Module 8:
Rheumatoid Arthritis and Seronegative Inflammatory Arthropathies

Objective 1:
Differentiate the three basic presentations of joint pain and develop a differential diagnosis for polyarthritis.

Sorting Out Synovitis
There are 3 basic presentation patterns to joint pain, determined by clinical history:
- Inflammatory
- Mechanical
- Fibromyalgia

There are 3 basic presentation patterns of joint swelling, based on clinical examination:
- Monoarthritis
- Pauciartritis
- Polyarthritis

Inflammatory
- Prolonged morning stiffness > 30 minutes; often several hours
- Swelling often present
- Patients stiffness improves with activity
- May have feeling of fatigue as well
- Examples: rheumatoid arthritis, psoriatic arthritis, polymyalgia rheumatica
### Mechanical or Noninflammatory
- Minimal morning stiffness (5-10 minutes)
- Progressive pain with increased activity
- Swelling may or may not be present
- No other systemic symptoms
- Examples: osteoarthritis, tendonitis

### Fibromyalgia
- Prolonged morning stiffness; can be present for several hours
- Pain with activity
- Pain may last several days after more vigorous activity
- Tender points typically present
- Fatigue/memory problems
- Other somatic conditions may be present (TMJ, HA, pelvic pain, etc.)

### Diagnosis of Joint Pain: Number of Joints Involved
**Monoarthritis:**
- Inflammatory
  - Septic arthritis
  - Crystalline arthritis, i.e., gout or pseudogout
  - Undifferentiated arthritis
- Noninflammatory
  - Osteoarthritis

### Diagnosis of Arthritis: Number of Joints Involved
**Pauciarthritis, i.e., 2-5 joints**
- Inflammatory
  - Septic arthritis
  - Spondyloarthropathies, such as psoriatic arthritis or reactive arthritis
  - Lyme disease
  - Gout
- Noninflammatory
  - Osteoarthritis
**Inflammatory Polyarthritis**

- Presentation patient is a classic case of inflammatory polyarthritis:
  - 90 minutes or more of morning stiffness
  - Better with activity
- Other features include:
  - Involvement of multiple small joints of the hands and feet (6 or more joints for polyarthritis)
  - Symmetrical involvement (both sides affected)
- Important demographic:
  - Women of childbearing age

**Major Causes of Inflammatory Polyarthritis**

- **Viral infections**
  - Hepatitis C
  - Hepatitis B
  - Parvovirus

- **Autoimmune disease**
  - Rheumatoid arthritis
  - Systemic lupus
  - Sjögren’s syndrome

- **Spondyloarthropathies**
  - Psoriatic arthritis
  - Reactive arthritis

- **Miscellaneous**
  - Polymyalgia rheumatica
  - Various vasculitides

**Viral Forms of Arthritis**

- **Viral arthritis**
  - Develops suddenly; generally resolves in weeks to months
  - Often have more pain than swelling; often accompanied by rash
- **Hepatitis C**
  - Blood exposure such as needle sharing
  - Polyarthralgias/polyarthritis
  - Rheumatoid factor positive in 70%
  - Check Hepatitis C antibody and if positive assay for viral RNA
- **Hepatitis B**
  - Arthritis develops before hepatitis; resolves with hepatitis
  - Usually accompanied by rash on trunk
  - Check HBsAg, HBsAb, and HBCAb
- **Parvovirus**
  - Children get fifth disease; “slapped cheek” and fever
  - Adults get arthritis along with rash on extremities and trunk
  - Check for IgM and IgG antibodies to parvovirus
  - 1/3 of adult women affected may have arthritis > 1 month

**Images courtesy of ©ACR - Rheumatology Image Bank, 2013.**
Autoimmune Diseases

- **Autoimmune diseases**
  - Subacute onset of inflammatory joint symptoms with other distinctive features and laboratory tests
- **Rheumatoid arthritis**
  - Occurs in women in their 20s to 40s, or men and women equally after age 60
  - Symmetric inflammatory polyarthritis involving the small joints
  - Rheumatoid factor and CCP testing very useful
- **Systemic Lupus**
  - Women predominately affected, but men are affected as well
  - Polyarthritis/polyarthralgias common but usually accompanied by other features of illness such as rash, serositis, nephritis, etc.
  - ANA testing critical for diagnosis
- **Sjögren’s syndrome**
  - Dryness of mouth, eyes, throat; also known as sicca
  - Arthritis may resemble rheumatoid arthritis but usually less severe
  - ANA testing critical for the diagnosis

Spondyloarthropathies

- **Spondyloarthropathies**
  - Often pauciarticular rather than polyarticular
  - Dactilitis, or “sausage” digit, should be a clue to these forms of arthritis
- **Psoriatic arthritis**
  - Psoriasis usually present but arthritis may appear first
  - Look closely at skin, including scalp and umbilicus
  - May have a rheumatoid arthritis-like presentation
- **Reactive arthritis (Reiter’s syndrome)**
  - Generally patients have other features that are a clue to reactive arthritis such as conjunctivitis or iritis, oral ulcers, skin rash on palms and/or soles, or tendonopathies
Miscellaneous Causes of Inflammatory Polyarthritis

- **Polymyalgia rheumatica**
  - Occurs in people generally over the age of 60 years
  - Characterized by marked stiffness in shoulder and hip regions
  - May have synovitis of hands, wrists, and knees; feet usually spared. Rheumatoid factor negative

- **Vasculitis**
  - Various forms of vasculitis may include inflammatory arthritis. Look for petechiae or purpura, weakness of hands or feet, abnormal chest x-ray, or urinalysis
  - Testing for ANCA may be helpful; if vasculitis is suspected, biopsy of affected tissue is important

Ockam’s Razor versus Hickam’s Dictum

**William of Ockam**

- “Entia non sunt multiplicanda praeter necessitatem”
- Entities should not be multiplied beyond necessity, i.e., the simplest explanation is usually correct

**John Hickam, MD**

- “The patient can have as many diseases as they desire well please.”


Patient History:
Ockam’s Razor versus Hickam’s Dictum

A 45-year old woman with a 10-year history of RA comes for evaluation. She reports two hours of morning stiffness, pain with activity especially in the left knee, and if she overdoes it, she has significant diffuse joint and muscle pain for a day or two. She also reports poor quality sleep.

Meds: Methotrexate 15 mg/week, naproxen 500 mg BID

Exam: No swelling of the small joints of the hands or feet. Small effusion in the left knee. She has multiple tenderpoints of fibromyalgia.

Testing: On x-rays, scattered erosion in the MCPs, diffuse loss of cartilage in the left knee; CBC normal, CRP normal

Which two patterns of joint presentation and examination is this patient exhibiting?
Thinking Like a Rheumatologist:
Clinical Pearl
Just because a patient carries a diagnosis of a chronic illness such as rheumatoid arthritis does not mean all of his/her symptoms are related to that illness! This person has quiet RA but active fibromyalgia plus post inflammatory osteoarthritis of the knee. Focus on the patient not the disease!

Epidemiology of RA in Adults
- Prevalence of RA differs by geographic location:
  - European/North American Caucasians: 0.5 to 2%
  - Asian/Far East: 0.2 to 0.5%
  - African: 0 to 1.4%
  - Native American (tribe dependent)
    - Pima - 5.3%
    - Southeast Alaskan 1.3-3.5%
- Higher prevalence found in women worldwide with the ratio of women to men is 3:1
- The incidence of RA increases dramatically in adulthood and continues through the 70s

Objective 2:
Describe the contributions of genes and environment to the development of RA.

Genetics of RA
Twin studies\(^1\):
- Monozygotic twins have a 15% concordance for RA
- Dizygotic twins have a 4% concordance rate
Risk of RA in a first-degree relative is similar to the dizygotic twin rate of 4%, or 2 to 4 times the general population risk in Caucasians. It is felt that overall genetics account for 50 to 60% of the risk of RA and the other 40 to 50% is due to environmental factors.

HLA Antigens and RA

HLA (human leukocyte antigen) are molecules found on the surface of cells and serve as recognition signals for the immune system. In RA, it has been discovered that the HLA-DR4 molecule increases the susceptibility of patients to RA. Specifically, the β1 chain has been found to hold the region that increases the risk.

- 3rd hypervariable region
- Amino acid sequences 70-74
- Shared epitope hypothesis

Other Risk Genes Identified

With each passing year, new genetic risk alleles are identified that could influence the onset or progression of RA. A combination of risk alleles are most certainly needed in RA.

