Reactive arthritis

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INTRODUCTION

Reactive arthritis is conventionally defined as an arthritis that arises following an infection, although the pathogens cannot be cultured from the affected joints. It is generally regarded as a form of spondyloarthritis (SpA).

The definition, clinical features, approach to diagnosis and differential diagnosis, and management of reactive arthritis will be reviewed here. Mechanisms that may play a role in reactive arthritis and in other spondyloarthritides are discussed separately. (See "Pathogenesis of spondyloarthritis".)

DEFINITION

The term "reactive arthritis" was introduced in 1969 as "an arthritis which developed soon after or during an infection elsewhere in the body, but in which the microorganisms cannot be recovered from the joint" [1]. The original definition did not specify the pathogens that were accepted as causes of reactive arthritis, and, in 1999, a panel of experts determined a specific list of gastrointestinal and urogenital pathogens that could be considered causative [2]. These included *Chlamydia trachomatis*, *Yersinia*, *Salmonella*, *Shigella*, and *Campylobacter* [2]. *Escherichia coli*, *Clostridioides* (formerly *Clostridium*) *difficile*, and *Chlamydia pneumoniae* have since been added to the list [3-7]. Reactive arthritis triggered by a sexually transmitted infection

is also referred to as sexually acquired reactive arthritis (SARA) [8].

Additional causative pathogens, alternative terms, and diagnostic and therapeutic strategies for reactive arthritis have subsequently been proposed [9]. However, none of the newer diagnostic or therapeutic approaches or alternate names has been adequately validated. Another problem is that many of the studies generating these approaches involved patients seen in rheumatology clinics or followed outbreaks of disease after exposure to a common pathogen; such patients are not likely to be representative of the affected patients in the general community. Thus, the definition of reactive arthritis is still evolving.

Two major clinical features that characterize reactive arthritis were identified [2]:

- An interval ranging from several days to weeks between the antecedent infection and arthritis
- A typically mono- or oligoarticular pattern of the arthritis, often involving the lower extremities, and sometimes associated with dactylitis and enthesitis

By convention, reactive arthritis of more than six months' duration was regarded as being chronic instead of acute.

The term "reactive arthritis" has sometimes been used historically to refer to the clinical triad of postinfectious arthritis, urethritis, and conjunctivitis, which was formerly called Reiter syndrome [10,11]. However, these patients represent only a subset of patients with reactive arthritis [10,12].

Patients suspected of having reactive arthritis whose features initially or subsequently satisfy the Assessment of SpondyloArthritis International Society (ASAS) criteria for axial or peripheral spondyloarthritis (SpA) are also considered as having a form of SpA. A preceding episode of genital or gastrointestinal infection is included among the ASAS criteria that may support a diagnosis of peripheral SpA and the inclusion of a patient with reactive arthritis in this group.

EPIDEMIOLOGY

Reactive arthritis is a relatively rare disease that typically occurs in young adults, affecting both men and women. Studies of the prevalence and annual incidence of reactive arthritis are highly heterogeneous with respect to the size of the cohort, collection of data, the definition of reactive arthritis, and the identification of the inducing pathogens. In a US population-based study in

Oregon and Minnesota, the incidence of reactive arthritis following documented enteric bacterial infections ranged from 0.6 to 3.1 cases per 100,000, depending upon the organism [13]. An analysis of the data in a 2013 systematic review found that the incidence of reactive arthritis following infection with *Campylobacter*, *Salmonella*, and *Shigella*, was estimated as 9, 12, and 12 per 1000 patients, respectively [14]. Globally, the annual incidence has been reported between 0.6 to 27 per 100,000, and the prevalence is estimated to be 30 to 40 per 100,000 adults [3,4,6,15]. Two publications in 2019 have suggested that the frequency of reactive arthritis has been diminishing [16,17].

Among patients with any of the spondyloarthritis (SpA) variants seen by rheumatologists, those with reactive arthritis are a small minority. This was illustrated by two registry-based studies from Spain in which 1.2 to 1.4 percent of all patients with SpA had been diagnosed with reactive arthritis [18,19].

Most cases of reactive arthritis appear sporadically, but outbreaks may follow single-source infections. In such outbreaks, the proportion of infected subjects who developed subsequent reactive arthritis has ranged from 0 to 21 percent [6,15].

The causative pathogens, incidence, and prevalence of reactive arthritis depend upon the geographic region. In general, among the pathogens, *Chlamydia* is probably the most endemic. A 2016 systematic review could identify only three studies of low to moderate quality reporting an incidence of sexually acquired reactive arthritis (SARA) of 3 to 8 percent among patients with a chlamydia infection [20]. A Japanese study reported that only one of 123 patients with clinical chlamydial infections developed arthritis [21]. Some epidemiologic studies include cases in which the preceding enterobacterial and chlamydial infections were silent [22].

CLINICAL MANIFESTATIONS

The onset of reactive arthritis is usually acute. Patients typically present with an asymmetric oligoarthritis, usually one to four weeks following the inciting infection [2,6,9,23].The extent of the interval between infection and the onset of arthritis considered consistent with a reactive arthritis by expert consensus is a minimum of several days and a maximum of several weeks [2]. In at least half of patients, all symptoms resolve in less than six months [24]; in most patients, symptoms resolve within one year. The several types of clinical manifestations of reactive arthritis include:

- Symptoms of preceding enteric or genitourinary infection (see 'Preceding infection' below)
- Axial and/or peripheral musculoskeletal signs and symptoms (see 'Musculoskeletal signs and symptoms' below)
- Extraarticular signs and symptoms (see 'Extraarticular signs and symptoms' below)

Other than those symptoms due to the infection that has triggered the arthritis, the articular and extraarticular manifestations are similar regardless of the particular enteric or genitourinary organism or species of organism causing the disorder [25].

Preceding infection — The characteristic symptoms of the enteric or genitourinary infections that can cause reactive arthritis are diarrhea or urethritis. Patients with arthritis induced by enteric bacteria can also develop aseptic urethritis. Many patients have been described in whom the preceding infections are clinically silent and detectable only by laboratory testing [22,23,26]. There are no data to indicate whether the disease course or prognosis of reactive arthritis differs between patients with or without an antecedent infection that is symptomatic. (See "Approach to the adult with acute diarrhea in resource-rich settings" and "Causes of acute infectious diarrhea and other foodborne illnesses in resource-rich settings" and "Approach to infectious causes of dysuria in the adult man" and "Clinical manifestations and diagnosis of Chlamydia trachomatis infections".)

The enteric bacteria commonly associated with reactive arthritis include:

- *Salmonella* of various serovars
- *Shigella*, especially *Shigella flexneri*, but also *Shigella dysenteriae* and *Shigella sonnei*
- *Yersinia*, including *Yersinia enterocolitica* 0:3 and 0:9 and *Yersinia pseudotuberculosis*
- *Campylobacter*, especially *Campylobacter jejuni*
- *C. difficile*

The genital pathogen commonly accepted to be the cause of reactive arthritis is *Chlamydia trachomatis*.

Other bacteria also reported to cause reactive arthritis include *Chlamydia pneumoniae*, *Escherichia coli*, *Ureaplasma urealyticum*, and *Mycoplasma genitalium*. Intravesical Bacillus Calmette-Guerin (BCG) treatment for bladder cancer has also been identified as a rare cause of reactive arthritis. (See 'Differential diagnosis' below and "Infectious complications of intravesical BCG immunotherapy".)

Reactive arthritis has also been reported in patients with human immunodeficiency virus (HIV)

infection, in which it is generally thought to be related to other infections to which patients have been exposed, rather than to HIV itself [27,28]. An association between reactive arthritis and human leukocyte antigen (HLA)-B27 has been noted in Caucasian HIV-infected patients but not in patients from sub-Saharan Africa, where the prevalence of HLA-B27 is much lower [29,30].

Although a large variety of pathogens, including streptococcus, have been described that may induce musculoskeletal symptoms, an arthritis is conventionally considered to be a reactive arthritis only if some of the typical musculoskeletal features occur (see 'Musculoskeletal signs and symptoms' below). Not infrequently, patients do not volunteer the history of infection until asked about this specifically, since most patients are not aware that the infections can be related to arthritis.

Musculoskeletal signs and symptoms — The musculoskeletal features of reactive arthritis include four major manifestations: arthritis, enthesitis, dactylitis, and back pain [31,32].

- **Peripheral arthritis** – The typical picture of peripheral arthritis, seen in rheumatology clinics, is an acute-onset asymmetric oligoarthritis, often affecting the lower extremities, especially the knees [33] (picture 1). However, about 50 percent of patients have arthritis in the upper extremities, and some have polyarthritis in the small joints [31]. By convention, the minority of patients with arthritis that does not resolve within six months is defined as having chronic reactive arthritis.

- **Enthesitis** – The enthesis is the site of insertion of ligaments, tendons, joint capsule, or fascia to bone; enthesitis (or enthesopathy), the term for inflammation around the enthesis, can occur in patients with reactive arthritis and other forms of spondyloarthritis (SpA). Swelling at the heels is among the most characteristic symptom of enthesitis. Common sites of heel involvement are at the insertions of the Achilles tendon and of the plantar fascia on the calcaneus. Pain, swelling, and local tenderness are suggestive clinical features. Estimates of the frequency of enthesitis in patients with reactive arthritis have ranged from 20 to 90 percent [13,31,34-36].

  In one study in the US of patients with documented enteric infections and a symptom of reactive arthritis, enthesitis was more common than arthritis or inflammatory back pain, occurring in 89 percent of patients [13,31].

  Enthesitis is discussed in more detail elsewhere. (See "Clinical manifestations of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in

adults", section on 'Enthesitis' and "Clinical manifestations and diagnosis of peripheral spondyloarthritis in adults", section on 'Musculoskeletal features'.)

- **Dactylitis** – Some patients also develop dactylitis, which typically presents as sausage digits (picture 2) [37]. The frequency of dactylitis in patients with chlamydia-induced reactive arthritis may be as high as 40 percent [32]. (See "Clinical manifestations and diagnosis of peripheral spondyloarthritis in adults", section on 'Musculoskeletal features'.)

