A Narrow Window of Opportunity:
Diagnosis and Management of Rheumatoid Arthritis in Underserved Populations

Matt Haney, DO





Disclosures



Speaker:

Matt Haney reports no financial relationships



Learning Objectives



Recognize signs and symptoms suggestive of RA

Determine when to refer patients with RA to a rheumatologist

Develop a comfort level in prescribing disease-modifying antirheumatic drugs (DMARDs)

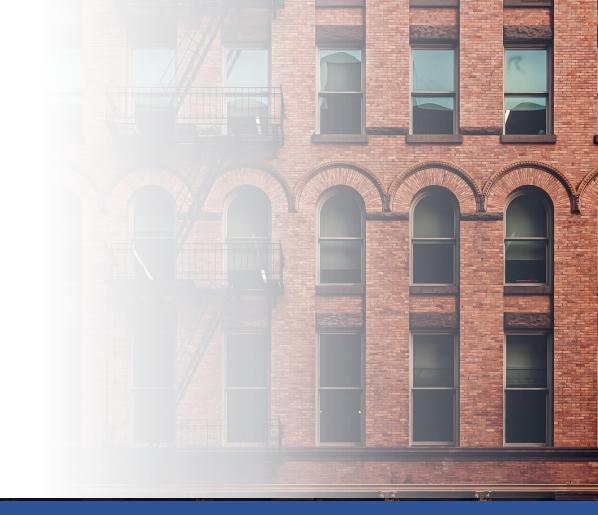
Help patients understand their disease and engage in shared decision making

Use motivational interviewing to recognize patients' concerns

Recognize and mitigate implicit bias to build a culture of equity in your practice



Rheumatoid Arthritis: Signs, Symptoms, and Impact





The Impact of RA



Most common type of autoimmune arthritis (1.3 million US adults)^{1,2}

Women account for 75% of diagnosed cases³

1-3% of women may be affected in their lifetimes³

Prevalence differs significantly across race, educational levels, and poverty-income ratio groups.¹

Independent of gender, non-Hispanic African Americans, individuals with an educational level of less than high school, and those with low family income had a significantly higher RA risk than age-adjusted comparator cohorts.¹

Total annual RA health cost for US is \$19.3 billion dollars (2010 data).4

Advances in treatment have shifted the economic burden from inpatient costs to indirect costs (e.g., disability, work absenteeism).⁵

What is RA?



A chronic autoimmune inflammatory disease in which the body's immune system attacks the lining of the joints^{1,2}

Damages the synovial tissue that envelops the ends of the bones within a joint, which differentiates it from the cartilage degeneration (or "wear and tear") that characterizes osteoarthritis

Inflammation eventually causes localized damage (e.g., bone erosion and joint deformity); more systemic effects reported in ~40% of RA patients³

Untreated RA may cause irreversible joint damage within the first year of onset²

Symptoms vary in severity across individuals and may "flare" or undergo periods of relative remission







Tender, warm, and swollen joints¹

Joint stiffness that is more notable in the morning or following a period of inactivity¹

Fatigue, fever, and loss of appetite¹

Can affect wrists, hands, elbows, shoulders, feet, spine, knees, and jaw²

Pain usually presents bilaterally³

RA "morning stiffness" usually lasts > 30 minutes but may lessen as the day's activity commences.



