

# Synovial Disorders

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## **INTRODUCTION**

In the evaluation of synovitis, the physician must be able to compartmentalize in his/her own mind the various categories of presentations. Is the symptomatology acute or chronic, occurring after an infection, concurrent with an infection, associated with another rheumatologic illness such as vasculitis, or is it consistent with the patient's previously known diagnoses (such as cystic fibrosis or glycogen storage disease)?

Chronic synovitis (duration equal to or greater than six weeks) is one of the criteria, according to the American College of Rheumatology, required to make the diagnosis of juvenile rheumatoid arthritis (JRA). Please see figure 1 for the approach to the child with chronic arthritis. In this chapter "acute" synovitis will be referred to as any arthritis of less than 6 weeks duration.

When gathering historical information from the patient and parents, the physician should direct questioning to elicit history that will aid in differentiating the acute causes of synovitis. Is there evidence of an active infectious synovitis? Are there fevers, sweats, chills, and/or a red-hot joint(s)? Was there a preceding streptococcal throat infection? Could the illness be consistent with that of rheumatic fever or post-streptococcal synovitis? Was there a viral illness preceding the onset of a painful large-joint arthritis consistent with toxic synovitis? Does the patient have a history of a tick bite or live in an endemic area for Lyme disease? Are there other signs or symptoms that indicate Kawasaki syndrome or Henoch-Schonlein purpura? Are there systemic signs of vasculitis, such as severe abdominal pain or cutaneous lesions, that suggest polyarteritis nodosa? In this chapter a few of the most common acute causes of synovitis, such as post-infectious and rheumatic fever, are discussed in this text but there are many more that are not reviewed because of the limited scope of this chapter.

Juvenile rheumatoid arthritis (JRA) and juvenile spondyloarthropathies (SpA) comprise the majority of the causes of chronic synovial disorders that rheumatologists see in the outpatient clinic setting; and thus much attention and time is spent in this chapter discussing these diagnoses. Other common autoimmune diseases, which may include chronic arthritis, such as systemic lupus erythematosus (SLE) and juvenile dermatomyositis (JDM), are also discussed in this chapter. The differential diagnoses of chronic and acute synovitis, or diseases mimicking synovitis, are more completely listed in Table 1.

### Physical examination of the child with arthritis:

The physical examination of any child suspected of having, or known to have, synovitis is similar. Aspects unique to the physical examination of individual arthritides will be discussed under those particular sections in this chapter. The first step of the exam should include observation of the joint versus its symmetrical counterpart. Is the joint erythematous? Is it warm to touch? The normal intra-articular temperature is below 37 degrees Celsius. Knees are approximately 32 degrees and ankles are approximately 29 degrees; therefore, if the knee is the same temperature as the rest of the leg it should raise suspicion that inflammation may be the cause.<sup>28</sup> Palpation includes ballotment, the bulge maneuver, and range of motion. Ballotment is a technique done on the knee. The joint is stabilized with the non-dominant hand, and then using either the thumb or the forefinger, the knee cap is gently pushed downward to see if it "bounces" off of the femur secondary to excessive joint fluid. Some joints are much larger than other joints and fluid may "hide" in the surrounding soft tissues. In the case of the knee, synovial fluid frequently communicates with the suprapatellar sac. To elicit a "bulge sign" the examiner's hand is used to "milk" the fluid into the suprapatellar sac, and then on the lateral side, one finger is slid from the superior aspect of the knee joint to the inferior pole. Careful observation may demonstrate a bulge along the medial aspect as the fluid is pushed medially. The examiner may notice that the "bulge" occurs slowly, this is due to the viscosity of the joint fluid.

Chronic synovitis frequently causes localized growth disturbances. Limb length discrepancies are common in children with JRA. Arthritis in the lower extremity causes accelerated growth in the ossification centers of the bone. The degree of bony maturation is likely responsible for whether inflammation will cause a limb to be longer or shorter than its unaffected counterpart. In a young child with greater potential for growth, the limb will likely become longer. Mild to moderate limb length discrepancies may resolve spontaneously in young children. In the older child, there may be premature closure of the growth plate and subsequently, the limb will be shortened. Limb-length discrepancy can be grossly observed in the supine child by bending the knees and comparing the height of the knees. At our center, a shoe insert or orthotic is not recommended until the discrepancy is greater than one centimeter. The difference that is usually compensated for is approximately half

of the defect. Other joints may have premature fusion of the physis or destruction of the joint. Micrognathia, resulting from arthritis of the temporomandibular joint, is one example of this.

Patients who have had arthritis in a particular joint may have muscle wasting surrounding that joint. If it unclear whether a patient has had swelling in the past, a discrepancy in the circumference of the nearby muscle groups may be telling. For example, if a patient has had synovitis of the knee for weeks at a time, he/she may have quadriceps wasting. The clinician should have a consistent and systematic approach to the child with arthritis. This organized examination allows for specific physical diagnostic skills when appropriate, such as measurement of quadriceps circumference and potential leg length discrepancy.

## **JUVENILE RHEUMATOID ARTHRITIS**

JRA is a term that encompasses a number of chronic synovial disorders in children. This identification causes some confusion and has been abandoned in Europe for the more general term of juvenile idiopathic arthritis. JRA should not be confused with adult-onset arthritides. The adult presentation of rheumatoid arthritis is quite uncommon in children. Likewise, the systemic presentation of juvenile arthritis (Still's Disease) and seronegative polyarticular arthritis is infrequent in adults. Seronegative pauciarticular arthritis is not seen in adults, whereas the older onset of seronegative spondyloarthropathy is diagnosed in older children and adults.

Although there was documentation of an inflammatory arthropathy in childhood by Cornil in 1864, it was not until 1890 that a review of published cases was presented by Diamantberger. He noted that the disease process was of an acute onset, involved exacerbations and remissions of large joints and was often accompanied by growth retardation. George Frederick Still, an English pediatrician and pathologist, described systemic onset of JRA in detail in 1897.

JRA is one of the most common diagnoses seen and treated by pediatric rheumatologists. Systemic onset, polyarticular, and pauciarticular are the subdivisions of JRA.

**Incidence and Epidemiology:** Published reports suggest the incidence of JRA is approximately 6-20 cases per 100,000 children at risk per year. This data includes information from both the United States and Finland.<sup>17</sup>

**Etiology:** The causes of JRA are unknown. Disease may occur in a genetically predisposed host initiated by some stimulus. Inciting agents may include an infection, physical trauma to the joint, emotional stress to the host, or an allergic reaction to environmental agents.

The genetic predisposition of JRA is of great interest. There appear to be different HLA associations with the different subtypes of disease (Table 2).

## **Systemic JRA**

**Presentation:** The systemic form of JRA can present at any age but is more common in younger age groups. It comprises 10-20% of all patients with JRA and has no gender bias. Onset of disease may be heralded by polyarticular joint inflammation, weight loss, and an evanescent salmon-colored rash which is usually worse with fevers. Systemic signs may precede arthritis by months and even rarely years. The fever curve in systemic JRA is referred to as "quotidian" or "biquotidian". Classically, the quotidian fever will spike (up to 40.5 degrees Celsius), and then drop to, or below, the baseline normal temperature once per day (or twice if biquotidian) without anti-inflammatory agents or antipyretics. The fever may occur at any time during the day, but is more common late in the afternoon or in the evening. Joint pain is frequently worse with fever spikes and involves small and large joints in a symmetrical manner. Approximately 20% of patients will develop chronic arthritis that continues for months or years after their initial systemic symptoms. Common to all forms of JRA, morning stiffness and/or gelling after inactivity are common in inflammatory arthritis. The young child may not complain of these symptoms, so the physician should inquire about a limp or disuse of a limb that improves as the day wears on. Pain is often described as an aching. Demonstration of discomfort on physical exam may only be elicited with extremes of range of motion.

One of the dangerous complications of systemic JRA is macrophage activation syndrome (MAS), otherwise known as hemophagocytic syndrome. MAS is caused by the overactivation and proliferation of well-differentiated macrophages. Clinically, patients appear acutely ill with one or all of the following findings: fever, hepatosplenomegaly, lymphadenopathy, depression of all three cell lines, low sedimentation rate,

elevated liver enzymes, prolonged prothrombin and partial thromboplastin times, and hypofibrinogenemia. Bone marrow aspirate reveals well-differentiated macrophages engulfing hematopoietic elements.<sup>24</sup> MAS is associated with significant morbidity and mortality, therefore the clinician should have a heightened awareness for this complication. In JRA patients, it has been associated with medications as well as poorly controlled disease activity. MAS can also occur in diagnoses other than JRA including adult Still's disease, malignancies, and infections.

Laboratories: Abnormal laboratories may include leukocytosis, anemia, thrombocytosis, elevated inflammatory markers (such as sedimentation rate and C-reactive protein), positive d-dimers, mild hyperbilirubinemia, elevated aldolase, and elevated transaminases. Only 10% of patients with systemic JRA will have a positive antinuclear antibody (ANA). Uveitis is more common in children with a positive ANA, but uveitis is rare in the systemic presentation of JRA. More information regarding uveitis will be presented in the section on pauciarticular JRA.

Laboratories are monitored on a regular basis in patients with JRA who are on medications. All of the pharmaceuticals used have toxicities, most of which are reversible. Nonsteroidal anti-inflammatory drugs (NSAIDs) may cause microcytic blood loss from the gastrointestinal tract, interstitial nephritis, thrombocytopenia, agranulocytosis, elevated transaminases, and renal compromise; but typically NSAIDs only cause stomach upset in a minority of children. Methotrexate may cause hepatotoxicity, leukopenia, anemia, and nephrotoxicity. Corticosteroids may cause gastritis with microscopic blood loss, hyperglycemia, adrenal insufficiency, and other side effects. Combination therapy, especially with medications that may have combined renal or hepatotoxicity, requires special attention.

Physical Examination:

Physical examination of the patient with systemic JRA may vary widely between patients and at different times for the same patient. The rash is evanescent and, as previously mentioned, is more remarkable and erythematous during periods of fever. The rash is classically described as "salmon" colored, but is frequently erythematous especially early in the disease course and with high fevers. The macules are often small (usually less than 5mm), but may coalesce and are found on the proximal extremities and trunk. The rash may also be seen on the hands, soles, and face. There may be a surrounding area of pallor. The lesions leave no scarring and may last hours at a time in a migratory and evanescent fashion (Figures 2a-b). Other physical findings that may be seen in the systemically ill child include pericardial or pleural fluid (which is frequently asymptomatic), hepatosplenomegaly, and/or lymphadenopathy.

Radiographic Studies: Plain films can show several characteristics of systemic JRA (Figures 3-4), including osteopenia, bony erosions, effusions, overgrowth, swelling, and enlargement.

Treatment: Treatment of the systemically ill patient includes steroids (usually starting at 2mg/kg/day divided twice daily) with or without initial pulse methylprednisolone for three consecutive days, weekly methotrexate (up to 1mg/kg/week), and nonsteroidal anti-inflammatories, typically Indomethacin.<sup>19</sup> At our institution we prefer to administer methotrexate subcutaneously as it avoids the first pass effect on the liver, whereas the absorption of oral methotrexate is highly variable and has a greater incidence of gastrointestinal upset.<sup>61</sup> Newer agents such as the tumor necrosis factor (TNF) inhibitors, Etanercept and Infliximab, are used as secondary disease-modifying medications. Steroids are slowly weaned and the disease modifying agents, such as methotrexate and TNF inhibitors, are used as primary therapy. A pediatric rheumatologist must monitor laboratories and disease course very closely.

Physical and occupational therapy are a mainstay for reducing pain, increasing mobility to restore function, and preventing disability in all forms of JRA. Splints, such as the cock-up splint, can be used to maintain a functional position of the wrist. Other splints, such as ring splints, may help prevent joint contractures of the digits. Dynamic splints are helpful in the elbow and knee joints.

A great deal of time and effort is spent on education of the patient, the family, and the school. Frequently, children who have limitations secondary to their arthritis are provided with letters of necessity for the use of elevators at school, extended periods of time to get to classes or to take written tests, and a second set of books at home. Teachers and school nurses need to be educated regarding the disease and any special needs the child may have so that adaptations can be made, if necessary, to promote the child's success. In general, children are encouraged to set their own limits on activities.

Disease Course: The disease course of systemic JRA varies. A subset of patients recovers completely, others have recurrent systemic signs and symptoms, and others have continued joint involvement and subsequent disability. Hopefully, the advent of newer medications will help to change these trends for the better.

An attempt has been made in the literature to identify those patients at risk for poorer outcomes. Some of these risk factors include disease onset at age <5 years, persistent disease greater than 5 years duration, and presence of cardiac disease. Poor prognosis was also shown to be associated with fever, thrombocytosis, and use of corticosteroids six months after initial diagnosis.<sup>50</sup>

Differential Diagnosis: The differential diagnosis of systemic JRA includes infections, Kawasaki disease, malignancies, and other connective tissue diseases such as rheumatic fever, systemic lupus erythematosus, and vasculitides. There are no diagnostic laboratories for JRA. The diagnosis of this disease is one of exclusion. The fever in a septic patient usually does not return to baseline, or less than baseline, as the quotidian fever of systemic-onset JRA does. In sepsis, the spikes are often more erratic and the patient continues to look systemically ill even between spikes. Excluding malignancies such as leukemia and neuroblastoma may be difficult and a bone marrow aspirate may be helpful. A manual differential of the complete blood count is necessary with examination of the peripheral smear for blasts. Patients with JRA may have significant lymphadenopathy so differentiating it from lymphoma may be difficult without a lymph node biopsy. Other connective tissue diseases that are included in the differential include rheumatic fever, polyarteritis nodosa, dermatomyositis, and systemic lupus erythematosus. The arthritis of rheumatic fever, although migratory, is exceptionally painful compared to physical findings. Appropriate screening for recent streptococcal infection should be done including antistreptolysin O. Other sensitive markers such as anti-deoxyribonuclease B, or, antihyaluronidase, and antistreptokinase increase the sensitivity of identifying streptococcal illnesses. Any evidence of myocarditis or valvular disease should make the clinician more suspect of the diagnosis of acute rheumatic fever. One of the vasculitides that may present as fever of unknown origin is polyarteritis nodosa. This disease does not have the classic JRA rash; rather it may have a painful purpuric rash. Hypertension or renal bruits are signs that should make the physician suspect this diagnosis.

### **Polyarticular JRA**

Presentation: Polyarticular JRA is defined as involvement of five or more joints during the first six months of disease. Forty percent of JRA cases are of polyarticular onset. Females outnumber males by approximately a three to one ratio. Onset may be any time during childhood but there is a peak during the toddler age group of one to three years of age. Joint involvement is usually symmetrical and involves the large joints including knees, ankles, hips, wrists, and elbows; however small joints may be involved, as well. The cervical spine and temporomandibular joints are often involved in polyarticular disease (Figure 5). Systemic symptoms may be present but are usually much milder than in the systemic presentation. Patients may have a low-grade fever, mild hepatosplenomegaly, and pericardial effusions. Chronic uveitis occurs in approximately 5% of these patients, most of whom are ANA positive.

