



GERD in the NICU



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Learning Objectives

- To determine the prevalence and economic burden of gastroesophageal reflux (GER) in infancy
- To appropriately utilize diagnostic testing in the evaluation of infants with complicated GER
- To understand the safety and outcome of current therapeutic approaches in the management infants with clinical GER

Why is GER in the NICU very important ??

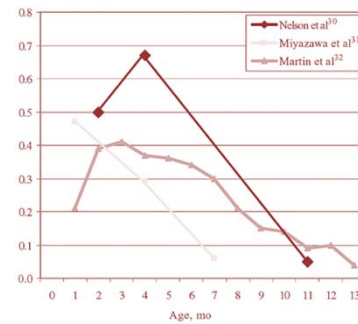
Great divide remains



Clinical practice

The use and abuse of anti-reflux medications is still a debate

GER is the passage of gastric contents into the esophagus and is a physiologic process



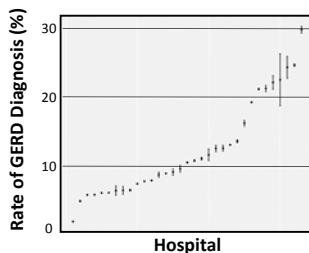
Natural history

Vandenplas & Rudolph. *JPGN*, 2009; (49):498-547
 Goldin A B et al. *Pediatrics* 2006;118:2326-2333

Variability in GERD Diagnosis Rates across the USA

Hospital Pediatrics 2013

- Rates of GERD diagnosis in preterm infants varied dramatically across NICUs from 2.4% to 29.9%¹



(Each dot represents a data point with upper and lower 95% CIs)

Prevalence of Neonatal Anti-reflux strategies

- Clinical significance of GERD also evident from the **7-fold** increase in use of acid suppressive medications
- ~ **48%** (range, 10% to 90%) of premature neonates are being discharged on acid suppressive medications
- ~**45%** of anti-reflux procedures are performed in infants

Malcolm et al. 2008 *Pediatrics*
 Clark et al. 2006 *Pediatrics*

GERD and Burden

- GERD diagnosis is associated with:

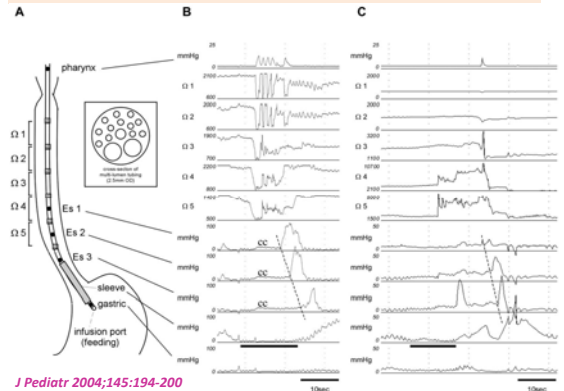


- \$70,489 additional costs per discharge and
- 29.9 additional days in LOS

Lighter birth weights, age >7 days, Aged 28 to 33 weeks at birth, Non-Hispanic patients

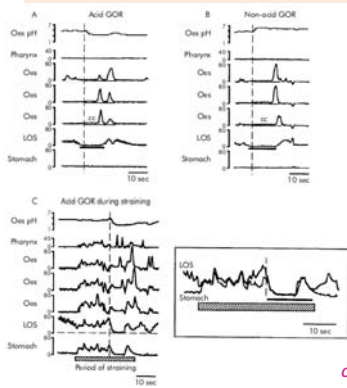
Hospital Pediatrics 2013

How does it happen?



J Pediatr 2004;145:194-200

Healthy infants vs infants with GERD



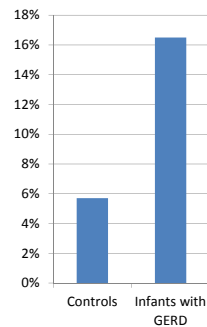
36 infants
22 normal healthy
14 infants with GERD

- TLESRs' occurrence is not affected by postmenstrual age
- Weak correlation between postnatal age and the rate of TLESRs, with older infants having fewer TLESRs ($r=0.32$, $p<0.05$)

Omari et al, Gut 2002;51:475-479

Mechanisms of reflux in neonates with GERD

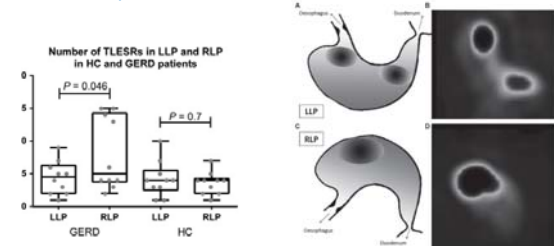
TLESR associated with acid GER



- In infants with GERD, the number of TLESRs overall was similar to healthy controls...
- but the proportion of TLESRs accompanied by acid GER was significantly higher.

