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JUVENILE RHEUMATOID ARTHRITIS
AND REACTIVE ARTHRITIS IN CHILDREN

Practical policies for students

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JUVENILE IDIOPATHIC ARTHRITIS

Juvenile idiopathic arthritis (JIA) is a broad term used to describe several different forms of chronic arthritis in children. All forms are characterized by joint pain and inflammation. The older term, juvenile rheumatoid arthritis, has been replaced by JIA to distinguish childhood arthritis from adult-onset rheumatoid arthritis and to emphasize the fact that arthritis in childhood is a distinct disease. JIA also includes more subtypes of arthritis than did juvenile rheumatoid arthritis.

Etiology

The etiology is not completely understood but is known to be multifactorial, with both genetic and environmental factors playing key roles. Malfunctioning of the immune system in JIA targets the lining of the joint, known as the synovial membrane. This causes inflammation. When the inflammation persists, joint damage may occur. (See diagram of normal joint versus inflamed joint below.)

It is not known what causes the immune system to malfunction in JIA. These conditions are not considered hereditary and rarely involve more than one family member. Research suggests that some individuals may have a genetic tendency to develop JIA, but develop the condition only after exposure to an infection or other unknown trigger. Dietary and emotional factors do not appear to play a role in the development of JIA.

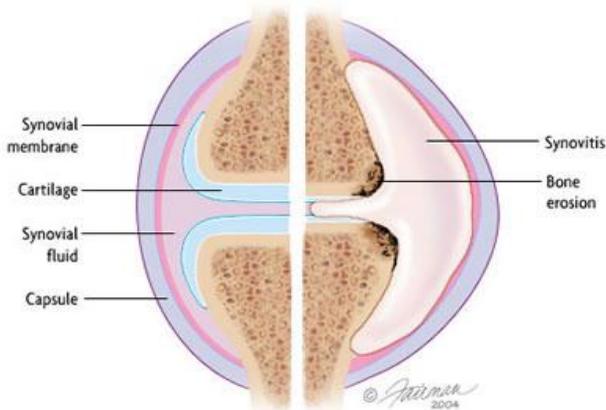


Fig. 1

JIA is the most common rheumatologic disease in children and is one of the more frequent chronic diseases of childhood. Without appropriate and early aggressive treatment, JIA may result in significant morbidity, such as leg-length discrepancy, joint contractures, permanent joint destruction, or blindness from chronic uveitis.

Arthritis is defined as joint effusion alone or the presence of two or more of the following signs: limitation of range of motion, tenderness or pain on motion, and increased warmth in one or more joints. JIA is broadly defined as arthritis of one or more joints occurring for at least 6 weeks in a child younger than 16 years of age.

JIA is a diagnosis of exclusion. A number of conditions, such as infections, malignancy, trauma, reactive arthritis, and connective tissue diseases such as systemic lupus erythematosus (SLE), must be excluded before a diagnosis of JIA can be made (*Table 1*).

Table 1 – Differential Diagnosis of Arthritis

Reactive	Poststreptococcal Rheumatic fever Serum sickness “Reiter syndrome”
Inflammatory	Juvenile idiopathic arthritis Inflammatory bowel disease Sarcoidosis
Infection	Septic joint Postinfectious: toxic synovitis Viral (eg, Epstein-Barr virus, parvovirus) Lyme disease Osteomyelitis Sacroilitis, bacterial Discitis
Systemic	Systemic lupus erythematosus Henoch-Schönlein purpura Serum sickness Dermatomyositis Mixed connective tissue disease Progressive systemic sclerosis Periodic fever syndromes Psoriasis Kawasaki disease Behçet disease
Malignancy	Leukemia Neuroblastoma Malignant bone tumors (eg, osteosarcoma, Ewing sarcoma, rhabdosarcoma)
Benign bone tumors	Osteoid osteoma Osteoblastoma
Immunodeficiency	Common variable immunodeficiency
Trauma	

JIA is subdivided into seven distinct subtypes in the classification scheme established by the International League of Associations for Rheumatology in 2001 (*Table 2*). The subtypes differ according to the number of joints involved, pattern of specific serologic markers, and systemic manifestations present during the first 6 months of disease. These categories were established to reflect similarities and differences among the different subtypes so as to facilitate communication among physicians worldwide, to facilitate research and to aid in understanding prognosis and therapy.

Table 2 – International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis

Category	Definition	Frequency (% of all JIA)	Age of Onset	Sex Ratio	Susceptibility Alleles
Systemic onset juvenile idiopathic arthritis (JIA)	Arthritis in one or more joints with or preceded by fever of at least 2 weeks' duration that is documented as daily ("quotidian") for at least 3 days and accompanied by one or more of the following: (1) rash (evanescent), (2) lymphadenopathy, (3) hepatomegaly or splenomegaly, (4) serositis	4–17	Childhood	F=M	HLA-DRB1*11
Oligo JIA	Arthritis affecting one to four joints during the first 6 months of disease	27–56	Early childhood; peak at 2–4 years	F>>>M	HLA-DRB1*08 HLA-DRB1*11 HLA-DQA1*04 HLA-DQA1*05
Persistent	Affects no more than four joints throughout the disease course				HLA-DQB1*04 HLA-A2 (early onset)
Extended	Affects more than four joints after the first 6 months of disease				

Category	Definition	Frequency (% of all JIA)	Age of Onset	Sex Ratio	Susceptibility Alleles
Polyarthritis (RF-negative)	Arthritis affects five or more joints in the first 6 months of disease. Tests for RF are negative	11–28	Biphasic distribution; early peak at 2–4 years and later peak at 6–12 years	F>>M	HLA-DRB1*0801
Polyarthritis (RF-positive)	Arthritis affects five or more joints in the first 6 months of disease. Tests for RF are positive on at least two occasions that are 3 months apart	2–7	Late childhood or adolescence	F>>M	HLA-B*04 HLA-DR4
Psoriatic arthritis	Arthritis and psoriasis, or arthritis and at least two of the following: (1) dactylitis, (2) nail pitting, (3) family history of psoriasis in a first-degree relative	2–11	Biphasic distribution; early peak at 2–4 years and later peak at 9–11 years	F>M	HLA-B*27 <i>IL23R</i> † (new association)
Enthesitis-related arthritis	Arthritis or enthesitis with at least two of the following: (1) sacroiliac tenderness or lumbosacral pain, (2) presence of HLA-B*27 antigen, (3) onset of arthritis in a male >6 years old, (4) acute anterior uveitis, (5) family history in a first-degree relative of HLA-B*27-associated disease	3–11	Late childhood or adolescence	M>>F	HLA-B*27 <i>ERAP1</i> † (new association)
Undifferentiated arthritis	Arthritis that fulfills criteria in no category or in two or more of the above categories	11–21			

Adapted from Ravelli A, Martini A. Juvenile idiopathic arthritis // Lancet. – 2007. – Vol. 369. – P. 767–768.

Diagnostic criteria of JRA

Clinical:

1. Duration of arthritis is more than 6 weeks and more (obligatory sign);
2. Affection of 3 joints during first 6 weeks of the disease;
3. Symmetric affection of small joints;
4. Affection of cervical spine;
5. Exudate in joint's cavity;
6. Morning stiffness;
7. Tendosynovitis or bursitis;
8. Uveitis;
9. Rheumatoid nodules;

Rentgenological:

10. Epiphyseal osteoporosis;
11. Narrowing of joint's fissure;
12. Signs of exudation in a joint;
13. Induration of periarticular tissues;

Laboratory:

14. Increase of ESR > 35 mm/h;
15. Presence of RF in blood serum;
16. Typical data of biopsy of synovial membrane.

At presence of 3 criteria diagnosis is considered to be probable, 4 – definite, 7 – classic (in every case presence of first criterion is obligatory). It's necessary also to exclude development of other diseases accompanied by affection of joints for diagnosing JRA.

