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Evaluation of the adult with polyarticular pain

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Literature review current through: Aug 2016. | **This topic last updated:** Jun 10, 2015.

INTRODUCTION — Polyarticular pain in an adult is encountered frequently in clinical practice. The causes include various self-limited illnesses and others that are potentially disabling and life-threatening. The history and physical examination generally provide the most useful diagnostic information; supporting or confirmatory data are obtained from laboratory and imaging studies or, more rarely, from tissue biopsy. A complete history and physical examination are appropriate for all patients presenting with polyarticular joint pain, since this symptom may be the initial manifestation of a systemic illness.

The list of causes of polyarticular pain is lengthy [1,2] and includes:

- Polyarthritis (table 1)
- Viral arthritis (table 2)
- Postinfectious or reactive arthritis
- Fibromyalgia
- Multiple sites of bursitis or tendinitis
- Soft tissue abnormalities
- Hypothyroidism
- Neuropathic pain
- Metabolic bone disease
- Depression

The diagnostic possibilities can be narrowed substantially depending upon whether or not arthritis is present (algorithm 1). Among those in whom there are symptoms and signs of synovitis, the further evaluation is limited to those diseases which cause polyarthritis. In the absence of clear-cut arthritis, the focus shifts to nonarticular sources of pain.

Despite the lengthy list of diseases that cause polyarthritis, many patients with inflammatory arthritis appear to have only one of a few possible disorders. Among over 200 patients with early synovitis (defined as less than one-year duration) evaluated at one academic center, 60 percent were diagnosed with either rheumatoid arthritis (RA) or a spondyloarthropathy at presentation or during the following year [3]. The prognosis is relatively good for those who remain unclassifiable, with nearly one-half of such patients undergoing remission and not requiring any pharmacologic therapy at follow-up at one year.

This topic review will address polyarticular joint pain in adults. Evaluations of the adult with monoarticular pain and of children with joint pain are presented separately. (See "Overview of monoarthritis in adults" and "Evaluation of the child with joint pain and/or swelling".)

HISTORY — Although the information obtained in the history is seldom sufficient to lead to a specific diagnosis, it allows substantial reduction in reasonable options. An acute presentation with migratory arthritis and fever, for example, is characteristic of rheumatic fever, disseminated gonococcal infection, and viral arthritis.

Musculoskeletal emergencies — The evaluation of polyarticular pain begins by ruling out potential musculoskeletal emergencies. These conditions generally have an acute presentation and are more commonly associated with monoarticular or oligoarticular pain. Some of these emergencies, however, can be seen in patients with polyarticular pain, and failure to make the correct diagnosis could lead to permanent harm to the patient. Important historical points include the following [2]:

- Hot or swollen joints may suggest infection (although bacterial infection more commonly presents with acute monoarthritis).
- Constitutional symptoms (fever, weight loss, malaise) are nonspecific but raise the suspicion of infection or sepsis.
- Joint pain greater than expected from physical findings may be a symptom of a compartment syndrome.

- Burning pain, numbness, or paresthesia may suggest an acute myelopathy, radiculopathy, or neuropathy.

Joint symptoms — It is important to obtain a detailed history of the character of the joint pain, including pain quality, time of onset, exacerbating or remitting factors, and duration.

The quality of the pain may be useful in distinguishing musculoskeletal from neurologic causes. The latter is suggested when pain is "burning" or is accompanied by numbness or paresthesias. Neuropathic pain is also likely to be constant, to be intensified at night, and to be unrelated to motion. However, an individual patient may experience more than one type of pain. As an example, patients with rheumatoid arthritis (RA) frequently have neuropathic pain due to carpal tunnel syndrome.

The two main categories of arthritis, inflammatory and noninflammatory, can often be distinguished based upon the character and distribution of joint pain:

- With inflammatory arthritis, symptoms tend to worsen with immobility; this accounts for the typical morning stiffness and "gelling" that typically accompanies inflammatory arthritis.
- In contrast, the pain of osteoarthritis (OA), the most common type of noninflammatory arthritis, is usually aggravated by motion and weightbearing and is relieved by rest.
- The joint involvement in RA is usually symmetrical, whereas asymmetry is frequent in OA, especially in the large joints. Problems such as bursitis, tendinitis, or sprains and strains are also asymmetrical in most cases.

