Joint pain is a common childhood complaint. Each year, as many as 1% of all children will be evaluated by a physician for joint pain (1). Approximately 15% of healthy children reported on a health questionnaire that they had episodes of musculoskeletal pain (2). Further, healthy children in day care centers have approximately one painful episode every 3 hours, arising from play, disciplining, or interaction with peers (3). The orthopaedic surgeon is often the first specialist to encounter the child with joint, limb, or back pain. In a study of subspecialty referrals of juvenile arthritis, most children with pauciarticular juvenile rheumatoid arthritis (JRA) (62%) were referred to orthopaedic surgeons prior to referral to pediatric rheumatology care (4). Among children who are evaluated by a physician for pain in the joints, only 1 in 100 will eventually be diagnosed as having arthritis, but among those who present to an orthopaedist, the frequency of arthritis is surely higher. Accordingly, it is important that the orthopaedic surgeon be able to identify the most likely cause of the pain and either initiate treatment or refer the patient to an appropriate medical specialist.

The purpose of this chapter is to provide the orthopaedic surgeon with an in-depth understanding of the presentation, differential diagnosis, and management of children with arthritis. With this framework, the orthopaedic specialist should be able to identify children with juvenile arthritis and to differentiate arthritis from benign pains of childhood, psychogenic pain syndromes, benign musculoskeletal back pain, infection, malignancy, or other systemic autoimmune diseases (lupus, dermatomyositis, and vasculitis). Infectious, malignant, congenital, mechanical, or traumatic causes of arthralgias and arthritis are presented in order to contrast the symptoms with those of juvenile arthritis; detailed presentations on these conditions can be found elsewhere in this text.

Juvenile arthritis is a term for persistent arthritis lasting >6 weeks of unclear etiology. A diagnosis of juvenile arthritis is made by taking a thorough history, performing a skilled and comprehensive physical examination, utilizing directed laboratory tests and imaging procedures, and following the child over time.

Over the past several decades, there have been three sets of criteria utilized for the diagnosis and classification of juvenile arthritis (Table 11-1). The first set of criteria was proposed in 1972 by the American College of Rheumatology (ACR) and defined three major categories of JRA: oligoarticular (pauciarticular), polyarticular, and systemic (5). The ACR JRA criteria exclude other causes of juvenile arthritis, such as spondyloarthopathies [JAS, inflammatory bowel disease (IBD)-associated arthritis, and related diseases], juvenile psoriatic arthritis, arthritis associated with other systemic inflammatory diseases [systemic lupus erythematosus (SLE), dermatomyositis, sarcoidosis, etc.], and infectious or neoplastic disorders. The second set of criteria was formulated in 1977 by the European League Against Rheumatism (EULAR) and coined the term juvenile chronic arthritis (JCA) (6). JCA is differentiated into the following subtypes: pauciarticular, polyarticular, juvenile rheumatoid [positive rheumatoid factor (RF)], systemic, juvenile ankylosing spondylitis (JAS), and juvenile psoriatic arthritis. The ACR and EULAR criteria, although similar, do not identify identical populations or spectra of disease. However, they have often been used interchangeably, leading to confusion in the interpretation of studies relating to the epidemiology, treatment, and outcome of juvenile arthritis.

In 1993, The International League of Associations of Rheumatologists (ILAR) proposed (7) and revised (8) criteria for the diagnosis and classification of juvenile arthritis (Table 11-2). The term juvenile idiopathic arthritis (JIA) has been proposed as a replacement for both JRA and JCA. The
### TABLE 11-1  
**Comparison of JRA, JCA, and JIA Classifications**

<table>
<thead>
<tr>
<th>Committee</th>
<th>JRA</th>
<th>JCA</th>
<th>JIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset</td>
<td>&gt;6 wk</td>
<td>&gt;3 mo</td>
<td>&gt;6 wk</td>
</tr>
<tr>
<td>Disease duration</td>
<td>Pauciarticular</td>
<td>Pauciarticular</td>
<td>Oligoarticular, persistent</td>
</tr>
<tr>
<td>Onset types</td>
<td>Polyarticular</td>
<td>Polyarticular RF-negative</td>
<td>Oligoarticular, extended</td>
</tr>
<tr>
<td></td>
<td>Systemic</td>
<td>Juvenile rheumatoid arthritis</td>
<td>Polyarticular RF-negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic</td>
<td>Polyarticular RF-positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Juvenile psoriatic arthritis</td>
<td>Systemic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Juvenile ankyllosing spondylitis</td>
<td>Psoriatic arthritis</td>
</tr>
<tr>
<td>Exclusions</td>
<td>Juvenile psoriatic arthritis</td>
<td>Juvenile ankyllosing spondylitis</td>
<td>Enthesitis-related arthritis</td>
</tr>
<tr>
<td></td>
<td>Juvenile ankylosing spondylitis</td>
<td>Other forms of juvenile arthritis</td>
<td>Other forms of juvenile arthritis</td>
</tr>
<tr>
<td></td>
<td>Inflammatory bowel disease</td>
<td>Other forms of juvenile arthritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other forms of juvenile arthritis</td>
<td>RF, rheumatoid factor.</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 11-2  
**Criteria for Classification of JIA**

<table>
<thead>
<tr>
<th>JIA Subtype</th>
<th>Exclusions&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Inclusion Criteria&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligoarthritis</td>
<td>1–5</td>
<td>≤4 joints during disease course</td>
</tr>
<tr>
<td>Persistent</td>
<td></td>
<td>&gt;4 joints after the first 6 mo</td>
</tr>
<tr>
<td>Extended</td>
<td></td>
<td>Arthritis affecting ≥5 joints during the first 6 mo, plus RF positivity on two occasions more than 3 mo apart</td>
</tr>
<tr>
<td>Polyarthritis RF-negative</td>
<td>1–5</td>
<td>Arthritis affecting ≥5 joints during the first 6 mo, plus RF positivity on two occasions more than 3 mo apart</td>
</tr>
<tr>
<td>Polyarthritis RF-positive</td>
<td>1–3, 5</td>
<td>Arthritis with or preceded by daily fever of at least 2 weeks’ duration, accompanied by one or more of the following: Evanescent, nonfixed erythematous rash, Generalized adenopathy, Hepatomegaly or splenomegaly, Serositis</td>
</tr>
<tr>
<td>Systemic</td>
<td>1–4</td>
<td>Arthritis and psoriasis, or arthritis and at least two of the following: a. Dactylitis, b. Nail abnormalities (pitting or onycholysis), c. Family history of psoriasis in a first-degree relative</td>
</tr>
<tr>
<td>Psoriatic</td>
<td>2–5</td>
<td>Arthritis and enthesitis, or arthritis or enthesitis with at least two of the following: 1. SI joint tenderness and/or inflammatory spinal pain, 2. Presence of HLA-B27, 3. Family history of HLA-B27–associated disease in a first-degree relative, 4. Onset of arthritis in a male after the age of 6 yr</td>
</tr>
<tr>
<td>Enthesitis-related</td>
<td>1, 4, 5</td>
<td>Children with arthritis of unknown cause that persists ≥6 wk, Does not fulfill criteria for any of the other categories, Fulfills criteria for ≥1 of the other categories</td>
</tr>
</tbody>
</table>

<sup>a</sup>Exclusions: 1, psoriasis in the patient or a first-degree relative; 2, arthritis in an HLA-B27 positive male beginning after the sixth birthday; 3, ankyllosing spondylitis, enthesitis-related arthritis, sacroiliitis with IBD, Reiter syndrome, or acute anterior uveitis in a first-degree relative; 4, IgM RF on at least two occasions more than 3 mo apart; 5, presence of systemic JIA.

<sup>b</sup>Inclusion criteria for all subtypes: 1, age at onset <16 yr; 2, arthritis in one or more joints; 3, duration of disease is at least 6 wk.

ILAR criteria allow for uniform interpretation of clinical and therapeutic data. Recent validation of the ILAR classification criteria has found that 80% to 88% of children could be classified, and 12% to 20% were classified as “Undifferentiated” because they either did not fit into any category or fulfilled the criteria under two categories (9–12). As genetic risk factors and specific triggers of juvenile arthritis are identified, modifications to the criteria can be made. In the remaining sections of this chapter, the emphasis will be on the JIA classification scheme. The terms JRA and JCA will be used only when referring to specific epidemiologic, therapeutic, or outcome data.