- **Axial, especially low back pain** – Inflammatory low back pain is frequent as an accompanying symptom, but seldom as the only presenting symptom [13,32]. Inflammation in the spine or at the sacroiliac joints may be seen [38]. (See "Clinical manifestations of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults", section on 'Low back pain and neck pain'.)

Extraarticular signs and symptoms — Extraarticular involvement in reactive arthritis is associated with a variety of manifestations, which may be present during the acute or chronic phase of illness [4,23]. The relative frequency of each of these manifestations has not been well-analyzed. In one European cohort of 186 patients enrolled in a clinical trial, the frequencies of eye and skin involvement were approximately 20 and 15 percent, respectively [34].

Extraarticular manifestations include:

- Ocular symptoms, such as conjunctivitis, and less frequently, anterior uveitis (picture 3), episcleritis, and keratitis. In one report, a third of those with conjunctivitis were found to have detectable chlamydia in scrapings off the conjunctiva [39].

- Genitourinary tract symptoms, such as dysuria, pelvic pain, urethritis, cervicitis, prostatitis, salpingo-oophoritis, or cystitis. Urethritis can occur even when the arthritis is induced by enterobacteriaceae [40].

- Gastrointestinal symptoms, such as diarrhea.

- Oral lesions, including painless mucosal ulcers (picture 4 and picture 5).

- Cutaneous eruptions and other skin changes, such as keratoderma blennorrhagica (hyperkeratotic skin lesions on soles and palms resembling pustular psoriasis) (picture 6) and, uncommonly, erythema nodosum (picture 7). (See "Neutrophilic dermatoses", section on 'Reactive arthritis'.)

- Nail changes that resemble those seen in psoriasis (picture 8 and picture 9).
- Genital lesions such as circinate balanitis (painless erythematous lesions with small, shallow ulcers on the glans penis and urethral meatus) (picture 10).
- Cardiac manifestations, which are uncommon, include valve disease, particularly aortic insufficiency, with greater chronicity of illness [41]. Pericarditis has been reported very rarely [42,43].

None of the mucocutaneous or other manifestations are specific for reactive arthritis [44].

LABORATORY AND IMAGING FINDINGS

Several types of findings may be present, including:

- Evidence of antecedent or concomitant infection
- Elevated acute phase reactants
- Positive testing for human leukocyte antigen (HLA)-B27
- Inflammatory synovitis
- Imaging abnormalities consistent with enthesitis or arthritis

Laboratory findings

Antecedent or concomitant infection — Laboratory tests, such as stool cultures to test for *Salmonella*, *Shigella*, *Campylobacter*, and *Yersinia*, can sometimes confirm a preceding or concomitant infection with one of the pathogens that classically induce reactive arthritis. However, by the time patients develop arthritis, the diarrhea has usually resolved, and the pathogens may no longer be retrievable. Urine and genital swab testing can sometimes detect *Chlamydial trachomatis* infection using nucleic acid amplification techniques. (See 'Chronic chlamydia-related arthritis' below and "Clinical manifestations and diagnosis of Chlamydia trachomatis infections", section on 'Nucleic acid amplification testing (test of choice)'.)

Serologic testing is used primarily in epidemiologic studies to test for preceding infections but is generally not useful in clinical practice [9,45,46]. Infections by *Yersinia*, *Salmonella*, *Campylobacter*, and *Chlamydia trachomatis* cause strong antibody responses, and the triggering enteric infections can still be identified by serology in more than 50 percent of *Yersinia*- or *Salmonella*-infected patients, if such testing is performed [47]. In communities in

which these infections are endemic and often clinically silent, serologic testing is not specific for recent episodes of infection.

Acute inflammatory changes — Acute phase reactants such as the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) may be elevated. In many patients, however, these studies may be normal; elevations in acute phase reactants were found in less than half of patients diagnosed with reactive arthritis in one study [13].

Genetic predisposition — The prevalence of HLA-B27, which is increased in patients with the various forms of spondyloarthritis (SpA), including reactive arthritis, is generally estimated at 30 to 50 percent in patients with reactive arthritis, although values range widely [6,23]. In hospital-based studies with more severely affected patients, frequencies as high as 60 to 80 percent have been reported [48]; however, estimates in population-based studies and analyses of disease outbreaks are generally much lower and occasionally have shown no increase in HLA-B27 prevalence compared with the general population [49]. (See "Pathogenesis of spondyloarthritis".)

Inflammatory synovitis — The findings in synovial fluid are nonspecific and are characteristic of inflammatory arthritis, with elevated leukocyte counts, predominantly neutrophils. White blood cell (WBC) counts are typically between 2000 and 64,000 WBC per mm^3 [9]. (See "Synovial fluid analysis" and "Monoarthritis in adults: Etiology and evaluation".)

Imaging abnormalities — There are no specific findings on plain radiographs that can establish a diagnosis of reactive arthritis. Changes are usually limited to those associated with joint swelling if inflammatory arthritis is present. Patients with concurrent or past heel pain may show calcaneal spurs, but such findings are nonspecific and can be seen in other forms of arthritis and in asymptomatic individuals [50].

Radiographic sacroiliitis, a feature of axial SpA, has been reported [51]. In patients with chronic joint disease, imaging studies such as ultrasonography and magnetic resonance imaging (MRI) can also identify changes consistent with peripheral synovitis, enthesitis, or sacroiliitis. (See "Clinical manifestations of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults", section on 'Musculoskeletal imaging'.)

DIAGNOSIS

The diagnosis of reactive arthritis is a clinical diagnosis based upon the pattern of findings and exclusion of other diseases. There is no single definitive diagnostic test, nor are there validated diagnostic criteria. The diagnosis can generally be suspected in patients who exhibit all three of the following:

- **Characteristic musculoskeletal findings** – Such findings include a combination of oligoarthritis of peripheral joints, most often with asymmetric involvement of the lower extremity, enthesitis, dactylitis, or inflammatory back pain. (See 'Musculoskeletal signs and symptoms' above and 'Inflammatory synovitis' above and 'Imaging abnormalities' above.)

- **Evidence of preceding extraarticular infection** – The presence of a preceding extraarticular infection may be indicated simply by a history of urethritis or diarrhea. In the case of urethritis, or suspected silent urethritis, chlamydia can usually be identified, if present, by nucleic acid amplification. Stool cultures are usually not done in patients in whom the preceding episode of diarrhea has resolved. (See "Clinical manifestations and diagnosis of Chlamydia trachomatis infections", section on 'Nucleic acid amplification testing (test of choice)'.)

  Inability to identify the causative pathogen does not exclude the diagnosis of reactive arthritis. Even in well-controlled studies, pathogens can be identified in only about 50 percent of the patients. In those cases, the diagnosis of infections would depend entirely upon the history. (See 'Preceding infection' above and 'Antecedent or concomitant infection' above.)

- **A lack of convincing evidence for another more likely cause of oligoarthritis, monoarthritis, or enthesitis** – It is particularly important for diagnosis of reactive arthritis to exclude another more likely cause of the patient's condition. Similar musculoskeletal findings may occur in patients with other disorders, such as other forms of spondyloarthritis (SpA); traumatic arthritis, crystal-induced arthritis; other forms of inflammatory polyarthritis, such as psoriatic arthritis, rheumatoid arthritis, and systemic lupus erythematosus; septic arthritis; poststreptococcal arthritis; or Lyme arthritis. These alternative diagnoses can usually be excluded based upon the history, physical examination, and laboratory examination. (See 'Diagnostic evaluation' below and 'Differential diagnosis' below.)

Algorithms derived from analysis of available cross-sectional data in the literature provide support for the above criteria; although the probabilities described below are estimates, given the lack of a definitive diagnostic test for reactive arthritis [47]:

- In patients with new onset of arthritis in a pattern characteristic of reactive arthritis (see 'Musculoskeletal signs and symptoms' above), in whom alternative diagnoses have been excluded (see 'Differential diagnosis' below), the probability of reactive arthritis has been estimated to be about 40 percent.

- In a patient with a typical musculoskeletal presentation, in whom other diagnoses have been excluded, **plus** symptomatic enteritis with a positive stool culture for bacteria associated with reactive arthritis, the probability of reactive arthritis is high.

- In a patient with a typical musculoskeletal presentation, in whom other diagnoses have been excluded, **plus** a history of proven symptomatic preceding infection by *Chlamydia trachomatis*, the probability of reactive arthritis is very high (increased to about 90 percent). If the patient does not have a symptomatic *Chlamydia trachomatis* infection but *Chlamydia trachomatis* can be detected in the urine, the probability is roughly 60 percent.

The diagnostic values of inflammatory spinal pain and extraarticular features, including conjunctivitis, balanitis, and keratoderma blennorrhagica, have not been systematically evaluated in longitudinal studies. (See 'Extraarticular signs and symptoms' above.)

Diagnostic evaluation — The diagnostic evaluation in a patient suspected of reactive arthritis depends upon the presenting symptoms and likely infectious etiology. In most patients, we do the following:

- A thorough history and physical examination. The history is directed, in particular, at distinguishing musculoskeletal manifestations characteristic of reactive arthritis from those suggesting an alternative diagnosis and at determining whether there are symptoms to indicate a preceding or concomitant infection, especially diarrhea or urethritis. (See 'Musculoskeletal signs and symptoms' above and 'Preceding infection' above and 'Extraarticular signs and symptoms' above and 'Differential diagnosis' below.)

  The physical examination should include a detailed examination of the joints, including the heels, digits, and spine, as well as the rest of the joint examination. The general examination should aim at excluding other systemic or localized arthritic disorders (eg, examination of the skin and nails to exclude psoriatic arthritis). (See 'Musculoskeletal signs and symptoms' above and 'Differential diagnosis' below.)

- Plain radiographs of affected joints and entheses, if necessary to exclude other causes of joint pain, including other forms of arthritis and stress fractures. Plain radiographs of

sacroiliac joints are performed in patients suspected of also fulfilling criteria for radiographic SpA (ankylosing spondylitis). MRI of the sacroiliac joints is performed in patients in whom radiographs of the sacroiliac joints are normal but are suspected of fulfilling criteria for nonradiographic axial SpA.

