Reactive arthritis (ReA) is an inflammatory arthritis that arises after certain types of gastrointestinal or genitourinary infections, representing the classic interplay of host and environment. It belongs to the group of arthritides known as the spondyloarthropathies (SpAs). The classic syndrome is a triad of symptoms, including the urethra, conjunctiva, and synovium; however, the majority of patients do not present with this classic triad.1 In general, there are two forms of ReA, postvenereal (Chlamydia trachomatis [Ct]) and postdysentery (Salmonella, Shigella, Campylobacter, and Yersinia), but several other bacteria have been implicated as potential causes. Epidemiologic and prospective studies have been difficult to perform on ReA for several reasons. The disease description and definition has been clouded by over-reliance on the complete classic triad of symptoms and the many different terms and eponyms used to describe the condition. Diagnostic criteria for ReA exist, including that of the American College of Rheumatology2 and the Third International Workshop on Reactive Arthritis in 1995,3 but data in this review suggest new criteria are needed. Although the postvenereal and postdysentery forms of the condition are clinically indistinct, these subtypes could have different long-term prognoses or treatment implications.

HISTORY OF REACTIVE ARTHRITIS

Considering the many terms and eponyms used in the literature to describe this condition, a brief review of the history of ReA is warranted. Although many attribute the earliest description of ReA to Hans Reiter in 1916, when he described the clinical triad of arthritis, nongonococcal urethritis, and conjunctivitis in a German soldier after an episode of bloody diarrhea,4 the syndrome also was described by two French physicians (Fiessinger and Leroy) in that same year.5 Therefore, it often was dubbed...
Reiter’s syndrome, but Fiessinger-Leroy syndrome also has been used. The literature, however, clearly describes cases of ReA many years before Reiter or Fiessinger and Leroy. The earliest description of ReA may date back to approximately 460 BC, when Hippocrates wrote, “A youth does not suffer from gout until sexual intercourse.” Although the term, gout, was used indiscriminately at the time to describe inflammatory arthritis, it is difficult to know whether or not this is a true description of ReA because it is not implicitly stated that the condition was preceded by a venereal infection. It has been speculated that Christopher Columbus developed ReA in 1494, when he developed fever and severe arthritis of the lower extremities after a case of dysentery (possibly Shigella flexneri). In 1498, Columbus had a flare of his articular inflammation that was accompanied by eye “hemorrhage and pain”; and in 1504 he was “paralyzed and bedridden” because of “gout.” Several others have described similar cases in the literature, including Pierre van Forest’s description of a case of “secondary arthritis and urethritis” in 1507, Thomas Sydenham’s association of arthritis with diarrhea in 1686, Stoll’s documentation of arthritis following dysentery in 1776, and Yvan’s description of a French captain who developed “ophthalmia” and inflammatory arthritis primarily of the lower extremities 15 days after a venereal infection. There were two clear descriptions of the classic triad of ReA; the first was in 1818 by Brodie and his documentation of five patients who had urethritis, arthritis, and conjunctivitis, and the second was in 1897 with Launois’ distinction of septic from aseptic arthritis, the latter occasionally developing cutaneous lesions on the plantar surface of the feet (keratoderma blenorrhagicum). During this same time period in 1824, Cooper proposed the concept of the relationship between venereal infection and arthritis, particularly of the lower extremities.

Baron Yvan was the surgeon-in-ordinary to Napoleon I. His description more than 200 years ago of a patient who had probable ReA was as follows:

40 year old invalid captain with a weak constitution entered the infirmary…to be treated for a gonorrhea he had caught 15 days previously. On the 12th day, the patient was immediately affected with intense ophthalmia in both eyes. He was very sensitive to light and the engorgement of the conjunctiva was extreme…On the 21st the patient suffered pains in the right foot joint. The pain was accompanied by a slight tumefaction which grew day by day; the knee joint as well as the right arm and forearm became painful.

Sir Benjamin Brodie, an English physiologist and surgeon who pioneered research in joint disease, described five patients who had classic ReA in his treatise, Pathologic and Surgical Observations on the Diseases of the Joints. He recognized the similar “train of symptoms” that all five patients experienced and clearly noted the relapsing course in the few who developed chronic disease:

A gentleman, 45 years of age, in the middle of June 1817, became affected with…a purulent discharge from the urethra…On the 23d of June he first experienced some degree of pain in his feet…June 25th, the pain in his feet was more severe; the tunica conjunctivae of his eyes were much inflamed, with a profuse discharge of pus…On the 27th of June the left knee became painful…exceedingly distended…The inflammation in his eyes and urethra was somewhat abated.

This patient’s symptoms resolved nearly completely in December 1817, but then he developed exacerbations that were similar in nature, including “inflammation seated in the tunicks of the eye.” Brodie recognized that these recurrent symptoms were related to the initial episode; his treatment of choice was vinum colchici seminis (wine of the Colchicum seed).
In 1942, the symptoms of ReA again were recognized as a syndrome by two Harvard researchers (Bauer and Engelmann) and in their review of the literature they realized that Reiter had described this same syndrome in 1916, so they coined the term, Reiter’s syndrome. A more thorough search might have revealed that Reiter was only one in a long line of previous physicians who described this postinfectious arthritis. Hans Reiter, however, did take the notion of ReA having an infectious etiology one step further, when he surmised that this condition was caused specifically by a spirochete. His terminology for the condition was “spirochetosis arthritica.” This supposition is now understood to be incorrect. The term, Reiter’s syndrome, has been widely used, although in recent years its use has been in decline. During World War II, Hans Reiter authorized medical experiments on concentration camp prisoners. Because of this, some have correctly argued against the use of the Reiter eponym. Because Hans Reiter was not the first to describe the syndrome, because many clinicians are reluctant to diagnose this condition in those who do not display the complete triad of symptoms, thereby missing the majority of cases, and because ReA is a more descriptive term, the term ReA has become the appropriate terminology for this disease process regardless of whether or not the symptoms involve the three classic organ systems.