Oligoarthritis

Definition. Oligoarthritis is the most common subtype of JIA and is defined by arthritis in four or fewer joints during the first 6 months of disease. Oligoarticular JIA is further divided into persistent and extended course. Persistent oligoarthritis affects a maximum of four joints throughout the disease course. Extended oligoarthritis affects a total of more than four joints after the first 6 months of disease. Exclusions to a diagnosis of oligoarticular JIA include the following: (a) psoriasis or a history of psoriasis in a first-degree relative; (b) arthritis in a first-degree relative after the age of 6 years; (c) ankylosing spondylitis (AS), enthesitis-related arthritis sacroiliitis with IBD, reactive arthritis, or acute anterior uveitis, or a history of one of these in a first-degree relative; (d) presence of IgM RF on at least two occasions, measured 3 months apart; and (e) systemic JIA (8).

Epidemiology. Most children with oligoarthritis present before 4 years of age and girls outnumber boys by a ratio of 4 to 1. Whites are affected more often than other races. It is the most frequent subtype of JIA, accounting for up to 40% of cases (13, 14). Prevalence is estimated at 60 per 100,000 children (15).

Etiology. The etiology of oligoarticular JIA is unknown, but associations with HLA-A2, DRB1*01, DRB1*08, DRB1*11, DRB1*13, DPB1*02, DQA1*04, and DQB1*04 have been reported (14, 16). Oligoarticular JIA is rarely familial. Approximately 70% of oligoarticular JIA patients are positive for antinuclear antibodies (ANA).

Clinical Features. Approximately 50% of children with oligoarticular JIA present with a single affected joint, most commonly the knee, followed by ankles and small joints of the hands. The hips and shoulders are rarely affected. Early wrist involvement is uncommon and may portend progression to a polyarticular or extended oligoarticular course. At presentation, the majority of children have morning stiffness, gelling, and pain. However, up to 25% of children have painless arthritis at presentation (17).

Most children with oligoarticular JIA have a mild and remitting course. However, in untreated children with longstanding unilateral knee arthritis, there can be overgrowth of the affected limb, resulting in a marked leg-length discrepancy (18, 19). Temporomandibular joint (TMJ) arthritis is present in a majority of children at disease onset (20) and if untreated, may cause localized growth disturbances, micrognathia, malocclusion, and chewing difficulties (21–23). Chronic uveitis is the most common extra-articular complication seen in oligoarthritis, is associated with ILAR criteria, and occurs in approximately 20% of children. Periodic screening for uveitis is necessary as the inflammation is typically asymptomatic and unable to be detected without the use of a slit lamp. Untreated uveitis may result in cataracts, band keratopathy, secondary glaucoma, and blindness.

Long-term, children with oligoarticular JIA have the greatest likelihood of remission of all JIA subtypes. In one study, 68% of persistent and 31% of extended oligoarticular JIA patients achieved long-term clinical remission off medication (24).

Polyarticular Arthritis

Definition. Polyarticular JIA is defined by arthritis in five or more joints during the first 6 months of disease. Polyarticular JIA is further divided into RF-positive and RF-negative disease. RF positivity is defined as the presence of IgM RF on at least two occasions, measured at least 3 months apart. Exclusions to a diagnosis of polyarticular JIA include the following: (a) psoriasis or a history of psoriasis in a first-degree relative; (b) arthritis in a first-degree relative after the age of 6 years; (c) AS, enthesitis-related arthritis sacroiliitis with IBD, reactive arthritis, or acute anterior uveitis, or a history of one of these in a first-degree relative; (d) presence of IgM RF on at least two occasions, measured 3 months apart; and (e) systemic JIA (8).

Epidemiology. RF-negative polyarthritis can occur at any age, with the median age of onset at 6.5 years (25), with girls outnumbering boys by a ratio of 3:1. RF-positive polyarticular JIA occurs most frequently in adolescent girls and is indistinguishable from adult rheumatoid arthritis (RA). Polyarticular JIA is the second most frequent subtype of JIA, accounting for up to 22% of cases (13, 14). Prevalence is estimated at 40 and 10 per 100,000 children for RF-negative and RF-positive subtypes, respectively (15).

Etiology. The etiology of polyarticular JIA is unknown. Multiple studies have examined the association of HLA genes and disease. RF-negative polyarticular JIA has been associated with HLA-A2, DRB1*08, DQA1*04, and DPB1*03. Associations of RF-positive polyarticular JIA with HLA-DQA1*03, DQB1*03, and DRB1*04, a gene also associated with adult RA, have been reported (14).

Clinical Features. Polyarticular-onset JIA is characterized by the insidious, but occasionally acute, onset of symmetric arthritis in five or more joints. It can involve both large and small joints and frequently affects the cervical spine and TMJs. Mild systemic features such as low-grade fever, lymphadenopathy, and hepatosplenomegaly may be present at diagnosis. The fevers are not typically the high quotidian temperature spikes that are diagnostic of systemic arthritis, and rash is rarely seen (26).
This RF-negative subgroup may be ANA positive (40% to 50%), and this is associated with an increased incidence of uveitis (5%) (27). Children with RF-positive polyarticular JIA are more likely to have a symmetric small-joint arthritis, rheumatoid nodules, and early erosive synovitis with a chronic course. However, these children rarely develop chronic uveitis.

Children with RF-positive polyarticular JIA are at risk for a prolonged and destructive course. These children are typically older girls with involvement of multiple joints (20 or more) including the small joints of the hands and feet, early erosions, and rheumatoid nodules. The presence of hip arthritis has been shown to be a poor prognostic sign and may lead to destruction of the femoral heads (28). If polyarthritis persists longer than 7 years, remission is unlikely. In a recent study, only 5% of RF-positive and 30% of RF-negative polyarticular JIA patients achieved long-term remission off medication (24).

**Systemic Arthritis**

**Definition.** Systemic-onset juvenile arthritis (29) was first completely described by Still in 1897, and is therefore often referred to as Still disease. Systemic JIA is defined by arthritis in at least one joint, fever of at least 2 weeks’ duration that is documented to be quotidian for at least 3 days, and at least one of the following: (a) evanescent and erythematous rash (Fig. 11-1); (b) generalized lymphadenopathy; (c) hepatosplenomegaly; and (d) serositis. Exclusions to a diagnosis of systemic JIA include the following: (a) psoriasis or a history of psoriasis in a first-degree relative; (b) arthritis in a first-degree relative after the age of 6 years; (c) AS, enthesitis-related arthritis sacroiliitis with IBD, reactive arthritis, or acute anterior uveitis, or a history of one of these in a first-degree relative; and (d) presence of IgM RF on at least two occasions, measured 3 months apart (8).

**Epidemiology.** Systemic JIA is one of the least common JIA subtypes, accounting for approximately 10% of all JIA cases (13). Onset can occur at anytime during childhood but peaks between 1 and 5 years of age (25). Boys and girls are affected equally. Prevalence of systemic JIA is estimated at 10 per 10,000 children (15).

**Etiology.** Etiology of systemic JIA is unknown. HLA associations that have been reported include DRB1*04, DRB1*11, and DQA1*05 (14). Non-HLA genetic associations have been found with macrophage migration inhibitory factor (30) and a variant of the interleukin-6 (IL-6) gene (8).

**Clinical Features.** The fever of systemic JIA is typically daily or twice-daily, usually to 39°C or higher (31). In between fever spikes, the temperature is often below normal. Children frequently appear quite ill while febrile but recover in between fevers. The fever often responds poorly to nonsteroidal anti-inflammatory drugs (NSAIDs) but will typically respond well to corticosteroids. In most children, the fever is accompanied by a characteristic rash that consists of discrete, transient, non-pruritic erythematous macules (Fig. 11-2) (32). The rash is typically more pronounced on the trunk but may occur on the extremities and the face. The most commonly involved joints are the knee, wrist, and ankle (33). Many children with systemic JIA will have extra-articular manifestations, including hepatosplenomegaly, pericarditis, pleuritis, lymphadenopathy, and abdominal pain. The extra-articular features may be present for weeks, months, and, occasionally, years prior to the onset of arthritis. Usually, the extra-articular manifestations of systemic JIA are self-limiting and will resolve spontaneously or with corticosteroid therapy. Occasionally, the pericarditis can result in tamponade.