We perform the following studies, depending upon the history and findings:

- In patients with a joint effusion, we perform arthrocentesis and examination of the synovial fluid, including total and differential white blood cell counts, crystal search, and examination for bacteria by Gram stain and culture to exclude septic arthritis. Techniques such as polymerase chain reaction (PCR) testing for pathogens in the synovial fluid or tissue are not indicated in the routine clinical evaluation and management of reactive arthritis. (See 'Inflammatory synovitis' above and "Joint aspiration or injection in adults: Technique and indications" and "Synovial fluid analysis".)

- In patients with ongoing active diarrhea, we obtain stool cultures to test for *Salmonella*, *Shigella*, *Campylobacter*, and *Yersinia*. Serologic testing for enteric pathogens is generally not indicated because of the limited specificity of such testing [47]. (See "Approach to the adult with acute diarrhea in resource-rich settings" and "Clinical manifestations and diagnosis of Yersinia infections", section on 'Diagnosis' and "Causes of acute infectious diarrhea and other foodborne illnesses in resource-rich settings", section on 'Inflammatory diarrhea'.)

- In patients suspected of infection with *Chlamydia trachomatis* and in patients with neither gastrointestinal nor genitourinary symptoms, we may obtain a first-catch urine sample (first portion of the urine specimen) or a vaginal swab, which may be self-administered by the patient or obtained by the clinician, for testing for chlamydia using nucleic acid amplification techniques. Testing for chlamydia is described in detail separately. (See "Clinical manifestations and diagnosis of Chlamydia trachomatis infections", section on 'Test performance'.)

Additional testing which may further increase or decrease support for the diagnosis, but which alone is not diagnostic or exclusionary, includes the following:

- Routine laboratory testing – We obtain a complete blood count and differential, acute phase reactants, renal and liver chemistries, and urinalysis to obtain supportive evidence of acute inflammation and to exclude other systemic disorders. (See 'Acute inflammatory changes'

above.)

- Testing for human leukocyte antigen (HLA)-B27 – We obtain HLA-B27 testing in patients with an intermediate likelihood of reactive arthritis. The prevalence of HLA-B27 in patients with reactive arthritis is generally estimated at 30 to 50 percent. Thus, a positive test would increase the likelihood of reactive arthritis being the correct diagnosis, rather than a different form of arthritis, other than another type of SpA. A negative HLA-B27 test does not exclude reactive arthritis.

- Serologic testing for rheumatoid arthritis – Rheumatoid factor and anticyclic citrullinated peptide antibody testing are obtained only in patients with polyarthritis suspected of possible rheumatoid arthritis. At least one of these antibodies is present in over 70 to 80 percent of patients with rheumatoid arthritis, but both are usually absent in patients with reactive arthritis. (See "Diagnosis and differential diagnosis of rheumatoid arthritis".)

DIFFERENTIAL DIAGNOSIS

Acute inflammatory monoarthritis or oligoarthritis may occur in a variety of disorders. Particularly important and/or common causes of arthritis to differentiate from reactive arthritis include crystal-induced inflammation, which is diagnosed by the history and identification of crystals (typically monosodium urate or calcium pyrophosphate) upon examination of the joint fluid, and bacterial infection (eg, septic arthritis and Lyme disease, which are identified by joint fluid examination and culture and by serologic testing of patients potentially exposed while in an endemic area, respectively). The general approaches to the evaluation of acute monoarthritis and polyarthritis are discussed separately. (See "Monoarthritis in adults: Etiology and evaluation" and "Synovial fluid analysis" and "Clinical manifestations and diagnosis of gout" and "Clinical manifestations and diagnosis of calcium pyrophosphate crystal deposition (CPPD) disease" and "Evaluation of the adult with polyarticular pain" and "Diagnosis of Lyme disease".)

The differential diagnosis of reactive arthritis can be guided, in part, by the pattern of symptoms and findings that are associated with the arthritis and that may suggest a related infectious or other systemic disorder. The following conditions should also be considered in the differential diagnosis:

- Monoarthritis – Common causes of acute monoarthritis such as traumatic arthritis, gout flares, septic arthritis, and Lyme arthritis should be considered. The evaluation and

differential diagnosis of monoarthritis are described in detail separately. (See "Monoarthritis in adults: Etiology and evaluation".)

- Diarrhea and arthritis – Various systemic conditions affecting the gastrointestinal tract and some infectious disorders may cause diarrhea in association with chronic or self-limited arthritis, features that may suggest reactive arthritis. Enteroviral infection-associated arthritis may represent a substantial number of cases of nonspecific, self-limited inflammatory joint disease; although arthritis is an uncommon manifestation of enterovirus infection, viral gastroenteritis is relatively common. Additional symptoms suggestive of a viral etiology include the presence of myalgias, an evanescent rash, and constitutional symptoms such as fever. Both large and small joints may be involved. Sore throat, pleuritic pain, and myocarditis are other features suggestive of enteroviral infection [52]. (See "Viruses that cause arthritis", section on 'Enterovirus infections: Coxsackie virus and echovirus'.)

  Inflammatory bowel diseases (eg, Crohn disease and ulcerative colitis), Behçet syndrome, celiac (sprue) disease, Whipple's disease, parasitic infections, and intestinal bypass surgery may cause diarrhea and arthritis. These conditions can usually be differentiated from reactive arthritis by the history, including the chronicity of the gastrointestinal symptoms and other features suggesting the alternative diagnosis; by physical examination; and, as indicated clinically, by serology, biopsy, or culture. These conditions are discussed in greater detail separately. (See "Clinical manifestations and diagnosis of arthritis associated with inflammatory bowel disease and other gastrointestinal diseases".)

- Genitourinary symptoms/disorders and arthritis – Disseminated gonococcal infection (DGI) is the primary cause to consider when urethral, uterine, cervical, or tuboovarian inflammation occurs in a patient with arthritis. The presence of a rash and tenosynovitis are suggestive. However, purulent arthritis due to gonococcal infection can occur in the absence of these findings. Culture of synovial fluid, the urethra, and other potentially infected mucosal sites is helpful in the diagnosis or exclusion of DGI or gonococcal arthritis. Nucleic acid amplification testing may be substituted for culture of genitourinary sites when it is available. The clinical manifestations and diagnosis of gonococcal infection and DGI are discussed in detail separately. (See "Clinical manifestations and diagnosis of Neisseria gonorrhoeae infection in adults and adolescents" and "Disseminated gonococcal infection".)

Arthritis and arthralgias are a rare complication of intravesical Bacillus Calmette-Guerin (BCG) treatment for bladder cancer, occurring in 1 to 2 percent of patients treated [53]. Affected patients commonly experience polyarthritis or oligoarthritis, predominantly of the lower extremities, within two weeks after instilling BCG. Approximately 20 percent of reported patients complain of axial pain compatible with spondyloarthritis (SpA), and over one-half of patients are human leukocyte antigen (HLA)-B27-positive. Associated genitourinary symptoms include cystitis, fever, and hematuria [54]. (See "Infectious complications of intravesical BCG immunotherapy".)

- Arthritis/SpA/enthesitis without preceding infectious symptoms – Other members of the SpA family, especially peripheral SpA related or unrelated to psoriasis or inflammatory bowel disease (undifferentiated SpA), may present with arthritis and sometimes enthesitis, which are indistinguishable from the musculoskeletal manifestations of reactive arthritis. Such conditions are distinguished from reactive arthritis by the lack of history and laboratory findings to suggest recent infection with the organisms associated with reactive arthritis. (See "Clinical manifestations and diagnosis of peripheral spondyloarthritis in adults".)

- Poststreptococcal arthritis – Arthritis is a common manifestation in patients with acute rheumatic fever (ARF) following streptococcal pharyngitis. These patients typically lack features common to the spondyloarthritides (eg, enthesitis), and this condition is generally not considered to be a form of reactive arthritis. Other clinical and laboratory manifestations of rheumatic fever and evidence of recent streptococcal infection distinguish these patients from those with reactive arthritis. A "poststreptococcal reactive arthritis" has been described in adults who have arthritis but do not satisfy criteria for ARF [55]. These issues are discussed in detail separately. (See "Acute rheumatic fever: Clinical manifestations and diagnosis", section on 'Poststreptococcal reactive arthritis'.)

TREATMENT

There are several major aspects to management. In some patients, particularly those with genitourinary infection, treatment of the infection that triggered the arthritis is indicated; arthritis and associated periarticular conditions should be treated in patients with symptomatic joint disease. Additional interventions may also be required for the treatment of extraarticular manifestations. (See 'Treatment of the infection' below and 'Treatment of arthritis' below and

'Treatment of other clinical features' below.)

Treatment of the infection — Antibiotics are not used to treat the arthritis specifically but may be indicated for treatment of the underlying infection if there is evidence of ongoing genitourinary infection or carriage of potentially pathogenic organisms. A role for antibiotic therapy in the treatment of chronic arthritis has not been established. (See 'Chronic chlamydia-related arthritis' below.)

A systematic review and meta-analysis of randomized trials comparing antibiotic therapy with placebo or no antibiotics for treatment of reactive arthritis found that antibiotic treatment did not significantly reduce the likelihood of failing to achieve remission of the reactive arthritis; although results of the studies were very heterogeneous, trial design varied substantially, and many trials were at risk of bias [56]. Rates of remission were able to be analyzed in 7 of the 12 trials included in the review, involving a total of 375 patients. Additionally, there were no significant effects of antibiotic therapy on pain, joint counts, or patient global assessment, but gastrointestinal side effects were nearly twice as likely in the patients receiving antibiotics.

Enteric infection — In general, antibiotics are not indicated for uncomplicated enteric infections, but some patients with active enteric infections may require treatment, depending upon their comorbidities and upon the specific organism. For example, therapy may be indicated in patients with severe gastrointestinal disease, in older adults, or in immunocompromised hosts. Treatment of enteric infections is discussed separately. (See "Approach to the adult with acute diarrhea in resource-rich settings" and "Travelers' diarrhea: Clinical manifestations, diagnosis, and treatment".)