**EPIDEMIOLOGY**

The lack of a disease definition or specific diagnostic criteria for ReA makes epidemiologic studies problematic. An epidemiologic discussion of ReA not only should include the typical analyses of incidence and prevalence but also an analysis of attack rate, which is of equal importance. Because only a percentage of subjects exposed to the known causative organisms of ReA develop the disease, the attack rate refers to that percentage. The incidence, prevalence, and attack rate of ReA vary widely among different studies. The variability of genetic background, including different prevalence of human leukocyte antigen-B27 (HLA-B27) in the various communities studied, might be a partial explanation. Local environmental factors also play a role in the apparent variable attack rate of ReA. For example, infection with one of the causative organisms, *Yersinia enterocolitica*, is uncommon in the United States but reported more commonly in Europe. As a further complication, infections with the same organisms in the same community can vary over time. An example was the recent outbreak of *Salmonella* in 2008 that affected approximately 1500 people in the United States and Canada. It also is likely that different species from the same genus of the triggering bacteria vary in their arthritogenic propensity. *Salmonella Saint Paul* was responsible for this recent outbreak in the United States and Canada. Although this is a less common *Salmonella* species, it had not previously been implicated as a cause of ReA. Other *Salmonella* species (eg, *S typhimurium* and *S enteritidis*) are well-documented causes of ReA. Finally, it is possible that local differences in the microbes themselves and that increased recognition and improved treatment of the causative organisms also may affect the incidence, prevalence, and attack rate of ReA.

Bacteria that commonly cause ReA are *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, and Ct. Ct is the most common etiologic agent causing ReA in the United States. Despite the obvious difference of initial route of infection (ie, gastrointestinal versus genitourinary), another distinction exists. The postdysentery form of ReA is preceded by a symptomatic infection, and recent data suggest that the more severe the initial gastrointestinal infectio, the more likely ReA develops. An initial Ct infection, however, often is asymptomatic. Data described later suggest that many cases of postchlamydial ReA follow an asymptomatic infection. Several published
studies also indicate that Chlamydia pneumoniae (Cpn), a related respiratory pathogen, is another causative agent in ReA, albeit at a lower frequency.31–33

The postdysentery form of ReA affects men and women with the same frequency, whereas the postvenereal form occurs at a male-to-female ratio of 9:1. Adults are more likely to develop ReA than children.22,34 The attack rate of postdysentery ReA generally ranges from 1.5%35 to approximately 30%36 depending on the study and causative organism; however one recent self-reported questionnaire study suggested that as many as 63% of patients experience symptoms consistent with ReA after an acute Salmonella infection.37 ReA is believed to occur in approximately 5% of individuals who develop an acute Chlamydia infection.38

It is likely that clinicians are under-diagnosing ReA. This contention is borne out by looking, specifically, at postchlamydial ReA. New genital infections with Ct must be reported to the Centers for Disease Control and Prevention, and that institution has estimated that as many as 3 million new cases per year occur in the United States, with as many as 4 to 6 million cases active at any one time.39,40 As discussed previously, data indicate that approximately 5% of patients develop objective features consistent with ReA after a Ct infection.38 By using an attack rate of 5%, as many as 150,000 cases of acute Chlamydia-induced ReA would occur in the United States each year (3 million/0.05). This is a low estimate representing half or fewer of the total cases, because it does not include those cases that result from the postdysentery organisms. For comparison, the estimated annual incidence of rheumatoid arthritis (RA) in the United States is 44.6 per 100,000.41 If the population is approximately 281 million (2000 census figure), approximately 125,000 new cases of RA per year occur. A 2002 study in Sweden found the annual incidence of ReA higher than that of RA.42 Thus, ReA represents a considerable burden on the United States health care system and that of other nations, and its impact on those systems well may be significantly under-recognized.

Data suggest that the incidence of certain types of ReA, specifically Ct-induced43 and Yersinia-induced ReA,44 might be in decline. The reasons for this are not entirely clear, but they may relate to better prevention and treatment of the causative organisms. There also are data that suggest that the use of antibiotics that are active against Ct, when patients present for treatment of their venereal disease, reduces the risk for postvenereal ReA.45 Data also suggest, however, that other types (eg, ReA secondary to Campylobacter and Salmonella) are on the rise.44 It has been demonstrated that the use of proton pump inhibitors increases the risk for developing ReA after a Campylobacter or Salmonella infection.46

A final issue complicating epidemiologic studies of ReA is the variable disease course. Patients’ initial features of ReA can range from fulminant to mild. Also, a significant percentage of patients’ disease course remits spontaneously in weeks to a few months. Generally, if the ReA symptoms last longer than 6 months, then the disease is considered chronic. Patients who progress to chronic ReA can display varying disease symptoms and, in some, disease features can relapse and remit.

