Indian Country ECHO Grand Rounds

Rheumatoid Arthritis: Introduction to Diagnosis and Management

November 1, 2022

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RA: Intro to Diagnosis and Management

I have no financial disclosures

RA: Intro to Diagnosis and Management

Agenda

- RA: epidemiology, pathogenesis, clinical spectrum
- RA in Indian Country
- Diagnosis of RA
- General treatment principles/initial therapy
- Case presentation
- Description of the Rheumatoid Arthritis ECHO curriculum

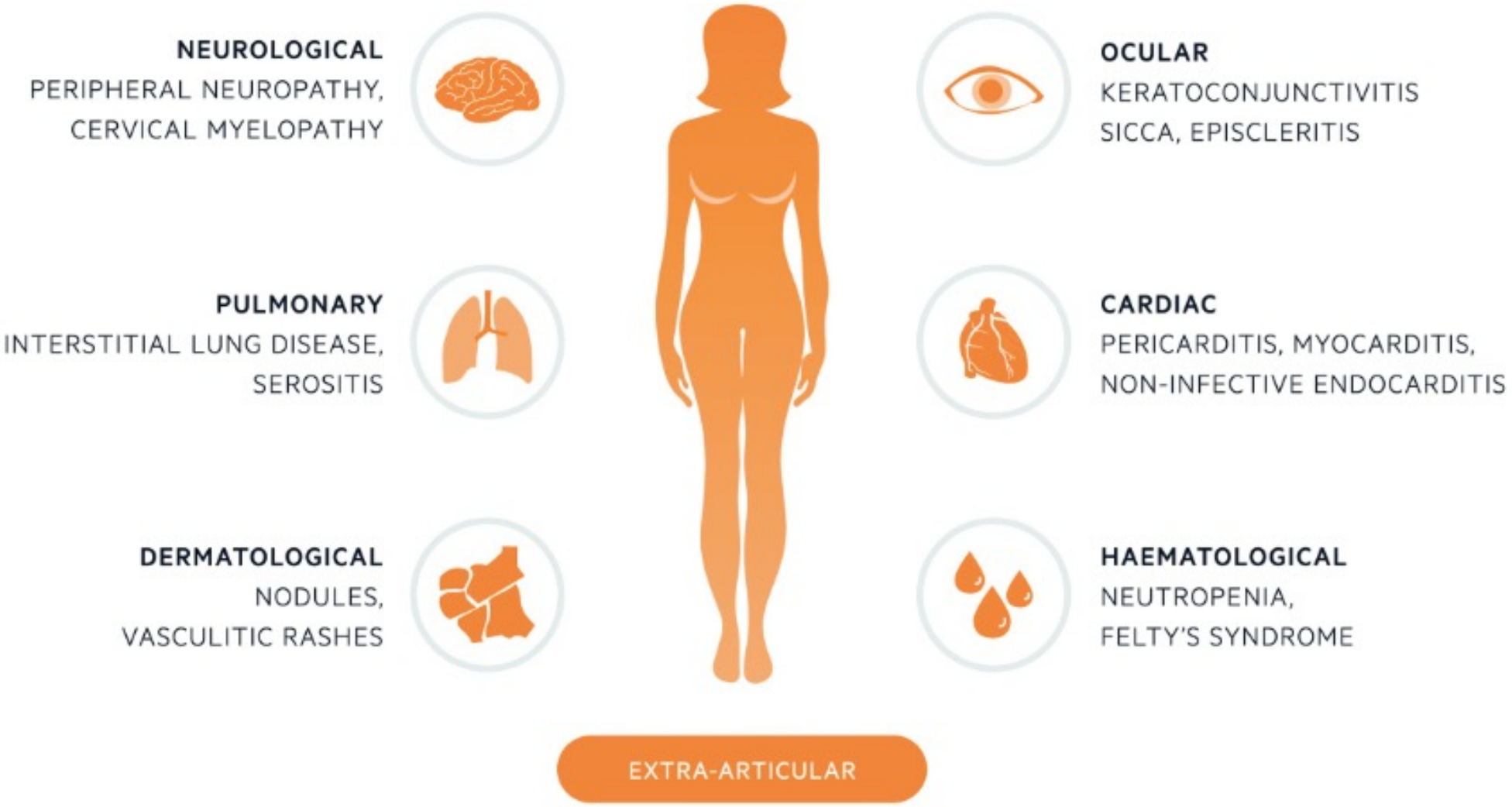
Poll questions

- Approximately how many patients with RA do you have under your care? (0; 1-5; 5-10; > 10)
- How comfortable do you feel making a diagnosis of RA without the input of a rheumatologist?
- How comfortable do you feel starting someone with RA on disease modifying medication without the input of a rheumatologist?
- How long do your patients (with RA or any rheumatologic condition) wait to see a rheumatologist? (1-3 months; 3-6 months; > 6 months)

Rheumatoid Arthritis: the basics

- RA is a systemic autoimmune disease characterized primarily by a symmetric inflammatory polyarthritis
- The US prevalence is 0.5-1%, with some populations having significantly higher rates of disease
- Women:men 2:1
- Age of onset: 30-50 most common
- 1st degree relative confers 3X higher odds
- 2nd degree relative confers 2X higher odds

Extra-Articular Manifestations of RA



Rheumatoid Arthritis: the basics

Pathogenesis

Likely a combination of genetic and environmental factors

Genetics:

- HLA-DRB1 genes are most closely associated with RA

Environmental:

- smoking (strongest known environmental RF for RA)
- chronic mucosal inflammation (periodontitis) and possibly gut dysbiosis are potential RF
- others: silica/other inhalants, sugary drinks, obesity, pollution

2 copies of the HLA-DRB1 gene + smoking = RR of 21

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RA Epidemiology among American Indians/Alaska Natives

Tlingit 2.4% (1991)

- 1.3% male
- 3.5% female

Yakima (1973)

- N/A male
- 3.4% female

Boyer et al. Rheumatic Diseases in Alaskan Indians of the Southeast Coast. JRheum1991;18:1477-84
Beasley et al. High prevalence of rheumatoid arthritis in Yakima Indians. Arth Rheum 1973; 16:743-8

RA Epidemiology among American Indians/Alaska Natives

- Pima (1989)
  - 3.2% male
  - 7.0% female
- Chippewa (1981,1983)
  - 4.8% male
  - 8.2 % female

DelPuente et al. High incidence and prevalence of rheumatoid arthritis in Pima Indians. Am J Epidemiol 1989; 129: 1170-8Harvey et al. Rheumatoid arthritis in a Chippewa Band. Arthritis Rheum 1981; 24: 717-21