Epidemiology

The incidence and prevalence of JIA vary worldwide. This difference likely reflects specific genetic (e.g., HLA antigen alleles) and environmental factors in a given geographic area. The incidence rate has been estimated as 4 to 14 cases per 100,000 children per year, and the prevalence rates have been reported as 1.6 to 86.0 cases per 100,000 children. JIA tends to occur more frequently in children of European ancestry, with the lowest incidence rates reported among Japanese and Filipino children.

In white populations with European ancestries, oligoarticular JIA is the most common subtype. In children of African American descent, however, JIA tends to occur at an older age and is associated with a higher rate of rheumatoid factor (RF)-positive polyarticular JIA and a lower risk of uveitis.

Different subtypes of JIA vary with respect to age and gender distributions (*Table 2*). Oligoarticular JIA, for example, occurs more frequently in girls, with a peak incidence in children between 2 and 4 years of age. Polyarticular JIA also occurs more frequently in girls and has a biphasic age of onset; the first peak is from 1 to 4 years of age and the second peak occurs at 6 to 12 years of age.

Pathogenesis

The cause of JIA is not well understood, but is believed to be influenced by both genetic and environmental factors. Twin and family studies strongly support a genetic basis of JIA; concordance rates in monozygotic twins range between 25% and 40%, and siblings of those affected by JIA have a prevalence of JIA that is 15 to 30-fold higher than the general population.

Strong evidence has been reported for the role of HLA class I and II alleles in the pathogenesis of different JIA subtypes.

Clinical features of systemic-onset JIA mostly resemble autoinflammatory syndromes, such as familial Mediterranean fever, and there is a lack of an association between systemic-onset JIA and HLA genes.

Cell-mediated and humoral immunity play a role in the pathogenesis of JIA. T cells release proinflammatory cytokines, such as tumor necrosis factor α (TNF- α), interleukin-6 (IL-6), and IL-1, which are found in high levels in patients who have polyarticular JIA and systemic-onset JIA.

The role of humoral immunity in JIA pathogenesis is supported by the increased level of autoantibodies, such as antinuclear antibodies (ANAs) and immunoglobulins, by complement activation, and by the presence of circulating immune complexes.

Clinical features

JIA is divided into seven subtypes defined by clinical features during the first 6 months of disease. The International League of Associations for Rheumatology classification of JIA includes the following subtypes: (1) Systemic-onset arthritis, (2) oligoarticular arthritis, (3) polyarticular RF-positive arthritis, (4) polyarticular RF-negative arthritis, (5) psoriatic arthritis, (6) enthesitis-related arthritis, and (7) undifferentiated arthritis, or “other.” Each subtype varies with respect to clinical presentation, pathogenesis, treatment outcomes, and prognosis. All subtypes of JIA, however, share common symptoms, such as morning stiffness or “gelling phenomenon” (stiffness after a joint remains in one position for a prolonged period) that improves throughout the day, limp, swollen joints, limitation of activities because of pain, and periods characterized by disease remission interspersed with disease flares. There is no diagnostic test for JIA; therefore, other causes of arthritis must be excluded carefully before the diagnosis is made.

Systemic-onset jia

Systemic-onset JIA is distinct compared with the other subtypes in that it is characterized by the presence of high-spiking fevers of at least 2 weeks' duration in addition to arthritis. The disease affects 10% to 15% of children who have JIA, and tends to affect boys and girls equally, with a peak age of onset between 1 and 5 years. Early in the disease course, patients can present with fatigue and anemia. The fever in systemic JIA is characterized by temperatures $>39^{\circ}\text{C}$ that occur daily or twice daily, with a rapid return to baseline or below baseline (quotidian pattern). Fever spikes usually occur in the

late afternoon or evening. Children often appear ill during febrile periods and look well when the fever subsides.

The rash in systemic JIA is described typically as an evanescent, salmon-colored macular rash that accompanies febrile periods. The rash generally is nonpruritic and occurs most commonly on the trunk and proximal extremities, including the axilla and inguinal areas. Other extra-articular manifestations that can be seen in systemic JIA include hepatosplenomegaly, lymphadenopathy, pulmonary disease, such as interstitial fibrosis, and serositis, such as pericarditis. The febrile period and other systemic features may precede the onset of arthritis by weeks to months. A definite diagnosis of JIA, however, cannot be made until arthritis is detected on physical examination.



Fig. 2. Salmon-colored rash in systemic juvenile idiopathic arthritis.
(Courtesy of Charles H. Spencer [<http://www.rheumatlas.org>].)

Laboratory abnormalities typically observed in systemic JIA include anemia, leukocytosis, thrombocytosis, elevated liver enzymes, and acute-phase reactants, such as erythrocyte sedimentation rate, C-reactive protein, and ferritin. ANA titer is usually negative and is not helpful in making the diagnosis.

Complications of systemic JIA include infection from immunosuppressive therapy, growth disturbances, osteoporosis, cardiac disease, amyloidosis, and macrophage-activation syndrome (MAS). MAS occurs in about 5% to 8% of children who have systemic JIA and is characterized by persistent fever, pancytopenia, hepatosplenomegaly, liver dysfunction, coagulopathy, and neurologic symptoms. Bone marrow examination in patients who have MAS reveals phagocytosis of hematopoietic cells by macrophages. Triggers of MAS include viral infections and certain changes in medications. Laboratory abnormalities include pancytopenia, prolongation of the prothrombin time and partial thromboplastin time, and elevated levels of D-dimer, triglycerides, and ferritin. Contrary to what would be expected, the erythrocyte sedimentation rate typically falls in MAS because of the low fibrinogen levels resulting from a

consumption coagulopathy and hepatic dysfunction. Because MAS carries a significant mortality rate of approximately 20% to 30%, early recognition and treatment of MAS with corticosteroids or cyclosporine is important to prevent multisystem organ failure.

Diagnosis of systemic JIA involves the exclusion of other conditions, such as infections, malignancy, collagen vascular diseases, and acute rheumatic fever (ARF). Infections tend to have less-predictable fever patterns than systemic JIA. Children who have leukemia tend to have leukopenia, thrombocytopenia, and elevated lactic dehydrogenase levels. In ARF, the fever tends to be persistent, the arthritis is migratory and asymmetric, cardiac involvement often is associated with endocarditis, and the rash (referred to as erythema marginatum) is associated with an expanding margin. Antistreptolysin O titers can be elevated in any inflammatory condition; however, the more specific antibodies for streptococcal infection, such as antideoxyribonuclease β , antistreptokinase, and antihyaluronidase, would be elevated only in ARF, indicating a recent group A streptococcal infection.

The prognosis of systemic JIA depends on the severity of the arthritis. Most systemic symptoms resolve over months to years, and mortality is associated mainly with MAS and infections secondary to immune suppression.

OLIGOARTICULAR JIA

Oligoarticular JIA is defined as arthritis that affects four or fewer joints in the first 6 months of disease. This subtype accounts for \approx 50% of cases of chronic arthritis in children and can be subdivided further into persistent oligoarthritis (affecting four or fewer joints throughout the disease course) or extended oligoarthritis (affecting more than four joints after the first 6 months of disease). The peak age of onset is between 2 and 4 years, with a female-to-male ratio of approximately 3:1.

Children who have oligoarticular JIA generally are well appearing and typically present with arthritis that affects the lower extremities (*Fig. 3*). In 30% to 50% of cases, one joint is affected at presentation, with the knee being the most commonly affected joint (approximately 89%). The hip joint is affected rarely in oligoarticular JIA. The typical presentation is that of a child who presents with a limp and is found to have a warm and swollen joint that is not very painful or tender. The pain tends to be worse in the morning or after being in one position for an extended period of time (the “gelling phenomenon”).

Growth disturbance may result from prolonged arthritis in a joint, resulting from increased blood flow to the growth plate at sites of inflammation, which leads to overgrowth. This complication is most common with knee arthritis and it leads to a leg length discrepancy. Later in the disease course, growth disturbances can result also from growth plate damage or premature fusion of the epiphyseal plates, leading to undergrowth of an affected extremity.



