Management Challenges of the Gastrointestinal Tract (GIT) in Systemic Sclerosis (SSc)

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OVERVIEW

- Systemic Sclerosis gastrointestinal tract basics
- The concept of “Personalized Medicine” as a management challenge
- Limitations of clinical assessment
  - Diagnostics
  - Treatments
- Why nutrition and gut homeostasis matters
- What the future holds
WHY GASTROINTESTINAL SYMPTOMS MATTER TO THE RHEUMATOLOGIST

- The gastrointestinal tract is the largest immune compartment of the human body.
- The major function of the intestinal immune cells is to maintain the integrity of the body at the huge interface between external stimuli:
  - Medications
  - Nutrition
  - Intestinal microflora
  - Brain-gut axis

SSc IS A PROGRESSIVE DISEASE OF THE MICROVASCULATURE

- Vascular dilatation
- Swelling
- Decreased oxygen and nutrient delivery to tissues
- Tissue death
- Immune dysregulation
- Scarring

CRITERIA FOR SYSTEMIC SCLEROSIS DO NOT CAPTURE GIT DISEASE

<table>
<thead>
<tr>
<th>Item</th>
<th>Sub-Item(s)</th>
<th>Weight/Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raynaud's phenomenon (with digital ischaemia during digital palpation)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Hypertension (systolic &gt;150 mmHg, diastolic &gt;90 mmHg)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Digital ulcers (with or without necrosis)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Palmar skin thickening</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Palmar skin hardening</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Palmar skin induration</td>
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<td></td>
</tr>
<tr>
<td>Dactyliitis</td>
<td>2</td>
<td></td>
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<tr>
<td>Arthritis</td>
<td>2</td>
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<tr>
<td>Periungual telangiectasia</td>
<td>2</td>
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</tr>
<tr>
<td>Nailfold capillary abnormality</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Median nerve sensory 80% slowing or more in all segments</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Nerve conduction abnormalities (in at least one sensory nerve to hand)</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

1. The MSA criteria is determined by the weighted mean weight given to each category.
2. Patients with a total score of 5.7 are significantly having definite scleroderma.
Over the course of the disease, GIT affects up to 90% of patients. GIT is the presenting feature in 10% of patients. In adults, women are at greater risk, ratio 4:1.
GIT SYMPTOMS ARE OBSERVED ACROSS LEVELS OF NUTRITIONAL STATUS

[Table 1: Description of the symptoms and their influence on overall health.]

<table>
<thead>
<tr>
<th>Symptom Description</th>
<th>Nutritional Status</th>
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<tbody>
<tr>
<td>Symptom A</td>
<td>High</td>
</tr>
<tr>
<td>Symptom B</td>
<td>Low</td>
</tr>
<tr>
<td>Symptom C</td>
<td>Ideal</td>
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</table>

[Table 2: Correlation between nutritional status and symptom severity.]

<table>
<thead>
<tr>
<th>Nutritional Status</th>
<th>Symptom A</th>
<th>Symptom B</th>
<th>Symptom C</th>
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<tbody>
<tr>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Ideal</td>
<td>Ideal</td>
<td>Ideal</td>
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</tr>
</tbody>
</table>

PERSONALIZED MEDICINE

CURRENT PRACTICE

IDEAL PRACTICE

CHALLENGE OF PERSONALIZED SS-GIT

- Upper tract and lower tract
- The GIT is 30 feet long

Digestion
- Mechanical digestion
- Chemical digestion
- Detoxification system
- All the chemicals (neurotransmitters) found in the brain, are also found in the GIT

Immune Function
- The largest immune organ in the body
- Continually exposed to substances from the outside world
- Has extremely thin lining providing the barrier between the internal body and the external world
**PHYSICAL EXAM: CAN IT HELP US?**

**Oral**
- Exam can guide referrals
- Dental
- Speech and swallow

**Abdominal**
- Exam is limited
- Pain
- Distention

**Rectal**
- Exam is usually only performed for prostate assessment

**INVESTIGATIONAL PROCEDURES: UPPER GIT**

**Esophageal Motility**
- Modified barium swallow
- Manometry
- Impedance-pH monitoring
- Scintigraphy

**Stomach Motility**
- Manometry
- Electrogastrography
- Gastric emptying
- Breath test
- Single Photon Emission CT
- Wireless pH monitoring
- MRI

**Tissue Evaluation**
- Endoscopy
- Capsule
SMALL INTESTINE BACTERIAL OVERGROWTH TESTING

- Breath Testing
  - Abnormal glucose hydrogen breath test
  - Abnormal lactulose hydrogen breath test

- Endoscopy
  - Jejunal aspiration

- Small bowel motility study

INVESTIGATIONAL PROCEDURES: LOWER GIT

Small Bowel Motility

- Manometry
- Scintigraphy
- Breath Testing
- MRI
- Tissue Evaluation
- Enteroscopy
- Capsule