Omari et al, Gut 2002;51:475-479

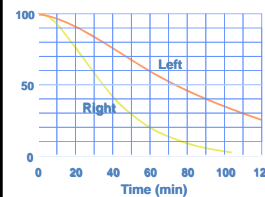
In GERD patients, TLESRs, GER, distension of proximal stomach, and gastric emptying are increased in RLP compared to LLP. This effect is not seen in HC.



Infants with GERD have a significantly higher number and proportion of TLESRs associated with acid GOR ($p<0.0001$)

Loots, et al, Neurogastroenterol Motil (2013)

Gastric Emptying



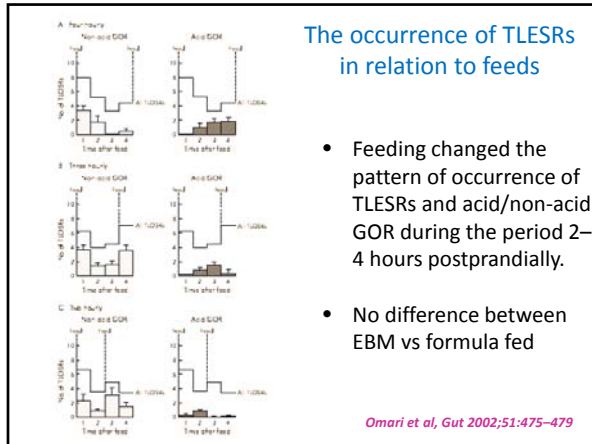
Omari et al. J Pediatr. 2004;145(2):194-200

TLESRs trigger 71-77% of GER events

	Right side	Left side
All GER		
Median (IQR) episodes	13 (12-14)	2 (1-6) ^{**}
Total No. of episodes	71	18 [#]
% Liquid	80	50 [#]
% Gas	12	22
% Mixed	8	28
TLESRs		
Median (IQR) TLESRs	14 (10-14)	2 (2-8)
Total No. of TLESRs	69	22 ^{###}
% Uneventful	29	23 ^{###}
% Liquid	63	36
% Gas	4	18
% Mixed	4	32

	Right side	Left side
Gastric emptying		
Mean $T_{1/2}$ (min)	34.9 ± 6.9	75.3 ± 5.3 ^{###}
Mean T_{min} (min)	22.5 ± 1.6	34.9 ± 2.1 ^{###}
Mean T_{lag} (min)	60.9 ± 4.3	91.7 ± 4.6 ^{###}
Mean gastric emptying coefficient	3.99 ± 0.22	3.40 ± 0.14 [#]

Significantly different, using Mann-Whitney U test (^{*} $P < .05$, [#] $P < .01$, ^{###} $P < .005$). Pairwise of GER significantly different, using χ^2 test (^{*} $P < .05$, [#] $P < .01$, ^{###} $P < .005$). Significantly different, using analysis of variance (^{*} $P < .05$, ^{##} $P < .01$, ^{###} $P < .005$).



Do infants have higher gastric acid production?

TABLE 1. Gastric acid secretion in infants and children after betazole stimulation

Mean age	Volume (mL/h)	Mean titratable acid (mEq/h)	Mean acid output (mEq/kg/h)
1 d	3.3	8.1	0.01
4 wk	3.1	26.4	0.02
12 wk	13.4	34.8	0.10
16 wk	44.0	41.6	0.17
24 wk	64.0	49.2	0.24
>4–9 yr	42.5	114.2	0.24
>11 yr to adults	143.2	91.2	0.19

*Scand J Gastroenterol. 1967;2(3):209-213
JPGN 37(Suppl):S12–S16, 2003*

How is GER received?

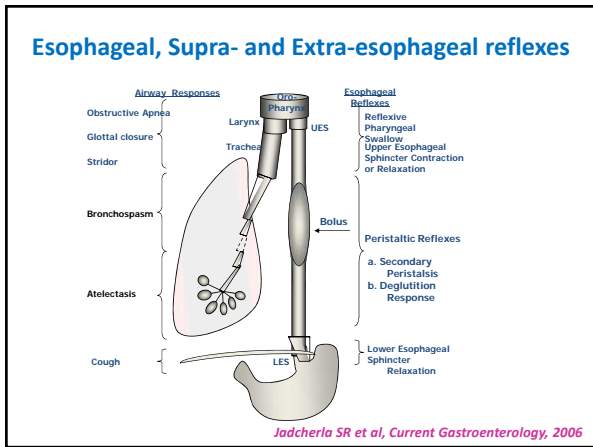
GER

- The retrograde movement of stomach contents into the esophagus
- Refluxate can be stomach acid, feeds, bile, gastric or pancreatic juices, or even air
- It can be a normal physiologic process that occurs throughout the day in healthy neonates, infants, children, and adults