Fig. 3. Swollen right knee in a patient with oligoarticular juvenile idiopathic arthritis. (Courtesy of Charles H. Spencer [<http://www.rheumatlas.org>].)

One of the most serious complications of JIA is iritis. Approximately 15% to 20% of children who have oligoarticular JIA are found to have iritis. The iritis tends to be a chronic, anterior, nongranulomatous inflammation affecting the iris and ciliary body and often is asymptomatic. This complication tends to occur in girls affected with oligoarticular JIA at a young age who have positive ANA titers. Appropriate ophthalmologic screening evaluation is imperative in all children who have JIA, especially those who have oligoarticular JIA and are ANA-positive (*Table 3*). If left untreated, complications include corneal clouding, cataracts, band keratopathy, synechiae, glaucoma, and visual loss. The outcome depends on early diagnosis and treatment.

Table 3 – American Academy of Pediatrics Guidelines for Screening Eye Examinations

Juvenile Idiopathic Arthritis (JIA) Subtype	Risk of Iritis	Examination Frequency
Oligoarticular or polyarticular, onset <7 years of age and antinuclear factor +	High risk	Every 3–4 months
Oligoarticular or polyarticular and antinuclear antibody (–) regardless of age	Medium risk	Every 6 months
Onset >7 years of age regardless of antinuclear antibody status	Medium risk	Every 6 months
Systemic onset JIA	Low risk	Every 12 months

Adapted from Ravelli A, Martini A. Juvenile idiopathic arthritis // *Lancet*. – 2007. – Vol. 369. – P. 767–768.



Fig. 4. Cataracts resulting from chronic uveitis in a patient with juvenile idiopathic arthritis

The differential diagnosis of a child with oligoarthritis includes trauma, septic arthritis, Lyme disease, postinfectious arthritis, and malignancy. In a child who presents with features of an infectious illness, synovial fluid analysis and cultures are important to distinguish inflammatory from infectious processes. In a septic joint, for example, there are usually more than 100,000 white blood cells/mm³ with 90% being polymorphonuclear neutrophils. Lyme arthritis can occur weeks to months after the initial infection, and children typically will present with acute onset of a large, swollen joint, typically the knee. In children who have oligoarticular JIA, laboratory evaluation may be normal or indicate a mild increase in inflammatory markers. Tests for RF often are negative, and tests for ANA may be positive in low titers in 70% to 80% of children who have oligoarthritis, especially girls and those who have iritis. Among children who have JIA, those with oligoarthritis have the best prognosis.

POLYARTICULAR JIA

Children affected by arthritis in five or more joints during the first 6 months of disease are diagnosed as having polyarticular JIA. Polyarticular JIA can be either RF-positive (seropositive) or RF-negative (seronegative). RF-positive disease affects approximately 5% to 10% of patients who have JIA and mainly affects girls in late childhood or early adolescence. Seropositive patients tend to develop arthritis similar to adult rheumatoid arthritis, having a more aggressive disease course. There tends to be symmetric, small joint involvement of both the hands and feet and the cervical spine and temporomandibular joints also may be affected (*Fig. 5*). Rheumatoid nodules and a more severe erosive disease characterized by joint deformities (ie, Boutonnière and Swan neck contractures) also may occur in patients who are RF-positive. Patients with RF-negative arthritis tend to have involvement of fewer joints and have a better overall functional outcome.



Fig. 5. Proximal interphalangeal joint and metacarpal-phalangeal joint swelling (see thumbs) typical of polyarticular juvenile idiopathic arthritis. (Courtesy of Charles H. Spencer [<http://www.rheumatlas.org>].)

Children who have polyarticular JIA may present with morning stiffness, joint swelling, and limited range of motion of the affected joints. In addition, they also may experience fatigue, growth disturbances, elevated inflammatory markers, and anemia of chronic disease. Iritis may develop, although less frequently than in patients who have oligoarticular disease. The differential diagnosis of patients presenting with polyarthritis includes infection, malignancy, and other collagen vascular diseases such as SLE. Polyarthritis in an adolescent girl could be an initial manifestation of SLE.

PSORIATIC ARTHRITIS

Juvenile psoriatic arthritis is characterized as an asymmetric arthritis that can affect both large and small joints and typically has an onset in mid childhood. The condition is defined more specifically by the presence of arthritis and the typical psoriatic rash, or any two of the following if the rash is absent: family history of psoriasis in a first-degree relative, dactylitis (diffuse swelling of fingers extending beyond the joint margin), and nail pitting. Children who have psoriatic arthritis may develop iritis and should therefore undergo slit-lamp evaluations every 6 months.



Fig. 6. Swelling of left third proximal phalangeal joint with “sausage” appearance of finger in a patient with psoriatic arthritis. (Courtesy of Charles H. Spencer [<http://www.rheumatlas.org>].)

ENTHESITIS-RELATED ARTHRITIS

Children affected by enthesitis-related arthritis generally are boys >8 years of age. This type of arthritis is characterized by the presence of enthesitis, or inflammation at the sites of tendon insertions onto bone. Most patients afflicted with this type of arthritis are HLA-B27–positive. Patients typically complain of pain, stiffness, and loss of mobility of the lower back, and can present with arthritis in lower extremity joints. Unlike other JIA subtypes, the sacroiliac joints can be involved at presentation. Children with this subtype

may experience anterior or acute iritis, which is characterized by injected, erythematous conjunctiva, photophobia, and pain. Many patients who have this type of arthritis have a positive family history of an HLA-B27–related disease, such as IBD, psoriasis, or ankylosing spondylitis (AS).

Complications

One of the more common and devastating complications associated with JIA is iridocyclitis, a form of chronic anterior uveitis. The condition occurs in approximately 15% to 20% of patients who have JIA and can lead to permanent blindness. It is critical that children who have JIA be screened routinely for iritis because the uveitis can be diagnosed early in the course only with a slit lamp examination by an ophthalmologist. The frequency of required examinations is determined by the child's age and his or her ANA status. Children <6 years of age who have a positive ANA titer are at highest risk and require evaluation every 3 to 4 months. Only the systemic subtype has a minimal risk of iritis and therefore does not require routine screening.

Growth disturbances (i.e., leg length discrepancy) must be considered and monitored in growing children who have chronic arthritis. Prolonged arthritis affecting a knee can result in accelerated growth of the affected leg. Prolonged arthritis in ankles or feet and wrists or hands usually results in local growth retardation. Arthritis of the temporomandibular joint can be particularly devastating because of the growth plate's close proximity to the joint space, resulting in micrognathia.

Osteopenia and osteoporosis, permanent joint damage, and persistent arthritis leading to significant disability and functional limitations are other complications of prolonged uncontrolled arthritis. Psychosocial factors, such as anxiety and school absenteeism, also can occur in children who have a more prolonged disease course.

Treatment

Treatment of JIA relies on a multidisciplinary approach that includes physical and occupational therapy, pharmacologic therapy, and psychosocial interventions. There is no cure for JIA at present, but current therapies, including the use of biologic medications, have improved the prognosis of this condition significantly. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first line of treatment for patients who have JIA. NSAIDs may be sufficient to control cases of mild arthritis. Most children tolerate NSAIDs well, but a few develop adverse effects, such as abdominal pain; hematologic, renal, hepatic, and neurologic adverse effects can occur also. Cox-2 inhibitors, such as celecoxib, occasionally are used in patients who have severe gastrointestinal complaints. In children who have IBD, traditional NSAIDs should be avoided because these can cause a flare in the bowel symptoms. Cox-2 inhibitors would be the choice in this condition.

Intra-articular corticosteroid injections may be very effective in controlling arthritis in patients who have limited disease, such as persistent oligoarthritis.

Triamcinolone hexacetonide is used commonly and may lead to rapid resolution of inflammation that may last for a prolonged time and replace the need for oral therapy. Oral or intravenous (IV) corticosteroids are used mainly for systemic manifestations of JIA and, in some cases, for severe polyarthritis.

