Spondyloarthritis Treatment and Research Update: The role of the Microbiome

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November 9, 2019
Disclosure of Conflicts of Interest
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Royalties: UpToDate
Mark J. Asquith, Ph.D.

In Memoriam
Outline

- What is spondyloarthritis?
- What is HLA B27?
- What does AxSpA affect besides the spine?
- How do we treat AxSpA?
- What causes AxSpA?
What is spondyloarthritis?
Ankylosing Spondylitis Progression

New York Criteria for AS (1966)

- Low back pain x 3 months improved by exercise
- Limited lumbar mobility
- Reduced chest expansion
- Grade 2 to 4 bilateral sacroiliitis or grade 3 to 4 unilateral sacroiliitis
- Last criteria plus one of top 3
Chronic Low Back Pain

- Inflammatory back pain  ✔  LR 3.1
- Heel pain (enthesitis)  LR 3.4
- Peripheral arthritis  LR 4.0
- Dactylitis  LR 4.5
- Acute anterior uveitis  LR 7.3
- Pos. Family history  LR 6.4
- Good response to NSAIDs  LR 5.1
- Elevated acute phase reactants  LR 2.5
- HLA-B27  ✔  LR 9.0
- MRI  ✔  LR 9.0

Axial SpA

\[3.1 \times 9.0 \times 9.0 = >200\]
(LR product)

Disease Probability

5%

> 90%
The dilemma of sensitivity versus specificity
Characteristics of inflammatory low back pain

- Insidious onset
- Morning stiffness
- Improvement with activity
- Non-dermatomal pain radiation/alternating buttock pain
- Positive family history
- Chronic duration
- Response to NSAIDs
- Onset before age 40
Other terms for ankylosing spondylitis

- Spondylitis
- Spondyloarthrits
- Spondyloarthropathy
- Axial spondyloarthropathy (AxSpA)
- Peripheral spondyloarthropathy
- Non-radiographic axial spondyloarthropathy (nrAxSpA)
Delayed diagnosis of AS

Average delay in diagnosis: 9 years

What is HLA B27 and How does it relate to ankylosing spondylitis?
High association of an HL-A antigen, W27, with ankylosing spondylitis.

Schlosstein L, Terasaki PI, Bluestone R, Pearson CM

New England Journal of Medicine

1973 Apr 5; 288(14):704-6
HLA B27

Structure of the HLA-B27 molecule

Expert Reviews in Molecular Medicine © 1999 Cambridge University Press
HLA B27

- Present in about 7% of Americans
- Increases the risk of developing ankylosing spondylitis about 100 fold
- 80% of HLA B27 + people do NOT develop AS
- Genes, Environment, and Chance each contribute to developing AS
What does AS affect besides the spine?
Targets of AS besides the Spine

- Peripheral joints and entheses
- Eye (Iritis/Uveitis)
- Skin (Psoriasis)
- Bowel (Crohn’s disease and Ulcerative colitis)
- Heart (Heart block and aortic valve disease)
- Atherosclerosis
How do we treat spondyloarthritis?
2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis

The Treatment of Ankylosing Spondylitis

- Diet, exercise, stress reduction, stop smoking
- NSAIDs
- Sulfasalazine (peripheral arthritis)
- (Methotrexate)
- TNF inhibitors
- IL-17 inhibitors
- (Tofacitinib)
#NSAID

non-steroidal anti-inflammatory drugs

Many cold, allergy, and sinus medications contain NSAIDs

SOME NSAIDS ARE:
- aspirin
- Motrin
- Advil
- ibuprofen
- Aleve

For an extensive list of NSAIDs visit www.clarityallergycenter.com
TNF inhibitors, 40% benefit rate

Please place a mark on each line below to indicate your answer to each question relating to the past week.

