Rheumatic Diseases of Childhood

Robert M. Rennebohm, MD*

The questions below should help focus the reading of this article.

1. What are the common clinical characteristics of juvenile rheumatoid arthritis?

2. What are the enthesopathy syndromes?

3. What are typical clinical and laboratory findings in patients with juvenile ankylosing spondylitis?

4. What is the association among Lyme disease, erythema chronicum migrans, and arthropathy?

5. What is the proposed mechanism of action of the nonsteroidal anti-inflammatory drugs?

The pediatrician frequently encounters children and adolescents with musculoskeletal complaints that raise the possibility of rheumatic disease. The purposes of this article are: to review an approach to the evaluation of "joint" symptoms and to review the pharmacology, use, and adverse effects of nonsteroidal anti-inflammatory drugs.

RHEUMATOLOGIC HISTORY

Systematic collection of the historical details is fundamental in the evaluation of "joint" complaints (Table 1).

Age and Sex

The child's age and sex provide initial clues. For example, suspicion that a young girl (less than 5 years of age) with knee swelling might have monoarticular juvenile rheumatoid arthritis is heightened simply because of her age and sex. (At onset of their disease, almost 20% of all patients with juvenile rheumatoid arthritis are young girls with pauciarthritis, most commonly involving the knee.) Suspicion that an older boy (10 years of age or older) with axioskeletal complaints might have an enthesopathy syndrome is increased, in part, because of his age and sex. Knowledge of the age and sex predilections of various rheumatic conditions is, therefore, helpful.

Chief Complaint

The chief complaint is often directive. For example, the complaint "his knees hurt every night" or "his legs hurt at night" is not characteristic of children who have juvenile rheumatoid arthritis or other well-defined inflammatory arthritides. Instead, these complaints are associated with benign nighttime leg pains. A complaint that "my back hurts" or "my heels hurt" raises the possibility of the enthesopathy/spondyloarthropathy spectrum. Chief complaints of joint "swelling" and "stiffness" increase the likelihood that the child has juvenile rheumatoid arthritis or one of the well-defined immune-mediated arthropathies. A complaint of joint "pain" but not swelling or stiffness, is not as directive and could be associated with a broad spectrum of possibilities, from the benign to the worrisome. For example, explanations for the complaint, "I hurt all over," include fibromyalgia, juvenile rheumatoid arthritis, lupus, and leukemia.

Location

Exactly which joint or other musculoskeletal areas have been symptomatic? Is the axial or peripheral skeleton involved? Are there symptoms in only one joint region or several? Are large or small joints involved? Are there symptoms at entheses? Is there bone or muscle pain?

Onset Characteristics

When did the musculoskeletal symptoms begin? Is the onset vaguely or sharply recalled? What, exactly, was first noticed? What was the patient doing at the time? Was there any trauma or unusual physical strain at onset? (Presence of trauma at onset, however, does not rule out immune-mediated disease.) Was the onset of musculoskeletal symptoms accompanied by fever or other symptoms? Was there sore throat or other infection, particularly gastrointestinal, genitourinary, or respiratory, during the 2 months prior to onset?

EDUCATIONAL OBJECTIVES

67. The pediatrician should be familiar with the pharmacologic properties of nonsteroidal anti-inflammatory drugs (Recent Advances, 88/89).
24. The pediatrician should have appropriate ability to manage children with Lyme disease (Recent Advances, 88/89).
113. The pediatrician should have appropriate ability to recognize the common pitfalls in the recognition and management of arthritis in children (Recent Advances, 88/89).

Duration

Are the joint symptoms *acute* (the differential diagnosis for which may include trauma, acute rheumatic fever, other reactive arthritides, transient synovitis, infectious arthritis, serum sickness-like reactions, Lyme disease, etc) or *chronic*?

