GER(D) in Preterm and Term Infants
Treat or not to Treat
Where is the Evidence?

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GER(D) in Preterm and Term Infants
Treat or not to Treat
Where is the Evidence?

- GER
- What is it?
- More likely physiological

- GERD
- What is it in Term and Preterm?
- More likely Pathological

Why GER is common in preterm and term infants?
More than 50% of NICU discharge prescription: GERD med
Different than older population

Physiology and Anatomy of GI tract development
Essential for preterm infants
May be for term infants if CNS injury i.e. stroke, HIE
GER(D) in Preterm and Term Infants

- Development of Suck, Swallow and coordination with respiration
- Suck: One of the primitive reflex of newborn
- Sustained strong suck vs. suck
- Creation of effective seal
- Development of buccal musculature
- Movement of tongue
- Oral Phase of Swallowing

- Swallow Pharyngeal
- Swallow Pharyngeal and laryngeal closure
- Swallow Pharyngeal, laryngeal closure and coordination with respiration

- Role of Lower Esophageal Sphincter (LES)
  - Smooth muscle thickening at JN
  - Control: Vagus; Contraction but REFLEX relaxation
  - External Ring by Diaphragm ligament
  - This two mechanism creates LESP:

GER(D) in Preterm and Term Infants

- Suck, Swallow and Co-ordination with respiration in Preterm
- Depends upon prematurity, CNS injury, oromotor stimulation, prolonged intubation and severity of lung disease in Preterm Infants
- Term infants should have all present unless CNS injury, Mitochondrial disease or myopathy affecting smooth muscle
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- LESP 5-10 mm Hg above intragastric pressure in term infants
- Preterm infants; earlier studies vs. newer study using Impedance Technology
- So LES isn’t similar as other sphincters in Neonates; Preterm or Term !!

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- What’s mechanism for Relaxation ?

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- Swallow Related LES; SLESR
  Pharyngeal Swallowing initiates LESR and primary peristaltic esophageal contraction
  It could be saliva, milk or even secretion from Respiratory tract

An example tracing of "typical" esophageal motility in the preterm infant

Omari, T. Neoreviews 2006;7:e13-e18
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- Transient LES Relaxation; **TLESR**

Important for forventing gas from the stomach to prevent GI bloating

That’s why there is “Burping”

Examples of manometric tracings of mechanisms of acid gastroesophageal reflux (GER) in preterm infants

- A: Spontaneous
- B: TLESR following Esophageal contraction
- C: Multiple swallow
- D: Peristalsis failure

- **TLESR**
  - Independent of Pharyngeal Swallow
  - Longer in duration; more than 10 seconds
  - Relax more completely as stretch from Cardia affects external Sphincter
  - Dependent on body position Lt vs. Rt

- **SLESR**
  - Dependent on Pharyngeal Swallow
  - Usually lasts 3-6 seconds
  - No effect on external sphincter
  - Independent body position
Postprandial occurrence of transient lower esophageal sphincter relaxations (TLESRs), TLESRs with common cavities (nonacid gastroesophageal reflux [GER]), and TLESRs with acid GER

**GER(D) in Preterm and Term Infants**

- Effect of body positioning on TLESR
- Right Vs Left side down after feeding?

**Right good for gastric emptying but BAD for TLESR and GER**

- So if you have residual after feeding, keep Right lateral position!
- But if you have Regurgitation problem, keep on Left lateral position!

**Abdominal-Thoracic Pressure gradient**

- Intragastric pressure positive compare to intrathoracic and intraabdominal which are negative.
- So there is pressure gradient favoring Reflux
- Increased abdominal or decreased thoracic pressure increases
The impact of straining and airways obstruction on intraesophageal pressure, intragastric pressure, and the abdominothoracic (A-T) pressure gradient

GER(D) in Preterm and Term Infants

- GER(D) and Apnea:
  - Earlier Studies:
    - Awake Apnea associated with Reflux; Spitzer A; J.Ped 1984
    - GER and relationship to Apnea; Walsh JK; J.Ped 1981

- Recent Studies:
  - Apnea isn’t prolonged by GER in preterm infants. Di Fiore et al; J Ped 2005
  - GER and Apnea of Prematurity; No Temporal relationship. Peter CS J. Ped 02
  - Apnea at discharge and GER. Barrington KJ. J Perinatology 2002

- So, where we stand today on Apnea and GER
  - Despite wide spread belief between GER and Apnea, no causative relationship has been found
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GER(D) and Chronic Lung Disease

- BAL pepsin, bile acid …in GER and CLD. Starstova et al. Chest 2007

At present, more than likely that Neonatologist and Pulmonologist treat GER in CLD preterm infants than NOT

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GER in VLBW infants: association with CLD and outcome at 1 yr of age. Fuloria et al. J of Perinatology 2000

- No difference in growth or development in either group in longer follow up.

GER(D) and behavior

- Irritability
- Arching back
- Very common observation by caregiver or parents while feeding

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GER(D) in Preterm and Term Infants

- Double blind placebo-controlled trial of Omeprazole in **irritable infants w GER**
  Moore DJ et al. J. Ped 2003

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- So, Irritability commonly with feeding but unlikely to be associated with GER in majority.
- In a few cases, CMA need to be excluded.

GER(D) in Preterm and Term Infants

- Growth in GER(D)
- Unlikely to be affected in majority of patients.
- Length of Stay in NICU is affected
- Preterm infants treated for reflux, stayed longer compare to control, more utilization of resources.