CLINICAL FEATURES

The clinical features of ReA are well described and generally congruent for the postvenereal and the postenteric forms. The acute and chronic symptoms can include articular, tendon, mucosal, cutaneous, ocular, and occasionally cardiac manifestations (Table 1) or systemic features (fever, malaise, and weight loss); the latter usually are confined to the acute stage. Symptoms typically start within 1 to 4 weeks of the
## Clinical manifestations of reactive arthritis

<table>
<thead>
<tr>
<th>Acute symptoms</th>
<th>Articular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most commonly present with oligoarthritis but also can present with polyarthritis or monoarthritis</td>
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<table>
<thead>
<tr>
<th>Articular</th>
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<tbody>
<tr>
<td>Axial</td>
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<tr>
<td>Frequently involved</td>
</tr>
<tr>
<td>Sacroiliac joints</td>
</tr>
<tr>
<td>Lumbar spine</td>
</tr>
<tr>
<td>Occasionally involved</td>
</tr>
<tr>
<td>Thoracic spine (usually seen in chronic ReA)</td>
</tr>
<tr>
<td>Cervical spine (usually seen in chronic ReA)</td>
</tr>
<tr>
<td>Cartilagenous joints (symphysis pubis; sternoclavicular and costosternal joints)</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Articular</th>
</tr>
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<tbody>
<tr>
<td>Peripheral</td>
</tr>
<tr>
<td>Frequently involved</td>
</tr>
<tr>
<td>Large joints of the lower extremities (especially knees)</td>
</tr>
<tr>
<td>Dactylitis (sausage digit)</td>
</tr>
<tr>
<td>Very specific for a spondyloarthropathy</td>
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<table>
<thead>
<tr>
<th>Enthesitis</th>
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<tbody>
<tr>
<td>Hallmark feature</td>
</tr>
<tr>
<td>Inflammation at the transitional zone where collagenous structures, such as tendons and ligaments insert into bone</td>
</tr>
<tr>
<td>Common sites: plantar fasciitis and Achilles tendonitis but any enthesis can be involved</td>
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<table>
<thead>
<tr>
<th>Mucosal</th>
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<tbody>
<tr>
<td>Oral ulcers (generally painless)</td>
</tr>
<tr>
<td>Sterile dysuria (occurs with both postvenereal and postdysentery forms)</td>
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<table>
<thead>
<tr>
<th>Cutaneous</th>
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<tbody>
<tr>
<td>Keratoderma blenorrhagicum</td>
</tr>
<tr>
<td>Pustular or plaque-like rash on the soles or palms</td>
</tr>
<tr>
<td>Grossly and histologically indistinguishable from pustular psoriasis</td>
</tr>
<tr>
<td>Also can involve nails (onycholysis, subungual keratosis, or nail pits), scalp, extremities</td>
</tr>
<tr>
<td>Circinate balanitis</td>
</tr>
<tr>
<td>Erythema or plaque-like lesions on the shaft or glans of penis</td>
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<table>
<thead>
<tr>
<th>Ocular</th>
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<tbody>
<tr>
<td>Conjunctivitis: typically during acute stages only</td>
</tr>
<tr>
<td>Anterior uveitis (iritis): often recurrent</td>
</tr>
<tr>
<td>Rarely described: scleritis, pars planitis, iridocyclitis, and others</td>
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<thead>
<tr>
<th>Cardiac</th>
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<tbody>
<tr>
<td>Pericarditis (uncommon)</td>
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<tr>
<td>Chronic symptoms (&gt;6 months)</td>
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</table>

<table>
<thead>
<tr>
<th>Cardiac</th>
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</thead>
<tbody>
<tr>
<td>Articular</td>
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<tr>
<td>Axial</td>
</tr>
<tr>
<td>Sacroiliac joints</td>
</tr>
<tr>
<td>Lumbar spine</td>
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<tr>
<td>Thoracic spine</td>
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</tbody>
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(continued on next page)
initial infection. As in the case of chlamydiae, however, the inciting infection could be asymptomatic; therefore, reliance on a symptomatic triggering infection results in underdiagnosis or misdiagnosis. Reports vary widely, but it generally is believed that approximately 30% to 50% of patients who develop ReA experience chronic symptoms. One study suggested the true figure might be as high as 63%.\(^\text{20}\) Patients who have chronic ReA often exhibit a relapsing disease course.

Enthesitis deserves special mention. Enthesitis is inflammation at the transitional zone in which collagenous structures, such as tendons and ligaments, insert into bone. This is a hallmark feature of any of the SpAs, including ReA. Common types of enthesitis in ReA are Achilles tendonitis and plantar fasciitis, but inflammation can occur at any enthesis. Sacroilitis, a major feature of all SpAs, represents a combination of synovitis and enthesitis.\(^\text{47}\) A recent report of more than 6000 cases of culture-confirmed infections with bacterial enteric pathogens revealed that enthesitis was the most common finding in those individuals who developed ReA, and arthritis was less frequent.\(^\text{27}\)

### TRIGGERING MICROBES

The triggering microbes of ReA are gram-negative bacteria with a lipopolysaccharide (LPS) component of their cell walls. All of these bacteria, or their bacterial products, have been demonstrated in the synovial tissue or fluid of patients who have ReA.

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This has been demonstrated in several studies involving many different laboratories. It is apparent that the entire bacteria or bacterial components traffic to the joints of patients who have ReA. Once these bacteria are in the synovium and other affected organs, their roles in the pathophysiology are less clear.

**Chlamydiae**

Ct is a common pathogen and believed the most common cause of ReA. Ct has been demonstrated in 50% of patients who have had a preceding symptomatic urogenital infection and who developed ReA. The routine presence of Ct has been demonstrated by polymerase chain reaction (PCR) in the synovial tissue of patients who have had ReA. These chlamydiae are viable, albeit in an aberrant state. These persistently infecting, viable chlamydiae have been demonstrated years after the initial infection. Similar PCR studies have demonstrated Cpn in the synovial tissue of patients who have had ReA, although it is detected less commonly. Ct and Cpn, however, occasionally have been demonstrated in the synovial tissue of patients who have had other types of arthritis or even asymptomatic individuals.

