Acid (Reflux) Related Disorders

Louis WC Liu
MD, MEng, PhD, FRCPC

OAG 14th Annual Post DDW Course
June 13, 2015
OAG 14th Annual Post DDW Course: Acid Related Disorders

CanMEDS Roles Covered in this Session:

<table>
<thead>
<tr>
<th>Role</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Expert</td>
<td>(as Medical Experts, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional attitudes in their provision of patient-centered care. Medical Expert is the central physician Role in the CanMEDS framework.)</td>
</tr>
<tr>
<td>Communicator</td>
<td>(as Communicators, physicians effectively facilitate the doctor-patient relationship and the dynamic exchanges that occur before, during, and after the medical encounter.)</td>
</tr>
<tr>
<td>Collaborator</td>
<td>(as Collaborators, physicians effectively work within a healthcare team to achieve optimal patient care.)</td>
</tr>
<tr>
<td>Manager</td>
<td>(as Managers, physicians are integral participants in healthcare organizations, organizing sustainable practices, making decisions about allocating resources, and contributing to the effectiveness of the healthcare system.)</td>
</tr>
<tr>
<td>Health Advocate</td>
<td>(as Health Advocates, physicians responsibly use their expertise and influence to advance the health and well-being of individual patients, communities, and populations.)</td>
</tr>
<tr>
<td>Scholar</td>
<td>(as Scholars, physicians demonstrate a lifelong commitment to reflective learning, as well as the creation, dissemination, application and translation of medical knowledge.)</td>
</tr>
<tr>
<td>Professional</td>
<td>(as Professionals, physicians are committed to the health and well-being of individuals and society through ethical practice, profession-led regulation, and high personal standards of behaviour.)</td>
</tr>
</tbody>
</table>
# Financial Interest Disclosure

(over the past 24 months)

**Dr. Louis Liu**

<table>
<thead>
<tr>
<th>Commercial Interest</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takeda Canada Inc.</td>
<td>Speaker, advisory board, consultant</td>
</tr>
<tr>
<td>Forest Laboratories</td>
<td>Speaker, advisory board</td>
</tr>
<tr>
<td>Actavis</td>
<td>Speaker, advisory board</td>
</tr>
<tr>
<td>AbbVie</td>
<td>Speaker, advisory board</td>
</tr>
</tbody>
</table>
Global Impact of GERD
Acid Pocket

• Only been demonstrated under stationary conditions in the postprandial period
• **Aim:** monitor the acid pocket during 24 hours using ambulatory multi-channel pH-impedance-pressure recording
• **Method:** 4 healthy volunteers. Catheters with 8-pH, 5-pressure, 8-Z sensors were clipped at Z-line (6.75 cm above and 9.75 cm below)
• **Results:** occurred 1-8 min after meals, lasting 52±9min, located 2.9±1.2 cm below GEJ, moved distally at night coupled with gastric contractions (likely associated with MMC III)
• **Discussion:**
  – Acid pocket, floating on top of a meal along with TLES relaxation during the post-prandial periods, promotes acid reflux
  – Acid pocket is increasingly recognized as therapeutic targets

Complex Antacids with Alginate

• Alginate: refined from brown seaweeds, absorbed water quickly, used extensively as an impression-making in industry (dentistry, prosthetics, life-casting)

• Compounded with antacids to neutralize and displace the acid pocket, as well as for a barrier for reflux

• 4 presentations on this topic in DDW 2015:
  – 3 clinical studies


Alginate-Antacid Chewable Tablets Reduce Esophageal Acid Exposure in Chinese Patients With Moderate Gastro-Esophageal Reflux Symptoms: A Randomized, Placebo-Controlled, Crossover Study. Y Yuan, N Levinson, B Ng, G Smith, J Wilkinson. Mo 1151, DDW 2015

- Chinese patients with moderately severe GERD, n = 44, randomized,
- A single dose of 4 tablets of chewable alginate with 2 antacids (CaCO$_3$ & NaHCO$_3$) vs placebo, 4-hr monitoring after a refluxogenic meal (McDonalds Big Mac, medium fries, med sized Fanta Orange drink), 1-week apart