There are two distinct groups of the polyarticular type. The first is rheumatoid factor (RF) positive disease and the second is the rheumatoid factor negative disease. Patients with a positive RF usually present later in childhood or adolescence and their disease more closely resembles adult onset rheumatoid arthritis. They may have early erosive disease, rheumatoid nodules, and a more chronic course of disease that waxes and wanes over time. Patients with RF negative disease are less likely to have as many joints involved as their RF positive counterparts, do not have rheumatoid nodules, and have a better prognosis for regression of disease.

Laboratories: There are no diagnostic laboratories for any of the subtypes of JRA. Some patients with polyarticular disease have a positive ANA, and these patients must be followed more closely for uveitis than patients without a positive ANA. (This will be discussed in more length in the pauciarticular JRA section) The seropositivity for ANA is 40 to 50 percent in the polyarticular group. The rate of uveitis is lower than the early age onset of pauciarticular JRA. Inflammatory markers such as sedimentation rate and C-reactive protein may be mildly elevated. Children frequently have a normocytic anemia of chronic disease.

Ten percent of patients with polyarticular JRA, or approximately 4% of all JRA patients have a positive RF. If a patient has RF positive disease or the disease process does not seem to be responding to standard

therapy, radiographs should be considered. If there is concern that pain in a joint is atypical or could represent another disease process, such as avascular necrosis, magnetic resonance imaging should be considered.

Physical examination: Patients with polyarticular disease will have synovitis as described earlier (Figures 6 through 9). They may have mild hepatosplenomegaly, mild lymphadenopathy, pericardial effusions (usually asymptomatic) and leg length discrepancies. Checking for a leg-length discrepancy should be a routine part of the exam in a patient with JRA.

A fundoscopic examination should always be done on every patient but a slit-lamp examination by an ophthalmologist is crucial for ruling out the “silent” uveitis of JRA. The plan of care should remind the families of when they are due to see ophthalmology.

Radiographic Studies: Plain films (Figures 10-11) can show several characteristics of polyarticular JRA, such as osteopenia, cortical irregularities, joint space narrowing and collapse, sclerosis, and erosions.

Treatment: Initial management of the patient with polyarticular disease depends on the degree of synovitis and if there are any other signs or symptoms such as pericarditis. If there is significant synovitis and/or organ involvement, treatment is usually initiated at our institution with corticosteroids and methotrexate. Nonsteroidal antiinflammatories are often used along with methotrexate for long-term therapy. The goal in management in any patient with arthritis is to wean and discontinue steroids as soon as possible. Other disease modifying agents such as parenteral gold and penicillamine are no longer used, but occasionally hydroxychloroquine and sulfasalazine are used as adjunctive therapy.<sup>19</sup> Recently, TNF inhibitors have proven to be effective in refractory cases of polyarticular JRA. Repeated physicals and laboratory examinations should guide treatment.

Intra-articular glucocorticoids are a useful method to reduce and, in some cases, resolve synovitis. This treatment modality can reduce joint contractures and may prevent leg-length discrepancies by minimizing or eradicating synovitis.<sup>49</sup> The uncommon side effects of intra-articular injections with glucocorticoids include subcutaneous atrophy and hypopigmentation at the site of injection, infection (1 in 100,000), chemical synovitis from the injection (usually of short duration), intra-articular calcification, and subchondral bone resorption. Although this list seems formidable, the inflammation of a joint is likely more dangerous than the minimal risk of the injection.<sup>31</sup>

Disease Course: Disease course is difficult to predict in the polyarticular JRA patients. Generally, the poorest outcome is in the older female patient with RF-positive disease, early and progressive erosions, nodules, and prolonged duration prior to therapy. Younger patients with a negative rheumatoid factor have a better prognosis. Hip involvement can occur with any of the JRA subtypes, but it can lead to significant disability if inflammation interferes with femoral head and acetabular development. Severe hip involvement may be a harbinger in a patient with a poorer prognosis.<sup>17</sup>

Differential diagnosis: The differential diagnosis in polyarticular JRA includes spondyloarthropathy, systemic lupus erythematosus, Lyme disease, reactive arthritis, sarcoidosis, and the mucopolysaccharidoses (which can mimic arthritis).<sup>17</sup>

## **Pauciarticular JRA**

Presentation: “Pauci” is derived from the Latin word “few” and infers that four or less joints are involved. Thirty to forty percent of all patients with JRA have pauciarticular disease. Age of presentation is usually in the toddler age group with the peak between one and two years of age. There is a female predominance with a female to male ratio of 5:1. Half of all patients with pauciarticular JRA will only have one joint involved (monoarthritis), with the knee being the most common. The next most common joints involved are the ankles and those of the fingers.<sup>47</sup> The patient may present with a limp or morning stiffness. The pain from pauciarticular JRA is usually much less severe than that felt in systemic JRA or that which is reported by adult patients with rheumatoid arthritis. A significant proportion of children with pauciarticular JRA have painless arthritis.<sup>48</sup>

Uveitis may be the first manifestation of the disease. Twenty percent of pauciarticular JRA patients will develop uveitis. Patients who present at an early age, are ANA positive, female, and HLA-DR5 are at highest risk. There is some data that report that ANA positivity is not as predictive as previously thought for the development of uveitis.<sup>26</sup> This extra-articular complication is often insidious, with most having no symptoms.

Nonetheless, the physician should inquire about photophobia, pain, redness, or any changes in vision. Uveitis usually develops within 5-7 years of onset of the arthritis, and 65% of disease is bilateral. The vast majority of cases develop within six weeks of disease onset.<sup>35</sup> Signs of disease that may be apparent to the pediatrician or rheumatologist include inflammatory cells within the anterior chamber (only seen without slit lamp if disease is very inflammatory) or synechiae which will make the shape of the iris appear irregular or cause a poorly reactive pupil. Poor and late outcomes include band keratopathy, glaucoma, and cataracts. Management by the ophthalmologist includes glucocorticoid eye drops, mydriatics, and intraocular injections of glucocorticoids in resistant cases. Collaborative therapy with the rheumatologist may be necessary, as systemic therapy can reduce the need for topical steroids. Systemic medications used successfully for uveitis include corticosteroids, methotrexate, cyclosporin, chlorambucil, and most recently etanercept (Table 3).<sup>54</sup>

Laboratories: As mentioned there is no diagnostic laboratory to diagnose JRA. ANA is present in 68% of patients with a pauciarticular presentation.<sup>47</sup> This laboratory allows the physician to predict those at highest risk of uveitis. Patients need to be screened for uveitis by an ophthalmologist every three months for the first two years of disease if they are ANA positive, rather than every six months if they are ANA negative. It is of utmost importance that the pediatrician realizes that an ANA is not used for diagnostic purposes. This test is used for prognostication for uveitis in a patient who has already been diagnosed with JRA. Approximately 1 in 10 healthy females has a positive ANA, which is likely inherited, and does not indicate a predilection to develop a connective tissue disorder. Children may have a chronic normocytic anemia and mild elevations in sedimentation rate or C-reactive protein. In our experience, these inflammatory markers are not as sensitive for disease activity as the physical examination.

Physical Examination: The maneuvers to determine synovitis on physical examination are the same in all of the JRA subtypes. The joints should be visualized and compared bilaterally, examined for warmth, balloted, inspected for a “bulge sign” and a determination regarding a leg-length discrepancy should be made. We observe the child’s gait at every visit to determine if orthotics are indicated or if the child should be referred for a gait analysis at physical therapy.

As mentioned, a fundoscopic examination should be performed at every visit and the care plan should include the patient’s follow-up with the ophthalmologist.

Treatment: Treatment modalities are similar in oligoarticular and polyarticular onset. There is usually no systemic involvement with oligoarticular onset, so administration of systemic steroids is usually not indicated. The mainstays of therapy include intra-articular corticosteroids, NSAIDs and methotrexate.<sup>19</sup> Other centers may use other disease modifying antirheumatics such as sulfasalazine and hydroxychloroquine more frequently. In general, early aggressive management with intra-articular steroids and subcutaneous methotrexate yields excellent results.

Intra-articular corticosteroid injections may yield the best results in this group. In one series, 82% of injections resulted in full remission with discontinuation of oral medications in 74% in those patients with oligoarticular disease.<sup>39</sup> In a series published from Germany, early onset pauciarticular JRA patients had the longest duration of efficacy following intra-articular triamcinolone hexacetonide, a long acting corticosteroid. The average duration of efficacy in this group was 121 weeks, followed by 105 weeks in rheumatoid factor negative JRA patients, 63 weeks in rheumatoid-factor JRA patients, and lastly 36 weeks in systemic-onset patients.<sup>8</sup>

Disease Course: The disease course of the patient who presents with oligoarticular onset is variable. The child may present with monoarticular disease, continue with pauciarticular disease, or progress to polyarticular disease.

Patients who have monoarticular disease usually have a good functional outcome. Some may have a remission of their disease within a couple of years. Other patients with pauciarticular involvement may have a waxing and waning of their disease course. In one group of patients, the pauciarticular disease extends to involve multiple joints.

The group of patients who progress to a polyarticular type of disease has a disease course that is similar to the polyarticular onset JRA subtype. These children have a higher risk of joint erosions. A French report attempted to define risk factors of pauciarticular patients that were markers of future progression to a polyarticular disease. They demonstrated that pauciarticular patients presenting with more than one joint and at

least one upper limb joint, or a high sedimentation rate were at an increased risk of developing polyarticular disease.<sup>26</sup> These children should be aggressively treated and every attempt should be made to minimize functional limitations.

**Differential Diagnosis:** The differential diagnosis of pauciarticular disease includes infection, reactive arthritis, rheumatic fever, toxic synovitis, Lyme arthritis, sarcoidosis, and malignancy. If there is any question that a joint may be infected, an arthrocentesis should be completed and synovial fluid should be sent for cell count with a differential, gram stain, and cultures. The history is the most helpful diagnostic tool available to the clinician. A history of a preceding upper respiratory infection, a preceding streptococcal infection, recent antibiotic use, tick bite, diarrheal illness, progressive weight loss with debilitation, night pain, or fevers should all be in the proper review of symptoms.

## **SPONDYLOARTHROPATHIES**

The spondyloarthropathies (SpA) are a group of HLA-B27 associated inflammatory disorders that involve arthritis, enthesitis, bursitis, and tendonitis. Enthesitis, or inflammation where tendons and ligaments insert into bone (usually around the knees and feet), distinguishes the spondyloarthropathies from JRA. Some of these illnesses may present with cutaneous manifestations. Serologies will reveal that a rheumatoid factor is absent and an ANA is typically absent but may be present. The subgroups of the spondyloarthropathies include the syndrome of seronegativity, enthesopathy, and arthropathy (SEA syndrome), psoriatic arthritis, arthritis associated with inflammatory bowel disease (IBD), Reiter syndrome and reactive arthritis, and juvenile ankylosing spondylitis (JAS).

**Epidemiology and Pathogenesis:** The incidence of juvenile SpA in the United States is not clear. Many children with SpA may be misdiagnosed with JRA and thus the incidence of juvenile SpA may have a prevalence approximating that of JRA. In our experience, careful examination for enthesitis, nail pitting and psoriatic patches (associated with psoriatic arthritis), poor lower back flexibility, and evaluation for HLA-B27 status will reveal a significant percentage of children with juvenile SpA who may have otherwise been misdiagnosed with JRA.

Multiple pathogenic triggers have been investigated in adult patients with SpA. Peptides bound within the groove of the HLA-B27 molecule, bacterial infections, gastrointestinal inflammation, and differences in immune responses have all been associated with these illnesses. Sixty to ninety percent of patients with SpA are HLA-B27 positive. HLA-B27\*05 is the most common subtype found in both the general population and in patients with SpA. Associations with *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *Chlamydia*, and *Klebsiella* have been suggested as possible inciting triggers, especially in reactive arthritis. Inflammatory changes in the terminal ileum or colon have been demonstrated in up to 70% of patients with SpA. Inflammation may allow increased permeability to bacterial antigens that can act as triggers of disease. Studies have demonstrated subclinical inflammatory bowel disease in 81% of patients with juvenile SpA.

**Clinical Manifestations:** Patients with either undifferentiated or a defined subtype of SpA may have a combination of arthritis, enthesitis, and bursitis/ tendonitis. An enthesitis occurs when inflammation is present at the site where a tendon or ligament inserts onto the bone. Enthesitis most frequently affects the lower extremities and enthesitis of the feet may be one of the most disabling features of children with SpA. On examination, there will be tenderness on palpation at the insertion of tendons, ligaments, or joint capsules into bone. Some of the more common sites include the insertion site of the Achilles' tendon, the insertion sites on the calcaneus and the metatarsal heads on the plantar fascia, and the insertion site of the patellar ligament onto the anterior tibia. There may or may not be demonstrable swelling, but these sites are tender to palpation. High definition ultrasound analysis may help to more objectively define an enthesitis. The clinician must be careful to recognize that tenderness at an enthesitis may represent a non-inflammatory disease such as Osgood-Schlatter disease or Sever's disease.

## **SEA Syndrome**

In the syndrome of seronegativity, enthesopathy, and arthropathy, patients do not have a rheumatoid factor or an ANA. SEA syndrome may be a form of SpA in a patient or it may be a harbinger of a separate subtype of SpA that may develop in the future. In one study, 70% of patients with SEA evolved into a different subtype of

SpA at 9-year follow-up.<sup>15</sup> There may be two forms of SEA syndrome, those children who are HLA-B27 negative and do not develop a separate subtype, and those children who are HLA-B27 positive and may progress to JAS.<sup>12</sup> Arthritis in the latter group often involves the small and large joints of the lower extremity. Approximately 72% of patients with SEA syndrome will be HLA-B27 positive.<sup>17</sup>

Management of SEA syndrome is usually NSAIDs and intra-articular corticosteroids.<sup>19</sup> If the arthritis is refractory to treatment, other disease modifying agents such as sulfasalazine and methotrexate may need to be initiated.

### **Psoriatic arthritis**

Juvenile onset psoriatic arthritis is defined as arthritis occurring at 16 years of age or less with a typical psoriatic rash. The alternative categorization is arthritis with three of the four minor criteria (dactylitis, nail pitting or onycholysis, psoriasis-like rash, and family history of a first or second-degree relative with psoriasis). This form of arthritis is more common in girls and the peak age of onset is between ages 7 and 13 years. There is less of an association with HLA-B27 than other spondyloarthropathies. Arthritis is the initial presentation in 50% and psoriasis is the initial symptom in 40%. In 10% of patients the skin and joint manifestations present simultaneously.

Oligoarticular involvement is the most common presentation of arthritis. The most frequently involved joints include knees, ankles, proximal interphalangeal joints (PIP's) of the feet and hands, and distal interphalangeal joints (DIP's) of the feet. Dactylitis, or "sausage digit", is also seen in psoriatic arthritis. As the disease progresses over time, polyarticular involvement of the elbows, DIP's of the fingers, wrists, temporomandibular joints, and cervical spine may become more prevalent. Findings on x-ray of involved joints may include periarticular osteopenia, joint space narrowing and erosions. An aggressive form of psoriatic arthritis is called arthritis mutilans for its severe erosive nature.

