

RHEUMATOID ARTHRITIS

OBJECTIVES

At the conclusion of this course, the learner will be able to:

1. List several types of arthritis.
2. Briefly describe osteoarthritis and gout.
3. Detail rheumatoid arthritis in terms of its prevalence, incidence, pathophysiology, signs and symptoms, diagnosis, and treatment, including pharmacological interventions and the latest research about the cardiovascular side effects of the COX-2 inhibitors and the effect of this research on the withdrawal some medications from the market.
4. Describe some rheumatoid arthritis resources and associations and the services that they provide.

INTRODUCTION

Arthritis is an inflammatory disease of the bone joints that is marked with a limitation of movement, swelling and pain. It can be caused by an infection in the joint, a buildup of uric acid or simply with the degeneration of a joint or joints as an individual grows older and perhaps, genetics.

Arthritis is the number one chronic disorder that leads to disability in our country among people 15 years of age and older. In 2005, it was estimated that 66 million people, that is, one out of every 3 adults in our nation is affected by arthritis. Additionally, it affects about 300,000 children and it is estimated that it costs the United States in excess of \$86.2 billion every year. Women are more affected than males. (Arthritis Foundation, 2004)

TYPES OF ARTHRITIS

There are more than 100 different types of arthritis. Some of these types include the below.

- *Osteoarthritis*- is the most common form of arthritis. It is a degenerative joint disease in which the cartilage that covers the ends of bones in the joint deteriorates, causing pain and a loss of movement as a result of the bone rubbing against bone rather than cartilage.

- *Rheumatoid arthritis*- is one of the most disabling forms of arthritis. It affects primarily women. This form is an autoimmune disease where the joint lining becomes inflamed as a result of the person's immune system.
- *Gout*- primarily affects mostly men. This form of arthritis affects small joints, specifically the great toe. A defect in body chemistry, that is, a buildup of uric acid leads to gout. This form can be successfully controlled with dietary changes and medications.
- *Ankylosing spondylitis*- when the bones of the spine become inflamed they fuse together, thus leading to ankylosing spondylitis, which affects the spine.
- *Juvenile arthritis*- this term encompasses all types of arthritis that can occur among the pediatric population. Some of these types are ankylosing spondylitis, juvenile rheumatoid arthritis and juvenile lupus among other types.
- *Systemic lupus erythematosus (lupus)*- is serious systemic disorder that inflames and damages joints as well as other connective tissue throughout the entire body.
- *Scleroderma*- is a disease that attacks the body's connective tissue. It causes a hardening and thickening of the skin.
- *Fibromyalgia*- affects primarily women. It leads to widespread pain that affects muscles and their attachments to the bone. (Arthritis Foundation, 2004)
- *Septic arthritis*- develops when a bacteria such as streptococcus (pneumoniae), staphylococcus, group B streptococcus, Mycobacterium tuberculosis and candida albicans. It occurs most often among children less than 3 years of age and primarily affects the hip. The onset is generally quite rapid with a low-grade fever, severe joint pain and joint swelling.
- *Psoriatic arthritis*- can be mild affecting only a couple of joints or it can be more severe affecting the spine. Genetics may play a role in this form of arthritis. Generally, people with psoriasis have a greater incidence of arthritis than those without this skin disorder.
- *Fungal arthritis*- this rare form of arthritis is also referred to as mycotic arthritis. Fungi that lead to this form include blastomycosis, histoplasmosis, candidiasis, coccidioidomycosis, sporotrichosis, and cryptococcosis. The infection typically begins in the lungs and then progresses. The knees are most often

affected. Immunocompromised patients are at greatest risk.
(MDchoice, Inc., 2005)

OSTEOARTHRITIS, RHEUMATOID ARTHRITIS AND GOUT

Osteoarthritis, known as degenerative joint disease, is the most commonly seen form of arthritis among the elderly population. Osteoarthritis results from the wearing out or deterioration of the smooth cartilage lining of the joint. This loss of cartilage makes the joints rougher than they had been when the cartilage was in place. Although it can also affect the hands, degenerative osteoarthritis is most often seen in the knees, spine and hips- the weight bearing joints of the body. This form of arthritis cannot be cured but those that suffer from it rarely become bedridden or crippled as a result of it. Post menopausal osteoarthritis is the result of the depletion of hormonal estrogen after menopause. It is a variation of the larger diagnosis of osteoarthritis from other causes.