Data exist corroborating the notion that chlamydial-induced ReA is vastly underdiagnosed. The explanation for this likely is twofold: the triggering chlamydial infection often might be asymptomatic, and clinical triad is expressed incompletely in most patients. In one study, 78% of subjects who developed ReA features after Ct or nongonococcal infections had an asymptomatic initial infection. The term, undifferentiated SpAs (uSpAs), is used to designate patients who have clinical and radiographic features consistent with the SpAs but who do not fulfill the classification criteria for any of the established disease categories. Because ReA is a type of SpA and the majority of patients who have ReA do not present with the classic triad of symptoms, the contention that Ct could function etiologically to engender uSpA is reasonable. It has been argued that uSpA is a forme fruste of ReA.

A recent study analyzed the PCR positivity for chlamydiae in the synovial tissue of patients diagnosed with uSpA. These data demonstrated that the rate of PCR positivity from patients who had uSpA (62%) was significantly higher than that found in synovial tissue from subjects who had osteoarthritis (12%), suggesting that chlamydial infection may be etiologic for uSpA in many patients. Among subjects who had a PCR-positive synovial tissue assay for Ct, 88% had an asymptomatic initial infection; this mirrors the data previous discussed. These, in part, could explain the disconnect between the expected and observed number of diagnosed cases of ReA.

The different chlamydial species also could have an additive or synergistic effect in determining ReA attack rate or incidence. Given that Cpn is a common infection, previous exposure to Cpn could have an effect on a subsequent response to a Ct infection or vice versa. Reports have demonstrated that prior Cpn infection primes a Th1 T-cell response to Ct antigens.

**Salmonella**

*Salmonella* is a rod-shaped, motile bacterium widespread in animals and environmental sources. It is one of the most common enteric infections in the United States and is the most frequently studied enteric bacteria associated with ReA. Cases of ReA secondary to ReA seem to be on the rise. After salmonellosis, individuals of Caucasian descent may be more likely than those of Asian descent to develop ReA, and children may be less susceptible than adults. The attack rate of *Salmonella*-induced ReA has ranged between 6% and 30%. As with the other causative organisms, efforts have been made to detect *Salmonella* in synovial tissue or fluid. *Salmonella* bacterial degradation products have been detected in the synovial fluid.
from patients who have *Salmonella*-induced ReA, but no viable organisms have been detected.\(^5^4\)

There have been large outbreaks of *S. typhimurium* and *S. enteritidis* with rheumatologic follow-up of affected individuals. Regarding the outbreaks of *S. typhimurium*, these occurred in three different countries and the attack rate of ReA ranged from 6% to 15% with the HLA-B27 prevalence ranging from 17% to 50% of these individuals.\(^6^5\)–\(^6^8\) The attack rate of ReA ranged from 7% to 29% with four different outbreaks of *S. enteritidis* in four different countries.\(^3^6\),\(^6^9\),\(^7^0\) A HLA-B27 prevalence of 33% affected individuals was reported in one of these outbreaks.\(^7^0\) A large study in Denmark comparing the different enteric pathogens known to cause ReA suggested that *Salmonella* was the second most common triggering infection (behind *Campylobacter*) and the second most arthritogenic, after *Yersinia*.\(^2^5\) There also has been one outbreak of *S. bovismorbificans* that resulted in 12% of individuals developing ReA, of whom 45% were HLA-B27 positive.\(^7^1\)

**Shigella**

All four of the species of *Shigella* (*S. flexneri*, *S. dysenteriae*, *S. sonnei*, and *S. boydii*) can cause ReA. In 1944, *Shigella* was the first bacteria to be implicated directly as a cause of ReA.\(^7^2\) *Shigella*, however, is the least common of the gastrointestinal-inducing organisms that are associated with ReA in developed countries.\(^7^3\) This is in large part due to the rarity of this organism in these communities. Previous data suggested that *S. flexneri* and *S. dysenteriae* are the most common causes, and *S. sonnei* is a rare cause worldwide.\(^7^3\) A study in 2005 from Finland, however, revealed cases of ReA to *S. sonnei*, *S. flexneri*, and *S. dysenteriae*, with *S. sonnei* the most common cause.\(^7^4\) The overall attack rate of *Shigella*-induced ReA in this study was 7% and another 2% had other reactive musculoskeletal symptoms including enthesitis. Of the subjects who developed ReA, 36% were HLA-B27 positive.

*Shigella* is phylogenetically indistinguishable from *Escherichia coli*, sharing all but 175 of 3235 open reading frames,\(^7^3\) and recent reports have suggested that *E. coli* might be an infrequent cause of ReA.\(^2^5\)–\(^2^7\) Despite these similarities, they behave differently. *Shigella* is a motile organism with the ability to invade human enterocytes, lyse intracellular vacuoles to enter the cytoplasm, and move from cell to cell. *E. coli* can do none of these.\(^7^2\) These capabilities likely are critical to the propensity to cause ReA. Similar to *Ct* and *Cpn*, bacterial DNA from *Shigella* has been demonstrated in the synovial tissue of patients who have ReA. In contrast, there have been no studies to detect viable organisms, only bacterial fragments.\(^4^8\),\(^5^2\)

**Campylobacter**

*C. jejuni* infections are the leading cause of bacterial gastroenteritis reported in the United States.\(^7^5\) It is estimated that 2.1 to 2.4 million cases of human campylobacter infections occur in the United States each year. The arthritis that develops usually is an oligo- or polyarticular arthritis, and it tends to be mild.\(^7^6\) In contrasting to other types of ReA, inflammatory back pain is believed uncommon.\(^7^7\)