Cutaneous manifestations may be mild in children, so the clinician must have a high index of suspicion. Locations for skin involvement include the umbilicus, scalp, anal area, and extensor surfaces of the limbs. Careful examination of the nails must include an investigation for pits, and striae.

### **Arthropathy Associated with Inflammatory Bowel Disease**

Joint disease in this group of patients may be divided into peripheral and axial (sacroiliac or spinal) disease. Peripheral joint involvement is usually of the lower extremity. Peripheral involvement is usually not HLA-B27 associated and only coincides with bowel symptoms 50% of the time.<sup>36</sup> Half of patients may only have one episode of arthritis that is self-limited. The rest of patients with peripheral joint involvement may have oligo- or monoarthritis that lasts for less than one month. Erosions may be evident by radiologic examination, but rarely are these patients functionally limited permanently.

Axial involvement tends to follow intestinal flares of the IBD and these children more frequently are in patients who are HLA-B27 positive.<sup>13</sup> Some patients with spondylitis will also have peripheral joint disease. A disease course resembling that of JAS may evolve in some patients whose IBD becomes quiescent.

### **Reactive Arthritis and Reiter Syndrome**

Reactive arthritis and Reiter syndrome are linked by their association of arthritis preceded by an infection. Infections (e.g. those mentioned previously in the epidemiology of SpA) usually antedate arthritis by approximately two to four weeks. The organisms implicated in these arthritides in children are usually of an enteric origin. In adolescents, sexually transmitted *Chlamydia trachomatis* is a common trigger. Reiter Syndrome consists of a triad of arthritis, conjunctivitis, and urethritis (or cervicitis).

Children with reactive arthritis or Reiter syndrome often have arthritis of acute nature. The arthritis is frequently asymmetric, usually involves few joints, and dactylitis is not uncommon. Knees and ankles are the most commonly affected. Enthesitis, especially at the patella and calcaneus, can be extremely painful.

Urethritis is present in 30% of children at the onset of disease and may present as dysuria, a sterile pyuria, inflammation at the meatus, or it may be completely asymptomatic. If symptoms are mild, or the physician suspects Reiter syndrome in a patient with conjunctivitis and arthritis, the urinary sediment should be centrifuged to look for white blood cells.<sup>17</sup>

Conjunctivitis is present in two-thirds of patients with Reiter syndrome and is usually bilateral. Symptomatology may include photophobia, erythema of the bulbar and/or palpebral conjunctiva, or a scratchy sensation of the eye. More severe complications can be seen, although less frequently, including mucopurulent discharge, iritis, keratitis, optic neuritis and corneal ulcerations.<sup>17</sup>

Occasionally, Reiter syndrome may be confused with Kawasaki disease.<sup>5</sup> Kawasaki disease presents with some of the same features including conjunctivitis, urethritis, and arthritis. The other signs and symptoms seen in Kawasaki include fever, lymphadenopathy, rash, and changes of the oral mucosa (dry fissured lips, “strawberry tongue”, and erythema of the oropharynx). Rashes are unusual in Reiter syndrome, but occasionally keratoderma blennorrhagicum and balanitis circinata can be seen. Mucocutaneous lesions, if present, tend to be short-lived.<sup>12</sup>

Laboratory abnormalities may include an elevated sedimentation rate (average equaling 50-60 mm/hr), an elevated white blood cell (WBC) count (up to 20,000/mm<sup>3</sup>) with a left shift, and pyuria (with 5-1000 WBCs per high power field). Microbiological cultures have been positive in some cases, but are usually negative. Examples of positive cultures include *Chlamydia* in conjunctivae and urethral swabs, and *Shigella* and *Salmonella* in stool samples. Radiographic changes that may be seen include peri-articular osteoporosis, erosions at ligamentous insertions, and asymmetric SI joint changes.<sup>17</sup>

The prognosis for children with reactive arthritis or Reiter syndrome tends to be good. A large proportion of patients remit and some may have waxing and waning disease. In one series of 26 patients with Reiter, two-thirds of patients were HLA-B27 positive.<sup>20</sup> It is possible that Reiter and reactive arthritis may be the initial presentation of a seronegative arthropathy that declares itself at a later time.

### **Juvenile-Onset Ankylosing Spondylitis**

Juvenile Ankylosing Spondylitis (JAS) is a chronic inflammatory arthritis that begins in children less than the age of sixteen. The arthritis affects the peripheral and axial skeleton, and may also involve inflammation of the entheses. The male to female ratio is approximately 7:1 and has a strong association with the presence of HLA-B27. True JAS is rare in childhood, whereas SEA syndrome is relatively common.

At presentation, peripheral joints of the lower extremities are more common than axial symptoms. The majority of patients present with four or fewer joints, but often this progresses to a polyarticular disease within one year. When axial disease begins, it usually appears in the lumbar and thoracic regions. Stiffening of the spine is a result of inflammation within the vertebral joints. Spinal and SI joint pain, stiffness, and decreased anterior flexion of the spine or decreased chest expansion usually increases after disease has been present 2 1/2 years and reaches a peak 5 to 10 years after onset. In adult patients, there is marked spinal stiffness in the morning that gradually improves with movement and time; it is just the opposite in children. Pain often worsens with activity and time and decreases with rest. Enthesitis can be quite disabling in JAS and is frequently an early manifestation of the disease. Radiographic findings may include periarticular osteopenia, joint-space narrowing, spur formation, erosion at ligamentous insertions and ankylosis of tarsal, hip, and axial joints.<sup>12</sup> Changes seen in the vertebral column, such as epiphysitis, anterior vertebral squaring, anterior ligament calcification, and “bamboo spine” are uncommon in childhood.<sup>17</sup>

There are a number of extra-articular manifestations of JAS. Acute iritis may occur and is characterized by a red, photophobic, painful eye. It usually does not cause long-term sequelae and usually does not precede the onset of the arthritis. Aortic insufficiency is less common in children than adults. Decreased vital capacity is possible secondary to impaired chest wall expansion secondary to arthritis. Atlantoaxial subluxation has only been reported in a few children with JAS.

Treatment of JAS patients includes medications and physical therapy. Nonsteroidal anti-inflammatory medications can be helpful in aiding with the pain of JAS, but likely do not alter disease progression. Indocin and Tolmetin sodium have both shown to be beneficial. Studies are underway to confirm initial reports that tumor necrosis factor inhibitors are effective in the management of ankylosing spondylitis.<sup>7</sup> Physical therapy is vital in order to limit functional disabilities and contractures as much as possible utilizing range of motion exercises and splints. Insoles can be made to help aid in the discomfort of painful enthesitis.<sup>17</sup>

### **RHEUMATIC FEVER AND POSTSTREPTOCOCCAL ARTHRITIS**

## **Rheumatic Fever**

**Incidence and Epidemiology:** Acute rheumatic fever (ARF) appears to be increasing in frequency beginning in the 1980's. Zanguill et al. initially published a report documenting the increased incidence of ARF in western Pennsylvania between 1985-1987. This report was then extended and they were able to demonstrate that the number of cases continued to increase between 1987 and 1990.<sup>62</sup> The change in incidence of rheumatic fever may be secondary to a change in the subtype of streptococci bacteria.

Rheumatic fever occurs equally between boys and girls with a peak in the age of onset between ages 5 to 15, and is uncommon in children less than the age of 4.<sup>17</sup> It occurs more frequently in highly populated areas with crowding and poverty.

**Etiology:** Rheumatic fever is precipitated by a pharyngeal infection with Group A beta hemolytic *Streptococci* (GABS). The pathogenesis of rheumatic fever likely is multifactorial. Investigations have demonstrated that the mechanisms responsible include cross-reactivity between GABS and host molecules, GABS virulence factors, and host susceptibility. There are a number of GABS antigens that have been shown to be associated with cross-reactivity with human tissue. One example of this is the M protein. Human antibodies directed against myosin also react against M protein. Antigens found within human synovium have been shown to be cross-reactive with streptococcal antigens. M protein can also function as a superantigen eliciting a cascade of inflammation. A variety of GABS virulence factors have been elucidated. Besides M protein, GABS may also be heavily encapsulated with hyaluronic acid, which may increase its resistance to being encapsulated by macrophages. Host factors include a B cell marker, identified by the monoclonal antibody D8/17, which most patients with ARF carry; this is inherited in an autosomal recessive fashion.<sup>37</sup> Genetic predisposition with HLA-DRB1\*01 has been shown to be associated with rheumatic fever.<sup>1</sup>

**Clinical Manifestations:** Clinical manifestations of rheumatic fever usually begin two weeks following a streptococcal pharyngitis. Patients usually have high fevers, which frequently subside after 3 weeks. Patients may not have a known history of streptococcal infection, so the clinician's index of suspicion must be high. The modified Jone's criteria (Table 4) aid the physician in diagnosing ARF, which like most other rheumatic illnesses is still a diagnosis of exclusion.

**Arthritis:** The arthritis of ARF is the most common symptom. It usually affects the large joints of the lower extremity, is asymmetric, migratory in nature, and frequently the degree of pain is out of proportion to the swelling. Pain may be so great that the patient cannot even bear passive range of motion. One of the identifying features of the arthritis seen in ARF is its migrating nature. The clinician may see significant erythema and pain on motion in one joint, and then a few hours later the joint is fine and a new joint has acquired the same symptomatology. The arthritis is remarkably sensitive to salicylates. If the arthritis is resistant to this medication and there are no other major criteria present, the diagnosis should be reevaluated. Arthritis usually will last a few days to a couple of weeks.<sup>4</sup> Erosive arthritis does not occur.

**Carditis:** Carditis is the most serious manifestation of ARF. It may manifest as a new murmur, tachycardia, electrocardiographic abnormalities, chest pain, and overt signs of congestive heart failure. Congestive heart failure is a poor prognostic sign. Carditis is more frequently seen in younger patients. The frequency of rheumatic fever carditis in the United States is approximately forty percent.<sup>17</sup>

**Sydenham's Chorea:** The onset of chorea is usually longer than arthritis or carditis, often occurring up to 3 months after the streptococcal infection. It is more common in girls than boys and in younger children. The choreiform movements most frequently involve the face, tongue, and hands. It usually does not occur during sleep. The patient may have difficulty fully controlling the movements and it may be exacerbated by stress. The chorea may last weeks to months.<sup>17</sup>

**Erythema marginatum:** This is an unusual manifestation of ARF, occurring in only 10% of patients. The rash may be transient in nature. It usually manifests on the trunk and is erythematous in quality with central clearing (Figure 12). Erythema marginatum is associated with those patients who develop carditis.<sup>17</sup>

**Subcutaneous Nodules:** Subcutaneous nodules are usually small (less than one centimeter), occur on bony prominences, and are painless. These lesions are uncommon, occurring in less than ten percent of patients and are usually found in sick patients with carditis or in children with recurrent ARF. Histologically, the nodules seen in JRA cannot be distinguished from those seen in ARF.

**Laboratories:** Laboratory studies to document a streptococcal infection are paramount. If a throat culture is not positive for GABS then antistreptolysin-O antibodies (ASO), anti-deoxyribonuclease B, antihyaluronidase, and/or antistreptokinase should be completed. A rise, or fall, in titers of fourfold should be sought over time. The specificity of the diagnosis is increased if more than one titer is documented as being elevated. A rise in the acute phase reactants (sedimentation rate and C-reactive protein) remains elevated for prolonged periods of time. If these levels are checked while the patient still has arthritis and/or carditis, the levels are usually still quite high. These markers may not be elevated if a patient presents only with chorea. Patients may also have a leukocytosis and mild anemia.

Cardiac evaluation should include both electrocardiogram (EKG) and echocardiogram. Abnormalities that can be seen on EKG include P-R prolongation and much less frequently second degree or complete heart block. S-T elevations across all leads may be indicative of pericarditis. Chest radiographs may demonstrate cardiomegaly if carditis occurs.

**Treatment:** Treatment of ARF includes eradication of the GABS infection, general management of disease manifestations, prophylaxis of rheumatic heart disease, and endocarditis prophylaxis. Treatment of the acute GABS should include a 10-day course of penicillin or an intramuscular injection of benzathine penicillin. If the patient is allergic to penicillin, erythromycin can be used.<sup>17</sup>

General management issues include bedrest for approximately 3 weeks or until the acute phase reactants are returning to normal. If carditis has been severe, the cardiologists may choose to have a more prolonged period of rest. Aspirin, 75-100mg/kg/d, should be used for fever and arthritis. As mentioned previously, the arthritis responds dramatically to salicylates. Aspirin is usually used for 6-12 weeks, however naproxen has also been shown to be effective.<sup>59</sup> Some physicians may choose to use glucocorticoids for initial management in patients with carditis. Doses at 1-2mg/kg/day are used initially and tapered after 2-3 weeks. Aspirin therapy is initiated, after glucocorticoids are weaned, and continued for an additional 3 weeks. Treatment of chorea is directed towards symptomatology.<sup>17</sup>

Prophylaxis is administered to prevent future cardiac manifestations of GABS infections. Benzathine penicillin intramuscularly every 3 weeks or oral penicillin V can be given. Prophylaxis is suggested until age 21 or throughout life if the patient is at high risk of GABS infection.<sup>17</sup>

Endocarditis prophylaxis for those with rheumatic heart disease is suggested for dental or surgical procedures. Doses and administration schedules depend on the procedure and invasiveness of the procedure to be performed.

**Disease Course and Prognosis:** Arthritis and carditis are the most frequent manifestations of ARF and occur within the first 2-6 weeks. Erythema marginatum, subcutaneous nodules, and chorea occur less frequently and may occur later in the disease process (Figure 13). Prognosis is determined by the severity of the carditis. ARF can recur and the risk of cardiac involvement increases with subsequent attacks. A prolonged course of rheumatic fever can occur (e.g. longer than 6 months), but this is rare.

**Differential Diagnosis:** The differential diagnosis of ARF will depend on the clinical manifestations. Arthritis and fever may be mistaken for Kawasaki disease, serum sickness, systemic JRA, or infectious arthritis. Confusion may occur when attempting to differentiate rheumatic fever without carditis, rash, or nodules from post-streptococcal arthritis.

### **Post-streptococcal Reactive Arthritis**

There are differing opinions as to whether post-streptococcal reactive arthritis (PSRA) is its own entity or rather whether it is on a continuum with rheumatic fever. Differences between the two conditions do appear to exist but these may be based on circular arguments/ definitions of the disease.