Rheumatoid arthritis also involves painful swelling of the joints but it is usually associated with the smaller, non weight bearing joints of the body. Also, it is not usually associated with old age onset, but instead, it primarily begins in the young adult from ages 30 to 50 from unknown causes. It can also develop in young child. This form of rheumatoid arthritis is referred to as Still's disease or juvenile rheumatoid arthritis. Unlike osteoarthritis, rheumatoid arthritis is associated with more profound physical deformities and crippling.

Gout is quite different from osteoarthritis and rheumatoid arthritis. Gout is a disease or disorder that occurs when the body cannot excrete the uric acid it produces because the body is overproducing it or the kidneys have a diminished ability to filter it out and excrete it. When uric acid builds up in the body the joints, as well as soft tissues, become affected by it. The buildup of uric acid in gout causes very painful attacks of arthritis and it is accompanied with a high concentration of uric acid in the bloodstream and the formation of uric acid crystals in the affected joints.

RHEUMATOID ARTHRITIS

Sadly, rheumatoid arthritis is a destructive and chronic inflammation of the joints that affects young adults and children, most commonly occurring in females. It is marked with symmetrical swelling in the smaller joints of the body such as the ankle, hand and wrist. The onset of the deforming and crippling disease can be sudden and unexpected

but most often it is somewhat gradual. This disorder is progressive and often without a hoped for remission despite treatment.

About 6.5 million people in the United States are affected with rheumatoid arthritis. Women are affected up to three times more than men. Although the onset can occur at any age, the onset is most frequent among those between 25 and 50 years of age.

Although the cause of this form of arthritis is largely unknown, there appears to be a genetic basis among the white race in that pentapeptide in the HLA-DR and locus of class II histocompatibility genes have been identified. (Langford & Thompson, 2000; Merck & Co., 2005)

Pathophysiology

This disease progresses from joint inflammation to edema and congestion in the joint's capsule and the synovial membrane. Later, granulation tissue develops and destroys the capsule and cartilage. This fibrous granulation leads to the deformity and immobilization of the affected joint(s). This degenerative process can also affect major bodily organs such as the kidneys, eyes, lungs and the heart. (Langford & Thompson, 2000; Merck & Co., 2005)

Signs and Symptoms

Some of the *early* signs may include:

- a low grade fever,
- malaise,
- fatigue,
- weight loss and
- anorexia.

The *middle stage* signs and symptoms are:

- tenderness in affected joints,
- joint pain and stiffness lasting 30 minutes or more after awakening and/or after a period of immobility,
- bilateral, symmetrical involvement of the small joints of the hands and/or foot, the elbows, wrists and/or the ankles,
- afternoon malaise and fatigue,
- decreasing joint function,

- contractures, especially flexion contractures,
- deformities such as those of the fingers, and
- carpal tunnel syndrome,

The *late* signs and symptoms of rheumatoid arthritis are:

- tenderness in affected joints,
- joint pain,
- subcutaneous and visceral nodules,
- fever that is typically low grade,
- vasculitis leading to leg ulcers,
- dryness of the mucus membranes,
- pericarditis,
- splenomegaly,
- pneumonitis,
- episcleritis, and
- lymphadenopathy. (Langford & Thompson, 2000; Merck & Co., 2005)

Diagnosis

The American Rheumatoid Association (ARA) has established diagnostic criteria. They are as follows:

- 1) morning stiffness in and around joints lasting at least 1 hour before maximal improvement;
- 2) soft tissue swelling (arthritis) of 3 or more joint areas observed by a physician;
- 3) swelling (arthritis) of the proximal interphalangeal, metacarpophalangeal, or wrist joints;
- 4) symmetric swelling (arthritis);
- 5) rheumatoid nodules;
- 6) the presence of rheumatoid factor; and
- 7) radiographic erosions and/or periarticular osteopenia in hand and/or wrist joints.

Criteria 1 through 4 must have been present for at least 6 weeks. Rheumatoid arthritis is defined by the presence of 4 or more criteria, and no further qualifications (classic, definite, or probable) or list of exclusions are required." (Arnett FC, Edworthy SM, Bloch DA,

McShane DJ, Fries JF, Cooper NS, Healey LA, Kaplan SR, Liang MH, Luthra HS, et al., 1988)

In addition to a complete physical exam and medical history, the following diagnostic tests can be done to facilitate the diagnosis of rheumatoid arthritis.