Autoantibodies in Rheumatoid Arthritis: Rheumatoid Factor (RF)

- Rheumatoid factor is an antibody directed against the patient's own IgG.
- Sensitivity of 75% and specificity of 50%
- RF can be seen in other diseases besides RA: Hepatitis B and C, TB, fungal infections, Sjögren’s syndrome, mixed connective tissue disease, Waldenstrom’s macroglobulinemia, etc.
- Higher level generally means worse prognosis
- May not appear until right before or just after the arthritis begins

1Plenge RM. Curr Opin Rheumatol. 2009.
Autoantibodies in Rheumatoid Arthritis: Anticitrullinated Protein Antibodies

- Citrulline is an amino acid not found in human proteins.
- Citrulline is formed by the action of PADs (peptidylarginine deiminases) induced during inflammation (i.e., lung inflammation from smoking), which deiminates arginine to form citrulline.
- In RA, sensitivity of ACPA is 70 to 80% and has a specificity of 95%.
- Level predicts severity of disease
- May be present years before clinical disease

Benign Autoimmunity: Specific Auto-Antibodies May Precede the Symptoms of RA

Study of 79 RA patients who had donated blood several times prior to onset of RA. 2,138 control sera: 1.1% tested + for RF; 0.6% + for anti-CCP

Prediction Model for Erosive versus Nonerosive RA Early in Disease Course

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Odds Ratio</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom duration: ≥6 weeks but &lt;6 months</td>
<td>0.96</td>
<td>0</td>
</tr>
<tr>
<td>≥6 months</td>
<td>1.44</td>
<td>0</td>
</tr>
<tr>
<td>Morning stiffness ≥ 1 hour</td>
<td>1.96</td>
<td>1</td>
</tr>
<tr>
<td>Arthritis in ≥ 3 joint groups</td>
<td>1.73</td>
<td>1</td>
</tr>
<tr>
<td>Bilateral compression pain in MTP joints</td>
<td>3.78</td>
<td>2</td>
</tr>
<tr>
<td>IgM-RF ≥ 5 IU/mL</td>
<td>2.99</td>
<td>2</td>
</tr>
<tr>
<td>Anti-CCP ≥ 92 IU/mL</td>
<td>4.58</td>
<td>3</td>
</tr>
<tr>
<td>Erosions on hand or foot x-ray</td>
<td>Infinite</td>
<td>Infinite</td>
</tr>
</tbody>
</table>

Note: 524 consecutive patients with early arthritis; total score corresponds to predictive value for erosive versus nonerosive arthritis given the presence of persistent RA.

Genetic Issues and Anticitrullinated Peptide Antibodies

The shared epitope sequence on the HLA-DR4 molecule has high affinity for citrullinated peptides that it can pass onto auto-reactive lymphocytes.

Both shared epitope and polymorphisms of a gene called PTPN22 appear to increase the risk of having anticitrullinated peptide antibodies (ACPA).

ACPA (anti-CCP, anti-Sa, etc.) is the strongest predictor of developing rheumatoid arthritis.
**Environmental Factors in RA**

Infectious agents: Several agents implicated over the last 20 years but none could be conclusively linked to RA
- Mycoplasma
- Ebstein-Barr virus
- Cytomegalovirus
- Parvovirus B19

Occupation and socioeconomic status: No consistent findings

Smoking:
- First recognized as a potential risk factor in the late 1980s
- Recent case-control and cohort studies have found a strong association with smoking and RA, as well as a risk factor for extra-articular manifestations such as nodules and vasculitis\(^6\)
- Tobacco, RA, and RA as a possible New World disease?\(^6\)


**Antiquity of RA**\(^8\)

- Rare reports and no suggestive skeletal remains of RA in the Old World prior to the exploration of the New World by Europeans
- Excellent examples of RA in Native American burial sites antedating the coming of Europeans
- Thomas Sydenham in 1676 reports the first definitive case of RA, after which RA becomes more commonly reported.


**Environment and RA: Tobacco?**

Study of 13 pairs of monozygotic twins discordant for smoking and RA found that in 12 of 13 pairs, the smoker had RA.\(^9\)

Smoking is capable of inducing citrullinated peptides in lung tissue based on BAL studies by inducing peptidylarginine deiminase-2 (PAD-2).\(^10\)


Interaction Between Genetic and Environmental Factors

Risk of RA by Smoking, Shared Epitope (SE), and CCP Status

Data demonstrates the dose relationship between smoking and SE. 21-fold increased risk of RA in those with two copies of SE and history of smoking. CCP positive and negative RA are different diseases.

Environment and RA: Periodontal Disease

- Sugar production in European Caribbean colonies in 1700s
  - Sugar use increases the risk of periodontal disease
- The same genetic markers associated with RA and periodontal disease; similar histology
- Periodontal disease associated with Porphyromonas gingivalis; RA patients have increased titers to P. gingivalis compared to non-RA patients
- P. gingivalis is the only prokaryotic organism that produces PAD leading to citrullization of peptides; antibody titer to P. gingivalis mirror CCP antibody levels in RA patients.

Benign Autoimmunity Precedes Clinical RA

- Environmental Exposure
  - Smoking?
  - Periodontal Disease?
- Genetic factors
  - Shared Epitope
  - PTPN22 Polymorphism?
  - etc.
- ACPA Formation
- Second immunological hit?
  - Joint inflammation with intra-articular citrullinated proteins developing
- Immune attack against joint citrullinated proteins
  - ACPA titer elevation
  - RF appears

Image courtesy of Dr. Greg Gardner, 2013.

Pregnancy and RA

- Data from the 1990s found that 75% of women with RA who are pregnant improve or go into remission during pregnancy
- The most recent numbers (2006):
  - 28% went into remission
  - 38% improved
  - 35% were considered worse
- Nelson, et al. found that women who had a mismatch at certain HLA antigens with the fetus had a high rate of remission in pregnancy. The immune system in such a situation seems to “quiet down.”
- Patients who are seropositive generally do less well during pregnancy than those who are seronegative.
Objective 3: Review the basic immunology of RA and the consequences of the immune upregulation.

Pathophysiology of RA

Harris suggests that one think about the pathophysiology of RA in terms of Ravel’s “Bolero”:
- The piece begins with a flute and drum alone
- Additional instruments are added with time
- In the end, the entire orchestra is playing in fortissimo

This concept helps illustrate why it becomes harder to control the disease as time goes on.

Control inflammation ASAP!

RA Progression: Think Bolero

Early 1990: RA immunologically staged by Harris, modified by Gardner

Stage 0-1: Benign autoimmunity to early RA; antigen processed/presented to T cells; autoantibody production
Stage 2: T cells proliferate and induce B cell proliferation; new blood vessels develop; acute joint inflammation
Stage 3: Marked synovial proliferation and inflammation develop with production of cytokines

RA and Bolero

Stage 4: Synovitis polarized into aggressively invasive front of macrophages and synovial cells that begins irreversible destruction of cartilage, ligaments, and bone
Stage 5: Progressive loss of articular cartilage and bone; tendon/ligamentous attenuation and loss; joint deformity

Current treatment focused on Stages 3-4. Why not 1-2?
Synovial Hypertrophy: A Look Inside the Joint

Note the hyperemia in the joint as new blood vessels have formed in early RA. There is marked synovial hypertrophy in established RA and impressive pannus in late RA. Also note the relative lack of hyperemia in late disease.

Consequences of Pannus

Joint Erosions in RA: From Bad to Worse


Immune Response Phase 1: Bolero begins

B Cell

B Cells Expand

Citrullinated peptide

MHC II

TCR

CD80/86

CD 28

CD4 T Cell (autoreactive)

Dendritic Cell

If foreign antigen with activating cytokines present, (IL2, TNF) T cell provides second signal and activates

T cells differentiate expand

Activated CD4 T Cell

ACPA Producing B Cell

CD4 T Cell

Chondrocytes

MMP

Osteoclasts

Bone Resorption

IL-1

IL-6

TNF-a

MMP

Synovial Fibroblasts

IL-1

IL-6

TNF-a

Macrophage

In the RA Joint: Bolero continues

Joint Damage!
RA Treatment Themes 2013

- Early recognition and early institution of therapy, especially for those with poor prognostic markers
  - Presence of erosions
  - High titer anti-CCP/RF
- Treat to DAS (disease activity score) or some other measure of disease activity (SDAI, CDAI, etc.)
- Methotrexate anchor therapy; dose to 15-20 mg/week
- Consider early institution of biologic therapy especially in patients with markers of poor methotrexate response at three months
- Persistent joint swelling
- Elevated CRP


Delayed Treatment Means More X-ray Damage

- Delayed treatment (median treatment lag time, 123 days; n = 109)
- Early treatment (median treatment lag time, 15 days; n = 97)

DMARDs = chloroquine or azathioprine
*p < 0.05 vs delayed-treatment group.

Can RA Go Away with Early Therapy?

- BeST remission/radiographic data at 4 years
- Patient with < 2 years of RA treated to DAS 44 score of <2.4 (remission <1.6)
- As patients went into remission, medications withdrawn
- Drug-free remission more likely to be males, seronegative, and shorter symptom duration before starting therapy

Conclusion: Stopping the Music Early

The pathophysiology of RA is one of relentless progression for most patients. Treat as early as possible to prevent joint damage:

- Goal: shut off inflammation before damage occurs
- Once cartilage is damaged, no repair is currently possible
- There can be some bone remodeling with TNF therapy
Objective 4: Describe the articular and extra-articular manifestations of RA.

Joint Involvement in RA
All patients with RA have, by definition, involvement of the small joints of the hands and almost always the feet. The “symmetry” of involvement is such that both sides are involved but various joints do not need to be involved to the same degree on both sides. 2nd and 3rd MCPs seem to be hardest hit and the side of handedness is more involved than the opposite side; sometimes the wrists are the most involved joints.