**Arthritis:** The joint symptoms of post-streptococcal arthritis typically present sooner than those in rheumatic fever. For the majority of patients with PSRA, onset of arthritis is within 10 days of the preceding streptococcal pharyngeal infection. The arthritis affects primarily large joints, but also small joints in 10-30%. Small joint involvement is very rare in ARF. Axial skeletal involvement, rare in ARF, was reported in almost one-quarter of patients with PSRA. The arthritis differs from that in rheumatic fever because it is not migratory, but is cumulative, and not as responsive to salicylates NSAIDs. Symptoms may last months after initiation of a

NSAID.<sup>4</sup> In contrast to the association of ARF with HLA-DRB1\*01, PSRA is associated with HLA-DRB1\*16.<sup>1</sup>

Carditis: Patients who have been diagnosed with PSRA do develop carditis in approximately 6% of cases; however, patients who had PSRA and were treated with antimicrobial prophylaxis did not develop carditis.<sup>1</sup> The carditis seen in PSRA tends to be “silent”.<sup>45</sup> No patients with PSRA develop Sydenham’s chorea or erythema marginatum; if seen, these patients most likely have ARF.

Treatment: Although the incidence of carditis is lower in PSRA patients, it is prudent to treat with prophylactic antibiotics. Opinions may differ as to the length of therapy, but given the dire complications of carditis one might consider therapy at least until the age of 21.

## **LYME DISEASE**

Incidence and Epidemiology: Lyme disease is a vector-borne systemic disease, which presents with symptoms that mimic many rheumatic, neurologic, and cardiovascular disorders. The disease was originally recognized in 1975 due to the geographic clustering of children diagnosed with JRA in Lyme, Connecticut.<sup>52</sup> Lyme disease has become the most prevalent (90%) vector borne disease in the United States.<sup>33, 40</sup> Almost 92% of reported cases occur in the northeastern and mid-Atlantic states of the U.S with most outbreaks occurring between April and October (Table 5). However, forested regions of Europe and Asia have reported cases, as well.<sup>33</sup>

Children between the ages of 5 and 9 years old represent the highest population reported with the disease annually, although adults have a high incidence as well.<sup>60</sup> The incidence of the disease continues to rise. In 2000, 13,309 cases were reported to the Center for Disease Control and in the past 11 years, approximately 158,448 cases were reported. However, some studies estimate that the number of reported cases accounts for only 50-60% of the actual occurrences of Lyme disease while others argue that the disease is over-diagnosed. Those who feel that Lyme disease is under-diagnosed attribute this to the strict regulations stated by the CDC for actual diagnosis coupled with the inaccuracy of lab results and overall complexity of the disease. The controversy over the diagnostic accuracy of Lyme disease is just one of the debates surrounding this highly publicized disease. Diagnostic methodology, treatment protocols, and preventative measures are also strongly debated between various members of the medical field.

Etiology: Lyme disease is caused by the spirochete, *Borrelia burgdorferi*, which thrives in the gut of the deer tick species, *Ixodes scapularis* (East coast strain) and *Ixodes pacificus* (along the Western U.S. seaboard). The deer tick undergoes three stages of development: larval, nymph, and adult. The *Ixodes* nymph, which is smaller than its adult counterpart and more abundant, causes the largest number of infections. This is attributed to the horizontal transmission pattern by which this disease is passed. The *Ixodes* larvae infect mice, deer, birds, and other small animals. The *Ixodes* nymph then feeds on these infected animals thereby acquiring the disease and passing it on to its hosts and offspring. A small percentage (1-3%) of *Ixodes pacificus* are infected with *B. burgdorferi*, which is most likely due to the feeding habits of the tick in its nymph stage.<sup>33</sup> *Ixodes pacificus* nymphs feed primarily on lizards, which are not susceptible to the spirochete and therefore do not aid in its transmission.

Unfortunately the *Ixodes* species is capable of transmitting more than one pathogen to its host which appears to increase the severity of symptoms. Patients suffering from multiple infections are often inflicted with Lyme disease as well as babesiosis and/or human granulocytic ehrlichiosis (HGE); fortunately these are all responsive to appropriate antibiotic therapy.

Presentation: Lyme disease presents with a variety in symptoms including flu-like symptoms, fever, headaches, Bell’s palsy, and erythema chronicum migrans (ECM) in over 60% of patients (Table 6). It is estimated that 2 out of 3 patients present with nonspecific systemic features<sup>33</sup> while others experience fevers, diffuse myalgias, arthralgias, headaches, fatigue, malaise, adenopathy, hepatosplenomegaly (rarely) and/or conjunctivitis.

Early Disease: Erythema chronicum migrans (ECM) occurs within in one month of infection in 50-70% of Lyme disease patients. ECM is an erythematous macule or papule usually found in the groin, thigh, or axilla areas. Approximately 1 out of 4 patients will develop secondary lesions, although these usually fade over time and are thought to result from an immunologic response to the pathogen.<sup>33</sup> The skin lesion is usually painless,

although some patients complain of tingling or burning sensations around the area. The rash expands concentrically giving the appearance of a bull's eye. It is possible to culture organism at expanding edge.<sup>33</sup> Early disseminated disease may result in satellite ECM lesions (Figure 14). Spirochetes are not found in the margins of these secondary rashes.

Lyme disease commonly results in joint involvement. The patient may experience brief and recurrent attacks of asymmetric swelling and pain in large joints, especially the knee.<sup>52</sup> Early neurologic manifestations of the disease include meningoencephalitis, cranial neuropathy (typically Bell's palsy), radiculoneuropathy, encephalopathy, and encephalomyelitis. Sensorineural hearing loss is a rare occurrence in the European form of the disease. Ocular manifestations of the disease have also been reported including a wide range of neuro-ophthalmologic disorders.<sup>60</sup>

Early Disseminated Disease: In the more progressive form of the disease, 60% of untreated patients experience migratory joint involvement of large joints, most commonly the knee. Synovial fluid counts may range from mild inflammation to appearing septic. Progressive neurologic manifestations occur in 10-15% of untreated patients resulting in encephalitis, meningitis, cranial and/or peripheral neuropathy, radiculitis, mild neck stiffness, memory and concentration problems, lymphocytic meningitis, and facial nerve palsy. Only 10% of untreated patients develop cardiac symptoms which includes fluctuating degrees of atrioventricular heart block, myocarditis, and mild congestive heart failure.<sup>33</sup>

Late Chronic Disease: Patients who do not receive treatment may suffer from serious joint and neurologic manifestations months to years following initial infection. These patients are almost always seropositive and may experience acute attacks of arthritis, arthralgia, joint erosion, tendonitis, bursitis, enthesitis affecting the back, neck, and upper body, fibromyalgia which results in sleep disturbances, and/or diffuse myalgias. The attacks of arthritis and arthralgia appear to decrease in frequency and duration over time and only a few large joints tend to be affected. Approximately 1% of untreated patients experience long-term neurologic manifestations including encephalomyopathy, polyneuritis, and/or cognition and psychiatric changes.<sup>33</sup>

Differential Diagnosis: Lyme disease has been called one of the "great imitators" due to its common and sometimes perplexing symptoms. The differential diagnosis for Lyme disease includes JRA, sarcoidosis, systemic lupus erythematosus, multiple sclerosis, myopathy, ehrlichiosis, Rocky Mountain spotted fever, primary fibromyalgia, rheumatic fever, gonococcal arthritis, temporomandibular joint syndrome, gout, polymyalgia rheumatica, psychogenic rheumatism, Reiter syndrome, seronegative rheumatoid arthritis, and syphilis (Table 7).<sup>33, 52</sup> The single most common diagnosis to exclude in pediatrics is pauciarticular JRA.<sup>52</sup>

Physical Examination and Laboratories: Due to the systemic nature of Lyme disease, it is essential for a careful examination to be performed at presentation. Recognizing the history and/or exposure risk for infected ticks (i.e. endemic area, outdoor activities), as well as noting symptoms, such as ECM at presentation, provide the physician with a high pretest probability of a positive blood test for Lyme.

The FDA approved a two-step diagnostic protocol for the serologic recognition of Lyme disease in 1987, which included an enzyme linked immunosorbent assay (ELISA) validated by an IgG (and/or IgM) Western blot. ELISA is the most effective screening tool as culturing the organism is impractical and blood cultures produce a low yield. ELISA is an effective test as it can be standardized, automated, and is easily reproducible. ELISA has a sensitivity of 94% and a specificity of 97%. Sonicated whole *B. burgdorferi* are most often used as an antigen with 41 kDa purified flagellin protein to increase IgM sensitivity. IgM ELISA are most responsive 2-4 weeks after infection whereas IgG response occurs within 6-8 weeks.<sup>33</sup> False positives may result from lack of standardization while false negatives are attributed to attenuation of the antibody response due to antibiotic therapy or testing very early in the course of infection. Recently, the accuracy of laboratory diagnosis has been improved by stipulating the presence of 5 of 10 bands on Western blots to determine a positive immunoblot.<sup>40</sup> Nevertheless, serology reports are not 100% consistent. True seronegativity is rare in patients with clinical manifestations of disseminated or chronic disease. Furthermore, it is estimated the 8% of populations in areas endemic to *Ixodes* ticks are serologically positive but asymptomatic for the disease.<sup>33</sup>

In 1995, the CDC expanded the diagnostic procedure for Lyme disease by issuing the following criteria: 1) patients must present with ECM, 2) patients must show one or more manifestations of the disease, and 3) these two criteria must be substantiated by positive laboratory findings.<sup>40</sup> However, criteria 1 is often absent in

pediatric Lyme disease. Criteria 2 may include the occurrence of arthritis, objective findings of CNS involvement, encephalopathy in conjunction with a CSF to serum Lyme ELISA ratio > 1, cardiovascular system involvement, or having been in an endemic county within 30 days of onset of symptoms. An endemic county is defined as a region where two cases have occurred or where infected ticks have been detected.<sup>33</sup> Unfortunately, Lyme disease remains difficult to diagnose.

Although diagnosis based on presence of ECM coupled with characteristic symptoms of articular, neurologic, and/or cardiac manifestations of Lyme disease with serologic confirmation is standard, new diagnostic techniques are currently being explored. Studies have begun to test the reliability and effectiveness of using recombinant chimeric *Borrelia* proteins with ELISA to gain diagnostic confirmation of the disease.<sup>60</sup>

Treatment and Disease Course: Although much controversy remains over the proper treatment for Lyme disease, most physicians treat the disease with oral antibiotic therapy (Tables 8a-b). Doxycycline (1-2 mg/kg twice daily for children over 8 years of age) or amoxicillin (50 mg/kg/d, divided into 2 doses) for 3-4 weeks is recommended for early localized or early disseminated Lyme disease in absence of neurologic and/or cardiovascular involvement. Intravenous ceftriaxone (75-100 mg/kg/d /iv in a single dose) or 3<sup>rd</sup> generation cephalosporin should be administered for patients suffering Lyme disease with neurologic involvement or cardiovascular block. Azithromycin (10 mg/kg/d) and clarithromycin (7.5 mg/kg twice daily) have also been found to be effective treatment methods. Some reports warn that patients may feel worse at the starting of antibiotics, which has been attributed as a Jarisch-Herxheimer reaction. This occurs as the antibiotics eradicate *B. Burgdorferi* organisms from the circulatory system. Symptoms of this reaction include fever, chills, aches, and fatigue. This occurs in 10-14% of patients treated for Lyme disease. Serology may remain positive for years after treatment. Therefore, response to treatment must be clinically determined.

Children who are diagnosed and treated for Lyme disease in a timely fashion have an excellent prognosis. If treatment failure occurs, retreatment with the same antibiotic is recommended. Left untreated, patients may suffer chronic neurologic or articular manifestations. Thus, recognition of the disease and timely treatment are essential for eradicating this disease in the pediatric population.

Additional controversy has arisen over prolonged antibiotic treatment for persistent Lyme-related symptoms such as joint pain. Some suggest that such symptoms result from permanent organ damage, slow resolution of the disease, persistence of the organism, and/or an ongoing immune response.<sup>60</sup> A recent study by Klempner et al (2001) reported that patients who were treated with prolonged antibiotic therapy to alleviate persistent Lyme-attributed symptoms showed no difference in relief of symptoms than those patients given placebo treatment.<sup>34</sup> Further research continues on this topic.

Research has provided additional insight to the physiological implications of Lyme disease. Some studies have indicated that the CD1d gene participates in host defense. Additionally, T cells have been shown to play an active role in the inflammatory response against *B. burgdorferi*. Arthritis Related Protein (ARP) appears to be a gene product of the organism that elicits an immune response from the host organism during infection. Recent studies have also found that the *B. burgdorferi* may use surface antigen modulation as a mechanism for evading the host's immune response.<sup>60</sup> Gross et al reported that a peptide from leukocyte function-associated antigen-1 (LFA-1) may act as an autoantigen in treatment-resistant Lyme arthritis.<sup>25</sup>

Prevention: The clear etiology of Lyme disease allows for easy methods of prevention. Some suggest wearing light-colored clothing in order to increase tick visibility. Children who play outdoors in tick-endemic areas should wear their pants tucked in and long-sleeved shirts. They should be encouraged to walk in the center of paths and avoid areas of tall grass. Insect repellent is another viable preventative measure. However, it is important recognize the risks of the use of insect repellent which contains the chemical N,N-Diethyl-3-Methylbenzamide (DEET). The EPA currently categorizes DEET with a low toxicity warning level and allows companies to label insect repellents as "child safe" if the product contains less than 15% of the active ingredient. It is recommended that insect repellent containing DEET not be applied to the hands or around the mouth of children. Parents should inspect their children after they have been outdoors, noting that ticks tend to prefer moist, warm locations on the body such as the groin area, neck, and behind the knees. If a tick is found, use tweezers to remove it, grasping the tick's mouthparts as close to the child's skin as possible. The tick should be removed by pulling upward steadily, taking care not to squeeze. The bitten area should then be cleaned with antiseptic and the child observed for signs of the disease and an ELISA performed within 6-8

weeks of the bite. If the child develops an ECM rash, treatment for Lyme disease should begin immediately. It is postulated that the tick must feed for at least 48 hours to infect a host and some studies have found that transmission is 100% if an infected tick feeds on a host for 72 hours or more.<sup>33</sup> Nevertheless, when infected ticks are removed within 24-36 hours, the risk of transmission remains very low. In areas non-endemic to deer tick and Lyme disease, the risk of acquiring the disease is negligible.

**Vaccine:** The Food and Drug Administration approved the Lymerix vaccine in December of 1998 for persons 15-70 years of age in order to aid in the prevention of Lyme disease.<sup>60</sup> The vaccine is comprised of lipidated recombinant OspA protein and works to eliminate and/or reduce the number of *B. Burgdorferi* present within the gut of a tick prior to spirochete entry into the host. Recipients of the vaccine receive three doses via intramuscular injection. Side effects for this vaccine have ranged from mild to severe and effectiveness is estimated at 78%. Recent studies have shown the vaccine for children ages 2-5 to be safe and immunogenic.<sup>60</sup> However, some studies have found that the vaccine may not be cost-effective.<sup>32</sup> Nevertheless, controversy continues to exist over its safety and effectiveness and further research is necessary to find definitive answers for these concerns.

