Spondyloarthropathies
(PsA, ERA, AS)

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What is Arthritis??

• Inflammation in one or more joints causing warmth, swelling, tenderness, pain, stiffness

• Acute (brief) inflammation may be a good thing: process by which the body’s white blood cells and chemicals try to protect us from bacteria and viruses

• Chronic (long duration) inflammation causes tissue/bone destruction

• Arthritis can be associated with inflammation in other organ systems (skin, GI tract, etc.)

• JA treatments aim to decrease inflammation
JIA: New Classification

• Oligio JIA : < 5 joints affected
  – Persistant oligio (Never 5 or more joints)
  – Extended oligio (Starts as < 5 joints, but more become involved over time)

• Polyarticular JIA : > 5 joints involved

• Psoriatic Arthritis

• Enthesitis related arthropathy (ERA)
  – Ankylosing spondylitis

• Systemic Onset JIA:
  – High fevers & rash
  – May include lymphadenopathy, HSM, pericarditis or pleuritis
Spondyloarthropathies

• The only type of JA that affects boys more than girls
• Generally starts in adolescent years
• Usually affects joints in lower extremities
• Over eventually affects the lower back (sacroiliac joints)
• PsA may or may not fall into the spondyloarthropathy category.
Spondyloarthropathies

- Generally RF negative
- AS and ERA usually ANA negative, but PsA often ANA positive
- Often HLA-B27 positive
- ERA and AS generally do not affect the small joints (fingers and toes), but PsA does.
- ERA and AS generally affect the SI joints. PsA may or may not affect SI joints.
- All are associated with enthesitis.
Spondyloarthropathy, Psoriasis and PsA

**Spondyloarthropathy (SpA)**
- The prevalence of SpA in adults is comparable to RA (0.5–1.9%)

**Psoriasis (PsO)**
- Psoriasis affects 2% of population
- 7% to 42% of patients with Pso will develop arthritis

**Psoriatic Arthritis (PsA)**
- A chronic and inflammatory arthritis in association with skin psoriasis
- Distinct from other forms of JIA or RA
- Psoriatic Arthritis is classified as one of the subtypes of spondyloarthropathies
  - Characterized by synovitis, enthesitis, dactylitis, spondylitis, skin and nail psoriasis
Enthesitis

- **Entheses** are the regions at which a tendon, ligament, or joint capsule attaches to bone\(^1\)

- **Inflammation at the entheses is called enthesitis** and is commonly seen in ERA, PsA, AS, etc.

- Pathogenesis of enthesitis has yet to be fully elucidated

- Patients may be initially diagnosed with Achilles tendonitis, Osgood-Schlatter’s, plantar fasciitis, etc. All forms of enthesitis.
Inflammatory Enthesopathy

- Subchondral bone inflammation and resorption
- Periosteal new bone formation
Enthesitis Related Arthropathy/Ankylosing Spondylitis

- Affects 10-20% of children with JIA
- Predominantly males affected
- Age of onset after 8 years
- Associated with sacroiliitis and HLA-B27
- ANA- negative, RF- negative
- Affected joints usually of lower limbs
Enthesitis Related Arthropathy/Ankylosing Spondylitis

Commonly complain of:

- Pain in the back & heel
- Morning stiffness
- Pain hips knees or ankles

**Arthritis &/or enthesitis plus** 2 of the following:

- Sacroiliac joint tenderness and/or Inflammatory back pain
- Positive family history
- Acute anterior uveitis
- Arthritis onset in boys > 8 yrs
- HLA-B 27 (higher likelihood of developing ankylosing spondylitis)
Psoriatic arthritis: classification/diagnosis

• Chronic, progressive inflammatory disorder of joints, ranging from mild, nondestructive to severe, aggressively destructive disease
• Initially thought to be a variant of rheumatoid arthritis
• Now classified as its own distinct form of arthritis
• In nearly 70% of patients, skin lesions precede the onset of joint pain, in 20% arthropathy starts before skin manifestations, and in 10% both are concurrent.
Main Features of PsA

**Clinical**
- Psoriasis of skin and nails
- Peripheral arthritis
- Distal interphalangeal (DIP) involvement
- Dactylitis
- Enthesopathy

**Laboratory**
- Rheumatoid factor (RF) & Anti-citrullinated protein antibodies (ACPA) negative*
  - Elevated Acute Phase**

**Radiographic**
- Erosions and resorptions
- Joint space narrowing or involvement of enthesal sites
- New bone growth at the enthesis
- Syndesmophytes***
- Sacroiliitis***

*Low levels of RF and ACPA can be found in 5-16% of patients; **To a lesser degree than in RA ***Spinal disease occurs in 40-70% of PsA patients