The prognosis of systemic JIA is determined predominantly by the course of arthritis. Approximately 50% of children with systemic arthritis will have a mild oligoarticular course, and in most of these children, the arthritis will ultimately remit. The remaining half of the children with systemic onset will develop a polyarticular arthritis that can remit, but progresses in approximately 50% of the cases (25% of all systemic-onset JIA) to a severe, unrelenting, and destructive course despite all currently available therapeutic interventions (34). Chronic anterior uveitis is extremely rare in systemic arthritis. Systemic amyloidosis, usually presenting with the onset of proteinuria and hypertension, can occur as a result of any chronic inflammatory disease. Approximately 8% of European children with systemic JIA have been shown to develop this life-threatening complication (35). The incidence of amyloidosis in North America is significantly lower.
Etiology. The etiology of psoriatic arthritis is unknown but genetic associations with HLA-Cw6, DRB1*01, and DQA1*0101 have been demonstrated (14, 43). There is often a strong family history of psoriasis or psoriatic arthritis in affected children.

Clinical Features. The arthritis in psoriatic JIA is often an asymmetric mono- or polyarthritis affecting both large and small joints. At onset, patients may have pitting of the nails (67%) (Fig. 11-2) and a family history of psoriasis (69%) or dactylitis (39%), while less than one-half of the children have the rash of psoriasis (13% to 43%) (25, 44, 45). JIA criteria do not require the development of psoriasis to confirm a diagnosis of psoriatic arthritis (Table 11-2) (46). In children younger than 5 years, the presentation is often characterized by the involvement of a small number of fingers or toes that are relatively asymptomatic, but leading to marked overgrowth of the digit(s).

Children with psoriatic arthritis may have chronic lifelong arthritis that follows a relapsing and remitting course. Arthritis mutilans and severe distal interphalangeal (DIP) joint disease are unusual. However, many of the children will have prolonged polyarthritis that may result in irreversible joint damage (47). Amyloidosis has been reported in the European literature as having resulted in the deaths of at least three children (47, 48). Chronic anterior uveitis has been observed in up to 17% of the children (44, 45) and is associated with a positive ANA titer; the uveitis associated with psoriatic JIA is clinically indistinguishable from the uveitis in oligoarticular and polyarticular JIA.

Enthesitis-Related Arthritis

Definition. The JIA criteria for classification of ERA describe a group of arthritides that includes undifferentiated spondyloarthritis, JAS, and IBD-associated arthritis. The JIA criteria include many of the children who were previously diagnosed with a syndrome of seronegativity, enthesopathy,
and arthropathy (SEA syndrome) who were shown to be at increased risk for development of classic spondyloarthritis or JAS (49, 50). ERA is defined as arthritis and enthesitis or arthritis or enthesitis with at least two of the following: (a) the presence or a history of sacroiliac (SI) tenderness or lumbosacral pain; (b) HLA-B27 antigen positivity; (c) onset of arthritis in a male after age of 6 years; (d) acute anterior uveitis; and (e) history of AS, ERA, sacroiliitis with IBD, reactive arthritis, or acute anterior uveitis in a first-degree relative. Exclusions for a diagnosis of ERA include (a) psoriasis or a history of psoriasis in the patient or a first-degree relative; (b) presence of IgM RF on at least two occasions, measured 3 months apart; and (c) systemic JIA.

Epidemiology. Unlike the other subtypes of JIA, ERA is more common in boys. Disease onset is typically after the age of 6 years. Prevalence is estimated at 50 per 100,000 children (15).

Etiology. The presence of HLA-B27 is part of the diagnostic criteria for ERA. In these children, molecular mimicry is thought to contribute to the pathogenesis. Other HLA genetic associations that have been found are HLA-DRB1*01, DQA1*0101, and DQB1*05 (14).

Clinical Features. ERA is often associated with enthesitis and arthralgias or arthritis long before any axial skeletal involvement is identified (50). Enthesitis is identified when marked tenderness is noted at the 6, 10, and 2 o’clock positions on the patella, at the tibial tuberosity, iliac crest, or the attachments of the Achilles tendon or plantar fascia (Fig. 11-3) (51). However, in ERA not all entheses are created equal; some entheses are more prone to trauma and mechanical damage such as in Sinding-Larsen-Johansson syndrome while other entheses are frequently tender in normal children such as the plantar fascia insertion into the metatarsal heads. One study suggested that “pathologic” enthesitis be defined as the presence of three tender entheses at the following sites: SI joints, inferior patellar pole, Achilles tendon insertion, and plantar fascia insertion into the calcaneus (52).

The primary extra-articular manifestation of ERA is acute anterior uveitis, which can occur in up to 27% of children with AS (53). The uveitis is manifested by an acute, painful, red, photophobic eye. ERA-associated uveitis may resolve with no ocular residua, but some of the children will have a persistent uveitis that is relatively resistant to therapy and can result in blindness (54, 55).

Juvenile Ankylosing Spondylitis

Definition. The definition of ERA overlaps with that of spondyloarthropathies, a group of conditions that includes JAS and reactive arthritis. Radiographic evidence of bilateral sacroiliitis is necessary to fulfill the New York criteria for AS (Table 11-3).

Epidemiology. JAS most often presents in late childhood or adolescence. Boys outnumber girls by a ratio of 6 to 1 (56). There is a high frequency of JAS in Pacific Canada Indians (57) and a low incidence in African Americans (58).

Etiology. The similarities between JAS and reactive arthritis, in which gastrointestinal and genitourinary infections trigger disease, suggest a role for infection. There is a strong genetic component to disease as AS occurs up to 16 times more frequently in HLA-B27–positive family members of patients with AS than in HLA-B27–positive individuals in the population at large (59). Further, children with JAS and SI involvement are frequently HLA-B27 positive (82% to 95%) (56).

Clinical Course. Children with early JAS often fulfill the diagnostic criteria for ERA. Epidemic arthritis of the lower extremity large joints, enthesitis, and tarsitis within 1 year of symptom onset predicts of progression to JAS (60). The presentation of JAS is most remarkable for the absence of axial involvement. Only 12% to 24% of children with JAS have pain, stiffness, or limitation of motion of the SI or lumbosacral spine at disease onset. A peripheral arthropathy or enthesopathy,

<table>
<thead>
<tr>
<th>TABLE 11-3</th>
<th>New York Criteria for AS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical criteria</strong></td>
<td>Limited lumbar motion in all three planes</td>
</tr>
<tr>
<td>History or presence of lumbar spinal pain</td>
<td>≤2.5 cm of chest expansion at the 4th intercostal space</td>
</tr>
<tr>
<td><strong>Definite AS</strong></td>
<td>Grade 3 or 4 bilateral radiographic SI changes plus at least 1 clinical criterion</td>
</tr>
<tr>
<td>Grade 3 or 4 unilateral or grade 2 bilateral radiographic SI changes plus clinical criterion 1 or criteria 2 and 3</td>
<td></td>
</tr>
<tr>
<td><strong>Probable AS</strong></td>
<td>Grade 3 or 4 bilateral radiographic SI changes without any clinical criteria</td>
</tr>
</tbody>
</table>

![Figure 11-3. Achilles tendonitis and enthesitis in a child with enthesitis-related arthritis. (Courtesy of Dr. Ruben Burgos-Vargas.)](image-url)
affecting predominantly the lower limb joints and entheses, is seen in 79% to 89.4%. These children tend to have fewer than 5 joints involved and rarely more than 10. At presentation, the pattern of involvement of the joints is usually asymmetric (61). Small joints of the toes are commonly involved in JAS but are seldom affected in other forms of JIA, with the exception of psoriatic arthritis. However, polyarticular and axial disease are usually evident after the 3rd year of illness (61). Children with long-standing JAS have been shown to develop tarsal bone coalition that has been termed **ankylosing tarsitis** (Fig. 11-4) (62).