**Summary:** Lyme disease is a treatable systemic disease known to mimic the symptoms of a wide range of medical disorders. Although it is the number one vector borne disease in the United States, the majority of cases arise in the limited geographical area of New England. The etiology of the disease has been traced to the spirochete, *B. Burgdorferi*, which is transmitted through the feeding habits of infected deer tick. The symptoms of the disease range from mild skin lesions and moderate joint pain to acute arthritis and cardiovascular or neurologic difficulties. Diagnostic confirmation is based on CDC criteria although no protocol is 100% accurate. Fortunately, the prognosis for this disease, once treated, is extremely favorable in both the pediatric and adult populations. Further research is necessary to alleviate much of the controversy that the diagnostic procedures and treatment protocols for Lyme disease have encountered.

### **Viral Arthritis**

A number of viruses have been implicated as causing arthritis and autoimmune disorders in patients. It may be difficult to prove a virus is the etiologic agent of arthritis. Signs of infection may precede arthritis or an autoimmune syndrome and they may be cleared by the immune system, such that testing only demonstrates previous infection by the time the patient presents for medical care. Arthritis and autoimmune processes are not uncommon and, therefore, infection with a virus may be coincidental. A few viruses have known clinical features when presenting with arthritis.

**Pathogenesis:** Mechanisms of viral arthritis in children are difficult to clearly delineate. Different viruses may cause inflammation in a variety of ways. Certain infections may initiate an immune complex reaction within a joint (e.g. varicella, Coxsackie B, and adenovirus) while others may cause direct cytopathic changes secondary to viral invasion of the joint (e.g. rubella and mumps).<sup>51</sup>

### **Rubella Arthritis**

Rubella is one of the best-described viral etiologies for arthritis. Rubella is known to cause direct cytopathic changes within the joint and viral replication has been demonstrated within the joint.<sup>30</sup> The arthritis occurs approximately one week after the onset of rash and is typically symmetrical involving the hands, wrists, ankles, and knees. The pain and morning stiffness are impressive. Most patients have resolution of symptoms within one to two weeks and anti-inflammatory medications are effective for the symptoms. In some patients, a more chronic course may be initiated, reminiscent of rheumatoid arthritis. An unusual pediatric presentation of rubella arthritis is called “catcher’s crouch” and involves acute inflammation and contraction of the knees occurring one to two weeks after infection.<sup>51</sup> IgM testing is available, but the diagnosis can be made clinically.

Arthritis occurring after rubella immunization can be seen. Its frequency is low and the course is more benign than wild-type virus infection.

### **Parvovirus B19 Arthritis**

Arthritis initiated by Parvovirus B19 should be suspected in a patient presenting with synovitis preceded by a nonspecific viral illness and/or rash consistent with erythema infectiosum (“slapped cheek” appearance). The

clinical course is usually that of acute onset, pain out of proportion to the amount of swelling, and both pauci- and polyarticular involvement is seen. Large joints are most common, including knee and hip involvement. The course in children is usually benign with symptoms lasting 2-4 weeks. Disease course in adults may be much different, with chronic arthritis and occasionally erosive manifestations. Synovitis may be secondary to the host's immune response or to persistent infection. Parvovirus DNA has been found in the bone marrow, synovial fluid, and synovium suggesting that failure to clear the organism may be responsible for disease manifestations. Parvovirus IgM should be tested as soon as possible in any patient suspected of having this post-infectious disease. IgG antibodies are nondiagnostic because of the high degree of seroprevalence in the general population. Cross reaction with other titers can occur such as the Lyme ELISA and ANA.<sup>44</sup> NSAIDs in children aid with pain and inflammation until symptoms subside.

### **Varicella Arthritis**

Arthritis occurring approximately 10 days after varicella infection does occur in a small proportion of children. The arthritis is usually not very painful and presents most commonly as a monoarthritis of the knee. Viral replication is not thought to be a cause of this manifestation, thus antiviral therapy may not be indicated. Conversely, viral replication may occur with zoster infection when the synovitis occurs in the affected dermatome.<sup>2</sup> NSAIDs should be used for pain; occasionally severe myalgias or arthralgias may require more aggressive pain management.

### **Ebstein-Barr Viral (EBV) Arthritis**

Patients with acute EBV (infectious mononucleosis) may present with a few days of a painful polyarthritis or polyarthralgia. The arthritis tends to be symmetrical involving the knees and knuckles. The joints may appear dusky in color. Systemic signs of infection including leukopenia, monocytosis, and thrombocytopenia should be sought. EBV serologies should be obtained including VCA IgM as a marker of acute infection. Manifestations of arthritis with EBV are rare and usually respond well to antiinflammatories.<sup>44</sup>

### **Infectious Hepatitis**

Both hepatitis B and C can cause an associated arthritis. The arthritis seen with hepatitis B is usually of an acute onset, symmetrical, and painful. Other manifestations may also be present including rash, lymphadenopathy, palpable purpura, and in children acropustulosis palmaris (Gianotti-Crosti syndrome). Antinuclear antibodies may be positive, and thus an investigation for SLE may be initiated. A few reports have been published of the rare occurrence of a transient arthritis occurring after immunization. Any patient with risk factors for hepatitis B presenting with an acute onset of arthritis should be tested.

Hepatitis C has been associated with a variety of autoimmune symptoms including arthritis, vasculitis, sicca symptoms (dry eyes and dry mouth), mixed cryoglobulinemia, and positive autoantibodies including a positive rheumatoid factor (RF). Arthritis is reported in approximately 4% of patients with HCV antibodies.<sup>14</sup> Similar to Hepatitis B, the arthritis is usually symmetrical, painful, and acute in onset. A positive rheumatoid factor should raise suspicion in a child with arthritis given that only 10% of patients with polyarticular JRA are RF positive. This infection should be suspected in those patients with risk factors for hepatitis C or in those patients who have a painful chronic arthritis that is poorly responsive to antiinflammatories.

## **OTHER CONNECTIVE TISSUE DISEASES WITH CHRONIC ARTHRITIS**

### **Systemic Lupus Erythematosus**

SLE is a multisystem autoimmune inflammatory disease, which involves the blood vessels and connective tissues. Serological markers (autoantibodies), some of which are highly specific for SLE, characterize it. Disease manifestations are variable from one subject to another and, therefore, so are treatment regimens.

**Epidemiology:** The incidence of SLE in children less than 15 years of age is approximately 1 per 200,000.<sup>27</sup> Ten percent of all patients seen in a pediatric rheumatology clinic have SLE.<sup>6</sup> Disease onset is rare in patients less than the age of 5, and steadily increases until, when in adolescence, the rate of onset is equivalent to that seen in adults. The sex ratio changes as the age of presentation does. The ratio of boys to girls in the 0-9 year

old age of onset has been shown to be 3:4, in the 10-14 year old age group it was 1:4, and in the 15-18 year old age group 1:5.<sup>18</sup>

Etiology: The etiology of SLE is unknown, but it is presumed that the disease is the manifestation of triggers (environmental, immune dysregulation, and/or hormonal) in a genetically predisposed host. In a study of 107 twin sets, in which one twin fulfilled American College of Rheumatology (ACR) criteria for SLE, the concordance for the disease was 24% in monozygotic twins and 2% in dizygotic twins.<sup>21</sup> There are HLA associations in SLE and some of these are strongly linked with race. A few examples include HLA-DR3 in northern European whites and HLA-DR2 in blacks, Chinese, and Japanese.<sup>17</sup> The immune dysregulation in SLE is complex and involves polyclonal immunoglobulin activation by B cells, T cell dysfunction, and production and deposition of immune complexes. (The immunological factors involved with the pathogenesis of SLE extend beyond the scope of this text.) An estrogen-mediated effect on SLE has also been suspected. Hormonal abnormalities in children with SLE have been demonstrated including low testosterone levels, high follicle-stimulating hormone, leutenizing hormone, and prolactin levels. Interestingly, patients with Klinefelter's (XXY) have low levels of testosterone, and also have a higher incidence of SLE than their normal male counterparts. SLE may also be precipitated after infection with viruses or bacteria, medication reactions, and exposure to sunlight.

Presentation: A patient is said to have SLE if 4 of 11 criteria are met. These criteria were revised in 1982, but a more recent letter suggests that antiphospholipid antibodies should be added to the criteria, and the LE prep eliminated from the list (Table 9).<sup>28</sup>

Arthritis and/or arthralgias are present in the majority of patients with SLE. The arthritis is often symmetrical, can involve any joint, but is most common in the small joints of the hands, wrists, and knees. The arthritis is almost never deforming in nature, may be of short duration or it may become chronic. Significant synovial fluid accumulation may be asymptomatic (e.g. in the knees) or some patients may describe an extremely painful arthritis (e.g. in the hands) with little to no objective findings. Patients with SLE may have ulnar deviation of the hands that is reducible. Swan neck deformities are common, and involve extension of the PIP, and flexion of the DIP. No erosions are seen on radiographic exams, even when subluxation occurs; this finding is called Jaccoud's arthritis. Tenosynovitis can be an early manifestation of disease, and may predispose a patient to developing a tendon rupture. This can be extremely painful, usually is not precipitated by trauma, and is frequently seen in patients who have had a prolonged course of steroids. Other etiologies of joint pain must be considered in patients with SLE. Patients are frequently on steroids and other immunosuppressive medications, so septic arthritis must be considered. Avascular necrosis is not uncommon in this group, especially those who have been on high doses and/or chronic steroids.

Constitutional symptoms: Constitutional symptoms are a common presentation for SLE. Patients may have fatigue, malaise, weight loss, and/or fevers. The clinician must have a high index of suspicion in a patient with such symptomatology. Children and adolescents may not always present with four criteria for SLE. They frequently develop the disease slowly and in stages. In retrospect, patients may have had constitutional symptoms for many months before the final diagnosis is made.

Skin manifestations: There are various rashes that may be seen in patients with SLE. "Lupus" originates from the Latin word for wolf, and referred to the facial rash of SLE resembling that of a wolf. The best recognized rash one is the 'butterfly' rash. Patients typically develop this over the nasal bridge and along the cheeks (with sparing of the nasolabial fold) secondary to sun exposure (Figures 15a-b). This lesion may last for days, weeks, or longer. Pathologically, there are immune complexes at the dermal-epidermal junction. Other SLE rashes may occur in this distribution, but are not limited to it. Discoid rashes are chronic cutaneous lesions that begin as erythematous plaques or papules, and progress to hypopigmented or hyperpigmented areas; central atrophy may occur. Discoid rashes may appear in a malar distribution, in the ears, scalp, torso, or on the extremities. The areas may have follicular plugging and be mistaken for severe acne. A thorough search must be made to discover subtle lesions. Patients may present with only discoid lesions and no systemic signs or symptoms; these patients are referred to as having 'discoid lupus'. Photosensitivity may occur without either a malar or discoid rash. Lymphocytes from patients with SLE appear to be sensitive to UV light, and may trigger a local or systemic inflammatory response. Alopecia, either patchy or diffuse, can present as a sign of active SLE, secondary to scarring discoid lesions, or as a consequence of corticosteroids and/or cytotoxic use.

Oral/nasal lesions: Non-painful oral or nasal lesions are a common manifestation of SLE. Characteristic oral sores are found on the hard palate and are nonpainful (Figure 16). Nasal lesions may present as recurrent epistaxis and are located on the septae. Septal perforations can occur. Similar mucous membrane changes can also be seen on the vagina. The ulcerations are usually shallow and well circumscribed.

Serositis: Serositis may present as pleural, pericardial, or peritoneal effusions. Pleuritis is more common than radiographic evidence of pleural effusions and autopsy findings of pleuritis is more common than clinical evidence. Pleural effusions are usually small, but can be quite large and may also be bilateral.

Pericarditis: Pericarditis is the most common manifestation of cardiac involvement in SLE. It is less common than pleuritis, being reported in 20-30% of patients, but in up to 60% on autopsy.<sup>10</sup> Pericarditis often presents as precordial chest pain, pericardial rub, and electrocardiographic changes. Although pericardial effusions are not uncommon, tamponade is very unusual.

Peritoneal inflammation: Peritoneal inflammation, although not a formal criteria for SLE, may cause nausea, vomiting, anorexia, and ascites. Autopsy findings of peritoneal involvement are found in 60% of cases, but clinical evidence is much less frequent.<sup>46</sup> Lupus ascites may become chronic, is often painless, and may be associated with few other signs or symptoms of active SLE. The differential diagnoses for chronic SLE ascites includes constrictive pericarditis, congestive heart failure, Budd-Chiari syndrome, intra-abdominal malignancy, and atypical infections. If infection is a possibility, aspiration of peritoneal fluid should be done as soon as possible.

Cardiopulmonary involvement: Cardiopulmonary involvement besides serositis can include pneumonitis, pulmonary hemorrhage, pulmonary hypertension, abnormal pulmonary function tests, endocarditis, myocarditis, and coronary artery disease. Coronary artery disease may be vasculitic in nature, but is more frequently atherosclerotic and is much less common in the teenage years.

Renal involvement: There is a wide array of renal lesions involved in SLE. Renal disease, along with CNS disease, accounts for the highest proportion of morbidity and mortality in SLE. The World Health Organization has classified these abnormalities (Table 10). The WHO classification characterizes renal involvement, but does not address the activity or the chronicity of the glomerulonephritis. Frequently, a patient may have a lesion that has characteristics that crosses classes.

Common presentations of patients with glomerulonephritis include asymptomatic hematuria, presence of casts, proteinuria, and pyuria on urine analysis. Patients may present with elevated creatinine, hypertension, and/or edema, especially if nephrotic. Details pertaining to renal involvement in SLE can be found in this text series which addresses nephrology.

Central Nervous System Disease: Nervous system involvement of SLE involves neurologic as well as psychiatric manifestations. Neurologic involvement includes headaches (most common CNS symptom), strokes, seizures, movement disorders, transverse myelitis, cranial neuropathy, and peripheral neuropathy. Psychiatric involvement includes psychosis, organic brain syndrome, neurocognitive dysfunction, and psychoneurosis.<sup>23</sup> This spectrum of presentations has a variety of pathogenic etiologies, and in some cases the pathogenesis is unknown. Some known pathologic findings include thrombotic occlusions of blood vessels, intimal proliferation of small blood vessels, microinfarcts, and rarely frank vasculitis. A few antibodies have been associated with neurologic disease in SLE. Antineuronal antibodies have been detected in the CSF and serum of patients with CNS disease and antiribosomal P protein can be observed in the serum.

Diagnosis of neuropsychiatric disease in SLE is usually clinical. Elevated white blood cell counts in the CSF, elevated protein, and/or reduced glucose may be present in one-third of cases. Elevation of immunoglobulins in the CSF has been suggested as evidence for CNS disease. Electroencephalograms are frequently abnormal in this population but lack specificity. A variety of radiographic scanning has been investigated in SLE including positron emission tomography (PET), magnetic resonance imaging (MRI), and <sup>32</sup>P nuclear magnetic resonance spectroscopy.<sup>23</sup> The utility of these methodologies for screening for CNS SLE is unclear.