Patients may be given low doses of prednisone to obtain symptomatic relief of pain and stiffness while waiting for a second-line agent to become effective. High-dose solumedrol or a “pulse” (30 mg/kg with a maximum of 1 g) may be given in systemic-onset JIA that is refractory to oral corticosteroids or to gain control over the disease rapidly with fewer adverse effects than high-dose oral corticosteroids. Adverse effects of corticosteroids are seen most commonly at higher dosages (e.g., >20 mg/d) and include immunosuppression, adrenal suppression, increased appetite and weight gain, acne, mood changes, osteoporosis and avascular necrosis, cataracts and increased intraocular pressures, cushingoid features, and diabetes.

Disease-modifying antirheumatic drugs are agents that slow the radiologic progression of disease and are required by two-thirds of children. These agents include sulfasalazine, azathioprine, hydroxychloroquine, leflunomide, cyclosporin, and methotrexate. Methotrexate, a folate antagonist, is the disease-modifying antirheumatic drug most commonly prescribed in children who have more aggressive arthritis. Methotrexate is given once weekly in either the oral or subcutaneous route. The effects of this medication generally are seen within 6 to 12 weeks. Adverse effects mainly include gastrointestinal manifestations, such as oral ulcers, abdominal pain, nausea, decreased appetite, and hepatic dysfunction (i.e., elevation of liver enzymes). Folic acid can be administered to decrease these gastrointestinal side effects.

Pulmonary toxicity is a known adverse effect that rarely occurs in children. There is an increased risk of immunosuppression while on methotrexate and patients should not receive any live virus vaccines such as measles-mumps-rubella, varicella, and intranasal flu vaccines. A child taking methotrexate who develops a fever or is unwell should be examined by the pediatrician and have studies sent (complete blood count, blood and urine cultures) to exclude an underlying bacterial infection. An increased risk of lymphoproliferative malignancies also is reported in children who take methotrexate. Blood counts and liver enzymes are monitored every 4 to 8 weeks while a child is taking methotrexate. Generally, a child is treated with methotrexate for at least 1 year after achieving disease remission. Overall, methotrexate is a very safe and effective drug and is now considered a “gold-standard” therapy for children who have JIA.

Use of biologic agents has improved the morbidity associated with JIA significantly. Biologic drugs are medications, such as monoclonal antibodies, soluble cytokine receptors, and receptor antagonists, that target specific proteins involved in the inflammatory cascade. All biologics are given through the IV or subcutaneous route. All of these agents carry a risk of immunosuppression and cytopenias.

As with methotrexate, a child taking a biologic who develops a fever or appears unwell even without a fever must be examined and have blood work to exclude a serious bacterial infection. Biologics should not be given while a child is acutely ill. Also, children on biologics should not be given live vaccines.

Elevated levels of TNF- α are found in patients who have JIA. Etanercept, infliximab, and adalimumab are biologic agents that block TNF- α . Etanercept is a soluble TNF receptor that binds and inhibits TNF- α and was approved by the FDA in 1999 for the treatment of JIA in children >2 years of age. The drug has been shown to be highly effective in patients who have extended oligoarthritis or polyarticular JIA who were not responsive to treatment with NSAIDs or methotrexate. In addition to the risk of immunosuppression, headache, upper respiratory tract infections, and injection site reactions are other common adverse effects.

Infliximab, a chimeric monoclonal antibody to TNF- α that is given through the IV route, has been shown to be efficacious in the treatment of JIA and uveitis. Adalimumab, a humanized monoclonal antibody to TNF, was the second biologic agent to be approved by the FDA in 2008 for moderate to severe JIA in children >4 years of age. Unlike etanercept, which is given once weekly, adalimumab is given once every 2 weeks and has been shown to be effective in patients who have polyarticular JIA.

Recently, anakinra, an anti-IL-1 receptor antagonist, and tocilizumab, an anti-IL-6 monoclonal antibody, which is now approved by the FDA, have demonstrated promising results in the treatment of patients who have systemic JIA. Abatacept, a recombinant fusion protein that down-regulates T-cell stimulation, was approved by the FDA in 2008 for moderate to severe polyarticular JIA in children >6 years old. Other therapies, such as rituximab and rilonacept, are being studied for the treatment of JIA. The duration of treatment with biologics is at least for 1 year after disease remission is achieved. Treatment of uveitis depends largely on the ophthalmologist's recommendations. If inflammation persists or the patient is unable to taper off corticosteroid ophthalmic drops, often methotrexate is started. Infliximab and adalimumab also have been found to be quite beneficial in the treatment of uveitis.

Autologous stem cell transplantation

Patients who have JIA that is refractory to the previously described medical interventions may undergo autologous stem cell transplantation. Autologous stem cell transplantation involves using immunosuppression to remove autoreactive lymphocytes followed by stem cell transplantation.

Other considerations

Other treatment considerations must include physical therapy and occupational therapy to improve mobility of affected joints and maintain muscle strength.

Prognosis

Approximately 50% of children who have JIA continue to have active disease into adulthood. In patients who have active disease into adulthood, there can be significant disability, such as joint deformity, growth abnormalities,

visual disturbance caused by uveitis, functional limitations because of pain, and so forth. Factors affecting disease outcome include disease duration, presence of polyarticular disease, and use of systemic corticosteroid treatment. The mortality rate in JIA based on reports from the United States and Canada is 0.29 per 100 patients, and most deaths occur in patients who have systemic JIA.

Reactive arthritis in children

Reactive arthritis (ReA), or Reiter syndrome (this eponym is not used because of Reiter's activities as a Nazi war criminal) is an autoimmune condition that develops in response to an infection. ReA has been associated with gastrointestinal (GI) infections with *Shigella*, *Campylobacter*, and other organisms, as well as with genitourinary (GU) infections (especially with *Chlamydia trachomatis*). The classic triad characteristically associated with this condition comprises noninfectious urethritis, arthritis, and conjunctivitis (though this triad is not found in all cases).

ReA is frequently associated with the human leukocyte antigen (HLA)-B27 haplotype and is classified in the category of seronegative spondyloarthropathies, which includes ankylosing spondylitis, psoriatic arthritis, the arthropathy of associated inflammatory bowel disease, juvenile-onset ankylosing spondylitis, juvenile chronic arthritis, and undifferentiated spondyloarthritis. Most ReA patients are young men. Young children tend to have the postdysenteric form, whereas adolescents and young men are most likely to develop ReA after a genitourinary infection. Some authors, interpreting the mucocutaneous findings as pustular psoriasis and the seronegative arthritis as psoriatic arthritis, believe that ReA is best classified as a type of psoriasis.

Defining criteria

The classic triad of ReA (arthritis, conjunctivitis or iridocyclitis, and nonbacterial urethritis or cervicitis) occurs in only about one third of patients at onset. Some prefer to describe it as a tetrad, adding the mucocutaneous findings of balanitis circinata and keratoderma blennorrhagicum to the classic triad. In this view, the complete and incomplete forms of ReA can be identified by the presence or absence of the mucocutaneous involvement.

Pathophysiology

ReA is usually triggered by a GU or GI infection. Evidence indicates that a preceding *Chlamydia* respiratory infection may also trigger ReA. The frequency of ReA after enteric infection averages 1-4% but varies greatly, even among outbreaks of the same organism. Although severely symptomatic GI infections are associated with an increased risk of ReA, asymptomatic venereal infections more frequently cause this disease. About 10% of patients have no preceding symptomatic infection.

ReA is associated with HLA-B27. Results for HLA-B27 are positive in 65-96% of patients with ReA.

The mechanism by which the interaction of the inciting organism with the host leads to the development of ReA is not known.

Synovial fluid cultures are negative for enteric organisms or Chlamydia species. However, a systemic and intra-synovial immune response to the organisms has been found with intra-articular antibody and bacterial reactive T cells. Furthermore, bacterial antigen has been found in the joints. Thus, the elements for an immune-mediated synovitis are present.