Outcome data for JAS are incomplete and at times contradictory. The prognosis of JAS has been reported as being worse according to some studies, and better according to others, than adult-onset AS (63, 64). Hip disease has been associated with a poor functional outcome (63, 65) and may require total hip arthroplasty.

**Inflammatory Bowel Disease–Associated Arthritis**

The frequency of arthritis in children with IBD has been reported to be 7% to 21%, and it usually occurs after the diagnosis of the bowel disease (66–68). Two different patterns of arthritis are seen (51). The most common type is oligo- or polyarticular arthritis of the lower limbs. This group is less likely to meet the criteria for ERA. This arthritis is often episodic, with exacerbation lasting 4 to 6 weeks or, rarely, for months. The activity of the peripheral arthritis is often related to the underlying bowel disease activity. The less common type of IBD-associated arthritis is an HLA-B27–associated oligoarticular arthritis of the lower limbs, with sacroilitis and enthesitis, and no relationship to bowel inflammation (51). This form is more likely to persist and progress despite adequate control of the bowel disease. The clinical course is similar to that in other children with ERA.

**DIFFERENTIAL DIAGNOSIS OF PAIN AND SWELLING IN THE JOINTS IN CHILDREN**

A comprehensive differential diagnosis of arthritis in childhood is beyond the scope of this chapter as there are over 100 disorders in which arthritis may be a significant manifestation (69). The most common classes of disorders that must be considered in the differential diagnosis of JIA include infection, postinfectious phenomenon, inflammatory arthropathies, systemic autoimmune disease, mechanical or orthopaedic conditions, trauma, and pain disorders. Often, the differential diagnosis will be determined by whether the presentation is acute, subacute, or chronic, whether the child has monoarticular or polyarticular arthritis, and whether there are systemic signs such as fever (Table 11-4).

**Infection-Related Arthritis**

**Septic Arthritis.** Septic arthritis generally affects a single joint and is associated with fever, elevated neutrophil count, ESR, C-reactive protein (CRP), and extreme pain. Synovial fluid analysis typically reveals white cell counts of >50,000 (70), neutrophil predominance, low glucose (<30 mg/dL), and a positive Gram stain. Oligoarticular JIA, in contrast, is seldom associated with systemic inflammation and joint effusions are often out of proportion to the reported pain. The most commonly infected joints in children are the knees, hips, ankles, and elbows. Gonococcal arthritis may present in a

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**TABLE 11-4 Differential Diagnosis of JIA**

<table>
<thead>
<tr>
<th>Monoarticular Arthritis</th>
<th>Polyarticular Arthritis</th>
<th>Febrile Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligoarthritis</td>
<td>Polyarthritis</td>
<td>Systemic arthritis</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>Psoriatic arthritis</td>
<td>Malignancy:</td>
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<tr>
<td>Enthesitis-related arthritis</td>
<td>Enthesitis-related arthritis</td>
<td>Lymphoid:</td>
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<tr>
<td>Sarcoidosis</td>
<td>Sarcoidosis</td>
<td>Neuroblastoma:</td>
</tr>
<tr>
<td>Transient synovitis of the hip</td>
<td>Systemic lupus erythematosus</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Trauma</td>
<td>Juvenile dermatomyositis</td>
<td>Juvenile dermatomyositis</td>
</tr>
<tr>
<td>Hemophilia</td>
<td>Systemic vasculitis</td>
<td>Systemic vasculitis</td>
</tr>
<tr>
<td>Pigmented villonodular synovitis</td>
<td>Scleroderma</td>
<td>Infection (viral or bacterial)</td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>Gonococcal septic arthritis</td>
<td>Reactive arthritis</td>
</tr>
<tr>
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<td>Reactive arthritis</td>
</tr>
</tbody>
</table>
sexually active adolescent as an oligoarticular, polyarticular, or migratory arthritis with significant tenosynovitis.

**Lyme Arthritis.** Lyme arthritis may occur weeks to months after infection with the tick-borne spirochete *Borrelia burgdorferi*. Up to 60% of patients with untreated disease develop arthritis, which may be manifested by intermittent or continuous swelling (71). Many patients with untreated Lyme disease complain of migratory arthralgias or arthritis (72). In a recent retrospective study of 90 children with Lyme arthritis, Gerber et al. (73) noted that the majority (63%) had monoarticular disease, but no child had more than four joints involved. The knee was affected most often (90%), followed by hip (14%), ankle (10%), wrist (9%), and elbow (7%), whereas small joints were rarely involved. Most children with Lyme arthritis do not recall a tick bite or erythema migrans (73, 74). Lyme arthritis is typically an inflammatory synovitis with a very large and relatively painless joint effusion (Fig. 11-5). The ESR can be normal or elevated (73). The diagnosis should be confirmed with serologic testing, which includes an enzyme-linked immunosorbent assay (ELISA) and Western blot. There is a high rate of false-positives with ELISA testing, so if the ELISA is positive, then a confirmatory Western blot should be performed. If the ELISA is negative, no further testing is needed. Synovial fluid analysis typically reveals white cell counts of 10,000 to 25,000. A small percentage of children may develop a persistent arthritis despite multiple courses of oral and/or intravenous antibiotics; persistence of swelling is associated with HLA-DR4 and HLA-DR2 alleles (75). In these patients, intra-articular corticosteroid injections are often helpful. Detection of *Borrelia burgdorferi* in the synovial fluid using polymerase chain reaction (PCR) can be confirmatory in seropositive patients. However, a positive PCR in the setting of negative serologies is likely to be a false-positive (76). Further a positive PCR is not proof of active infection as remnant DNA may persist for some time after *Borrelia burgdorferi* killing has occurred (76).

**Postinfectious Arthritis.** Postinfectious or reactive arthritis results in a sterile synovitis that is an immune response to a non-articular infection. In most children, the reactive arthritis occurs after upper respiratory or gastrointestinal infections, whereas in adult patients it is more likely to occur following a genitourinary infection (77–79). The classic presentation of reactive arthritis is the triad of conjunctivitis, urethritis, and arthritis. The complete triad of reactive arthritis is very uncommon in childhood. The ratio of boys to girls is 4 to 1 (79, 80). Most patients with reactive arthritis carry the *HLA-B27* allele (79, 81).

**Transient Synovitis of the Hip.** Transient synovitis of the hip is a self-limiting, postinfectious, inflammatory arthritis. Transient synovitis of the hip has a peak incidence, predominantly in boys (70%), at between 3 and 10 years of age. It is an idiopathic disorder often preceded by a nonspecific upper respiratory tract infection (82). The onset of pain is often gradual, is rarely bilateral, and lasts for an average of 6 days. There is often low-grade fever and mild elevation of inflammatory markers (83). With rest and NSAIDs, most children will have complete resolution of symptoms within 2 weeks. Most children with transient synovitis of the hip will have only a single event; however, 4% to 17% have a recurrence within 6 months (84).

**Acute Rheumatic Fever.** Acute rheumatic fever (ARF) is a postinfectious reaction to an untreated group A β-hemolytic streptococcus infection of the pharynx (85). Arthritis, which is the most common but least specific ARF manifestation, classically appears 2 to 3 weeks after the streptococcal infection. The classic arthritis of ARF is a migratory polyarthritis. The affected joints are erythematous, swollen, and extremely painful. The joint pain is exquisitely responsive to aspirin or NSAIDs; dramatic relief is often obtained within several hours after the first dose. Since children with ARF are at an increased risk for rheumatic carditis, streptococcal prophylaxis is recommended until age 21. The diagnosis can be confirmed by the presence of the other major JONES criteria (Table 11-5), which include carditis, migratory subcutaneous nodules, chorea, and erythema marginatum.