In patients with chronic reactive arthritis induced by enteric bacteria, the available evidence does not support the use of long-term antibiotics [31,34,57-60].

Genitourinary tract infection — In contrast with most patients with enteritis, patients with acute *Chlamydia trachomatis* infection of the genitourinary tract and their sexual partners should receive a standard antimicrobial treatment for chlamydial infection of the genital tract. Treatment regimens are presented elsewhere. (See "Treatment of Chlamydia trachomatis infection".)

Patients with a history of chlamydia-induced arthritis should be evaluated for recurrent genitourinary infection if arthritis or genitourinary symptoms recur and should be retreated with antibiotics if testing for chlamydia infection is positive. Antibiotic treatment of the infection might

prevent relapses of arthritis in patients with recurrent genitourinary tract symptoms alone [61]. It has not been proven whether prompt treatment of acute chlamydia infections prior to the development of reactive arthritis, in both patients and partners, may lower the probability of developing reactive arthritis.

The approach to the evaluation and treatment of persistent or recurrent genitourinary tract symptoms despite initial antibiotic therapy is discussed in detail separately. (See "Treatment of Chlamydia trachomatis infection", section on 'Persistent or recurrent symptoms'.)

Chronic chlamydia-related arthritis — We do not advise the routine use of long-term antibiotics to treat chronic reactive arthritis. Results are mixed in randomized trials of long-term therapy with single antibiotics, and most do not show benefit [34,57-60,62].

By contrast, one 2010 study (included in the meta-analysis) provides limited evidence to suggest that combination antibiotics might be useful in the subset of patients with polymerase chain reaction (PCR)-proven chlamydia-induced arthritis [63]. This trial involved 42 patients with reactive arthritis of at least six months' duration who tested positive for *Chlamydia trachomatis* or *Chlamydia pneumoniae* by a special PCR technique in blood or affected synovial tissue [63]. Patients were randomly assigned to receive six months of treatment with rifampin plus either doxycycline or azithromycin or to receive placebo. The composite endpoint for improvement in musculoskeletal signs and symptoms was reached more often by the patients receiving combination antibiotics (17 of 27 [63 percent] versus 3 of 15 [20 percent], p = 0.01). Adverse events were mild and comparable between groups. However, there were limitations to the study: the numbers in each group were too small to compare the different antibiotic regimens, and the study was limited to patients with evidence of persistent chlamydial infection by a special PCR using peripheral blood or synovial samples instead of routine urine samples. Serologic tests did not correlate with these PCR results, and the PCR assays that were used in the study are not yet available for routine clinical use and are not of proven clinical utility. Further studies with larger numbers of patients are required to confirm these findings. There is no evidence of benefit for such treatment in patients with any other form of reactive arthritis. Evaluation of the synovial tissues or peripheral blood for *Chlamydia* by PCR is not indicated in clinical practice.

Treatment of arthritis — The treatment of arthritis with antiinflammatory and immunosuppressive agents can be divided into two stages: the treatment of acute reactive arthritis and the treatment of refractory (chronic) reactive arthritis, usually defined as disease of

greater than six months' duration. (See 'Acute reactive arthritis' below and 'Chronic reactive arthritis' below.)

The initial treatment goal is symptomatic relief of the arthritis, because the disease is self-limited in a substantial majority of patients, and joint injury with significant continued symptoms is infrequent. (See 'Prognosis' below.)

The approach to therapy is based upon both clinical experience in reactive arthritis and upon evidence of benefit for these therapies in other inflammatory arthritides, particularly other forms of spondyloarthritis (SpA), given the paucity of randomized trials and longitudinal observational studies in patients with reactive arthritis. (See "Clinical manifestations and diagnosis of peripheral spondyloarthritis in adults" and "Treatment of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults" and "Treatment of psoriatic arthritis".)

In clinical practice, disease activity and the response to therapy are assessed by the swollen or tender joint counts, the intensity of pain and disability, the presence and severity of enthesitis, and global assessments by the clinician and patient. There are no specific validated indices for assessment of disease activity in reactive arthritis.

Acute reactive arthritis — In patients with acute reactive arthritis, we initiate treatment with nonsteroidal antiinflammatory drugs (NSAIDs), which are usually the principal form of therapy, and may administer intraarticular and/or systemic glucocorticoids in patients with disease resistant to NSAIDs. (See 'Initial therapy' below and 'Intraarticular glucocorticoids' below and 'Systemic glucocorticoids' below.)

Initial therapy — We suggest treatment with antiinflammatory doses of NSAIDs (eg, naproxen 500 mg two to three times daily, diclofenac 50 mg three times daily, or indomethacin 50 mg three to four times daily) for symptomatic therapy for most patients, unless contraindicated (eg, by a history of gastrointestinal bleeding, allergy, cardiovascular disease, or compromised renal status). Maximum antiinflammatory doses and continuous use may be necessary to control pain and inflammation. An adequate trial of a given NSAID is usually at least two weeks in duration. Individual responses vary, and more than one NSAID may need to be tried before identifying an effective agent. There is no evidence that NSAIDs shorten or otherwise affect the course of the disease.

NSAIDs are used initially as the major modality because treatment of the infection does not

alleviate the signs or symptoms of arthritis, because the disease is most frequently self-limited, and because most patients will not require disease-modifying antirheumatic drugs (DMARDs) to control inflammation or to prevent erosive joint changes. The use of NSAIDs is based upon their ability to provide significant symptomatic relief in other forms of SpA and upon clinical experience with their use in reactive arthritis [6,23,64-66]; there have been few formal trials of NSAIDs in reactive arthritis [67,68]. (See "Treatment of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults".)

Patients receiving NSAIDs should be cautioned regarding the risk of gastrointestinal, renal, hepatic, and cardiovascular adverse effects, including the risk of NSAID gastropathy and gastrointestinal bleeding. Complete blood counts, renal function, and hepatic aminotransferases should be measured after two months on a given agent and then every six months thereafter in patients continuing to require antiinflammatory dosing regimens of NSAIDs, depending upon the comorbidities present. (See "NSAIDs: Therapeutic use and variability of response in adults" and "Nonselective NSAIDs: Overview of adverse effects" and "Overview of COX-2 selective NSAIDs".)

Inadequate response to NSAIDs — Intraarticular glucocorticoids can be administered in patients with persistent symptoms despite treatment with NSAIDs, and oral glucocorticoids may be of benefit in patients who do not respond to these therapies.

Intraarticular glucocorticoids — In patients with monoarthritis or oligoarthritis who do not respond adequately to NSAIDs, we suggest injection of major affected joints with intraarticular glucocorticoids. In our experience, intraarticular injection with triamcinolone acetonide (40 mg for a large joint, such as the knee, and lower doses for smaller joints), or an alternative agent in equivalent doses, is generally effective in reducing joint inflammation and in providing symptomatic relief similar to that seen in other forms of SpA or in rheumatoid arthritis. These may result in symptomatic relief sufficient to avoid the need for oral glucocorticoids or DMARD therapy and the side effects associated with use of these agents. (See "Use of glucocorticoids in the treatment of rheumatoid arthritis", section on 'Intraarticular therapy'.)

There is no evidence in our experience, nor are there any reports, of a greater frequency of adverse events or of disease worsening associated with the use of intraarticular or systemic glucocorticoids, despite the infectious etiology of reactive arthritis and the detection of the causative microbes in the joints of some patients with reactive arthritis. This issue has not been systematically evaluated. Pain and swelling of the plantar fascia can also be relieved by local

glucocorticoid injections. (See "Intraarticular and soft tissue injections: What agent(s) to inject and how frequently?" and "Use of glucocorticoids in the treatment of rheumatoid arthritis" and "Joint aspiration or injection in adults: Technique and indications" and "Joint aspiration or injection in adults: Complications".)

Systemic glucocorticoids — In patients who do not respond adequately to NSAIDs and intraarticular glucocorticoid injections or in those with a large number of involved joints, we suggest low to moderate doses of oral glucocorticoids (eg, a starting dose of prednisone 20 mg daily), which should be reduced gradually to the lowest dose required to control symptoms. In our experience, use of these agents for a limited period and in a tolerable dose range may preclude need for use of DMARD therapy. There are no randomized trials of systemic glucocorticoids in reactive arthritis. The use of glucocorticoids for inflammatory joint disease, the adverse effects of these agents, and strategies for the prevention of glucocorticoid-induced osteoporosis are described in detail elsewhere. (See "Use of glucocorticoids in the treatment of rheumatoid arthritis" and "Major side effects of systemic glucocorticoids" and "Prevention and treatment of glucocorticoid-induced osteoporosis".)

Resistant to NSAIDs and glucocorticoids — Treatment with a DMARD is indicated in patients who do not respond adequately to initial therapies. The duration prior to beginning DMARDs depends upon the degree of disease activity and upon the relative risks and benefits of NSAIDs and glucocorticoids in a given patient, given the comorbidities that are present and the dose of glucocorticoids required to control symptoms. We generally use DMARDs in patients who have not responded adequately to at least two different NSAIDs over a total of four weeks and who require ongoing therapy with more than 7.5 mg of prednisone or equivalent for more than three to six months. (See 'Chronic reactive arthritis' below.)

Chronic reactive arthritis — In patients who develop refractory reactive arthritis, usually defined as disease lasting greater than six months, or who are resistant to initial therapy for acute arthritis with NSAIDs and glucocorticoids, we initiate therapy with a nonbiologic (traditional) DMARD, usually sulfasalazine (SSZ) or, alternatively, methotrexate (MTX). In patients with disease that is refractory to a nonbiologic DMARD, we administer therapy with a tumor necrosis factor (TNF) inhibitor. The use of these medications for reactive arthritis is based upon limited data and upon clinical experience. (See 'Resistant to NSAIDs and glucocorticoids' above and 'Nonbiologic DMARD use' below and 'Resistant to nonbiologic DMARDs' below.)