RA Usually Occurs As a Slowly Progressive Disease Process
- **Early Symptoms**
  - Fatigue due to systemic manifestations of inflammatory cytokines
  - AM joint stiffness due to fluid accumulation during inactivity
- **Weeks to Months**
  - Joint pain from swelling and inflammation
  - Progressive joint deformity caused by progressive destruction of bone and cartilage and attenuation of supporting structures such as the joint capsule, ligaments, and tendons
- **Months to Years**
  - Gradual functional impairment
  - Extra-articular involvement (TBD)

2010 ACR/EULAR RA Criteria
- Joint involvement Score
  - 1 large joint: 0
  - 2-10 large joints: 1
  - 1-3 small joints: 2
  - 4-10 small joints: 3
  - > 10 small joints: 5
- Serology Score
  - Negative RF ACPA: 0
  - Low positive RF ACPA: 2
  - High level RF ACPA: 3
- Acute phase reactants Score
  - Normal CRP or ESR: 0
  - Abnormal CRP or ESR: 1
- Duration Score
  - < 6 weeks: 0
  - > 6 weeks: 1

6/10 points needed for classification

Small joints:
- MCPs
- PIPs
- Wrists
- 2-5 MTPs

High RF/ACPA > 3x ULN
**Joint Distribution**
- Cervical spine
- Shoulders
- Elbows
- Wrists
- Hands
  - PIPs
  - MCPs
  - SPARES DIPs
- Hips
- Knees
- Ankles
  - Tibiotalar
  - Subtalar
- Feet
  - MTPs

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**Hand Involvement Is the Hallmark of RA**
*Illustrated in the pictures that follow*

- Stiffness followed by fusiform swelling of the PIPs and swelling of the MCPs and wrists.
- Progressive hand changes include:
  - Ulnar deviation
  - MCP subluxation
  - Intrinsic muscle wasting
- Other changes:
  - Swan neck and/or boutonnière deformities
  - Finger nodules
  - Telescoping of joints
  - Tendons ruptures

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**Early Stage RA**

- Symptoms for only 6-8 weeks; note fullness in 3rd and 4th PIPs.

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**Close-up of Early RA**

- Note fullness in PIP joints of index, ring, and little fingers, in particular. Compare to your own fingers. Palpation of these joints would give you a sense of bogginess or fullness.

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*Image courtesy of Dr. Greg Gardner, 2013.*
Earliest RA

Below: Note fusiform swelling of the PIP joints, i.e., swelling contained by the capsule and fullness at the MCP joints.

Above: See how the normally loose skin creases over the joint are distended; the IP joint of the thumb is a PIP joint rather than DIP.

Image courtesy of Dr. Greg Gardner, 2013.

Early RA

Yet another example of early RA with swelling of PIPs, MCP, and the wrists.

Image courtesy of Dr. Greg Gardner, 2013.

Advancing RA

Note the swelling in the MCPs and PIPs, the mild atrophy of the intrinsic muscles, and early ulnar deviation, especially in the photo on the right.

Images courtesy of Dr. Greg Gardner, 2013.

Advancing RA

Above: Note the marked ulnar deviation in the right hand; this patient is most likely right handed.

Right: Moderate subluxation of the MCPs.

End-stage RA Hand Changes

Note severe ulnar deviation of the MCPs and subluxation of these same joints; this patient had just been treated with a TNF inhibitor and his swelling was markedly improved.

Advanced RA

Subluxation, ulnar deviation, and nodulosis

Left: Swan neck deformity (on ring, middle, and index) with hyperextension of DIP and hyperflexion of PIP. In the little finger, Boutonniere deformity shows hyperextension of PIP and hyperflexion of DIP.

Other Hand Deformities in RA

Right: Severe joint damage with telescoping fingers (fingers foreshortened), so called ‘opera glass’ deformity.
Luncheon of the Boating Party, 1881
Phillips Collection, Washington, D.C.

The Arthritis Begins
1896 1901

The Family of the Artist, 1896
The Barnes Foundation

The Arthritis Progresses
1903 1911

RA in Other Joints

- The feet are the joints most frequently involved, other than the hands and wrists.
  - MTP joint subluxation can lead to “cock-up” deformities of toes.
  - “Fibular deviation” of the toes, i.e., toes angling toward the fibula, is the equivalent to ulnar deviation.
- Elbow involvement typically leads to contracture.
- Shoulder disease occurs at the rotator cuff, as well as the glenohumeral joint.
- The ankle can be involved at both the tibiotalar and subtalar joints.
- Knee and hip involvement occurs in more serious disease.
- C-spine is also affected in more serious disease and can lead to significant neurological sequela.

RA at the Feet

**RA at the Feet**

Note the cock-up deformities of the MTPs and prominence of the MTP heads. This prominence can lead to pain with walking and even skin breakdown and can be a source of infection. It is important to examine the bottom of the feet in an RA patient.

Important Extra-articular and Periarticular Manifestations of RA

RA is a systemic disease. The hallmark of more serious RA is the presence of extra-articular disease. These include:

- Nodules
- Eye involvement
- Rheumatoid lung disease
- Felty’s syndrome
- Rheumatoid vasculitis

Many of these important extra-articular features appear to be much less common than in years past due to current treatment approaches. Important articular or periarticular complications include:

- Tenosynovitis with tendon rupture or carpal tunnel syndrome
- Upper cervical spine disease
RA Nodule or Gouty Tophus?

Elbows Nodules

Nodules form at pressure points and are most often seen at the elbows but can also be seen over the fingers and in rare instances in the lung. It is important to remember that gouty tophi can form at the elbow and mimic RA nodules. The nodule to the left is RA and below is a gout tophus. The presence of nodules in RA is a sign of more aggressive disease.

Eye Involvement

Scleritis is inflammation of the scleral layer of the eye causing thinning and blue discoloration. If thinned significantly, perforation can occur (below left). The cornea can also be involved (keratitis) and may lead to significant visual impairment.

Pulmonary Disease

Pulmonary nodules (left) occur in patients with nodules elsewhere. Solitary nodules need to be followed and evaluated for infection or tumor like any pulmonary nodule. Treatment of RA will often reduce the size of the nodule. Pulmonary fibrosis (below) occurs in RA as well. High resolution CT and PFTs can be used to diagnose this complication.

Felty’s syndrome

Felty’s syndrome is defined as the triad of:
- Rheumatoid arthritis
- Splenomegaly
- Leukopenia

It occurs in patients with long-standing seropositive (rheumatoid factor or CCP+) RA. Manifestations include:
- Recurrent bacterial infections
- Lower extremity ulcers
- Thrombocytopenia
- Development of large granulocyte lymphocytosis (LGL) and rarely LGL leukemia

Treatment is to more aggressively treat the underlying RA. Rarely, splenectomy may help the cytopenias.
Rheumatoid Vasculitis

Serious vasculitis, similar to polyarteritis nodosa, can occur in RA. It usually occurs in men with long-standing, severe RA. Common manifestations include:

- Digital necrosis (left)
- Neuropathy (foot or wrist drop)
- Intestinal bleeding
- Coronary vasculitis with MI

This is a life-threatening complication of RA.

Digital infarct from vasculitis

Right: Less serious small vessel vasculitis can also occur in RA and presents as nail fold infarcts. This form of vasculitis is not life threatening.

Tenosynovitis of the five finger extensor tendon

Tendon Involvement

Tendonitis, or tenosynovitis, can affect both flexor and extensor tendons. Extensor tendon rupture of the ring and little finger is a recognized complication of persistent tenosynovitis at the wrist and extensor tendons (left). When there is significant flexor tenosynovitis, the swelling can lead to pressure on the median nerve and carpal tunnel syndrome. Note thenal wasting in this case.

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Upper Cervical Spine Disease

Excess movement of the odontoid can be either anteroposterior (left) or it can move superiority into the foramen magnum and impinge the midbrain (below).

In the film on the left, the anterior arch of C1 is seen on the right and the odontoid is on the left. Normal spacing is 3 mm and this space is >5 mm.

Symptoms and exam findings are related to:

- Myelopathy
- Vertebral artery occlusion

Diagnosis:

- Flexion/Extension X-rays
- MRI scan of the cervical spine

Treatment:

- Surgery for severe symptoms
Objective 5:
Describe the utility of the current diagnostic testing and identify the basic radiographic findings in RA.

Rheumatoid Factor: Other Disease Associations

**Rheumatologic Diseases**
- RA
- SLE
- Sjogren’s syndrome
- Mixed connective tissue disease
- Myositis
- Cryoglobulinemia (usually associated with Hepatitis C)

**Infectious Diseases**
- Subacute bacterial endocarditis
- Tuberculosis
- Syphilis
- Hepatitis C
  - 70% of hepatitis C patients are RF+

**Other**
- 5% of healthy older people
- 2% of healthy younger people
- Idiopathic pulmonary fibrosis
- Cirrhosis
- Sarcoidosis
- Waldenstrom’s macroglobulinemia
  - A hematologic malignancy

**Bottom line:** Rheumatoid Factor is not a specific test for rheumatoid arthritis!

What is Rheumatoid Factor (RF)?

- Rheumatoid factor (RF), as generally measured, is an IgM molecule that is directed against the Fc portion of the patient’s own IgG.
- Why would the immune system want to make antibodies against its own antibodies?
  - One thought is that RF might help remove immune complexes from the circulation more efficiently, and thus RF provides a protective function.
- RF can also be IgG or even IgA antibodies
  - The presence of IgA RF is felt to predict worse prognosis but is rarely measured clinically

Using Rheumatoid Factor

- Sensitivity of RF 70 to 80%; so, up to 30% of people with RA will not develop a RF
- May not be present early in disease
- Useful to confirm a clinical impression when present
- As noted in the previous slide, the specificity of RF is such that when present, one needs to think about other possible diseases, especially hepatitis C.
Anti-cyclic Citrullinated Peptide (CCP)\textsuperscript{20}

- Anti-CCP antibodies have a sensitivity of 78% and specificity of 96% for RA.
- 40% of "seronegative RA" patients are anti-CCP+.
- The level of CCP is predictive of disease severity.
- CCP is not typically present in people with hepatitis C and is helpful in sorting out hepatitis C arthralgias from rheumatoid arthritis.
- May be present months prior to onset of clinical symptoms.
- When present, CCP is very reassuring that the patient does indeed have rheumatoid arthritis.