- *Blood tests* may reveal elevated white blood cells (WBCs), hypochromic anemia, thrombocytosis, polyclonal hypergammaglobulinemia, the presence of γ -globulin antibodies (the "rheumatoid factors") which is positive in 95% of the cases, and an elevated erythrocyte sedimentation rate which occurs in 90% of the cases.
- *Synovial fluid* takes on an opaque color with decreased viscosity. The WBCs are between 3,000 and 50,000/ μ L.
- Initially the *x-ray* may only reveal soft tissue swelling. Later, marginal erosions and narrowing of the joint space's articular cartilage may be seen. (Langford & Thompson, 2000; Merck & Co., 2005)

Treatment

The goals of treatment for rheumatoid arthritis aim to control the inflammatory process and to relieve the troublesome and painful symptoms. Currently, there is no treatment available to repair any existing damage to the joints.

Treatment consists of one or more of the following modalities, as based on the unique needs of the patient.

- *Rest.* During the active painful stages of the disease, complete bed rest is necessary. Otherwise, regular rest and sleep is recommended.
- *Nutrition.* A regular, nutritious diet is necessary. Plant oil and/or fish oil supplements may helpful to some because they decrease the production of prostaglandins.
- *Exercise.* Range of motion and active exercise (ambulation and other exercises) should be done after the inflammation has subsided in order to prevent flexion contractions. Serial splinting, orthopedic interventions and intensive exercise are necessary once flexion contractures become established so prevention is vitally important. Passive range of motion should be done during episodes of acute inflammation to prevent contractures, again, within the limits of pain. These exercises preserve and restore

normal or near normal range of motion, muscle mass and muscular strength.

- *Physical therapy* is often indicated and ordered. Some of the treatments that are used include, cool, moist compresses; paraffin treatments and paraffin gloves to reduce the swelling and pain; and endurance and strength exercises. Ambulatory assistive devices, such as a walker, and splints may also be incorporated into the plan of care. Orthopedic shoes with special inserts, including bars, may help to increase mobility and decrease pain. Splints are also used to decrease inflammation and pain.
- *Occupational therapy* may also be incorporated in the plan of care to enable the patient to better perform the activities of daily living. Self help device, such as grasping tools, may be used.
- *Salicylates and nonsteroidal anti-inflammatory medications (NSAIDs)*. These medications serve as both anti-inflammatory agents and analgesics. Examples are aspirin, ibuprofen, diclofenac, fenoprofen, flurbiprofen, indomethacin, ketoprofen, meclofenamate, nabumetone, naproxen, oxaprofen, piroxicam, sulindac and tolmetin.

Some of the side effects and adverse drug reactions to the NSAIDs are GI irritation, cardiovascular complications, blood dyscrasias, nephrotoxicity (oliguria, azotemia, hematuria and dysuria), abdominal pain, cholestatic hepatitis, anorexia, dizziness and drowsiness. Antacids, H₂ blockers and sucralfate can be given between meals for mild GI side effects of aspirin. 100 to 200 µg bid to qid of misoprostol or a proton pump inhibitor can be used with aspirin and other NSAIDs to reduce the risk of GI bleeding among high risk patients.

The NSAIDS are contraindicated among patients with asthma, severe liver and/or renal disease, and hypersensitivity. They can be used with caution among the elderly and children, during lactation and pregnancy and for patients with GI, cardiac and/or bleeding disorders.

The patient's blood, renal and hepatic function must be monitored when NSAIDS are used. Baseline hearing and eye exams are also recommended so that changes can be identified. Toxicity may be signaled with tinnitus and/or blurred vision.

Current concerns about COX-2 inhibitors and NSAIDs are described below.

- *Gold compounds.* When the NSAIDs have not effectively reduced the pain and swelling after 2 to 4 months, gold or methotrexate is generally considered to relieve the pain, reduce the inflammation, decrease further bony erosion, and to modify the progression of the disease to a clinical remission.

Auranofin is the oral preparation of gold. Parenteral gold preparations include gold thioglucose and gold sodium thiomalate. These preparations are given IM every week, starting with 10 mg for the first week which is increased to 25 mg the next week and then increased to 50mg a week or more until the therapeutic effect is achieved. Prolonged maintenance therapy can sustain an improvement for several years, however, a relapse can be expected in 3 to 6 months if and when the medication is stopped,.

