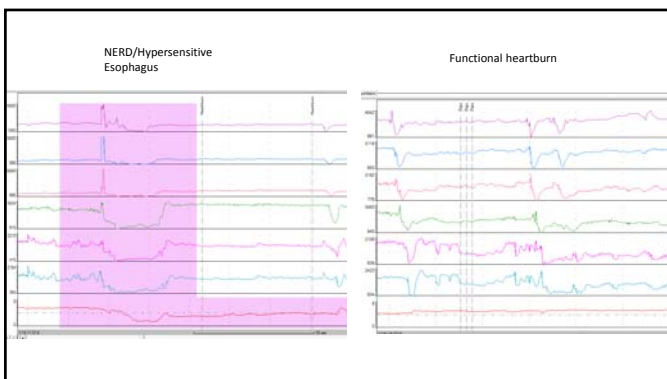
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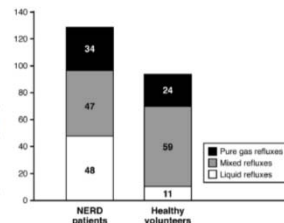
## Manometry in NERD patients

Ribolsi et al Clin Gastro Hep 2014

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

	Mean TLESRs	Mean reflux during TLESRs
Patients	11.7 ± 2.1	9.2 ± 2.8
Healthy volunteers	12.7 ± 3.4	8.5 ± 2.1

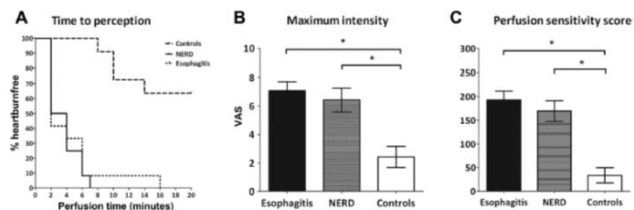
NOTE. Data are expressed as mean ± standard error of the mean.



**Figure 3.** Characteristics of reflux episodes associated with TLESRs, in patients and healthy volunteers.

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

Weijenborg et al AJP-Gastrointest Liver Physiol 2014



**Fig. 1.** Parameters of acid perception in patients with esophagitis, patients with nonerosive reflux disease (NERD), and control subjects. A: lag time to initial heartburn perception. B: maximum symptom intensity. VAS, visual analog scale. C: perfusion sensitivity scores. \* $P < 0.05$ .

## Regional sensitivity of the esophagus in NERD patients

Emerenziani et al NGM 2009

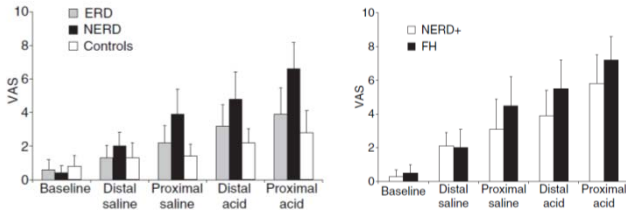
**Table 1** Proportion (%) of symptomatic events according to the acidity at each esophageal site

	All NERD	NERD pH+ (n = 8)	NERD pH- (n = 6)
<b>Acidic reflux (%)</b>			
5 cm above LOS	11 ± 2	11 ± 3	10 ± 5
15 cm above LOS	18 ± 5*	17 ± 6*	18 ± 7*
20 cm above LOS	25 ± 8*	20 ± 8*	30 ± 19*
<b>Weakly acidic reflux (%)</b>			
5 cm above LOS	8 ± 2	7 ± 4	8 ± 4
15 cm above LOS	19 ± 7*	16 ± 11*	22 ± 8*
20 cm above LOS	27 ± 8*	23 ± 12*	32 ± 9*

\* $P < 0.05$  vs distal.