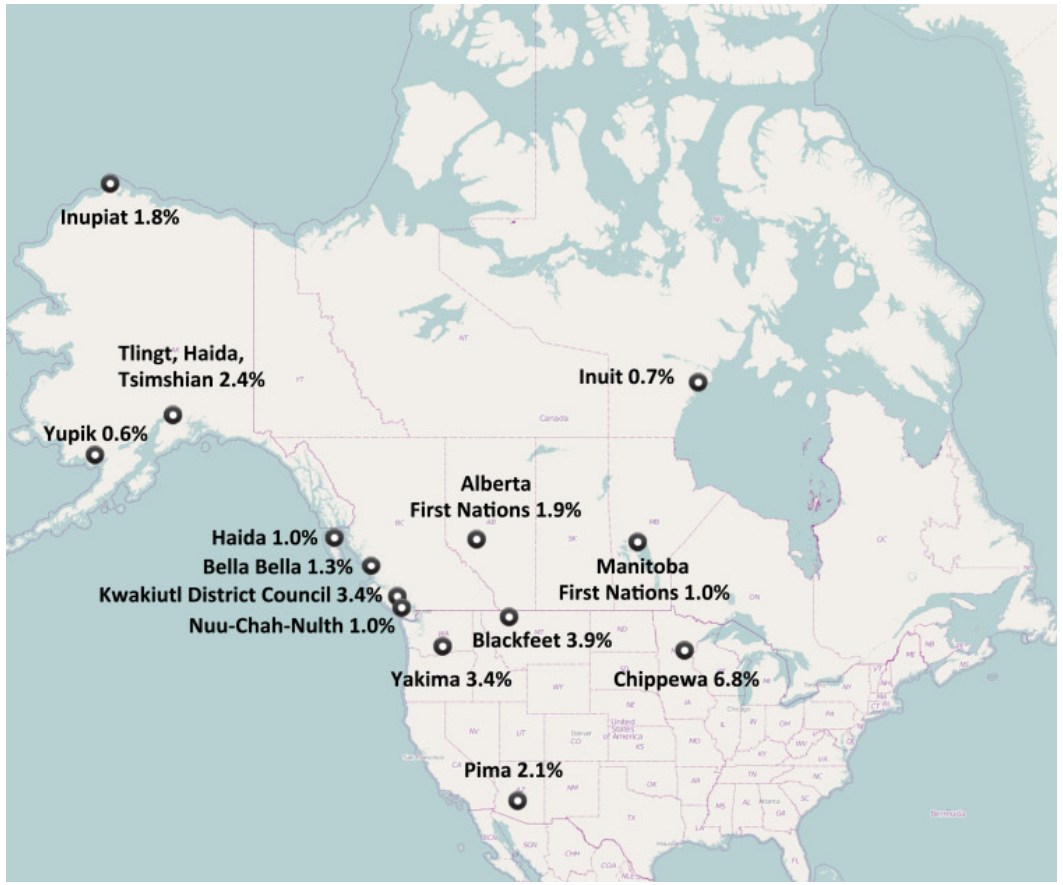
RA Epidemiology Among American Indians/Alaska Natives

Table 1: Prevalence and Incidence Rates of Rheumatoid Arthritis in Caucasians and Native North Americans

Population	Geographic Region	Prevalence	Annual Incidence
Pima Indians (22, 41, 54)	Arizona	2.5-5.3%	422/100,000
Chippewa Indians (4)	Central Minnesota	5.3%	—
Blackfeet Indians (40)	Montana	5% females, 4% males	—
Yakima Indians (43)	Central Washington	3.4% females	—
Tlingit, Tsimshian, & Haida Indians (6)	Southeast Alaska	2.4%	122/100,000 women 46/100,000 men
Algonkian Indians (44)	Central Canada	2.0%	—
Nuu-Chah-Nulth (12)	Vancouver Island	1.4%	—
Haida Indians (46)	Queen Charlotte Islands	1-1.5% females, 0.5-1% males	—
Inupiat Eskimos (6)	Northwest Alaska	1.0%	—
Yupik Eskimos (13)	Southwest Alaska	1.1%	—
Inuit Eskimos (11)	Northwest Territories	0.6%	48/100,000
National Health Examination Survey (37)	USA	1.6% females, 0.7% males, 0.9% total	—
Rochester (38)	Minnesota	1.0%	22/100,000 men 48/100,000 women
England (39)	England	1.1%	—

Peschken CA, Esdaile JM. Seminars in Arthritis and Rheum 1999;28:368–391.

RA in Native American populations



RA Epidemiology among American Indians/Alaska Natives

2010 study comparing NAN patients (Cree, Ojibway, Metis, Sioux, Dakota) to white patients with RA

20 years of follow up

In the NAN group:

- Younger age of onset
- Higher rate of RF positivity
- Higher rate of ANA positivity
- Higher lifetime number of DMARDs
- More frequent combination therapy
- More frequent prednisone use

Peschken et al. Rheumatoid arthritis in a North American Native population: longitudinal followup and comparison with a white population. JRheum 2010; 37: 1589-95

Table 3: Summary Of Unusual Clinical and Serological Features in Native North Americans With Rheumatoid Arthritis

Tribal Group	Prevalence	Age at Onset (years)	RF Positive (%)	ANA Positive (%)	Shared Epitope Frequency		Comments
					RA Patients (%)	Controls (%)	
Tlingit (5, 47)	⇑	51% <35	97	71	Dw16: 91	Dw16: 85	44% rheumatoid nodules
					DR9: 18	DR9: 8	24% extraarticular features
Yakima (43, 53)	⇑	Peak prevalence <35	94	53	Dw16: 83	Dw16: 60	50% rheumatoid nodules 100% erosive disease 64% stage IV x-ray changes
Chippewa (4, 48)	⇑	58% <40	92	75	DR4: 100	DR4: 68	42% rheumatoid nodules

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DIAGNOSIS: 2010 ACR/EULAR CRITERIA

1. Synovitis must be present; no other diagnosis to explain it

2. RA diagnosed if **≥6 points** from the following:

JOINTS:

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1-3 small joints (wrists, any hand joint).....2 points

4-10 small joints.....3 points

>10 joints, including ≥1 small joint.....5 points

SEROLOGY:

RF or anti-CCP low-positive (above ULN).....2 points

RF or anti-CCP high-titer (3x >ULN).....3 points

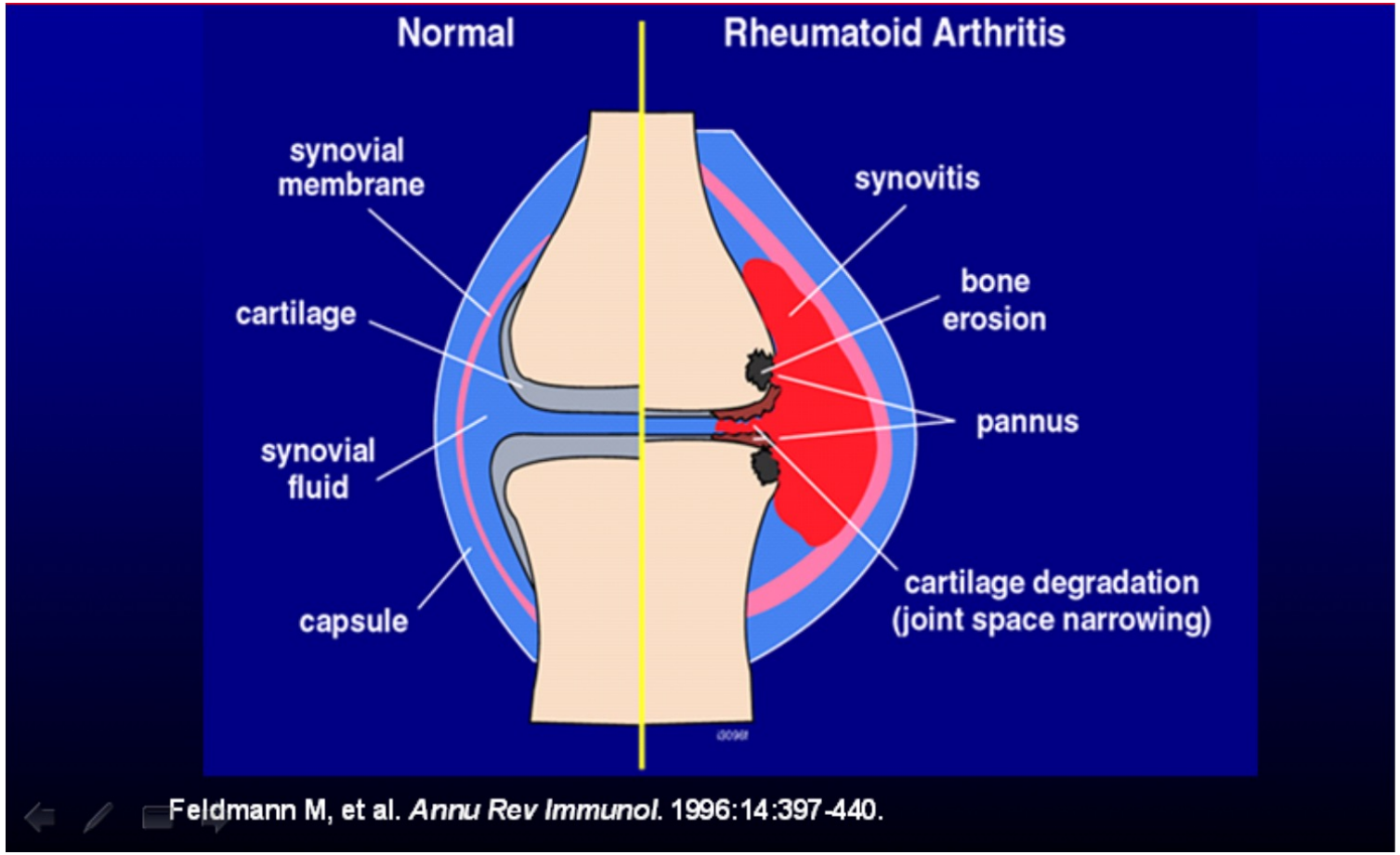
ESR **or** CRP ELEVATED.....1 point

SYMPTOM DURATION ≥6 weeks.....1 point

Hallmarks of synovitis

- **History**
  - Stiffness
  - Swelling
  - +/- warmth
  - Improvement with movement/NSAIDs
  - Exacerbated by inactivity (morning stiffness > one hour)
- **Exam**
  - Swelling
  - “bounciness” to palpation

Synovitis


Normal
Rheumatoid Arthritis
synovial membrane
cartilage
synovial fluid
capsule
synovitis
bone erosion
pannus
cartilage degradation (joint space narrowing)
Feldmann M, et al. *Annu Rev Immunol.* 1996:14:397-440.

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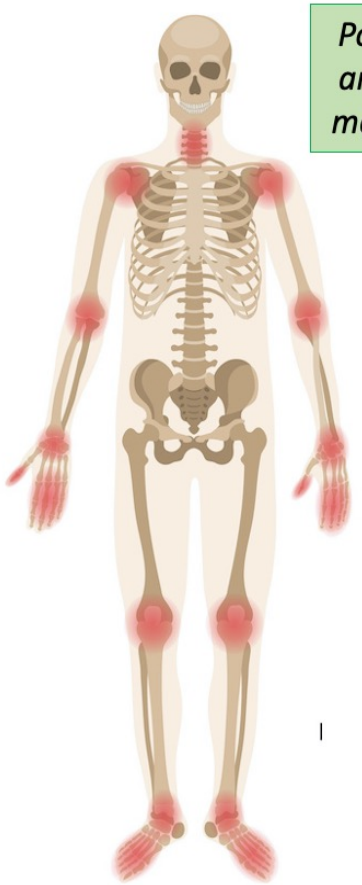
SYMPTOM DURATION ≥6 weeks.....1 point

Joint distribution in RA

Rheumatoid arthritis



Polyarticular, symmetric arthritis affecting small, medium, and large joints

Neck
Shoulders
Elbows
Wrists
Hands (MCPs, PIPs)
Knee
Toes

Spares the:

- **Low back**
- **DIPs**

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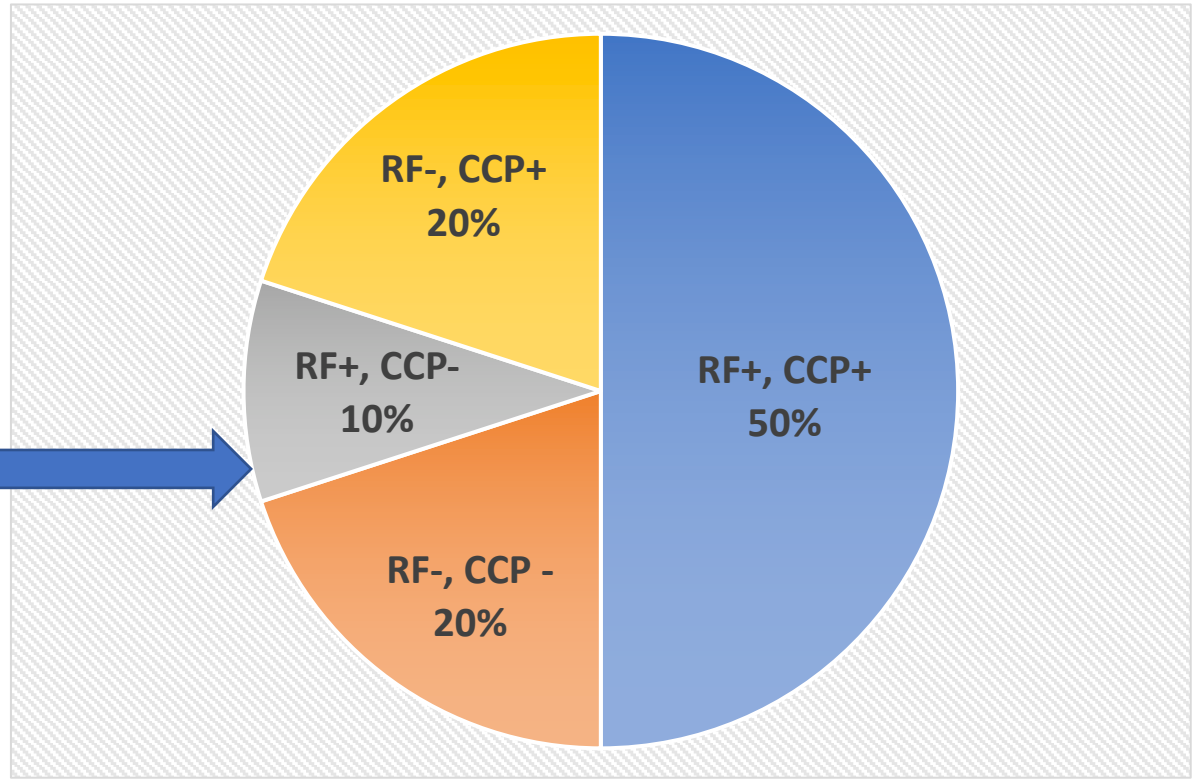
SYMPTOM DURATION ≥6 weeks.....1 point