Swelling

Presence or absence of joint swelling is an extremely important historical detail. Has there ever been any joint swelling? (It is unusual, eg, for patients with juvenile rheumatoid arthritis to complain of a long history of arthralgias and deny ever noticing any joint swelling.) Has the swelling been episodic (as in Lyme disease, acute rheumatic fever) or persistent (as in juvenile rheumatoid arthritis)? When swelling has been present, how long has it lasted? If swelling has been episodic, has the joint truly been asymptomatic and without swelling between episodes? Has swelling been objectively documented by a physician? How severe has the swelling been? How painful? Has redness or heat accompanied the swelling?

* *Associated Professor of Clinical Pediatrics, Columbus Children's Hospital and Ohio State University College of Medicine, Columbus.*

TABLE 1. Rheumatologic History

1. Age and sex
2. Chief complaint
3. Location of musculoskeletal discomfort
4. Onset characteristics
5. Duration of symptomatology
6. Swelling?
7. Morning stiffness?
8. Time of day when most symptomatic
9. Aggravating factors
10. Course, frequency of complaints
11. Severity
12. Associated symptoms
13. Psychosocial history
14. Family history

Morning Stiffness

Morning stiffness is a subjective feeling, noted upon arising, that a joint(s) does not move as freely through its usual range of motion as it is apt to later in the day. This same "stiffness" (or gel phenomenon) may occur after napping or after prolonged sitting.

Morning stiffness is a nonspecific indication of joint region inflammation. Its presence, although strongly suggestive, does not assure that a rheumatic disease is present. Its duration and severity correlate with the severity of inflammation. The more spontaneously the patient mentions morning stiffness and the greater the duration, severity, and predictability of it, the more likely it is that a rheumatic disease is present.

Time of Day When Most Symptomatic

During what time(s) of the day is the patient symptomatic? (Only at night?, mostly in the mornings?, mostly after exercise?, throughout the day?).

Aggravating Factors

Physical Activities. Are symptoms aggravated by or primarily noted during stair climbing, running, prolonged walking, bicycling, opening jars or doors, buttoning, prolonged writing, etc?

Weather Changes. Barometric pressure changes do not actually worsen inflammatory processes but often make inflammation more symptomatic.

Course and Frequency of Complaints

Since onset, how constantly and how frequently has the child complained of joint symptoms? Has the problem been evident on virtually a daily basis (typical of juvenile rheumatoid arthritis)? Or, has the patient only complained intermittently and variably? If joint symptoms have been of recent onset, have they been migratory, rapidly additive, or slowly cumulative? Has there been a recent trend of worsening or improvement?

Severity

How severe or disabling have these symptoms been? To what extent have activities of daily living and play been affected? How has the problem affected school performance and attendance? How have the symptoms affected the child's mood.

Associated Symptoms

What other symptoms have accompanied joint complaints? (Table 2).

Psychosocial History

Are psychosocial factors playing a role in the initiation or exacerbation of joint symptoms?

Family History

Is there a family history of arthritis or other rheumatic disease? For example, it is particularly productive to ask patients who may have a disease along the enthesopathy/spondyloarthropathy spectrum whether there is a family history of chronic low back pain, "arthritis of the spine," inflammatory bowel disease, or psoriasis.

TYPICAL HISTORIES ASSOCIATED WITH VARIOUS CLINICAL ENTITIES

Details regarding joint complaints associated with several common or otherwise important musculoskeletal disorders follow. These examples

TABLE 2. Rheumatologic Review of Systems

Constitutional
- Malaise
- Fatigue
- Fever
- Anorexia
- Weight loss
- Irritability
- Nonrestorative sleep

Skin
- Past or present rash
- Nodules
- Alopecia
- Photosensitivity
- Vasomotor phenomenon
- Raynaud phenomenon
- Skin tightening
- Increased bruising
- History of desquamation

EENT
- Red eyes
- Dry eyes
- Dry mouth
- Mouth sores
- Nasal mucosal sores
- Sore throat
- Epistaxis
- Parotid enlargement