The duration of symptoms may also be helpful. Synovitis that has been present for less than six weeks could represent a viral arthritis or systemic rheumatic disease, whereas a longer duration would increase the likelihood of the latter. The ability to accurately classify patients with early inflammatory arthritis is difficult. In one study of 211 patients with recent-onset synovitis, 36 percent could not be classified and were designated as having "undifferentiated arthropathy" after follow-up of 33 weeks [4]. (See "Specific viruses that cause arthritis".)

Associated symptoms — The presence of extraarticular symptoms may help to narrow the differential diagnosis. Weakness suggests a neurologic or myopathic disorder. On the other hand, signs and symptoms of multisystem involvement (such as fatigue, rash, adenopathy, alopecia, oral and nasal ulcers, pleuritic chest pain, Raynaud phenomenon, or dry eyes and mouth) are common in patients with systemic rheumatic diseases. Fever, night sweats, and weight loss may also suggest systemic illness.

Other clues from the history — The remainder of the history should focus on the usual areas, including past medical history, family history, social history, and system review. Particular attention should be paid to the following:

- Functional capacity – This includes assessing the patient's ability to perform usual activities of daily living. Changes in functional status may lead to depression, anxiety, and loss of independence.
- History of joint injury – A past medical history of previous trauma, fracture, or surgical procedures on symptomatic joints may help identify the cause of pain.
- Risk factors for or a history of infection – For example, exposure to or past infection with viral hepatitis may suggest the diagnosis of viral arthralgia. Exposure to ticks or young children may suggest Lyme disease or parvovirus infection, respectively.
- A complete medication list – A review of medications may lead to a specific diagnosis, such as drug-induced lupus, or may alter treatment choices.
- Psychologic state and social support system – The more chronic conditions can greatly affect the life of the patient and his or her family.

PHYSICAL SIGNS — After a complete history, the physical examination is used to further narrow the differential diagnosis. As an example, acute lower-extremity pain may have many causes; however, septic arthritis, crystal-induced arthritis, or fracture should be suspected when the pain results in inability to bear weight, or is associated with soft tissue swelling and other signs of inflammation extending far above or below the involved joint.

Joint examination — An important objective of the physical examination is to establish the presence or absence of synovitis [2]. Detecting synovitis increases the likelihood of an inflammatory arthritis or systemic rheumatic diseases. The hallmarks of synovitis include:

- Soft tissue swelling
- Warmth over a joint

- Joint effusion
- Loss of motion

Reduced active range of motion with preserved passive range of motion suggests soft tissue disorders such as bursitis, tendinitis, or muscle injury. If both active and passive ranges of motion are decreased, soft tissue contracture, inflammatory or noninflammatory joint disease, or a structural abnormality of the joint should be considered [2].

Joint examination is also helpful to confirm the absence of synovitis or the presence of bony enlargement or crepitus, as is typical of osteoarthritis (OA).

General examination — Findings on general examination may point to a systemic condition. These findings include lymphadenopathy, parotid enlargement, oral ulcerations, heart murmurs, pericardial or pleural friction rubs, or fine inspiratory rales due to interstitial lung disease.

Fever suggests a subset of infectious and rheumatic illnesses including [1]:

- Infectious arthritis
- Postinfectious or reactive arthritis (post-enteric infection, rheumatic fever)
- Systemic rheumatic disease, including Still's disease, vasculitis, or systemic lupus erythematosus (SLE)
- Crystal-induced arthritis (gout and pseudogout)
- Other diseases such as cancer, sarcoidosis, and mucocutaneous disorders

Additional findings may suggest a specific disease process. Examples of such findings include:

- The presence of subcutaneous nodules may be due to rheumatoid nodules or tophi.
- Skin lesions may suggest that the joint symptoms are due to psoriatic arthritis, SLE, viral infection, or Still's disease.
- Eye disease, including keratoconjunctivitis sicca, uveitis, conjunctivitis, and episcleritis, is also a feature of certain rheumatic illnesses.
- Concomitant axial pain or stiffness suggests the possibility of axial spondyloarthritis or another seronegative spondyloarthritis. As a result, spinal tenderness, deformity, and range of motion should always be ascertained in patients with polyarticular joint pain.