Risk Factors for RA



Age: Onset increases with age, peaking for individuals in their sixties

Gender: Women are 2-3 times more likely to develop RA than men

Smoking

Obesity

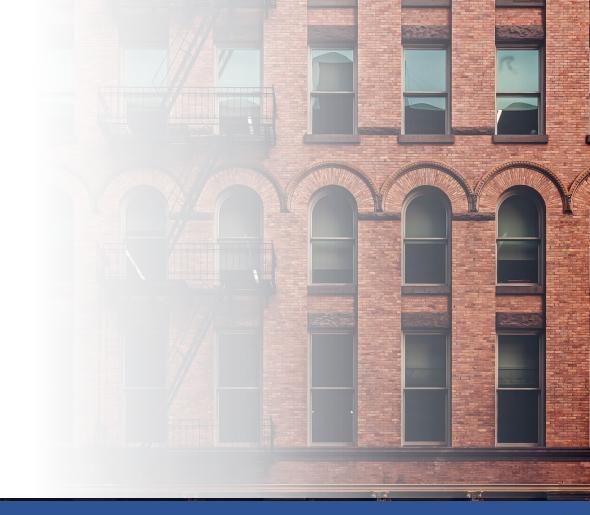
Human leukocyte antigen (HLA) Class II genes

Early life exposure to secondhand smoke may increase risk of developing RA as an adult

Women who have never given birth may be at greater risk of developing RA, while women who breastfeed their infants may have a *decreased* risk of RA



Diagnosing RA in Primary Care





Diagnosing RA



Early diagnosis and prompt treatment will slow disease progression, minimize potential disability, and improve outcome and quality of life.

Early symptoms can resemble those of other forms of arthritis.

Physical examination/medical history, imaging, and laboratory tests can help to rule out other conditions.

RA symptoms usually need to be present >3 months to consider a diagnosis of RA, although some patients are diagnosed sooner.

No single blood test or physical finding unequivocally confirms a diagnosis of RA.



What to Ask a Patient with RA Signs and Symptoms



A review of joint symptoms—location, when/how the patient noted their presence, changes over time

Limitations that symptoms have imposed on the patient's activities

Other symptoms that could indicate chronic inflammation (e.g., weight loss, fever, fatigue, weakness, difficulty breathing)

Other medical conditions (depression/anxiety)

Family history of RA or family members with similar symptoms

Medication history

Diet and activity

Smoking history

Vaccination status and relevant cancer screenings



Imaging in RA Diagnosis



X-rays, MRI, and ultrasound can help diagnose or monitor disease progression.

X-rays are often normal during the early stages of RA but can sometimes rule out other conditions.

MRI of symptomatic areas (e.g., hand or wrist) may support a diagnosis of RA or inflammatory arthritis.

Early-stage RA is associated with periarticular osteoporosis;¹ hand BMD measurement can predict severity/progression of joint destruction.

Ultrasound can indicate synovitis, synovial hypertrophy, or increased circulation associated with inflammation.



Blood Tests: Serology



Rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACPA) are serologic markers that can be diagnostic and prognostic indicators of autoimmune disease.

High-titer RF indicates increased risk for extra-articular involvement, and ACPA suggests aggressive disease with risk for erosive disease.

Both are negative on presentation in up to 25% of patients with RA and can remain so during follow-up in 20% of these individuals.¹

Positive results on both tests increase specificity compared to either test alone.

Seronegative RA patients can become seropositive over time.



Blood Tests: Acute-phase Reactants



Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are acute-phase reactants—markers that undergo significant serum concentration changes in response to inflammation.

Both are typically elevated in RA and can be used to monitor systemic inflammation following initial evaluation and/or diagnosis.¹

Changes in ESR and CRP levels can be monitored serially to assess treatment response.



Blood Tests: Antinuclear Antibody (ANA) Panels



ANA panel testing using immunofluorescence (IF) confirms the presence of ANAs associated with autoimmune rheumatic diseases (e.g., RA, lupus [SLE], systemic sclerosis, mixed connective tissue disease) and some viruses (e.g., EBV, HIV, hepatitis C, parvovirus).

A positive ANA test indicates an autoimmune reaction process, although up to 15% of healthy people have positive ANA test results.¹

ANA may be positive in up to one-third of patients with RA.²

ANA testing has limited value in patients who present solely with nonspecific symptoms (e.g., malaise, fatigue).³



Reading ANA Test Results



ANA results are reported in titers (levels) and patterns.

Titer refers to the highest dilution of serum that produces visible fluorescence.