ReA can occur in patients with HIV infection or AIDS—most likely because both conditions can be sexually acquired, rather than because ReA is triggered by HIV.

Etiology

Infectious causes

Organisms that have been associated with ReA include the following:

- *C. trachomatis* (L2b serotype)
- *Ureaplasma urealyticum*
- *Neisseria gonorrhoeae*
- *Shigella flexneri*
- *Salmonella enterica* serovars Typhimurium, Enteritidis, and Hadar
- *Mycoplasma pneumoniae*
- *Mycobacterium tuberculosis*
- *Cyclospora*
- *Yersinia enterocolitica* and pseudotuberculosis
- *Campylobacter jejuni* and *coli*
- *Clostridium difficile*
- Beta-hemolytic (eg, group A) and viridans streptococci

Other possible linkages include infection with *C. difficile* and with bacillus Calmette-Guérin (BCG). ReA has also been shown to occur after tetanus and rabies vaccination.

Genetic factors

ReA has an important genetic component; it tends to cluster in certain families and almost exclusively affects males, and HLA-B27 is identified in 70–80% of patients. HLA-B27 may share molecular characteristics with bacterial epitopes, facilitating an autoimmune cross-reaction instrumental in pathogenesis. HLA-B27 contributes to the pathogenesis of the disease and reportedly increases the risk of ReA 50-fold.

Epidemiology

International statistics

The infections that incite ReA may vary with geographic location. For example, *Y. enterocolitica* is more commonly identified in Europe than in North America and thus is responsible for more cases of ReA in countries such as Finland and Norway. More than 40 subtypes of HLA-B27 are known; those associated with the spondyloarthropathies are HLA-B2702, B2704, and B2705. These subtypes may be somewhat geographically segregated. For example, the subtype B2705 is found predominantly in Latin America, Brazil, Taiwan, and parts of India. It is noteworthy that subtypes HLA-B2706 and B2709—found in native Indonesia and Sardinia, respectively—may be partially protective against ReA.

Age-, sex-, and race-related demographics

ReA is most common in young men, with the peak onset in the third decade of life. It rarely occurs in children; when it does, the enteric form of the disease is predominant. Most pediatric patients present with symptoms after the age of 9 years.

ReA after foodborne enteric infections is equally common in males and females. However, the male-to-female ratio for disease associated with venereally acquired infections has been estimated to range from 5:1 to 10:1. A possible prostatic focus of persistent infection is postulated to explain the male predominance of ReA.

The frequency of ReA appears to be related to the prevalence of HLA-B27 in the population. As with other spondyloarthropathies, HLA-B27 and ReA are more common in white people than in black people. When ReA occurs in black persons, it is frequently B27-negative.

Prognosis

ReA has a variable natural history but typically follows a self-limited course, with resolution of symptoms by 3-12 months, even in patients who are acutely incapacitated. A fatal outcome is seldom reported, but death can occur, and it is usually related to the adverse effects of treatment. Post-dysenteric cases are associated with a better prognosis than post-venereal cases. ReA has a high tendency to recur (15-50% of cases), particularly in individuals who are HLA-B27-positive. A new infection or other stress factor could cause reactivation of the disease. Approximately 15–30% of patients with ReA develop a long-term, sometimes destructive, arthritis or enthesitis or spondylitis.

Physical Examination

Physical findings in ReA may involve the musculoskeletal system, the skin and nails, the eyes, the GU tract, the GI tract, and other systems.

A scoring system for diagnostic points in ReA-like spondyloarthropathies exists. In this system, the presence of 2 or more of the following points (1 of which must pertain to the musculoskeletal system) establishes the diagnosis:

- Asymmetric oligoarthritis, predominantly of the lower extremity
- Sausage-shaped finger (dactylitis), toe or heel pain, or other enthesitis
- Cervicitis or acute diarrhea within 1 month of the onset of arthritis
- Conjunctivitis or iritis
- Genital ulceration or urethritis

Joints, axial skeleton, and entheses

Articular involvement in ReA is typically asymmetric and usually affects the weight-bearing joints (i.e., knees, ankles, and hips), but the shoulders, wrists, and elbows may also be affected. In more chronic and severe cases, the small joints of the hands and feet may be involved as well. Dactylitis (i.e., sausage digits) may develop. In children, joint involvement is oligoarticular in 69% of cases, polyarticular in 27%, and monoarticular in 4%.

Joints are commonly described as tender, warm, swollen, and, sometimes, red. Symptoms may occur initially or several weeks after onset of other symptoms. Migratory or symmetric involvement is also reported. Periostitis and

tendinitis may occur, especially involving the Achilles tendon, which produces pain in the heel. The arthritis is usually remittent and rarely leads to severe limitation of functional capacity. Muscular atrophy can develop in severely symptomatic cases.



Fig. 7. Swelling of right knee with effusion caused by arthritis. Image courtesy of Gun Phongsamart, MD



Fig. 8. Remarkable tenderness of left sacroiliac joint caused by sacroiliitis. Image courtesy of Gun Phongsamart, MD



Fig. 9. Plaques on soles of patient with reactive arthritis



Fig. 10. Painful erosions on fingers in patient with reactive arthritis

Enthesopathy, or enthesitis (i.e., inflammation of ligament and tendon insertions into bone), is thought to be a characteristic feature of ReA. The Achilles insertion is the most common site; other sites include the plantar fascial insertion on the calcaneus, ischial tuberosities, iliac crests, tibial tuberosities, and ribs.

Sacroiliitis frequently occurs in adults who are positive for human leukocyte antigen (HLA)–B27 (though it is apparently less common in children). It is typically self-limiting. Whereas 50% of patients with ReA may develop low-back pain, most physical examination findings in patients with acute disease are minimal except for decreased lumbar flexion. Patients with more chronic and severe axial disease may develop physical findings similar to, or even indistinguishable from, those of ankylosing spondylitis.

Skin and nails

Skin and mucocutaneous lesions are commonly observed in ReA. The dermal lesions are typified by keratoderma blennorrhagicum, in which hyperkeratotic skin begins as clear vesicles on erythematous bases and progresses to macules, papules, and nodules – found on the soles of the feet, palms, scrotum, trunk, or scalp – and eventually coalescing to form a hyperkeratotic erythematous dermatitis resembling pustular psoriasis.



Fig. 11. Plaques and erosions of tongue in patient with reactive arthritis

Distal involvement with painful and erosive lesions in the tips of the fingers and toes, with pustules and subungual pustular collections, also occurs.

In some patients, typical keratoderma blennorrhagicum develops 1–2 months after the onset of arthritis, with keratotic papules and plaques that are painful under pressure; sometimes, these can be disabling.

Erythematous macules and plaques, diffuse erythema, erosions, and bleeding can appear on the oral and pharyngeal mucosae in 30–60% of patients. Circinate lesions on the tongue resemble geographic tongue.

Erythema nodosum may develop but is uncommon.

Nail dystrophy is present in 20–30% of patients. The nails can become thickened and ridged and may crumble, in a manner resembling mycotic infection or psoriatic onychodystrophy, but nail pitting is not observed. Nail shedding is common.

Eyes

Conjunctivitis is a component of the original triad and is one of the hallmarks of the disease, reported to appear in 33–100% of patients. It tends to occur early in the disease, especially during the initial attack; it may be missed if patients are seen only during subsequent attacks.

An intense red, velvet like conjunctival injection characterizes the conjunctivitis. Bilateral involvement is common. Edema and a purulent discharge are not rare. The conjunctivitis may be mild and painless or may cause severe symptoms with blepharospasm and photophobia. It usually resolves spontaneously within 2 weeks.

Anterior uveitis (including iritis, iridocyclitis, or cyclitis) is the second most common ocular finding. Iridocyclitis may be the initial ocular manifestation in some patients. Uveitis may occur in 12–37% (or possibly as many as 50%) of patients with ReA and is more frequently found in patients with HLA-B27 and those with sacroiliitis. At clinical examination, redness, pain, impaired vision, and exudation with hypopyon can suggest iritis. Rarely, an ReA patient may have permanent visual loss from macular infarction or foveal scarring.