In addition, soft tissue tender points characteristic of fibromyalgia are particularly important to identify in patients who have no objective abnormalities in the joints (see "Clinical manifestations and diagnosis of fibromyalgia in adults"). However, joint tenderness may occur in some fibromyalgia patients, and patients with various types of polyarthritis, including rheumatoid arthritis (RA), SLE, and Lyme disease, may have superimposed fibromyalgia.

LABORATORY STUDIES — Laboratory studies are not always necessary to make a diagnosis and, in fact, can be misleading. As an example, some patients with osteoarthritis (OA) may have abnormal results that actually reflect other unrelated conditions. In addition, in some patients with arthralgias and myalgias without physical findings, managing symptoms and carefully following the patient over several weeks may be more prudent than an initial battery of tests. Laboratory testing is also unnecessary when a mechanical or extraarticular problem has been identified [2].

When the initial history and physical exam do not yield a diagnosis, however, some diagnostic testing may be indicated. Standard hematologic tests, urinalysis, and biochemical tests (renal and liver function) may help to identify patients with systemic illnesses. Other more specialized tests are discussed below.

Erythrocyte sedimentation rate — Nonspecific indicators of inflammation, such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are helpful in distinguishing between inflammatory and noninflammatory conditions. However, these tests are never diagnostic and may be abnormal in a vast array of infectious, malignant, rheumatic, and other diseases [5]. The CRP is sometimes a more reliable indicator of the acute phase response than the ESR [6], as the latter may be influenced by abnormal red blood cell morphology and a host of other factors [5].

Furthermore, there are numerous examples of the ESR yielding results that are not consistent with the actual rheumatologic process:

- Some patients with an inflammatory rheumatic disease have a normal ESR. As an example, in one series of 9,135 patients with active rheumatoid arthritis (RA), the ESR was normal in 71 percent [7].
- In noninflammatory arthritis, the ESR may be elevated because of another problem, such as renal failure, diabetes, hyperlipoproteinemia, dysproteinemia, or occult malignancy.

- The ESR may increase with age in the general population [8]. This phenomenon may be the basis for apparent ESR elevations in some OA patients.

Despite these limitations, the ESR may provide confirmatory information when a certain diagnosis is favored based upon the history and physical findings. In an older patient with aching and stiffness in the hip and shoulder girdle areas, for example, the post-test probability of polymyalgia rheumatica increases if the ESR is markedly elevated. However, a normal ESR does not preclude the diagnosis.

Antibody tests — Antibody tests can identify exposure to potential pathogens (group A streptococcus, viruses such as parvovirus or hepatitis B and C, *Borrelia burgdorferi*) (see "Specific viruses that cause arthritis"). In addition, certain autoantibodies are associated with a limited group of illnesses and may add diagnostic specificity to a clinical suspicion of rheumatic disease (such as anti-native DNA or anti-Sm in systemic lupus erythematosus [SLE]) (see "Antibodies to double-stranded (ds)DNA, Sm, and U1 RNP"). These antibody tests should not be ordered routinely but should be reserved for cases in which there is a reasonable clinical suspicion [9] (see below). The indiscriminate use of panels of these tests will result in a high frequency of false-positive results and in additional expensive and unnecessary testing [9-11].

Antinuclear antibody — The antinuclear antibody (ANA) test has high sensitivity but low specificity for SLE. Therefore, unless another cause is evident, it is generally appropriate to order an ANA in patients with polyarthritis since a negative test essentially rules out a diagnosis of SLE. A positive ANA may occur, however, in many rheumatic and non-rheumatic illnesses. Thus, a patient with few or no clinical features of SLE is unlikely to have the disease, even in the presence of a positive ANA. (See "Measurement and clinical significance of antinuclear antibodies".)