Helliwell PS & Taylor WJ. Ann Rheum Dis 2005;64(2:ii)3-8
Fitzgerald "Psoriatic Arthritis" in Kelley’s Textbook of Rheumatology, 2009
Hallmark Clinical Features in PsA

Psoriatic Arthritis

- Dactylitis
- Enthesitis
Psoriatic Arthritis

PsA: Cutaneous Features
PsA: Cutaneous features

Psoriatic plaques

Fingernail pitting
PsA: Dactylitis

- Diffuse swelling of a digit may be acute, with painful inflammatory changes, or chronic wherein the digit remains swollen despite the disappearance of acute inflammation¹

- Also referred to as “sausage digit”¹

- Recognized as one of the main features of PsA, occurring in up to 40% of patients

- Feet most commonly affected

- Dactylitis involved digits show more radiographic damage
PsA: Not Rheumatoid Arthritis

- Enthesopathy (38%)²
  - DIP involvement (39%)²
  - Nail psoriasis (80%)⁴, ⁵
  - Dactylitis (48%)³
  - Back involvement (50%)¹

PsA: Laboratory Studies

• HLA association—it’s complicated
  – HLA-B27 commonly seen
    ▪ less than ankylosing spondylitis or reactive arthritis
    ▪ some psoriasis and SpA are HLA-B27 (-)
    ▪ PsA and HLA B27 who do not have SpA
  – predictors for disease progression:
    ▪ HLA-B27 in the presence of HLA-DR7
    ▪ HLA-DQ3 in the absence of HLA-DR7
    ▪ HLA-B39
  – protective: HLA-B22
Changes in Treatments of JA

1984
• Aspirin
• NSAIDS: naproxen, tolmentin, indomethacin
• Steroids
• Methotrexate first used in late 1980s

2015
• Many new NSAIDS
• Cox-2 inhibitors
• Corticosteroids
• Local steroid injections
• Early use methotrexate
• BIOLOGICS
Treatments for ERA

- Stretching, stretching, PT, stretching
- NSAIDS sometimes work
- One of the only types of JIA that responds well to SSZ
- Methotrexate often used and may be very successful
- Biologics (anti-TNF agents) generally very successful in treating the arthritis of ERA.
Common NSAIDS
(Non-Steroidal Anti-inflammatory drugs)

- Ibuprofen (Motrin, Advil)
  - Works, but wears off in 4-6 hours
- Naproxen (Naprosyn, Aleve)
  - Lasts longer, taken twice daily, comes in liquid
- Many newer NSAIDS
  - Relafen, Daypro, Voltaren, Arthrotec,
    Can be given once daily, do not come in liquid
Main Problems with NSAIDS

• GI upset--worse with some than others

• Increased bruising/bleeding

• Rarely can affect kidneys

• Often take 4-6 weeks to start working
Cox-2 Inhibitors

- Traditional NSAIDS inhibit Cox-1 and Cox-2
- Most side effects due to Cox-1 inhibition
  - GI upset
  - bruising/bleeding, etc
- Only Celebrex currently on the market and approved for JIA
- Mobic (meloxicam) is a “mostly” Cox-2 inhibitor, comes in a liquid, once daily dosing
STEROIDS

- Often needed to control severe flares
- Only anti-inflammatory medication that works very quickly
- Can be given by mouth, IV, topically or intra-articularly
- Can have rebound flares, especially in psoriasis
- Many side effects with systemic steroids
DMARDs
(Disease Modifying Anti-Rheumatic Drugs)

- Methotrexate
- Sulfasalazine (azulfadine)
- Hydroxychloroquine (plaquenil)
- Cyclosporine
- Cyclophosphamide
- Cellcept
- Gold
- Gamma Globulin
Methotrexate in Rheumatic Diseases

• Very successful in controlling arthritis, uveitis and myositis. Often used for scleroderma, vasculitis

• Given once / week, either by mouth or injections

• Side effects much less than previously thought

• Must monitor labs (blood counts, liver functions)

• Can cause significant nausea, especially at higher doses.
Sulfasalazine

- Works best for the spondyloarthropathies/ERA
- 30% efficacy – often “all or none” response
- 25% develop severe rash
- Persistent nausea and/or dizziness often occur
- Generally considered very safe
Medications for JA

• Almost all DMARDs were borrowed from other specialties
• Gold for pulmonary TB
• Antimalarials (Plaquenil)
• Sulfasalazine for inflammatory bowel disease
• Methotrexate and Cytoxan for cancer
Anti-Cytokine Therapy (Biologics)

Specifically developed for the treatment of rheumatic disorders
Cytokines

• Protein messengers in the body
• Involved in immunity, inflammation, cell growth, differentiation, etc.
• Currently about 150 defined
  → (probably >300 exist)
Cytokine Receptors

- Cytokines bind to cell surface receptors
- Receptors are linked to signal transduction pathways that alter gene expression, and thus define the biologic effects of the cytokine
Cytokines

• Proinflammatory:
  – IL-1, IL-6, TNFα, IL-12, IL-15, IL-17, INFγ, etc

• Anti-inflammatory
  – IL-4, IL-10, IL-1Ra, TGFβ, IL-11, IL-13, etc.