Reported as a ratio that reflects the number of serial 1:1 saline dilutions of the plasma; commonly reported titers include 1:40, 1:80, 1:160, 1:320, and 1:640.

A titer of 1:160 is a common standard to define a positive ANA, but labs vary in their qualification standards.

Titers may change during the course of the disease; fluctuations do not necessarily correlate with disease activity.¹

ANA patterns (e.g., homogeneous, speckled, centromere) refer to the distribution of staining observed when ANA reacts with antigens in the human HEp-2 cell line commonly used as a substrate in the IF assays. ANA patterns can inform about the type of autoimmune disease and appropriate treatments.



ACR/EULAR Classification Criteria for RA

Category	Value	Score
Joint involvement	1 large joint	0
	2-10 large joints	1
	1-3 small joints (w/ or w/o large joints)	2
	4-10 small joints (w/ or w/o large joints)	3
	> 10 joints (at least one small joint)	5
Serology (at least 1 result needed)	Negative RF and negative ACPA	0
	Low-positive RF or low-positive ACPA	2
	High-positive RF or high-positive ACPA	3
Acute-phase reactants (at least 1 result needed)	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
Symptom duration	Less than 6 weeks	0
	Six weeks or longer	1





Post-viral Arthritis



Several common viruses, including parvovirus B19, hepatitis B and C, HIV, alphaviruses, and COVID-19 can cause an acute polyarthritis syndrome that could be mistaken for RA.^{1,2}

However, virally induced polyarthritis rarely lasts more than six weeks, in contrast to RA's chronic and persistent symptoms.

Patients who experience symptoms for < 6 weeks should be considered for RA but may possibly have post-viral arthritis.

Clinicians should monitor these patients closely and ask them about recent acute infections and travel.







Results from a gradual breakdown ("wear and tear") in the cartilage between heavily used joints

Onsets slowly over a period of years, usually later in life

Often begins unilaterally and may be limited to one set of joints

Joint tenderness and pain, but little or no swelling

Morning stiffness transient if present

Not associated with whole-body symptoms (e.g., fever, fatigue)



Systemic Lupus Erythematosus (SLE)



Chronic autoimmune disorder that may present with joint pain/ swelling/stiffness, fever, and fatigue¹

Symptoms may "flare" and vary widely but can include rashes, chest pain, hair loss, sun/light sensitivity, mouth sores, anemia, renal issues, and ocular sequelae

~98% of individuals with lupus test positive for ANA²

~20% of women are weakly ANA+; most never develop signs of lupus²

Evidence to support a diagnosis of SLE includes additional symptoms and full ANA panel (anti-dsDNA, anti-Smith, anti-U1RNP, anti-Ro/SSA, and anti-La/SSB)



Inflammatory Bowel Disease (IBD)



Chronic GI tract inflammation leads to arthritis in \sim 30% of IBD patients, most commonly peripheral arthritis of the arms and legs and axial arthritis of the spine and hip¹

Typically does not cause joint deformity or breakdown

Swelling may be sudden/severe, move among joints, and affect larger joints

IBD-associated arthritis is RF-negative¹

Common symptoms include diarrhea, abdominal pain, loss of appetite, unintended weight loss, fatigue, and bloody stools^{2,3}

Clinicians should assess for abdominal tenderness and ask about family history of GI conditions in patients who present with joint pain





Treatment Goals



Early diagnosis and proactive treatment can slow progressive joint damage in up to 90% of patients with RA.¹

- Aim to achieve remission or low disease activity.^{2,3}
- Treat to target—i.e., aim toward a clearly defined goal—regardless of disease activity level.³
- Monitor patients regularly.
- Incorporate medical, social, and emotional support.

RA treatment should aim to achieve

remission or low disease activity.