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Alginate (n=44) LS Mean</th>
<th>Placebo (n=44) LS Mean</th>
<th>Difference Alginate-Placebo LS Mean (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Efficacy endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time pH&lt;4.0 (%)</td>
<td>5.14</td>
<td>14.94</td>
<td>-9.79 (-14.85, -4.74)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Secondary Efficacy endpoints</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time pH&lt;5.0 (%)</td>
<td>10.40</td>
<td>26.16</td>
<td>-15.76 (-22.82, -8.71)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Occasions when pH&lt;4.0</td>
<td>11.50</td>
<td>30.90</td>
<td>-19.40 (-29.60, -9.20)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Occasions when pH&lt;5.0</td>
<td>17.30</td>
<td>33.60</td>
<td>-16.30 (-26.20, -6.40)</td>
<td>0.0019</td>
</tr>
<tr>
<td>Reflux episodes with pH&lt;4 for at least 5 minutes</td>
<td>0.60</td>
<td>1.40</td>
<td>-0.80 (-1.60, -0.10)</td>
<td>0.0290</td>
</tr>
<tr>
<td>Longest reflux time (minutes)</td>
<td>3.30</td>
<td>9.60</td>
<td>-6.30 (-10.90, -1.80)</td>
<td>0.0075</td>
</tr>
<tr>
<td>DeMeester scores</td>
<td>14.84</td>
<td>38.99</td>
<td>-24.15 (-37.43, -10.86)</td>
<td>0.0007</td>
</tr>
</tbody>
</table>
Double Action Alginate-Antacid Tablets Provide Effective and Safe Relief of Acid Reflux and Dyspepsia Symptoms in Chinese Patients With Gastro-Esophageal Reflux Disease (GERD). Y Yuan, J Sun, C Yang, H Zhao, P Zheng, G Smith, N Levinson, J Wilkinson, B Ng. Mo1150, DDW 2015

- 31 centers in China, patients with mild/moderate GERD symptoms (n=1107)
- Chewable alginate with 2 antacids (CaCO₃ & NaHCO₃), DA (n=552), compared with matched placebo (n=555) for 7 days

<table>
<thead>
<tr>
<th>Variable</th>
<th>DA</th>
<th>Placebo</th>
<th>Least-squares mean difference (DA vs. placebo)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS mean change from baseline in RDQ GERD* dimension (95% CI)</td>
<td>-1.27 (-1.37, -1.16)</td>
<td>-1.06 (-1.17, -0.95)</td>
<td>-0.21</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LS mean change from baseline in RDQ Dyspepsia dimension (95% CI)</td>
<td>-0.98 (-1.10, -0.86)</td>
<td>-0.80 (0.91, -0.68)</td>
<td>-0.18</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

Combined heartburn and acid regurgitation RDQ dimensions. CI, confidence interval; ITT, intent-to-treat; LS, least-squares
Concentrated Alginate As Add-On Therapy in Gastro-Esophageal Reflux Disease (GERD) Patients With Inadequate Response to Once Daily Proton Pump Inhibitor (PPI): A Multicentre, Randomized, Double-Blind, Placebo-Controlled Pilot Study. C Reimer, B Ng, G Smith, J Wilkinson, S Reader, P Bytzer 691, DDW 2015

- Pilot study in 5 Denmark centers, 3 German centers
- Refractory symptoms on PPI daily
  - Moderate severity using HRDQ during 7 days run-in using HRDQ (e.g. moderate heartburn on 3 occasions/day on 3 days during screening)
- Randomize to Gaviscon® Advance (10 ml after meals and qhs) vs placebo x 7 days on top of daily PPI
- Results (n = 134, 35% males, BMI 28.1, mean age 56.4 yr)
  - Alginate (n=65) improved HB (-2.7 vs -1.9), regurgitation (-1.2 vs -0.8) in HRDQ and reduced days with NT symptoms (-1.7 vs 0.6), but not dyspepsia
  - No difference in AE
- Promising effective adjuvant therapy but will need longer term and large scale study
Classifica7on of patients with refractory reflux symptoms (heartburn)

<table>
<thead>
<tr>
<th></th>
<th>Esophagitis by EGD</th>
<th>Abnormal 24-hr pH (off PPI)</th>
<th>SI/SAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>NERD</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Acid Hypersensitive Esophagus</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Functional Heartburn</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