Other Laboratory Abnormalities

- ESR and CRP are frequently, but not invariably, elevated in RA.
- Lowering of an elevated acute phase reactant such as ESR is a marker of treatment success.
- Normochromic, normocytic anemia, that is, anemia of chronic disease
  - Hematocrit in the low to mid 30s is not unusual
  - Need to differentiate from iron deficiency anemia from NSAID use or other medication side effect causing bone marrow suppression
- As with any active inflammatory disease, albumin may be slightly low and fibrinogen elevated.
- Synovial fluid (SF):
  - Cell counts generally run 5,000 to 20,000 WBC/cc\textsuperscript{3} and are mostly neutrophils. Cell count can be higher though.
  - SF complement and glucose levels are typically low, although these are rarely measured.

Synovial Fluid in RA

The middle fluid is typical of RA. The number of WBCs in the fluid makes it impossible to read the newsprint through the fluid. The second vial from left is typical of OA, while the fourth from left is septic, and the fifth is a hemorrhagic fluid.

Radiology of RA

Classic radiographic features of RA include:
- Periarticular osteopenia
- Marginal erosions
- Uniform joint space narrowing
- Less commonly, subchondral cysts
- Periarticular soft tissue swelling

Features not typical of RA and suggestive of OA include:
- Osteophytes
- Subchondral sclerosis

One can see the above changes in someone with long-standing RA who has developed a post-inflammatory OA; that is, the joint has been damaged by RA and develops OA in the affected joint.
But First… Anatomy Review

Bones of the Hand
Proper terminology for the bones of the hand are shown at right, although naming the digits by thumb, ring finger, middle finger, index finger, little finger, and so on can sometimes avoid confusion.

X-ray views for hands
- AP
- ballcatchers

Progressive Radiographic Changes in RA

X-rays A-C show progressive changes in one PIP joint. Panel A shows periarticular osteopenia. B demonstrates the beginnings of joint space narrowing and the start of a marginal erosion. C shows an erosion and marked joint space narrowing.

Early RA

Note the early marginal erosion at the thumb and third MCP. There is little joint space narrowing at this point.

Progressive RA

In this radiograph, there are marked erosive changes at the index and middle finger MCP joints with joint space loss. The thumb also shows joint space narrowing with a small marginal erosion.
This is an end-stage hand with marked destruction of all the MCPs and subluxation of the MCP joints, as well as ulnar deviation. The wrist is also globally involved by RA.

Can you spot the erosions indicated by the arrows? Try looking at films systematically, i.e., start at DIPs, then PIPs, then MCP, then the wrist. Don’t forget to look at bone mineralization and soft tissues as well.

This film shows a close-up of a wrist and in particular the ulnar styloid. This is a location where erosions might first be seen in RAC. Can you name the carpal bones?

Carpal Bones

End-stage RA of the Wrist

Note radiocarpal and ulnocarpal joint space loss, along with complete loss of cartilage between the other carpal bones.

Progressive changes in the wrist of a patient with RA. Note the gradual loss of joint space and progressive appearance of erosions.

Normal Shoulder X-ray and Named Structures

When ordering shoulder x-rays in RA, order three views:
- External rotation
- Internal rotation
- Axillary

This x-ray shows RA affecting the shoulder girdle. RA can damage the rotator cuff tendons, leading to cuff tear and a high-riding humeral head as noted here. In addition, the glenohumeral joint cartilage has been lost and note the erosions at the humeral head at the margin of the cartilage and synovium. Also note the osteopenia present.
Classic demonstration of a rotator cuff tear in a patient with RA. Note the position of the humeral head in relationship to the glenoid. The upward migration of the humeral head causes the humerus to actually articulate with the undersurface of the acromion.

Elbow Radiographs Typically Include at Least an AP and Lateral in RA

Elbow in RA
Above lateral and left AP x-ray of the elbow showing erosions and cartilage loss. Upper right is an MRI showing marked synovitis surrounding the elbow.

Normal X-ray Anatomy of the Hip
Usual view in RA includes an AP pelvis and frog leg view of the hip in question.
1. Moderate progressing to severe RA hip involvement. Note the diffuse joint space narrowing subchondral cysts and no osteophytes more typical of OA.

2. Close-up of the diffuse joint space narrowing

3. Severe disease in hips, called 'protrusio'

There is severe diffuse joint space narrowing typical of an inflammatory disorder. All three compartments can be affected.

In RA, AP standing, lateral, and sunrise views are typical views used to assess the knee.

Joint spaces are maintained and there is a small erosion present at the margin of the medial tibial plateau.
Examples of severe foot involvement in RA with damage to all MTPs, cock-up deformities, subluxation, and fibular deviation of the toes. Note the soft-tissue swelling upper left on the right 5th MTP. (Also note ghost rheumatologist in 1.) In x-ray 2, there is end-stage foot changes.

Advancing RA of the Feet

AP and oblique views of the feet demonstrate erosive changes at the 3rd and 5th MTPs. Note how the oblique view demonstrates the damage to the 5th MTP.
To evaluate C-spine disease in RA, neutral and flexion views are useful to look for C1-C2 subluxation.

MRI scans of the wrist in RA. The pink arrows indicate areas of erosion or synovitis.

Ultrasound has emerged as an important tool in rheumatology, capable of detecting synovitis and erosions in RA. Below is an US of the shoulder in an RA patient.

Identify current assessment methods, the utility of outcome measure tools, and “treat to target” monitoring.

Objective 6:
Outcome Measures in RA

Outcome measures in RA have focused on four main areas:
1. Measurement of inflammatory activity
2. Measurement of joint damage
3. Functional and global status
4. Long-term outcome status

Most of these measures have been utilized in studies, but recently they have found their way into everyday practice as well.

Measurement of Inflammatory Activity

There are two main clinical outcome measures in treatment trials for inflammatory activity in RA:
1. American College of Rheumatology (ACR) criteria for improvement
   - Measures the percent change from baseline and is useful for discriminating between treatment for RA
   - ACR 20, 50, 70 indicates the level of improvement observed (see the next few slides for more explanation)
2. European League Against Rheumatism (EULAR) criteria for improvement - Disease Activity Score (DAS)
   - The DAS provides a current level of activity as opposed to relative activity
   - Currently includes DAS 28 ESR, DAS 28 CRP, DAS remission

ACR Criteria for Improvement

Developed for use in clinical trials, not for daily practice.
Seven core criteria:
1. Swollen joint count (28 joints)
2. Tender joint count (28 joints)
3. Health Assessment Questionnaire
4. Pain on Visual Analog Scale (VAS)
5. Physicians global assessment VAS
6. Patients global assessment VAS
7. ESR/CRP

ACR 20 = 20% improvement in SJ and TJ and 20% improvement in 3/5
ACR 50 and ACR 70 have less discriminating power for detecting differences between treatments than ACR 20.

Disease Activity Score (DAS)

Original DAS used a 44-joint count.
Current DAS is the DAS 28:
- Swollen joint count of 28 joints
- Tender joint count of 28 joints
- Omits the joints of the feet
- General health assessment on VAS 100
- ESR or CRP
- 0-10 scale
- Has to include joint counts and ESR/CRP but can omit VAS
**DAS 28 Equation**

\[
\text{DAS28} = 0.56 \times \sqrt{(\text{TJ28})} + 0.28 \times \sqrt{(\text{SJ28})} + 0.70 \times \log(\text{ESR \text{mm/hr}}) + 0.014 \times \text{Global health assessment VAS in mm (0-100)}
\]

Online or handheld calculators can do this math for you; it’s too cumbersome without help. Online calculator can be found at:  

---

**DAS Scores (Based on DAS 28)**

<table>
<thead>
<tr>
<th>DAS Score</th>
<th>Disease Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2.6</td>
<td>Remission!</td>
</tr>
<tr>
<td>2.6 - 3.1</td>
<td>Low disease activity</td>
</tr>
<tr>
<td>3.2 - 5.1</td>
<td>Moderate disease activity</td>
</tr>
<tr>
<td>&gt; 5.1</td>
<td>High disease activity</td>
</tr>
</tbody>
</table>

---

**EULAR Response Table Used in Clinical Trials**

<table>
<thead>
<tr>
<th>Present DAS 28</th>
<th>DAS 28 Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3.2 Low disease activity</td>
<td>&gt;1.2 Good response, 0.6-1.2 Moderate response, &lt; 0.6 No response</td>
</tr>
<tr>
<td>3.2 - 5.1 Moderate disease activity</td>
<td>Moderate response, Moderate response, No response</td>
</tr>
<tr>
<td>5.1 High disease activity</td>
<td>Moderate response, No response, No response</td>
</tr>
</tbody>
</table>

---

**Using the DAS Calculator**

Cut and paste the URL into another window of your browser:  
[http://www.das-score.nl/](http://www.das-score.nl/)  
On the DAS home page, click on Online DAS calculator. Choose DAS 28.

**Problem - Part 1**
- Patient on methotrexate for 4 months at 10 mg/week and 5 mg of prednisone per day  
- Has 12 tender joints, 10 swollen joints, an ESR of 35 mm/hr, and a VAS of 50 on a 100 mm scale for global sense of health
- Plug in the numbers
- Press calculate

**Problem - Part 2**
- A DAS of 6.02!  
- This is high disease activity and this person should be counseled to accept additional therapy

**Problem – Part 3**
- Patient placed on a TNF inhibitor. At 8 weeks, patient has 1 tender joint, 1 swollen joint, an ESR of 10 mm/hr, and VAS of 10

**Problem – Part 4**
- DAS of 2.59  
- Much better
ACR versus EULAR Summary

<table>
<thead>
<tr>
<th>Developed to distinguish between</th>
<th>Active and placebo prescription</th>
<th>High and Low Disease Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Components</td>
<td>7 core set variables</td>
<td>DAS (3-4 core set variables)</td>
</tr>
<tr>
<td>Improvement definition</td>
<td>Relative change</td>
<td>Significant change and reached level</td>
</tr>
<tr>
<td>Classification of improvement</td>
<td>20, 50, 70, 90% improvement</td>
<td>Good, moderate, non-responder; remission</td>
</tr>
</tbody>
</table>

Correlation finds the ACR and EULAR equal in terms of determining change in randomized placebo controlled trials.