Overview of Modalities



The Holistic RA Treatment Plan

Pharmacotherapy

- NSAIDs
- Glucocorticoids
- DMARDs

Physical Activity or Therapy

Diet

- Anti-inflammatory
- Mediterranean diet



Pharmacotherapy: NSAIDs



Inhibit prostaglandin formation by blocking the active site of the cyclooxygenase enzymes COX-1 and COX-2¹

Have independent anti-inflammatory effects and mild-to-moderate analgesic properties¹

Despite improving pain and stiffness, NSAIDs alone <u>do not</u> modify RA progression or prevent joint destruction^{1,2}

Agents are comparably efficacious and are associated with risk of GI bleeding and cardiovascular risks^{2,3}

Responsiveness to NSAIDs does not correlate with changes in serologic marker levels



Pharmacotherapy: Corticosteroids



Low-dose corticosteroids can slow radiographic progression of articular disease in early RA¹

Long-term use is associated with increased mortality, CV events, and bone fractures, and there is no consensus about optimal tapering²

Appropriate as a temporary "bridge" therapy while awaiting DMARDs to take effect or as chronic adjunctive therapy in patients with severe disease that is poorly controlled with NSAIDs and DMARDs³

ACR and EULAR recommend using low-dose glucocorticoids (≤10 mg daily of a prednisone equivalent) when starting a DMARD or for ≤3 months when treating a flare^{4,5}

ACR strongly recommends initiating a conventional DMARD without longer-term (\geq 3 months) glucocorticoids over doing so with them⁶



Pharmacotherapy: Disease-modifying Antirheumatic Drugs (DMARDs)



DMARDs improve symptoms, alter the disease course, and improve radiographic outcomes in patients with RA.¹

Although DMARDs generally act more slowly on RA (onset can take up to 6 weeks) than do NSAIDs or glucocorticoids, their introduction effectively shifted the goal of therapy from symptom relief to sustained remission.^{2,3}



Conventional DMARDs Approved for RA*

Category	Agents (Alphabetical)	
Conventional DMARDs	Hydroxychloroquine	
	Leflunomide	
	Methotrexate	
	Sulfasalazine	



Biologic DMARDs Approved for RA*

Category	Mechanism of Action	Agents (Alphabetical)
Biologic DMARDs (bDMARDs)	TNF Inhibitor	Adalimumab Certolizumab pegol Etanercept Golimumab Infliximab
	IL-6 Receptor Inhibitor	Sarilumab Tocilizumab
	Anti-CD20 Antibody	Rituximab
	T-cell Costimulatory Inhibitor	Abatacept
	IL-1 Receptor Antagonist	Anakinra



Targeted Synthetic DMARDs Approved for RA*

Category	Mechanism of Action	Agents (Alphabetical)
Targeted Synthetic DMARDs (tsDMARDs)	JAK Inhibitors	Baricitinib
		Tofacitinib
		Upadacitinib



Guiding Principles for Prescribing DMARDs



2021 ACR RA treatment guidelines focus on using DMARDs, with strong and conditional recommendations based on various scenarios. DMARD treatment decisions should:

- Follow a shared decision-making process
- Be reevaluated within a minimum of 3 months based on efficacy and tolerability of the chosen agent(s)
- Follow a systematic, treat-to-target approach that involves frequent monitoring of disease activity and modifying treatment to reach a pre-defined target of low disease activity or remission
- Consider tapering only when patients have been at target for at least DMARDs should generally be initiated when RA diagnosis is confirmed.2



ACR Recommendations for Prescribing DMARDs (1)



For DMARD-naïve patients with symptomatic early RA, consider DMARD monotherapy (preferably methotrexate) over combination DMARD therapy.¹

For DMARD-naïve patients with moderate to high disease activity, use methotrexate monotherapy over hydroxychloroquine or sulfasalazine, bDMARD or tsDMARD monotherapy, or the combination of methotrexate plus a non-TNF inhibitor bDMARD or tsDMARD.²

Switching RA therapies when low disease activity or clinical remission is achieved should be considered only at the clinician's discretion in consult with the patient.¹
A treat-to-target strategy to reduce disease activity by >50% within 3 months and achieve remission/low disease activity within 6 months can improve outcomes and prevent disability.³



ACR Recommendations for Prescribing DMARDs (2)



Move to combined therapy if moderate or high disease activity persists despite DMARD monotherapy (with or without glucocorticoids).¹

Add another DMARD, a TNF inhibitor, or a non-TNF biologic agent (all choices with or without methotrexate and in no order of preference) rather than continue DMARD monotherapy.