## Visceral hypersensitivity throughout the esophagus

Thoua et al APT 2008

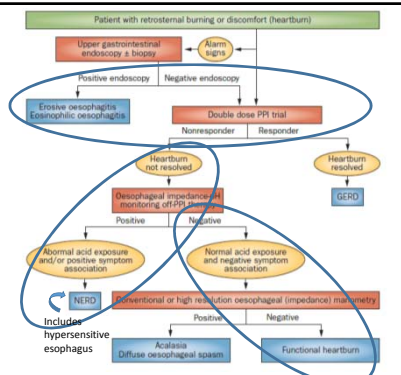


## NERD Algorithm

Savarino et al Nat Reviews Gastro 2013

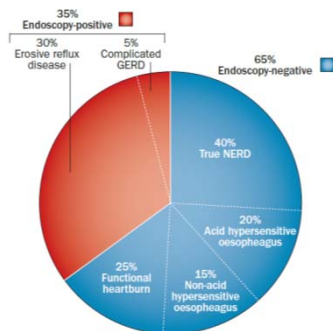
Adults suggest functional heartburn is not NERD

NERD by definition needs some abnormal reflux testing, not just symptoms



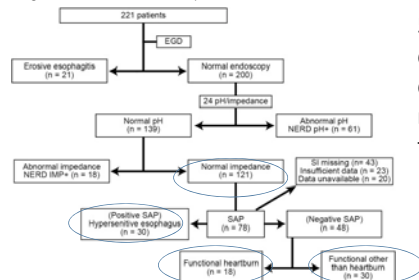
## Incidence of subtypes

Savarino Nat Med Rev 2013



## Incidence of functional heartburn and hypersensitive esophagus

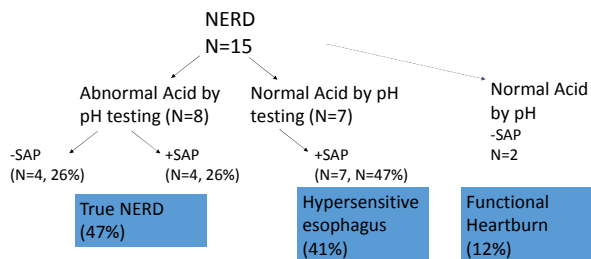
Fong-Kuei et al Clinical Gastro Hepatol 2015



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

## Frequency of Subtypes in Pediatrics

Borelli et al NGM 2012

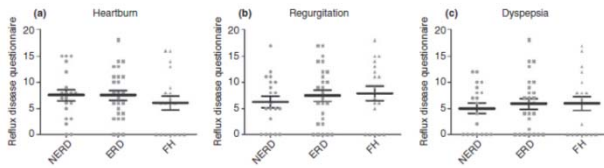


Can we diagnose NERD by:

- Symptoms
- Proton pump inhibitor trial
- Endoscopy
- Impedance

## Can you tell based on history who has which diagnosis?

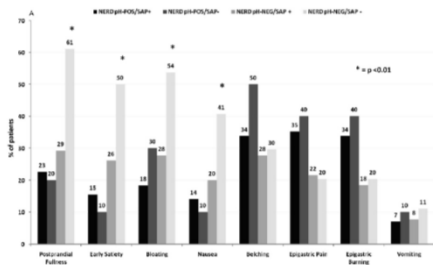
Kandulski et al APT 2013



**Figure 2 |** Symptom characteristics according to the reflux disease questionnaire. Panels a + b display the reflux items for heartburn (a) and regurgitation (b). Panel c shows the dyspepsia score. For all items, no significant differences were obtained between the diagnoses.

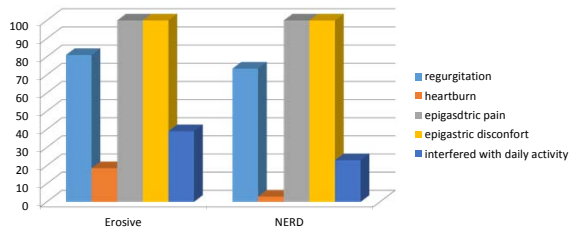
## What about other symptoms besides heartburn?

Savarino et al Gut 2009



## Can you tell based on history who has which diagnosis?

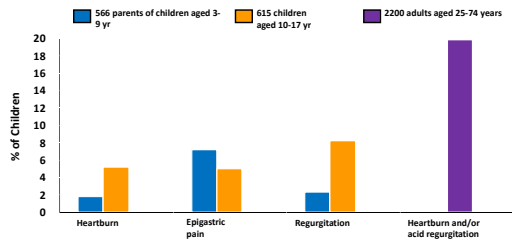
Lee et al Archives Dis Child 2010



43 children with ERD, 34 children with NERD

Prevalence of GER Symptoms in Children

Nelson et al Arch Pediatr Adolesc Med 2000



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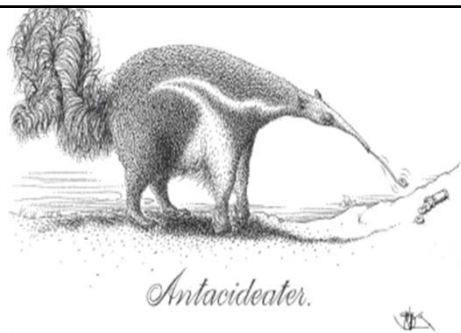
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PPI Trial