Rheumatoid Factor and CCP ab

- RF and CCP (cyclic citrullinated peptide) should always be ordered together
- RF is 70-80% sensitive, 75% specific for RA
- CCP (cyclic citrullinated peptide) ab is 80% sensitive, > 95% specific
- A positive RF can be seen in multiple other settings (other rheumatologic disease, chronic infection, healthy individuals)
- RF and CCP are used in diagnosis of RA but generally do not correlate with disease activity, so not helpful to follow over time
- High titers tend to correlate with severity of disease

RF and CCP in rheumatoid arthritis

Be suspicious!



Diagnosis: Exceptions

Very early RA

< 6 weeks, but high CCP/RF, typical joint distribution and no other reasonable explanation

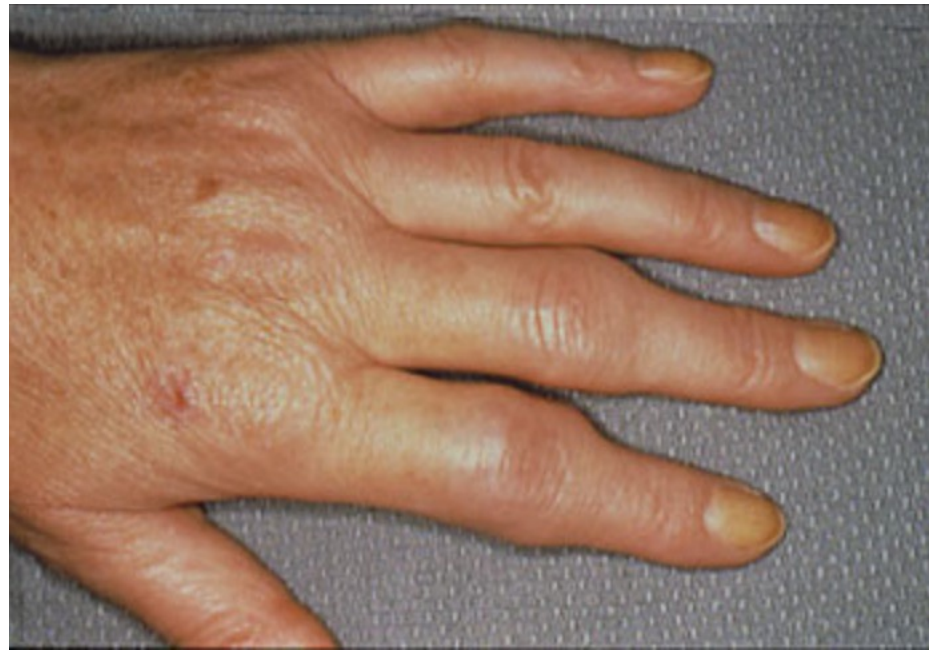
Very late RA

No ongoing inflammation (normal CRP/ESR); no active synovitis, but joint erosions/deformities consistent with RA

Scenario #1

- 34 year old woman

- 2-3 months joint pain, stiffness in hands, feet, wrists
- Better with movement, NSAIDs; worse in the morning or after inactivity
- Exam: swelling and tenderness of both wrists, left index and third finger PIP joints
- RF negative
- CCP > 250 (< 20)
- CRP 15 (< 10)



Poll Question

- Does this person have RA?
  - Yes
  - No
  - Maybe

Scenario #1

- 34 year old woman

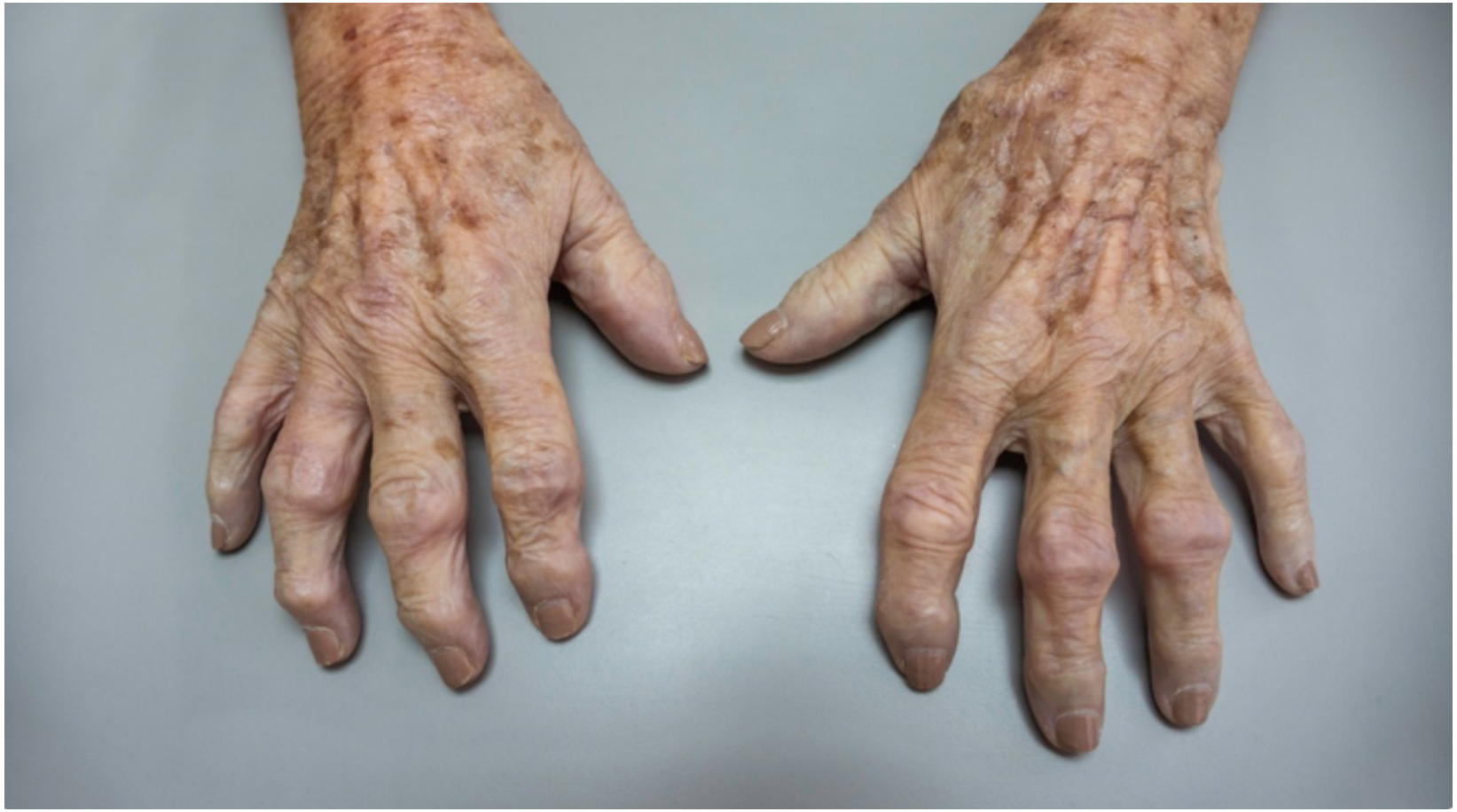
• 2-3 months joint pain, stiffness in hands, feet, wrists	1 point
• Exam: swelling and tenderness of both wrists, left index and third PIP joints	3 points
• RF negative	0 points
• CCP > 250 (normal < 20)	3 points
• CRP 15	1 point