Cardiopulmonary
- Pleuritic chest pain
- Chest wall pain
- Other chest pain
- Dyspnea
- Orthopnea
- Cough
- Syncope
- History of wheezing/asthma
- History of heart condition

Gastrointestinal
- Ulcer symptoms
- Heartburn
- Abdominal pain
- Diarrhea
- Nausea
- Vomiting
- Melena/hematochezia
- Dysphagia

Genitourinary
- Genital ulcers
- Urethral discharge
- Vaginal discharge

Neuromuscular/Psychiatric
- Muscle pain
- Muscle weakness
- Dysphonia
- Headaches
- Forgetfulness
- Confusion
- Personality change
- Depression
- Psychosis
- Seizures
- Paresthesias
- Chorea

serve to emphasize the value of collecting the kinds of historical information mentioned above.

Juvenile Rheumatoid Arthritis

The arthritis of juvenile rheumatoid arthritis is typically characterized by *mono*, *pauci* (four or fewer), or *polyarticular* (five or more) joint *swelling* which is present *constantly* and *daily* for *at least 6 weeks* and *usually persist for months or years*. Of patients with this disease, 70% are girls, and at least 50% of all patients have a pauciarticular onset. Of patients with pauciarticular onset, 43% have onset prior to 5 years of age, often while toddlers.

Juvenile rheumatoid arthritis is characterized by mono-, pauci-, or polyarticular swelling which is present constantly and daily for at least 6 weeks and usually months or years.

The chief complaints of most patients with juvenile rheumatoid arthritis usually include mention of both *joint pain and joint swelling*. It is almost always possible to elicit a history of *morning stiffness*. Typically, the child is stiff every morning, then "loosens up" or "limbers up" as the day progresses, such that the child appears normal or near normal in the afternoon. The child may again appear stiff after naps and may begin complaining of joint pain again toward the end of the day.

Sometimes the onset of arthritis is acute, but more commonly the process develops gradually, such that days, weeks, or even months pass before the family fully recognizes that a genuine problem exists. Often, parents initially assume the joint complaints stem from trauma. The falsely reassuring observation that the child seems "fine" by late morning or early afternoon may dissipate their concern and postpone the seeking of medical attention.

Lupus

The joint complaints of lupus differ from juvenile rheumatoid arthritis in the following ways: Commonly, patients with lupus complain primarily of *intermittent arthralgias*. Actual joint swelling may not be noted. When joint swelling is present, it may persist for months but is often *episodic* or intermittent and may be only fleetingly present. Lupus joint inflammation is often more acute and painful than juvenile rheumatoid arthritis inflammation, and the pain is often out of proportion to physical findings. In contrast, juvenile rheumatoid arthritis often causes swelling out of proportion to pain. Any joints can be involved in lupus. Finger involvement is particularly common. Some patients with lupus have symptoms mimicking enthesitis. Many state, "I ache all over" and are unable to localize the pain.

Acute Rheumatic Fever

The resurgence of acute rheumatic fever mandates review of poststreptococcal arthropathy. The classical course of the arthritis of untreated acute rheumatic fever is as follows. Approximately 2½ weeks (range 1 to 5 weeks) after group A streptoccocal infection, painful, tender arthritis in one or more joints develops, usually starting in the lower extremity. The inflammation in a single joint rapidly reaches maximum severity in 12 to 24 hours and then remains maximally inflammed for the next two to six days. As arthritis in the initial joint(s) subsides, fresh arthritis develops in previously uninvolved joints (*migratory arthritis*). Often, there is overlap, such that arthritis in new joints is developing before arthritis in previously involved joints has subsided (*rapidly additive arthritis*). The arthritis may "migrate" or be rapidly additive during a period ranging from a few days to several weeks. Usually, the entire bout of polyarthritis is severe only for 1 week (in approximately 66% of patients) or for 2 to 3 weeks (in 33%). Then, it may continue in milder form for 1 to 2 weeks. Only rarely do symptoms in one joint persist for more than 2 to 3 weeks.