A particularly serious ocular manifestation is recurrent nongranulomatous iridocyclitis. Recurrences are usually associated with an acute iridocyclitis that has a rapid onset with conjunctival and episcleral edema and injection. The corneal endothelium has cellular debris and poorly defined, small- to medium-sized keratic precipitates. Heavy flare and cells and a very early tendency toward formation of posterior synechiae are characteristic, more so than in most other forms of acute iridocyclitis.

Even the most aggressive pupil-dilation management is sometimes inadequate to prevent synechiae formation. A peripheral iridectomy may be necessary to prevent iris bombé and angle closure if the synechiae cannot be broken.

Other ocular findings that may be noted in ReA include the following:

- Scleritis
- Episcleritis
- Keratitis – Rarely (4% of cases), patients may develop a punctate epithelial keratitis that may lead to central loss of the corneal epithelium and subepithelial infiltrates
 - Cataracts – Lens clouding and posterior subcapsular cataracts occur with prolonged or repeated episodes
 - Hypotony – This may occur after a severe or prolonged course and may persist after resolution
 - Glaucoma – Secondary open-angle glaucoma may occur because of the anterior chamber reaction and the trabecular obstruction or trabeculitis; it usually resolves with aggressive anti-inflammatory therapy; with repeated recurrences, damage to the trabecular meshwork may occur, resulting in secondary glaucoma

- Corneal ulceration
- Disc or retinal edema
- Retinal vasculitis
- Optic neuritis
- Dacryoadenitis (occurs rarely in the setting of chlamydial urethritis)

Genitourinary tract

Urogenital symptoms may be primary or postdysenteric and may include the following:

- Meatal edema and erythema and clear mucoid discharge
- Prostatitis causing tenderness (up to 80%) and vulvovaginitis
- Circinate balanitis (balanitis circinata)
- Cervicitis
- Cystitis
- Salpingo-oophoritis

Circinate balanitis, consisting of small shallow painless ulcers of the urethral meatus or the glans penis, is characteristic. The condition is characterized by circinate or gyrate white plaques that grow centrifugally and eventually cover the entire surface of the glans penis. The penile shaft and scrotum can be involved. On an uncircumcised penis, the lesions typically remain moist; on a circumcised penis, they may harden and crust, causing pain and scarring in 50% of patients.

Circinate vulvitis is reported in women. Balanitis and vulvitis are rare in children; when they occur, they are suggestive of ReA.

Prostatitis, cystitis, and pyelonephritis are rare but possible urogenital manifestations of reactive arthritis. Bartholinitis can be present in women. Proctitis caused by *Chlamydia* species can occur in both sexes after anal intercourse.

Urethritis is difficult to diagnose in children but is present in 30% of pediatric patients at onset. Obtaining a history of dysuria from children is difficult, possibly because the urinary abnormality is mild or absent. In patients with painless discharge, staining of the underpants may be evident.



Fig. 12. Balanitis circinata in patient with reactive arthritis.
Image courtesy of Gun Phongsamart, MD

Gastrointestinal tract

Enteric infections may trigger ReA. Pathogens include Salmonella, Shigella, Yersinia, and Campylobacter species. The frequency of ReA after these enteric infections is about 1%–4%. Other enteric bacteria that have been associated with ReA include C difficile, E coli, and Helicobacter pylori.

Other findings

Aortic regurgitation caused by inflammation of aortic wall and valve may occur. This proximal aortitis can be found in 1–2% of cases. Aortitis may be accompanied by coronary inflammation, which can be fatal in rare cases. Transient conduction abnormalities may develop but are of little significance; rarely, patients may be affected by myocarditis or pericarditis.

Other manifestations of ReA include mild renal pathology with proteinuria and microhematuria. In severe chronic cases, amyloid deposits and immunoglobulin A (IgA) nephropathy have been reported in association with reactive arthritis. IgA nephropathy is the most common type of primary glomerulonephritis worldwide.

Complications

Complications of ReA include the following:

- Recurrent arthritis (15-50%)
- Chronic arthritis or sacroiliitis (15-30%)
- Ankylosing spondylitis (30-50% of HLA-B27–positive patients)
- Urethral stricture
- Aortic root necrosis
- Secondary glaucoma

- Cataracts
- Cystoid macular edema
- Posterior and anterior synechiae
- Cyclitic membrane
- Vitreous opacification
- Ankylosing spondylitis, psoriatic arthritis, and sacroiliitis
- Erythroderma (rare)

In severe cases, functional impairment may be severe, and a chronic and prolonged clinical course is followed by sequelae (e.g., urethral stenosis, chronic arthritis, or ocular impairment).

Diagnostic Considerations

Gonorrhea and other types of infectious urethritis must be ruled out by means of microbiologic cultures of the urethral exudate. Gonococcal arthritis does not involve the spine.

Rheumatoid arthritis and psoriatic arthritis, as well as ankylosing spondylitis, must be differentiated from ReA.

Septic arthritis must be ruled out if suspected before a diagnosis of ReA is made. Oligoarticular and asymmetrical involvement, together with the clinical course, may contribute to the diagnostic suspicion.

Rheumatic fever and serum sickness are characterized by a course that is more acute than that of ReA.

Syphilis may mimic ReA, especially secondary syphilis in its so-called malignant form with polymorphic vesicular pustules covered with thick crusts.

Other conditions to be considered include the following:

- Acute lymphoblastic leukemia
- Immunotherapy/immunization–related arthropathy
- Synovitis, acne, pustulosis, hyperostosis, and osteomyelitis (SAPHO) syndrome
- Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome
- Systemic autoinflammatory disorders

Approach Considerations

The diagnosis of reactive arthritis (ReA) is clinical, based on the history and physical examination findings. A high index of suspicion is required. No laboratory study or imaging finding is diagnostic of ReA. No specific tests or markers are indicated. Indicators of inflammation are usually abnormal.

Laboratory Studies

The values of acute-phase reactants, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are usually elevated markedly (e.g., ESR of 50–60 mm/hr) but later return to the reference range when the inflammation subsides. C1, C4, and C5 levels are within the reference range. C1 inhibitor functional assay (C1INH) and C2 levels may be elevated.

Other laboratory findings include a normocytic normochromic anemia along with mild leukocytosis (up to 20,000/ μ L) and thrombocytosis during the acute phase. Immunoglobulin A (IgA) antibodies to specific bacterial antigens

have been reported. Test results for rheumatoid factor and antinuclear antibodies are negative.

Referral for HIV should be considered in patients presenting with history, symptoms, or findings suggesting increased risk for the disease.

White blood cells (WBCs), red blood cells (RBCs), and small amounts of protein are present in urinalysis findings, indicating pyuria. Urine culture findings may be positive for Chlamydia or Ureaplasma, though test results may be negative if obtained several weeks after the onset of symptoms.

Chlamydia should be sought in every case of ReA. Serology is useful in some cases; however, culture techniques may not be reliable, causative agents are only identified in only 58% of cases with genitourinary (GU) symptoms, and there is a high positive rate in control populations.

If urethritis or cervicitis is present, cervical or urethral cultures should be obtained.

Results of routine urine cultures are negative. Stool cultures can be helpful for enteric pathogens (e.g., Salmonella, Shigella, and Yersinia).

The presence of human leukocyte antigen (HLA)-B27 correlates with axial disease, carditis, and uveitis. HLA-B27 test results are positive in 67–92% of pediatric cases of ReA. HLA-B27 testing is not diagnostic of ReA.

A tuberculin skin test may be appropriate in certain individuals, particularly those with demographics strongly suggestive of infectious tuberculosis (TB).

Radiologic examination may demonstrate various arthritic changes. These changes tend to be asymmetric and oligoarticular and are more common in the lower extremities. However, radiologic signs are present in only 40–70% of cases, and they may be completely absent even in instances of severe disease. Early in the disease process, radiography often reveals no abnormalities at all.