Large Bowel Motility

- Radio-opaque Markers
- Scintigraphy
- Wireless Motility Capsule
- MRI
- Tissue Evaluation
- Colonoscopy
- Capsule

Anorectal

- Manometry
- Endosonography
- Scintigraphy
- Electromyography
- Dynamic MRI
- Defecography
- Balloon-Expulsion Test
- MR fluoroscopic and scintigraphic defecography

The American Journal of Gastroenterology
THE PROBLEM WITH GIT PROCEDURES

- Invasive
- Expensive
- Often times do not provide guidance:
  - "Findings consistent with Systemic Sclerosis"
- Empiric treatments often the standard of care

HEARTBURN

### Behavioral
- Smaller meals
- No eating 4 hours before bedtime
- Elevate head of the bed
- Avoid esophageal irritants
- Avoid tight fitting clothes
- Avoid alcohol
- Avoid tobacco

### Invasive
- Medications:
  - Coating
  - Sucralfate/carafate
  - Acid neutralization
  - Acid suppression
  - Pro-motility
- Procedure:
  - Partial Nissen

ANTACIDS

Other Antacids:
- NaHCO₃ (bubbling w/ CO₂)
- Mg(OH)₂ (bubbling w/ OH⁻)
- Al(OH)₃ (bubbling w/ OH⁻)

### Common Symptoms
- Heartburn
- Acid Reflux
- Esophagitis

Other Guidelines:
- Use of antacids is usually limited to short-term relief
- Avoiding antacids may lead to rebound acid production
- Always consult with a healthcare provider before use

Procedure:
- Take antacids with meals or at bedtime
- Avoid lying down after taking antacids
<table>
<thead>
<tr>
<th>Product</th>
<th>Alkaline Ion</th>
<th>Abnormalities</th>
<th>Calcium</th>
<th>Magnesium</th>
<th>Potassium</th>
<th>Sodium</th>
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<tr>
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<td>Equate bicarbonate</td>
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<td>Maalox (liquid) bicarbonate</td>
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<td>Maalox (tablet) bicarbonate</td>
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<td>Milk of Magnesia hydroxide</td>
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<td>Ranit (tablets) bicarbonate</td>
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<td>Droxygel hydroxide</td>
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<td>Gelusil hydroxide</td>
<td>X</td>
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</table>

**ACID SUPPRESSION: PPI**

**Proton Pump Inhibitors**
- Omeprazole (Prilosec, Zegrid)
- Lansoprazole (Prevacid)
- Esomeprazole (Nexium)
- Pantoprazole (Protonix)
- Rabeprazole (Acidphex)

**Cautions**
- Gastric acid is important for breakdown of food and release of micronutrients.
- High dose and/or long-term use, increased risk of bone fractures.
- Small bacterial overgrowth.

**Indications**
- Symptomatic GERD
- Peptic ulcer disease
- As part of Helicobacter pylori eradication therapy
- Barrett's esophagus
- Eosinophilic esophagitis
- Laryngopharyngeal reflux causing laryngitis and chronic cough

**ACID SUPPRESSION: H2 BLOCKERS**

**H2 Blockers**
- Ranitidine (Zantac)
- Famotidine (Pepcid)

**Cautions**
- Many drug interactions, including calcium channel blockers.

**Indications**
- Peptic ulcer disease
- GERD
SURGICAL OPTIONS: REFLUX

Patients with Normal Motility
- Nissen Laparoscopic Fundoplication
- Toupet Partial Fundoplication

PRO-MOTILITY: UPPER GIT

Dietary
- High-fiber foods can make gastroparesis worse
- Oranges, broccoli, apple with the skin on, wheat, beans, nuts, kale, ...

Medications
- Tricyclic antidepressants
- Calcium channel blockers
- Clonidine
- Dopamine agonists
- Lithium
- Nicotine
- Progesterone

Us Medication Options
- Metoclopromide (Reglan®)
- Erythromycin (low dosages, not antibiotic dosing levels)
- Domperidone (Motilium®, now only available outside US; for nausea due to delayed gastric emptying; not FDA approved)

SURGICAL OPTIONS: GASTROPARESIS

Gastric Pacemaker
- Battery-operated device is implanted into the abdomen
- Sends electrical pulses to the muscles of the abdomen to increase gastric emptying

Feeding Tube
- Usually inserted directly into the small intestine through the abdomen
SMALL INTESTINAL BACTERIAL OVERGROWTH

**Characteristics**
- Abdominal Pain
- Distention
- Diarrhea

**Behavioral**
- Minimize medications
- Hormone replacement
- PPI

**Therapeutics**
- Pro-motility drugs
- Initiate or cycle antibiotics
- Probiotic
- Nutrition

CONSTIPATION

**Behavioral**
- Physical activity
- Adequate fluid intake
- Stop constipating medications

**Therapeutics**
- Osmotic Laxatives
- Stimulants:
  - Lubiprostone
  - Linaclotide
- Pro-motility:
  - Pyridostigmine
  - Biofeedback
  - Sacral Nerve Stimulation