GER(D) in Preterm and Term Infants

**Diagnosis:**
- Reflux questionnaire/History
- Barium Swallow
- Ph Probe
- Impedence technology
- Litmus test
GER(D) in Preterm and Term Infants

- Reflux Questionnaire or History of Regurg/behavior problem
- Poor correlation with GERD and treatment outcome; Both
  - Barium Swallow/Upper GI
  - Barium Swallow usually for swallowing dysfunction; more importantly with CLD and/or Apnea in preterm infants or term infants with CNS problems
  - Upper GI
  - NORMAL TEST DOESN'T RULE OUT REFLUX
  - Abnormal test doesn’t establish “Significant” problem
  - More important to rule out Pyloric stenosis in persistent vomiting

GER(D) in Preterm and Term Infants

- Ph Probe:
  - Currently ‘Gold Standard’ for diagnosis
  - More importantly, it provides reflux frequency/24 hr, reflux index; % day that Ph is <4, number of episodes longer than 5 minutes and duration of longest episodes
  - Drawbacks
  - Norms are not validated in preterm infants
  - Requires 18-24 hr time
  - Upper value of Reflux 12% is significantly higher than older infants (6%)
  - Detects only acid GER
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- Multiple Intraluminal Impedance; MII Technology
  - New Technology that evaluates bolus transit through the esophagus and detects acid and nonacid GER events with no time delay.
  - Even better than Ph Probe
  - Drawbacks: Time consuming, difficult to interpret and normal not yet established for term and preterm infants

- Litmus test
  - Novel Test but older concept
  - Oropharyngeal secretion test for more than 2 acid event by litmus
  - 89% sensitivity and 80% specificity compare to Ph probe study

Treat or not to?

- Non Pharmacological Treatment
  - Positioning:
    - Increases/Aggravates GER: Infant Car seat, right lateral and supine
    - Decreases GER: Prone positioning with 30 degree elevation and left lateral position.
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- Formula or Dietary alteration
- CMA:
  - In cases with frequent vomiting associated with cow milk, 2 week trial of protein hydrolysate or amino acid based formula may be considered to exclude intolerance to cow’s milk protein as a cause of reflux symptom
  - Recommendation of North American Society of Ped. GE 2001

Thickened Feed (Cereal or Guar Gum):
- Reduces number and height of non-acid reflux episodes and regurgitation but not acid reflux events

Methods of Feeding
- NG tube Vs. NJ feeding
- Continuous Vs Bolus feeding
- Continuous Vs Intermittent NG/OG placement

Medications:
- Prokinetic Agents
- H2 Receptor antagonists
- Proton pump inhibitors
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- Prokinetic Agents:
  - Cisapride
  - Domperidone
  - Metoclopramide
  - Erythromycin

Metoclopramide
- Tested in Preterm
- Safety profile better compare to others!
- Limited usefulness in meta-analyses
- May be of value in gastric residual compare to reflux

Erythromycin
- Increases antral contractility thr’ motilin receptor
- It can improve gastric emptying in PMA 33 weeks and older infant
- Can decrease TPN associated cholestasis

Erythromycin and Infantile Hypertrophic Pyloric stenosis
- Cause vs Coincidental?
- Very Early EES & IHP
Arch Ped 02 from TenC are Data over 300,000 patient
- Con: Early treatment before 2 weeks “8 fold” increase in IHP
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- Acid Suppression Therapies
  - H2Ra decreases acid secretion
  - Ranitidine studied in preterm but not famotidine
  - Useful in steroid induced ulcer with CLD
  - Decreases regurg and crying time in Term infants older than 1 month

GER(D) in Preterm and Term Infants
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- Acid suppression therapies
  - PPI: Acts by irreversible inhibition of H/K-ATPase in Parietal cell
  - Superior than H2Ra in Acid suppression
  - Omeprazole studied most in preterm
  - Indicated for abnormal ph Probe study
  - Three distinct phenotype metabolizer
  - Long term safety not established in preterms

GER(D) in Preterm and Term Infants
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- Dangers of acid suppression (Chronic)
  - Increased risk of NEC; not standard on TPN
  - Late onset sepsis (seven times)
  - Can increase Community Acquired Pneumonia and gastroenteritis
  - Decreases absorption of calcium and B12

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- Summary
  - One of the most common problem encountered by Ped and Neo
  - Rule out CMA particularly if family history
  - Wait before considering treatment
  - Document Ph probe if possible if warranting treatment
  - Consider Co-Morbidities for treatment
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- Always use non pharmacological treatment first
- Restrict use of Erythromycin for less than 2 weeks old preterm

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- 21 days old neonate who was born full term present to you 3rd time in two weeks for persistent vomiting. His mother is breast feeding with adequate supply of milk. It was normal delivery without any complication. He weighed 9.8 at birth. He went down to 7.5 and now at 8.9. What would you do?
  - A: Stop breast feeding
  - B: Start on supplemental formula (non cow milk based)
  - C: Start on antireflux medication
  - D: Order Ph Probe
  - E: Order Upper GI
  - F: Reassurance

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6 weeks old preterm who was born at 27 weeks has problem with feeding for last 2-3 weeks with persistent residuals and regurg. of more than 30% on three different formulas. His history is remarkable for extubation in 24 hrs, no PDA, no IVH and room air for two weeks prior to last two weeks. What would you do?
- A: Wait for another two weeks
- B: Order Upper GI
- C: Consult GI
- D: Start on antireflux treatment
- E: Order Ph Probe

Thank you