Hematological abnormalities: Hematological abnormalities seen in SLE include anemia, leukopenia/lymphopenia, and thrombocytopenia. Anemia may originate from many causes, including renal disease, chronic disease, or blood loss, but the hemolytic anemia mediated by autoantibodies is one of the classification criteria for SLE. A Coomb's autoantibody test should be done on all SLE patients with anemia of

unclear etiology. Active SLE frequently causes a leukopenia in the range of 2500-4000 white blood cells/mm<sup>3</sup>. Leukopenia can be complicated by medications known to lower the WBC count. SLE patients frequently have antibodies to their own lymphocytes causing a lymphopenia. Thrombocytopenia less than 150,000 cells/mm<sup>3</sup> is common in children with SLE. Patients may have anti-platelet antibodies, but sometimes these may not be clinically relevant because patients with these antibodies may not be thrombocytopenic. Both immune thrombocytopenic purpura and thrombotic thrombocytopenic purpura may be complications of SLE and must be considered in the appropriate clinical setting.

**Immunoserologic abnormalities:** There are a number of antibodies that may be seen in patients with SLE. According to the ACR criteria, anti-double stranded DNA antibodies (anti-dsDNA), anti-Smith antibodies (anti-Sm), and/or a false positive VDRL test constitute serologic evidence for SLE. In particular, anti-dsDNA and anti-Sm antibodies are very specific for SLE. Approximately 50-60 % of patients have antibodies to dsDNA and 25 % have anti Sm antibodies. The false positive VDRL test for syphilis suggests antibodies to phospholipid proteins. Antiphospholipid antibodies predispose some patients to having coagulation and thrombotic disorders. In the future, new ACR criteria may be more specific regarding antiphospholipid status as a requirement for SLE.

A positive antinuclear antibody (ANA) is present in almost all patients with SLE. A positive ANA alone is never sufficient evidence to suspect a diagnosis of SLE. Ten to twenty percent of healthy young women have a positive ANA without any predisposition to an autoimmune process.<sup>56</sup> ANA's may also be present in patients with other autoimmune processes, infections, malignancies, and those taking certain medications.

**Laboratories:** There are many possible laboratory abnormalities seen in SLE, many of which have been discussed under "Presentation". Other serologic evidence of disease activity may include an elevated sedimentation rate (ESR) and low complement levels (C3 and C4). An elevated sedimentation rate may indicate increased disease activity or in some patients may remain elevated for prolonged periods of time despite disease quiescence. C3 and C4 frequently drop during an acute flare, indicating consumption in an immune-complex mediated process. There are a number of other autoantibodies that can be seen in SLE. Anti-Ro (SS-A) and anti-LA (SS-B) antibodies are seen in SLE and Sjogren's syndrome. These antibodies are associated with neonatal lupus, with SS-A having a greater implication for congenital heart block. Anti-histone antibodies should be tested in any patient suspected of having drug-induced SLE. Drugs that have been proven to be associated with drug-induced SLE include hydralazine, procainamide, isoniazid, methyldopa, and chlorpromazine.

**Physical Examination:** SLE is a multisystem disease and, thus, the physical examination should be a complete one from head to toe. The hair should be examined for follicular stability. The fundus and eye should be examined for the complications seen with vasculitis, hypertension, corticosteroids, and superimposed infections. The oral and nasal orifices should be checked for lesions. The skin on and around the face should be examined for malar or discoid rashes. The heart should be auscultated for any evidence of new murmurs or rubs and the lungs should be auscultated for any possible effusions or intrathoracic disease. The abdomen should be examined for hepatosplenomegaly, ascites, or tenderness. If vasculitis is suspected within the abdomen, a rectal exam and stool hemocults should be done. A thorough exam of the joints should be completed to look for synovitis or limitation of movement. A complete neurological exam should be done and must test for CNS disease as well as peripheral nerve disease. Deconditioning frequently occurs if a patient is unable to maintain physical activity, and strength should be assessed at each visit. Capillary nail fold loop dilatation is less frequently seen in SLE than in JDM or scleroderma, but its presence may indicate a vasculitic process (Figure 17). Raynaud's phenomena is common in SLE. Patients present with the classic color changes of white, blue, and red of the fingertips on cold exposure. Occasionally, patients may have ulcerations from ischemia at the tips of the fingers secondary to severe Raynaud's (Figure 18).

**Treatment:** A cornerstone of the management of patients with SLE is prevention. SLE activity may wax and wane and certain measures may prevent a flare. Patients must be reminded to avoid sun exposure. Sun blocks with high level of effective UV blockade must be used even in colder weather. Use of long sleeves and hats with brims further sun protective measures. Patients are advised to avoid sulfa-containing antibiotics, as these may exacerbate SLE disease activity. Regular follow-up appointments with the pediatrician and/or rheumatologist are important to check urinalyses, blood pressure, laboratories, and signs of systemic involvement. Pregnancy often exacerbates disease activity and can place the mother and fetus at risk if not

closely followed and managed by a high-risk obstetrician; therefore, family planning should be discussed early. If a patient with SLE wishes to become pregnant, it is best to plan the pregnancy at a time when her disease is in remission. Some of the medications used in SLE management are contraindicated in pregnancy (such as cytotoxics). Birth control pills containing estrogen may place patients at a higher risk of thromboembolic disease. A large multicenter trial, the Safety of Estrogen in Lupus Erythematosus - National Assessment (SELENA), is presently underway to evaluate the risk of estrogen containing birth control pills. Routine immunizations should be given to children with SLE, but live vaccines should not be administered to patients on immunosuppressive medications, including corticosteroids.

Medications: NSAIDs are used primarily for the musculoskeletal complaints associated with SLE. This class of medications helps to alleviate the discomfort from arthralgias, myalgias, or arthritis. NSAIDs can also be used for the pain and inflammation associated with recurrent pericarditis or pleuritis. Laboratories must be checked for any alterations in liver function tests and for any blood or white blood cells in the urine as consequences of these medications. Patients with severe thrombocytopenia should not be given NSAIDs because of the anti-platelet effects

Antimalarials such as hydroxychloroquine (Plaquenil) are used as adjunctive therapy. Hydroxychloroquine is helpful in the management of cutaneous and constitutional symptoms. It has a very low toxicity profile, but visits every six months to one year are required to monitor for any retinal damage, including visual field and color testing. Chloroquine, another antimalarial, can be used in cases of severe cutaneous disease that is refractory to hydroxychloroquine alone. Liver function tests must be monitored with this medication. Other possible side effects of the antimalarials include dyspepsia, diarrhea, and rash. Hydroxychloroquine has been shown to have a modest lipid lowering effect.<sup>41</sup> The dose is typically 5-6 mg/kg/day, with a maximum dosage of 400 mg per day.

Corticosteroids are widely used in patients with SLE. They are effective in decreasing inflammation quickly that results from active disease. The dose of steroids is dependent on the complication being treated. Low-dose therapy is typically less than 0.5 mg/kg/day. The arthritis of SLE is usually sensitive to low-dose therapy. Manifestations such as serositis and fever are usually also sensitive to these doses. The dosage is weaned according to the indication for treatment. Higher doses of steroids (1-2 mg/kg/day usually divided twice per day) are used for glomerulonephritis, CNS disease, hemolytic anemia, and vasculitis. Occasionally pulse-intravenous therapy must be used in a crisis situation (30 mg/kg/day). The side effects of long-term steroid use is vast and includes cataracts, insulin resistance, weight gain with cushingoid features, striae of the skin, and avascular necrosis. The dose should be weaned as is appropriate and this should be managed by the rheumatologist, often in conjunction with the nephrologist if glomerulonephritis or hypertension is present).

Cyclophosphamide (Cytosan) is a nitrogen mustard-alkylating agent used in the management of some glomerulonephritides, some neuropsychiatric disease, some hematologic manifestations, and in some cases of vasculitis. Cyclophosphamide is metabolized by the liver and excreted by the kidney. Patients with either liver or kidney dysfunction may need to have the dose of the medication altered appropriately. Intravenous cyclophosphamide has been shown to be effective in the management of lupus nephritis and reduces the risk of end-stage renal disease.<sup>3</sup> The possible side effects of cyclophosphamide are substantial. Patients may have nausea and vomiting with administration of the medication and usually require antiemetic medications. Alopecia may result from therapy, but is often the result of uncontrolled SLE disease activity. Immune suppression is expected, with the nadir in the white blood cell count occurring 7-14 days after the intravenous dose. Daily oral therapy with cyclophosphamide is occasionally used and requires frequent blood counts. Patients are at greater risk of infection and may require *pneumocystis pneumoniae* prophylaxis. Bladder damage may result from use of cyclophosphamide, including acute cystitis, hemorrhagic cystitis, fibrosis, and carcinoma. It is routine at our institution, that patients are given mesna (2-mercaptoethanesulfonate) which binds the toxic metabolite known to cause cystitis. Intravenous fluids are also administered before and after the medication to ensure adequate hydration for bladder irrigation.

Purine analogs such as azathioprine and mycophenolate mofetil (MMF) are used in some patients with SLE. MMF is a relatively new medication in the treatment of SLE and has been shown to be effective in membranous nephritis in children and as a steroid sparing drug.<sup>11</sup> Azathioprine has been used for a longer periods of time and has been efficacious as an immunosuppressant and steroid-sparing medication for non-renal manifestations.

In older studies it has been shown to reduce proteinuria, stabilize renal disease, and reduce mortality in patients with diffuse proliferative glomerulonephritis.<sup>22</sup> Side effects include bone marrow suppression; therefore blood counts must be monitored regularly. There are reports of patients with SLE who were treated with azathioprine who developed leukemia and non-Hodgkin's lymphoma.<sup>23</sup>

Other treatments used in SLE, but less frequently, include Dapsone, cyclosporine A, methotrexate, immune globulin, danazol, and plasmapheresis.

**Disease Course:** The disease course for SLE is one of remissions and exacerbations. Some patients may have a benign course of disease marked by constitutional symptoms, positive serologies, and rash; where others have multiorgan involvement and significant morbidity. Morbidity may be a result of the disease or of the treatment. Mortality rates have declined over the years and patients are dealing with the long-term consequences of prolonged inflammatory processes and immunosuppressive medications. Complications include the need for dialysis or kidney transplantation, neuropsychiatric alterations, atherosclerosis, and osteoporosis, growth delays, infections, malignancies, diabetes, glaucoma, and cataracts.

Prognosis is affected by socioeconomic status. Non-Caucasian race and lower levels of education predispose patients to a poorer outcome. Longer disease duration and a higher disease activity also predict a poorer outcome with a larger degree of organ damage.<sup>53</sup>

**Differential Diagnoses:** The differential diagnosis for a patient suspected of having SLE is broad and depends on the symptomatology presented. Involvement of specialists may play a key role in differentiating the causes of a patient's complaints; e.g. psychiatry for CNS symptoms, hematology for cytopenias, and nephrology for declining renal function to name just a few.

### **Juvenile Dermatomyositis**

JDM is a chronic, systemic vasculopathy that affects the musculature, skin, joints and occasionally visceral organs. It is an uncommon disease, but is the most common of the idiopathic myopathies in children.

**Epidemiology:** JDM occurs in approximately 3 per 1 million children. The average age of onset of disease is 7 years. In girls there appears to be two age peaks, one at 6 years of age and one at 10 years. Boys appear to only have one age peak at 6 years of age. There is some evidence for geographic and seasonal clustering of cases of JDM.

**Etiology:** The etiology of JDM is unclear. Viral causes have been sought without clear evidence and immunological factors may play a role. Most studies agree that JDM is an autoimmune condition. Pathogenesis of this disease involves both cell-mediated and immune-complex elements. IgG, IgM, and components of C3 have been identified within affected vessel walls in JDM. Genetic predisposition may also predetermine who may be afflicted. There are few familial cases of JDM, but both HLA-B8 and DR3 occur in a higher proportion of patients with JDM than in the general population.

**Presentation:** The most common presentation of JDM includes fatigue, proximal muscle weakness, fever, and rash. Fatigue is common in children with JDM, and in young patients it may represent how parents interpret muscle weakness. Patients may also complain of muscle pain. Muscle disease usually manifests as weakness of the limb-girdle musculature of the lower extremities. Other muscle groups that may be affected include the neck flexors, abdominal musculature, shoulder girdle, facial and extraocular muscles, and less frequently distal muscles. Two of the most life-threatening complications are aspiration or choking as a complication of pharyngeal involvement and bowel perforation from vasculitis of the gastrointestinal tract.<sup>17</sup>

Cutaneous disease is pathognomonic in three-quarters of patients with JDM. A less characteristic rash is usually seen in the rest of patients. The most common rashes seen in this disease include heliotropic rash of the eyelids, Gottron's papules, and capillary nailfold loop changes. The heliotropic rash is an erythematous-purplish discoloration of the eyelids (Figure 19). There may be marked periorbital edema in patients presenting with JDM. The clinician must be careful to examine along the superior aspect of the eyelid, along the lashes, if JDM is suspected and an obvious heliotropic rash is not present. Gottron's papules are erythematous, shiny patches located over the extensor surfaces. The most common location is at the proximal interphalangeal joints (PIP's), and less commonly can be seen over the metacarpal phalangeal joints (MCP's), distal interphalangeal joints (DIP'S), elbows, patellas, and maleoli. Capillary nail fold loop dilatation, arborization, and drop out is characteristic in JDM. Although this also is seen in scleroderma, and less frequently in systemic lupus, it is

typical of this disease. The nailbeds of the fingers can be examined by capillaroscopy. If this diagnostic tool is unavailable, the clinician may use the 40X lens of the ophthalmoscope. We find that petroleum jelly acts as an inexpensive magnifying agent when placed along the nailbed. Dilatation and drop out of capillaries indicates active disease and may denote a disease with a more severe, chronic course.<sup>17</sup>

Arthritis is a frequent manifestation of JDM. In one series of 80 patients, 61% reported arthritis. Frequently affected joints included the knees, wrists, elbows, and fingers. The arthritis appeared at an average of 4.5 months after the diagnosis of the disease. The initial involvement was oligoarthritis in one-third of patients and polyarticular in two-thirds. All patients responded to the therapy instituted for the JDM (41% were on corticosteroids only), but the arthritis recurred in 39% as the steroids were tapered. In all patients, the arthritis was non-erosive.<sup>58</sup> Arthritis can be a major sequelae in JDM and appropriate measures must be taken to prevent morbidity.

Calcinosis is the accumulation of calcium within the soft tissues; this is a cause of long-term morbidity in JDM. Collections frequently appear at sites of trauma such as the elbows and knees. These areas may exsanguinate a milky white fluid when traumatized further. The deposition may cause calcified plaques, nodules, bridging calcification across a joint, clumps in the interfacial planes of muscle, (Figures 20a-b) or even exoskeletons on some children. The acute phase of the calcinosis can be inflammatory and painful. Severe calcinosis is thought to occur in patients who have had a delay in therapy, and/or those with an aggressive and chronic course. Ulcerated calcium plaques can create a nidus of infection caused by cutaneous microorganisms, and these are often exacerbated in these immunocompromised hosts.