A study in Finland in 2002 of 870 patients who had *Campylobacter*-positive stool cultures found that 7% of these individuals developed ReA.\(^7^6\) The development of ReA was not associated with HLA-B27 in this study. Fourteen percent of affected individuals were HLA-B27 positive (similar to the background prevalence in Finland). The majority of cases were associated with *C. jejuni* but *C. coli* was another cause. Similar to patients who had *Salmonella* infection, children were far less likely to develop ReA after a *Campylobacter* infection. A recent systematic review suggested an attack
rate of 1% to 5% of ReA after a Campylobacter infection and no significant association with HLA-B27.77

Yersinia

There are three species in the genus Yersinia, but only Y enterocolitica and Y pseudotuberculosis cause gastroenteritis. Y enterocolitica and Y pseudotuberculosis have been associated with ReA. Although Yersinia infections are not as common as some of the other enteric pathogens, some data suggest that Yersinia is particularly arthritogenic. A follow-up study in Denmark suggests that it was the most likely to cause ReA, with an attack rate of 23%.25 In 1998, two different outbreaks of Y pseudotuberculosis were reported.78,79 One occurred in Finland (serotype O:3) and resulted in 12% of affected individuals developing ReA.78 The other occurred in Canada (serotype Ib) and 12% reported “joint pain” after their infection.79

As with the majority of the other known triggering microbes, two studies have attempted to localize Yersinia in the synovial tissue or fluid of affected individuals. Although both studies demonstrated that Yersinia does traffic to the joints,49,53 one suggested that these Yersiniae are metabolically active49 and the other demonstrated only bacterial degradation products.53

Other Possible Triggering Microbes

Many other organisms have been implicated as potential causes of ReA. These include Ureaplasma urealyticum, Helicobacter pylori, and various intestinal parasites. The majority of these are of single cases or small series. Because of the limited numbers, the pathophysiology is not well studied with these other organisms. Reports of ReA secondary to E coli,25–27 Clostridium difficile,80 and intravesicular bacille Calmette-Guérin81 have garnered recent recognition.

PATHOPHYSIOLOGY

Triggering Microbes Persist

The triggering microbes and their associated molecular biology in relation to arthritis, specifically ReA, are discussed elsewhere in this issue in the article by Gerard and colleagues. A brief review is warranted. PCR technology occasionally has demonstrated the presence of chromosomal DNA from the known triggers in the synovial tissue of patients who have the postdysentery form of ReA.48,52–54 Recent studies from many laboratories have demonstrated that Ct and Cpn, such as Mycobacterium tuberculosis, can undergo long-term, persistent infections,50,51,58,59 and the role persistent Ct infections play in the genesis of ReA has been established. The role of bacterial persistence in chronic ReA is less well established. One difference is that these chlamydiae exist in a persistent metabolically active state whereas the postenteric organisms do not, with the possible exception of Yersinia.49

The causative bacteria (or bacterial fragments) of ReA occasionally have been demonstrated in the synovial tissue of who have with various types of arthritis, so the importance of this finding has been questioned.82–84 Furthermore, bacterial DNA from various pathogens not associated with ReA have been discovered in synovial tissue.60,85 Even viable chlamydial infections have been documented in the synovial tissue of patients who have osteoarthritis and asymptomatic volunteers, albeit to a much lower degree; background PCR positivity rates of approximately 5% to 20% for Ct in synovial samples have been reported.59,61,86

The importance of host genetic variability and host tolerance is highlighted by a certain percentage of the population harboring bacterial DNA from the enteric
organisms or persistently viable chlamydial infections in their synovium. Various hosts might respond differently to the same pathogen, thereby manifesting different phenotypic expressions to these same organisms. Furthermore, in the case of Ct, there are several different serovars; these different serovars may portend diverse prognoses that include variable pathogenic sequelae. Despite this background PCR-positivity rate, data suggest these other groups of patients are far less likely to be positive for these organisms. A study comparing synovial tissue chlamydial PCR-positivity in patients who have suspected chlamydial-induced ReA versus an osteoarthritis control population demonstrated that the ReA subjects were significantly more likely to be positive for Ct or Cpn.59

The pattern of gene expression associated with persistently viable chlamydiae is significantly different from that seen during normal active infections. For example, during the persistent state, expression of the major outer membrane protein (omp1) gene and several genes required for the cell division process is severely down-regulated; this is coupled with an up-regulation of heat shock proteins (HSPs). HSPs in general are paramount to the persistent state of Ct and Cpn because they provide many functions involved with cell survival. Under stressful conditions, HSPs allow cells to survive lethal assaults by preventing protein denaturation.87,88 The HSP-60 molecule, specifically, has many functions that seem important to the pathophysiology of ReA. HSP-60 has been shown to be pivotal in the inability of chlamydial-infected cells to undergo apoptosis.59 These same molecules also are believed to play a role in antibiotic resistance87 and potentially be immunogenic.90 Despite HSPs’ important role in the pathophysiology of Chlamydia-induced ReA, there are differences even within the Chlamydia genus. In the case of Ct, specifically, the persistent state is characterized by the differential up-regulation of three paralog HSP-60 genes (Ct110, Ct604, and Ct755).91 There also are differences in cytokine and chemokine mRNA profiles demonstrated in human synovial tissue chronically infected with Ct versus Cpn.58 Regardless of these differences, elimination of the HSPs likely is important in abrogating the pathogenic sequelae of Chlamydia-induced ReA or ReA in general. Such an accomplishment eliminates the immunogenic nidus itself or renders the infected cell more susceptible to apoptosis or therapy.

**Host Response**

The causative bacteria of ReA are incorporated intracellularly, in part or in whole, then taken from the site of initial infection and trafficked to the synovium. That which governs this process, however, is not yet evident. It also is not clear if their presence in the affected organs represents a trigger for an autoimmune response or if these organisms are the source of the inflammatory process. It seems that this phenomenon of host tolerance is multifactorial in nature.

