Acid Mediated Disorders

Current Topics
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## Topics for Discussion

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<td>• <em>Helicobacter pylori</em></td>
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### Causative Factors

**TABLE 1. Pathophysiologic determinants of GERD**

- **Refluxate toxicity**
  - Gastric acid secretion
  - Duodenogastric reflux

- **Intrinsic gastric volume and pressure**
  - Gastric compliance
  - Gastric emptying (20)
  - Gastric acid volume secretion

- **Extrinsic pressure on gastric contents**
  - Weight (obesity (22))
  - Somatic motor tone (spasticity (34))
  - Somatic and crural episodic contractions (cough, wheeze, ... (35,36))

- **Gastroesophageal barrier**
  - Lower esophageal sphincter tone
  - Gastric fundic sensory thresholds
    - (for Transient Lower Esophageal Sphincter Relaxations)
  - Cural diaphragm location (relative to sphincter location) and function

- **Esophageal defenses**
  - Salivary secretion
  - Peristaltic motor function
  - Esophageal cytoprotection

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Genetics of GERD

- Familial clustering
  - GERD
  - Hiatal hernia
  - Barrett’s esophagus and adenocarcinoma

- “Severe pediatric GERD” locus: chromosome 13q14
  - Conflicting studies linking locus to phenotype
  - Specific gene defect suspected but excluded

- Multifactorial pathogenesis
  - Implies genetic heterogeneity in pediatric GERD

**GER Disease**

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>SIGNS/FINDINGS</th>
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<tr>
<td>Recurrent vomiting</td>
<td>Esophagitis</td>
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<tr>
<td>Poor weight gain</td>
<td>Stricture</td>
</tr>
<tr>
<td>Irritability</td>
<td>Laryngitis</td>
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<tr>
<td>Heartburn/epigastric pain</td>
<td>Recurrent pneumonia</td>
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<tr>
<td>Hematemesis</td>
<td>Sandifer posturing</td>
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<tr>
<td>Dysphagia</td>
<td>Anemia</td>
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<tr>
<td>Feeding refusal</td>
<td>Dental erosions</td>
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<tr>
<td>Globus sensation</td>
<td></td>
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<tr>
<td>Chronic cough/wheeze</td>
<td></td>
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<td>Hoarseness</td>
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Diagnostic Approach

- H & P
- Empiric acid suppression therapy
  - Time-limited trial is cost-effective
  - Long term therapy requires accurate diagnosis
- UGI: anatomic abnormalities
- EGD/Bx
  - Assess for esophagitis presence and severity
  - Exclude infx, Crohn’s, EE
- pH monitoring
  - Temporal assn. between acid reflux and frequent sx
  - Adequacy of acid suppression therapy
  - Diurnal variation
  - Provocative feeds or regular diet?
  - What about non-acid reflux?

Evidence from ≥1 well designed case-control or cohort study
Non-acid reflux

• 1/3 of all GER events
• Predominantly in 1\textsuperscript{st} hr after meal
• Impedance monitoring
  – Detects resistance to current flow
  – EM catheter with electrodes
  – Combination with pH probe
    • picks up both acid and non-acid GER
    • May be useful in cases of GERD not responsive to PPI or in extraesophageal reflux disease
    • Proposed therapies: Baclofen, EndoCinch (studies in adults)

**DIAGNOSIS**

- EGD/bx useful to exclude other disorders
- Perform esoph. bx even if mucosa appears grossly nl
- EGD useful in child over 2 y/o with recurrent vomiting

**TREATMENT**

- Elevation of HOB and left side positioning helpful
  - Children over 1 year old
- H2-blockers relieve sx and heal mucosa, but PPIs are superior to them for both
- Initial tx of esophagitis = lifestyle changes + PPI
- Histologic esophagitis: follow degree of sx relief
- Erosive esophagitis: follow endoscopically

Rudolph CD et al. (2001) JPGN 32, suppl. 2.
Esophagitis

FIG. 4. An algorithm for the continued management of a child or adolescent with esophagitis.