A baseline Hb level, platelet count, total and differential WBC count as well as a urinalysis should be done prior to the administration of gold, Thereafter, these diagnostic tests should be repeated every week for the first month and then two times a month.

Gold is contraindicated among patients who have significant renal disease, hepatic disease and/or blood dyscrasias.

Some of the toxic reactions to gold include stomatitis, albuminuria, pruritus, dermatitis, agranulocytosis, aplastic anemia, and thrombocytopenic purpura. Hepatitis, diarrhea, neuropathy and pneumoniti are less common side effects. Pruritis and eosinphilia (more than 5%) can be the precursor of a rash and a red flag of impending danger - a rash and dermatitis that can lead to deadly exfoliation. The gold should be held temporarily if these side effects occur and the patient should be given prednisone orally or a topical corticosteroid if the reaction is mild. Dimercaprol, a gold chelating medication, should be given for severe reactions.

Auranofin, which is an oral gold compound, can also be administered for rheumatoid arthritis although it is not as effective as parenteral gold compounds. A baseline Hb level, platelet count, total and differential WBC count and a urinalysis should also be done. Thereafter, these diagnostic tests should be minimally repeated every month. The side effects oral gold are GI symptoms and diarrhea. Mucocutaneous and renal side

effects are less than parenteral gold, however, they can still occur.

The usual dosage is 6 mg orally once a day or 3 mg bid. This dosage can be increased to 3 mg three times a day for 3 months, if, after 6 months, the 6 mg daily dosage does not achieve the desired therapeutic effect.

- *Oral penicillamine* produces many of the benefits that gold does, in fact, it is often used when gold fails to produce its desired effects or the patient is experiencing toxic side effects to the gold. However, penicillamine has to be discontinued more often than gold because of its side effects.

The side effects of this medication include proteinuria, bone marrow suppression, nephrosis, polymyositis, Goodpasture's syndrome, myasthenia gravis, a lupus type syndrome, a foul taste and a rash. The risk of side effects can be decreased if the dosage is started low and kept as low as possible as long as the desired effects have been realized.

The initial daily dosage of penicillamine is 250 mg. This dose should be continued for 1 to 3 months after which the dosage is 500 mg a day for another 1 to 3 months. The dosage can be increased to 750 mg a day if these recommended dosages do not produce and maintain the desired effect. Again, the lowest possible dose should be used.

- *Hydroxychloroquine* is another medication that can be used to treat rheumatoid arthritis. Its toxic side effects include myopathy, dermatitis and retinal degeneration, which is usually reversible. These side effects are generally not as pronounced as they can be with gold and penicillamine, nonetheless, irreversible retinal degeneration can occur. Visual field testing is done before the therapy begins and then every 6 months as long as the hydroxychloroquine is being taken.

The initial dosage of hydroxychloroquine 200 mg orally with breakfast and dinner (bid). If, after 6 to 9 months of treatment, the patient does not favorably respond to the medication, **this dosage should be decreased to 200 mg a day.**

- *Sulfasalazine*, a medication that has and continues to be used for colitis, is now being used for rheumatoid arthritis. The initial dosage of this enteric coated tablet is 500 mg a day with an increasing dosage of 500 mg every week until the dosage is 3 to 3 g per day. Serum chemistries and CBC must be monitored throughout the course of this therapy.

The toxic side effects of this medication are neutropenia, hemolysis, rash, gastric symptoms and hepatitis.

- *Corticosteroids* are, at least during the initial phases of therapy, highly effective. Unfortunately, their usefulness and benefits decrease over time and a rebound back to active disease occurs when the corticosteroid therapy is ceased. These medications should only be used when others fail because their long term side effects are quite serious.

Corticosteroids are contraindicated and/or used with caution among patients who have diabetes, untreated or untreatable infections, peptic ulcer, TB, fungal infections, amebiasis, hypersensitivity, seizures, glaucoma, CHF, hypertension, impaired renal function, myasthenia gravis and ulcerative colitis. Cautious use is also recommended with the elderly, children, lactation and pregnancy.