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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 GERD Patients With and Without Erosive Esophagitis and in Non-GERD Patients

	GERD		NERD	Non-GERD
	Esophagitis	No esophagitis		
All patients (n = 296)	57% (64/112) <sup>a</sup>	49% (42/85)		35% (35/99)
Placebo nonresponders (n = 253)	54% (53/98) <sup>a</sup>	44% (31/71) <sup>a</sup>		27% (23/84)
Patients with symptoms typical for GERD (n = 127)	72% (57/72)	61% (30/50)		56% (14/25)
Patients without symptoms typical for GERD (n = 169)	30% (12/40)	40% (22/55)		28% (21/74)

NOTE. Symptoms typical for GERD were defined as heartburn, regurgitation, dysphagia, or central chest pain as the most bothersome symptom. <sup>a</sup>P < .01, <sup>b</sup>P < .05, vs non-GERD (Fisher exact test).

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## PPI trial cannot differential patients with and with and without GERD symptoms

Bytzer et al 2012

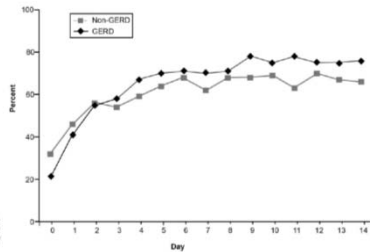


Figure 2. Proportion of patients with relief of reflux symptoms in response to PPI day by day.

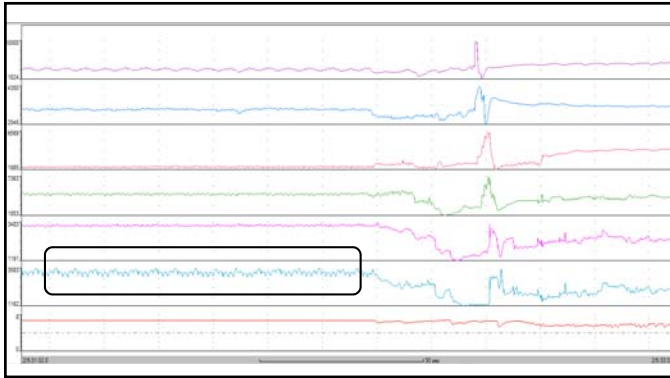
## Response of Symptoms to PPI

- 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



No such thing as an impedance cartoon but since impedance goes in the nose, we are going with a nose joke.....




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Can I get by just using baseline impedance values?

Borrelli et al NGM 2012

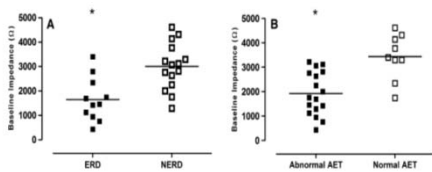


Figure 1 Baseline impedance levels in (A) NERD and ERD groups, and (B) children with pathological and physiological AET. The bars indicate the means. ERD: erosive reflux disease; NERD: non erosive reflux disease.

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Baseline impedance correlates with other reflux parameters

Borrelli et al NGM 2012

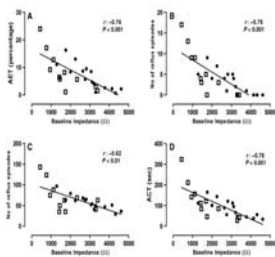


Figure 3 Correlation between baseline impedance levels and acid exposure time (AET). A) long-lasting reflux episodes (s) and B) acid reflux episodes (%). C) acid duration time (ACT, s) in the whole study population. □ ERD (erosive reflux disease); ● NERD (non erosive reflux disease).