In more advanced or long-term ReA, periosteal reaction and proliferation at sites of tendon insertion are visible. Exuberant plantar spurs are a common sign in long-term ReA. Changes consistent with chronic plantar fasciitis or Achilles tendinitis may be seen. In the hands and feet, marginal erosions with adjacent bone proliferation occur. The erosions typically have indistinct margins and are surrounded by periosteal new bone and periostitis (see the images below).

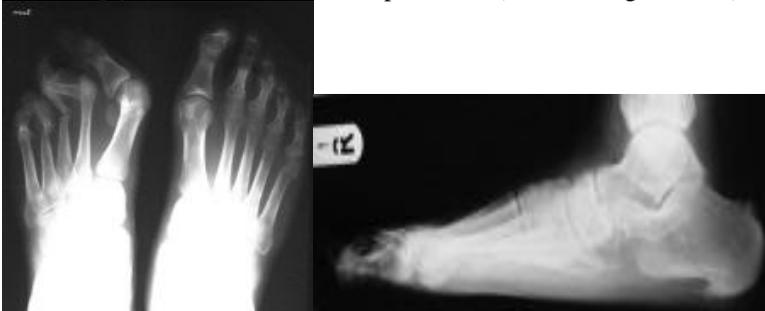


Fig. 13

Radiograph of feet of 27-year-old man shows erosions in all left metatarsophalangeal (MTP) joints with subluxation and valgus deformity of most toes. Smaller erosions are also visible in fourth and fifth MTP joints of right foot. Lateral radiograph of foot reveals calcaneal spur and enthesitis.



Fig. 14

Radiograph of both hands shows small erosive changes in both first metacarpal heads associated with minimal subluxation. Bone density is normal.

Spinal radiographic findings include sacroiliitis and syndesmophytes. Sacroiliitis (unilateral or bilateral) occurs in fewer than 10% of acute cases but develops in half of patients with chronic severe disease (see the image below). Specifically ordering a radiograph of the sacroiliac joint is advisable. Such a film provides a more

sensitive tunnel view than a routine film of the lumbosacral spine does.

Radiography of pelvis reveals bilateral asymmetric sacroiliitis.

Syndesmophytes are asymmetric, paravertebral, bulky, discontinuous, comma-shaped ossifications that most commonly involve the lower thoracic and upper lumbar vertebrae (see the image below).



Fig. 15



Fig. 16

Radiograph in 40-year-old man shows nonmarginal syndesmophytes predominantly in lower thoracic and upper lumbar spine.

Severe ankylosing spondylitis occurs in fewer than 5% of cases.

Whole-body scintigraphy is a sensible diagnostic tool for use in screening for enthesopathy and arthropathy.

Positron emission tomography has been found to allow recognition of enthesitis in the early stage of ReA, before other modalities would be able to detect it.

Magnetic resonance imaging (MRI) of the sacroiliac joints may reveal disease earlier than conventional radiography would. MRI is more sensitive than computed tomography (CT) or scintigraphy in detecting sacroiliitis and may be necessary in children who do not usually exhibit sacroiliac symptoms.

Ultrasonography may reveal enthesitis (as periosteal reaction and tendinosis) more accurately than physical examination would. Echocardiography may reveal carditis or valvular dysfunction in patients with poststreptococcal ReA.

Arthrocentesis and fluid analysis are often needed to rule out an infectious process, especially in monoarticular arthritis with constitutional symptoms. Synovial fluid analysis reveals a high WBC count (10,000–40,000/ μ L), most often with polymorphonuclear leukocytes (PMNs) predominating. CH50, C1INH, C4, C5, and C3 levels are elevated.

PCR assay has been used to detect *Chlamydia* and *Yersinia* antigenic DNA in synovial fluid.

Synovial biopsy typically yields nonspecific inflammatory changes; infectious antigens have been found in the synovium. Immunohistochemistry (IHC), PCR assay, and molecular hybridization may become more useful.

Antistreptolysin O (ASO) or anti-DNase B testing may be considered if poststreptococcal infection is suspected.

Electrocardiography (ECG) should be performed in patients with a prolonged course of ReA to evaluate for conduction disturbances.

Histopathologic findings of the early cutaneous lesions are essentially the same as in psoriasis.

Approach Considerations

No curative treatment for reactive arthritis (ReA) exists. Instead, treatment aims at relieving symptoms and is based on symptom severity. Almost two thirds of patients have a self-limited course and need no treatment other than symptomatic and supportive care. As many as 30% of patients develop chronic symptoms, posing a therapeutic challenge.

Physical therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), and intralesional corticosteroids may be helpful for joint, tendon, and fascial inflammation. Phenylbutazone may be effective when other NSAIDs fail. Low-dose prednisone may be prescribed, but prolonged treatment is not advisable. Antibiotics may be given to treat underlying infection, and disease-modifying antirheumatic drugs (DMARDs) such as sulfasalazine and methotrexate may be used safely and are often beneficial. No specific surgical treatment is indicated.

Hospitalization of a patient with uncomplicated ReA is not usually indicated. Inpatient care may be considered for patients who are unable to tolerate oral administration of medications, who are unable to ambulate because of significant joint involvement, who have intractable pain, or who have concomitant disease necessitating admission.

No dietary limitations are necessary unless the patient is receiving steroid therapy. Efforts should be made to maintain joint function with physical activity, joint protection, and suppression of inflammation. Physical therapy may be instituted to avoid muscle wasting and to reduce pain in severe cases. Although no limitations on physical activity need be imposed, symptoms of arthritis will usually limit patients' activity to some extent.

Pharmacologic Therapy

NSAIDs (e.g., indomethacin and naproxen) are the foundation of therapy for ReA. Etretinate/acitretin has been shown to decrease the required dosage of NSAIDs. Sulfasalazine or methotrexate may be used for patients who do not experience relief with NSAIDs after 1 month or who have contraindications to NSAIDs. In addition, sulfasalazine-resistant ReA may be successfully treated with methotrexate.

Antibiotic treatment is indicated for cervicitis or urethritis but generally not for post-dysenteric ReA. In *Chlamydia*-induced ReA, some data suggest that prolonged combination antibiotic therapy could be an effective treatment strategy.

Case reports exist that demonstrate the effectiveness of anti-tumor necrosis factor (TNF) medications, such as etanercept and infliximab. No published data are available on the effectiveness of selective cyclooxygenase (COX)-2 inhibitors; however, COX-2 inhibitors may be tried in patients who do not tolerate NSAIDs and in whom no preexisting contraindication to COX-2 use exists.

Symptom-specific approaches

Arthritis and enthesitis

Joint symptoms are best treated with aspirin or other short-acting and long-acting anti-inflammatory drugs (e.g., indomethacin, naproxen). A combination of NSAIDs is reportedly effective in severe cases. There are no published data to suggest that any NSAID is more effective or less toxic than another (controlled treatment trials are difficult to conduct with an uncommon disease).

Varying success in treating severe cases of ReA with other medications (e.g., sulfasalazine, methotrexate, etretinate, ketoconazole, azathioprine, or intra-articular steroid injections) has been reported. In a refractory case or a patient with HIV-associated ReA, the anti-TNF- α agent infliximab may be successful. Depending on the culture results, a short course of antibiotics may be needed; however, treatment may not affect the disease course. Longer-term administration of antibiotics to treat joint symptoms provides no established benefits.

Conjunctivitis and uveitis

Transient and mild conjunctivitis is usually not treated. Mydriatics and cycloplegics (e.g., atropine) with topical corticosteroids may be administered in patients with acute anterior uveitis. Patients with recurrent ocular involvement may require systemic corticosteroid therapy and immunomodulators to preserve vision and prevent ocular morbidity.