Involved joints may be exquisitely tender, with marked pain during movement. The pain is often out of proportion to physical findings.

An important characteristic of the arthritis of acute rheumatic fever is its impressive response to nonsteroidal anti-inflammatory drugs. Most patients display marked improvement within 24 to 36 hours after such therapy. Objective evidence of synovitis is usually gone within five days. Failure to respond dramatically to nonsteroidal anti-inflammatory drug therapy should raise questions about the diagnosis.

Caveats regarding diagnosis of acute rheumatic fever: Although Jones' criteria stipulate presence of arthritis in two or more joints, acute rheumatic fever may affect only one joint or the patient may complain of arthralgias only. A high percentage of patients have no history of preceding sore throat and have a throat culture negative for *Streptococcus*. Fever may be absent.

Enthesopathy Syndromes

Enthesopathy is an underrecognized cause of childhood musculoskeletal discomfort. The term denotes a pathologic condition at an enthesis—an attachment site of a ligament, tendon, or fascia to bone. *Enthesitis* denotes inflammation at an enthesis. Common enthesopathy sites are listed in Table 3. Patients with enthesopathy complain of pain and tenderness near joints or at nonarticular entheses. Swelling may or may not be present at involved entheses.

Entheses are sites of attachment of ligaments, tendons, and fasciae to bone; potential sites of immune-mediated inflammation; and sources of tenderness and pain in the spondylarthropathies.

The prototype enthesopathy syndromes are the classical spondylarthropathies (ankylosing spondylitis, Reiter syndrome, psoriatic spondyloarthropathy, and spondyloarthropathy associated with inflammatory bowel disease).

Juvenile ankylosing spondylitis primarily occurs in older boys (10 years

TABLE 3. Enthesopathic Sites

Posterior heel
Plantar heel
Metatarsal phalangeal region
Tibial tuberosities
Peripheral patella
Iliac crest
Ischial tuberosity
Back
Cervical spine
Chest wall

Enthesopathy near the following joints
- Fingers
- Wrists
- Elbows
- Shoulders
- Knees
- Ankles
- Toes

of age or more) and is typically characterized by chronic low back pain and stiffness (due to arthropathy and enthesopathy of the spine), limited back mobility, limited chest expansion, sacroiliitis, chronic or episodic peripheral arthritis (usually in large joints of lower extremities), peripheral enthesopathy (eg, at the heels), episodic acute iritis, and HLA B27 positivity. A significant percentage of older boys with apparent pauciarticular onset juvenile rheumatoid arthritis eventually prove to have ankylosing spondylitis.

Reiter syndrome is characterized by axial and peripheral enthesopathy, plus the triad of conjunctivitis/uveitis, urethritis/cervicitis, and arthritis.

Psoriatic spondyloarthropathy is characterized by psoriatic skin lesions, nail pitting, and axial and peripheral arthropathy/enthesopathy. Spondyloarthropathy/enthesopathy that is accompanied by chronic diarrhea is suggestive of *inflammatory bowel disease.*

The seronegative enthesopathy and arthropathy syndrome is characterized by presence of enthesopathy and arthropathy but absence of sufficient criteria for a definite diagnosis of one of the more specific (and usually more worrisome) spondyloarthropathy syndromes mentioned before. Patients with seronegative enthesopathy and arthropathy also tend to be older boys and HLA B27 positive. They may have arthralgias or arthritis. Their arthritis may be episodic or chronic.

Reactive Arthritis

The term reactive arthritis denotes arthritis which develops during or soon after infection elsewhere in the body but is not associated with demonstration of the infectious agent within the involved joints. It is assumed that the arthritis represents an immune-mediated reaction to the microorganism. The prototype reactive arthritides include postenteric and postvenereal arthritis and rheumatic fever. Postviral reactive arthritis occurs and is probably common. Reactive arthritis also occurs after infection with *Mycoplasma*, *Haemophilus influenzae*, *Meningococcus*, *Mycobacterium tuberculosis*, and a variety of other organisms.