Additional information may help clarify the meaning of a positive ANA. The higher the ANA titer, the more likely that the patient has either SLE or another ANA-associated disease [2]. Additional serologic tests, such as anti-double-stranded (ds)DNA antibodies, may be diagnostic or at least may further limit the differential diagnosis.

Rheumatoid factor — Rheumatoid factor should be ordered when RA is suspected due to signs or symptoms of inflammatory arthritis; however, the test has limited diagnostic value [12]. Approximately one-third of patients with RA remain seronegative throughout their course [12]. Furthermore, patients with other inflammatory or infectious diseases (such as SLE, infective endocarditis, vasculitis, viral infection) may have a positive test (table 3). High rheumatoid factor titers have a better predictive value for the diagnosis of RA and may also predict poor outcomes. (See "Origin and utility of measurement of rheumatoid factors".)

Antibodies to citrullinated peptides — Anti-citrullinated peptide/protein antibodies (ACPA) are frequently found in patients with RA. ACPA, detected by anti-cyclic citrullinated peptide (anti-CCP) antibody testing, are more specific than rheumatoid factor for diagnosing RA and may predict erosive disease more effectively [13,14]. (See "Biologic markers in the diagnosis and assessment of rheumatoid arthritis", section on 'Anti-citrullinated peptide antibodies'.)

Serum uric acid concentration — Serum uric acid levels are usually elevated in gout, but, since asymptomatic hyperuricemia has a high prevalence in the general population, the finding of hyperuricemia has little diagnostic value. In addition, normal uric acid levels are fairly common during an attack of gout, including in patients with polyarticular involvement [15,16], although the finding of a uric acid level below the lower limit of the normal reference range would make the diagnosis of gout much less likely.

Synovial fluid analysis — Synovial fluid analysis may be diagnostic in patients with bacterial infections or crystal-induced synovitis. Synovial fluid analysis is also valuable to permit classification into an inflammatory or noninflammatory category, to identify hemarthrosis, and to identify crystals and infectious organisms. Patients with established rheumatic disease present a particular challenge as it may be difficult to distinguish a flare of the underlying disease from a new, concomitant disorder, including infectious arthritis. While the American College of Rheumatology (ACR) clinical guidelines suggest that synovial fluid analysis be performed in the febrile patient with an acute flare of established arthritis [2], such testing can be recommended for any patient, with or without prior rheumatic disease, when the diagnosis is uncertain after history, physical examination, and standard laboratory tests. This is especially important when crystal-induced arthritis or septic arthritis are suspected. (See "Joint aspiration or injection in adults: Technique and indications".)

The white cell count, differential count, cultures, Gram stain, and polarized light microscopy are the most valuable studies [2,17]. Noninflammatory fluids generally have fewer than 2000 white blood cells/mm^3, with fewer than 75 percent polymorphonuclear leukocytes (table 4) [17]. The ACR guidelines suggest that unexplained inflammatory fluid, particularly in a febrile patient, should be assumed to be infected until proven otherwise. (See "Synovial fluid analysis".)

IMAGING STUDIES — Imaging studies are expensive and are not required routinely in the evaluation of polyarticular pain. Even when useful, it is seldom necessary to obtain radiographs of all involved joints; those joints with the highest yield in the differential diagnosis should be chosen. As an example, if RA is the suspected diagnosis, erosions are best visualized in the wrist, hand, and foot.

In acute conditions, radiographs usually lack diagnostic specificity and are generally not helpful for patients with new onset of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), gout, tendinitis, or bursitis. In several acute settings, however, plain films may be useful. Chondrocalcinosis, for example, may be seen in calcium pyrophosphate deposition disease (see "Clinical manifestations and diagnosis of calcium pyrophosphate crystal deposition (CPPD) disease"). On the other hand, abnormalities of the sacroiliac (SI) joints are the earliest radiographic finding in ankylosing spondylitis and serve to point toward seronegative spondyloarthropathy as the cause of peripheral polyarthritis. Magnetic resonance imaging (MRI) is more sensitive than plain film radiography in detecting early SI joint abnormalities. (See "Diagnosis and differential diagnosis of ankylosing spondylitis and non-radiographic axial spondyloarthritis in adults".)