Add 1-2 DMARDs to TNF inhibitor therapy if disease activity remains moderate or high despite TNF inhibitor monotherapy in a DMARD-naïve patient.

If disease activity is low, continue DMARD therapy.¹

If disease is in remission, do not discontinue all RA therapies.

Do not routinely consider dose reduction for patients in remission for < 6 months.²



DMARDs, Pregnancy, and Family Planning



Methotrexate and leflunomide are considered teratogens (FDA Pregnancy Category X) and <u>should not</u> be prescribed to women with RA at pre-conception, during pregnancy, or while breastfeeding.¹

The ACR conditionally recommends discontinuing anakinra, abatacept, rituximab, and tocilizumab during pregnancy.

Hydroxychloroquine, sulfasalazine, and certolizumab are strongly recommended to be continued pre-conception, during pregnancy, and during breastfeeding.

Other TNF inhibitors are conditionally recommended in preconception and during the first and second trimesters but strongly recommended during breastfeeding.

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Vaccines and RA



Patients who initiate or take DMARDs should receive all recommended pneumococcal, influenza, hepatitis B, and HPV vaccines.¹

CDC recommends that adults \geq 50 years and immunocompromised adults aged \geq 19 years who have RA receive the recombinant zoster vaccine for shingles.²

ACR strongly recommends prophylactic antiviral therapy over frequent monitoring alone for HBV+ patients who are initiating any bDMARD or tsDMARD.³

Patients should be tested for tuberculosis (TB) before initiating bDMARDs and tsDMARDs. TNF inhibitor treatment is associated with up to 25X increased relative risk for TB, depending on clinical setting and agent used.⁴



Physical Activity



RA is associated with "rheumatoid cachexia" that includes decreased joint health, fatigue, increased incidence and progression of CVD, and accelerated loss of muscle mass.¹

Exercise training can reverse cachexia and improve function without exacerbating disease activity.^{1,2}

The EULAR recommends exercise and maintenance of healthy body weight for people with rheumatic and musculoskeletal diseases.³

RA patients should be encouraged to be active within appropriate contexts.



Dietary Interventions



"Anti-inflammatory" or "Mediterranean" diets are rich in whole foods (e.g., fruits, vegetables, fish, nuts, beans, olive oil) but low in processed foods and saturated fats.¹

Foods commonly included in these diets can lower blood pressure, protect against chronic conditions, reduce inflammation, and support weight-loss regimens.

Obesity is a strong predictor of worse clinical outcomes and treatment responses in patients with early RA.²

Anti-inflammatory diets are part of a healthy lifestyle that may positively impact RA.





The Role of the Primary Care Clinician



Identify patients at risk for RA or other connective tissue or autoimmune disorders

Assess and determine referral needs

Understand cultural factors and patient preferences for treatment

Discuss treatment options and adjunctive interventions

Coordinate efforts with an RA care team (e.g., rheumatologist, physical therapist, gynecologist, pulmonologist, dietitian, social worker)

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Talking with Your Patient about RA (1)



Remind the patient that they are not at fault for developing RA.

Stress that many effective pharmacologic options can treat RA.

Stress that approved treatments will improve pain symptoms and prevent joint damage.

Discuss medication side effects and onset of efficacy.

Discourage the use of non-evidence based practices and agents.

Recognize that managing RA is a journey.



Talking with Your Patient about RA (2)



Reiterate that proper management will enable the patient to live a meaningful life with RA.

Initiate a conversation about how lifestyle changes favorably affect RA symptoms and management.

Discuss reproductive issues and family planning in the context of RA management with appropriate patients.