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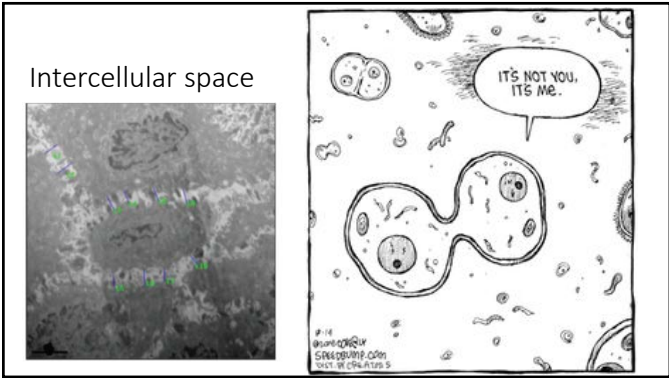
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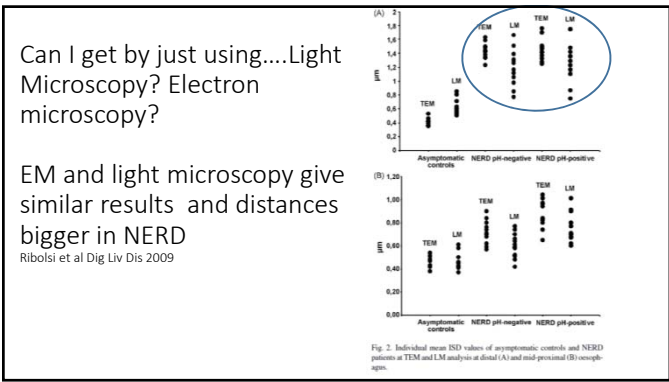
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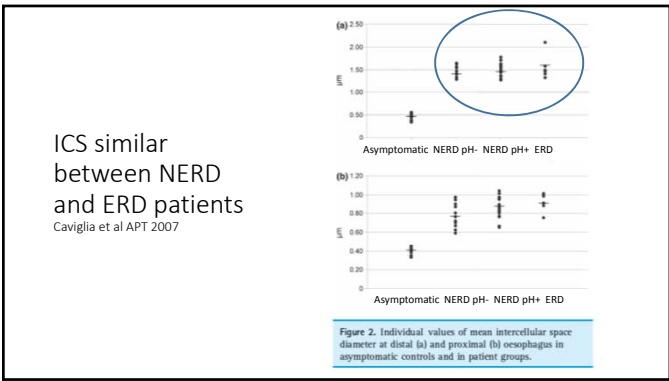
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## No difference in ISD in children with NERD versus ERD

Borrelli et al NGM 2012

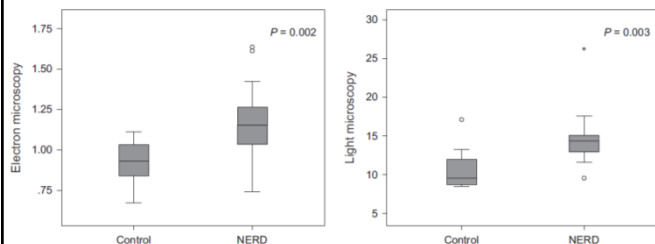
Table 2 Mean intercellular space diameter (ISD), mean of maximum is values and mean of minimum ISD values in the two groups of patients

ISD ( $\mu\text{m}$ )	NERD (n = 15)	ERD (n = 11)
Mean value $\pm$ SD (95% CI)	1 $\pm$ 0.3 (0.9-1.2)	1.1 $\pm$ 0.3 (0.9-1.2)
Mean of Maximum value $\pm$ SD (95% CI)	1.4 $\pm$ 0.4 (1.2-1.6)	1.7 $\pm$ 0.6 (1.3-2.1)
Mean of Minimum value of DIS $\pm$ D (95% CI)	0.4 $\pm$ 0.1 (0.4-0.5)	0.5 $\pm$ 0.2 (0.3-0.6)

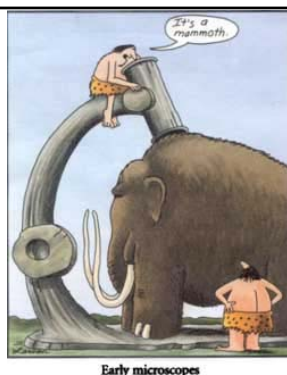
NERD, non-erosive reflux disease; ERD, erosive reflux disease.

