Juvenile Idiopathic Arthritis: An Update

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ABSTRACT
Juvenile idiopathic arthritis (JIA) is the most common chronic arthropathy of childhood. Previous terminology identified this entity as juvenile rheumatoid arthritis. The 7 subsets of JIA identified under the new classification system are discussed, as are current treatments. A differential diagnosis of JIA is included as this condition continues to be diagnosed by exclusion. Recent studies, which discuss the outcome of adults with previous childhood arthritis, are reviewed.

INTRODUCTION
Many different types of arthritis affect children. Some are acute and self-limiting, such as viral arthritis. Other forms of arthritis represent chronic conditions. The purpose of this article is to review and highlight new developments in chronic arthritis of childhood. The new classification system of juvenile idiopathic arthritis (JIA), formerly juvenile rheumatoid arthritis (JRA), will be discussed. Additionally, information on the occurrence, diagnosis, clinical features, management, and outcome of this disorder will be updated and reviewed.

EPIDEMIOLOGY
The exact incidence and prevalence of juvenile arthritis (JA) is not known. A recent meta-analysis of 34 epidemiological studies showed wide variability in both the reported incidence and prevalence of JA (inclusive of the different classification systems of JRA, JIA, and juvenile chronic arthritis [JCA]). Incidence numbers varied considerably from 0.008 to 0.226/1000 children per year. Prevalence numbers varied even more widely and ranged from 0.07 to 4.01/1000 children. No specific study has been performed to address the incidence and prevalence of juvenile arthritis in Wisconsin.

DISEASES OF EUROPEAN ORIGIN
Arthralgias and arthritis are common in children and adolescents in Europe. The most common cause of acute arthralgias is infection, especially streptococcal. Infections of the skin, such as impetigo, can cause generalized arthralgias. The occurrence of arthritis is more common in children with chronic diseases, such as systemic lupus erythematosus (SLE) and scleroderma.

IMMUNOSUPPRESSIVE THERAPY
The treatment of juvenile idiopathic arthritis (JIA) has evolved over the past few decades. Initially, systemic gold was used for treatment, but it was associated with serious side effects. Methotrexate is now the first-line treatment for JIA. It is an immunosuppressive agent that has been shown to be effective in the treatment of JIA.

Other immunosuppressive medications, such as cyclosporine and azathioprine, are also used in the treatment of JIA. These medications are effective in reducing inflammation and pain, but they also have significant side effects. Long-term use of these medications can increase the risk of infections, cancer, and other serious conditions.

OUTCOME
The outcome of juvenile idiopathic arthritis (JIA) is variable. Some children have complete resolution of their symptoms, while others have persistent arthritis. The outcome of JIA is affected by many factors, including the type of JIA, the duration of symptoms, and the effectiveness of the treatment.

Conclusions
Juvenile idiopathic arthritis (JIA) is a common chronic condition that affects children. The new classification system of JIA has helped researchers better understand the condition and improve treatment options. Continued research is needed to improve outcomes for children with JIA.
these disorders. Septic arthritis needs to be considered when there is a monarticular arthritis accompanied by fever, severe pain, and exquisite tenderness.

Perhaps one of the most concerning aspects of the diagnosis of JIA is the recognition that some childhood malignancies, such as leukemia and neuroblastoma, may present with musculoskeletal pain or arthritis. The severity of pain, lack of morning stiffness, nocturnal nature of the pain, and the ability to localize the site of pain to the bones on palpation are clinical measures that can direct the examiner to the consideration of a malignancy. In a series of 12 children with leukemia who initially were presumed to have JRA, Wallendahl found that there were no differences in white count, hemoglobin or platelet count that enabled these children to be diagnosed with malignancy. Elevated lactate dehydrogenase was the only test where differences were noted in some children. 

It is important to consider and distinguish between persistent oligoarthritis and extended oligoarthritis. Extended oligoarthritis occurs when 5 or more joints are involved after the first 6 months of illness. This type of arthritis is female predominant and its peak occurrence is in toddlers and preschoolers. Most of these children appear healthy. They may have morning stiffness and want to be carried in the morning. Later in the day, their activity and ambulation may appear normal. Pain complaints may be minimal as the children limit their joint movement to the area of pain-free range of motion. This may result in the development of joint contractures. The joint involvement may be asymmetric and lead to leg length discrepancies. The affected leg often overgrows and has accelerated maturation because of the increased vascularity that accompanies inflammation.