Issues of Relative Improvement

Both patients have an ACR 50 response, but which one needs more therapy? This demonstrates the weakness of the ACR Criteria for clinical practice.

Simplified Disease Activity Index (S-DAI)\textsuperscript{21}

Designed to be used in clinical practice

\[
S-DAI = TJC + SJC + PtGA + PhGA + CRP
\]

- TJC (0–28)
- SJC (0–28)
- Patient Global Assessment, 0–10 cm VAS
- Physician Global Assessment, 0–10 cm VAS
- CRP (mg/dL)

Clinical improvement by the S-DAI:
- Remission $<3.3$
- Low disease activity $<11$
- Moderate disease activity $<26$
- High disease activity $>26$

Clinical Disease Activity Index (CDAI)\textsuperscript{21}

Designed for use in clinical practice; omits CRP

\[
C-DAI = TJC + SJC + PtGA + PhGA (No CRP)
\]

- TJC (0–28)
- SJC (0–28)
- Patient Global Assessment, 0–10 cm VAS
- Physician Global Assessment, 0–10 cm VAS

Clinical improvement by the C-DAI:
- Remission $<2.8$
- Low disease activity $<10$
- Moderate disease activity $<22$
- High disease activity $>22$

Routine Assessment of Patient Index Data (Rapid 3) in RA

Rapid 3:
• Patient questionnaire
• No physician input except to score

Components total 30 points:
• Patient global scale VAS 0–10
• MDHAQ 10 ADL for physical functioning 0–10
• Patient pain VAS 0–10

Score:
• Remission < 3.0
• Low disease activity 3.1 – 6
• Moderate disease activity 6.1 – 12
• High disease activity > 12

Example of RAPID 3 with detailed scoring explanation
http://echo.unm.edu/.../clinic-rheumatology-rapid3.pdf

ACR/EULAR 2011 Criteria for Remission in Rheumatoid Arthritis

For clinical trials:
• Boolean
  – SJC, TJS, PtGA, CRP all ≤1
• Index-based
  – SDAI ≤3.3

For clinical practice:
• Boolean
  – SJC, TJC, PtGA all ≤1
• Index-based
  – CDAI ≤2.8

SDAI = SJC + TJC + PhGA + PtGA + CRP (mg/dl)
CDAI = SJC + TJC + PhGA + PtGA

Measures of Function: Health Assessment Questionnaire (HAQ)

• The HAQ was first introduced in 1980 and questionnaires have become an important instrument in assessing RA patients.
• They can be completed by the patient or by an interviewer and generally can be done in five minutes or less.
• Found to correlate as effectively as other objective measures of disease assessment and are sensitive to changes in activity
• Now included in most major clinical trials
• Some rheumatologist are using them in the office to track patient status

HAQ Variations

Over the years, several versions have appeared
- HAQ
- Modified HAQ (MHAQ)
- Multidimensional HAQ (MDHAQ)

The MDHAQ has been correlated with the HAQ (a longer questionnaire) and with joint counts, radiographs, and laboratory markers of disease activity. The MDHAQ is available for download from the ACR website (www.rheumatology.org - see next slide) under ‘Practice Management,’ then ‘Clinical Support.’ Some versions of the MDHAQ also include a fatigue VAS.

MDHAQ

- Can be self-administered or conducted by patient interview
- Four dimensions (or indexes) with multiple components
- Scores range from 0 (no difficulty) to 3 (unable to perform)


Use of HAQ as Predictor of Outcome in RA Patients

- Functional loss at five years is 4x more likely in patients with baseline HAQ > 1
- High HAQ score has been associated with 3x to 6x higher rate of joint replacement
- High HAQ scores correlated with a high risk of work disability
- Minimally Clinically Important Change (MCID) is considered to be -0.22 for studies (see Additional Reading/Resources section for where to find more information on the HAQ)

ACR 1991 Revised Criteria:

Global Functional Status in RA

A global score provides healthcare providers with an overall sense of the level of the impact of the disease in someone’s life:
- Class I: performs usual activities of daily living
- Class II: performs usual self-care and vocational activities, but limited in avocational activities
- Class III: performs usual self-care activities, but limited in vocational and avocational activities
- Class IV: limited in ability to perform usual self-care, vocational, and avocational activities

Measurement of Joint Damage: Radiographic Evaluation of RA Progression

There have been numerous methods for measuring radiographic progression in RA over the years. Various modifications have been proposed. The basic methods include:

- Sharp
- Larsen
- Genant

You may see different names in front of the method, such as the Van der Heijde modification of the Sharp method, but they basically measure the same thing: joint damage.

What the Radiographic Scores Measure

Example: Modified Sharp score from 1985

- Erosion score
  - 17 joint areas scored for erosions of hands/wrists
  - 0 – 5 for each joint with each erosion counted 1 point
  - Maximum score 170

- Joint space narrowing score of hands/wrists
  - 18 joint areas scored for narrowing
  - 0 – 4 for narrowing (4 = ankylosis)
  - Maximum score of 144

- Total Sharp score maximum is 314

For clinical trials, an increasing Sharp score indicates progressive disease. The Sharp score is a sensitive indicator for progression.

Progressive Radiographic Changes in RA

Modified Sharp score for A is 0, for B is 2 (i.e., no erosion and half of joint space gone), and C is 4 [i.e., complete loss of joint space without ankylosis (3) and one erosion (1)].

Ultrasound\(^{26}\) and MRI\(^{27}\) Scoring in RA

It is anticipated that imaging will be used in the future definitions of remission given their power to discern disease activity. Ultrasound has been used in studies to monitor response to therapy; but to date, no universally accepted scoring method has been agreed upon. MRI scoring method is currently under assessment.

Objective 7: Describe the rationale for medication choices, including hoped for efficacy, side effects, and safety issues.

Treatment Milestones in RA

1929 Gold: the first disease-modifying antirheumatic drug (DMARD)
- Forestier began using gold compounds for RA based on their use in tuberculosis and the notion that tuberculosis and RA were linked.
- The Empire Rheumatism Council in Great Britain and the Cooperating Clinics of the American Rheumatism Association trials demonstrated that gold is a true DMARD.
- A long-term open study of 47 years by Lockie and Smith reported a 4% remission rate with gold the first year and a 10% rate of remission in patients on gold 6 to 7 years.28
- Disadvantages of gold include the slow onset of action, the intensive monitoring and administration schedule, and its toxicity.


1936 Sulfasalazine: first designer drug for RA
- Svartz and colleagues at the Karolinska Institute in Sweden combined sulfapyridine with 5-aminosalicylic acid (5-ASA) to treat RA with an antibiotic and an anti-inflammatory.
- Initial success was followed by negative studies and sulfasalazine was "lost" until rediscovery by McConkey and colleagues in the late 1970s in Great Britain.
- The mechanism of action is felt to depend on the sulfapyridine moiety liberated from the 5-ASA portion of the compound by gut bacteria. Sulfapyridine has the ability to inhibit production of interleukin 1 (IL-1) and tumor necrosis factor (TNF), as well as production of lipoxygenase and cyclo-oxygenase products.
- Sulfasalazine continues to be used, especially in Europe.

1948 Cortisone: the “miracle” drug
- Work of Reichstein in Switzerland, and especially Kendall in the US at the Mayo Clinic, led to the discovery of cortisone.
- Synthesized by Sarett at Merck and made available to Hench at Mayo Clinic.
- Initial use and dramatic results held out the hope for cortisone as a miracle agent.
- The next slide details the results with its use in the first RA patients treated with cortisone.
**Cortisone and Arthritis**

Hench inquires about compound E (cortisone) for Mrs. G, who suffered from severe RA. On September 21, 1948, the first dose was given to Mrs. G, and she becomes Patient No. 1. Two days later, she is able to get out of bed and walk. By September 28th (one week later), she went out shopping for three hours.

Patient 5 was given controlled trial of compound E versus cholesterol injections.

Patient 6 was given ACTH with similar benefit.

Data presented on May 3, 1949 at the Association of American Physicians to a large crowd.

Reichstein, Kendall, and Hench receive the Nobel Prize in Medicine in 1950.

---

**The Miracle and Reality**

- Realization that cortisone had significant side effects led to its rejection by many physicians
- Hench advocated for reasonable doses in RA but he became embittered in the debate
- Current use of steroids in RA is with small doses to control symptoms, bridge therapy (until DMARDs begin to work), and in Europe, as an induction agent in higher doses
- Recently low-dose prednisone in combination with methotrexate was found to provide significant additive therapeutic benefit for RA patients\(^\text{29}\); however, long-term side effects of such therapy is a concern.


