THE GUT, THE BUGS AND SPONDYLITIS
from basic research to an integrative approach

Alexander Shikhman MD, PhD
Institute for Specialized Medicine
July 20, 2013
SPONDYLOARTHROPATHIES

The spondyloarthropathy family consists of the following entities:

- Ankylosing spondylitis
- Undifferentiated spondyloarthritis
- Reactive arthritis
- Psoriatic arthritis
- Spondyloarthritis associated with IBD
- Juvenile onset spondyloarthritis
ANKYLOSING SPONDYLITIS AND GUT

- Subclinical gut inflammation has been described in up to two-thirds of patients with spondyloarthropathies

- Two histologic types of gut inflammation in patients with SpA can be distinguished: acute and chronic inflammation
ANKYLOSING SPONDYLITIS AND GUT

The **acute type** mimics the acute bacterial enterocolitis and is mainly seen in patients with **reactive arthritis**:

- The mucosal architecture is well preserved
- There is a polymorphonuclear infiltration of the ileal villi and crypts
- There is an increased number of inflammatory cells (granulocytes, lymphocytes and plasma cells) in the lamina propria
ANKYLOSING SPONDYLITIS AND GUT

The **chronic type** is often indistinguishable from Crohn’s disease (CD):

- The mucosal architecture is clearly disturbed
- The villi are irregular, blunted and fused
- The crypts are distorted
- The lamina propria is edematous and infiltrated by mononuclear cells
- In some cases aphthoid ulcers and sarcoid-like granulomas are present

Chronic lesions are more present in undifferentiated SpA and AS.
ANKYLOSING SPONDYLITIS AND GUT

- Increased intestinal permeability or leaky gut syndrome is a key mechanism contributing to the development and chronic course of ankylosing spondylitis and other autoimmune diseases and inflammatory arthritis.

- The leaky gut allows substances such as toxins, microbial antigens, undigested food, waste, or larger than normal macromolecules to leak through an abnormally permeable gut wall and trigger cascades of inflammatory reactions.

Tight junctions (TJs) represent the major barrier within the pathway between intestinal epithelial cells that line the digestion tract.
ANKYLOSING SPONDYLITIS AND GUT

- Zonulin is a protein regulating intestinal permeability via modulation of tight junction.

- Small intestines exposed to enteric bacteria secrete zonulin.

- This secretion occurs only on the luminal aspect of the bacteria-exposed small intestinal mucosa and is followed by an increase in intestinal permeability.
ANKYLOSING SPONDYLITIS AND GUT


ANKYLOSING SPONDYLITIS AND GUT MICROBIOTA

- Gut microbiota consists of a complex of microorganism species that live in the digestive tract.
- The human body carries about 100 trillion microorganisms in its intestines, a number ten times greater than the total number of human cells in the body.
- The metabolic activities performed by these bacteria resemble those of an organ, leading some to liken gut bacteria to a "forgotten" organ.
ANKYLOSING SPONDYLITIS AND GUT MICROBIOTA

- Gut microbiota primary benefits the host by generating energy from the fermentation of undigested carbohydrates and the subsequent absorption of short chain fatty acids.

- The most important of these are butyrates, metabolized by the colonic epithelium and normalizing intestinal permeability.
ANKYLOSING SPONDYLITIS AND GUT MICROBIOTA

Ankylosing spondylitis (AS) - HLA-B27 association

• AS patients: >95% HLA-B27 positive
• <5% chance of AS if are HLA-B27 +
  – But family history of AS increases risk
• How does HLA-B27 cause disease:
  – fails to eliminate organism?
  – presents arthritogenic peptide?
  – Answer is not known
ANKYLOSING SPONDYLITIS AND GUT MICROBIOTA

THE HLA-B27 CONNECTION

- HLA B27 influences the composition of the body’s endogenous flora and the ‘B27-shaped flora’ predisposes to ankylosing spondylitis
- HLA-B27 transgenic mice do not develop spondylitis-like lesions in germ-free environment
- Antibiotic therapy prevents spondylitis and colitis in HLA-B27 transgenic rats
ANKYLOSING SPONDYLITIS
THERAPEUTIC GOALS