**TABLE 11-5** Modified Jones Criteria for Acute Rheumatic Fever

<table>
<thead>
<tr>
<th>Major Manifestations</th>
<th>Minor Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carditis</td>
<td>Fever</td>
</tr>
<tr>
<td>Polyarthritis</td>
<td>Arthralgia</td>
</tr>
<tr>
<td>Subcutaneous nodules</td>
<td>Prolonged PR interval</td>
</tr>
<tr>
<td>Erythema marginatum</td>
<td>Increased ESR or CRP</td>
</tr>
<tr>
<td>Chorea</td>
<td></td>
</tr>
</tbody>
</table>

Diagnosis requires the presence of two major criteria, or one major and two minor criteria, with supporting evidence of a preceding streptococcal infection (rising streptococcal antibody titers, positive throat culture, or rapid streptococcal antigen test). ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

**FIGURE 11-5.** Right knee effusion in a child with Lyme arthritis.
Poststreptococcal Arthritis. Poststreptococcal-reactive arthritis is a postinfectious reaction to a streptococcal infection that does not fulfill ARF criteria. It typically presents as a nonmigratory oligo- or polyarthritis. Unlike ARF, it is poorly responsive to aspirin or other nonsteroidal drugs. Limited studies have suggested that further episodes of streptococcal pharyngitis lead to an increased risk for ARF and rheumatic carditis and that streptococcal prophylaxis is indicated for 1 to 2 years (86, 87).

Serum Sickness. Serum sickness is a clinical syndrome resulting from an adverse immunologic response to foreign antigens mediated by the deposition of immune complexes. The most common culprits are antibiotics (penicillins and sulfonamides) and infections (88–90). Serum sickness is characterized by fever, arthralgia or arthritis, lymphadenopathy, cutaneous eruptions (urticarial or morbilliform), and angioedema. Both serum sickness and allergic angioedema can be mistaken for acute-onset JIA. However, most children with serum sickness will spontaneously improve within a few weeks. For mild disease, removal of the offending antigen and treatment with antihistamines and nonsteroidal anti-inflammatory medications is sufficient. In severe cases, a several-week course of corticosteroids may be required.

Other Inflammatory Arthropathies

Gout. Gouty arthritis is characterized by hyperuricemia and deposition of monosodium urate crystals into the joint. The major clinical manifestations include acute mono- or oligoarthritis, frequently involving the first metatarsophalangeal joint. Gout may result from either increased production or decreased excretion of uric acid. Gout is extremely rare in children (91). The diagnosis can be confirmed by demonstration of negatively birefringent, monosodium urate crystals in the synovial fluid. Acute gout is treated with nonsteroidal anti-inflammatory medications and allopurinol is utilized to prevent recurrences. The use of allopurinol is not recommended during the acute phase of gout.

Cystic Fibrosis–Associated Arthritis. Cystic fibrosis (CF)-associated arthritis (92) is an episodic transient arthritis often associated with pulmonary exacerbations (93–97). The joint symptoms typically last for 1 to 10 days and may be associated with a pruritic and nodular rash. Additionally, CF patients have a higher-than-expected occurrence of RF-positive polyarticular JIA or adult RA (98). Some children with CF may develop secondary hypertrophic osteoarthropathy, demonstrable on radiographs (99, 100).

Systemic Autoimmune Diseases. Many of the systemic autoimmune diseases can cause acute or chronic arthritis. There are often signs, symptoms, or laboratory abnormalities that will aid in the diagnosis of these conditions. For a thorough discussion of these diseases in children, several excellent texts and reviews are available (51, 69, 101).

SLE is an episodic, autoimmune inflammatory disease characterized by multiorgan system inflammation. Arthralgia and arthritis affect 75% of the children with SLE. It is usually polyarticular, and the joint pain is often out of proportion to the physical findings. Typically, the arthritis responds readily to corticosteroids, is rarely erosive (102), and does not result in deformity.

Sarcoidosis is uncommon in childhood (103). However, arthritis is frequent in childhood-onset sarcoidosis, and typically presents as an oligoarthritis affecting the knees, ankles, and/or elbows. Large and boggy effusions with minimal discomfort characterize the arthritis. A synovial biopsy is often diagnostic, showing the presence of noncaseating granulomas.

Vasculitis in childhood may be associated with arthritis. The disease most likely to be seen by the orthopaedic surgeon is Henoch-Schönlein purpura (HSP). HSP is the most common vasculitic syndrome in childhood, occurring in slightly more than 1 in 10,000 children per year (104). The classic manifestations of HSP are nonthrombocytopenic palpable purpura, arthritis, abdominal pain, gastrointestinal hemorrhage, and glomerulonephritis. In the complete syndrome, the diagnosis is often clear. However, the arthritis can precede the appearance of the rash, and the rash may be unrecognized if a comprehensive skin examination is not done. The rash of HSP often begins on the lower extremities as an urticarial eruption, followed by petechiae and purpura, which are most often concentrated on the buttocks and lower extremities. The arthritis of HSP presents as a periarticular swelling and tenderness, most commonly of large joints, with severe pain and limitation of motion. The younger child will often refuse to use the affected joint. The arthritis is usually transient, and resolves without sequelae in a few days to weeks.

Foreign Body Synovitis. Plant thorns and wood splinters in the joint space can cause a chronic synovitis or tenonitis (105). Typically, the injury has been long forgotten, because many months may pass between entry of the thorn into the skin and passage into the joint. Surgical removal of the splinter and synovectomy are the only effective treatments.

Coagulopathies and Hemoglobinopathies. Children with congenital coagulopathies (hemophilia) and hemoglobinopathies (sickle cell disease) will present with acute pain and swelling in the joints, resulting from hemarthrosis and localized ischemia, respectively. A comprehensive discussion of these conditions is found in Chapter 11.

Malignancy. It is not uncommon for malignancies such as childhood leukemia to present as musculoskeletal pain and joint swelling. Often these symptoms present before blasts are detectable in the peripheral blood, making diagnosis challenging (106). In a recent study of 277 children ultimately diagnosed with either JIA or acute lymphocytic leukemia (ALL), the features that best predicted a diagnosis of ALL were leukopenia (<4 × 10^9/L), borderline low platelet count (150–200 × 10^9/L), and a history of nighttime pain (106). Plain radiographs may show subperiosteal elevation, osteolytic reaction, or metaphyseal rarefaction.

Pigmented Villonodular Synovitis. Pigmented villonodular synovitis (PVNS) is a benign tumor of the synovium.
PVNS is a rare cause of episodic joint effusions (107, 108). The effusions are minimally painful and cause progressive cartilage destruction and bone erosions (Fig. 11-6A). Synovial aspirates that are very bloody should arouse suspicion of the diagnosis. Magnetic resonance imaging (MRI) can be helpful, but confirmation of the diagnosis is made by synovial biopsy showing nodular hypertrophy, with proliferating fibroblasts and synovial cells, and hemosiderin-laden macrophages (Fig. 11-6B). Treatment consists of surgical excision. However, recurrence is frequent and multifocal disease can occur.

**Benign Nocturnal Pains of Childhood.** Growing pains, or benign nocturnal pains of childhood, are common and may affect up to 20% of all children (109). These pains typically occur in school-age children. The pain typically affects the lower extremities symmetrically. Characteristically, the pain occurs in the early evening or at night and often awakens the child from sleep. The pains are always resolved by the morning and respond well to massage or analgesics. The physical examination and laboratory studies are always normal. Children with recurring nighttime pains often have significant relief from a single bedtime dose of acetaminophen, ibuprofen, or naproxen.

** Reflex Sympathetic Dystrophy.** Reflex sympathetic dystrophy (RSD) is likely underrecognized in children (110–113). The onset of RSD often occurs after minor trauma or after a fracture has healed and the cast has been removed. There is an initial pain that causes the child to stop using the affected limb. The disuse perpetuates the pain and the extremity involved becomes painful to light touch (allodynia), swollen, cold, and discolored. Plain radiographs of the affected limb may show soft-tissue swelling and, after 6 to 8 weeks, a generalized osteoporosis. Technetium-99m bone scans may show either a diffuse increase (early) or decrease (late) in uptake of isotope (Fig. 11-7). The most effective treatment for RSD is vigorous physical therapy and careful attention to the underlying psychosocial stressors (110, 111, 114). The affected limb should never be immobilized, because this will uniformly cause a worsening of the pain during or after the period of immobilization.