Nonbiologic DMARD use

Sulfasalazine — We suggest the use of SSZ in patients with refractory reactive arthritis or with reactive arthritis resistant to initial therapy for acute arthritis. We initiate treatment with 500 mg once or twice daily and increase the daily dose stepwise (in increments of 500 mg each week) to 1000 mg twice daily. The dose can be increased to a maximum of 3000 mg/day (taken in two or three divided doses) if required. (See 'Resistant to NSAIDs and glucocorticoids' above and 'Chronic reactive arthritis' above.)

The use of SSZ in patients with reactive arthritis is based primarily upon one randomized trial in patients with reactive arthritis [69] and is further supported by a meta-analysis and randomized trials comparing it with placebo in patients with ankylosing spondylitis and with psoriatic arthritis; and by randomized trials comparing it with placebo and other nonbiologic DMARDs in rheumatoid arthritis. We prefer SSZ over MTX because of its better documented efficacy in patients with peripheral SpA, including psoriatic arthritis. (See "Sulfasalazine: Pharmacology, administration, and adverse effects in the treatment of rheumatoid arthritis" and "Treatment of psoriatic arthritis", section on 'Sulfasalazine' and "Treatment of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults".)

Benefit from SSZ was suggested by a 36-week randomized trial involving 134 patients with chronic reactive arthritis who had not responded adequately to NSAIDs [69]. Response in the trial was defined by a composite measure that included patient self-assessment, clinician assessment, and improvement in joint pain or tenderness and in joint swelling. Results for the primary outcome measure showed a trend toward benefit with SSZ that was not statistically significant but that might be clinically meaningful if real. SSZ was well-tolerated, with minor gastrointestinal side effects in some patients.

In general, the most common adverse effect causing discontinuation of therapy with SSZ is gastrointestinal upset, but central nervous system symptoms, rash, and other infrequent side effects may also occur. The use and monitoring of SSZ, as well as its adverse effects, are discussed in detail separately. (See "Sulfasalazine: Pharmacology, administration, and adverse effects in the treatment of rheumatoid arthritis", section on 'Adverse effects'.)

Methotrexate — MTX may be used as an alternative nonbiologic DMARD for patients who may be allergic to or intolerant of SSZ or who do not respond to SSZ treatment. However, MTX has not been formally studied in patients with reactive arthritis, and there is a lack of evidence to support the use of MTX for axial disease in ankylosing spondylitis, even though clinical experience suggests it may be of benefit for treating peripheral arthritis in such patients.

(See "Treatment of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults".)

The use of MTX is based upon clinical experience with its use for peripheral SpA, including psoriatic arthritis, and upon evidence in meta-analyses and in randomized trials for its efficacy in rheumatoid arthritis. In reactive arthritis, we use MTX in the same fashion and doses (15 to 25 mg given on one day weekly) as are employed in psoriatic arthritis and rheumatoid arthritis. The use and adverse effects of MTX are described in detail elsewhere. (See "Use of methotrexate in the treatment of rheumatoid arthritis" and "Major side effects of low-dose methotrexate" and "Treatment of psoriatic arthritis" and "Treatment of psoriatic arthritis", section on 'Methotrexate'.)

Duration of therapy — The nonbiologic DMARDs are continued for at least four months (SSZ) or three months (MTX) at the maximally tolerated therapeutic dose (up to 3 g/day SSZ or up to 25 mg/week MTX) to determine if there is a response to therapy and are then discontinued three to six months after the patient has entered into remission, with resolution of clinical signs and symptoms of disease activity. Some patients who do not respond to the initial DMARD therapy may respond to the alternative agent, in our experience; however, whether to use a second nonbiologic DMARD or to proceed directly to the use a biologic agent in such patients has not been formally evaluated. If disease recurs, we resume therapy with the previously effective agent.

Resistant to nonbiologic DMARDs — For patients who have reactive arthritis that is refractory to NSAIDs and glucocorticoids and who do not respond to or have a contraindication to the use of SSZ and MTX, an anti-TNF agent is often effective [70]. Examples include etanercept 50 mg/week administered by subcutaneous injection; and infliximab 3 to 5 mg/kg administered intravenously on weeks zero, two, and six and then every eight weeks. In patients who do not respond to an initial trial of one agent after three months of therapy, another TNF inhibitor can be tried instead. An effort can be made to discontinue therapy in patients who have been in remission induced by a TNF inhibitor for at least three months, but treatment should be resumed with the medication if disease then recurs.

The use of TNF inhibitors in patients with reactive arthritis is directly supported only by case reports and by small case series. Their use, rather than the use of other nonbiologic or biologic DMARDs, is also supported by clinical experience and by their effectiveness in the treatment of other spondyloarthropathies, including axial and peripheral SpA and the various forms of

psoriatic arthritis. The dosing and agents, the evidence supporting their use in patients with other types of SpA, and the adverse effects of TNF inhibitors are described in detail elsewhere. (See "Treatment of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults", section on 'TNF inhibitors' and "Tumor necrosis factor-alpha inhibitors: An overview of adverse effects" and "Treatment of psoriatic arthritis".)

Evidence directly supporting the use of TNF inhibitors in reactive arthritis is illustrated by the following examples [71,72]:

- A group of patients with reactive arthritis (seven patients) or undifferentiated SpA (nine patients) were treated with etanercept for six months; a treatment response (a composite of pain score and tender and swollen joint counts) was achieved by 9 of the 10 patients who completed the study, including patients from both groups [71]. None of the patients experienced a worsening of arthritis or an exacerbation of any suspected underlying infections.

- An observational study in France reported the efficacy and safety of anti-TNF therapies in 10 patients with reactive arthritis of recent onset (within 12 months) [72]. Five, four, and one patient(s) each received infliximab, etanercept, and adalimumab, respectively. Nine of 10 patients met response criteria, with reduction in tender and swollen joint counts, pain score, and serum C-reactive protein (CRP) levels. All eight patients taking glucocorticoids successfully discontinued them after a median of four months. Six patients discontinued the anti-TNF therapy after a median of 7.5 months; three relapsed after stopping but responded to retreatment.

There are no studies of patients with reactive arthritis refractory to the above therapies, although other approaches to the treatment of chronic inflammatory arthritis have been evaluated in SpA, including psoriatic arthritis, and in rheumatoid arthritis. Other biologics have been tried in individual patients. In the very uncommon patients who are resistant to treatment with the agents noted above, including at least two TNF inhibitors, alternative diagnoses such as other forms of SpA or central pain should be reevaluated. (See "Treatment of rheumatoid arthritis in adults resistant to initial biologic DMARD therapy" and "Treatment of psoriatic arthritis" and "Treatment of rheumatoid arthritis in adults resistant to initial conventional nonbiologic DMARD therapy" and "Treatment of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults".)

Treatment of other clinical features — Some extraarticular manifestations, including ocular

involvement and mucous membrane and skin manifestations, require additional interventions. The management approaches are based upon the treatments used for these or for similar manifestations in patients with other disorders and upon clinical experience [73-75].

None of these interventions has been systematically evaluated in randomized trials or has been the subject of observational studies in patients with reactive arthritis, and most treatment studies of antiarthritic or antibiotic therapy for reactive arthritis and reviews of this disease do not discuss the effects of such therapies on these manifestations or the recommended approaches for their treatment. Extraarticular manifestations that may require treatment include the following:

- Ocular manifestations – Patients with eye pain, visual disturbance, or abnormal eye findings should be referred for ophthalmologic evaluation, as a slit-lamp examination may be required to determine if uveitis is present. The diagnosis and treatment of conjunctivitis and anterior uveitis are discussed separately. (See "Conjunctivitis" and "Uveitis: Etiology, clinical manifestations, and diagnosis" and "Uveitis: Treatment".)

- Skin and mucous membrane lesions – Patients with very mild skin involvement or oral ulcers may not require intervention [73]. Symptomatic treatment may be sufficient in patients with oral mucosal ulcers, and topical steroids are effective in some patients [75]. The treatment of oral mucosal ulcers is discussed in detail elsewhere. (See "Oral lesions", section on 'Erosions and ulcerations'.)

  More symptomatic involvement with mild to moderate keratoderma blennorrhagica may benefit from the use of topical steroids, and some skin lesions can be treated with topical salicylates [23,74-76]. In general, treatment of these manifestations is very similar to the approach in patients with palmoplantar pustulosis from other causes. The treatment of circinate balanitis is discussed separately. (See "Neutrophilic dermatoses", section on 'Palmoplantar pustulosis' and "Balanitis in adults".)

  Patients with more severe keratoderma blennorrhagica and pustular lesions who do not respond to topical medications may require systemic DMARDs, such as MTX or a TNF inhibitor [72,76]. Other treatments that may be of benefit in keratoderma blennorrhagica include topical vitamin D (calcipotriol/calcipotriene) in mild to moderate cases [77] and retinoids in patients with more severe involvement [74,78,79]. Therapy of these skin findings and of nail involvement is similar to that used in patients with psoriasis. (See "Treatment of psoriasis in adults".)

PROGNOSIS

The course of reactive arthritis varies considerably, probably depending upon the triggering pathogen and the genetic background of the host [6,9]. The typical disease duration is three to five months. Most patients either remit completely or have little active disease within 6 to 12 months after presentation, but 15 to 20 percent may experience more chronic persistent arthritis. After entering remission of peripheral joint arthritis, pain is occasionally still noted in the joints, at entheses, or in the spine. Representative results are illustrated by the following:

- A European League Against Rheumatism (EULAR) study evaluated 152 patients with reactive arthritis who were enrolled within two months of the onset of arthritis [34]. By the end of an additional 24 weeks of observation, almost all patients had very low disease activity as determined by clinician- and patient-global assessments.

- In other studies, reactive arthritis that lasted for more than one year occurred in 4 to 19 percent of patients in Finland whose arthritis was induced by *Yersinia*, *Salmonella*, *Shigella*, and *Chlamydia* [6,15]. It is difficult to know whether this proportion of patients who develop chronic disease can be generalized to other geographic regions.