One of the most well recognized associations of JIA is for children with oligoarticular arthritis to develop a chronic, frequently asymptomatic iritis. This occurs in approximately 15%-20% of children with oligoarticular arthritis. Antinuclear antibodies detected by Hep-2 cell substrate have been detected in 55% of children with both iritis and JIA. It is well known that this chronic iritis may be asymptomatic, particularly in early disease. Because of the lack of symptoms, clinical guidelines for routine ophthalmologic screening have been developed and published by the American Academy of Pediatrics.6

Children with involvement of 5 or more joints in the first 6 months of illness are classified as having polyarticular disease and, as previously mentioned, these subtypes are differentiated by the presence or absence of rheumatoid factor. Generally, polyarticular disease tends to be more symmetric and is more likely to involve the small joints of the hands and feet. Local growth disturbances can occur. Some are distinctive, such as the micrognathia, which can develop from arthritis of the temporomandibular joint. Cervical spine involvement may occur in the polyarticular and systemic subtypes and be characterized by posterior fusion of the vertebrae.

Systemic arthritis is the least common subtype of JIA. It is also the most dramatic in its presentation, as children have high spiking fevers that accompany the arthritis. The differential diagnosis of this type of arthritis often involves an initial extensive diagnostic work-up for the wide range of disorders that can present as a fever of unknown origin. This type of arthritis is considered when the fever has been present at least 2 weeks. Frequently, a rheumatoid rash may be present. This rash is characteristically intensified by fever or heat. It is evanescent by nature and has a tendency for Koebner’s
phenomenon. This is the occurrence of typically linear skin lesions at a site of previously uninvolved skin after trauma or scratching. Serositis, anemia of chronic disease, hepatosplenomegaly, and lymphadenopathy all may be seen. Children with systemic arthritis typically have both negative rheumatoid factors and antinuclear antibody (ANA) serology. A prominent leukocytosis and thrombocytosis are seen. While rare, there is a life-threatening syndrome that can occur in systemic arthritis, known as macrophage activation syndrome. Following a history of intercurrent illness or recent medication change, these children often develop sustained (not spiking) fevers along with marked pancytopenia, coagulopathy, hepatic involvement, and hypoalbuminemia. Despite the severity of these symptoms, the erythrocyte sedimentation rate may fall into the normal range, presumably from impairment of the acute phase response due to liver dysfunction. These children require emergent treatment with corticosteroid medications or immunosuppressive therapy. It is thought that this syndrome is related to other hemophagocytosis syndromes and recent investigations have shown abnormalities of natural killer cell function.

While systemic arthritis is unique in its febrile presentation, the number and pattern of joint involvement, as well as the presence or absence of rheumatoid factor, distinguish the other 6 types of JIA. Two of the subtypes of JIA, psoriatic arthritis and enthesitis-related arthritis, have previously been included under the generic terminology of spondyloarthropathy. These conditions share features of arthritis, enthesopathy (tenderness at ligamentous attachment sites to bone) and the tendency to be associated with HLA-B27. Historically, it has been recognized that school age children, particularly boys, may have presented with features of pauciarticular JRA and then followed a course more consistent with one of the spondyloarthropathy syndromes. These disorders may be associated with back or sacroiliac joint involvement. They may also develop an iritis, which often presents as the acute red eye. Other conditions, generally thought to occur in the spondyloarthropathy spectrum, such as reactive arthritis associated with enteric or chlamydia infections and the arthropathy of inflammatory bowel disease, are not included in this classification system as they are not considered to be “idiopathic.” However, it is important for clinicians to consider these disorders, as the arthritis may be an initial manifestation of a different systemic disease.

TREATMENT AND MANAGEMENT
The care of children with arthritis has seen definite advancements over the last several years. Initial management of children with arthritis includes the use of nonsteroidal anti-inflammatory drugs (NSAIDs) to reduce pain, enhance mobility, and reduce morning stiffness. The armamentarium of approved NSAIDs for childhood arthritis is limited, compared to the availability of these agents for the adult population, and includes ibuprofen, naproxen, and tolmetin. A review of the clinical trials of these agents by the Pediatric Rheumatology Collaborative Study Group showed that 65% of children responded to a particular agent by 1 month, but that some children were late responders and could take up to 3 months to respond to a particular agent. A spirin therapy is not routinely used because of alternatives with reduced frequency of dosing schedules, less frequent liver enzyme elevation, and concerns of Reye’s syndrome in children exposed to viral infections, particularly varicella or influenza. While selective COX-2 inhibitors have been approved for adults with arthritis, these agents have not yet received FDA approval for pediatric use.