Some of the adverse reactions and side effects associated with corticosteroids include insomnia, euphoria, behavioral changes, peptic ulcer (GI irritation), sodium and fluid retention, hypokalemia, hyperglycemia, and carbohydrate intolerance (metabolic reactions). GI symptoms can be prevented when the dose is administered or taken with food or milk. Monitor blood sugar, potassium, weight, I & O, plasma cortisol levels, adrenal insufficiency and for any signs of infection. The patient must also be assessed for mood changes, particularly depression.

The recommended adult dosage of prednisone should not exceed 7.5 mg per day unless the patient has severe and systemic symptoms, such as pericarditis or vasculitis.

- *Intra-articular injections* of corticosteroid esters offer some the temporary relief of local synovitis. Among the preparations used are triamcinolone hexacetonide and prednisolone tertiary-butylacetate. Soluble 21-phosphate preparations of prednisolone and dexamethasone are not recommended. These medications have a very short term of actions
- *Immunosuppressive/cytotoxic agents* decrease inflammation and they also allow a reduced dosage of a corticosteroid. Some of the side effects include bone marrow suppression, liver disease, azathioprine, malignancy and pneumonitis.

The dosage of methotrexate is 2.5 to 20 mg in a single dose once weekly, starting at 7.5 mg a week with gradual increases as needed in order to achieve the desired dosage. Liver function must be monitored throughout the course of therapy. A liver biopsy should also be done when the liver function test is not

normal and the patient needs to continue the methotrexate. This medication is contraindicated among heavy drinkers and diabetics.

The initial dosage of azathioprine is 1 mg/kg/day or 50 to 100 mg per day that can be given bid or once a day. The dosage can be increased by 0.5 mg/kg/day after 6 to 8 weeks for every 4 week interval until a maximum of 2.5 mg/kg/day or when the therapeutic effect is achieved. Again, the lowest dosage possible should be used.

Cyclosporine is effective in treatment of rheumatoid arthritis and may be especially useful in combination with other slow-acting drugs. Dosages generally should not exceed 5 mg/kg/day to minimize toxic effects on blood pressure and renal function.

Etanercept, which is a tissue necrosis factor antagonist, is given with a dosage of 25 mg subcutaneously two times a week. This medication is reconstituted. Do not shake the bottle, swirl it or gently rotate it. Additionally, the injection sites must be rotated at least 1 inch away from a previous site.

Some of the side effects include dyspepsia, abdominal pain, rash, cough, an injection site reaction, headache, dizziness, pharyngitis, sinusitis, rhinitis, sepsis, and hypersensitivity. It should be used cautiously with pregnant women.

- *Surgery.* A synovectomy may be done to maintain joint function and to relieve some of the pain and inflammation; the excision of subluxations of the metatarsophalangeal joints or the neck may be done in the presence of severe pain; and an osteotomy may help to change the patient's weight bearing surfaces.

(Langford & Thompson, 2000; Merck & Co., 2005)

RECENT NEWS ABOUT COX-2 INHIBITORS AND NSAIDS

In 2005, research indicated that some popularly used and intensely marketed COX-2 inhibitors, used for arthritis, increased the risk of cardiovascular events. On April 7, 2004 the U.S. Food and Drug Administration (FDA) asked Pfizer Inc. to voluntarily take Bextra off the market and to place strong warnings on Celebrex as a result of this research. This advice news lead to the withdrawal of Bextra (valdecoxib) from the market and to the strong warning that Celebrex (celecoxib), too, is associated with cardiovascular complications. Vioxx (rofecoxib) had been previously taken off the market by Merck because of its cardiovascular disease risk as well.

The FDA has also asked the numerous manufacturers of over the counter NSAIDs, other than aspirin and acetaminophen, to include additional information about the potential for gastrointestinal and cardiovascular side effects and risks.

At the current time it appears that the cardiovascular side effects are dose dependent, therefore, decisions about whether or not to take available NSAIDs and Celebrex should be up to the patient and their physician. Additionally, if the decision is to use or continue to use one of these medication, the dosage should be the lowest possible to achieve the desired effect. (Arthritis Foundation, 2005)

REUMATOID ARTHRITIS RESOURCES AND ORGANIZATIONS

Arthritis Foundation

Contact Information:

Phone Number- (404) 872-7100
Address- Arthritis Foundation
P.O. Box 7669
Atlanta, GA 30357-0669

Web Page: <http://www.arthritis.org>

Mission and Services:

"The Arthritis Foundation efforts center on the three-fold mission of the organization: research, prevention and quality of life. The Arthritis Foundation currently provides nearly \$20 million in grants to nearly 300 researchers to help find a cure, prevention or better treatment for arthritis. The Arthritis Foundation's sponsorship of research for more than 50 years has resulted in major treatment advances for most arthritis diseases.