- In a 2018 study in Guatemala 15 of 32 patients showed persistence of symptoms two years after onset [24].

Some patients with chronic reactive arthritis later develop features characteristic of another of the spondyloarthritides, eg, psoriatic arthritis, ankylosing spondylitis, or the arthritis associated with inflammatory bowel disease. Human leukocyte antigen (HLA)-B27 testing has been associated with a worse prognosis in some, but not all studies, with findings suggesting that patients who are HLA-B27-positive are more likely to develop a chronic spondyloarthropathy with radiographic changes [9,34,80]. Patients with the triad of postinfectious arthritis, urethritis, and conjunctivitis may also have a poorer prognosis [81,82].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Spondyloarthritis".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

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

- Basics topic (see "Patient education: Reactive arthritis (The Basics)")
- Beyond the Basics topic (see "Patient education: Reactive arthritis (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Reactive arthritis is a rare disease even among rheumatology practices.
- Reactive arthritis has been defined by consensus as a form of arthritis that is associated with a coexisting or recent antecedent extraarticular infection. Only certain enteric and genitourinary pathogens are conventionally accepted as capable of causing reactive arthritis. These include *Chlamydia trachomatis*, *Yersinia*, *Salmonella*, *Shigella*, *Campylobacter*, *Clostridioides* (formerly *Clostridium*) *difficile*, and *Chlamydia pneumoniae*. Various other bacterial and viral infections have been suggested as triggers for postinfectious arthritis but they are by convention not considered as "reactive arthritis." (See 'Definition' above and 'Preceding infection' above.)
- Musculoskeletal features of reactive arthritis typically develop one to four weeks following an acute infection with one of the triggering organisms. At least one of the following is seen in all patients with this condition: asymmetric oligoarthritis (often affecting the lower extremities), enthesitis, dactylitis, and inflammatory back pain. (See 'Musculoskeletal signs

and symptoms' above.)

- Extraarticular manifestations occur in some patients, but none are specific for reactive arthritis. These include eye involvement, most often with conjunctivitis, but infrequently with anterior uveitis; genitourinary tract symptoms; oral mucosal ulcers; and cutaneous manifestations such as keratoderma blennorrhagica, circinate balanitis, and psoriasis-like nail changes. (See 'Extraarticular signs and symptoms' above.)

- Laboratory findings may include evidence of the antecedent infection, elevated acute phase reactants, and findings of inflammatory joint fluid in patients with arthritis. Plain radiographs are generally nondiagnostic. (See 'Laboratory findings' above and 'Imaging abnormalities' above.)

- The diagnosis is based upon the presence of characteristic musculoskeletal and other clinical features in a patient with a preceding or ongoing enteric or genitourinary infection, in whom other causes of arthritis have been excluded. There is no single definitive test for reactive arthritis. Laboratory testing to confirm infection if feasible may be helpful but is not required to make the diagnosis; such testing may include stool cultures in patients with ongoing gastrointestinal symptoms and testing for *Chlamydia trachomatis* with a vaginal swab or urine sample for nucleic acid amplification testing in patients with genitourinary symptoms and those without localizing symptoms of infection. Serologic testing for preceding infections is used primarily in epidemiologic studies but is generally not useful in clinical care. Human leukocyte antigen (HLA)-B27 testing may be useful in selected patients. (See 'Diagnostic evaluation' above and 'Antecedent or concomitant infection' above.)

- It is mandatory to consider the various differential diagnoses before diagnosing a patient as having reactive arthritis. The differential diagnosis encompasses disorders that can cause acute mono- or oligoarthritis, particularly those associated with bowel diseases or genitourinary symptoms (eg, enterovirus infection, inflammatory bowel disease, and disseminated gonococcal infection), acute septic or crystal arthritis, undifferentiated spondyloarthritis (SpA), and other postinfectious arthritic disorders. (See 'Differential diagnosis' above.)

- Antibiotic therapy should be used for treatment of active *Chlamydia trachomatis* infection, if present. In general, antibiotics are not indicated for uncomplicated enteric infections or for treatment of the arthritis itself. (See 'Genitourinary tract infection' above and 'Enteric

infection' above and 'Treatment of the infection' above.)

- We suggest treatment of arthritis in most patients initially with nonsteroidal antiinflammatory drugs (NSAIDs) in antiinflammatory doses (eg, naproxen 500 mg two to three times daily, diclofenac 50 mg three times daily, or indomethacin 50 mg three times daily), rather than starting a disease-modifying antirheumatic drugs (DMARD) upon diagnosis (**Grade 2B**). (See 'Initial therapy' above.)

- In patients who do not respond adequately to NSAIDs, we suggest intraarticular glucocorticoids, rather than initiating therapy with daily oral glucocorticoids or a DMARD. (**Grade 2C**). (See 'Intraarticular glucocorticoids' above.)

- In patients who do not respond adequately to NSAIDs and intraarticular glucocorticoid injections, we suggest low to moderate doses of systemic glucocorticoids, rather than initiating treatment with a DMARD. (**Grade 2C**). A typical dose would be prednisone, 20 mg daily, titrated to the lowest dose required to control symptoms (See 'Systemic glucocorticoids' above.)

- In patients who have not responded adequately to NSAIDs over at least four weeks and who require ongoing therapy with more than 7.5 mg of prednisone or equivalent for more than three to six months we suggest a trial of a nonbiologic DMARD, rather than continuing moderate to high dose glucocorticoids without a DMARD (**Grade 2B**). We usually prescribe sulfasalazine (SSZ, beginning with 500 to 1000 mg daily and titrating the dose to a maximum of 3 g daily). Methotrexate (MTX, up to 25 mg one day weekly) is an alternative to SSZ. Treatment with a tumor necrosis factor (TNF) blocker may be used in the rare patients who are resistant to NSAIDs and nonbiologic DMARD therapy. (See 'Nonbiologic DMARD use' above and 'Sulfasalazine' above and 'Methotrexate' above and 'Resistant to nonbiologic DMARDs' above.)

- The prognosis is good in the majority of patients, with spontaneous remission within 6 to 12 months of onset of arthritis. However, some patients have persistent but mild musculoskeletal symptoms, and others develop radiologic evidence of joint injury and evolve to a more chronic form of SpA. (See 'Prognosis' above.)

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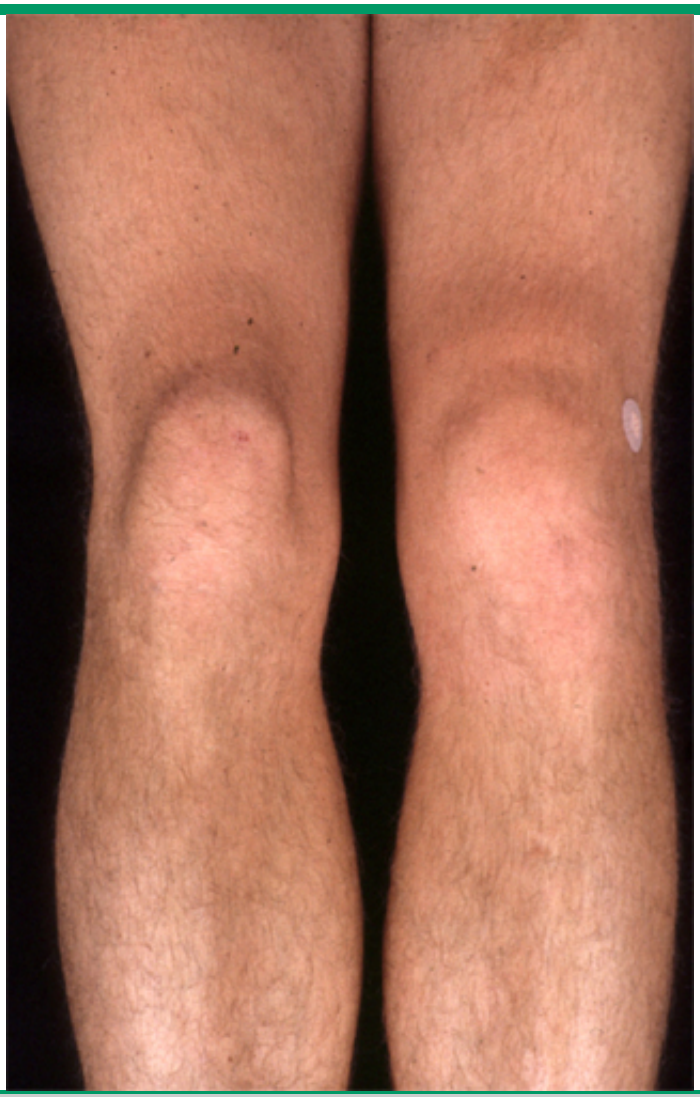
Topic 7794 Version 23.0