Discuss the patient's role in adhering to and modifying treatment plans.

Encourage the patient to use the practice's patient portal.



When to Refer to a Rheumatologist



The Expert Panel recommends referring any patient for whom you are confident of an RA diagnosis. Other situations that warrant referral include:

- Canonical RA symptoms but normal serology
- Family history of RA or autoimmune disease
- Other organ involvement, especially lung nodules
- High CCP levels or other markers of systemic inflammation
- Clinician discomfort with prescribing and managing DMARDs
- Requirement of medications beyond DMARDs

The American College of Rheumatology provides a searchable directory of rheumatologists at https://my.rheumatology.org/find-a-rheumatologist.





The Culturally Informed Office



Language- and topic-appropriate materials

Staff to match population served

Bilingual or language-appropriate wall posters and signs

Written text geared for comprehension

A trained medical interpreter or access to interpretation services

Staff trained to overcome cultural misconceptions

Establishing a culturally informed office is the first step toward providing culturally appropriate care.



Considerations for Providing Culturally Appropriate Care (1)



Education level and health literacy (i.e., ability to understand concepts)

Family integration and support systems (church, community)

Cultural judgments about disease and norms regarding body image

Knowledge about RA

Learning styles and motivational strategies



Considerations for Providing Culturally Appropriate Care (2)



Spiritual beliefs (e.g., belief that events are predetermined by fate)

Nutritional preferences

Alternative/herbal practices and folk remedies

Language issues





Partnering with Minority Patients



Appreciate value system associated with patient's cultural heritage

Emphasize holistic care by recognizing biologic, psychological, and faith-based components

Provide framework to understand level of disease severity and realistic treatment options

Promote trust through engaged attitude

Avoid paternalistic stance

Culturally informed care is based on a partnership between the patient and the healthcare provider.



Cross-cultural Interviewing



Establish trust through "small talk"

Use open body language

Speak slowly and directly to the patient (rather than to the interpreter)

Use short sentences and a normal tone of voice

Avoid use of idioms

Ask patient what illness means to her and about her current treatments

Provide treatment instructions in writing

Have patient repeat instructions in his/her own words



Cross-cultural Interview Questions (1)



What is your native country?

How long have you been here?

What do you think is wrong?

What do you call the illness?

What do you think has caused the illness?

Why do you think that the illness began when it did?

What problems do you think that the illness causes?





Cross-cultural Interview Questions (2)



How severe is your illness?

What kind of treatment do you think is necessary?

What are the most important results you hope to receive from this treatment?

What do you fear most about the illness?

How do you cope with your feelings?

What can you change?

What types of support do you have to help you deal with this illness?





The "Teach-back" Approach





"Teaching back"

Have the patient repeat your statements in their own words.

- Assesses patient's health literacy and language proficiency
- Promotes understanding of cultural issues
- May facilitate adherence to an intervention



Culturally Informed Care for Latino Patients



Listen for somatic presentation of complaints

Recognize that disease may be perceived as internal/external imbalance (e.g., body and soul)

Be aware of folk-healing traditions

Incorporate support systems into treatment (family, clergy, social workers, counselors)

Recognize central role of male family members

Provide trained medical interpreter when needed



Culturally Informed Care for African- American Patients



Respect the patient's understanding of illness

Use open-ended questions to ensure that you and the patient have common meaning

Recognize the patient's medical beliefs, including folk-, home-, and herbal-based remedies

Recognize the role of spirituality as a coping mechanism

Incorporate beneficial or neutral folk remedies into the plan of care

Recognize that medication cost and complex dosage instructions may promote non-adherence.





30 y/o African-American woman who complains that both hands have hurt off and on for ~3 months.