NASPGHAN Clinical Practice Guidelines, 2001
**Eosinophilic Esophagitis**

**Dx requires EGD/bx**
- Typical allergy tests not effective for dx
- Infiltrates can be in mid or distal esophagus
- Inflammation extends into submucosa
- Often normal pH probe study

Linear furrowing, white specks, fragile mucosa, trachealized rings *(but mucosa can be grossly normal)*

>20 eos/HPF confirms dx
**Eosinophilic Esophagitis**

- **Increasing incidence**
  - Function of dx technology and increased index of suspicion

- **Etiology unclear**
  - Allergic disorder
    - Non-IgE mediated
    - Food allergy involved
      - Aeroallergens may play role
  - Immune dysregulation
  - Severe GERD?

**CHILD**
- Vomiting
- Epigastric pain

**ADOLESCENT**
- Dysphagia

**ADULT**
- Dysphagia
- Stricture

Treatment of EE

- **Most effective**
  - Elimination diet
  - Elemental formula
  - LT inhibitors (montelukast)

- **Less effective**
  - Acid suppression
    - May improve sx but no effect on histology
  - Corticosteroids
    - sx and histologic relapses

- **Not effective**
  - Cromolyn sodium
  - Surgical GERD therapy
Barrett’s Esophagus

Major risk factors = DURATION + SEVERITY of GERD
Barrett’s

• Prevalence
  – Adults w/GERD: 15%
  – Children: 0.02-0.38%
  – 400 neurol. nl pts age 18m-25 y with GERD
    • Erosive esophagitis: 34%
    • Barrett’s: 0

• Management
  – Surveillance EGD q 1-5 y
  – Aggressive acid blockade
  – Fundoplication
  – Endoscopic mucosal resection + photodynamic therapy
  – COX-2 inhibitors?

Are there any published pediatric guidelines?
Paradigm 2005
GERD is a lifelong disorder, but its severity is not necessarily progressive

Proportion of adults who had childhood GERD symptoms:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Adult refluxers (n = 225)</th>
<th>Adult nonrefluxers (n = 154)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spit up as infant</td>
<td>23 (8.8%)</td>
<td>6 (3.8%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Abdominal pain (epigastric pain)</td>
<td>48 (21.3%)</td>
<td>17 (11.0%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Heartburn/ chest pain</td>
<td>67 (29.7%)</td>
<td>14 (9.0%)</td>
<td>0.000001</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>52 (23.1%)</td>
<td>20 (12.9%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Underweight</td>
<td>47 (20.1%)</td>
<td>18 (11.6%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Asthma</td>
<td>50 (22.2%)</td>
<td>9 (5.8%)</td>
<td>0.00002</td>
</tr>
</tbody>
</table>

P < 0.05 was considered statistically significant.
Adapted from Waring et al., 2002 (20).
Medical Therapy
PPI

- Similar healing of erosive and nonerosive esophagitis in children and adults
- **Key is using enough drug and using it right**
  - Children 1-10 y/o need higher per kg dosing
    - Increased metabolism of PPI thru cyt 2A19, 3A4
    - Omeprazole: 0.7-3.3 mg/kg/d (15-80 mg/d)
    - Lansoprazole: 1-1.5 mg/kg/d
  - Administer q AM just before 1st meal of day
    - Dose BID (or PM H2-blocker) in severe cases
    - Switch between PPIs if necessary
  - Safety
    - Omeprazole has been studied up to 2 years duration in children (11 y in adults)
    - Lansoprazole only up to 6 months duration
    - Benign fundic gland polyps unrelated to duration of therapy or dosing

Medical Therapy

Prokinetics

**Metoclopramide**
- Not efficacious
  - 12 studies in children since 1985
  - 7/9 controlled studies: NO significant improvement in GER sx
    - Increasing dose above 0.1 mg/kg/d: no improved response
- Adverse effects
  - Extrapyramidal sx can occur even at lower doses
  - Incidence of EPS higher in children
  - Tardive dyskinesia can be prolonged

**Erythromycin**
- Improves feeding tolerance in infants
  - 8/9 placebo-controlled studies
  - Dosing: 1.5-12.5 mg/kg q 6 h
  - Limited evidence in older children with GERD or gastroparesis
    - Need better outcome measures
- Risks
  - Pyloric stenosis
    - In preterms or neonates
  - QT prolongation
    - IV form in infants
  - Bacterial resistance