GRAPHICS

Asymmetical arthritis of the knees

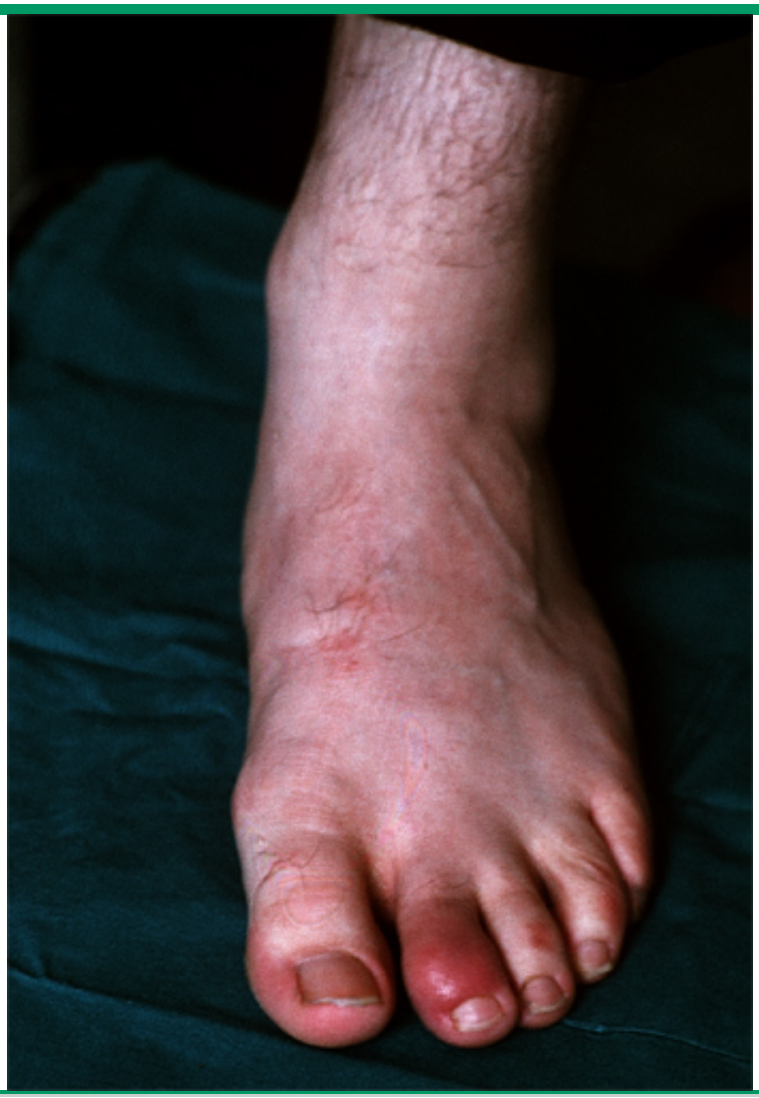


Asymmetrical swelling due to reactive arthritis is apparent in this photograph. The patellar borders are effaced and there is suprapatellar fullness of the left knee.

Courtesy of Filip de Keyser.

Graphic 67863 Version 1.0

Sausage digit (left 2nd toe)

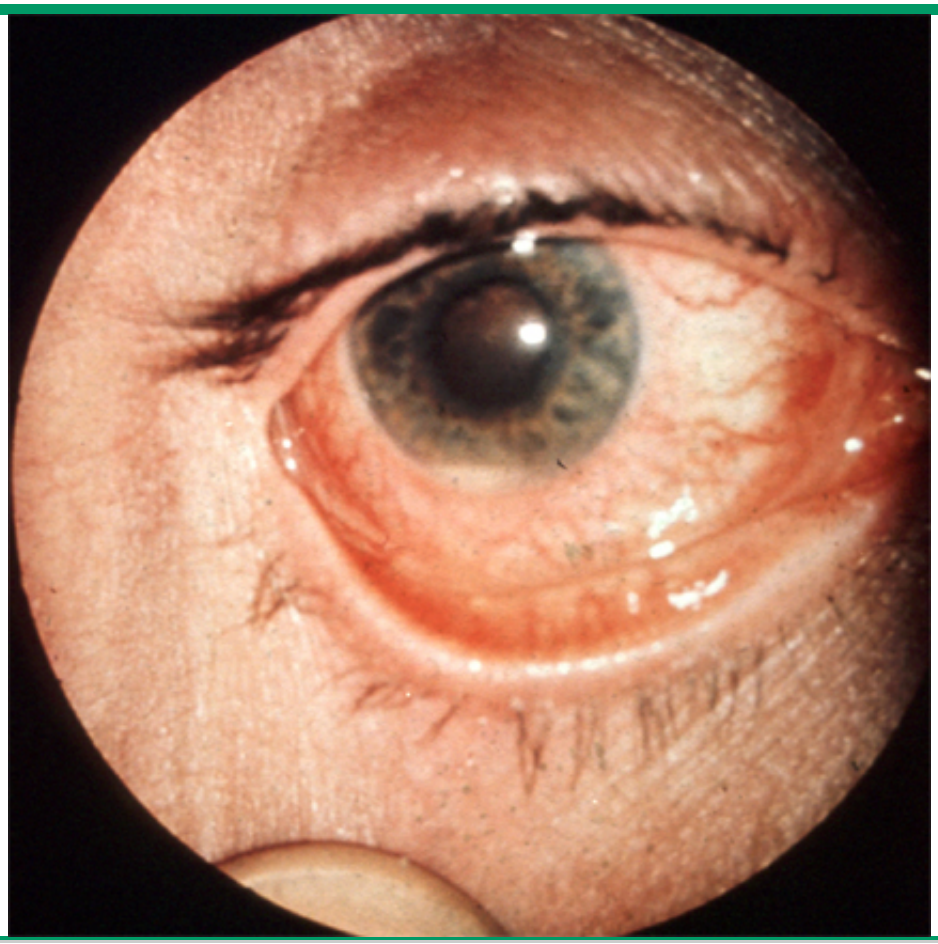


Sausage like swelling of the left second toe is apparent in this photograph of a patient with reactive arthritis.

Courtesy of Henning Zeidler.

Graphic 50959 Version 1.0

Conjunctivitis and anterior uveitis in reactive arthritis

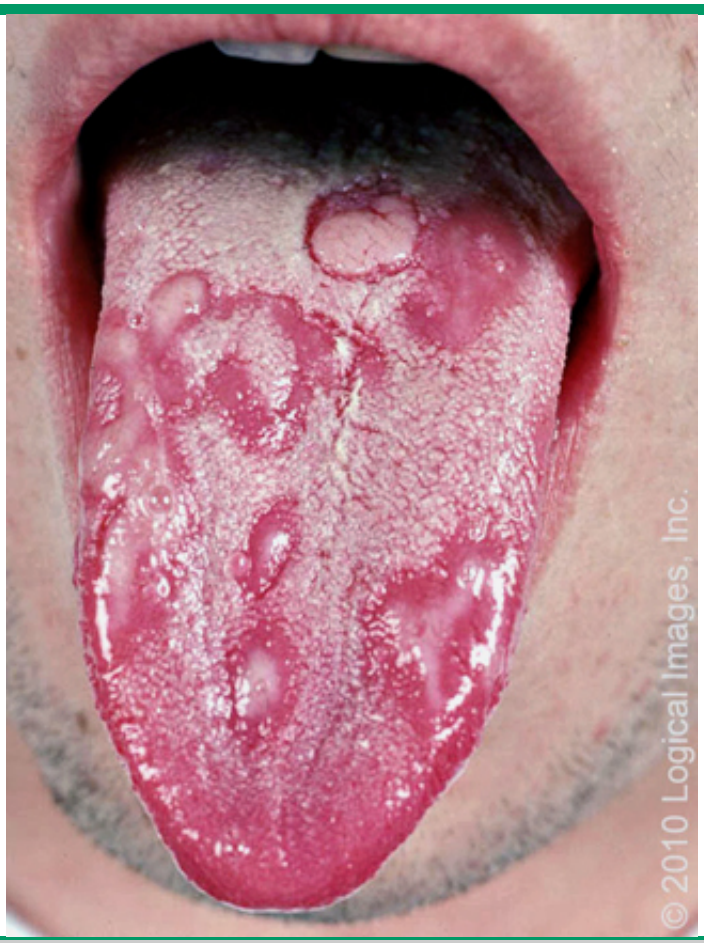


Conjunctival injection and anterior uveitis (iritis) with hypopyon are noted in the photograph of the eye of a patient with reactive arthritis (formerly Reiter's Syndrome).

Courtesy of Filip de Keyser.

Graphic 77483 Version 2.0

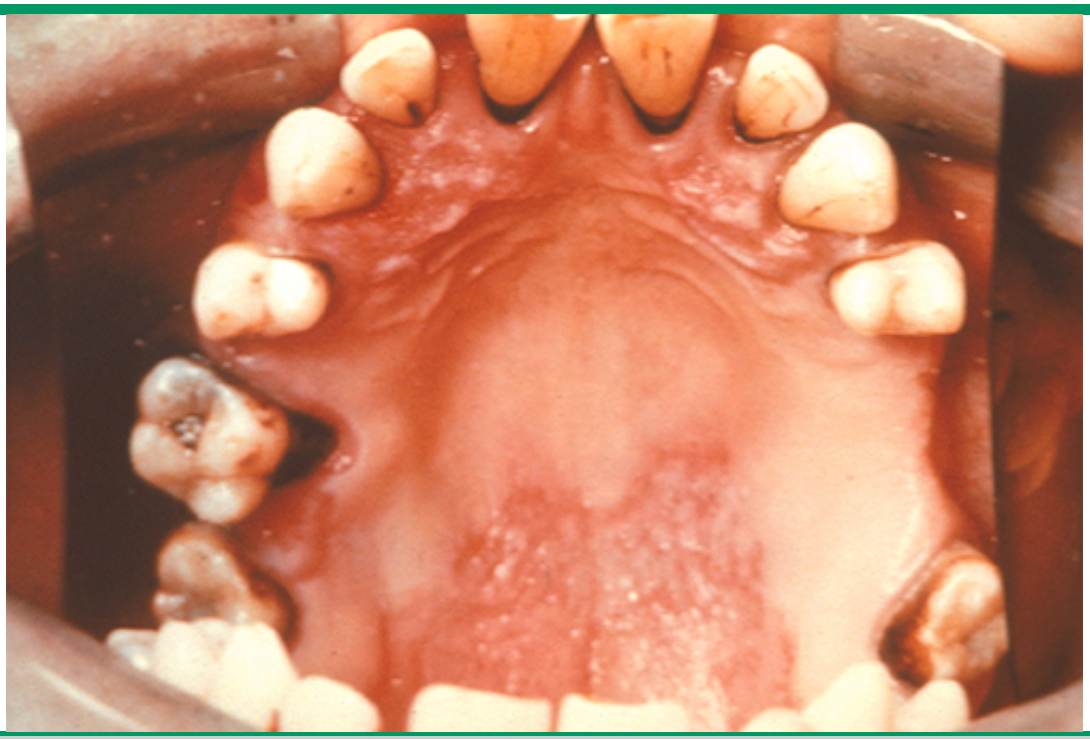
Oral lesions in reactive arthritis



Gray plaques are present on the tongue.