There are other less common manifestations of disease. Lipoatrophy is a localized loss of subcutaneous tissue that frequently occurs in the hands. Pericarditis has been described as well as nonspecific cardiac enlargement and EKG findings. Subclinical myocarditis may be more frequent than previously thought as demonstrated by radioisotope scanning.<sup>9</sup> Vasculitis of the intestines can be life threatening. Children present with abdominal pain, melena, and hematemesis. Investigations to rule out intestinal infarction and/or perforation must be made as quickly as possible. Vasculitis of other visceral organs, such as the urinary bladder, uterus, and testes can also occur. Respiratory weakness can result in restrictive lung disease, but the interstitial lung disease seen in some adults with myositis is less common in children.

Laboratory Examinations: Some of the laboratory abnormalities in JDM include nonspecific markers of inflammation, muscle enzyme elevations, and autoantibodies. Nonspecific markers of inflammation include erythrocyte sedimentation rate and C-reactive protein. These markers can be used to follow disease activity during therapy. Muscle enzymes include creatinine kinase (CK), aldolase, aspartate aminotransferase (AST), and lactic dehydrogenase (LDH). Aldolase and CK are more specific muscle enzymes, and thus baseline evaluations should be done to determine how the disease is responding to therapy. CK may be elevated to 20-40 times higher than baseline in acute disease. In some children, CK may not be elevated and other enzymes must be used as markers of disease. There are a number of myositis-specific autoantibodies (MSA) that can be seen in myopathies. A few of these antibodies can be seen in JDM. In adults, identification of a certain MSA may help predict disease course and response to therapy. Approximately 80% of JDM patients have no identifiable MSA. Anti Mi-2 antibody is one autoantibody detected in some patients with JDM. This autoantibody is associated with disease that responds well to therapy and has a good prognosis.<sup>43</sup>

Muscle biopsy may be a vital piece of information in a patient to identify the cause of a myopathy if other signs are not prominent. Electromyography (EMG) used to be used frequently to identify a muscle group to biopsy. This proved to be problematic for a few reasons; EMG can be painful (especially in a young child), the biopsy cannot be done on the same leg as the EMG because of abnormalities seen on biopsy as a consequence of the EMG, and involvement may be patchy. Magnetic resonance imaging is frequently used now to identify muscle groups, and skin, that is inflamed secondary to disease involvement. MRI imaging of the muscles, usually the quadriceps, can aid the surgeon in precisely localizing the proper site for biopsy without the use of EMG. MRI can also be helpful in a patient that presents with acute pain in proximal musculature when it is not clear if symptomatology is secondary to acute muscle swelling or inflammation from calcinosis around muscle groups. (Figures 20b)

Physical examination: The physical exam in a patient suspected with JDM or in a patient followed for JDM should pay particular attention to skin, joints, and the musculature. Muscle strength should be assessed in

an organized and reproducible fashion such that the clinician can compare the patient's performance over time. The physician should measure how long the patient can perform certain tasks; such as neck flexion to the chest (the starting position should be with the head extended over the edge of the table) and straight leg extensions against gravity. Muscle strength, of proximal and distal musculature, should be graded. The child should be asked to test proximal muscles including their ability to complete a sit-up and the Gower's maneuver. A positive Gower's sign is said to be present if a patient uses his/her arms to push up the trunk and "climb up the legs" when rising from the floor.

The skin examination should include a thorough search for rash and calcinosis, although calcinosis is usually a late finding. The heliotrope rash may be subtle, especially in dark-skinned children. Gottron's papules appear over the knuckles, but other extensor surfaces such as the knees and elbows can develop a similar erythematous shiny appearance. Calcinosis may also be subtle in the beginning. A thorough investigation of the entire body surface area should be completed and the skin felt for any subcutaneous irregularities. The ophthalmoscope, or if available capillaroscopy, should be utilized to examine the nail beds for dilation and drop out of capillary nail fold loops. Interestingly, a careful inspection of the gumline may reveal dilated blood vessels.

Treatment: The rarity of this disease prevents large, controlled, randomized trials from taking place. Reports of success with treatment regimens are often from single centers and frequently are retrospective. At our center, we use 2 mg/kg/day of corticosteroids orally in the initial stages after diagnosis and frequently until labs normalize. If there is any evidence of swallowing difficulty or severe compromise in function, then high dose intravenous Solumedrol is administered promptly. Disease modifying medications are started almost immediately, in order to control disease and allow the weaning of steroids when appropriate. Methotrexate subcutaneously is frequently a first-line therapy. Hydroxychloroquine is also used in JDM, primarily for skin, arthritis, and constitutional effects. One of the more dangerous total dose-related side effects of hydroxychloroquine is retinal toxicity. Children should have yearly ophthalmologic examinations when using this medication that should include slit-lamp examination, color vision, visual acuity, and visual fields. Other drugs that have been used with variable success include intravenous immune globulin, cyclosporine, azothiaprine, and cyclophosphomide.

Disease course: Prior to the use of steroids, mortality from JDM was near forty percent. Mortality in the post-corticosteroid era is down to 3% and is primarily from gastrointestinal hemorrhage, intestinal infarction, cardiopulmonary complications, and sepsis. The survival rate presently is approximately 90%. There appear to be four phases involved in the disease course of JDM. The first phase is a prodromal period that lasts weeks to months and involves nonspecific symptoms. In the second phase, the affected child develops muscle weakness and rash lasting days to weeks. Continued myositis, weakness, and rash, which can last up to two years, marks the third phase. The final stage is the recovery period, in which the child is left with residual weakness, scarring, and calcinosis. The best prognostic factor in predicting a good outcome is the rapidity of steroid initiation. Disease courses may vary greatly, ranging from signs and symptoms lasting less than one year to a persistent waxing and waning of symptoms with little resolution. Approximately 20% of children have a more progressive course with poor outcomes. Poor prognosis and mortality are associated with a disease course of rapid onset, cutaneous and/or cutaneous vasculitis, severe vascular disease and infarction on muscle biopsy, delay in the institution of therapy, inadequate therapy, and poor response to initial treatment with steroids. Although malignancy is associated with dermatomyositis in adult patients, this is rarely the case with children.<sup>17</sup>

Differential Diagnosis: The list of differential diagnoses of myopathies and neuromuscular disorders is a long one; however, most of these are rare. Very few diseases present with the classic JDM rash and muscle symptoms. In atypical cases, ones in which the rash is not classic, other etiologies of muscle weakness and/or inflammation should be investigated.

Infectious etiologies may present with an acute onset of muscle pain. Influenza A and B, Coxsackie B, toxoplasmosis, trichinosis, staphylococcal bacteremia, schistosomiasis, and trypanosomiasis have all been implicated in acute myopathies. Infection with *Trichenella spiralis* usually presents with fever and diarrhea, but may be followed by periorbital edema. Swelling of involved muscles, including those of the face, neck, and chest, would be extremely unusual in JDM. Biopsy of the muscles demonstrates the larvae and cysts.

Other connective tissue diseases (CTD), such as mixed connective tissue disease (MCTD), scleroderma, and SLE may manifest with myositis and skin involvement. Usually the serologies and other systemic complications make differentiation of these disease from JDM an easy one. The myositis of JDM is usually much more severe, disabling, and involves elevations of CK to a much greater degree. Vasculopathy is not seen on muscle biopsies in SLE, JRA, or scleroderma. The skin involvement if atypical or early can be mistaken for other entities. Children with JDM may have a malar blush, but it is not usually as intense as that of SLE and there is not the typical sparing of the nasolabial folds as in SLE. Capillary nail fold changes can be seen in other CTD's that involve vasculitis, such as scleroderma, SLE, and MCTD. The classic heliotropic rash and Gottron's papules are not seen in other CTD's.

There are many neuromuscular diseases and myopathies that may have similar signs or symptoms in a patient with an atypical presentation of JDM. Muscular dystrophy is usually a slowly progressive disease and does not evolve as quickly as JDM. There may be similar involvement of the proximal musculature and elevations in CK. Patients with Duchenne's muscular dystrophy frequently have calf hypertrophy, a sign not seen in JDM. Myoadenylate deaminase deficiency is an autosomal recessive deficiency of an enzyme that causes muscle fatigue, cramping, and stiffness after exercise. It frequently presents in childhood and may be secondarily associated with a rheumatic disorder. These patients may have decreased muscle mass, and usually the elevation of CK is only modest in nature. The diagnostic laboratory test is a failure to produce increased plasma ammonia after exercise of the forearm. Lack of the enzyme can be detected on muscle biopsy. Medications may induce a myopathy; some of these include hydroxychloroquine, steroids, alcohol, HMG CoA reductase inhibitors, and penicillamine. The list of neuromuscular disorders is a long one and if indicated, a pediatric neurologist should evaluate the child.

### **Malignancies Presenting with Rheumatic Complaints**

Musculoskeletal complaints may be one of the initial symptoms in a child with a malignancy. The clinician must have a high index of suspicion and know what signs and symptoms are consistent with malignancy versus a rheumatologic disorder. In a review of 29 children initially referred for a rheumatic disease and later identified as malignancies, 48% of patients had clinical features atypical for any rheumatic disorder.<sup>16</sup> Signs and symptoms in this series that were considered "worrisome" were monoarticular bone pain and bone tenderness, back pain, severe constitutional symptoms discordantly high ESR and low platelet count, elevated lactic dehydrogenase (LDH), and CBC results. The authors make the point that back pain is a very unusual complaint in pediatric rheumatologic disorders, even JAS and spondyloarthritis. Back pain is usually a late manifestation in these diseases. They also point out that night sweats, a constitutional sign, is extremely unusual in rheumatologic disorders (despite having high spiking fevers), where they are not as uncommon in malignancies. Referring diagnoses included JRA, SpA, SLE, Kawasaki disease, mixed connective tissue disorder, Lyme disease, and JDM. Ostrov et al compared the cases of ten children with acute leukemia to ten children with systemic onset JRA. Some of their findings are summarized in Table 11. They found that certain laboratory findings did not significantly differ between the two groups, including ANA, RF, uric acid, LDH, and ESR. White blood cell (WBC) counts and the differentials varied between the two groups depending on time of onset of signs and symptoms versus time at diagnosis. The total WBC count was not significantly different between the two groups, rather the composition of the total WBC did differ, and only at the time of diagnosis. Specifically, in SoJRA, there was a neutrophilia and in leukemia there was a lymphocytosis.<sup>38</sup> In a series examining ten patients initially complaining of musculoskeletal symptoms who were later determined to have malignancies, the diagnoses included acute leukemia, non-Hodgkin's lymphoma, Ewing's sarcoma, and neuroblastoma.<sup>57</sup> The preliminary diagnoses included JRA, PSRA, "post-viral arthralgia", septic arthritis, JDM, and "rheumatic disorder". This group found that common complaints included a monoarticular arthritis either of the elbow or knee, which was usually transient in nature, pain out of proportion to the degree of swelling, and lack of morning stiffness. Other symptoms included night sweats, hepatosplenomegaly, and lymphadenopathy. Diagnostic procedures included lymph node biopsy and bone marrow aspiration. Interestingly, initial diagnostic aspirates in three out of seven patients only revealed cellular hypoplasia. Unfortunately, repeat aspirations were required to make the diagnosis of malignancy.

A misdiagnosis of a rheumatic disease in a patient with a malignancy may delay the time to appropriate treatment. Treatment with corticosteroids could also worsen the prognosis in patients with leukemia.<sup>42</sup> The clinician must maintain a high degree of suspicion and continue to reevaluate the patient who presents with atypical symptomatology.

### **Summary**

In summary, there are many causes of acute and chronic synovitis in children. JRA and SpA account for a large majority of chronic arthritides, while viral, post-infectious, Lyme, and rheumatic fever account for some of the more frequently seen acute causes. SLE and JDM are two of the autoimmune diseases consisting of chronic arthritis that are cared for by pediatric rheumatologists. Searching for and discovering specific history and physical findings will increase the clinical suspicion of particular diagnoses and will increase the pretest probability of certain tests (e.g. HLA-B27 and Lyme ELISA). Worrisome signs and symptoms (such as nighttime pain, pain out of proportion to findings, and lymphocytosis) should direct diagnostic testing to rule out malignancies that can be disguised as rheumatic illnesses and can delay diagnosis. Hopefully this review has elucidated when appropriate testing should and should not be done (e.g. ANA and RF). Chronic arthritis in children is not uncommon, but it can be appropriately managed when identified early.

## Figure Legends

**Figure 1** Approach to the Child with Chronic Arthritis. \*Cassidy JT, Petty RE, editors: Textbook of Pediatric Rheumatology, 4<sup>th</sup> ed, Philadelphia, 2001, W.B. Saunders. \*\*Chandrasekaran AN, Rajendran CP, Madhavan R: Juvenile rheumatoid arthritis-madras experience, Indian J Pediatr July-Aug 63(4):501-510, 1996.

**Figure 2** Systemic JRA rash on the **a)** abdomen and **b)** perineum and legs of an infant.

**Figure 3** Plain radiographs of an 11-year-old female with RF-negative systemic JRA showing osteopenia of both wrists as well as narrowing of intercarpal spaces. Several bony erosions (arrows), including subchondral cysts, radial epiphyseal erosion and carpal erosion are shown.

**Figure 4 a-b)** Plain radiograph of a 12-year-old female with systemic JRA showing knee effusions (arrows), diffuse osteopenia, and enlargement (white lines) and overgrowth of the distal femoral, proximal tibial, and fibular epiphyses.

**Figure 5** A patient with polyarticular JRA with involvement of the temporomandibular joint resulting in micrognathia.

**Figure 6** Patient with polyarticular JRA with symmetric PIP inflammation, left greater than right.

**Figure 7** Patient with polyarticular JRA with active arthritis in the wrists preventing complete dorsiflexion: known as a “prayer sign”.

**Figure 8** Patient with JRA with elbow arthritis.

**Figure 9** Evidence of arthritis in fourth toe and ankle.

**Figure 10** Plain radiographs of a 10-year-old female with RF-positive polyarticular JRA. **a)** Osteopenia of the left hand is noted with irregularity of distal radial epiphysis. Cortical irregularities of carpal bones with erosions of triquetrum and navicular bone (arrows) as well as radio-lunate joint space narrowing is apparent. **b)** Radiograph of the right hand also shows osteopenia, cortical irregularities and erosions of the scaphoid and triquetrum (arrow).

**Figure 11** Plain radiographs of a 14-year-old female with RF-positive polyarticular JRA. **a)** Radiographs of the wrists show diffuse osteopenia, poorly defined articular surfaces, fusion of 2<sup>nd</sup> and 3<sup>rd</sup> metacarpal joints, and erosion and deformity of the 2<sup>nd</sup> proximal, phalangeal epiphysis (arrow) and 1<sup>st</sup> proximal, interphalangeal epiphysis (arrow) in the right hand. Fusion of the 3<sup>rd</sup> metacarpal joint (arrow) with diffuse osteopenia is also apparent in the left hand. **b)** Joint space narrowing of the hips with sclerosis (arrow), collapse, and bony irregularities of the left femoral head (arrows) are visible on a pelvic radiograph.

