From Current Diagnosis & Treatment in Rheumatology, Third Edition
John Imboden, David Hellmann, and John Stone, Editors

Chapter 4. Approach to the Patient with Arthritis

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(Abridged and edited by Dr. Eli Miloslavsky)

Approach to the Patient with Arthritis: Introduction

Many diseases can cause arthritis. Obtaining a history and performing a physical examination are the first steps in allowing the clinician to accurately characterize the arthritis and approach the differential diagnosis in a focused, logical fashion based on the duration of symptoms, the presence or absence of joint inflammation, the number of joints affected, and the pattern of joint involvement (Table 4–1).

Table 4–1. Initial Clinical Characterization of Arthritis.

- Duration: acute (presenting within hours to days) or chronic (persisting for weeks or longer)
- Number of joints involved: monoarticular, oligoarticular (2–4 joints), or polyarticular (5 joints or more) If more than one joint is involved: symmetric or asymmetric; additive or migratory
- Accurate delineation of the involved joints
- Inflammatory or noninflammatory

When evaluating a patient with joint symptoms, it is important to determine whether the symptoms are due to an articular process and not to bursitis, tendinitis, or other soft tissue conditions. The physical examination should also establish whether there are objective findings of arthritis, such as swelling, in the symptomatic joints. Arthralgias in the absence of objective arthritis commonly occur in systemic lupus erythematosus (SLE) and acute viral illnesses but have less diagnostic significance than true arthritis.

Laboratory tests cannot substitute for clinical evaluation and should never be used as a "screen" for disease. Musculoskeletal complaints are common in the general population, but the prevalence of inflammatory rheumatic diseases is relatively low. Hence, the positive predictive value of many rheumatologic tests is low when tests these are ordered indiscriminately. In general, radiographs add little to the evaluation of acute presentations of arthritis (except in cases of suspected trauma) but often are critical for the assessment of chronic arthritis.

Inflammatory versus Noninflammatory Arthritis

The distinction between inflammatory arthritis and noninflammatory arthritis is a critical bifurcation point in the differential diagnosis of arthritis. The most reliable means for making this distinction is analysis of the white blood cell (WBC) count in the synovial fluid. The synovial fluid WBC count is >2000/mcL in inflammatory arthritis and is <2000/mcL in noninflammatory arthritis. Arthrocentesis should be performed whenever feasible because although clinical features and other laboratory investigations also help distinguish inflammatory and noninflammatory arthritis, no single finding is definitive.

Patients with an inflammatory arthritis usually complain of pain and stiffness in involved joints;

typically these symptoms are worse in the morning or after periods of inactivity and improve with mild to moderate activity. On examination, the larger joints can be warm and, when severely inflamed as in acute gout or septic arthritis, can have erythema of the overlying skin. In contrast, patients with noninflammatory arthritis have pain that worsens with activity and improves with rest. Stiffness is generally mild, lasts <30 minutes in the morning, and is not a prominent symptom.

Constitutional Symptoms

The presence of fever raises the possibility of infection. Fever can also accompany arthritis that is not due to active infection. Constitutional symptoms rarely accompany noninflammatory forms of arthritis.

Extra-Articular Manifestations

Extra-articular manifestations, such as kidney abnormalities, pulmonary abnormalities, oral ulcerations, ocular inflammation, and peripheral neuropathy, may signal that arthritis is a manifestation of a systemic rheumatic disease or vasculitis. The presence of rash can be a very helpful clue to the diagnosis.

Family History

A positive family history, particularly among first-degree relatives, increases the likelihood of certain forms of arthritis. Most notably, the risk of ankylosing spondylitis for children or siblings of a patient with ankylosing spondylitis is as much as 75-fold that of the general population. The relative risk for SLE among first-degree relatives ranges from 20 to 30. A positive family history of rheumatoid arthritis is less helpful. The relative risk for siblings may be as low as 3, and family histories of rheumatoid arthritis can be inaccurate due to confusion with osteoarthritis.

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Acute Arthritis

Except in cases of trauma, arthritis that is acute in onset is usually inflammatory. Septic arthritis and crystal- induced arthritis typically have an acute onset, and patients often seek medical attention within hours to days after the onset of symptoms. These disease processes, therefore, always warrant serious consideration in cases of acute arthritis.

Acute Monoarthritis

Essential Features

- Septic arthritis is the major diagnostic concern.
- Arthrocentesis is the most important diagnostic test.