Graphic 53868 Version 5.0

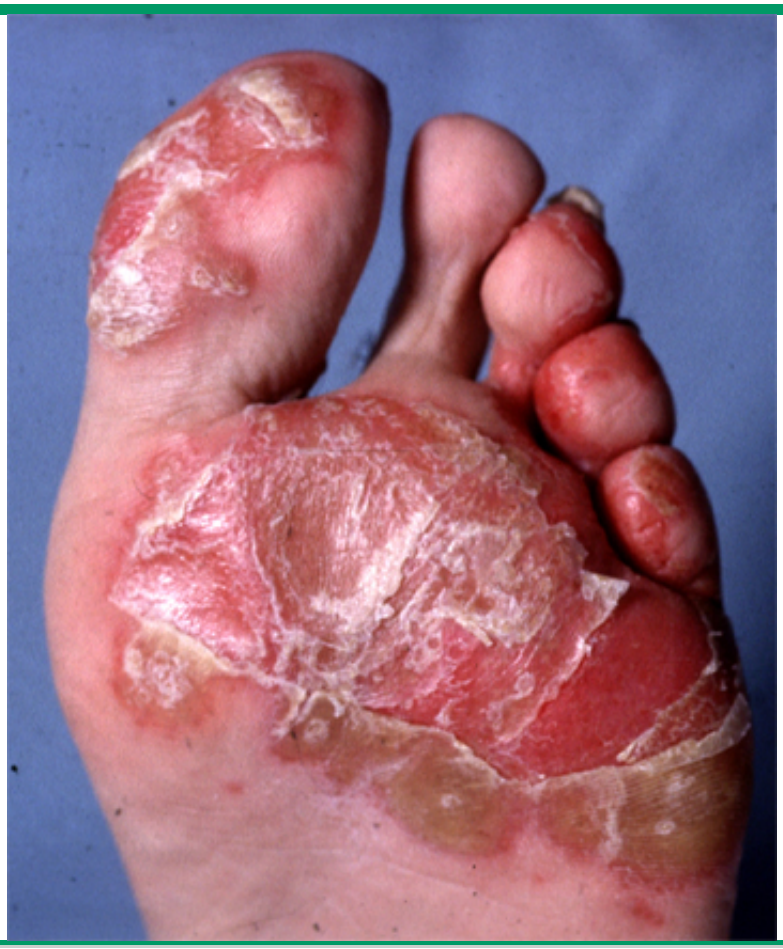
Palatal erosion in reactive arthritis



A sharply demarcated erosion of the hard palate is shown. This is among the more common of the oral manifestations of reactive arthritis.

Graphic 83797 Version 12.0

Keratoderma blennorrhagicum

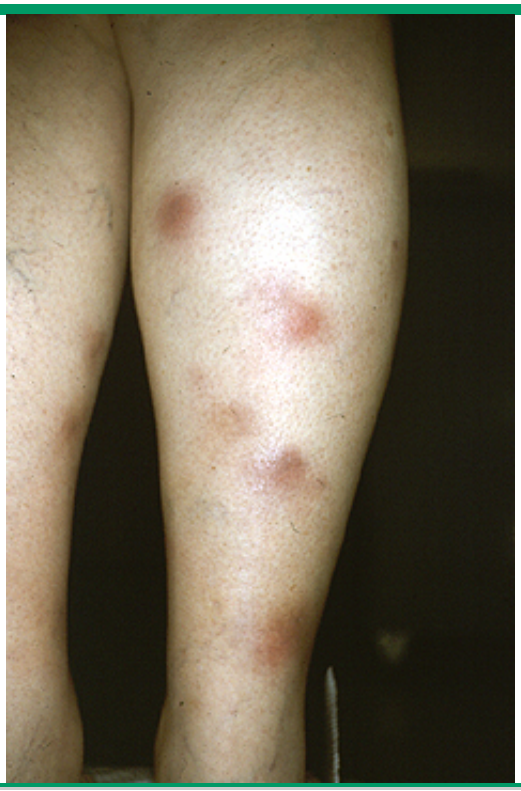


This close-up photograph shows the erythematous, scaly plaques of keratoderma blennorrhagicum in a patient with reactive arthritis (formerly Reiter's Syndrome).

Courtesy of Filip de Keyser.

Graphic 50133 Version 2.0

Erythema nodosum



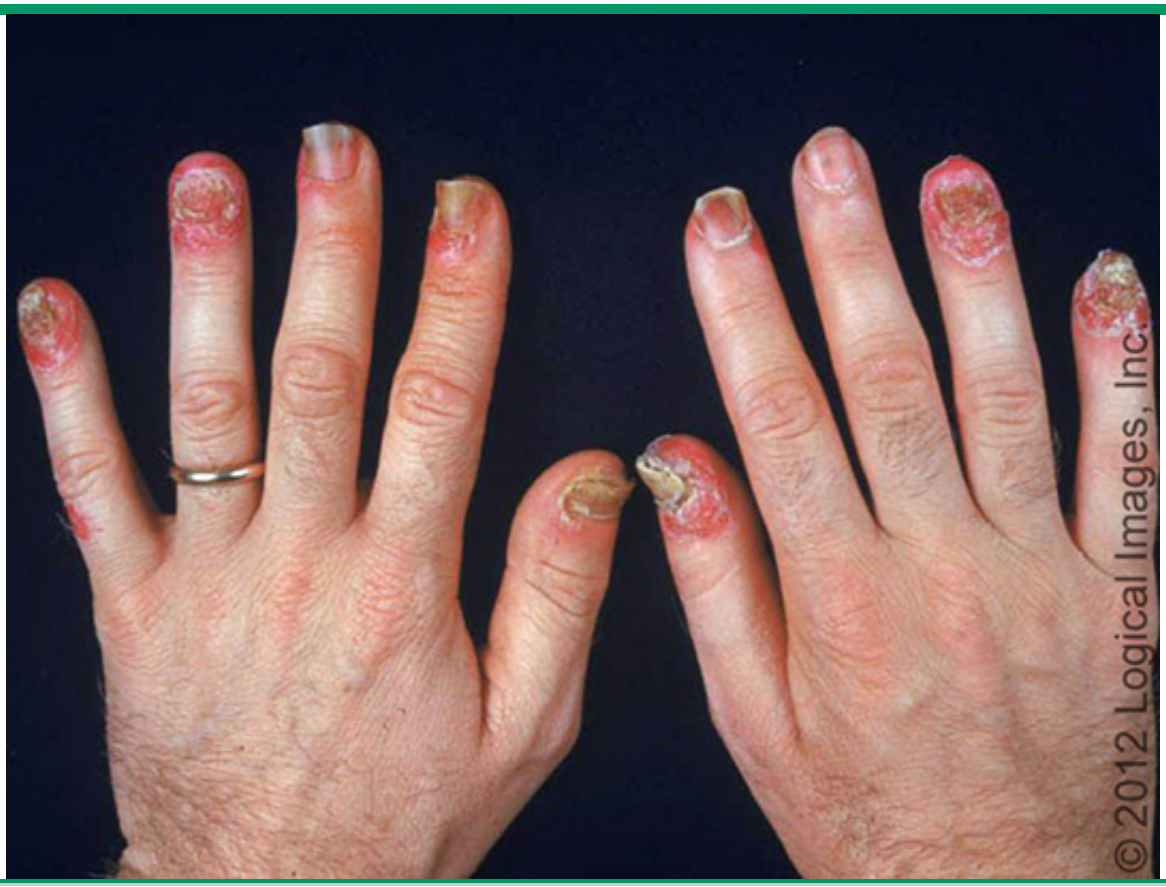
Painful erythematous nodules of erythema nodosum are often found in a symmetric distribution on the legs. The nodules can also appear to be pigmented.

Courtesy of Lee T Nesbitt, Jr. The Skin and Infection: A Color Atlas and Text, Sanders CV, Nesbitt LT Jr (Eds), Williams & Wilkins, Baltimore. 1995.

http://www.lww.com

Graphic 80056 Version 5.0

Nail changes in reactive arthritis



Subungual hyperkeratosis, onycholysis, and periungual erythematous scaly plaques are present on the hands of this patient with reactive arthritis.

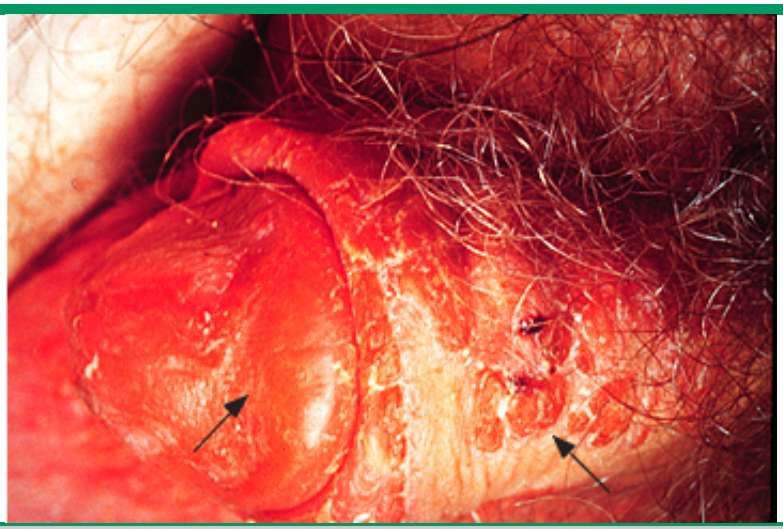
Graphic 83793 Version 4.0

Nail changes in reactive arthritis

Separation of the distal portion of the nails (onycholysis), accumulation of subungual keratotic debris, and periungual scale and erythema can occur in both reactive arthritis and psoriasis. Arthritis is present in addition to the dystrophic nail changes.

Graphic 83796 Version 14.0

Circinate balanitis



Circinate balanitis characterized by shallow ulcers on the glans penis and the shaft of the penis (arrows). The lesions are generally asymptomatic.

Courtesy of Professor Victor Newcomer, UCLA.

Graphic 62093 Version 1.0

Contributor Disclosures

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