This person has rheumatoid arthritis

Scenario #2

- 68 year old woman

- 10 years of joint pain and stiffness in the hands, gradually progressive
- Stiffness in hands in the mornings x 15-20 minutes
- Relief from NSAIDs; worse with use
- Exam: enlarged PIP and DIP joints; decreased flexion; no direct tenderness
- RF 34 (normal < 14)
- CCP negative
- Normal CRP



Poll Question

- Does this person have RA?
  - Yes
  - No
  - Maybe

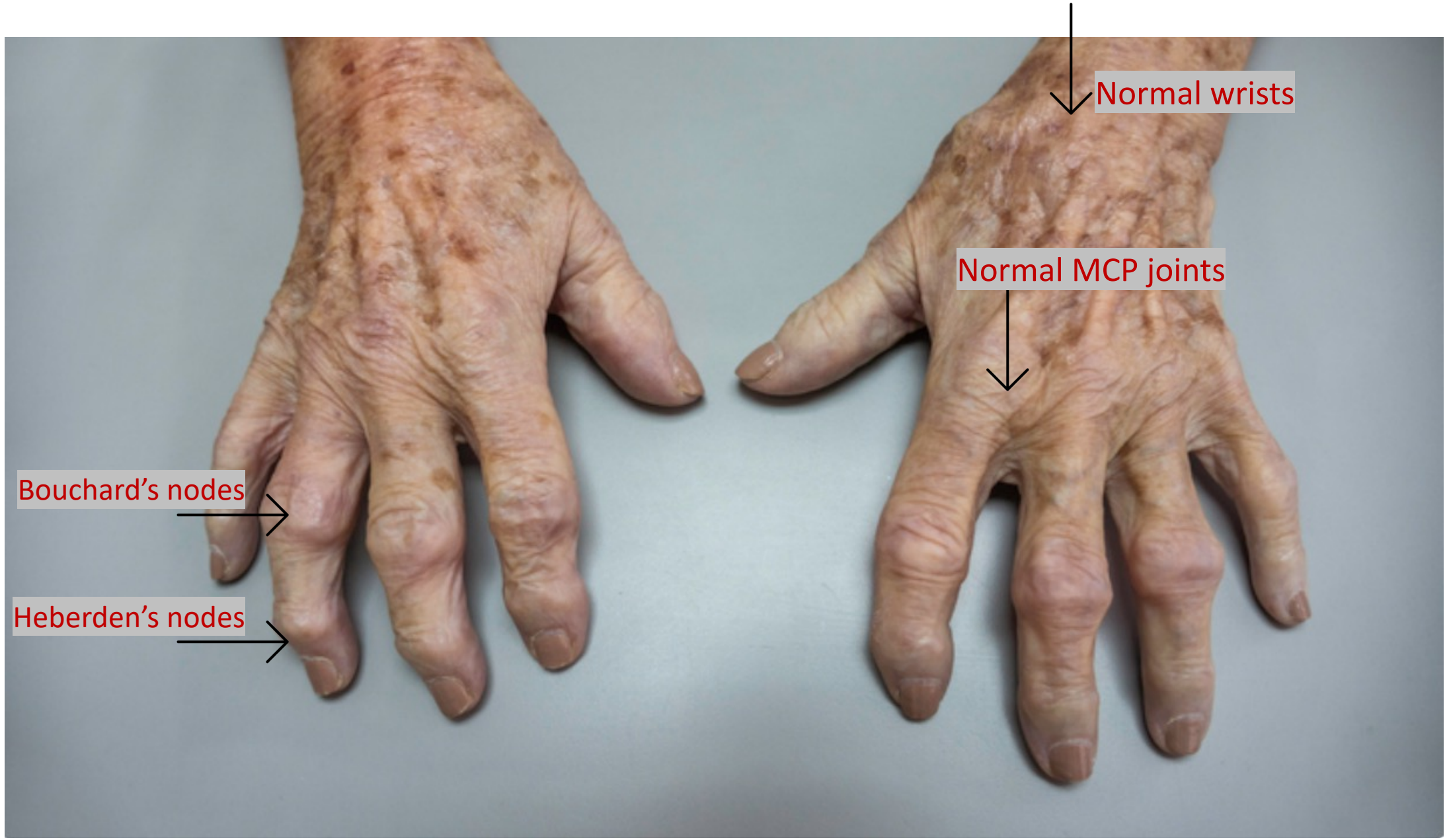
Scenario #2

- 68 year old woman

• 10 years of joint pain in the hands	1 point
• Exam: enlarged PIP and DIP joints; decreased flexion	0 points
• no synovitis	
• RF 34	2 points
• CCP negative	0 points
• Normal CRP	0 points