## Differences cellular spaces on esophageal histology

Altaf et al JPGN 2014

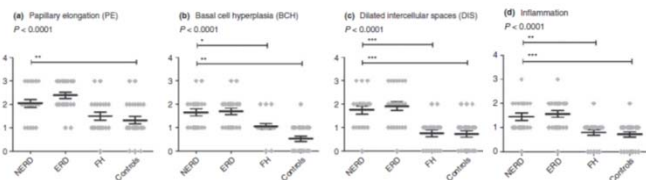


The value of inflammation on histology ?



## Microscopically, you cannot tell NERD from ERD

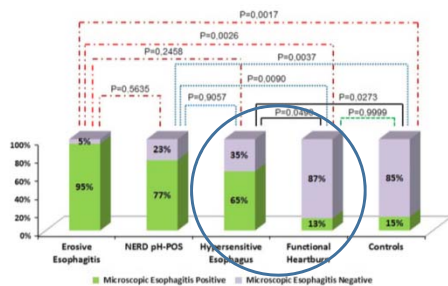
Kandulski et al APT 2013



## Role of microscopic inflammation and NERD

Savarino et al J Gastro 2014

**Fig. 2** Percentages of microscopic esophagitis, identified by light microscopy using a histological global score of  $\geq 0.35$ , among our different subgroups of patients and healthy volunteers (HVs) (pairwise comparison with adjusted  $p$  values)



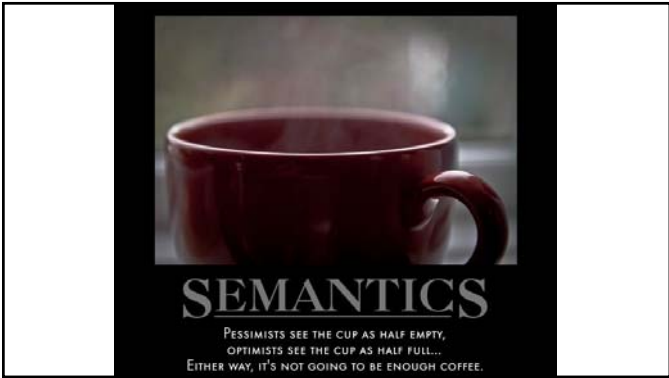
## Can I differentiate patients based on Histology?

**Table 1** Demographics and baseline disease characteristics in the two groups of GERD patient

	NERD	ERD
No. of cases	15	11
Age (years; median and ranges)	11.2 (4-18)	9.6 (4.2-14)
MF	9/6	7/4
Disease duration (weeks; median and ranges)	12 (9-17)	13 (10-19)
Symptoms and signs, n (%)		
Regurgitation/vomiting	12/15 (80)	9/11 (82)
Epigastric pain	11/15 (73)	9/11 (82)
Pyrosis	4/15 (27)	5/11 (45)
Dysphagia	1/15 (7)	2/11 (18)
Emetocesis	0/15 (0)	2/11 (18)
Wheezing/asthma	2/15 (13)	0/11 (0)
Cough	6/15 (40)	2/11 (18)
Grade of esophagitis <sup>1</sup> , n (%)		
Grade A	-	7/11 (64)
Grade B	-	3/11 (27)
Grade C	-	1/11 (9)
Grade D	-	-
Hiatal hernia	-	1/11 (9)
Presence of esophagitis <sup>1</sup> , n (%)	7/15 (47)	10/11 (91) <sup>2</sup>
Abnormal AET, n (%)	8/15 (53)	8/11 (73)

NERD, non-erosive reflux disease; ERD, erosive reflux disease; AET, acid exposure time. <sup>1</sup> $P < 0.05$  by Fisher's exact test. <sup>2</sup>According to Los Angeles classification. <sup>3</sup>According to histology.