TECHNIQUE

**How it works**

**SOLUTION**

Squatty Potty

Squatting helps you pooping

Technical issues

How it works
DIARRHEA & SOILAGE

Important Considerations

- Medication review
- Magnesium
- Cholesterol-lowering
- Gout medication
- Anti-inflammatories
- Metformin
- Thyroid medication
- Recent antibiotics
- C. Difficile toxin
- Travel
- Giardia antigen
- Ova/ parasites

Behavioral

- Pelvic floor exercises
- Biofeedback

Therapeutics

- Octreotide
- Bile acid sequestrants
- Anti-depressants

Dietary Considerations

- Lactose intolerance
- Sugar substitutes
- Food allergies
- Gluten

NUTRITIONAL CONSIDERATIONS

The physical ability to digest food including chewing, swallowing, absorption, and elimination.

- Appetite fluctuations
- Taste changes
- Food/drug interactions

Skills and ability to comply with dietary lifestyle changes.

FODMAP Diet:

- Short-chain carbohydrates
- Poorly absorbed
- Osmotically active
- Rapidly fermented
- Result in symptoms of abdominal bloating and pain.

FODMAP EDUCATION

- Low FODMAP education consists of initially eliminating FODMAPs from the diet for 6-8 weeks.
- Following symptom resolution, gradual re-introduction of foods to determine individual tolerance.
- FODMAP dietary education should be provided by a trained dietician.
ALLERGEN TESTING

- The role of food allergy in SSc is unclear.
- Immunoassay methods used in evaluating food allergies may include:
  - Skin prick testing
  - Allergy patch testing
  - Blood RAST testing
- Goal is to identify trigger and restore gut balance.

GOOD GUT BACTERIA

- Changes in the distribution or composition of the GIT microbiota may alter intestinal physiology and immunity.
- Environmental, nutritional, and gut-derived triggers that cause microbiome perturbations can drive an abnormal overload of dysbiosis, influencing gut barrier.
- The change in composition of the GIT biofilm communities in response to immunosuppressive therapies has not been well-characterized.

SSc-GIT HOMEOSTASIS

Probiotics
- Live microorganisms that, when administered in adequate amounts, have shown potential benefits in SSc patients.

Prebiotics
- Non-absorbable carbohydrate polymers that promote metabolic activity and expansion of potential beneficial gut bacteria.

Rifaximin
- Non-absorbable antibacterial activity, including prevention of gut mucosal adherence and bacterial translocation.

Fecal Microbiota
- Recipients following transplantation become more diverse and more similar to the donor profile.
WHAT THE FUTURE HOLDS

- Improved natural history studies
- Improved non-invasive imaging
- Improved use of biopsy specimens

### Table

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (n=35)</th>
<th>Year 1 (n=17)</th>
<th>Year 2 (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total GIT 2.0</td>
<td>Median 0.32, IQR 0.45</td>
<td>Median 0.19, IQR 0.33</td>
<td>Median 0.26, IQR 0.34</td>
</tr>
<tr>
<td>Reflux</td>
<td>Median 0.38, IQR 0.75</td>
<td>Median 0.83, IQR 0.75</td>
<td>Median 0.5, IQR 0.56</td>
</tr>
<tr>
<td>Distention/Bloating</td>
<td>Median 0.5, IQR 1.25</td>
<td>Median 0.75, IQR 0.75</td>
<td>Median 0.63, IQR 0.63</td>
</tr>
<tr>
<td>Fecal Sillage</td>
<td>Median 0.0, IQR 0.0</td>
<td>Median 0.0, IQR 0.0</td>
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<td>Diarrhea</td>
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<td>Social Functioning</td>
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<tr>
<td>Emotional</td>
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<td>Median 0.0, IQR 0.22</td>
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<tr>
<td>Well-being</td>
<td>Median 0.0, IQR 0.5</td>
<td>Median 0.0, IQR 0.5</td>
<td>Median 0.0, IQR 0.5</td>
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</tbody>
</table>
BEDSIDE CLINICAL TOOLS

GIT BIOPSIES

- Tissue studies
  - Stains (ie, ANA)
- Metabolomics
  - Analysis of complete set of metabolites
  - End-products of gene expression
  - Reflects the physiological state of a biological system

In Summary

- GIT symptoms in SSc are common.
- A personalized approach to each patient and a focus on nutrition is critical.
- Improved use of questionnaires, bedside testing, and biopsy specimens will improve management.
- The role of dysbiosis and immune dysfunction in SSc-GIT needs to be defined in management.
Acknowledgements

- SSc Patients
- Utah SSc Clinical Care Team
  - Kathryn Peterson, MD
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  - Bryan Jones, PhD
- Donato Lab

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- CCTS Pilot Personalized Health Care
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QUESTIONS?