GERD

- GERD occurs when GER causes symptoms
- It is a pathological process manifesting as:
 - Poor Oral Feeding
 - Poor weight gain
 - Aversion
 - Irritability/Pain
 - Swallowing Problems
 - Esophagitis
 - Hematemesis
 - ENT problems
 - airway symptoms (apnea, aspiration, recurrent pneumonia, chronic lung disease (CLD))

Jadcherla SR, Rudolph CD. NeoReviews 2005;6:e87-e98



GER in the NICU is still a controversy!!

Great divide remains

Red flags Apnea?? Aspiration!!

Maturation

Myth: Gastroesophageal reflux is a pathological entity in the preterm infant
Christian F. Poethig, Pablo E. Bruckmann

The use and abuse of anti-reflux medications is still a debate

How and when to evaluate?


MH1 How much is GER predictable with questionnaires, pH-metry, endoscopy and histology?

- **Poor diagnostic accuracy** of a clinical questionnaire (compared to pH monitoring and esophageal biopsy)
 - 100 infants suspected of having GER compared to 100 healthy controls.
- A normal questionnaire score in 26% of those with confirmed GERD.
- The score was abnormal in 81% of infants with a normal biopsy and pH study result,


J Pediatr Gastroenterol Nutr 2005;40:210e5.

Appropriate Use of the Upper GI Series to Evaluate for GERD


- Useful to detect anatomic abnormalities
 - Intestinal malrotation (or non-rotation), hiatal hernia, achalasia, stricture or mass
- Not a test to definitively diagnose reflux
- Many false positives and negatives (< 50% sensitive/specific)



Intestinal malrotation in an 8 year-old with chronic vomiting and heartburn



Achalasia in a 14 year-old girl with chronic vomiting. Previous diagnosis 'psychogenic vomiting'



Stricture in a 13 year-old post-bezoar removal

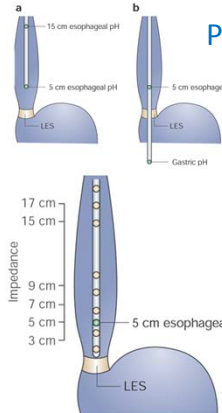
Rudolph, et al. J Pediatr Gastroenterol Nutr. 2001;32:51.

The benefits of UGI in evaluating a patient with GERD

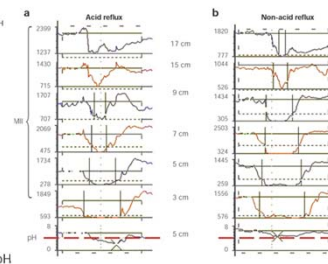
Finding	No. of patients (%)
Malrotation	22 (3.3)
Esophageal stricture	5 (0.76)
Delayed gastric emptying	2 (0.30)
Possible duodenal obstruction	1 (0.15)

J Pediatr Surg (2010) 45, 1169–1172

Ph-metry vs Ph-impedance



15 cm esophageal pH
5 cm esophageal pH
LES
Gastric pH



a Acid reflux
b Non-acid reflux

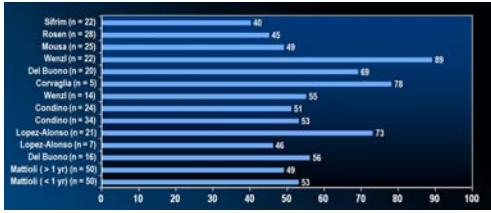
- pH Reproducibility 70's
- The sensitivity of the pH probe is 40% (compared with pH-II)

Normal values for non-acid reflux

Variable	Percentile	Upright	Recumbent	Total	
%NAGER	Median (IQR)	1 (0.6-1.55)	0.4 (0.1-1.1)	0.7 (0.45-1.2)	
Infants (n=46)	90 th	2.7	1.74	1.78	
	95 th	3.4	2.15	2.48	
(birth-11.9 mo)	NAGER Frequency	Median (IQR)	11 (6-19.5)	11 (7-23)	32 (16-45)
	90 th	39.2	44.2	57.6	
	95 th	45.5	48.1	67.1	
	#Proximal NAGER Episodes	Median (IQR)	7.5 (3-15)	7.5 (1.75-17.3)	21.5 (8.5-32.5)
	90 th	30.3	37.6	49.6	
	95 th	45.5	40	57	

Mousa, et al Curr Gastroenterol 2014

- Ability to measure nonacid reflux
- Ability to assess chemical clearance vs bolus clearance
- Ability to evaluate the possible association between GER and other symptoms