Initial Clinical Evaluation

The history and physical examination should determine whether the process is acute (onset over hours to days), involves the joint rather than surrounding tissues or bone, and is truly monoarticular. The most common causes of acute monoarthritis are infection, crystal-induced arthritis (e.g. gout), and trauma. In cases of suspected trauma, it is important to ascertain whether the reported trauma was sufficiently severe to account for the joint findings. (Patients with new-onset joint effusions often attribute the joint abnormality to incidental bumps, turns, or other minor trauma.) Joint space infection is the foremost concern in patients with acute pain and swelling in a single joint not clearly due to trauma.

Laboratory Evaluation

Arthrocentesis is indicated for all cases of unexplained acute monoarthritis. Synovial fluid should be sent for culture (for bacteria, mycobacteria, and fungus), cell count, Gram stain, and examination for crystals by polarized light microscopy.

The characteristics of the synovial fluid guide the initial differential diagnosis. Septic arthritis usually causes synovial fluid WBC counts >50,000/mcL and often generates very high counts (>100,000/mcL). Crystal- induced arthritis is also very inflammatory, with synovial fluid WBC often <50,000/mcL, but WBC counts >50,000mcL can be seen as well.

Gram staining for bacteria in synovial fluid is relatively insensitive (false-negative rates range from 25% to 50%). On the other hand, examination of synovial fluid by polarized light microscopy is a sensitive test for urate crystals. Thus, the absence of crystals is a strong argument against microcrystalline disease, but a negative Gram stain does not exclude infection. Occasionally, infection and microcrystalline disease coexist; therefore, the finding of crystals in the synovial fluid does not exclude the possibility of infection.

Properly performed cultures of synovial fluid are a sensitive test for septic arthritis (positive in up to 90% of cases).

Imaging Studies

Radiographs can demonstrate fractures in cases of trauma but usually contribute little to the diagnosis of nontraumatic monoarthritis if the process is truly acute. Occasionally, imaging studies can be misleading. For example, radiographs may demonstrate osteoarthritis or other chronic conditions that predispose to the development of septic arthritis but are not the proximal cause of the acute joint inflammation.

Chronic Arthritis

Essential Features

- Distinguishing between inflammatory and noninflammatory arthritis is a key step toward establishing a diagnosis.
- Rheumatoid arthritis and osteoarthritis are the leading causes of chronic polyarthritis.
- Careful delineation of the joints involved, particularly in the hands, can help point to the correct diagnosis.

Initial Clinical Evaluation

It is important to determine whether the symptoms and signs point to an inflammatory or noninflammatory process. The particular joint involved influences the differential diagnosis.

Differential Diagnosis

Noninflammatory

Osteoarthritis is the leading cause of chronic noninflammatory monoarthritis, particularly when the hip, knee, first carpometacarpal joint, or acromioclavicular joint is involved. Internal derangements, such as a torn meniscus in the knee, often produce mechanical symptoms and characteristic findings on physical examination.

Inflammatory

There are many causes of inflammatory arthritis which you will encounter in this course as outlined in Table 4-9. These will be discussed in more details in future sessions.

Table 4–9. Differential Diagnosis of inflammatory arthritis.

INFLAMMATORY CAUSES	NON-INFLAMMATORY CAUSES

• Rheumatoid arthritis
• Spondyloarthropathy
  o Reactive arthritis
  o Ankylosing spondylitis
  o Psoriatic arthritis
  o Inflammatory bowel disease
• Systemic lupus erythematosus (SLE)
• Sarcoidosis
• Dermatomyositis and polymyositis
• Vasculitis
• Crystal arthropathy (gout and pseudogout)
	• Osteoarthritis

Initial Clinical Evaluation

Rheumatoid arthritis is the leading cause of chronic inflammatory polyarthritis, and osteoarthritis is the most common cause of chronic noninflammatory polyarthritis. As is the case with other forms of arthritis, the distinction between inflammatory and noninflammatory processes is critical.

Imaging Studies

Radiographs are indicated in most cases of chronic polyarthritis of the hand. Radiographs of the hand usually show characteristic changes at the time of presentation of primary generalized osteoarthritis, calcium pyrophosphate deposition disease, and chronic tophaceous gout. In cases of rheumatoid arthritis and the spondyloarthropathies, however, the likelihood of radiographic joint erosions and other characteristic findings increases with the duration of the polyarthritis; hand radiographs may be normal or demonstrate nonspecific changes only, for months or longer.