**RADIOGRAPHIC FEATURES OF JIA**

Plain radiographs are useful in the initial evaluation of children with pain and/or swelling in the joints, predominantly for identifying periarticular osteopenia, fractures, or other bony lesions. Radiographic changes associated with JIA include the following, in order of appearance: (a) soft-tissue swelling and widening of the joint space, (b) generalized osteoporosis, (c) joint space narrowing, (d) erosions, (e) subluxation, and (f) ankylosis (Figs. 11-8 and 11-9). However, the diagnosis of JIA is often made before radiographic changes are detectable. Eroded changes, with the exception of the TMJs, are uncommon before 2 years of active disease. Children with chronic polyarthritis may develop bony ankylosis of the carpal and tarsal joints, and in the cervical spine. Radiologic abnormalities of the cervical spine (Fig. 11-10) can result from apophysal joint inflammation and bony fusion, often initially at the C2–C3 level. Atlantoaxial instability, which is not uncommon with cervical disease, is identified when the atlanto-odontoid space is >4 mm. If instability is identified, special care should be used if intubation is required for a surgical procedure.

Children with AS will develop radiographically visible changes in the SI joints, but this may not occur for 1 to 15 (average 6.5) years after diagnosis (53). These findings can include pseudo-widening caused by erosions, sclerosis, and fusion (Fig. 11-11). Radiologic changes in the lumbosacral spine occur later in the course of JAS and are less frequent (115). Chronic enthesitis, particularly at the calcaneus, can result in erosion at the insertion of the Achilles tendon or plantar fascia.

**OTHER DIAGNOSTIC STUDIES FOR JIA**

**Laboratory Tests.** There are no diagnostic laboratory tests for JIA. The selection of specific laboratory evaluations should be guided by the history and physical examination. A complete blood count with differential, CRP, and ESR should be part of the initial evaluation of any child with joint swelling. These tests will help to identify hematologic abnormalities suggesting malignancy, and to document the presence or absence of systemic inflammation. Systemic JIA, malignancies, systemic autoimmune diseases, and infections typically have an elevated ESR, often >100 mm/hour. However, most children with oligoarticular and some with polyarticular JIA will have a normal ESR and CRP. The addition of a CRP test can be helpful in situations in which infection is strongly suspected, because the short half-life of this acute-phase protein results in a rapid decline in concentration with effective antibiotic treatment, whereas the ESR may continue to rise. In addition, serologic testing for Lyme is appropriate in the setting of monoarthritis if the patient is from a Lyme endemic area.

The ANA titer is a measure of serum antibodies that can bind to one of many potential antigens present in the nucleus of normal human cells. ANA titer at a dilution of >1 to 40 is considered positive. The presence of an elevated ANA is not diagnostic of JIA and should not be used as a screening test for arthritis. ANA can be positive in up to 20% of the normal population and may be induced by illness or be present in first- or second-degree relatives with SLE (120, 121). Unless there is a high index of suspicion of JIA, a positive ANA test results in unnecessary subspecialty referrals and parental anxiety.
FIGURE 11-6. Reflex sympathetic dystrophy in a child with a 1 month history of hand swelling and pain. A: Right hand after 1 month of symptoms. B: Technetium-99m bone scan showing diffuse increased isotope uptake in the affected hand. C: Right hand after 3 weeks of intensive physical therapy and psychotherapy.
Children who have a positive ANA in the absence of systemic inflammation and arthritis are unlikely to subsequently develop a significant autoimmune disease (120, 122). In children with an established JIA diagnosis, the frequency of ANA positivity is greatest in young girls with oligoarticular disease, and represents an increased risk for anterior uveitis (123). If JIA is suspected on the basis of a history and physical exam, positive ANA should prompt an immediate referral to an ophthalmologist for a slit-lamp examination to evaluate for the presence of uveitis.

The RF is an autoreactive IgM, anti-IgG that is commonly used to help diagnose adult RA. In contrast to adults with RA, RF positivity is infrequent in children with JIA. Therefore, like the ANA, RF is not a good screening test for JIA. When present, it is most commonly associated with polyarticular JIA. RF is associated with a higher frequency of erosive synovitis and a poorer prognosis (124, 125).

Anti-citrullinated cyclic peptide (anti-CCP) antibodies have a sensitivity and specificity of 48% and 98%, respectively, for adult RA (126). Additionally, adult CCP-positive RA patients have a more aggressive disease course manifested by joint erosions and destruction (127, 128). Anti-CCP antibodies are mainly detected in polyarticular RF-positive JIA patients and are of limited diagnostic value. However, in a child with established polyarticular disease, seropositivity for anti-CCP antibodies may portend a more destructive disease course and, therefore, help to identify patients who might benefit from more aggressive therapy at diagnosis.

The presence of HLA-B27 is strongly associated with transient reactive arthritis, IBD, and ERA. The high familial occurrence of AS is directly related to the presence of HLA-B27 (129). Although HLA-B27 is found in approximately 8% of the white population, it can be useful in the diagnosis of...
FIGURE 11-9. The cervical spine in a child with polyarticular JIA. A. At 6 years of age, there are no radiographic abnormalities. B. At 21 years of age there is ankylosis of C2–C5.

ERA. It is especially important in boys above the age of 6, where there is a family history of HLA-B27–associated illness, or SI joint or spinal inflammatory pain.

Synovial Fluid Analysis. Arthrocentesis with synovial fluid analysis and culture should be performed in all children with an acute arthritis accompanied by fever or in children for whom the diagnosis is unclear. In JIA, synovial fluid is type II, or inflammatory. The appearance is typically yellow and cloudy with decreased viscosity. Leukocyte counts are generally between 15 and 20,000 cells/mm³; however, they may range as high as 100,000 cells/mm³ (130–132). There is typically a neutrophil predominance (130).

Synovial Biopsy. A synovial biopsy should be performed if the diagnosis remains unclear after laboratories, imaging, and synovial fluid analysis. Biopsy is particularly helpful if a diagnosis of tuberculosis, PVNS, or sarcoidosis is being considered.

TREATMENT RECOMMENDATIONS

Medications. The fundamental purpose of pharmacologic therapy is to achieve pain control, decrease inflammation, prevent joint destruction, and to maintain remission. The medications used are individualized for each patient, depending on their subtype of arthritis, degree of inflammation, and previous pharmacologic response.

Nonsteroidal Anti-Inflammatory Drugs. NSAIDs are the initial therapeutic intervention in many children with JIA. NSAIDs provide both analgesia and anti-inflammatory effects. NSAIDs affect the biosynthesis of prostaglandins by direct inhibition of cyclo-oxygenase (COX) (133). There are two isoforms
of the COX enzyme. COX-1 is constitutively expressed and is involved in gastric cytoprotection, maintenance of renal perfusion, and platelet aggregation. COX-2 is upregulated at sites of inflammation. Most NSAIDs inhibit both COX isoforms, with consequential side effects such as GI toxicity or renal hypoperfusion. NSAIDs are generally safe and well tolerated in most children. Abdominal pain, nausea, and vomiting are the most common side effects, and gastrointestinal hemorrhage is rare (134). Gastroduodenal injury is more frequent in children who are receiving high doses, or more than one NSAID at a time (135). The use of aspirin in JIA is no longer recommended because of the risk of Reye syndrome.

In the United States, the most commonly used NSAID for JIA is naproxen (10 to 20 mg/kg/d). In children with fevers, serositis, or pericarditis associated with systemic arthritis, reactive arthritis, or JAS, indomethacin is often the most effective NSAID (51).

The doses of NSAIDs in children are based on body weight, and are often proportionally greater than in adult rheumatic diseases (Table 11-6). Preparations that come in a liquid form and have once- or twice-daily dosing are preferred. Children on long-term NSAID therapy should have a complete blood count, renal and liver function tests, and urine analysis at baseline, within 6 weeks of therapy initiation, and every 6 to 12 months thereafter. The average time required for a therapeutic response to NSAIDs is 2 to 12 weeks (136). Therefore, an NSAID is usually tried for several weeks before another is substituted. Approximately 50% of children respond to the first NSAID; of those who do not respond, 50% respond to an alternate NSAID (137). Nearly two-thirds of children with juvenile arthritis are inadequately treated with NSAIDs alone (138). These children require additional pharmacologic interventions.