Systemic corticosteroids are not routinely utilized in the care of children with JIA because of side effects, primarily osteopenia and growth retardation, which are already concerns for children because of their underlying disease process. Steroid medications are reserved for life-threatening or severe manifestations, such as macrophage activation syndrome, pericarditis, or severe anemia of chronic illness. They may be used to maintain ambulation if other strategies have failed, or treat severe sight-threatening iritis, but these cases are rare. Steroid medications are preferable as a local measure. Examples include the use of topical ophthalmic drops for iritis or the use of intra-articular triamcinolone hexacetonide. Studies of triamcinolone hexacetonide have shown a sustained local response to this agent. In 60% of children, this response lasts 6 months and in 45% the response may last a year. Unfortunately, this steroid preparation, which has been the most studied and has shown the most sustained responses, has been unavailable due to commercial shortages of this agent.

While a variety of second line agents have been used, methotrexate administered once a week has become the agent of choice for persistent disease. A controlled clinical trial of this agent showed improvement in 72% of children. It is recognized that there may be improved efficacy of this agent with subcutaneous rather than oral administration of this agent. Use of this medication requires ongoing monitoring of blood counts and transaminases. A recent advance in the care and treat-
ment of children with JRA has been the arrival of etan-
cept. This drug, which represents a new generation of
cytokine modifying agents, works by blocking the
tumor necrosis factor receptor. In a controlled study of
patients with severe JRA whose disease did not re-
respond to methotrexate, 74% patients improved at 3
months. Subsequent studies have now shown sus-
tained improvement for as long as 2 years. In the
primary care of children receiving these agents, it is im-
portant to recognize that they are receiving immuno-
suppressive treatment as they are evaluated for fevers
and intercurrent illnesses. Live virus vaccines should be
avoided while these children are on immunosuppres-
sive therapy. Other cytokine modifying drugs have re-
cently been approved for use in adult rheumatoid
arthritis, but have not yet received pediatric approval.
Occasionally, other agents such as sulfasalazine have
been utilized.

Children with JIA are known to have an increased
risk of osteopenia from their disease. It has now been
shown that this risk exists independent of the use of
corticosteroid medications. Strategies to minimize the
consequences of osteopenia should be employed.
Encouragement of physical activity is important.
Klepper has shown that children with JIA are less
physically fit than children without JIA and that most
children with JIA can exercise without exacerbating the
symptoms of their disease. The provision of ade-
quate calcium either by diet or with calcium supple-
mentation is important. A standard age-appropriate
multivitamin containing vitamin D is also suggested.

It is important to encourage physical activity to
maintain bone density, prevent disuse weakness and
muscle atrophy, and minimize contractures. The severity
of disease and symptoms experienced by some children
may suggest the need for adaptations and modifications.
Swimming and bicycling are often well-tolerated activ-
ities for individuals with arthritis. Heat may help re-
duce the accompanying inactivity stiffness. For chil-
dren experiencing increased disease activity, physical
and occupational therapy may be needed. Therapy is
often provided to complement a home exercise pro-
gram performed by the child and supervised by the
parents.

In addition to the care of the arthritis, it is important
to establish routine ophthalmologic care for children
with JIA. Because of the asymptomatic nature of the
iritis regularly scheduled, routine slit lamp eye exami-
nations are recommended. The American Academy of
Pediatrics has issued guidelines for ophthalmologic ex-
aminations for children with JIA. Children at the high-
est risk are recommended to have eye exams at 3-
month intervals. Intervals of follow-up differ by the
age of the child at onset of arthritis, ANA status, and
duration of the disease. Some authors have reported
improvements in visual outcome of children with JIA
and they speculate that adherence to a regular program
of eye screening have led to the reported improvements
in outcome.

Children with arthritis may have symptoms that im-
pact their school performance. For example, children
with hand involvement may have difficulty with writ-
ing and require adaptations. Children with lower ex-
tremity involvement may experience difficulties in run-
ning and other activities in their physical education
courses. Impairments in ambulation may create diffi-
culties changing classes, standing in line, or utilizing
stairs. Providers of care may need to work with families
to coordinate the needs their children may have in the
school setting.