Differential Diagnosis

Osteoarthritis and rheumatoid arthritis have different patterns of joint involvement in the hand. Osteoarthritis involves the distal interphalangeal (DIP) and PIP joints and the first carpometacarpal joint. Rheumatoid arthritis, in contrast, involves the PIP and MCP joints and the wrists. Both can affect the large joints such as the hips and knees.

Osteoarthritis and rheumatoid arthritis typically spare certain joints. Osteoarthritis usually does not involve the MCP joints, wrists, elbows, glenohumeral joints, and ankles; degenerative arthritis of these joints raises the possibility of other processes. Rheumatoid arthritis usually spares DIP joints, the thoracic and lumbosacral spine, and sacroiliac joints.

In generalized osteoarthritis, interphalangeal joints, particularly the DIPs, may appear to be inflamed (“inflammatory osteoarthritis”) and thus cause some diagnostic uncertainty. Radiographs, however, usually show typical degenerative changes (irregular joint-space narrowing, sclerosis, and osteophytes). Psoriatic arthritis also commonly involves the DIP joints, usually with radiographic changes distinct from those of osteoarthritis.

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Chapter 3. Laboratory Diagnosis

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(Abridged and edited by Dr. Eli Miloslavsky)

Laboratory Diagnosis: Introduction

In general, laboratory tests are useful adjuncts in establishing a rheumatologic diagnosis but are not absolutely diagnostic of any specific disease. Two features of rheumatologic diseases contribute to the difficulties of interpreting laboratory tests. First, many rheumatic diseases are chronic systemic inflammatory diseases and, therefore, share many laboratory abnormalities with other such diseases, particularly chronic infections and malignancies. Second, the prevalence of certain rheumatologic diseases is low in most patient populations. Therefore, even if sensitivity and specificity of a test are high for a specific disease, the positive predictive value of the test may be low. Considering these statistical characteristics of laboratory tests can help the clinician interpret the data within the context of the clinical case.

Statistical Characteristics of Laboratory Tests

Appropriate use of laboratory tests requires awareness of the rates and causes of false-positive and false-negative test results. The **sensitivity** of a test demonstrates the ability of the test to detect a patient with disease and is measured by the proportion of people with disease who have a positive test result. The **specificity** of a test demonstrates the ability of the test to avoid detecting patients without disease and is measured by the proportion of people without disease who have a negative test result. The usefulness of a laboratory test is best reflected in the **positive predictive value**, which determines the proportion of patients with a positive test result who truly have the disease. The **positive predictive value** of a test depends on the **prevalence** of the disease in the population being examined (or the pretest probability of disease); thus, even if the sensitivity and specificity of a test are 99%, the positive predictive value of the test can be low if the prevalence of disease in the population is extremely low. The **negative predictive value** of a test determines how many patients with a negative test result truly do not have the disease. The negative predictive value also depends on the prevalence of the disease. The generally low prevalence of rheumatologic disease in the overall population means that many rheumatologic laboratory tests will only have a high positive predictive value when the tests are selected on the basis of clinical presentations that are highly suggestive of a rheumatologic disorder, which increases the pretest probability of disease.

Autoantibodies

A variety of basic assays are used to detect autoantibodies. In general, there has been a trend away from labor-intensive tests, such as agglutination assays and countercurrent immunoelectrophoresis, and toward assays amenable to automation, such as nephelometry, enzyme-linked immunoabsorbent assay (ELISA), and high throughput multiplex bead assays.

Indirect immunofluorescence assays identify autoantibodies reactive with antigens, in particular tissues or subcellular compartments (eg, nuclear antigens). Fixed tissue samples or cells are overlayed with patient sera and then washed. The presence of autoantibodies bound to the tissue sample is revealed by staining with a fluorescein-labeled antiserum against human immunoglobulin and observed by immunofluorescent microscopy. The antinuclear antibody (ANA) test has traditionally been done by this method.

ELISA uses an enzymatic readout to detect reactive antibodies. Sera to be tested for an autoantibody is incubated with the relevant autoantigen immobilized on a surface. After extensive washing, a detecting antibody (eg, an antiserum to human immunoglobulin) that has been conjugated to an enzyme is added. In the final step, substrate is added, and the product of the enzymatic reaction is measured. The amount of product reflects the quantity of detecting antibody bound to the autoantibody. There are several modifications of the basic ELISA, but all take advantage of the remarkable sensitivity imparted by the enzymatic readout.