Urethritis and gastroenteritis

Antibiotics may be considered for urethritis and gastroenteritis, depending on the cultures used and their sensitivity. In general, urethritis may be treated with a 7- to 10-day course of erythromycin or tetracycline. Antibiotic treatment of enteritis is controversial.

Mucocutaneous lesions

Only local care is necessary for mucosal lesions. Topical steroids may be needed for psoriasiform lesions; the use of hydrocortisone or triamcinolone may be beneficial. A topical keratolytic, such as 10% salicylic acid ointment, can be added if needed. Topical salicylic acid and hydrocortisone with oral aspirin has also been suggested.

Hydrocortisone 2.5% cream and salicylic acid 10% ointment are effective in treating chronic keratoderma blennorrhagicum and circinate balanitis, though either condition may heal without medical treatment. Circinate balanitis usually responds to topical steroids; however, it can be recurrent and create a therapeutic challenge. Balanitis refractory to conventional therapy can be successfully treated with the complementary use of topical 0.1% tacrolimus.

Systemic therapy, if required, consists of the administration of oral acitretin, PUVA, methotrexate, cyclosporine, or some combination thereof.

Surgical Intervention

No surgical therapy for ReA is recommended. However, surgical intervention may be warranted for certain ocular manifestations of the disease.

Preoperative ultrasonography is helpful in determining the degree of vitreous opacification, the thickening of the choroid, and the presence of a cyclitic membrane, which can create significant problems at surgery.

Prevention

In *Chlamydia* -induced ReA, studies have suggested that appropriate treatment of the acute GU infection can prevent ReA and that treatment of acute ReA with a 3-month course of antibiotics can reduce the duration of illness. Currently, there is no evidence to indicate that antibiotic therapy is effective for enteric-related ReA or chronic ReA of any cause. Education on the prevention of the spread of sexually transmitted diseases with condoms has been associated with a decrease in the incidence of postvenereal ReA.

Control questions

1. It's typical for arthritis:

- | | |
|---|--|
| <i>A) Articular pain</i> | <i>D) Disorder of joint's function</i> |
| <i>B) Increase of joint's volume</i> | <i>Ⓓ) All above mentioned</i> |
| <i>C) Increase of local temperature</i> | |

2. A child of 5 years old was admitted at the hospital with preliminary diagnosis: Juvenile rheumatoid arthritis, articular, 2 degree of activity. What additional data will help to refine diagnosis?

- | | |
|------------------------------------|--|
| <i>A) Indices of acute phase</i> | <i>D) Antibodies to articular joints</i> |
| <i>B) Rheumatoid factor</i> | <i>E) All above mentioned</i> |
| <i>C) X-ray of affected joints</i> | |

3. A boy of 5 years is hospitalized due to pains in upper part of vertebral column, knee and ankle joints, elevation of temperature up to 39°C , inconstant small spotted maculopapular rash on extremities. There are joint stiffness and limitation of head movements in the morning. Objectively: pallor of skin and mucous membranes, knee and ankle joints are defigured. Movements in these joints and cervical spine are limited and painful. Please, put preliminary diagnosis.

- A) *Reactive arthritis*
- B) *Juvenile rheumatoid arthritis*
- C) *Acute rheumatic fever*
- D) *Meningitis*
- E) *Dermatomyositis*

4. The most typical clinical sign for rheumatoid arthritis is:

- A) *Affection of big joints*
- B) *Shifting character of affection*
- C) *Morning joint stiffness*
- D) *Absence of steady deformations of joints*
- E) *All above mentioned*

5. The following diagnosis was made in a child of 5 years: Juvenile rheumatoid arthritis, articular-visceral form (myocarditis, pulmonitis, glomerulonephritis), high degree of activity. Standard therapy (sodium diclophenac, prednisolon 1,5 mg/kg, methothrexate) was ineffective. It's necessary to prescribe:

- A) *Antibiotic of cephalosporine group*
- B) *Second drug from NSAID group*
- C) *Antihistaminic drug*
- D) *Pulse-therapy with prednisolon and cyclophosphane*
- E) *Drug from quinolone group*

6. Rheumatoid factor in blood is determined with the help of:

- A) *Reaction of Wasserman*
- B) *Reaction of Greguersen*
- C) *Reaction of Vaaler-Rouse*
- D) *Reaction of complement binding*
- E) *PCR*

7. Diagnosis of juvenile arthritis, articular-visceral form, high degree of activity was established in a girl of 8 years. Which drugs are referred to base therapy?

- A) *Non-steroid anti-inflammatory drugs*
- B) *Glucocorticoids*
- C) *Cytostatics*
- D) *Membrane stabilizers*
- E) *Metabolic drugs*

8. In a child of 10 years who suffered from ARI 2 weeks ago there is elevation of temperature up to 38°C , erythematous annular rash on skin of extremities, pain in knee joints. Joints were edematic, hot, volume of movements was limited. In several days local changes in knee joints disappeared but similar affection of left elbow joint appeared. What disease can you think about?

- A) *Reactive arthritis*
- B) *Juvenile rheumatoid arthritis*
- C) *Acute rheumatic fever*
- D) *Gout arthritis*
- E) *Traumatic arthritis*

9. Diagnosis of reactive arthritis of left ankle joint is established in a child of 14 years. It's necessary to prescribe:

- A) *Non-steroid anti-inflammatory drug*
- B) *Prednisolon*
- C) *Methotrexate*
- D) *Delagil*
- E) *All above mentioned*

10. A child of 6 years old stays at a hospital with diagnosis: juvenile rheumatoid arthritis, articular-visceral form, moderate degree of activity. He receives voltaren and prednisolon during a month. Abdominal pains appeared. What examination is it necessary to perform in order to diagnose GIT bleeding?

- A) *Reaction of Greguersen (feces for occult blood)*
- B) *X-ray of GIT with barium*
- C) *Fibrogastroscope*
- D) *Rectoromanoscopy*
- E) *Ultrasound examination*

11. Main mechanisms of joints affection in JRA are all, EXCEPT:

- A) *Hyperemia of skin*
- B) *Destruction of cartilage*
- C) *Bone erosion*
- D) *Formation of pannus*
- E) *Development of sinovitis*

12. Peculiarity of articular syndrome in JRA is the following:

- A) *Symmetric affection of small joints*
- B) *Duration of arthritis 3 months and more*
- C) *Effusion in articular cavity*
- D) *Morning stiffness*
- E) *All above mentioned*

13. Pains in left knee joint appeared in a child of 6 years old after ARI. General condition isn't disturbed, temperature is normal. Left knee joint is enlarged; local temperature above joint is increased, volume of movements is limited. Inner organs – without pathology. What is your preliminary diagnosis?

- A) *Reactive arthritis*
- B) *Juvenile rheumatoid arthritis*
- C) *Acute rheumatic fever*
- D) *Meningitis*
- E) *Dermatomyositis*

14. Function of joint is determined by:

- A) *Edema of surrounding tissues*
- B) *Volume of active and passive movements*
- C) *Hyperemia of skin.*
- D) *Pain syndrome*
- E) *Increase of local temperature*

15. Which mechanism lies in the base of JRA pathogenesis?

- A) *Autoimmune reactions*
- B) *Formation of immune complexes*
- C) *Activation of immunocompetent cells*
- D) *Hyperproduction of pro-inflammatory cytokines*
- E) *All above mentioned signs*

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Навчальне видання

МОДУЛЬ 1
ЗМІСТОВИЙ МОДУЛЬ 4
ТЕМА 10
ЮВЕНІЛЬНИЙ РЕВМАТОЇДНИЙ АРТРИТ
ТА РЕАКТИВНИЙ АРТРИТ У ДІТЕЙ

Методичні вказівки
для студентів

Упорядники Одинець Юрій Васильович
 Піддубна Ірина Миколаївна

Відповідальний за випуск Ю. В. Одинець



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MODULE 1
SUBSTANTIAL MODULE 4

THEME 10
JUVENILE RHEUMATOID ARTHRITIS
AND REACTIVE ARTHRITIS IN CHILDREN

Practical policies for students