Borelli NGM 2012



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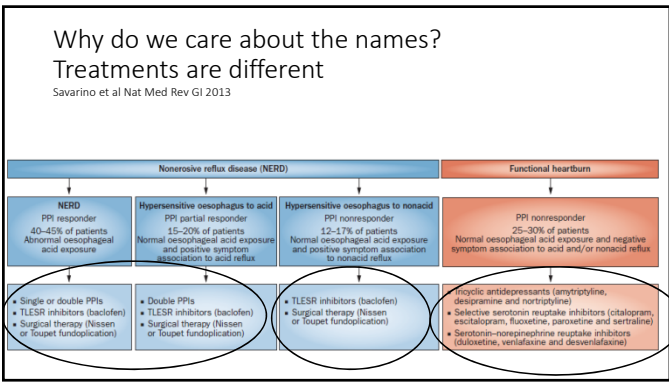
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PPI response in NERD  
Dean et al Clinical Gastro Hepatol 2004

**Table 5.** Symptomatic Response Rates and Therapeutic Gains at 4 Weeks Among Patients With NERD and EE

Study population	PPI symptomatic response pooled rate (95% CI)	Placebo symptomatic response pooled rate (95% CI)	Therapeutic gain – difference (95% CI)
NERD (n = 1854)	36.7 (34.1–39.3)	9.5 (7.1–11.9)	27.2 (20.9–35.3)
EE (n = 705)	55.5 (51.5–59.5)	7.5 (2.5–12.5)	48.0 (24.6–93.8)

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## 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

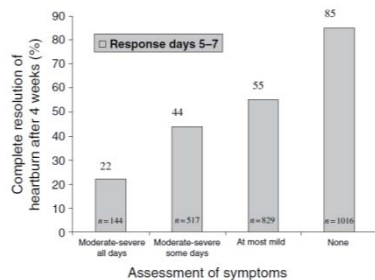


Figure 1. Complete resolution of heartburn (%) after 4 weeks by symptom response during days 5–7 of the first week of treatment.

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



Lee et al Archives Dis Child 2010

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

Broeders et al Br J Surg 2010

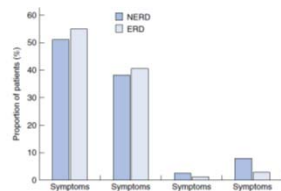


Fig 2 Self-rated change in reflux symptoms 5 years after surgery compared with the preoperative state in 76 patients with non-erosive (NERD) and 69 with erosive (ERD) reflux disease (Vnick score)

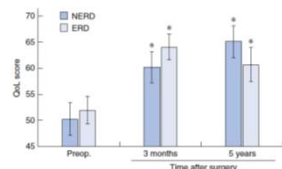
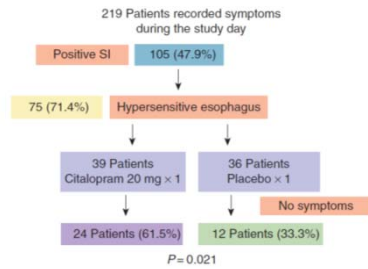


Fig 3 Mean (s.e.m.) quality of life (QoL) score, measured on a visual analogue scale from 0 to 100, in 69 patients with non-erosive reflux disease (NERD) and 89 with erosive reflux disease (ERD) before surgery and 3 months after surgery, and in 68 and 64 patients respectively 5 years after surgery. \* $P < 0.050$  versus preoperative score (paired-samples  $t$  test)

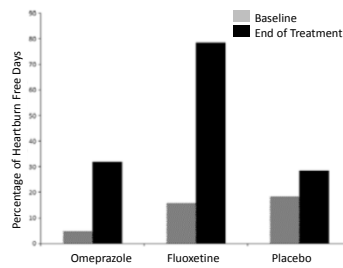
## SSRI for hypersensitive esophagus

Viazis et al Am J Gastro 2012

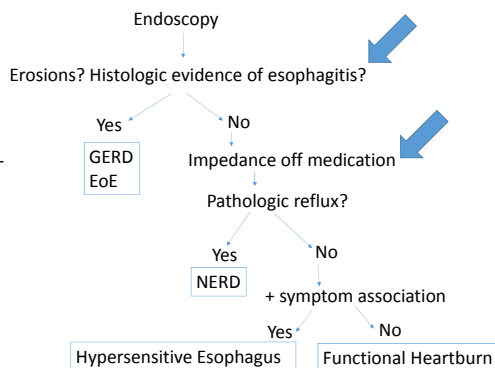


## SSRI for functional heartburn

Ostovaneh et al NGM 2014



Proposal for  
PPI  
Non-  
Responders





## 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

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“Be nice  
To nerds.  
Chances are you'll  
End up working for  
One.” -Bill Gates

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