Study (n)	Non-acid reflux (%)
Sillem (n = 22)	40
Rosser (n = 28)	45
Mousa (n = 25)	49
Wenzl (n = 22)	69
Del Buono (n = 20)	78
Corngaglia (n = 5)	89
Wenzl (n = 14)	95
Condino (n = 24)	51
Condino (n = 34)	53
Lopez-Alonso (n = 21)	73
Lopez-Alonso (n = 7)	46
Del Buono (n = 16)	56
Mattoli (> 1 yr) (n = 50)	49
Mattoli (< 1 yr) (n = 50)	53

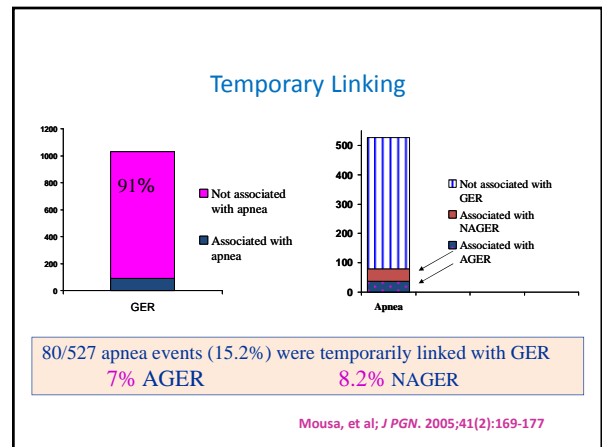
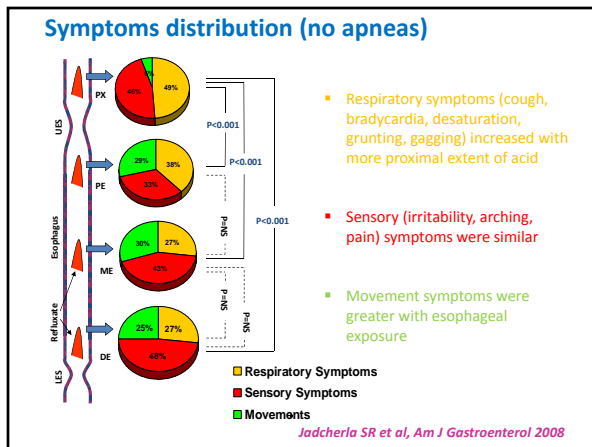
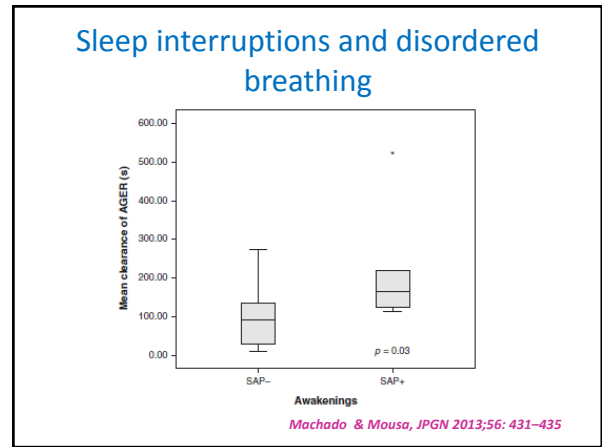
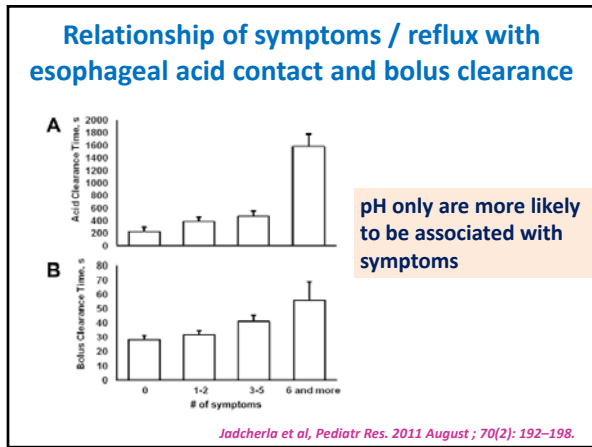
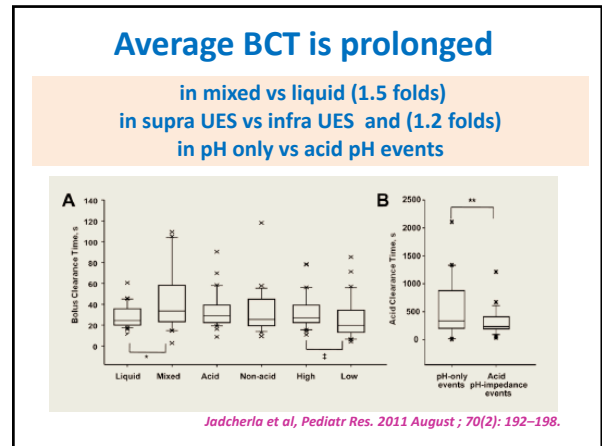
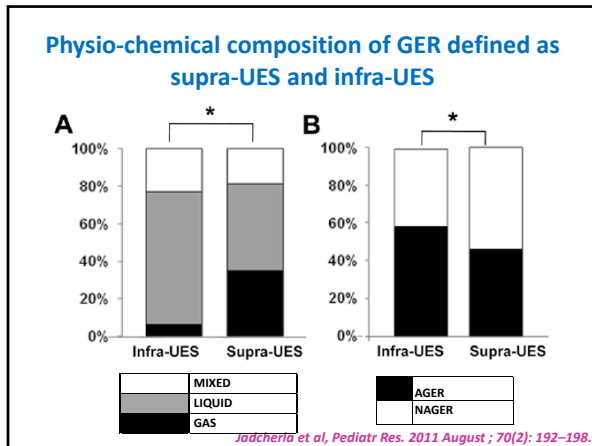
Acta Paediatr. 2007;96(7):956-62
Gastroenterology. 2001;120(7):1599-606