Postenteric (eg, *Shigella*, *Salmonella*, *Yersinia*, *Campylobacter*, and *Clostridium difficile* infection) and postvenereal (eg, *Chlamydia trachomatis* and *Ureaplasma urealytica*) reactive arthritis are similar clinically. Typically, a mono- or an asymmetric pauciarticular (but sometimes polyarticular) arthritis develops within 1 to 2 weeks after the triggering infection. During a period ranging from a few days to 2 weeks, joints become involved in rapid succession. Usually, no further joints are affected thereafter. The most commonly involved joints are the weight-bearing joints of the lower extremities (with predilection for knees and metatarsal phalangeal joints). Enthesopathy is also common.

Fever usually occurs at the onset of postenteric arthritis but is less common in children with postvenereal arthritis. Conjunctivitis is common but may be so transient or so mild as to be overlooked. Urethritis may also be present.

The arthritis is usually self-limited, usually reaches its peak within 2 weeks, and gradually resolves during 2 to 6 months. The postenteric and postvenereal reactive arthritides respond less dramatically to nonsteroidal anti-inflammatory drugs than does acute rheumatic fever.

Lyme Arthritis

Because of its increasing incidence, expanding geographic spread, and protean manifestations, pediatricians need to be familiar with Lyme disease. Lyme disease is caused by the spirochete, *Borrelia burgdorferi*. This organism is carried by a variety of ticks, most notably *Ixodes dammini.* Although Lyme disease develops after a tick bite, a history of tick bite is often not recalled. Lyme disease is multisystemic, and patients may first seek medical attention during any of three clinical phases.

Acute (Initial) Phase. Within three to 32 days after a tick bite, a slowly expanding, circular erythema chronicum migrans rash develops at the site of the bite. The erythema chronicum migrans lesion typically has a maculopapular border and a flat, sometimes partially clearing, center. It ranges from 2.5 cm (1 in) to more than 30 cm (12 in) in diameter and may be painless, slightly burning, or pruritic. It usually fades within 3 to 4 weeks.

A variety of symptoms may accompany the rash or precede it by a few days. Fever, chills, malaise, fatigue, headaches, and stiff neck are most common. Other symptoms include arthralgias, myalgias, backache, lymphadenopathy, sore throat, and gastrointestinal complaints. Usually, these symptoms last only a few days.

Lyme disease can be a cause of recurrent episodes of mono- or pauciarthralgia; migratory polyarthralgias; recurrent episodes of mono-, pauci, or polyarthritis; or chronic arthritis which resembles pauciarticular juvenile rheumatoid arthritis.

Subacute (Second) Phase. Within a few weeks to several months after appearance of the rash, joint, cardiac, and/or neurologic symptoms and signs may occur. The arthropathy is usually characterized by brief, recurrent, self-limited *episodes* of either monoarticular, pauciarticular, or migratory polyarticular discomfort,

often without joint swelling. Individual *episodes* usually last 1 to 2 weeks but can last as many as 3 months. Episodes can recur several times within several weeks, months, or years. A common example: Four weeks after onset of the erythema chronicum migrans rash, knee swelling abruptly develops, which fully resolves within 1 to 2 weeks but recurs four times within the next 6 months. The child's joints are asymptomatic between episodes.

Chronic (Late) Phase. In 5% to 10% of patients, the episodic course of pauciarthritis ceases and a chronic arthritis that strongly resembles pauciarticular juvenile rheumatoid arthritis develops. Also, a chronic phase of neurologic involvement has been described. The chronic phase of Lyme disease usually occurs months to years after onset of the erythema chronicum migrans rash.

