



Reactive Arthritis (ReA) / Inflammatory Bowel Disease (IBD) Arthritis

Introduction: For as long as scientists have studied rheumatic disease, bacterial infections have been believed to trigger certain types of arthritis. The strongest support for this theory is seen in ReA and IBD arthritis. In ReA, bacterial infections of the intestines, genitals, and upper respiratory tract typically precede the onset of arthritis, while in arthritis related to IBD (*Crohn's disease, ulcerative colitis*), bacteria in the intestines is believed to invade the bloodstream and trigger arthritis.

In ReA, bacterial forms of diarrhea known as *dysentery*, sexually transmitted diseases such as *gonorrhea* or *chlamydia*, or the common “strep throat” have all been found to trigger joint inflammation. While well recognized, only a small minority of individuals contracting such illnesses develop ReA. When investigating these conditions, researchers have found no evidence for an active infection, but it appears that following the infection, the immune system recognizes something in the body that is similar to the bacteria and begins attacking it. It is also noteworthy that some patients with human immunodeficiency virus (HIV) infection are at risk for developing ReA.

IBD arthritis develops in up to 20% of those with Crohn's disease or ulcerative colitis. Joint involvement tends to correlate with the level of intestinal inflammation in ulcerative colitis, but for some reason not in Crohn's disease. Arthritis has also been described in association with other intestinal disorders such as *celiac disease, Whipple's disease*, and a recently described condition known as *collagenous colitis*.

All of these conditions fall into the category of illnesses known as *spondyloarthropathies* (spon-di-lo-ar-thráw-pa-thees), which include *ankylosing spondylitis (AS)* and *psoriatic arthritis (PsA)* (see related sections). These forms of arthritis tend to involve the spine and/or a small number of additional joints as well as the areas around joints where tendons and ligaments attach. All of these conditions are also associated to some extent with a gene known as HLA-B27.

Features of ReA: Typically, joint symptoms and swelling begins about 2 to 4 weeks after the triggering infection, although sometimes this infection is unrecognized. The joints most commonly affected are located below the waist (i.e. – knees, ankles, and feet), typically in an asymmetric pattern, with different joints being affected on each side. Less commonly, arthritis may occur in the hands, wrists, elbows, or shoulders, resembling rheumatoid arthritis (RA). When spinal symptoms are present, the *sacroiliac* joint,

located below the waist at the junction of the spine and pelvis, is typically involved. Tendinitis, particularly of the heel, may also be a dominant feature of ReA.

Inflammation in other parts of the body also commonly occurs. The most common manifestation is *conjunctivitis*, commonly referred to as “pink eye.” Redness, irritation, excessive tearing, and crusting of the eyelashes are typical symptoms. Less commonly, a deeper inflammation of the eye known as *iritis* may occur, which is usually more painful, results in more blurring of vision, and may result in vision loss if not treated. Inflammation of the genital region, including the urethra, penis, testicles, prostate gland, or cervix, may also occur in the absence of an active infection. Burning with urination, discharge from the urethra, and a scaly rash in the genital region are symptoms or findings that may be present. Mouth ulcers and a scaly rash on the palms or soles resembling psoriasis (known as *keratoderma blenorrhagicum*) are other commonly observed features of ReA.

The outcome of ReA is variable. While up to 1/3 of patients recover completely from their joint symptoms within 2 years, over 15% have recurring or chronic joint inflammation, and most of the remaining patients have continued joint pain in the absence of signs of inflammation. While less commonly seen than in RA, deforming changes of the joints may occur in ReA and become an ongoing source of pain and limitation in function.

Features of IBD Arthritis: The arthritis in patients with IBD occurs slightly more commonly in the spine than in other joints. As in those with ReA, the sacroiliac joint is the most frequent location that becomes inflamed. This joint may be involved on x-rays without the patient having symptoms, but lower back pain is frequently seen. Sacroiliac inflammation may begin either before or after the IBD is diagnosed, and bowel and lower back symptoms do not seem to correlate well or mirror each other.

In contrast to spinal arthritis, inflammation in other joints may correlate more closely with disease activity in the bowel. The most common joints involved include the knuckle and finger joints of the hands, the knees, the ankles, the elbows, and the shoulders. The upper limbs are involved more frequently in patients with IBD than in ReA, and a greater number of joints tend to become inflamed in these patients overall. While joint damage may occur, the inflammation does not typically produce destruction of the bone or joint. Because patients with IBD are at risk for joint infections as well as loss of blood supply to the bones (a complication known as *avascular necrosis*), an acutely swollen or painful joint should be investigated accordingly to rule out these problems.

Other complications of IBD occurring in other parts of the body include iritis, red nodules over the shins known as *erythema nodosum*, painful ulcerations of the skin known as *pyoderma gangrenosum*, sores in the mouth known as *aphthous ulcers*, and complications involving the liver. While all of these features have been well described in IBD patients, they all occur in less than 20% of these individuals and are less frequently seen than the arthritis described above.

Diagnosis: Both ReA and IBD arthritis are best diagnosed by carefully examining the joints for swelling, tenderness, limited motion, and other signs of inflammation. Arthritis fitting the patterns described above in a patient with a known recent infection or either known or suspected IBD should raise the suspicion for these disorders. For patients with abnormal skin findings, oral ulcers, eye inflammation, genital involvement, or other features common to either ReA or IBD, the diagnosis is further supported.