• There is a fine balance between pro- and anti-inflammatory cytokines
Tumor Necrosis Factor

• In mice, over expression of human TNF leads to RA

• If mice given anti-TNF therapy form birth, no arthritis seen

• Anti-TNF therapy first used in humans early 1990s

• 3-4 hrs after IV infusion, decreased levels of IL-6. Few days later decreased CRP.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HUMIRA™</th>
<th>ENBREL®</th>
<th>REMICADE®</th>
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<tbody>
<tr>
<td>Class</td>
<td>TNF-α mAb</td>
<td>sTNFR</td>
<td>TNF-α mAb</td>
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<tr>
<td>Construct</td>
<td>Recombinant</td>
<td>Recombinant</td>
<td>Chimeric mAb</td>
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<td></td>
<td>human mAb</td>
<td>fusion protein</td>
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<tr>
<td>Half-life</td>
<td>10–20 days</td>
<td>4 days</td>
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<tr>
<td>Binding target</td>
<td>TNF-α</td>
<td>TNF-α/LT-α</td>
<td>TNF-α</td>
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<tr>
<td>Administration</td>
<td>40 mg SC</td>
<td>25 mg SC</td>
<td>3–10 mg/kg IV</td>
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<tr>
<td></td>
<td>Every other</td>
<td>Twice weekly</td>
<td>Every 4–8</td>
</tr>
<tr>
<td></td>
<td>week*</td>
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<td>MTX</td>
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## TNF inhibitors

<table>
<thead>
<tr>
<th>Medication</th>
<th>Remicade (infliximab)</th>
<th>Enbrel (etanercept)</th>
<th>Humira (adalimumab)</th>
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<tbody>
<tr>
<td><strong>Class</strong></td>
<td>TNF-α mAb</td>
<td>sTNFR</td>
<td>TNF-α mAb</td>
</tr>
<tr>
<td><strong>Construct</strong></td>
<td>Chimeric Ab</td>
<td>Recombinant fusion protein</td>
<td>Recombinant human mAb</td>
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<td><strong>Binding target</strong></td>
<td>TNF-α</td>
<td>TNF-α/ LT-α</td>
<td>TNF-α</td>
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<tr>
<td><strong>Administered</strong></td>
<td>IV q 4-12 weeks, with methotrexate</td>
<td>SQ weekly or twice weekly, +/- methotrexate</td>
<td>SQ q 2 weeks +/- methotrexate</td>
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<tr>
<td><strong>Problems</strong></td>
<td>Injusion reactions</td>
<td>Not useful for uveitis or Crohn’s</td>
<td>Burns</td>
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</table>
Ustekinumab (IL-12 and 23 inhibitor)

- It has been shown that psoriasis susceptibility is associated with single-nucleotide changes within the interleukin-23 receptor (IL-23R) and IL-12B, the gene that encodes for subunit of ligand of IL-23R
- Ustekinumab has been used in pediatric patients with PsA, psoriasis and Crohn’s Disease
- Interleukin-12 expression is focally enhanced in the gastric mucosa of **pediatric** patients with Crohn's disease
<table>
<thead>
<tr>
<th>Biologic</th>
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<td>Infliximab</td>
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<td>Etanercept</td>
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<td>Adalimumab</td>
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<td>IL-12/23</td>
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<td>Secukinumab</td>
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# Topical Psoriasis Therapy

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<tr>
<th>CLASS</th>
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<tr>
<td>vitamin D analogs</td>
<td>Dovonex, Vectical</td>
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<td>calcineurin inhibitors</td>
<td>Elidel, Protopic</td>
<td>Black Box</td>
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<td>anthralin</td>
<td>Drithranol</td>
<td>irritation, staining</td>
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<tr>
<td>salicylic acid</td>
<td>Keralyt</td>
<td>irritation</td>
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</table>
Future for JA

• New biologics (oral)
• Combined biologics
• Research to find cause of autoimmune disorders, so we can finally cure and not just treat them!