The Arthritis Foundation also provides a large number of community-based services nationwide to make life with arthritis easier, including:

- Self-help courses
- Water and land-based exercise classes
- Support groups
- Home study groups
- Instructional videotapes
- Public forums
- A wide variety of free educational brochures and booklets
- The national, bimonthly consumer magazine *Arthritis Today*

- Continuing education courses and publications for health professionals

Arthritis Foundation volunteers serve as advocates to local and national governments on behalf of the nearly 70 million Americans with arthritis and chronic joint symptoms. Their successes include the federal establishment of a national institute for arthritis among the National Institutes of Health, increased federal funding for arthritis research and state funding for arthritis medications. An Arthritis Foundation telephone and e-mail information service answers questions from more than 140,000 people per year." (Arthritis Foundation, 2004)

American College of Rheumatology

Contact Information:

Phone Number- (404) 633-3777

Address- American College of Rheumatology
1800 Century Place, Suite 250
Atlanta, GA 30345-4300

Web Page: <http://www.rheumatology.org>

Mission and Services:

"The American College of Rheumatology (ACR) is the professional organization of rheumatologists and associated health professionals who share a dedication to healing, preventing disability, and curing the more than 100 types of arthritis and related disabling and sometimes fatal disorders of the joints, muscles, and bones. Members include practicing physicians, research scientists, nurses, physical and occupational therapists, psychologists, and social workers.

The ACR provides professional education for its members through several venues. The Annual Scientific Meeting, held each fall, is the premier scientific meeting devoted to the rheumatic diseases. This meeting draws thousands of rheumatologists and arthritis health professionals from around the world. A winter rheumatology symposium, spring clinical meetings, and other topical conferences round out the ACR's educational offerings.

The ACR publishes *Arthritis & Rheumatism*, the premier scientific journal for research in the rheumatic diseases. *Arthritis Care and Research* is published by the Association of Rheumatology Health Professionals, a division of the ACR. This journal focuses on the health services and clinical aspects of rheumatology.

REF

Through the ACR Research and Education Foundation (REF), the ACR seeks to increase research in the rheumatic diseases while fostering the careers of young investigators. The ACR also works to increase federal funding for research in the rheumatic diseases. The College is also an advocate in the formulation of public policy relating to the care of people with arthritis and other rheumatic diseases.

ARHP

The Association of Rheumatology Health Professionals, a division of the American College of Rheumatology, is a professional membership society composed of non-physician health care professionals specializing in rheumatology, such as advanced practice nurses, nurses, occupational therapists, physical therapists, psychologists, social workers, epidemiologists, physician assistants, educators, clinicians, and researchers." (American College of Rheumatology, 2004)

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REFERENCES

American College of Rheumatology (2004). "About the American College of Rheumatology."
<http://www.rheumatology.org/about/index.asp?aud=mem>

Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, Healey LA, Kaplan SR, Liang MH, Luthra HS, et al.(1988). "The American Rheumatism Association 1987 Revised Criteria for the

Classification of Rheumatoid Arthritis". Arthritis Rheum. 1988
Mar;31(3):315-24
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3358796&dopt=Abstract

Arthritis Foundation (2004). "The Facts About Arthritis".
<http://www.arthritis.org/resources/gettingstarted/default.asp>

Arthritis Foundation (2005). "Straight Talk About Selective COX-2
Inhibitors and NSAIDs".
http://www.arthritis.org/conditions/NSAIDS/Straight_Talk_FAQ.asp

Langford, Rae W. and June D. Thompson (2000). Mosby's Handbook
of Diseases, 2nd Edition. Mosby Inc.

MDchoice, Inc. (2005). "Fungal Arthritis."
<http://www.drkoop.com/ency/93/000444.html>

MDchoice, Inc. (2005). "Non-gonococcal (septic) Bacterial Arthritis"
<http://www.drkoop.com/ency/93/000430.html>

MDchoice, Inc. (2005). "Psoritic Arthritis"
<http://www.drkoop.com/ency/93/000413.html>