**Cellular Uptake**

The causative organisms of ReA are incorporated into peripheral blood mononuclear cells (PBMCs) and persist intracellularly in synovial cells (primarily macrophages). How this process of intracellular uptake occurs is less apparent. Chlamydial infection, specifically, is initiated when the elementary body (EB) binds to the target eukaryotic cell. Intriguing recent evidence suggests that apolipoprotein E (ApoE4) that is adherent to the surface of Cpn EBs attaches to the host cell low-density lipoprotein receptor family carrying the EB with it; this is not true for Ct.92 This could represent a truly remarkable adaptation of chlamydiae using a basic cellular function involving cell homeostasis as its pathway to host cell attachment and uptake.
**Toll-like Receptors**

The Toll-like receptors (TLRs) recognize extracellular pathogens and activate immune cell responses as part of the innate immune system. TLR-4 recognizes LPS, thereby potentially playing a role in the pathophysiology of ReA. TLR-4 deficient mice exposed to Salmonella demonstrate dramatically increased bacterial growth and demise.\(^93\) Other animal data have shown that effective host clearance of Ct depends on appropriate TLR-4 expression by neutrophils.\(^94\) TLR-4 functions as a coreceptor with CD14 for the detection of bacterial LPS.\(^95\) PBMCs from eight patients who had Salmonella infections (four who had and four who did not have ReA) have been analyzed in the acute and recovery phases of the infection.\(^96\) During the recovery phase, the patients who had ReA demonstrated down-regulation of CD14 whereas the response of those who did not have ReA was similar to that of healthy controls. Despite these animal and in vitro human studies implicating TLR-4 in the pathophysiology of ReA, in vivo human data suggest that genetic variants of TLR-2, but not TLR-4, are important in the development of ReA after a \(S\) enteritidis infection.\(^97\)

**Th1 Versus Th2 Response**

Although the Th1 cytokines, such as tumor necrosis factor (TNF)-\(\alpha\), play a role in the clinical manifestations of ReA, their importance seems less important than that in other types of inflammatory arthritis.\(^98–100\) This might be true particularly for chronic ReA. Data suggest that a Th2 cytokine profile is more typical. Compared with patients who have RA, patients who have ReA demonstrated significantly lower levels of TNF-\(\alpha\) in their peripheral blood, and patients who had disease duration of greater than 6 months secreted significantly less TNF-\(\alpha\).\(^98\) Similar findings have been demonstrated in the joints of patients who have ReA (ie, higher levels of interleukin 10 and lower levels of TNF-\(\alpha\) and interferon (IFN)-\(\gamma\), favoring a Th2 profile).\(^99,100\)

Temporal relationships of these different Th1 and Th2 cytokines or blunting of initial cytokine response also might be important in disease manifestations and maintenance. Slight changes in the Th1/Th2 balance may explain the relapsing course frequently seen in chronic ReA. Alterations in the initial Th1/Th2 balance also may predispose to disease initiation. Animal data have demonstrated a lesser initial TNF-\(\alpha\), IFN-\(\gamma\), and interleukin 4 response to chlamydial infection leading to decreased bacterial clearance.\(^101\) Therefore, lower initial responses of these Th1 cytokines may increase the likelihood of developing ReA compared with those patients who are exposed to the causative organism, exhibit a more robust initial Th1 response, and do not develop ReA. Along these same lines, background cytokine levels favoring a Th2 response might contribute to bacterial persistence; in vitro data reveal that low levels of TNF-\(\alpha\) and IFN-\(\gamma\) help promote the persistent state of Ct and Cpn.\(^102–104\)

Other data suggest a role for the Th3 response with expression of transforming growth factor \(\beta2\) and granulocyte monocyte-colony stimulating factor.\(^105\)

**HLA-B27**

The host factor associated most notably with the pathogenesis of the SpAs in general, and which has been associated with ReA, has an equally mysterious role as that of the entire host response. There are many theories regarding the precise role of HLA-B27, but none are proved. Because HLA-B27 is a class I histocompatibility antigen, it has been postulated that HLA-B27 presents arthritogenic microbial peptides to T cells, stimulating an autoimmune response, so-called molecular mimicry.\(^106\) Conversely, B27 itself may serve as the autoantigen that is targeted by the immune system.\(^107\) It also is possible that exposure to the triggering bacteria may subvert self-tolerance
to the B27 antigen, and animal data exist to support this notion. Another theory suggests that the role of HLA-B27 may be to enhance invasion of the causative organisms, specifically *Salmonella*, into human intestinal epithelial cells. It also has been suggested that *Salmonella* invasion leads to significant recognizable changes in the B27-bound peptide repertoire. A similar study, however, found only minimal changes in the peptide repertoire. Intracellular uptake of chlamydiae may not be altered by HLA-B27, but intracellular replication and formation of inclusion bodies might be suppressed by the cytoplasmic tail of this antigen. If true, this could predispose the cell to chlamydial persistence. Conversely, it has been suggested that HLA-B27 has no influence on invasion or replication of Ct serovar L2 within cell lines.

HLA-B27 has multiple alleles that could influence host response and disease susceptibility. Few studies have analyzed the specific HLA-B27 alleles in the setting of ReA. One recent study suggests that although HLA-B*2705 is the most common allele observed in B27 positive ReA patients, this allele is seen less frequently than in the other SpAs and in B27 healthy controls. Another study suggests that HLA-B*5703 increases the risk for the classic triad of symptoms of ReA in a specific population.

HLA-B27 is believed to increase susceptibility to ReA, but the data suggest there is too much emphasis placed on this HLA haplotype. The literature often states a HLA-B27 prevalence of 75% to 85% in ReA. A thorough search, however, reveals a reported range of 0% to 88%, with the majority of the data suggesting an HLA-B27 prevalence of 30% to 50%. Recent reports dictate that HLA-B27 has no role in determining postenteric ReA susceptibility; the same likely is true for postchlamydial ReA.