This person has osteoarthritis

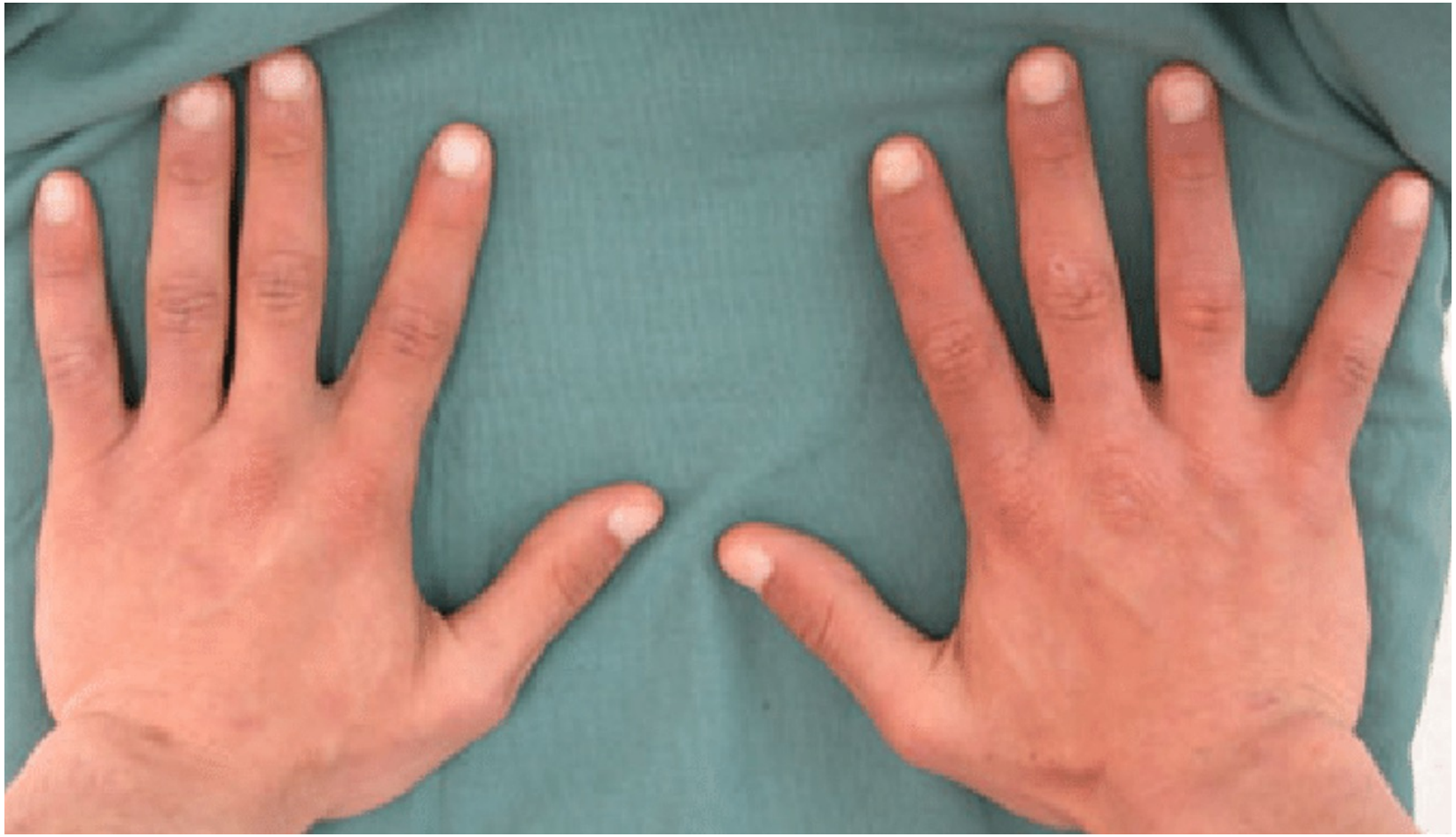
Osteoarthritis in the hands



Scenario #3

- 55 year old woman

- 3 months of pain/stiffness in hands
- Worse in AM; better with NSAIDs
- Exam: tenderness in several PIP joints; no swollen joints; full grip
- RF negative
- CCP 50 (normal < 20)
- CRP 12 (normal < 10)



Poll Question

- Does this person have RA?
  - Yes
  - No
  - Maybe

Scenario #3

- 55 year old woman

• 3 months of pain in hands		1 point
• Exam: tender joints; no obvious synovitis	0 points	
• RF negative		
• CCP 50 (normal < 20)		2 points
• CRP 12 (normal < 10)		1 point

This person does not meet the criteria for RA, but should be followed closely

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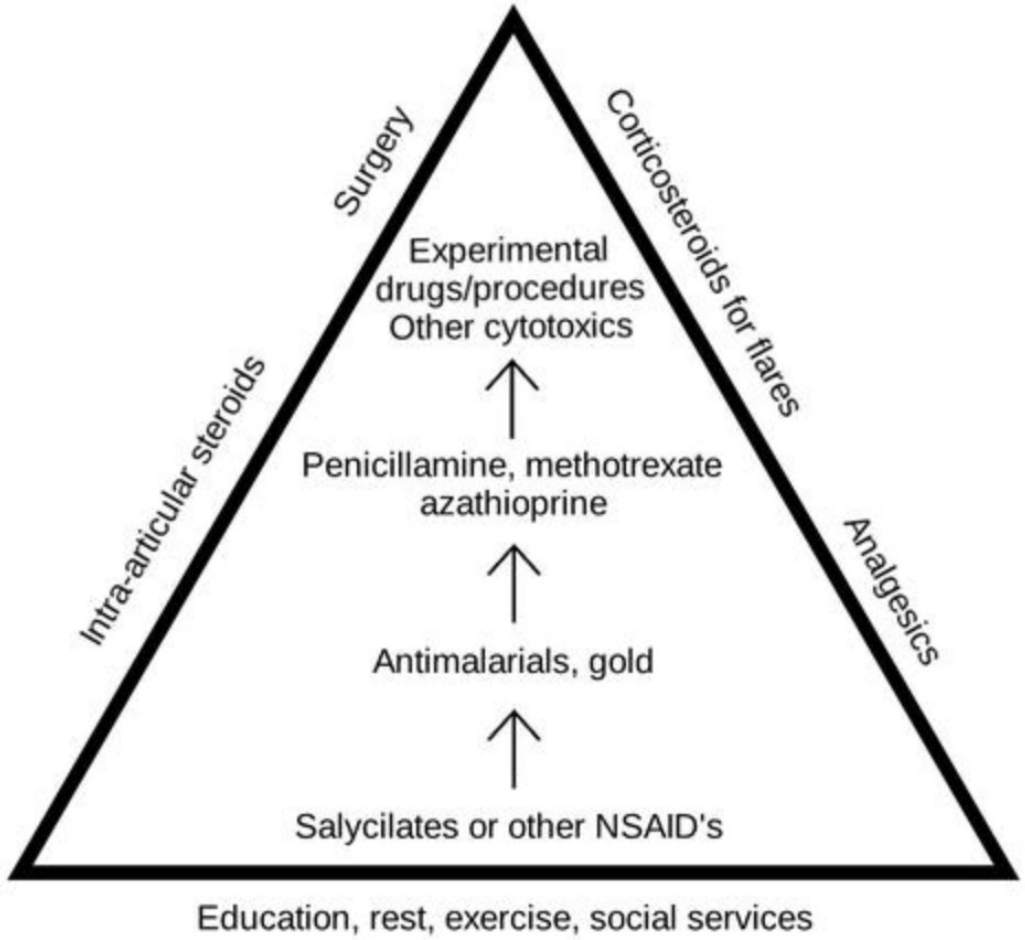
Principles of Treatment

The old "pyramid approach"