1. How would you describe the overall level of fatigue/tiredness you have experienced?

   NONE ________________________________ VERY SEVERE

2. How would you describe the overall level of AS neck, back or hip pain you have had?

   NONE ________________________________ VERY SEVERE

3. How would you describe the overall level of pain/swelling in joints other than neck, back, hips you have had?

   NONE ________________________________ VERY SEVERE

4. How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?

   NONE ________________________________ VERY SEVERE

5. How would you describe the overall level of morning stiffness you have had from the time you wake up?

   NONE ________________________________ VERY SEVERE

6. How long does your morning stiffness last from the time you wake up?

   0 hrs  ½  1  1½  2 or more hours
Side effects include:

- GI upset, bleeding, fluid retention, mood changes with NSAIDs
- Infections with biologics as well as allergic reactions, injection site reactions, immunological disease
What causes spondyloarthritis?
“this type of genetic control of specific immune responses may play an important role in susceptibility to a variety of diseases in both animals and man” SCIENCE, January, 1972.
The Concept of the Microbiome

- Bacteria in our body outnumber the cells in our body. (We are holobionts.)
- 99% of all the transcripts expressed in the body are derived from microbes.
- We are holobionts.
- Only a fraction of the microbial world that we host is easily cultured.
- Without bacteria, no vitamin K and no immune system.
Hypothesis: Time for a gut check. HLA B27 predisposes to ankylosing spondylitis by altering the microbiome

- Rosenbaum, JT
- Davey, MP
- Arthritis & Rheumatism
The Human Microbiome Project

Meta Hit Project in Europe

Turnbaugh, P, Ley, R, Hamady, M, Fraser-Liggett, CM, Knight, R, Gordon, J
Cost for human genome sequencing

Cost per Genome

Moore's Law

NIH National Human Genome Research Institute

genome.gov/sequencingcosts

Metabolic Syndrome and Altered Gut Microbiota in Mice Lacking Toll-Like Receptor 5

Vijay-Kumar et. al.
April 9, 2010
Gut-residing segmented filamentous bacteria drive autoimmune arthritis via T helper 17 cells

K/BxN Model

Immunity, June 25, 2010
Does the microbiome contribute to the pathogenesis of ankylosing spondylitis?
Immunopathology of HLA-B27 Transgenic Rats

Disease features

- Peripheral arthritis
- Spinal lesions
- Inflammatory bowel disease
- Epididymo-orchitis
- Skin lesions

Determined by

- HLA-B27 gene copy number
- Human β2 microglobulin gene copy number
- Strain and sex
- Gut flora
- Haematopoietic cells

Tran TM et al. Arthritis Rheum 2006;54:1317-27 (with permission)
The germfree state prevents development of gut and joint inflammatory disease in HLA-B27 transgenic rats

Taurog, JD, et.al., 180: 2359, 1994.
HLA B27

MICROBIOME

ALTERED GUT PERMEABILITY

IMMUNE RESPONSE

SPONDYLOARTHRITIS AND UVEITIS
Do HLA molecules shape the microbiome?
HLA alleles associated with risk of ankylosing spondylitis and rheumatoid arthritis influence the gut microbiome
Gut Bacterial DNA Translocation is an Independent Risk Factor of Flare at Short Term in Patients With Crohn’s Disease

Ana Gutiérrez, MD, PhD1,2, Pedro Zapater, MD, PhD2, Oriol Juanola2, Laura Sempere, MD1, Marifé García, MD, PhD3, Raquel Laveda, MD4, Antonio Martínez, MD4, Michael Scharl, MD, PhD5, José M. González-Navajas, PhD2, José Such, MD, PhD6, Reiner Wiest, MD, PhD7, Gerhard Rogler, MD, PhD5 and Rubén Francés, PhD2,a

- 288 patients
- 34% with detectable bacterial DNA in blood
- HR for flare if DNA present = 8.75

- American Journal of Gastroenterology, April, 2016
ANTIGEN-PRESENTING CELLS CONTAINING BACTERIAL PEPTIDOGLYCAN IN SYNOVIAL TISSUES OF RHEUMATOID ARTHRITIS PATIENTS COEXPRESS COSTIMULATORY MOLECULES AND CYTOKINES

INGRID A. SCHRIJVER, MARIE-JOSÉ MELIEF, PAUL P. TAK, MAARTEN P. HAZENBERG, and JON D. LAMAN
Important Caveat:

- Different aspects of spondyloarthritis (e.g. axial disease, peripheral disease, uveitis) might have similar but also different etiopathogenesis
Therapeutic implications

Rosenbaum and Asquith
Nature Reviews. Rheumatology
December, 2018
Fecal Microbiota Transplantation for Dysbiosis — Predictable Risks

Martin J. Blaser, M.D.