**Figure 12** Example of erythema marginatum in a patient with rheumatic fever.

**Figure 13** Expected occurrence of major manifestations of acute rheumatic fever. Maximum clinical activity is represented by the peak of shaded area. Expected frequency is represented by relative heights of shaded area.

**Figure 14** Patient with Lyme disease showing erythema chronicum migrans. Shows several secondary lesions on the leg. Note the bull’s-eye pattern.

**Figure 15 a) and b)** Patients with systemic lupus and malar rashes.

**Figure 16** Patient with systemic lupus with palatal ulcers.

**Figure 17** Example of grossly visible dilated capillary nail fold loops.

**Figure 18** Patient with systemic lupus and Raynaud phenomena with ulcer..

**Figure 19** Patient with dermatomyositis and heliotrope rash of the eyelids.

**Figure 20** Patient with dermatomyositis who presented with diffuse muscle pain of the quadriceps. **a)** X-ray revealed diffuse soft tissue calcification. **b)** MRI revealed T2 uptake in soft tissues surrounding muscle groups consistent with inflammation secondary to calcification, not myositis.

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**Table 1.** Causes of Synovial Disorders in Children

Juvenile Rheumatoid Arthritis <ul style="list-style-type: none"><li>Pauciarticular</li><li>Polyarticular</li><li>Systemic</li></ul>
Spondyloarthropathies <ul style="list-style-type: none"><li>Psoriatic arthritis</li><li>Reiter's Syndrome</li><li>Inflammatory Bowel Arthropathy</li><li>Seronegative Entesopathy and Arthropathy (SEA)</li><li>Juvenile Ankylosing Spondylitis</li></ul>
Systemic Lupus Erythematosus
Mixed Connective Tissue Disease
Juvenile Dermatomyositis
Systemic Sclerosis
Eosinophilic Fasciitis
Vasculitic Syndromes <ul style="list-style-type: none"><li>Leukocytoclastic Vasculitis<ul style="list-style-type: none"><li>Henoch-Schonlein Purpura</li><li>Hypersensitivity Angiitis</li><li>Hypocomplementemic Urticarial Vasculitis</li><li>Mixed Cryoglobulinemia</li></ul></li><li>Polyarteritis<ul style="list-style-type: none"><li>Polyarteritis Nodosa (PAN)</li><li>Kawasaki Disease</li><li>Cutaneous Polyarteritis</li></ul></li><li>Granulomatous Vasculitis<ul style="list-style-type: none"><li>Wegener's Granulomatosis</li></ul></li><li>Giant Cell Arteritis<ul style="list-style-type: none"><li>Takayasu's Arteritis</li></ul></li><li>Behcet's Disease</li><li>Mucha-Habermann Disease</li></ul>
Sarcoidosis
Relapsing Polychondritis
Sweet's Syndrome
Septic Arthritis (Bacterial)
Arthritis Caused by Viruses
Parvovirus
Rubella
Hepatitis B and C
Alpha viruses
Mumps
HIV
HTLV-1
Herpes viruses
Arthritis Caused by Other Infections
Fungal
Mycobacteria

- Spirochetes
  - Lyme
  - Leptospirosis
  - Syphilis
- Sporotrichosis
- Plant Thorn Synovitis
- Infective Endocarditis
- Rheumatic Fever
- Serum Sickness
  - Secondary to drugs
  - Secondary to infections
- Reactive Arthritis
  - Post-Streptococcal Arthritis
  - Post-Dysenteric Arthritis
  - Mycoplasma
- Immunodeficiencies with Arthritis
  - Chronic Granulomatous Disease
  - Familial Lipochrome Histiocytosis
  - Complement deficiencies
  - Combined immunodeficiency
    - Severe Combined Immunodeficiency (SCID)
    - Wiskott-Aldrich Syndrome
  - T-Cell Deficiencies
    - DiGeorge Syndrome
  - Hypogammaglobulin Syndromes
    - Selective IgA Deficiency
    - X-linked agammaglobulinemia
    - Common Variable Immune Deficiency (CVID)
- Mucopolysaccharidoses
- Sphingolipidoses
- Metabolic Deficiencies
  - Gout (to name just a few causes)
    - Lesch-Nyhan Syndrome
    - Becker Syndrome
    - Gaucher's disease
    - Renal Disease with decreased urate excretion
    - Glycogen Storage Disease Type 1
  - Pseudogout (Calcium Pyrophosphate Deposition Disease)
  - Ochronosis
  - Hyperlipoproteinemia
- Hematologic Disorders
  - Sickle-Cell Disease
  - Thalassemia
  - Hemophilia
- Hemochromatosis
- Multicentric Histiocytosis
- Cystic Fibrosis
- Familial Mediterranean Fever
- Hypothyroidism
- Plant thorn synovitis



**Table 2.** HLA Associations with Different JRA and Spondyloarthropathy Subtypes

<b><u>Disease Type</u></b>	<b><u>Antigen</u></b>
Pauciarticular – Young age onset	HLA-A2
	HLA DR5
	HLA-DR6
	HLA-DR8
	HLA-DPw2
	HLA-DR4
Pauciarticular – Spondyloarthropathies	HLA-B27
Polyarticular – Rheumatoid factor +	HLA-DR4
	HLA-DR7
Polyarticular – rheumatoid factor -	HLA-DR8
	HLA-DPw3
	HLA-DQw4
Systemic	HLA-DR4
	HLA-DR5
	HLA-DR8
Spondyloarthropathy	HLA-B27

Adapted pending permission from Cassidy JT, Petty RE, editors: Textbook of Pediatric Rheumatology, 4<sup>th</sup> ed, Philadelphia, 2001, W.B. Saunders.

**Table 3.** Ophthalmological Screening for JRA

	1 <sup>st</sup> 2 years of arthritis	>2 years after diagnosis
ANA + Pauci JRA	Every 3 months	Every 6 months
ANA – Pauci JRA	Every 6 months	Every 6 months
ANA + Polyarticular JRA	Every 3 months	Every 3 months
ANA – Polyarticular JRA	Every 6 months	Every 6 months
Systemic JRA	Every year	Every year

**Table 4.** Revised Jones Criteria for Rheumatic Fever

<b>Revised Jones Criteria for Rheumatic Fever</b>	
<u>Major Criteria</u>	<u>Minor Criteria</u>
Carditis Polyarthrititis Chorea Erythema Marginatum Subcutaneous Nodules	Clinical: Fever Arthralgia  Laboratories: High sedimentation rate Or C-reactive protein Prolonged P-R interval
<u>PLUS</u> Evidence of preceding streptococcal infection: Elevated anti-streptococcal antibodies and/or positive throat culture or rapid streptococcal antigen test	

The presence of 2 major criteria or of one major and two minor criteria indicate a high probability of ARF; if supported by evidence of preceding streptococcal infection.

**Table 5.** State distribution of Lyme disease. (1992-1998)

<b>State</b>	<b>Cases, n (% of total)</b>	<b>Cases/100,000 persons</b>
New York	29,172 (32.8)	23.3
Connecticut	15,523 (17.4)	67.9
Pennsylvania	13,020 (14.6)	15.4
New Jersey	10,852 (12.2)	19.9
Wisconsin	3,237 (3.6)	9.5
Rhode Island	3,128 (3.5)	44.8
Maryland	2,758 (3.1)	8.3
Massachusetts	2,118 (2.4)	5.1
Delaware	883 (1.0)	18.5
Minnesota	1,522 (1.7)	5.0

Adapted pending permission from: Van Solingen RM, Evans J: Lyme disease, Curr Opin Rheumatol 13(4):293-299, July 2001.

**Table 6.** Symptoms of Lyme disease.

<p><b>Early Disease: Stage I (1-4 weeks)</b></p> <ul style="list-style-type: none"><li>• ECM rash (erythema chronicum migrans)</li><li>• Muscle and joint aches</li><li>• Headache</li><li>• Fever</li><li>• Fatigue</li></ul>
<p><b>Early Disseminated Disease: Stage II (Months)</b></p> <ul style="list-style-type: none"><li>• Multiple ECM lesions</li><li>• Facial paralysis (Bell's palsy)</li><li>• Meningitis</li><li>• Radiculitis (numbness, tingling, burning)</li><li>• Brief episodes of joint pain and swelling</li></ul>
<p><b>Late Chronic Disease: Stage III (Months to years)</b></p> <ul style="list-style-type: none"><li>• Arthritis, intermittent or chronic</li><li>• Encephalopathy (mild to moderate confusion)</li></ul>
<p><b>Less Common Symptoms of Lyme Disease</b></p> <ul style="list-style-type: none"><li>• Heart abnormalities</li><li>• Eye problems such as conjunctivitis</li><li>• Chronic skin disorders</li><li>• Encephalomyelitis (limb weakness, motor coordination)</li></ul>

Adapted with permission from the National Institutes of Health. How Lyme disease is diagnosed (online) 1999). <http://www.niaid.nih.gov/publications/lyme/diagnosis.htm>

**Table 7.** Differential Diagnoses for Lyme disease.

Juvenile rheumatoid arthritis (JRA), specifically pauciarticular
Seronegative rheumatoid arthritis
Gonococcal arthritis
Sarcoidosis
Systemic lupus erythematosus
Multiple sclerosis
Myopathy, ehrlichiosis
Rocky Mountain spotted fever
Primary fibromyalgia
Rheumatic fever
Temporomandibular joint syndrome
Gout
Polymyalgia rheumatica
Psychogenic rheumatism
Reiter syndrome
Syphilis

**Table 8.** Treatment options for patients with Lyme disease.

**a.** Drug Therapy

<b>Drug</b>	<b>Dosage for children</b>
<b>Preferred oral</b>	
Amoxicillin <sup>o</sup>	50 mg/kg/d divided into 3 doses (max: 500 mg/dose)
	Age < 8 yr: not recommended
Doxycycline <sup>o</sup>	Age ≥ 8 yr: 1-2 mg/kg 2x daily (max: 100 mg/dose)
<b>Alternative Oral</b>	
Cefuroxime axetil <sup>o</sup>	30 mg/kg/d divided into 2 doses (max: 500 mg/dose)
<b>Preferred parenteral</b>	
Ceftriaxone	75-100 mg/kg/d IV in a single dose (max: 2 g)
<b>Alternative parenteral</b>	
Cefotaxime	150-200 mg/kg/d IV divided into 3 or 4 doses (max: 6 g/d)
	200,000-400,000 units/kg/d, divided into doses given every
Pencillin G	4 hours (max: 18-24 million units/d)*

\*The penicillin dosage should be reduced for patients with impaired renal function.

<sup>o</sup>For children intolerant of amoxicillin, doxycycline, and cefuroxime axetil, alternatives are azithromycin, 10 mg/kg/d (max: 500 mg/d), erythromycin, 12.5 mg/kg 4x daily (max: 500 mg/dose), clarithromycin, 7.5 mg/kg 2x daily (max: 500 mg/dose). Patients treated with macrolides should be followed closely.

**b. Symptom-based Therapy**

<b>Indication</b>	<b>Treatment</b>	<b>Duration (days)</b>
Tick bite	Observe	
Erythema chronicum migrans	Oral <sup>ε</sup>	14-21
Acute neurologic disease		
Meningitis or radiculopathy	Parenteral <sup>ε</sup>	14-28
Cranial-nerve palsy	Oral <sup>ε</sup>	14-21
Cardiac disease		
1 <sup>st</sup> or 2 <sup>nd</sup> degree heart block	Oral <sup>ε</sup>	14-21
3 <sup>rd</sup> degree heart block	Parenteral <sup>ε</sup>	14-21
Late disease		
Arthritis without neurologic disease	Oral <sup>ε</sup>	28
Recurrent arthritis after oral regimen	Oral or Parenteral <sup>ε</sup>	28
Persistent arthritis after 2 courses of antibiotics	Symptomatic therapy	
Central nervous system or peripheral nervous system disease	Parenteral <sup>ε</sup>	14-28
Chronic Lyme disease or post-Lyme disease symptoms	Symptomatic therapy	

<sup>ε</sup> See Table 8a

Table recreated pending permission from: Van Solingen RM, Evans J: Lyme disease, Curr Opin Rheumatol 13(4):293-299, July 2001.

**Table 9.** 1982 American College of Rheumatology Revised Criteria for Classification of

Systemic Lupus Erythematosus

<b><u>Criterion</u></b>	<b><u>Definition</u></b>
1. Malar Rash	1. Erythema over the malar eminences, tending to spare the nasolabial folds
2. Discoid Rash	2. Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	3. Skin rash as a result of unusual reaction to sunlight
4. Oral or nasal ulcers	4. Usually painless, observed by physician
5. Arthritis	5. Non-erosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	6. a) Pleuritis: pleuritic pain, rub heard by physician, or evidence of pleural effusion OR b) Pericarditis: documented by EKG or rub or evidence of pericardial effusion
7. Renal disorder	7. a) Proteinuria > 0.5 grams per day or > 3+ if quantitation not performed OR b) cellular casts
8. Neurologic Disorder	8. Psychosis in the absence of offending drugs or metabolic derangements
9. Hematologic Disorder	9. Hemolytic Anemia, OR Leukopenia (<4,000 on 2 or more occasions), OR Thrombocytopenia in the absence of offending drugs
10. Immunologic Disorder	10. Anti-double stranded DNA antibody, OR Anti-smith antibody, OR Positive finding of antiphospholipid antibodies based on
11. Antinuclear Antibody	1) an abnormal serum level of IgG or IgM anticardiolipin antibodies, 2) a positive test result for lupus anticoagulant using a standard method, or 3) a false-positive serologic test for syphilis 11. Abnormal ANA titer not associated with drug

A person is said to have SLE if 4 of the 11 criteria are present.<sup>55</sup>

Table recreated with permission of American College of Rheumatology

Criteria #10 adapted.<sup>28</sup>

**Table 10.** WHO Classification of SLE Nephritis

<b><u>World Health Organization Classification of SLE Nephritis</u></b>	
Class I	Normal or minimal change in disease
Class II	Mesangial Glomerulonephritis
Class III	Focal Proliferative Glomerulonephritis
Class IV	Diffuse Proliferative Glomerulonephritis
Class V	Membranous Glomerulonephritis
Class VI	Advanced Sclerosing Glomerulonephritis

**Table 11.** Findings at Time of Diagnosis: Acute Leukemia vs. Systemic Onset JRA (SoJRA)

	Morning stiffness with high spiking fevers	Nighttime pain with awakenings	Boney Pain (not articular)	Thrombocytosis	WBC Differential	Tc99 Bone Scan	Arthralgia without arthritis	Arthritis
Leukemia	+	++++	++++	+	Lymphocytosis	Multiple "hot" areas or single "cold" lesions	++++	++
SoJRA	++++	None	None	++++	Neutrophilia	arthritis	None	++++

Abbreviations: systemic onset JRA (SoJRA), Technetium 99 (Tc99)  
 <25%= (+), 25-50% = (++) , 51-75% = (+++) , >75% = (++++)<sup>38</sup>