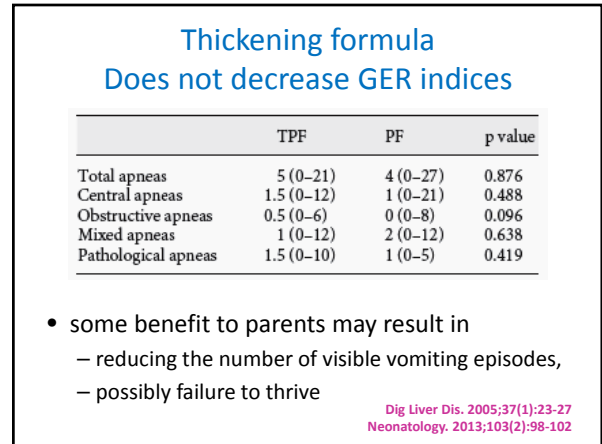
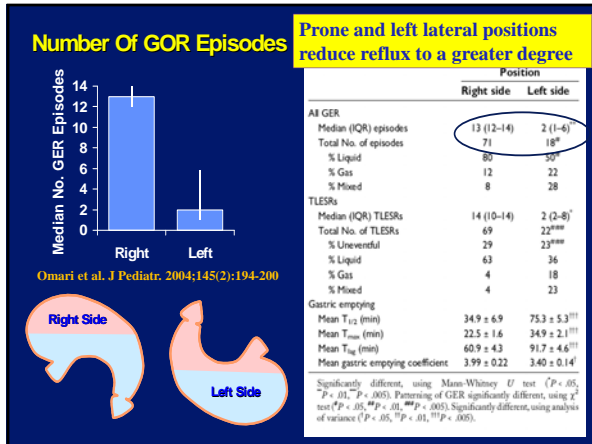
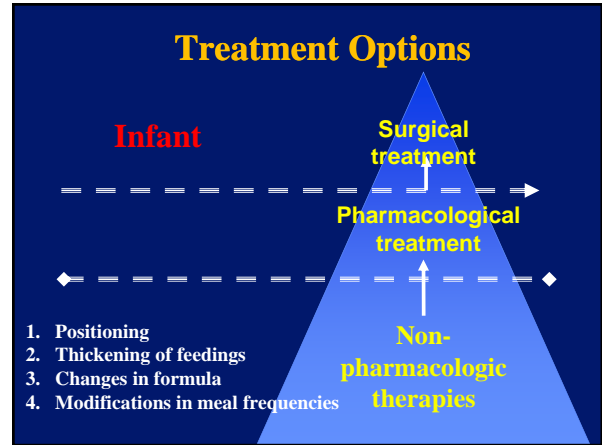
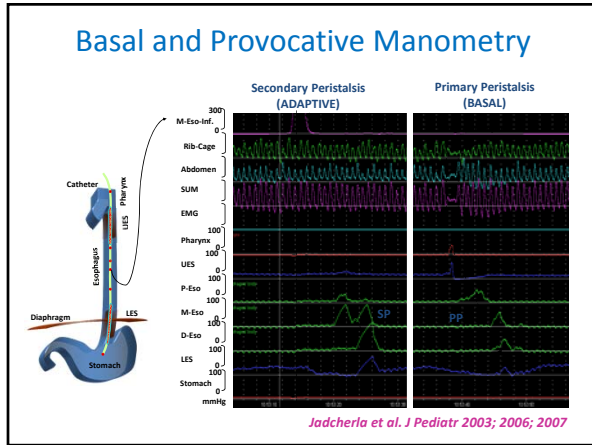
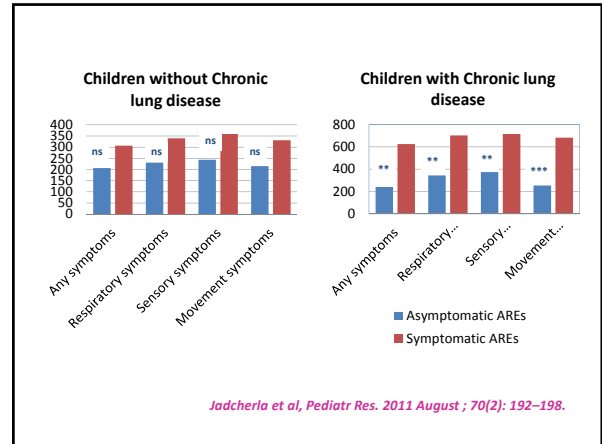
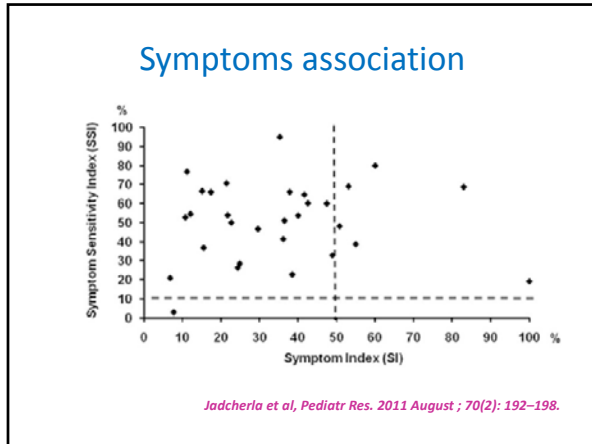
Slide 19