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**Pyramid Approach for Treatment of RA**

A standardized approach was developed in the 1960s and utilized in various forms until the mid- to late 1980s. This slow and steady approach resulted from the notion that RA was disabling but an otherwise benign disease.
**Treatment Milestones in RA**

1972 Methotrexate: workhorse drug in RA
- Hoffmeister reported the use of methotrexate in RA patients in his practice in abstract form in 1972
- In 1980, Willkens, et al., published the use of methotrexate in 32 RA patients. In the mid-1980s Willkens was instrumental in two controlled trials demonstrating the efficacy of methotrexate in RA
- The mechanism of action of methotrexate is to modulate an increase in the anti-inflammatory compound adenosine, which affects lymphocyte and monocyte function
- Methotrexate is a true DMARD and is currently first-line therapy in RA and is utilized in a variety of combinations for the treatment of RA

**Late 1980s: Inverting the Pyramid**

Data accumulated indicating that RA was a disabling disease and was not a benign disease in many respects. The following are some of the data that changed minds about the slow and steady approach to RA:
- > 90% of RA patients have erosions after 2 years
- 5% to 10% of RA patients become disabled each year
- Only 18% of RA patients achieve a period of remission during the course of their disease.
- Median life expectancy decreased 4 years for men and 10 years for women with RA. Primary cause was ???

In 1989, Healey and Wilske wrote an editorial suggesting the pyramid be inverted, i.e., treat aggressively and as soon as possible to stifle inflammation. Wilske KR, Healey LA. *J Rheumatol.* 1989.

"Time and comparative observations will be needed to show the optimum combination of drugs and whether the step-down bridge concept will achieve the sought-for and presently unobtainable goal of early and sustained control of inflammation, improved quality of life, and prevention of bone and joint damage." Wilske KR, Healey LA. *J Rheumatol.* 1989.


“What we need in RA is a drug for which one does not need a statistician to see the beneficial effects.”
Changes in Treatment Approaches to RA

Early intervention
Combination therapy
Single-drug therapy

Treatment pyramid


RA Treatment Themes 2012

• Early recognition, early institution of therapy, especially for those with poor prognostic markers (which is true of other diseases as well)
  - Extra-articular manifestations, i.e., nodules
  - Presence of erosions
  - High titer anti-CCP/RF
• Treat to DAS (disease activity score) or some other measure of disease activity (SDAI, CDAI, etc.)
• Methotrexate anchor therapy; dose to 15-20 mg/week
• Consider adding biologic therapy/additional DMARD, especially after three months if low disease activity or remission is not achieved
  - Persistent joint swelling
  - Elevated CRP

2012 ACR Paradigm for Treating RA of Less Than Six Months Duration

Patients were categorized based on the presence or absence of one or more of the following poor prognostic features: functional limitation (e.g., Health Assessment Questionnaire score or similar valid tools), extra-articular disease (e.g., presence of rheumatoid nodules), positive rheumatoid factor or anti-CCP antibodies, and bony erosions by radiograph.

DMARD Treatment: The Earlier, the Better

Early treatment, even with mild DMARDs, can make a difference in radiographic damage later on.

DMARDs = chloroquine or azathioprine
*p < 0.05 vs delayed-treatment group.
Current Medications to Treat RA

**Methotrexate (MTX)**

**History:**
- Developed in 1940s to treat childhood forms of leukemia
- First used in 1972 for RA and studied in late 1970s and early 1980s; found to slow the progression of RA

**Current uses:**
- RA, SLE, psoriasis, PsA, IBD, scleroderma, and others

**Mechanism of action:**
- DHFR inhibitor but anti-inflammatory action is thought to be mediated by methotrexate-mediated increases in adenosine

**Dosage:**
- 7.5 mg to 25 mg SC or PO once weekly
- SC found to be more effective than PO with similar tolerability
- Onset of activity 3 to 8 weeks

**Toxicity:**
- Liver – minimize ethanol use; use folic acid supplementation
- Bone marrow – folic acid supplementation may reduce toxicity
- GI symptoms – anorexia, nausea especially day after
- Teratogen/abortifacient – three months off drug before conception

**Initial evaluation and monitoring:**
- Baseline CBC, creatinine (decrease in GFR increases methotrexate toxicity), chemistry panel, Hepatitis B and C
- CBC, LFTs monthly for 6 months then every 1 to 3 months thereafter; consider intermittent check of albumin and creatinine

**Immunizations:**
- UTD influenza and pneumococcal; can receive zoster if appropriate, provided methotrexate dose is equal or less than 0.4 mg/kg/week


**Sulfasalazine (SSZ)**

**Medication forms:** oral tablets in 500 mg

**Initial dose:** 1000 to 2000 mg/day in divided doses
- Patients can be started on 500 BID and then increase the dose to 500 mg every five days until reaching the standard dose of 2000 mg/day

**Maximum dose:** 3000 mg/day
- Little additional benefit of this dose but increase in toxicity. It can be used when it appears patients are losing their previous benefit from the medication

**Time to effect:** 4 to 12 weeks

**Other:** Can be used during pregnancy; avoid in sulfa allergic patient
Hydroxychloroquine (HCQ)

History:
- Derivative of quinine, which originally came from the bark of the cinchona tree in South America
- Quinine was used to treat lupus as early as 1894
- Hydroxychloroquine was developed during WWII and was first used to treat RA in 1951

Current uses:
- RA, SLE, discoid lupus, and a multitude of other conditions!

Mechanism of action:
- Raises the pH inside lysosomes of APC and modifies how antigens are presented to T cells
- Interferes with activation of toll-like receptors on inflammatory cells

Clinical effects (wonder drug!):
- Modifies inflammation
- Reduced risk of thrombosis in SLE patients with APL abs
- Reduces risk of diabetes in patients with inflammatory disease
- Reduces LDL, VLDL, TG, raises HDL

Dosage:
- 6.5 mg/kg lean body weight

Potential side effects:
- Ocular: corneal deposits; retinopathy (dosage 6.5 mg/kg max dose)
- Skin: drug rash, gray skin pigmentation with chronic use
- Rare bone marrow toxicity
- Neuromyopathy cardiomyopathy (unexplained CHF in older patient on HCQ?)

Hydroxychloroquine and the Eye

American Academy of Ophthalmology recommendations for antimalarial screening:
- High-risk patients (over 60 years old, diabetes, renal or hepatic disease, obesity) should have baseline and yearly eye evaluation
- Low-risk patients should have baseline and again at 5 years; then yearly screening

Leflunomide (LEF)

Medication forms: oral tablets 10, 20
MOA: inhibition of dihydroorotate and tyrosine kinase that affects the activity of activated lymphocytes

Drug has a half-life of two weeks!

Dose: 10 to 20 mg/day
- Time to effect: 4 to 12 weeks
- Side effects: Avoid in pregnancy as LEF is a teratogen
Other Non-biologic DMARDs

Other agents occasionally used in RA:
- Azathioprine
- Cyclosporine
- Minocycline/doxycycline
- Gold
- Penicillamine

These agents are beyond the scope of this introductory course. Consult an experienced colleague or textbook for more information on these little used drugs for RA.

Important Side Effects of Commonly Used Non-biologic DMARDs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Minor side effect</th>
<th>Major side effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>GI intolerance, anorexia, stomatitis, alopecia</td>
<td>Myelosuppression, hepatic dysfunction, cirrhosis, pneumonitis, infection</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>GI intolerance, rash, orange urine color (expected), azospermia</td>
<td>Myelosuppression, agranulocytosis, hepatitis</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Rash, diarrhea</td>
<td>Retinopathy with diminished peripheral vision, neuromyopathy, including cardiomyopathy</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>GI intolerance, diarrhea, alopecia</td>
<td>Myelosuppression, infection, hepatitis/cirrhosis</td>
</tr>
</tbody>
</table>

Baseline/Monitoring Schedule for Commonly Used Non-biologic DMARDs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Baseline</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>CBC, creatinine, LFTs (albumin, transaminases, alkaline phosphatase), CXR, hepatitis B and C (avoid in chronic viral hepatitis)</td>
<td>CBC, transaminases monthly for 6 months, then every 2 months for 6 months then every 3 months. Repeat testing for minor elevations of AST/ALT. Hold dose and repeat for &gt; 2-3x normal; restart at lower dose.</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>CBC, LFTs</td>
<td>Every 2 to 4 weeks for 3 months then every 3 months</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Baseline eye exam (if patient tolerates drug), document reflexes</td>
<td>Eye exam as noted, reflex testing (if loss of reflexes, harbinger of neuromyopathy)</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>Same as for MTX</td>
<td>Same as MTX</td>
</tr>
</tbody>
</table>

Naming Biologics

- Biologics are isolated, naturally occurring molecules created through recombinant DNA technology
- Monoclonal antibodies (mab)
  - muminab = fully human protein
  - zumab = humanized, i.e., 10% mouse
  - ximab = chimeric, i.e., 33% mouse
- Fusion proteins
  - Molecule (receptor or ligand) fused to the Fc portion of IgG1
  - -cept suffix is used to identify these agents
- Recombinant receptor antagonists
  - -inra suffix is used to identify these agents
TNF Agents in RA
Five agents currently available (2013):
- Etanercept (Enbrel) 50 mg SC weekly
- Infliximab (Remicade) 3 to 5 mg/kg IV 8 weeks
- Adalimumab (Humira) 40 mg SC 2 weeks
- Certolizumab pegol (Cimzia) 200 mg SC 2 weeks
- Golimumab (Simponi) 50 mg SC monthly

Biologic DMARDs: Issues Using TNF Agents
- Avoid in patients with NYHA III or IV CHF; apparently does not cause CHF but may worsen
- Avoid live vaccines in patients receiving TNF agents
- Plan major elective surgeries for end of dosing interval and hold for two weeks before restarting
- Current recommendation is to avoid in pregnancy
- Monitor for demyelinating disease (weakness, parathesias)
- Rare leukopenia
- Reactivation of hepatitis B; check hepatitis B at baseline
- Hepatitis C not a contraindication to use TNF agents
- TNF agents may reactivate TB (see next slide for screening algorithm)