Plain radiographs may also be helpful in the diagnosis of the following chronic conditions:

- In OA, plain films can be used not only to confirm the diagnosis but also to assess the severity. Radiographs can, however, be normal in OA, and the finding of radiographic OA may not be related to the patient's symptoms [2].
- In RA, marginal erosions in the joint can be diagnostic. MRI and ultrasound may be able to detect erosions before plain radiographs [18].
- Chronic gout may also cause joint erosions, but these often have an "overhanging edge" suggestive of reparative changes that distinguishes them from erosions due to RA [2]. Ultrasound may provide more specific information than conventional radiographs for the diagnosis of gout [19].

Radionuclide scans and other imaging procedures are occasionally useful in identifying involvement of both relatively inaccessible joints (eg, hip, SI) and bone (eg, malignancy, infection, Paget disease).

TISSUE BIOPSY — In some instances, the correct diagnosis in a patient with polyarticular pain will depend upon a tissue biopsy. As an example, synovial biopsy may be useful in the diagnosis of tuberculosis, fungal infection, and sarcoidosis. Biopsy of other tissues may help establish the presence of rheumatoid nodules, Whipple's disease, vasculitis, and hemochromatosis.

DISEASE COURSE — Although it may not be possible to make a definitive diagnosis at the time of a patient's initial presentation with polyarticular pain, some progress has been made in predicting the disease course for those with definite polyarthritis of recent onset. A combination of clinical, laboratory, and imaging data can help to differentiate patients likely to have self-limited disease from those likely to have persistent arthritis. Prediction models based upon patients with early arthritis have identified a number of features associated with persistent and/or erosive disease, including [20-23]:

- Duration of symptoms prior to presentation
- Older age
- Male gender
- High BMI
- Duration of morning stiffness
- Number of tender or swollen joints
- Involvement of lower extremities
- Elevated acute phase reactants
- Rheumatoid factor
- Anti-cyclic citrullinated peptide antibody
- Erosive change on baseline radiograph
- Human leukocyte antigen (HLA)-DRB1 shared epitope alleles

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient

education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Beyond the Basics topics (see "Patient education: Arthritis (Beyond the Basics)")

SUMMARY — When the history and physical examination are used in concert with selected sequential laboratory and imaging studies, the cause of polyarticular joint pain can be identified in most cases. The American College of Rheumatology (ACR) guidelines make the following general recommendations after completion of a thorough history and physical examination (algorithm 1) [2]:

- In the presence of synovitis and symptoms greater than six weeks in duration, consider rheumatoid arthritis (RA) and other systemic rheumatic diseases (table 1). A complete blood count, erythrocyte sedimentation rate (ESR), rheumatoid factor, anti-cyclic citrullinated peptide (anti-CCP), antinuclear antibody (ANA), plasma creatinine concentration, and urinalysis should be obtained. Joint aspiration should be considered if an effusion is present and if the diagnosis is uncertain, especially if septic or crystal-induced arthritis is suspected.
- In the presence of synovitis and symptoms less than six weeks in duration, a complete blood count, measures of liver function tests, and, in some cases, serologic testing for hepatitis B and C and parvovirus may be helpful (table 2).
- In the absence of synovitis, the physical examination finding of tender points suggests fibromyalgia or multiple sites of bursitis or tendinitis; further diagnostic testing is not needed. (See "Clinical manifestations and diagnosis of fibromyalgia in adults" and "Bursitis: An overview of clinical manifestations, diagnosis, and management".)
- In the absence of synovitis and tender points, consider the remainder of the differential diagnosis (algorithm 1) and consider liver function tests, hepatitis B and C serology, radiographs, and serum levels of thyrotropin (TSH), calcium, albumin, and alkaline phosphatase.