Antireflux Surgery

- Historical mainstay of Rx of severe GERD
  - Remains widely used
    - Increasing rate of use in 12-24 month age group
    - 14% of pediatric pts w/suspected GERD had fundoplication w/o diagnostic evaluation

- Not curative or even long-term solution
  - High rates of failure
    - Recurrence of GERD sx
    - Morbidity
      - Gas bloat syndrome
      - Esophageal dysmotility and pseudo-obstruction
      - Occasional mortality

Antireflux Surgery

- High-risk GERD pts most likely to have problems
  - Neurologic impairment (“static encephalopathy”)
    - Double complication rate, 3X morbidity, 4X re-operation rate
    - Within mean 3.5 y, 71% recurrence of sx, 25% operative failure
  - Esophageal surgery (repaired esoph. atresia)
  - Chronic lung dz (BPD, CF, asthma)

- Beware the flawed study (Fonkalsrud EW et al. Pediatrics 1998)
  - Reported “good” to “excellent” results in 85% of NI and 94% of NN children
  - No hypothesis, objective endpoints or outcome measures
  - Subjective outcomes not defined and “poor” not offered

- Best candidates for fundoplication
  - Neurologically normal
  - Well-established GERD by endoscopy
  - Prior response to PPI therapy

GER and Asthma

GER is associated with asthma and other airway problems.

Acid suppression helps control asthma flares.

- Asthma promotes GER by altering intrathoracic and intra-abdominal pressures
- GER promotes asthma
  - Reflux theory: refluxate directly stimulates airway bronchospasm and inflammation
  - Reflex theory: refluxate stimulates vagal reflex and bronchospasm thru shared innervation

Asthma and GER

Who to work up for GER

- Frequent exacerbations
  - Despite good compliance
- Nocturnal sx > once/wk
- GER sx precede resp. sx
- Lack of response to corticosteroids
  - > 2 bursts/yr prednisone
- Asthma beginning after 3 y/o
- Recurrent pneumonia

Recommended approach

3-month therapeutic trial of PPI in higher than std doses (even BID)

The Dreaded Helicobacter

- Infects $\geq$ 50% humans
  - Most are asymptomatic
  - Almost always acquired in childhood
  - Risk factors
    - Infected family member
    - Crowded living conditions
    - Lower socioeconomic status
    - Daycare
    - Immigrant/intl. adoptee
  - Transmission
    - Fecal-oral
    - Oral-oral
    - Within families

Why care about H. pylori infection?
- Duodenal ulcer disease
- Atrophic corpus gastritis: precursor to gastric adenocarcinoma or MALT lymphoma
- Iron deficiency anemia
- Growth retardation (possible association)

**Diagnosis**

**Indications for testing**
- DU or GU
  - Endoscopically dx’d
  - Radiographically definitive
- MALT lymphoma
- Follow-up of documented H. pylori disease

**Not recommended**
- Asymptomatic children
- Recurrent abdominal pain without documented PUD
- Family hx of gastric cancer or recurrent PUD

Gold BD et al. (2000) NASPGHAN Guidelines
_JPGN_ 31: 490-97.
Treatment

• Indications
  – DU/GU with Hp on bx
  – Prior hx DU/GU with active Hp
  – Atrophic gastritis w/intestinal metaplasia + Hp
  – Judgement call:
    • Hp+ gastritis w/o PUD

• Not recommended
  – Asymptomatic child + family member w/Hp, PUD, or gastric cancer
  – Hp+ child with nonulcer dyspepsia or functional abdominal pain

Table. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Position Statement: Recommended Regimens for Helicobacter pylori Treatment

First-line regimens, each agent administered twice-daily for 10 to 14 days
- Proton pump inhibitor (1-2 mg/kg/day) plus amoxicillin (50 mg/kg/day) plus clarithromycin (15 mg/kg/day)
- Proton pump inhibitor (1-2 mg/kg/day) plus amoxicillin (50 mg/kg/day) plus metronidazole (20 mg/kg/day)
- Proton pump inhibitor (1-2 mg/kg/day) plus metronidazole (20 mg/kg/day) plus clarithromycin (15 mg/kg/day)

Functional GI Problems in the Adolescent