Rather than truly increasing disease susceptibility, HLA-B27 might portend a different prognostication. Several large studies are in agreement that patients who are HLA-B27 positive have more severe symptoms, thereby making the condition more clinically apparent. This haplotype also might increase risk for developing the complete triad of symptoms. Therefore, HLA-B27 actually could function as a diagnostic bias rather than a true genetic susceptibility locus. This requires further study.

**DIAGNOSTIC TESTS**

There are diagnostic criteria available, but these are broad and rely on clinical symptoms only. The American College of Rheumatology criteria, published in 1981, require the presence of a peripheral arthritis occurring in association with urethritis or cervicitis. The Third International Workshop on Reactive Arthritis in 1995 requires a peripheral arthritis with sacroiliac involvement and a preceding gastrointestinal or genitourinary infection. The current American College of Rheumatology definition might be too limited in scope and the latter’s reliance on a preceding infection could lead to underdiagnosis. Difficulties with these diagnostic criteria have been raised. The traditional disease definition also suggests that ReA represents a sterile inflammatory arthritis, but data presented herein, specifically pertaining to chlamydiae, call this into question.

Although not pathognomonic for the condition, the documentation of the DNA presence of one of the causative organisms by PCR in synovial tissue or fluid of patients who fulfill the clinical criteria for ReA represents the most accurate means of diagnosing the condition. The contention that the synovium yields the most accurate results is supported by studies comparing the PCR results from synovial tissue and
PBMC in patients who have ReA. These data suggest that only a small minority of patients who are PCR positive for Ct in synovium were PCR positive in their PBMC.\textsuperscript{59,123} Unfortunately, such synovial tissue analysis is not readily available for the majority of clinicians. Even when synovial tissue or fluid is obtained, the concordance rate of PCR results between PCR testing laboratories is low, suggesting it is a learned science.\textsuperscript{124} It has been suggested that chlamydial IgG or IgA titers are useful at diagnosing patients who have persistent chlamydia infections.\textsuperscript{125,126} The majority of these data, however, apply only to Cpn in disease states other than ReA. There also is cross-reactivity between chlamydial serotypes, so their usefulness has been questioned. Recent data advocate that serology positive for anti–HSP-60 IgG might be diagnostic of Ct-induced ReA,\textsuperscript{124} but HSP is a conserved molecule with high potential for false-positive results. This contention merits further study. Stool and urogenital sampling for the causative organisms in patients who have chronic disease have been analyzed, but many patients test negative, limiting the usefulness of this approach.\textsuperscript{127,128} Because more than half of affected patients are HLA-B27 negative and recent reports cited suggest it has no role in disease predilection, HLA-B27 should not be used as a diagnostic tool. Therefore, currently there is no practical diagnostic test.

ReA can follow two disease courses. The first is an acute syndrome occurring shortly after the triggering infection followed by gradual resolution of the symptoms; the second begins in a similar fashion yet can progress to chronicity, sometimes years. During the acute stage, individuals often display elevated acute phase reactants, such as an elevated erythrocyte sedimentation rate or C-reactive protein level. Conversely, patients who have chronic ReA typically display normal levels. Patients in the acute phase also might display other indicators of inflammatory response, including leukocytosis or thrombocytosis.

The radiographic features of ReA include sacroiliitis, periostitis, nonmarginal syndesmophytes, periosteal new bone formation, joint erosions, and joint space narrowing. These findings are apparent only on plain radiographs, however, with chronic disease. Syndesmophytes and sacroiliitis are more common in patients who have postvenereal ReA rather than in those who have postenteric ReA, but radiologic findings in lumbosacral spine radiographs are characteristically similar.\textsuperscript{129} There may be a role for MRI or ultrasound (of the sacroiliac or other joints) to detect earlier changes, but neither has been formally studied in ReA.

**TREATMENT**

**Nonsteroidal Anti-Inflammatory Drugs**

A breadth of clinical experience suggests that nonsteroidal anti-inflammatory drugs (NSAIDs) help with the inflammatory arthritis associated with ReA, but there are no well-designed prospective trials analyzing their efficacy for this indication. Although helpful for the articular symptoms, they are not believed efficacious for the potential extra-articular symptoms of ReA. Data suggest that continuous use of NSAIDs might reduce radiographic progression for other types of SpAs, in particular ankylosing spondylitis,\textsuperscript{130} however, it is not clear if the same might be true for chronic ReA.

**Corticosteroids**

Corticosteroids have limited benefit for the axial symptoms and may be more effective for the peripheral arthritis of ReA.\textsuperscript{22} Local corticosteroid injections into affected joints may provide short-term relief. Topical corticosteroids also seem helpful for some of the extra-articular manifestations, such as iritis, circinate balanitis, and keratoderma.
blenorrhagicum. Because bacterial persistence is a hallmark pathophysiologic feature of ReA, there could be theoretic concerns with the use of systemic corticosteroids in ReA, particularly early in the disease course. There are no data, however, to distinguish whether or not corticosteroids have any impact on the long-term outcome of ReA.