In some patients presenting with polyarticular pain, the differential may be reduced to two or three reasonable possibilities. Close follow-up may soon reveal the correct diagnosis.

ACKNOWLEDGMENT — The editorial staff at UpToDate would like to acknowledge Robert Pinals, MD, who contributed to an earlier version of this topic review.

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Topic 1821 Version 14.0

GRAPHICS

Major causes of inflammatory polyarthritis

Infectious arthritis
Bacterial
Lyme disease
Bacterial endocarditis
Viral
Other infections
Postinfectious (reactive) arthritis
Rheumatic fever
Reactive arthritis
Enteric infection
Other seronegative spondyloarthritides
Ankylosing spondylitis
Psoriatic arthritis
Inflammatory bowel disease
Rheumatoid arthritis
Inflammatory osteoarthritis

Crystal-induced arthritis
Systemic rheumatic illnesses
Systemic lupus erythematosus
Systemic vasculitis
Systemic sclerosis
Polymyositis/dermatomyositis
Still's disease
Behçet's disease
Relapsing polychondritis
Autoinflammatory disorders
Other systemic illnesses
Sarcoidosis
Palindromic rheumatism
Familial Mediterranean fever
Malignancy
Hyperlipoproteinemias

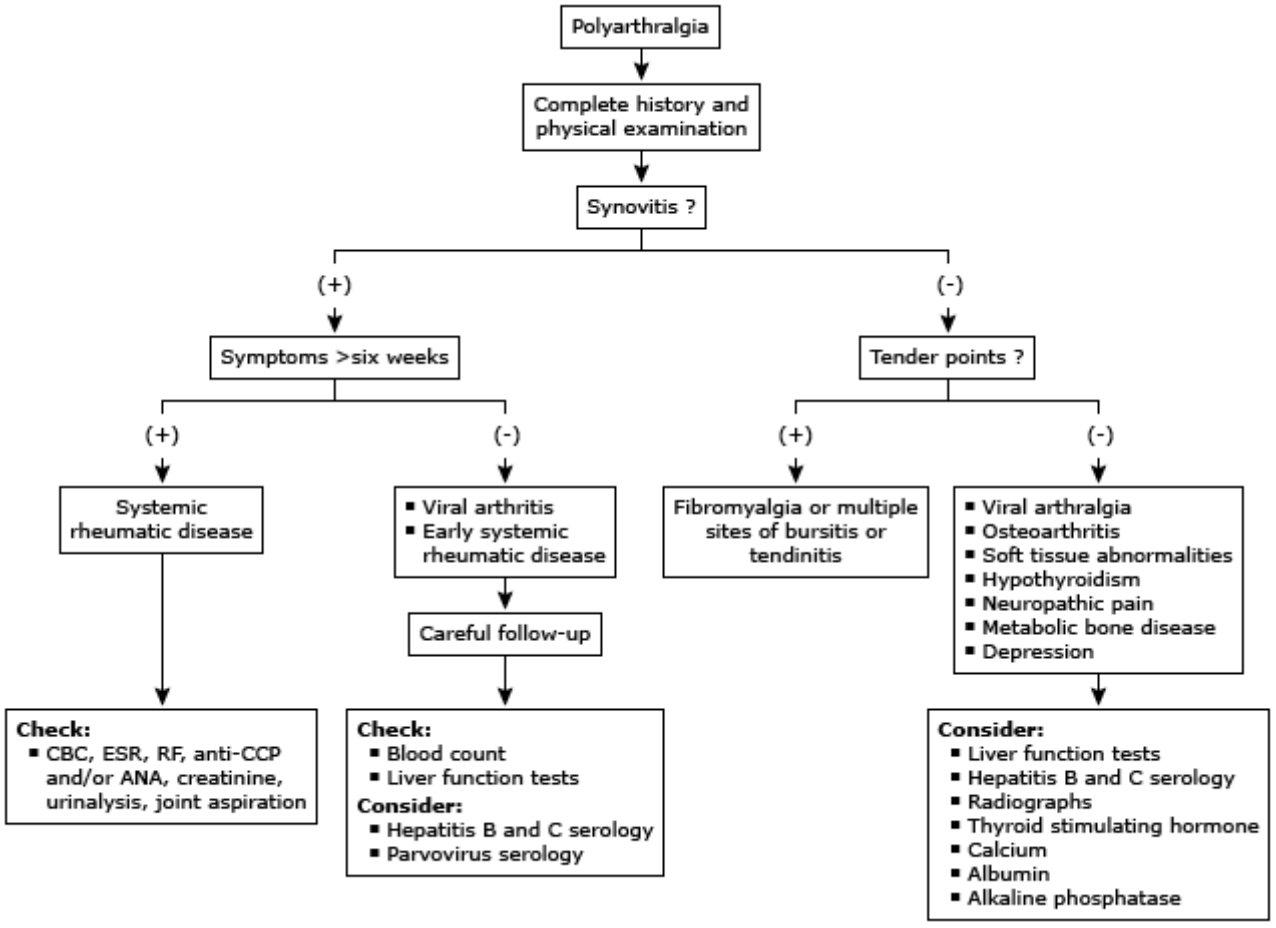
Graphic 74266 Version 4.0

Viruses that cause arthralgia

Commonly seen
Hepatitis B and C
Rubella and vaccine
Parvovirus
Alphaviruses
Dengue virus
Occasionally seen
Epstein Barr virus
Human immunodeficiency virus
Mumps
Hepatitis A
Coxsackie virus
Echovirus
Adenovirus
Varicella-zoster
Herpes simplex
Cytomegalovirus

Graphic 73403 Version 5.0

Evaluation of polyarthritis or polyarthralgia



An initial approach to the patient with polyarticular joint symptoms.

CCP: citrulline containing peptide; CBC: complete blood cell count; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor; ANA: antinuclear antibodies.