MH1

add graph

Mousa, Hayat, 10/21/2014





Frequent feedings

- BCT and ACT during each hour of the 3 hour feeding cycle

Postprandial Hour	BCT, s	ACT, s	P Value
1	26.2 = 30.9 (18.7, 36.3)	218.4 = 716.7 (0, 7.4)	.9
2	15.3 = 23.0 (4.9, 21.7)	419.1 = 940.8 (0, 271.1)	.001
3	13.5 = 24.1 (1.8, 18.0)	589.6 = 709.2 (432.4, 863.7)	<.0001

- Caloric density and (feeding volume) did not change reflux burden in preterm infants
- Faster flow rates and shorter durations resulted in a higher reflux burden.

JPEN, 2012;36(4):449-455
Omari et al, Gut 2002;51:475-479

Hypoallergenic formula

- Symptoms of milk protein intolerance are similar to reflux symptoms, including fussiness, regurgitation, arching, and colic
- A 2-week trial of a hypoallergenic formula has been suggested to treat symptoms of GER (NASPGHAN guidelines)

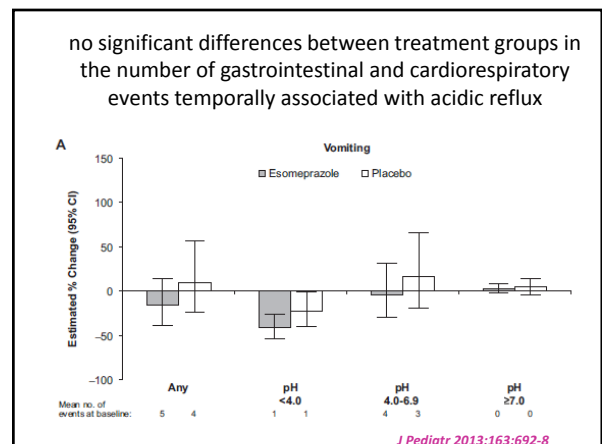
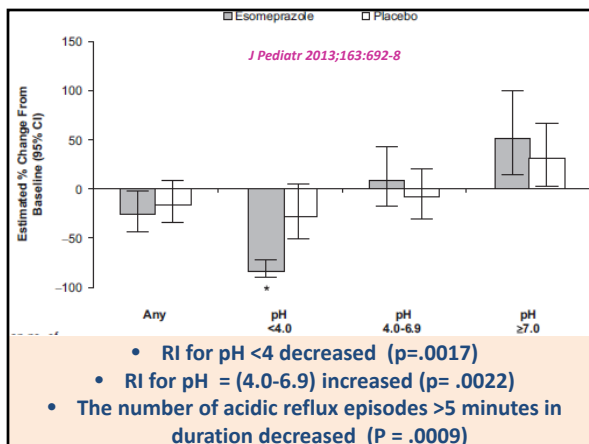
J Pediatr. 2012;161(3):476-481