SI – symptom index
SAP– symptom association probabiity

Extracted from Sifrim & Zerbib. Diagnosis and Management of patients with refractory to PPI. GUT 2012; 61: 1340-1345
Surgery in refractory GERD patients

- Patients with typical reflux symptoms and inadequate response to PPIs and have abnormal esophageal acid exposure and/or positive symptom association analysis (‘off’ PPI therapy)
  - Lotus trial: esomeprazole and surgery achieved similar high remission rates in patients initially well controlled by PPI therapy at 5 years
  - Improve belching and weakly acidic reflux

- 24-h pH + impedance monitoring performed ‘on’ PPIs may add value but requires further prospective outcome studies to determine its utility.
  - Small non-randomized prospective studies shows improved post-surgical symptom control in patients
    - Normal acid exposure but elevated reflux episodes
    - Positive SI for non-acid reflux (18 out of 19 patients improved)


- 266 consecutive patients (52.7±0.8 yr), over 5 yr
- FRH: positive SAP, negative AET (pH+/-Z), off/on PPI, 77 pt (28.9%) identified
- Referral physician decided independently on medical therapy vs anti-reflux surgery (ARS)
- Patients (n=53) were able to be contacted for symptomatic outcome assessment: Dominant Symptom Intensity (DSI), 5-pt Likert Scales, Global Symptom Severity (GSS)
  - 37 patients were on medical therapy and 16 had ARS. F/u = 3.3±0.2 yr
- Symptoms were significantly better controlled by ARS
  - >50% improvement in DSI & GSS = 86.7% & 91.7%
  - LESP was significantly lower in ARS
  - Presence of HH positively predict and acid sensitivity negatively predict improvement
- ARS may improve FRH in those with HH and low resting LESP
Management algorithm in patients with refractory reflux symptoms

**NERD**
- Anti-secretary therapy*
- Baclofen

  **Refractory symptoms**
  - pH +/- Z abnormal & positive SA

  **Surgery**

**Acid Hypersensitive**
- Antidepressants
- (+) PPI

  **Refractory symptoms**
  - pH + Z abnormal & positive SA

  **Consider surgery**

**Functional heartburn**
- PPI BID trial (stop if no response)
- Antidepressants
- Address other psychiatric co-morbidities (CBT, relaxation ...)

* Change PPI, BID
  PPI, H$_2$RA qhs prn

---

Increased Number of Risk Factors Predicts Esophageal Injury and Metaplasia: Results From a Large Prospective Population-Based Study


- MN residents aged 50 yr or older without known BE or recent endoscopy were recruited (n=205)
- Esophageal injury (n=38, 18.5%): defined as presence of BE and/or esophagitis LA criteria grade B, C, or D
  - 46% males, 98% Caucasians, 33% with GERD
- Male sex and central obesity are independent risk factors of esophageal injury
- Odds of esophageal injury increase with increase RF: 0-1, 2-3, 4-6 = 6.1%, 20%, 30%

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Male Sex</td>
<td>4.2 (1.9, 9.2)</td>
<td>0.0004*</td>
</tr>
<tr>
<td>Age &gt; 75 years old</td>
<td>2.1 (0.99, 4.4)</td>
<td>0.05</td>
</tr>
<tr>
<td>Central Obesity</td>
<td>3.5 (1.4, 8.8)</td>
<td>0.008*</td>
</tr>
<tr>
<td>GERD</td>
<td>1.6 (0.8, 3.2)</td>
<td>0.22</td>
</tr>
<tr>
<td>Ever Tobacco Use (yes)</td>
<td>0.9 (0.5, 1.9)</td>
<td>0.86</td>
</tr>
<tr>
<td>Family History (yes)</td>
<td>0.7 (0.3, 1.6)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Central obesity (WHR): males >0.94 and females >0.85
Summary of Reflux Disorders: DDW 2015

• Alginate antacids target the acid pocket and appear to improve reflux symptom control

• Patients with refractory reflux symptoms and with positive SAP in pH-Z monitoring may benefit from ARS
  – Presence of a HH and lax LESP are associated with satisfactory outcome

• Reinforce known associated RF of BE
  – Males (older) with central obesity