Measurement of the Acute Phase Response

The acute phase response develops in the setting of a wide range of acute and chronic inflammatory conditions: severe bacterial, viral, or fungal infections; rheumatic and other inflammatory diseases; malignancy; and tissue injury or necrosis. These conditions elicit a response in which interleukin-6 and other cytokines trigger the synthesis by the liver of a variety of plasma proteins, including C-reactive protein (CRP) and fibrinogen. The detection and monitoring of this response can be clinically useful and is accomplished by measuring the level of CRP or by determining the erythrocyte sedimentation rate (ESR), which is influenced by the binding of protein, particularly fibrinogen, to erythrocytes. As a general rule, CRP is a more sensitive and dynamic reflection of the acute phase response than the ESR.

C-Reactive Protein

CRP likely has a physiologic role in the innate immune response to infection and may participate in the clearance of necrotic and apoptotic cells. The baseline levels of CRP increase with age and with body mass index. During the acute phase response, levels of CRP rapidly increase up to 1000-fold, reaching a peak at 48 hours. With resolution of the acute phase response, CRP declines with a relatively short half-life of 18 hours. Because there are a large number of disparate conditions that can induce CRP production, an elevated CRP level does not have diagnostic specificity. An elevated CRP level, however, can provide support for the presence of a clinically suspected inflammatory disease. Monitoring CRP levels can provide useful
nformation on the activity of diseases such as rheumatoid arthritis and giant cell arteritis.

Erythrocyte Sedimentation Rate

The ESR is determined by allowing anticoagulated blood to sediment for 1 hour in a glass tube. Normal ranges for the ESR are 0–10 mm/hour and 0–15 mm/hour for men and women, respectively, but the upper limit of normal increases with age and with obesity.

Because fibrinogen and certain other acute phase proteins (not including CRP) bind to erythrocytes and increase their sedimentation rate, the ESR is a measure of the acute phase response. The ESR responds slower (over days) to the onset and resolution of an acute phase response than does the level of CRP, and the dynamic range of the ESR is less than that of CRP. More so than CRP, the ESR can be influenced by factors other than the acute phase response.

Elevations of the ESR in the absence of clinically important inflammation also occur in pregnancy, anemia, kidney disease, obesity and hypercholesterolemia.

From Graff's Textbook of Routine Urinalysis and Body Fluids.
Chapter 11: Synovial Fluid

Table 11-2 Classification of Synovial Fluids

GROUP	CATEGORY	VISUAL	VISCOSITY	MUCIN CLOT	CELL COUNT	GLUCOSE BLOOD: SF	OTHER
	Normal	Colorless—straw Clear	High	Good	150 WBCs 25% neutrophils	0–10	
I	Noninflammatory	Yellow Slightly cloudy	Decreased	Fair	1,000 WBCs 30% neutrophils	0–10	
II	Inflammatory	White, gray, yellow Cloudy, turbid	Absent	Poor	100,000 WBCs 50% neutrophils	0–4	
III	Septic	White, gray, yellow, or green Cloudy, purulent	Absent	Poor	50,000–200,000 WBCs 90% neutrophils	20–100	Positive cultures
IV	Crystal induced	White Cloudy, turbid, opaque, milky	Absent	Poor	500–200,000 WBCs 90% neutrophils	0–80	Crystals present
V	Hemorrhagic	Sanguinous, xanthochromic, red, or brown Cloudy	Absent	Poor	50–10,000 WBCs 50% neutrophils	0–20	RBCs present

From: Approach to Arthritis, Chapter 35

Liyakat Ali Gauri, BR Ajay, Asim Khan, Nadeem Liyakat, Qadir Fatima

Table: Distinctive features of regional syndromes

	Periarticular pain	**Articular pain**	**Neurogenic pain**	**Referred pain**
Enquiry	Only a few selective movements are painful	All joint movements are painful	Dysaesthesic; aggravated by compression of nerve or movement of the spine	Unrelated to movement; 'visceral' timing; poorly localised, may be improved by rubbing
Pain on motion	Active> passive; selected movements	Active~passive; several directions	Normal; if root pain: pain on movement of the affected spine segment	Normal
Range of motion	Active movement may be limited by pain; passive movement: full	May be limited equally for both active and passive movement	Normal	Normal
Resisted active movement	Pain on specific manoeuvres	No effect	No effect	No effect
Local palpation	Tenderness over affected periarticular structure (away from joint line)	Possible tenderness over joint line, crepitus, capsular swelling, effusion, increased heat	Normal	Normal
Neurological examination	Normal	Normal	May be abnormal	Normal

Arthritis aproach