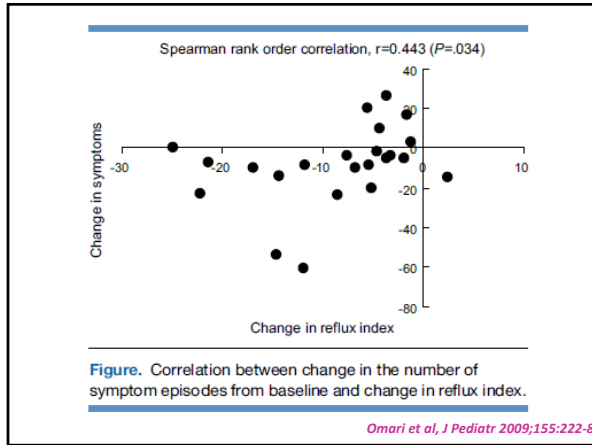
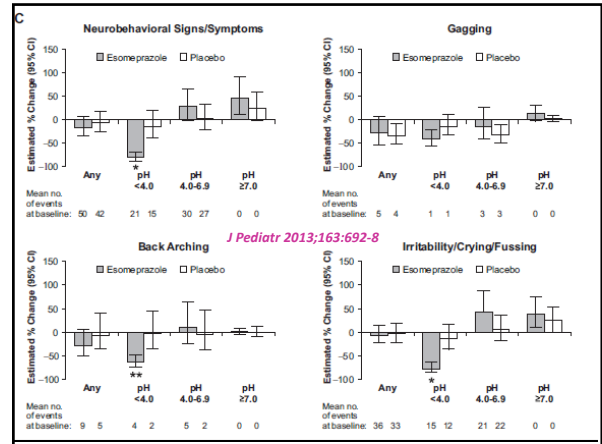
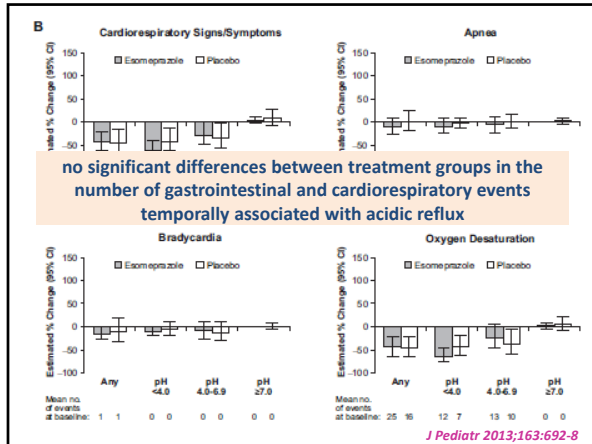
Outcome of conservative therapy in 50 infants

- 78% of the study population improved
- 25% completely resolved to normal
- Individual symptoms of regurgitation, crying, and arching improved significantly

Orenstein SR, et al J Pediatr 2008

Pharmacotherapy





Orenstein et al; J Pediatr 2009; 154:514-20

- Randomized, doubleblind, placebo-controlled study
- 162 infants with symptomatic GERD
- No differences between lansoprazole and placebo
- In percentage of feedings with crying episodes or duration of crying episodes averaged across feedings

Risks of using acid suppression medications in infancy
Hospital Pediatrics 2013;3:16

Study Author	Type of Study	Age	Location	Medications Investigated	Outcome Assessed	OR (95% CI)
Guillet et al ^a	Retrospective	Neonates	NICU	Ranitidine, famotidine, cimetidine, Ranitidine	NEC	1.71 (1.34-2.19), $P<.0001$
Terrin et al ^a	Prospective	Neonates	NICU	Ranitidine	NEC, sepsis, pneumonia, UTI	Infections: 5.5 (2.9-10.4), $P<.001$ NEC: 6.6 (1.7-25), $P=.003$ 2.9, $P=.008$
Beck-Sague et al ^a	Prospective	Neonates	NICU	H ₂ antagonists	Bloodstream infection	3 (1.1-7.7)
Rojas et al ^a	Prospective	Neonates	NICU	H ₂ antagonists	Nosocomial infection	3.1 (0.96-10.2), $P=.059$
Graham et al ^b	Retrospective	Neonates	NICU	H ₂ antagonists or PPI	Gram-negative bacterial	6.99 (3.78-12.94), $P<.0001$
Bianconi et al ^b	Retrospective	Neonates	NICU	Ranitidine	Late-onset sepsis	$P=.006$
Elward et al ^b	Prospective	≤18 y	PICU	H ₂ antagonists	VAP	$P=.963$
Yildizdas et al ^b	Prospective	Pediatric, age range not specified	PICU	Omeprazole, ranitidine, sucralfate	VAP	-
Lopriore et al ^b	Retrospective	Pediatric, age range not specified	PICU	Ranitidine, sucralfate	VAP	$P=.025$
Sharma et al ^b	Prospective	1 mo-15 y	PICU	Ranitidine	VAP	Univariate $P<.0001$
Singh-Naz et al ^b	Prospective	Pediatrics, age range not specified	PICU	H ₂ antagonists	Nosocomial infection	$P=.05$
Canani et al ^b	Prospective	4-36 mo	Pediatric GI centers	Omeprazole and ranitidine	Pneumonia, gastroenteritis	Pneumonia: 6.39 (1.38-29.7), $P<.05$ Gastroenteritis: 3.58 (1.87-6.86), $P=.001$ $P=.032$
Orenstein et al ^b	Prospective	28 d-12 mo	Primary care centers	Lansoprazole	Lower respiratory tract infection	1.2 (1.04-1.39), $P=.008$
Turco et al ^b	Retrospective	1-18 y	Hospital	PPI, H ₂ antagonist	C difficile colitis	