Wrists swollen, red, and tender

Ibuprofen and running hands under hot water provide temporary relief

Reports feeling tired lately and sometimes awakens at night because her hand is asleep

Difficulty lifting objects such as a suitcase

Planning to start a family and concerned that she will be unable to care for a baby without pain





Could Sheila have RA?

a) Yes. She shows the hallmark bilateral presentation of swollen joints, which suggests RA. RA often onsets in women of Sheila's age, and RA symptoms commonly flare and may remit.

a) No. RA is unlikely to affect a young and healthy woman, and the pain associated with RA usually does not remit.





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Sheila's exam results:

BP: 130/80 mm Hg

Pulse: 78 beats/minute

Physical exam: Normal

BMI: 28 kg/m²

Alcohol or tobacco use: No

Prescription medications: None.





What other questions should you ask to help diagnose RA?

- a) Do other joints besides your wrists hurt?
- b) At what time of day do you feel the pain most acutely?
- c) Did you first notice the pain in conjunction with any specific event? (e.g., viral infection, life stress)
- d) Do you have a family history of arthritis or similar conditions?
- e) All of the above.





What other questions should you ask to help diagnose RA?

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States that knuckles and feet sometimes hurt.

Pain peaks in the morning.

Palpation of her hands indicates tenderness in the second, third, and fourth metacarpophalangeal (MCP) joints.

Proximal interphalangeal (ICP) joints feel warm.





You order CBC and liver/renal function tests, but what other tests will be helpful to proceed?

- a) Routine lipid panel
- b) Immunofluorescent ANA test
- c) Hepatitis panel
- d) Serology (RF, ACPA)
- e) Acute-phase reactants (ESR, CRP)
- f) Thyroid stimulating hormone (TSH)
- g) All of the above.





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Sheila is up to date on flu and COVID-19 vaccines but contracted COVID about one year ago. Are her symptoms consistent with post-viral arthritis?

- a) Yes. Post-viral arthritis is a long-term condition that typically lasts up to one year post-infection.
- b) No. Virally induced polyarthritis rarely lasts more than six weeks, in contrast to RA's chronic and persistent symptoms. Patients who report experiencing symptoms for fewer than six weeks should be considered for RA but may possibly have post-viral arthritis.





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Are her symptoms consistent with a diagnosis of osteoarthritis (OA)?

- a) Yes
- b) No



Are her symptoms consistent with a diagnosis of osteoarthritis (OA)?

a) Yes

b) No





Sheila's lab results indicate elevated acute-phase reactants (ESR and CRP) and positive ANA, but she is negative for RF and ACPA. The first two results are consistent with a diagnosis of RA, but what about the seronegative results?

- a) A seronegative result is inconsistent with a diagnosis of RA, and you should consider another diagnosis.
- b) A seronegative result is relatively common in patients with RA and is consistent with a diagnosis of RA.
- c) Serology results may change over time with disease progression, and Sheila has symptoms of early-stage RA.
- d) Both b and c are correct.





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What points should you discuss with Sheila now?

- a) RA can be treated using safe and effective therapies.
- b) Approved treatments will improve pain symptoms and prevent irreversible joint damage.
- c) Successful RA management is a journey that involves shared decision-making.
- d) Family planning will likely impact the course of treatment.
- e) Initiating lifestyle changes can favorably affect RA outcomes.
- f) Sheila will play an active role in adhering to treatment and discussing changes to treatment plans.
- g) All of the above.





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RA Resources for Clinicians and Patients



American College of Rheumatology (ACR)	rheumatology.org
The Arthritis Foundation	arthritis.org
National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)	niams.nih.gov
The Mayo Clinic	mayoclinic.org
Centers for Disease Control and Prevention	cdc.gov



Conclusion and Clinical Pearls

RA is treatable and can often be managed in the primary care setting.

Early diagnosis and prompt treatment are central components of successful management.

Treatment should aim to achieve remission or low disease activity.

DMARDs are highly effective pharmacologic options to manage RA and will improve pain symptoms and prevent joint damage.

Disparities occur in the diagnosis and treatment of RA, with minority populations being underserved.

Informed care is based on a partnership between the patient and clinician that incorporates biological and psychological aspects within a holistic framework.



Questions?