Adapted from American College of Rheumatology Ad Hoc Committee on Clinical Guidelines, Arthritis Rheum 1996; 39:1.

Graphic 79481 Version 3.0

The major nonrheumatic diseases associated with rheumatoid factor (RF)-positivity

Condition	Frequency of RF, percent
Aging (>age 60)	5 to 25
Infection	
Bacterial endocarditis*	25 to 50
Hepatitis B or hepatitis C*	20 to 75
Tuberculosis	8
Syphilis*	Up to 13
Parasitic diseases	20 to 90
Leprosy*	5 to 58
Other viral infection*	15 to 65
Pulmonary disease	
Sarcoidosis*	3 to 33
Interstitial pulmonary fibrosis	10 to 50
Silicosis	30 to 50
Asbestosis	30
Miscellaneous diseases	
Primary biliary cholangitis*	45 to 70
Malignancy*	5 to 25
After multiple immunizations	10 to 15

* Refers to disorders that may cause symptoms suggestive of rheumatoid arthritis. The best-documented examples of viral infection (in addition to hepatitis B and C) are rubella, mumps, influenza, and HIV. Chagas' disease, Leishmaniasis, onchocerciasis, and schistosomiasis are major parasitic diseases. B cell neoplasms are the most common malignancies.

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Graphic 74945 Version 8.0

Categories of synovial fluid based upon clinical and laboratory findings

Measure	Normal	Noninflammatory	Inflammatory	Septic	Hemorrha
Volume, mL (knee)	<3.5	Often >3.5	Often >3.5	Often >3.5	Usually >3.5
Clarity	Transparent	Transparent	Translucent-opaque	Opaque	Bloody
Color	Clear	Yellow	Yellow to opalescent	Yellow to green	Red
Viscosity	High	High	Low	Variable	Variable
White blood cell, per mm^3	<200	0 to 2000	2000 to 100,000	15,000 to >100,000*	200 to 2000
Polymorphonuclear leukocytes, percent	<25	<25	≥50	≥75	50 to 75
Culture	Negative	Negative	Negative	Often positive	Negative

* Lower part of range with infections caused by partially treated or low virulence organisms.

Graphic 76506 Version 5.0