Ranitidine is Associated With Infections, Necrotizing Enterocolitis, and Fatal Outcome in Newborns

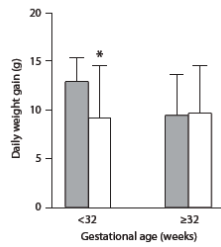
	Not exposed to Ranitidine (n = 183)	Exposed to Ranitidine (n = 91)	P
Overall infections, n (%)	18 (9.8)	34 (37.4)	<.001
Sepsis, n (%)	16 (8.7)	23 (25.3)	<.001
Pneumonia, n (%)	1 (0.5)	4 (4.4)	.043
Urinary tract infections, n (%)	1 (0.5)	7 (7.7)	.002

➤ Ranitidine use should be avoided in preterm infants.
➤ Ranitidine administration is associated with increased incidence of NEC (level 2b).

Terrin et al, Pediatrics 2012

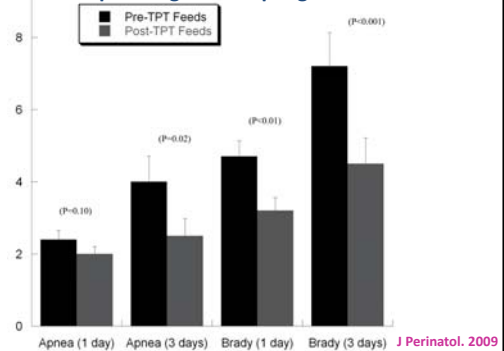
Erythromycin

Neonatology 2011;100:290-294

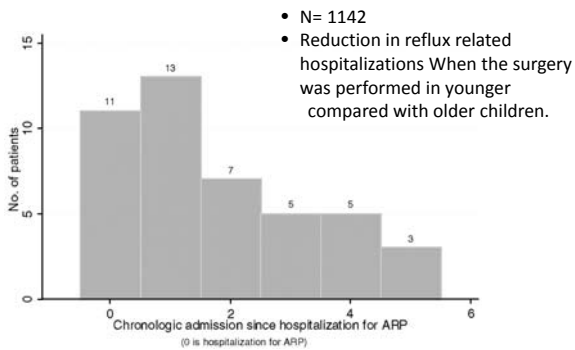


1. The ideal dosage??
2. The effect on children older than 32 weeks' gestation?
3. The effect on acid and nonacid reflux?

Transpyloric feedings may safely reduce episodes of apnea and bradycardia in preterm infants with suspected gastroesophageal



Fundoplication



- N= 1142
- Reduction in reflux related hospitalizations When the surgery was performed in younger compared with older children.

Goldin A B et al. Pediatrics 2006;118:2326-2333

Conclusion (1)

- GER is commonly diagnosed in the NICU, and in most of the cases, is a self-limited physiologic process
- Maturation of reflux protective mechanisms should be considered in evaluating for GER in the NICU
- Non-pharmacologic measures should be the first line therapy for GER
- A role for acid suppression exists in infants with evidence of esophagitis or with gastrointestinal tract bleeding

However...

Conclusion (2)

- Acid suppression therapy increases the burden of non-acid reflux and is associated with increased risk of NEC and infections
- If indicated, acid suppression therapy should be :
 - continued only with clear benefit,
 - monitored closely, and
 - discontinued empirically in consideration of maturational changes

Conclusion (3)

- Anti-reflux treatment should thus be individualized carefully in each patient to reduce the widespread use of acid suppression medications unless clear evidence of pathologic GER exists