Biologic DMARDs: Issues Using TNF Agents
- Rare hepatitis
- Rare lupus-like illness (induces ANA/DSDNA)
- Increased risk of respiratory infections
- Rates of lymphoma under close scrutiny; RA patients, in general, are at increased risk of lymphoma related to disease activity
- Infusion reactions occur with infliximab; premedicate with Benadryl and Tylenol and keep infusion to the slow end of infusion rate; use MTX as this will decrease the incidence of anti-infliximab antibodies so-called HACA (human anti-chimeric antibodies)
- Monitoring labs:
  - Baseline: CBC, LFTs, hepatitis B status
  - Monitoring: CBC, LFTs every 2 to 4 months; CBC with infection

B Cells and Autoimmunity in RA
- Produce autoantibodies, i.e., RF, anti-CCP, DSDNA
- Autoantibodies capable of fixing complement and attract other inflammatory cells such as PMNs
- B cells activate T cells and thus influence downstream events; can act as antigen-presenting cells
- Produce cytokines, IL-6, TNF, IL-10
- Rituximab has a long history of use in lymphoma; targets CD20 antigen on B-cell surface
- Currently approved for use in RA
## Issues in Using Rituximab
- Dosed 1000 mg IV at baseline and then 1000 mg IV two weeks later
- Redosing in majority of RA patients
- Infusion reactions can rarely be severe (rash, anaphylactic reactions, urticaria, laryngeal edema). Pre-medicate with acetaminophen and Benadryl; some clinicians will give 100 mg of solumedrol IV as a premed as well.
- Other important side effect includes concern about infection, especially in patients taking multiple immunosuppressant drugs. Several cases of progressive multifocal leukodystrophy (PML) reported in lupus patients (not RA) from reactivation of JC virus in the CNS
- Need to screen for TB and Hepatitis B prior to prescribing

## Issues in Using Abatacept
IV dosing as follows:
- In those weighing less than 60 kg, 500 mg of abatacept given IV monthly
- Patients weighing 60 to 100 kg, receive 750 mg
- Patients weighing more than 100 kg, receive 1000 mg of abatacept
It is now available for subcutaneous injection, as well as 125 mg SC weekly
Abatacept is also approved as first-line therapy for RA
Side effects of concern include:
- Increased risk of respiratory tract infections
- Exacerbations of COPD
- There is some concern for lung tumors in smokers and should currently be used with caution in this group of patients
- Infusion reactions do occur and the usual pre-meds of acetaminophen and Benadryl do not have to be used as pre-medications

## T Cell Costimulatory Blockade
Recall our discussion of the pathophysiology of RA in Objective 3, where the T cell can be downregulated if the CTLA-4 ligand on the T cell is presented to the APC rather than CD-28.
Abatacept is a CTLA-4 molecule fused to a human IgG constant region and it inhibits the presentation of antigen to T cells. Fusion to IgG tail increases the half-life of the molecule.

## Anti-IL6 Therapy in RA
- Tocilizumab (Actemra) prevents IL-6 from interacting with its receptor and activating cell
- Dosed 4 to 8 mg/kg IV monthly
- Rapidly reduces acute phase reactants such as CRP
- Need premeds with infusion
- Side effects: TB reactivation, infection, elevation of LFTs, and elevation of lipids
Janus Kinase (JAK) 3 Inhibitors

New class of medication approved for RA in 2012
Rather than targeting cytokines directly, these drugs interrupt the signal from the cytokine receptors (STAT) to the nucleus where inflammatory molecules are made
Tofacitinib, an oral agent, has recently been approved for RA
Initial efficacy data suggests comparable to TNF agents
Side effects are similar to tolcilizumab, which inhibits IL-6, in that it uses the JAK/STAT pathway for cell activation:
- Neutropenia
- Elevation of lipids
- Elevated liver tests

RA Treatment in Action

Combination Therapy in RA: “Triple Therapy”
Combination of MTX/HCQ, MTX/SSZ, or MTX/HCQ/SSZ in patients who have failed MTX alone over two years

Does Triple Therapy Slow Radiographic Progression?
A Finnish study looked at triple therapy versus single DMARD therapy in RA at two and five years with regard to radiographic progression. In spite of a 40% “remission” rate in the combination group at two years, there was still radiographic progression—although significantly less than single therapy at both endpoints.
A similar study done in 2012 compared triple prescription to MTX and etanercept. Although there was equal clinical efficacy, biologics had better radiographic data.

The Power of Anti-TNF Therapy: TEMPO Study at Three Years

TEMPO: Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (682 patients with average seven years of disease)

% Remission: DAS 44 <1.6

TEMPO Study Mean Change in Total Sharp Score* from Baseline at Two Years

<table>
<thead>
<tr>
<th></th>
<th>MTX</th>
<th>Etanercept</th>
<th>MTX + Etanercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Year</td>
<td></td>
<td>0.3†</td>
<td>0.1</td>
</tr>
<tr>
<td>2 Years</td>
<td></td>
<td>0.8†</td>
<td>0.6†</td>
</tr>
</tbody>
</table>

Note negative scores for combination. Does this mean healing?

‡p < 0.05 versus etanercept
†p < 0.05 versus etanercept

TEMPO: Impact of Therapy on X-ray Progression at One Year

TEMPO: Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (682 patients with average of seven years of disease)

% subjects with NO X-ray progression

If Not Healing, Then Remodeling

42-year old woman started on etanercept in 1998 and was reimaged by x-ray in 2005. Note remodeling of 3rd and 4th MTP heads.

Images courtesy of Dr. Greg Gardner, 2013.
**PREMIER study: Adalimumab, Methotrexate, or Combination**

799 patients who were methotrexate naïve and mean disease duration < one year. Graph shows percent remission over two years by DAS 28 in patients with early RA.

![Graph showing percent remission over two years by DAS 28 in patients with early RA.](image)

**PREMIER Study: Radiographic Changes of Combination Better than MTX Alone**

RA patients with <3 years of disease and methotrexate naïve

![Graph showing radiographic changes.](image)

---

**COMET Trial**

Combination of Methotrexate and Etanercept in Active, Early, Moderate to Severe Rheumatoid Arthritis

- Methotrexate versus methotrexate + etanercept in early RA; endpoint at 52 weeks
- 542 patients with early RA (<2 years) and methotrexate naïve
- MTX alone versus MTX + etanercept with remission being primary endpoint
- SAE is 12% combo versus 13% MTX alone

![Graph showing remission in early RA.](image)

**Strategies for Using Therapy in RA**

BeST (Behandel Strategieen) Study at One Year

<table>
<thead>
<tr>
<th>Group</th>
<th>Sequential monotherapy N=122</th>
<th>Step-up therapy N=115</th>
<th>Combination with prednisone N=128</th>
<th>Methotrexate + infliximab N=126</th>
</tr>
</thead>
<tbody>
<tr>
<td>% DAS Low Disease Activity</td>
<td>53</td>
<td>64</td>
<td>71</td>
<td>74</td>
</tr>
<tr>
<td>% No radiographic progression</td>
<td>67</td>
<td>73</td>
<td>87</td>
<td>93</td>
</tr>
<tr>
<td>% Staying on initial therapy</td>
<td>30</td>
<td>37</td>
<td>73</td>
<td>81</td>
</tr>
</tbody>
</table>

Patients with RA of less than two years of disease Therapy changed every three months IF subjects did not reach DAS goal.

---

BeST study: Remission Induction??

Results of using methotrexate + infliximab as “induction” therapy (Group 4):
- 55% of Group 4 patients had discontinued infliximab (mean of 26 months off infliximab) and had a DAS low-disease activity level while continuing on MTX
- 15% of Group 4 patients off all meds and in DAS clinical remission

Is remission induction possible and how do we predict which patients will go into remission?

Can We Stop Therapy in RA?

BeST remission/radiographic data at four years
- Patient with < 2 years of RA treated to DAS44 score of <2.4 (remission <1.6)
- As patients went into remission, medications withdrawn
- Drug-free remission was more likely to be males, seronegative, and have shorter symptom duration before starting therapy

<table>
<thead>
<tr>
<th>Group</th>
<th>No X-ray progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Mono DMARD</td>
<td>48%</td>
</tr>
<tr>
<td>2 Combo DMARD</td>
<td>46%</td>
</tr>
<tr>
<td>3 COBRA</td>
<td>62%</td>
</tr>
<tr>
<td>4 MTX &amp; INF</td>
<td>69%</td>
</tr>
</tbody>
</table>

Rituximab in MTX-Resistant RA

The Randomized Evaluation of Long-Term Efficacy of Rituximab in RA (REFLEX) Trial. Patients failed >3 months of MTX; 209 RA patients randomized to MTX/placebo and 311 to MTX/rituximab. ACR response data at 24 months.

Abatacept + DMARD versus Placebo + DMARD Over Six months in RA patients Who Had Failed Previous TNF Therapy

258 patients randomized to DMARD/abatacept (mostly MTX)
133 patients randomized to DMARD/placebo

SUMURAI Trial: Tocilizumab

306 patients in Japan with RA <5 years were randomized to tocilizumab 8 mg/kg IV monthly or conventional DMARDs; failed at least one DMARD. Followed for 52 weeks; primary endpoints were radiographic progression and clinical efficacy.

RADIATE: IL-6 Receptor Antagonist in RA patients Refractory to TNF Therapy

24-week trial of MTX + tocilizumab at 8 or 4 mg/kg IV monthly versus MTX alone in 498 patients with long-standing RA

All failed at least one TNF, 30 to 40% two TNFs, and 14 to 18% failed three TNFs.