Corticosteroids. Intra-articular corticosteroid injections have been shown to be safe and effective in controlling the synovitis in JIA (139, 140). A recent decision analysis reported that initial intra-articular injection, rather than a trial of NSAIDs, is the optimal treatment for monoarthritis (141). In order to avoid a singled intra-articular injection, 3.8 children need to be treated with an initial trial of NSAIDs; the cost of initial therapy with NSAIDs was an expected additional

**FIGURE 11-11.** Iritis in oligoarticular JIA. Posterior synechiae with an irregular pupil.

**TABLE 11-6 NSAIDs for the Treatment of JIA**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (mg/kg/d)</th>
<th>Maximum Daily Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TID medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indomethacin (Indocin)†,‡</td>
<td>2–3</td>
<td>200</td>
</tr>
<tr>
<td>Salicylsalicylic acid (Aspirin)§</td>
<td>80–100</td>
<td>5200</td>
</tr>
<tr>
<td>Ibuprofen (Motrin, Advil, etc.)†,§</td>
<td>45</td>
<td>3200</td>
</tr>
<tr>
<td>Tolmetin (Tolectin)§</td>
<td>30–40</td>
<td>1800</td>
</tr>
<tr>
<td>BID medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulindac (Clinoril)</td>
<td>4–6</td>
<td>400</td>
</tr>
<tr>
<td>Choline magnesium trisalicylate (Trilisate)§</td>
<td>50–65</td>
<td>4500</td>
</tr>
<tr>
<td>Naproxen (Naprosyn)†,§</td>
<td>15–20</td>
<td>1000</td>
</tr>
<tr>
<td>Diclofenac sodium (Voltaren)</td>
<td>2–3</td>
<td>150</td>
</tr>
<tr>
<td>Celecoxib (Celebrex)§</td>
<td>4–6</td>
<td>400</td>
</tr>
<tr>
<td>Daily medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nabumetone (Relafen)</td>
<td>20–30</td>
<td>2000</td>
</tr>
<tr>
<td>Meloxicam (Mobic)†,§</td>
<td>0.25</td>
<td>15</td>
</tr>
<tr>
<td>Feldene</td>
<td>0.25–0.4</td>
<td>20</td>
</tr>
</tbody>
</table>

†Liquid preparation available.
‡U.S. Food and Drug Administration (FDA)-labeled for use in children.
6.7 months of active arthritis (141). Further, early intra-articular corticosteroid injections are associated with less leg-length discrepancy (LLD) in young children with oligoarthritis (142).

Triamcinolone hexacetonide (1 mg/kg for large joints and 0.5 mg/kg for medium joints) is the most commonly used agent and often provides long-term control of inflammation. The most frequent adverse consequence of intra-articular corticosteroids is the development of subcutaneous atrophy at the site of injection. Other side effects of intra-articular injections include infection, chemical irritation, and periarticular calcifications.

Systemic corticosteroids can be used for rapid control of severe arthritis. However, long-term use should be restricted to those children who have severe arthritis or systemic features that do not respond to other interventions.

**Methotrexate.** The efficacy of methotrexate in JIA is well established (143, 144). It is a folic acid analogue, a competitive inhibitor of dihydrofolate reductase, and an inhibitor of purine biosynthesis.

Methotrexate is typically given at a dosage of 0.5 to 1 mg/kg/wk or 15 mg/m²/wk (with a maximum of 25 mg) once weekly, either orally or by subcutaneous injection (145, 146). The most common side effects of methotrexate are nausea, fatigue, and liver transaminitis. Supplementation with folic acid (1 mg/d) can usually prevent gastrointestinal complications. Subcutaneous methotrexate should be considered for children who require doses >20 mg or who have significant gastrointestinal toxicity with the oral formulation. The average time course for clinical response to methotrexate is 6 to 8 weeks. Children on methotrexate should have a complete blood count and liver function tests at baseline, within 6 weeks of therapy initiation and then every 2 to 3 months thereafter.

**Sulfasalazine.** Sulfasalazine has been used extensively in Europe, and increasingly in North America for the treatment of JIA. It was developed on the idea that RA was caused by an infection; therefore, it has both antibacterial and anti-inflammatory properties. A randomized, double-blind, placebo-controlled trial showed that sulfasalazine is both safe and effective for the treatment of oligo- and polyarticular juvenile arthritis (156).

It is typically given in an enteric-coated form at a dose of 50 mg/kg/d in two divided doses. Serious side effects have been noted in children with systemic arthritis, and the routine use of sulfasalazine is not recommended for this subgroup (157, 158). Side effects occur in up to 30% of patients (159) and include cytopenias, severe allergic reactions such as Stevens-Johnson syndrome, hypogammaglobulinemia, and IgA deficiency. Children taking sulfasalazine should have a complete blood count, liver function tests, and urinalysis at baseline and every 2 to 3 months thereafter. Immunglobulin levels should be monitored every 6 months.

**Abatacept.** Abatacept (Orencia) is a fully human monoclonal antibody (MRA) that consists of the extracellular domain of the CTLA-4 receptor attached to the Fc portion of a type 1 human immunoglobulin. Abatacept binds TNF-α in circulation and prevents subsequent cell activation. A multicenter placebo-controlled, double-blinded trial showed that abatacept was efficacious in treatment of juvenile arthritis that was resistant to initial therapy with methotrexate (147, 148). Further, the safety and efficacy of abatacept is maintained for up to 8 years (149). Abatacept is given subcutaneously at a dose of 0.8 mg/kg/wk.

**Anti-Interleukin 1 Agents.** Anakinra (kineret) is an IL-1 receptor antagonist. It has been shown to be safe and efficacious in combination with methotrexate for adult RA (162). A recent randomized, placebo-controlled trial showed that anakinra was safe and well tolerated at a dose of
1 mg/kg/d (maximum 100 mg) but did not significantly reduce disease flares in children with polyarticular JIA (163). In JIA, it has been anecdotally used for systemic JIA, although there are no randomized controlled trials published at this time. The major side effects of anakinra are injection site reactions and infection.

**Anti-Interleukin 6 Agents.** IL-6 is a key inflammatory cytokine in RA and JIA. Anti–IL-6 receptor MRA has been studied for the treatment of systemic JIA in open label phase II trials. These preliminary trials have demonstrated that MRA is safe, well tolerated, and resulted in improvement in symptoms and inflammatory markers (164, 165). Tocilizumab (RoActemra or Actemra) is a recombinant humanized MRA that acts as an IL-6 receptor antagonist. A recent double-blinded trial demonstrated that Tocilizumab monotherapy was superior to methotrexate monotherapy in RA, with a rapid improvement in symptoms and a favorable safety profile (166). Tocilizumab trials in children have not been published yet.

**PHYSICAL AND OCCUPATIONAL THERAPY**

All children with prolonged arthritis should be evaluated by a physical and/or occupational therapist to provide an appropriate teaching and treatment program. Most treatment programs for JIA will include active and passive range-of-motion exercises, strengthening, and other modalities such as use of hot paraffin for relief of hand stiffness. Swimming has the advantage of providing muscle strengthening and active range of motion without significant weight bearing. Splinting may be used for maintaining alignment, providing rest, and reducing flexion contractures. For children with severe flexion contractures, a dynamic tension splint or serial casting can be used to correct the contracture. Physical therapy for range of motion in JAS is primarily to prevent loss of mobility and poor functional positioning.

**Surgical Interventions.** For most children with JIA, orthopaedic surgery has a limited role in the management plan. With early detection and aggressive medical management, the majority of children with JIA have a satisfactory outcome without significant disability. However, for those children with persistent arthritis despite medical therapy, continued pain, or progressive leg-length discrepancy, there is often significant benefit from individualized orthopaedic surgical intervention. Surgical intervention in JIA presents unique challenges to the management team. The small size of children and their growth potential must be taken into consideration. Also, in the postsurgical period, prolonged immobilization can lead to decreased strength and range of motion. Intensive physical therapy is frequently required during the recovery period. There is no universal agreement about which procedures are indicated for the treatment of complications of JIA. However, the overall goal is to provide symptomatic relief and improved functioning.