Disease Modifying Antirheumatic Drugs

DMARDs have been used as treatments in patients who have chronic ReA because these patients can develop radiographic abnormalities with subsequent joint deformities if left untreated. The best-studied DMARD in the setting of ReA is sulfasalazine (SSZ). A placebo-controlled prospective trial of 134 subjects demonstrated a trend toward improvement with 62% of the participants on SSZ versus 47% on placebo demonstrating overall response ($P = .089$). There were no significant improvements, however, in any of the individual clinical measures followed compared with placebo, including swollen and tender joint counts. Because SSZ is a treatment of inflammatory bowel disease and 67% of patients who have ReA have histologic evidence consistent with IBD on bowel biopsies, this medication might be a good therapeutic option for patients who have chronic disease, particularly of the postenteric variety. Methotrexate, azathioprine, and cyclosporine have been advocated as potential treatments for ReA but never formally evaluated in a prospective trial.

Tumor Necrosis Factor Antagonists

The TNF-α antagonists have demonstrated great success in the treatment of other types of SpAs. There are potential theoretic concerns, however, regarding TNF-α antagonism in ReA. As discussed previously, lower levels of TNF-α have been demonstrated in ReA compared with other types of inflammatory arthritis and ReA is believed more of a Th2-driven disease. Also, chlamydiae are the most common trigger of ReA and might be a common cause of uSpA. In vitro data suggest that persistent Ct and Cpn levels are inversely associated with TNF-α levels. Conversely, patients who have ReA exhibit higher serum levels of TNF-α levels compared with normal controls, so this might suggest that these patients would benefit from TNF-α antagonists.

There are no randomized trials in ReA to accurately assess the efficacy of anti-TNF therapy. Several case reports and a small open-label study suggest clinical benefit with these drugs in the treatment of ReA, however, one patient in the small open-label trial required total knee replacement 6 months after beginning therapy. In this same open-label study of etanercept, synovial PCR positivity for chlamydiae was followed with equivocal results, including two patients who became positive for this organism on treatment. In preliminary experiments, the relative bacterial load in paired synovial tissue samples from a patient who had Ct-induced arthritis was assessed before and after several months of treatment with etanercept. Real-time PCR analyses demonstrated that the second biopsy sample held a bacterial load that was several-fold higher than that of the initial, pretreatment sample (A.P. Hudson, unpublished data, 2008). These initial observations support the contention that anti-TNF-α therapy may not be appropriate for extended use in patients who have chronic Chlamydia-induced arthritis. The general lack of viability of the postenteric organisms in the setting of ReA suggests that anti-TNF therapy might have more of a role in these patients. The usefulness of TNF-α antagonists in the treatment of ReA is unanswered.
Because ReA clearly is triggered by bacteria and because, in the case of Chlamydia-induced ReA, the synovial-based long-term viability of the organism has been demonstrated, a potential role for antibiotics is suggested. Similar to the results with the TNF-antagonists, treatment of ReA with antibiotics has produced equivocal results, although these data are more abundant. The majority of the studies have proved antibiotic therapy ineffective, but some studies suggest benefit. Potential explanations for these apparent discordant results are discussed.

Studies assessing the long-term administration of doxycycline, ciprofloxacin, and azithromycin in ReA failed to show benefit. There was no effort to separate postenteric from postvenereal patients in these trials, however. A trial assessing 3 months of treatment with lymecycline showed no benefit in patients who had postdy-sentery ReA, whereas there was improvement in patients who had Chlamydia-induced ReA. A subgroup analysis of another trial demonstrating that ciprofloxacin had no benefit as a treatment for ReA suggested improvement in postchlamydial patients. A follow-up of one of the aforementioned “negative” ciprofloxacin trials suggested that this antibiotic significantly improved long-term prognosis. Finally, another study suggested significant improvement in patients who had postchlamydial ReA with a combination of knee synovectomy and 3 months of azithromycin. Therefore, it seems that there may be benefit in the postchlamydial form but not ReA that is secondary to the postdysentery organisms.

Such inconsistent outcomes sometimes derive from the particular antibiotic used in a given study, because not all such drugs have equal efficacy against the triggering bacteria. To date little meaningful information is available relating to the synovial accessibility of antibiotics after standard oral administration. In general practice, the efficacy of antibiotic treatment for Ct or Cpn is assayed using in vitro systems during the acute chlamydial life cycle. Individuals who have Chlamydia-induced ReA, however, harbor persistent organisms with an attenuated life cycle, thus equivocating the validity of the standard means of testing for drug efficacy. The in vitro effect of standard concentrations of ciprofloxacin, ofloxacin, doxycycline, or azithromycin induced the persistent state rather than clearing the organism. These same in vitro data suggest synergistic eradication of the persistent chlamydial infection with a combination of azithromycin and rifampin. Furthermore, a 2004 study revealed significant improvement in patients who had presumed Chlamydia-induced ReA after 9 months of a combination of rifampin and doxycycline compared with doxycycline monotherapy; however, there was no placebo control. Therefore, it is possible that a prolonged combination of antibiotics may eradicate the persistent state of chlamydiae along with its pathogenic sequelae, but more studies are needed.

**SUMMARY**

Although environmental exposures have been implicated as potential causes for nearly all chronic diseases, ReA is one of the few with a known bacterial trigger. This insight into disease initiation has led to significant advances in the pathophysiology of this condition. As disease pathophysiology often stays one step ahead of science, however, many of the mysteries that surrounded ReA remain unsolved, including the clinical implications of bacterial persistence. In similar fashion, HLA-B27 is believed important in determining disease susceptibility, yet recent data downplay its importance and suggest it might be a better predictor of disease severity. Although bacteria are known to trigger ReA, the role of antibiotics remains ill defined, although recent studies lend hope for combination antibiotics. Anti-TNF therapy has
proved efficacious in the other SpAs, but sufficient data are lacking and theoretic concerns with their use remain. Just as epidemiologic studies have been hampered by an incomplete historical review resulting in multiple eponyms for ReA, it is likely that the pathophysiology that surrounds disease initiation needs to be targeted in hopes of finding a definitive treatment.

REFERENCES