Primary endpoint ACR 20

Side effect: increase in lipids in tocilizumab groups (LDL and HDL increased)

Starting Therapy: Minimizing Risk

Baseline labs
- CBC, chemistry panel, LFTs, Hepatitis B and C
- Hepatitis C actually not an issue for TNF agents, HCQ
- Hepatitis B reactivation can occur with biologics in particular

TB screening (see next slide)
- TST versus IGRA

Immunizations
- See 2012 ACR recommendation in 2 slides
- Newer recommendations from the CDC may be out for pneumococcal immunizations soon
- Generally avoid live virus vaccines in patients currently on biologics

TNF and TB
A and B: TNF primes macrophages and T cells.
C: TNF along with interferon γ recruit mononuclear cells to form granulomas.
D: Anti-TNF therapy disrupts granuloma organization releasing TB.
Pearl: fusion protein etanercept less granuloma disruptive; sTNF versus tmTNF.

2012 ACR Recommendations for Vaccinations in RA Patients

Table 1. 2012 American College of Rheumatology recommendations update regarding the use of vaccines in patients with RA starting or currently receiving BiDMAs or biologic agents.

<table>
<thead>
<tr>
<th>Killed vaccine</th>
<th>Recombinant vaccine</th>
<th>Live attenuated vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parvovirus B19</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Influenza</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Mumps</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Rubella</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tetanus</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Haemophilus B</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Bordetella</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Typhoid</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Use of Biologics in Various Clinical Scenarios

Table 2. 2012 American College of Rheumatology recommendations for the use of biologic agents in patients otherwise qualifying for the conventional arthritis treatment with a history of leprosy, malignancy, or congenital heart failure.

<table>
<thead>
<tr>
<th>Comorbidity/clinical circumstance</th>
<th>Recommended</th>
<th>Not recommended</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis</td>
<td>Etanercept</td>
<td>Any biologic agent</td>
<td>C</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Anti-TNF</td>
<td>Anti-TNF</td>
<td>C</td>
</tr>
<tr>
<td>Other chronic biologic disease</td>
<td>Anti-TNF</td>
<td>Anti-TNF</td>
<td>C</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Anti-TNF</td>
<td>Anti-TNF</td>
<td>C</td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td>Anti-TNF</td>
<td>Anti-TNF</td>
<td>C</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>Anti-TNF</td>
<td>Anti-TNF</td>
<td>C</td>
</tr>
</tbody>
</table>

Treatment of Inflammation Reduces Mortality in RA\textsuperscript{53}

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Observations</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No MTX/TNF</td>
<td>35,309</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>34,638</td>
<td>0.82</td>
<td>0.72 - 0.94</td>
</tr>
<tr>
<td>Etanercept</td>
<td>6,649</td>
<td>0.62</td>
<td>0.46 - 0.84</td>
</tr>
<tr>
<td>Infliximab</td>
<td>9,407</td>
<td>0.95</td>
<td>0.70 - 1.29</td>
</tr>
<tr>
<td>MTX+Etan</td>
<td>5,767</td>
<td>0.59</td>
<td>0.41 - 0.84</td>
</tr>
<tr>
<td>MTX+Inflix</td>
<td>21,397</td>
<td>0.69</td>
<td>0.55 - 0.87</td>
</tr>
</tbody>
</table>

19,580 patients; 63,811 patient years of observation; deaths: 33% CV, 22% malignancy, 19% lung


“La Cortisone”
Painted in 1951 by Dufy and given to Roussel in gratitude for making cortisone available for his treatment.\textsuperscript{54}

Objective 8:
Review perioperative issues that should be considered in the RA patient.

Perioperative Concerns in RA

Postoperative MI:
- RA patients at increased risk of CVD; SMR 2x general population and similar to DM
- Particularly important in patients with poorly controlled or long-standing disease

Pulmonary disease
- Mild asymptomatic abnormalities common
- Rheumatoid lung disease – fibrosis, bronchiolitis, pleuritis

Cricoarytenoid arthritis
- Up to 75% of patients may be affected via bronchoscopy
- May affect intubation or cause postoperative airway obstruction

TM joints

Perioperative Concerns
Cervical spine disease
Three types:
- C1-C2 subluxation
- Atlantoaxial impaction
- Subaxial disease
Patients undergoing orthopaedic surgery are a group to worry about. 38% of 154 patients undergoing surgery had evidence of cervical spine disease. All patients undergoing orthopaedic surgery for their disease, with >5 years of disease or any neurologic abnormality, warrant cervical spine films (flexion/extension views; MRI if abnormal).

Corticosteroids
Under normal physiologic conditions, the body produces 10 to 12 mg of cortisol per day. With moderate stress the level of cortisol production is approximately 25 to 50 mg per day, and with major stress, up to 75 to 150 mg cortisol may be released into the circulation.

Patients treated with as little as 20 mg of prednisone a day for five days can manifest physiologic changes of mild adrenal insufficiency (AI). Patients on long-term therapy may require up to a year to fully recover adrenal function when the external glucocorticoids are tapered and stopped.

How long and how much will require CS coverage?
### Table 1: Guidelines for Adrenal Supplementation Therapy*

<table>
<thead>
<tr>
<th>Surgical Stress</th>
<th>Corticosteroid Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor Procedures (local anesthesia)</td>
<td>25 mg of hydrocortisone or 5 mg of methylprednisolone IV on day of procedure</td>
</tr>
<tr>
<td>Surgical Stress</td>
<td>Corticosteroid Dosage</td>
</tr>
<tr>
<td>Minor Procedures (local anesthesia)</td>
<td>25 mg of hydrocortisone or 5 mg of methylprednisolone IV on day of procedure</td>
</tr>
<tr>
<td>Moderate</td>
<td>50-75 mg of hydrocortisone or 10-15 mg of methyprednisolone IV on day of procedure</td>
</tr>
<tr>
<td>Single Joint Arthroplasty</td>
<td>-Taper quickly over 1-2 days to preoperative dose</td>
</tr>
<tr>
<td>Moderate</td>
<td>100-150 mg of hydrocortisone or 20-30 mg of methyprednisolone IV on day of procedure</td>
</tr>
<tr>
<td>ORIF Acetabulum</td>
<td>-Taper quickly over 1-2 days to preoperative dose</td>
</tr>
<tr>
<td>Critically Ill</td>
<td>50-100 mg of hydrocortisone IV every 6-8 h or 0.18 mg/kg/h as a continuous infusion + 50 µg/d of fludrocortisone until shock resolved</td>
</tr>
<tr>
<td>Polytraumatized Patients</td>
<td>-Gradually taper, closely following vital signs and serum sodium</td>
</tr>
</tbody>
</table>


### NSAIDs

Not utilized as intensely as in years gone by Its use puts patients at risk for intra-operative bleeding and post-op GI bleeding:

- Sponge weights and suction volumes indicate that NSAIDs used up to the time of surgery increases blood loss by a factor of two and increases transfusion requirements (mortality?)

Recommendation is to stop NSAIDs five half-lives before surgery

ASA should be stopped 10 to 14 days before surgery

- What about primary and secondary prophylaxis? High risk?

### Methotrexate

**Continue for most surgeries**

- Grennan demonstrated fewer infections and flares in group of RA patients who continued methotrexate perioperatively

**Consider temporary stop for:**

- Rising creatinine
- Post-operative infection
- Long period of NPO
- Patients over 70 years old

**Toxicity:** bone marrow suppression, severe stomatitis

- Rx with folinic acid po or IV

---

**Other Non-Biologic DMARDs**

**Leflunomide**

- Half-life of two weeks
- Two studies with opposite conclusions regarding wound healing issues
- Consider stopping one month before surgery where large wounds are expected

**Sulfasalazine** – no reason to stop except for NPO

- May be protective against infection

**Hydroxychloroquine** – no reason to stop

- Used as postoperative anticoagulant years ago
TNF Agents

Six studies exploring TNF and infection and wound healing: five showed no risk, and one study showed significant risk.

Only one prospective study continued TNF or non-biologic DMARD through foot and ankle surgery. It found a LOWER rate of combined wound-healing issues and infection in the TNF group.

Mushtaq, et al.\(^5\) reviewed data regarding infliximab and abdominal surgery in patients with inflammatory bowel disease and found no concern for infection or wound healing in this group of patients.


Other Biologic DMARDs

Abatacept
- No data, no signals in trials
- Hold at least two half-lives for moderate to intense surgeries
- Half-life 12.6 days
- Pneumonias and exacerbations in COPD patients
- Hold for 10 to 14 days

Rituximab
- Depletes B cells up to 100 days post-infusion
- Check immunoglobulin levels; if ok and at least 100 days since dosing, okay to proceed
- May infuse 10 to 14 days post-op

TNF Agents

For now, suggest holding TNF agent for moderate to intense procedures; continue for minor

Hold is based on half-life; hold at least two half lives:
- Enbrel – 3.5 to 5.5 days
- Humira – 10 to 20 days
- Infliximab – 9.5 days
- Cimzia – 14 days
- Golumimab – 14 days

Restart 10 to 14 days postop

Other Biologic DMARDs

Tocilizumab
- Two studies looking at wound healing and infection: one held, the other continued, and neither found signal
- Did find that tocilizumab prevented rise in acute-phase reactants and fever that might mask infection
- Hold for at least two half-lives for moderate to intense procedures (T ½ 11 to 13 days)
Herbal Supplements

Ginkgo
- Antiplatelet effects
- Hold for 36 hours before surgery

Ginseng
- Antiplatelet effects as well
- Hold for seven days

Valerian
- May potentiate effects of benzodiazepines and anesthetic agents
- Modulates anxiety and insomnia via its effects on GABA receptors
- May have withdrawal symptoms so needs to be tapered several weeks before surgery

References