X-rays of involved joints, particularly the pelvis if sacroiliac disease is suspected, can provide additional evidence for these forms of arthritis. While x-rays are often normal initially and may remain normal throughout the course of the disease (particularly in IBD patients), joint films may demonstrate erosions or joint damage suggesting the need for more aggressive treatment or provide evidence for another explanation for the patient's joint symptoms.

Laboratory testing is of less value in the diagnosis of both ReA and IBD arthritis. While both conditions are usually associated with elevations in markers of inflammation, these findings are not specific and can be seen in a number of inflammatory conditions. The HLA-B27 gene can be measured, but this finding is not necessary to establish the diagnosis of either condition. While the presence of this gene may be helpful in supporting the diagnosis, a significant percentage of individuals with ReA and IBD arthritis lack this finding, and a negative test certainly does not rule out these forms of arthritis. Crohn's disease patients may exhibit antibodies to a yeast known as *Saccharomyces cerevisiae*, and ulcerative colitis patients may demonstrate *anti-neutrophil cytoplasmic antibodies* (ANCA), but once again these tests are frequently negative and do not need to be ordered in every patient.

The procedures required to diagnose IBD are beyond the scope of this discussion, but in general the diagnosis is made by *endoscopy*, a procedure where a lighted flexible tube is inserted through the rectum to look into the colon, or by barium studies done in the x-ray department. Other specialists, such as gastroenterologists or surgeons, are usually more involved in the diagnosis and treatment of the bowel component of the disease.

Therapy: As in many forms of arthritis, the treatment of ReA and IBD arthritis depends on the severity of the joint involvement and the potential for causing damage. In patients with IBD, many of the therapies that treat the bowel disease will also treat the joint disease, but we will focus our discussion on the treatment of IBD arthritis.

Non-steroidal anti-inflammatory drugs (NSAIDs) are useful in treating joint symptoms and may be sufficient in mild cases of either ReA or IBD arthritis. Examples of drugs in this category include ibuprofen, naproxen, and indomethacin, the latter being a preferred drug by many physicians for spondyloarthropathies. One problem with these agents in IBD is that they have the potential to aggravate gut inflammation in addition to placing patients at risk for damage to the lining of the stomach or ulcers. Newer NSAIDs that are "COX-2 selective" greatly reduce the risk of stomach damage and may also cause

less exacerbation of bowel inflammation, but this issue has not been addressed in well-designed studies as of yet.

Corticosteroids such as prednisone are effective for treating flares of IBD, but are less effective in treating associated arthritis or ReA. Injections of steroids directly into inflamed joints or soft tissues may, however, be effective in controlling acute symptoms accompanying arthritis or tendinitis flares.

Sulfasalazine (SSZ) is a well-established treatment for inflammatory bowel disease and is often helpful in treating joint inflammation in these patients as well as those with ReA who do not respond to NSAIDs. SSZ is slow-acting, taking effect in 2-3 months but often providing more consistent relief of symptoms than NSAIDs alone. The most common side effects are nausea, abdominal discomfort, and allergic reactions, but less common side effects, such as a drop in white blood cells and elevated liver enzymes, must be monitored while taking SSZ.

Antibiotics given to patients with ReA may reduce the severity or duration of arthritis, but they are more effective in doing so if targeting a specific infection. Both *tetracycline*-based antibiotics (doxycycline, e.g.) and *ciprofloxacin* have been shown to be beneficial when given over a period of three months in ReA triggered by genital infections and infectious diarrhea, respectively. While the studies yield somewhat mixed results, it is reasonable to treat a recognized triggering infection with appropriate antibiotic therapy.

Immune suppressing drugs such as *methotrexate (MTX)*, and *azathioprine (AZA)* may be useful in certain patients. There are few well-designed studies examining their specific effects on these types of arthritis, but since they are frequently used in treating IBD, many have made the observation that the joint symptoms also improve in these patients. The effectiveness of these agents in treating ReA is variable and may be greater in treating inflammatory arthritis in joints other than the spine. Before starting a patient with ReA on one of these medications, checking for exposure to HIV infection is prudent, as these patients are at greater risk for side effects. For more details regarding side effects of these drugs, see *Medications* section or the *Rheumatoid Arthritis* section, where they are covered in greater detail.

Tumor necrosis factor (TNF) antagonists have represented a major advance in the treatment of spondyloarthropathies and IBD. These drugs block the effects of TNF, a protein involved in inflammation in various parts of the body and have been used extensively in RA. While more studies have documented their benefit in treating patients with AS and PsA, they appear to be useful in treating ReA and IBD arthritis.

The drugs in this class that are currently in use include *etanercept* (trade name *Enbrel*), *infliximab* (trade name *Remicade*), and *adalimumab* (trade name *Humira*). Enbrel and Humira are administered by weekly or every two week injections, respectively, and Remicade is given by intravenous infusion every 8 weeks. While some evidence exists that each agent benefits patients with spondyloarthropathy in general, only Remicade seems to be beneficial for the bowel disease in patients with IBD.

Because TNF antagonists suppress the immune system, infections must be monitored while taking these therapies, and exposure to tuberculosis should be assessed by performing a skin test prior to starting on of these drugs. Injection site reactions, infusion reactions, worsening of heart function in patients with heart failure, and worsening of disease in patients with multiple sclerosis are additional potential side effects.

Given the above risks and the cost of these medications, TNF antagonists are not for every patient with ReA or IBD arthritis, but in those with severe or resistant disease, they represent a major advance in therapy. The physician and patient working together can best decide which combination of the above treatments is most appropriate for each individual with ReA or IBD-associated arthritis.