**Synovectomy.** Synovectomy may be indicated in JIA for relief of persistent joint pain, swelling, and loss of range of motion related to synovial hypertrophy. Several recent studies suggest that arthroscopic synovectomy for treatment-refractory monoarthritis only partially effective JRA and that recurrence was common (167, 168). In one study, two-thirds of children relapsed within 24 months of the procedure (167), and in a second study, 67%, 95%, and 100% of children with oligo-, poly-, and psoriatic JIA relapsed after an average of 1 year (168). Predictors of a good response were normal inflammatory markers and short disease duration at the time of the procedure (167).

**Soft-Tissue Release.** Soft-tissue release may be useful in a child with a severe contracture of the knee or hip that is resistant to splinting or serial casting. Reports have demonstrated various results. The most recent publications have shown only a modest benefit (169, 170).

**Arthrodesis.** Arthrodesis may be indicated for severe joint destruction of the ankles or cervical spine secondary to prolonged synovitis. After puberty, a fixed and painful deformity of the ankle may be corrected by a triple arthrodesis. Occasionally, in children with isolated damage of the subtalar or talonavicular joint, a single joint fusion may be appropriate (171). Although many children with JIA have cervical spine arthritis and atlantoaxial instability, there is no consensus on the indications for prophylactic fusion. In many cases, a simple cervical orthosis may stabilize the neck and prevent further subluxation. However, fusion of the cervical spine (C1–C2) is indicated in children who have progressive neurologic involvement (172, 173).

**Epiphysiodesis.** An appropriately timed epiphysiodesis can be successfully used to correct leg-length discrepancies in oligoarticular JIA (174, 175). The discrepancy can be predicted using the method of Moseley (92). Simon et al. (175) reported that 15 such patients were followed up to skeletal maturity and showed satisfactory results.

**Total Joint Arthroplasty.** Total joint arthroplasty is indicated for children with JIA who have severe destructive joint changes with functional impairment. The most common joints replaced are the hip and knee, followed by the shoulder and elbow.

Cemented hip replacements may reduce pain and improve functional ability; however, there is a significant rate of loosening and need for subsequent revision (176, 177). A recent study has suggested that bipolar hemiarthroplasty of the hip, with a 79% 10-year survival, may be an alternative to conventional joint arthroplasty (178).

Results of total knee arthroplasty in JIA have been encouraging, with few revisions required (179–183). Cementless total knee arthroplasty has been used in selected cases (184). Recent studies have confirmed the efficacy of the procedure by reporting an overall 99% survival for nonconstrained anatomically graduated components prosthesis with cementless fixation (183).
In a recent review, Connor and Morrey (185) evaluated the long-term outcome for 19 children (23 elbows) who had been managed with total elbow arthroplasty and followed up for at least 2 years. Only three (13%) had poor results caused by late complications: aseptic loosening, instability, and worn bushings (185).

**COMPLICATIONS**

**Uveitis.** Uveitis is one of the most severe extra-articular complications of JIA. It is often asymptomatic and, if untreated, can lead to synchiae, cataracts, glaucoma, retinal detachment, and visual loss (Fig. 11-11). Significant predictors of uveal inflammation include JIA subtype, younger age at disease onset, and ANA positivity (186). Oligoarticular JIA has the highest cumulative incidence of uveitis, occurring in up to 25% and 16% of children with extended and persistent courses, respectively (186). Uveitis is much less frequent in polyarticular and systemic JIA patients, 4% and 1%, respectively. In ERA, ocular inflammation occurs in up to 7% of children; in two-thirds of children, it is manifested by pain, photophobia, and conjunctival erythema (186). Uveitis is present in up to 10% of psoriatic JIA patients and is typically asymptomatic (186). Although the overall incidence and severity of uveitis seem to be decreasing (187, 188), even a low-grade, asymptomatic (186). Although the overall incidence and severity of uveitis seem to be decreasing (187, 188), even a low-grade, asymptomatic (186).

**Growth Retardation.** Chronic inflammation and corticosteroid therapy adversely impact the growth of children with JIA (Fig. 11-9A,B). Growth failure, as defined by at least two of the following, is present in up to 19% of children with JIA (191): (a) less than the 3rd percentile height for age, (b) growth velocity less than the 3rd percentile for age >6 months, and (c) crossing two or more percentiles on the height for age growth chart. Once remission is achieved and corticosteroid therapy is discontinued, as much as 70% have catch-up growth; however, the remaining 30% may have persistent growth retardation (192). Preliminary results of recombinant growth hormone look promising (193); however, use of growth hormone in the JIA population is not part of currently recommended routine therapy.

**Osteoporosis.** Risk factors for osteoporosis in JIA include chronic corticosteroid use, physical inactivity, delayed puberty, and malnutrition (194). Recent studies have demonstrated that children with chronic arthritis are at risk for low volumetric bone mineral density and bone strength (195). Furthermore, a recent population-based study demonstrated an elevated risk of fracture in children with chronic arthritis (196). Careful attention to calcium and 25-OH vitamin D status may help minimize osteoporosis in the JIA population.

**Leg-Length Discrepancy.** Increased blood flow to inflamed joints also results in increased nutrient delivery to adjacent growth plates, resulting in increased bone growth. If arthritis is asymmetric in the lower extremities, this may result in LLD over time. LLD < 1 cm are probably clinically insignificant and may be a variant of normal. LLD > 1 cm, however, may result in strain on the shorter leg and back. Early treatment of arthritis may prevent LLD. One study showed that early and continued use of intra-articular corticosteroid injections help prevent LLD and decrease the need for shoe lifts (142).

### TABLE 11-7 Guidelines for Initial Frequency of Screening Eye Exams in JIA

<table>
<thead>
<tr>
<th>JIA Onset Type</th>
<th>Minimum Screening Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Onset</td>
<td>&lt;7 yr</td>
</tr>
<tr>
<td>Oligoarticular</td>
<td></td>
</tr>
<tr>
<td>ANA+</td>
<td>3 mo</td>
</tr>
<tr>
<td>ANA−</td>
<td>6 mo</td>
</tr>
<tr>
<td>Polynartic</td>
<td></td>
</tr>
<tr>
<td>ANA+</td>
<td>3–4 mo</td>
</tr>
<tr>
<td>ANA−</td>
<td>6 mo</td>
</tr>
<tr>
<td>Systemic</td>
<td></td>
</tr>
<tr>
<td>Psoriatic</td>
<td></td>
</tr>
<tr>
<td>ANA+</td>
<td>3 mo</td>
</tr>
<tr>
<td>ANA−</td>
<td>6 mo</td>
</tr>
<tr>
<td>Enthesitis-related arthritis</td>
<td>1 yr</td>
</tr>
</tbody>
</table>

All patients with an irregular iris, or an acute red, painful, or photophobic eye, should be examined immediately.

ANA, antinuclear antibodies.

**PEARLS AND PITFALLS**

- JIA has been proposed as a replacement for both JCA and JRA.
- Oligoarthritis is the most common subtype of JIA.
- Only 5% of RF-positive and 30% of RF-negative polyarticular JIA patients achieve long-term remission off medication.
- Less than one-fourth of children with JAS have pain, stiffness, or limitation of motion of the SI or lumbosacral spine at disease onset.
- Small joints of the toes are commonly involved in JAS and are seldom affected in other forms of JIA, with the exception of psoriatic arthritis.
- Initial laboratory evaluation of arthritis should include a CBC, ESR, and CRP. Lyme ELISA should also be considered if living in a Lyme endemic area.
- RF and ANA positivity are not diagnostic of JIA
- Plain radiographs are useful in the initial evaluation for identifying osteopenia, fractures, or other bony lesions.
- Radiographic features associated with JIA include soft-tissue swelling and widening of the joint space, generalized...
osteoporosis, joint space narrowing, erosions, subluxation, and ankylosis.

- Screening flexion and extension films are recommended prior to anesthesia if cervical disease is suspected.
- ANA positivity is a marker of risk for JIA-associated uveitis.
- All children with JIA should be evaluated for uveitis at diagnosis and routinely thereafter.
- JIA patients are at risk for growth failure, osteoporosis, and LLD.

REFERENCES