October 31, 2019
Publications on FMT Trials, May 27, 2019

- C. Difficile and other refractory bowel infections
- Ulcerative colitis
- Crohn’s disease
- Irritable bowel syndrome
- Sclerosing cholangitis
- Constipation
- Cirrhosis
- Hepatic encephalopathy
- Psoriatic arthritis
- Graft vs Host Disease
- Diabetic neuropathy
- Metabolic syndrome

Rosenbaum, JT, Expert Reviews of Clinical Immunology, August 15, 2019
<table>
<thead>
<tr>
<th>FMT Trials as listed in clinicaltrials.gov*</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Acute myeloid leukemia</td>
</tr>
<tr>
<td>- Alcoholic hepatitis</td>
</tr>
<tr>
<td>- Amyotrophic lateral sclerosis</td>
</tr>
<tr>
<td>- Ankylosing spondylitis</td>
</tr>
<tr>
<td>- Anorexia nervosa</td>
</tr>
<tr>
<td>- Autism</td>
</tr>
<tr>
<td>- Bipolar disorder</td>
</tr>
<tr>
<td>- Chronic fatigue syndrome</td>
</tr>
<tr>
<td>- Depression</td>
</tr>
<tr>
<td>- Diabetes mellitus, type II</td>
</tr>
<tr>
<td>- Epilepsy</td>
</tr>
<tr>
<td>- Hepatitis B infection</td>
</tr>
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</table>

Rosenbaum, JT, Expert Reviews of Clinical Immunology, August 15, 2019

May 27, 2019
FMT Trials as listed in clinicaltrials.gov*

- HIV infection
- IgA nephropathy
- Immune thrombocytopenia
- Kidney transplantation
- Liver transplantation
- Malnutrition
- Melanoma
- Multiple myeloma
- Multiple sclerosis
- Non-alcoholic steatohepatitis
- Obesity
- Pancreatitis
- Parkinson’s disease
- Peanut allergy
- Pouchitis
- Rheumatoid arthritis refractory to methotrexate therapy
- Sjogren’s syndrome
- Squamous cell cancer
- Urinary tract infection

May 27, 2019

Rosenbaum, JT, Expert Reviews of Clinical Immunology, August 15, 2019
Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial

Sudarshan Paramsothy, Michael A Kamm, Nadeem O Kaakouch, Alissa J Walsh, Johan van den Bogaerde, Douglas Samuel, Rupert W L Leong, Susan Connor, Watson Ng, Ramesh Paramsothy, Wei Xuan, Enmoore Lin, Hazel M Mitchell, Thomas J Borody

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>Faecal microbiota transplantation (n=41)</th>
<th>Placebo (n=40)</th>
<th>Risk ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid-free clinical remission and endoscopic remission or response*</td>
<td>11 (27%)</td>
<td>3 (8%)</td>
<td>3.6 (1.1–11.9)</td>
<td>0.021</td>
</tr>
</tbody>
</table>

Secondary outcomes

<table>
<thead>
<tr>
<th>Secondary outcomes</th>
<th>Faecal microbiota transplantation (n=41)</th>
<th>Placebo (n=40)</th>
<th>Risk ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid-free clinical remission†</td>
<td>18 (44%)</td>
<td>8 (20%)</td>
<td>2.2 (1.1–4.5)</td>
<td>0.021</td>
</tr>
<tr>
<td>Steroid-free clinical response‡</td>
<td>22 (54%)</td>
<td>9 (23%)</td>
<td>2.4 (1.3–4.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>Steroid-free endoscopic remission§</td>
<td>5 (12%)</td>
<td>3 (8%)</td>
<td>1.6 (0.4–6.4)</td>
<td>0.48</td>
</tr>
<tr>
<td>Steroid-free endoscopic response¶</td>
<td>13 (32%)</td>
<td>4 (10%)</td>
<td>3.2 (1.1–8.9)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

Enemas 5 days/week for 8 weeks

Clinicaltrials.gov lists >300 FMT trials for various diseases

Lancet, 389:1218, 2017
Challenges affecting FMT

- Optimal route of delivery
- Frequency
- Choice of donor
- Safety
- Substituting a defined consortium
The Promise of Poop

Fecal transplants offer hope for treating many diseases. But they need to be studied more scientifically, says one of the treatment’s pioneers.
Acknowledgements

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☐ Matthew Schleisman
☐ Tammy Martin
CONCLUSIONS:

- Spondyloarthritis is a common disease.
- New therapies for spondyloarthritis are emerging but treatment is still imperfect.
- The microbiome MIGHT be the key to understanding and preventing spondyloarthritis.