Current approach to treatment of RA

- **Early initiation of treatment** with disease modifying anti-rheumatic drugs (DMARDs) is critical to slow disease progression and prevent irreversible damage and disability
- **"Treat to target"** approach: titrate/change DMARDs until patient achieves low disease activity
- There are now more than 20 FDA-approved medications for the treatment of RA!
- **NSAIDS and glucocorticoids** are helpful adjuncts to treatment, particularly early on, but are not disease modifying agents
- **Glucocorticoids** should be used in the lowest dose possible for the shortest duration possible
- **Opioids are not effective** treatment for RA and should be avoided

Terminology: DMARDs
Disease Modifying Anti-Rheumatic Drugs

- "Conventional DMARDs":
  - Methotrexate, Hydroxychloroquine, Sulfasalazine, Leflunomide

- "Biologic DMARDs":
  - TNF inhibitors: etanercept/Enbrel (SQ), adalimumab/Humira (SQ), infliximab/Remicade (IV)
  - Others: abatacept (T cell costimulatory inhibitor), rituximab (anti-CD20), tocilizumab/sarilumab (IL-6 inhibitors), tofacitinib/upadacitinib (JAK inhibitors)

”Treat to Target” Approach

General principles of treatment:

- Choose initial DMARD based on disease severity, baseline labs, and comorbidities (MTX is most common first-line tx)
- Start DMARD ASAP to avoid progressive joint damage
- **Goal is remission or low disease activity** (RAPID-3 ≤2 or CDAI ≤10)
- Evaluate patient q3 months until this is achieved
- Vast majority of patients will require life-long medication

Contraindications to Methotrexate

- Chronic liver disease
- GFR < 30/hemodialysis
- Severe COPD or other chronic lung disease (risk of methotrexate pneumonitis)
- Potential for conception

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Case presentation

- 22 year old Navajo woman, college student with 1 year of joint pain, initially intermittent, now daily
- Affected joints: hands, feet, knees, elbows; more right-sided than left
- Swelling in hands, feet
- Symptoms are better with Advil, hot shower, activity
- Worse in the mornings and after sitting (knees)
- Not able to do her usual running for exercise
- Sometimes hard to get to class on time in the mornings

Case presentation

- College student
- No tobacco, alcohol, drug use
- Exercises regularly when able
- Not sexually active currently

- Great aunt with RA

- No medications aside from OTC NSAIDs
- Prior LARC but d/c secondary to arthritis sx

Case presentation

Pertinent review of systems positives and negatives:

Const: no fevers, chills, weight loss; + fatigue
HEENT: no sicca symptoms; no oral ulcers
Resp: no dyspnea or cough
CV: no chest pain or palpitations
Skin: no rash or photosensitivity; no Raynaud's phenomenon
Neuro: no h/a, dizziness, paresthesia
Lymph: no adenopathy

Case presentation

EXAM

- Swelling/tenderness at the MCP joints of the right > left hand
- Swelling/tenderness/pain with ROM of both wrists
- Swelling/tenderness of the right foot MTP joints
- Stiff with ROM of the knees, ankles, elbows. No swelling/effusions present in these joints

Case presentation

LAB DATA

- **RF 100 (CCP not done)**
- **ANA 1:320; SSA 2.0**
- **HLA B27 +**
- **ESR 33 (< 20)**
- **CRP 10.1 (< 3)**
- **CBC, CMP without abnormalities**
- **TSH normal**

- **No imaging**

Poll Question

- What is the diagnosis?

- RA
- Sjogren’s syndrome
- Lupus
- Reactive arthritis
- Fibromyalgia

Case presentation

- Using the diagnostic criteria
  - Synovitis in > 10 joints, including 1 small joint — 5 points
  - High titer RF — 3 points
  - Elevated inflammatory markers — 1 point
  - Duration > 6 weeks — 1 point

Case presentation

- But what about the ANA of 1:320 and positive SSA?
  - 30% of RA patients have a positive ANA
  - Higher in some AI/NA populations
  - SSA is very low positive; no sicca symptoms but she should be monitored for development of concomitant Sjogren's
- What about the positive HLA B27? Why not a spondyloarthritis?
  - High rate of HLA B27 positivity in Navajo population (40%) so not a very helpful test
  - Pattern of involvement (symmetric, small joints) more c/w RA
  - No associated sx (psoriasis, uveitis)

Poll Question

- What would be your first-choice medication regimen for this patient?

Methotrexate

Hydroxychloroquine

Sulfasalazine

Combination therapy (MTX + HCQ + SSZ)

TNF inhibitor

Poll Question

Methotrexate	contraindicated; no contraception
Hydroxychloroquine	safe, but not likely to control disease
Sulfasalazine	ditto
Combination therapy (MTX + HCQ + SSZ)	contains methotrexate
TNF inhibitor	most likely to get disease under control

RA: Intro to Diagnosis and Management

- RA is more common among Native American populations
- Early diagnosis and treatment is critical in preserving function and preventing joint damage
- RF and CCP should always be ordered in tandem
- Treat to target approach is recommended, with goal of remission or low disease activity
- First choice of therapy is usually methotrexate, with some important exceptions

Overview of Project RAE (Rheumatoid Arthritis ECHO)

The purpose of Project RAE is to provide education and support to primary care providers, enabling them to diagnose RA and initiate treatment among their patients

The format is a 12 week program with didactics and case discussions

DIAGNOSIS & MANAGEMENT OF RHEUMATOID ARTHRITIS

Initial visit checklist:

- ❑ LABWORK: RF, CCP, CBC, CMP, ESR, CRP, PPD or Quantiferon, HBV sAg/sAb/cAb, HCV Ab
- ❑ IMAGING: bilateral hand and foot xrays (to establish baseline and screen for alternate diagnoses)
- ❑ MEDS: consider scheduled NSAIDs vs. prednisone 5-10mg daily (temporary measure until patient is stable on DMARD therapy)
- ❑ Pneumovax/Prevnar, flu shot, Shingrix, HBV vaccine, COVID19 vaccine as early as possible.
- ❑ If TB screen positive (and active TB has been ruled out), start LTBI treatment at least 1 week before starting methotrexate
- ❑ Schedule follow-up to review labs/xrays and discuss DMARD initiation

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ESR **or** CRP ELEVATED.....1 point

SYMPTOM DURATION ≥6 weeks.....1 point

General principles of treatment:

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- Start DMARD ASAP to avoid progressive joint damage
- **Goal is remission or low disease activity** (RAPID-3 ≤2 or CDAI ≤10)
- Evaluate patient q3 months until this is achieved
- Vast majority of patients will require life-long medication

less common

common

VERY MILD RA
ALL of the following: <5 joints involved, no extra-articular disease, minimal limitation in joint function, RAPID-3 ≤2 or CDAI ≤10.