- NORMALIZATION OF INTESTINAL PERMEABILITY
- OPTIMIZATION OF GUT MICROFLORA
- OPTIMIZATION OF TOXIN REMOVAL
- REDUCTION OF LOCAL/MUCOSAL INFLAMMATION
- REDUCTION OF SYSTEMIC INFLAMMATORY RESPONSES AND PREVENTION OF ANKYLOSIS
NORMALIZATION OF INTESTINAL PERMEABILITY

- **BUTYRATE**

- **L-GLUTAMINE**

- **BERBERINE**
OPTIMIZATION OF GUT MICROBIOTA

- **PROBIOTICS**
  live microorganisms which beneficially improve intestinal microbial balance

- **PREBIOTICS**
  non-digestible polysaccharides that stimulate the growth and/or activity of ‘good’ bacteria in the digestive system

- **SYNBIOTICS**
  nutritional supplements combining probiotics and prebiotics

- **BUTYRATE**

- **DIGESTIVE ENZYMES**
OPTIMIZATION OF GUT MICROBIOTA

CLINICAL TRIALS UTILIZING PROBIOTICS IN ANKYLOSING SPONDYLITIS

- limited number of published clinical trials
- insufficient number of participants to make any meaningful conclusions
- absence of reliable clinical or/and laboratory markers to measure the trials outcome
- poor clinical design (low dose of probiotics, poor selection of the probiotic strains)
OPTIMIZATION OF GUT MICROBIOTA

PROBIOTICS

- THE RIGHT DOSE
- THE RIGHT STRAIN(S)
- THE RIGHT TIME OF ADMINISTRATION
- SPACING OUT PROBIOTICS FROM ANTIBIOTICS AND DMARDs
OPTIMIZATION OF GUT MICROBIOTA

PREBIOTICS

- no published clinical trials
- experimental data utilizing beta-glucan and mannano-oligosaccharides based prebiotics demonstrated negative effect in animals with experimental colitis and Crohn’s disease
OPTIMIZATION OF GUT MICROBIOTA

DIGESTIVE ENZYMES

- enzymes of animal origin (pancreatic enzymes/pancreatin)
- plant-based enzymes
- medicinal mushrooms/medicinal molds-based enzymes
OPTIMIZATION OF TOXIN REMOVAL

- Calcium glucarate
- Psyllium/apple pectin
- Triphala
- Citrulline malate
- Acetyl-L-carnitine
REDUCTION OF LOCAL/MUCOSAL INFLAMMATION

<table>
<thead>
<tr>
<th>TRADITIONAL THERAPY</th>
<th>COMPLEMENTARY THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfasalazine</td>
<td>Curcumin</td>
</tr>
<tr>
<td>5-ASA</td>
<td>Boswellia</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Devil’s claw</td>
</tr>
<tr>
<td></td>
<td>Berberine</td>
</tr>
<tr>
<td></td>
<td>N-acetylglucosamine</td>
</tr>
<tr>
<td></td>
<td>Omega-3 polyunsaturated fatty acids</td>
</tr>
<tr>
<td></td>
<td>Oral bovine immunoglobulins</td>
</tr>
</tbody>
</table>
REDUCTION OF SYSTEMIC INFLAMMATORY RESPONSES

<table>
<thead>
<tr>
<th>TRADITIONAL THERAPY</th>
<th>COMPLEMENTARY THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biologics</td>
<td>Curcumin</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Boswellia</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Devil’s claw</td>
</tr>
<tr>
<td>5-ASA</td>
<td>Omega-3 polyunsaturated fatty acids</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td></td>
</tr>
</tbody>
</table>
GUT-FOCUSED THERAPY IN ANKYLOSING SPONDYLITIS

TRADITIONAL THERAPY + COMPLEMENTARY THERAPY = INTEGRATIVE APPROACH

SULFASALAZINE + BUTYRATE/GLUTAMINE + BERBERINE

TRIPHALA + CALCIUM GLUCARATE + CITRULLINE MALATE

BACILLUS COAGULANS + DIGESTIVE ENZYMES + BOVINE IMMUNOGLOBULINS

OMEGA-3 + DEVIL’S CLAW + BOSWELLIA/CURCUMIN