Measures to help the child and their family realize
that they are not the only ones coping with the chal-
lenge of arthritis can help facilitate their adjustment to
the disease. Internet sources such as www.arthritis.org
sponsored by the Arthritis Foundation can provide in-
formation and links to the American Juvenile Arthritis
Organization (AJAO). There is a Wisconsin chapter of
the AJAO, which provides families in the state with an
opportunity for information and support. Opportuni-
ties for group interaction, such as Camp MASH (Make
Arthritis Stop Hurting), coordinated by the Arthritis
Foundation, Wisconsin Chapter, allow children to meet
other children dealing with similar issues. The Ameri-
can College of Rheumatology has published a position
statement on the referral of children and adolescents
to pediatric rheumatologists. One of the 5 stated goals in
this document is to provide families with specialized
input to help the family cope with the disease process,
accept treatment plans, allay anxiety, and provide edu-
cation.

OUTCOME

Families faced with the challenge of dealing with arthri-
tis often want to know what the future holds. While
unable to predict the future for a specific family, the
outcome studies performed on JIA can give some in-
sight. Older studies show that adults with JIA develop
more limitations in self-care function as the follow-up
interval becomes longer. Patients in Steinbrocker func-
tional class III or IV have marked limitations in self-
care activities. Wallace and Levinson showed an in-
crease in functional impairment over time.
9% of patients were in functional class III or IV, but at 15-20 years of follow-up, the numbers increased to 17%.17

Recently, a new generation of studies reporting the outcome of adults with JIA have become available. These studies utilize more refined outcome measures than the Steinbrocker classification system. Peterson et al performed a study comparing adults with JIA to a control group. At a mean time of follow-up of 24.7 years, these individuals experienced more disability, pain, fatigue, poorer health perception, and decreased physical function compared to the control group. They also found that educational level, income, insurance status, and rates of pregnancy and childbirth were similar in the cases and controls.18 Another study by these authors showed an increased mortality rate of 0.27 deaths/100 years of patient follow-up compared to the expected mortality rate of 0.068 deaths/100 years for the general population. In their series, the deaths were all associated with other autoimmune diseases.19 Thomas et al also reported increased mortality rates for adults with a history of JIA. This Scottish study reported a standardized mortality rate of 3.39 for males and 5.09 for females.20

Packham et al reported a series of 246 adults with JIA with a mean disease duration of 28.3 years (range of 8-73 years) and noted that 56.7% of patients had no signs of active inflammation at follow-up. These authors noted that both male and female heights were decreased compared to the general population. Fifty-one percent of their patient group had required at least 1 joint replacement surgery.21 Oen et al reported rates of arthroplasty of 23% for rheumatoid factor positive patients and 17% for systemic onset disease. The lower rates may reflect a shorter median duration of follow-up of 10.5 years. These authors also reported on probability of remission at 10 years after onset. The remission rate were as follows: systemic 37%, oligoarticular 47%, polyarticular RF- 23%, and polyarticular RF + 6%.22

Foster et al reported on 82 adults with JIA and a mean duration of disease of 21 years. Using the Health Assessment Questionnaire they found that patients with oligoarticular onset disease had less functional impairment compared to patients with systemic or polyarticular disease. They used the SF-36 instrument and found that compared to controls, patients had worse scores for physical function, vitality, pain, general health, social function, and emotional role. Most of the patients included in their study had excellent educational achievement, but despite this had lower rates of employment than the control population.23 It is important to realize that for all the studies of adults with JIA their disease began before the wide availability of newer proven therapies, such as methotrexate and etanercept.

There are some data addressing the outcome of children treated during the methotrexate era, but prior to the use of etanercept. At 5 years after onset, 25% of children with polyarticular onset disease and approximately 50% of children with systemic onset disease had functional limitations that required modifications in their school schedule. These authors noted that over half of the children with systemic onset arthritis required admission to the hospital during the first year of disease. At 5 years, 12% of children with polyarticular disease and 30% of those with systemic disease were in Steinbrocker class III or IV reflecting significant impairments in self-care activities. At 5 years, 67% of children with polyarticular arthritis showed joint space narrowing and the numbers were higher for children with systemic arthritis as 75% of the patients had radiographs showing joint space narrowing.24

Hopefully, the newer therapies will show improved long-term results for children now being treated during the age of biologic agents. Currently, many children with JIA will enter adulthood with inactive disease and with good functional outcome. Yet it is clear that there are a significant number of individuals who have had JIA, who did not “outgrow” their disease and have experienced significant impairments continuing into adulthood.

The field of pediatric rheumatology has been a dynamic one in the past several years. Standardization of terminology will enhance comparisons of studies performed throughout the world. Increased awareness should help children receive appropriate therapy early in their disease course. Newer treatments hopefully will improve the outcome and consequences of JIA, which are now being better understood. Research studies also continue to better understand the etiologies of this heterogeneous group of chronic childhood arthritides and hopefully will lead to novel therapies in the future.

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REFERENCES


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