MODERATE or SEVERE RA
ANY of the following: >5 joints involved, extra-articular disease, erosions on baseline x- rays, function limited, RAPID-3 >2 or CDAI >10

1st line for most RA patients

HYDROXYCHLOROQUINE
200-400mg PO daily [max dose 5mg/kg]
* May reduce risk of diabetes and improve lipids
* Well-tolerated, safe in pregnancy
* Retinal exam at baseline and q1yr

OR

SULFASALAZINE
500mg BID x 1 week → 1000mg BID
* Better efficacy than hydroxychloroquine, but more likely to cause GI upset
* Monitor WBC q2 months

After 3 months, if moderate or high disease activity

METHOTREXATE
10mg PO qWEEK x 4 weeks, then check labs. If no side effects and labs stable then increase to **20mg PO qWEEK**. Recheck labs after 4 weeks.
If RA activity still mod-high after 3 months: switch to **25mg subcutaneous qWEEK**
MTX monitoring:
* CBC, liver panel, Cr q3months once the dose is stable
* Must take with **folic acid 1mg daily** (increase to 2mg daily if mild side effects)

If not tolerating MTX, might consider:

LEFLUNOMIDE
10mg PO daily x 6 weeks, then check labs. If tolerating, increase to **20mg PO daily**
* Diarrhea in 20%
* Labs and contraindications same as for MTX (see page 2); Avoid in women of childbearing age: risk of birth defects up to 2 years after cessation!

After 3 months, if moderate or high disease activity

preferred

"TRIPLE THERAPY"
Methotrexate + Sulfasalazine + Hydroxychloroquine
- Large pill burden makes adherence challenging
- Lower infectious risk compared to TNFi
- Can be considered in patients who strongly prefer pills over injections

TNF-INHIBITOR
Adalimumab (Humira) 40mg SC q2weeks
or Etanercept (Enbrel) 50mg SC qweek
or Certolizumab pegol (Cimzia) 200mg SC q2weeks
* Ideally, give TNFi AND weekly methotrexate
* Adalimumab and Etanercept are more readily available
* Certolizumab is specifically preferred in pregnancy

If still not controlled, discuss second-line biologic options with a rheumatologist

When to use prednisone in RA?

Prednisone 5-10mg daily may be considered initially (<3 months, while waiting for DMARD to take effect), but should be avoided as chronic therapy whenever possible, due to long term side effects.

Originally developed by: Sara K. Tedeschi, MD[1]; Paul Dellaripa, MD[1]; Anneliese Flynn, MD[2]; Michael Weinblatt, MD[1]; [1]Brigham and Women's Hospital, Division of Rheumatology, [2]Northern Navajo Medical Center

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Conventional DMARD Safety & Monitoring:

Methotrexate:

Contraindicated in: pregnancy, breastfeeding, chronic liver disease, heavy alcohol use, CKD stage 4/5

Caution in: CKD 3 (decrease dose)

Side effects: GI upset, oral ulcers, transaminitis (if AST/ALT <2x ULN: ok to monitor; >2x ULN: reduce dose or discontinue), infections, cytopenias, macrocytosis, pneumonitis (very rare)

Pearls: Dosed once WEEKLY. Splitting the oral dose (half in AM, half in PM) or switching to SQ formulation can improve absorption/efficacy. Always prescribe along with folic acid 1-5mg daily. In case of overdose: IV leucovorin.

Monitoring: CBC, Cr, LFTs q 3 months

Hydroxychloroquine:

Caution in: advanced renal impairment (decrease dose)

Side effects: Retinal toxicity (risk increases with duration of therapy), GI upset, skin hyperpigmentation. Rare myopathy, rare cardiotoxicity (avoid with known QT prolongation).

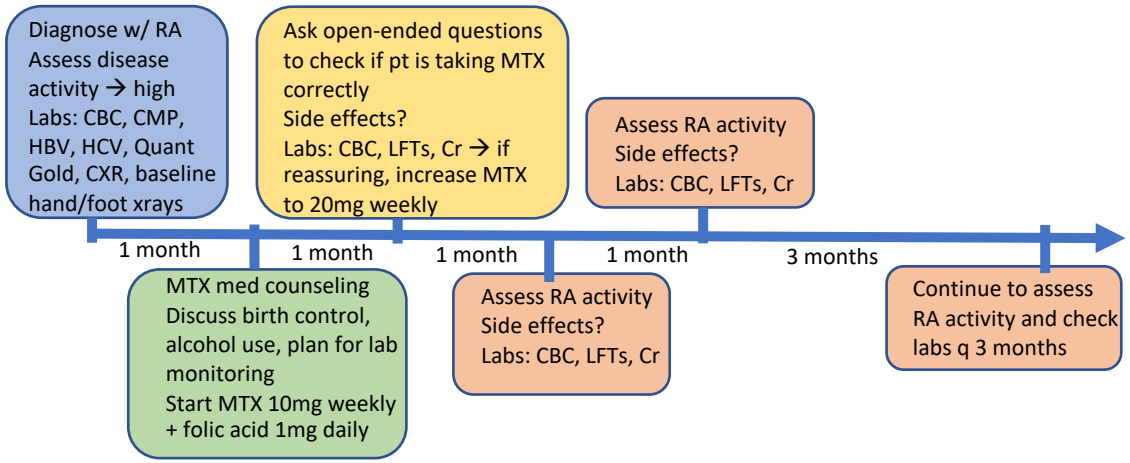
Pearls: Not immunosuppressive. Safe in pregnancy/breastfeeding.

Monitoring: Annual retinal exam (q6 months after >10 years on therapy). No lab monitoring required.

Sulfasalazine:

Side effects: GI upset, hepatotoxicity, leukopenia, hemolytic anemia (higher risk in G6PD deficiency)

Typical Timeline for Starting Methotrexate:



Pregnancy & Breastfeeding:

Safe	Contraindicated	Insufficient/Limited Data
Hydroxychloroquine, Sulfasalazine, TNFi (certolizumab has most data)	Methotrexate, Leflunomide	Abatacept, IL-6 inhibitors, Rituximab, JAK inhibitors

Overview of Biologic DMARDs for RA:

Generic	Trade	Class	Administration	Frequency	Pearls
Etanercept Adalimumab Golimumab Certolizumab Infliximab	Enbrel Humira Simponi Cimzia Remicade	TNF inhibitor	SQ SQ SQ SQ IV	Weekly Q 14 days Monthly Monthly Q 4-8 weeks	Typically used as first-line biologic therapy. Often try 2 different TNFi before moving on to another class. Avoid in class III/IV CHF, SLE-overlap, demyelinating disease.
Abatacept	Orencia	Costim blocker	SQ/IV	Weekly/monthly	Pro: Fewer infectious complications. Con: Longer time to efficacy
Tocilizumab Sarilumab	Actemra Kevzara	IL-6 inhibitor	SQ/IV SQ/IV	Weekly/monthly Weekly/monthly	Pro: Well-tolerated Con: Can cause hyperlipidemia, intestinal perforation
Rituximab	Rituxan	Anti-CD20	IV	2 IV doses every 6 months	Pros: May help RA-ILD, q6 month dosing can help with compliance, lowest risk of activating TB. Cons: B cell depletion = high risk of severe COVID, poor response to vaccines.
Tofacitinib Baricitinib Upadacitinib	Xeljanz Olumient Rinvoq	JAK inhibitor	PO PO PO	Daily or BID Daily Daily	Pro: Oral Con: high rate of zoster, increased risk of CVE/VTE in at-risk patients