Urticaria With Arthritis

A common phenomenon in children is the development of a self-limited serum sickness-like illness characterized by the acute onset of painful polyarticular arthritis, urticaria, and/or erythema of the skin overlying joints. Joints most commonly affected are the ankles, metacarpal phalangeals, wrists, and knees. Most patients with lower extremity synovitis refuse to walk. A minority of patients have fever, an elevated ESR, and an increased WBC count. The average duration of joint symptoms is six days. In most patients, symptoms fully resolve within 2 weeks. Hypersensitivity to drugs, notably to penicillin and cefaclor, is a major cause of this syndrome. In other cases, the phenomenon appears to be idiopathic or triggered by viral infection.

Chondropathy of the Patella

Chondropathy of the patella occurs primarily in older children and adolescents. The chief complaint usually is "my knees hurt." Knee pain is primarily noted during running (especially up hills), bicycle riding, jumping, stair climbing, and deep knee bending. The knee pain is usually described as being on the "undersurface of the kneecap." Usually, there is no history of morning stiffness or swelling. Another common complaint is "my knee gives way."

Acute Transient Synovitis of the Hip

The typical patient is a boy, 2 to 7 years of age, who wakes up in the morning with unilateral pain in the anterior thigh or hip region or with referred pain in the knee. He may limp or refuse to bear weight. There may or may not be a history of trauma or upper respiratory tract infection. Commonly, there is low-grade fever, rarely high fever, and often no fever. Often, the pain subsides considerably by the time the child is seen by the physician later that day but returns more impressively the next day. Symptoms usually resolve within several days or 1 to 2 weeks. A small percentage of children experience recurrences.

Benign Nighttime Knee Pains

One of the most common musculoskeletal complaints of childhood is nighttime leg pains. The child typically screams or cries in the middle of the night, says "my legs hurt," and points to the anterior thighs, knees, or shins. The child is often awakened from sleep by these pains. The pain responds to massage and acetaminophen, and he or she feels "perfectly fine" the next morning.

The key historical features are that the complaints occur almost exclusively at night or in the evening, and there is no upper extremity discomfort. If there is morning stiffness or considerable symptomatology during the day, concern should be raised that a more significant problem is present.

Benign nighttime leg pains can occur nightly for weeks, months, or ever a few years. Frequency of complaints may vary from month to month for a given patient. The pathogenesis of benign nighttime leg pains remains unclear.

RHEUMATOLOGIC PHYSICAL EXAMINATION

It is beyond the scope of this article to discuss the rheumatologic physical examination in detail. Only a few points will be emphasized.

A complete joint examination includes assessment for joint swelling, effusion, warmth, erythema, tenderness, pain during movement, limitation of motion, and deformity. When joints appear swollen, it should be documented whether the swelling appears to be due mostly to bony enlargement, synovial proliferation, joint effusion, swelling of periarticular soft tissues, or combinations of these. By definition, objective evidence of arthritis is present when the joint is swollen, when effusion is present, or when two or more of the following conditions exist: limitation of motion, tenderness or pain during movement, and increased heat.

The musculoskeletal examination should also include detection of tenderness or swelling at enthesopathic sites, palpation at "fibrositis" trigger points, performance of patellar compression tests, examination of muscles for tenderness and strength, and palpation to elicit bone pain. Avoid the pitfall of assuming a child's pain is due to arthralgia or enthesalgia, when careful physical examination would reveal the bone pain of leukemia. The rheumatologic physical examination includes thorough general physical examination to detect other stigmata of rheumatic disease.

LABORATORY EVALUATION OF SUSPECTED RHEUMATIC DISEASE

A suggested list of initial screening tests for rheumatic disease is given in Table 4. The complete blood cell count, differential, and platelet count screen, for example, for leukopenia of lupus or leukemia; leukocytosis of systemic onset juvenile rheumatoid arthritis, other acute arthritides, or leukemia; blast cells of leukemia; atypical lymphocytes of Ebstein-Barr virus infection; anemia of chronic inflammatory disease, hemolytic anemia of lupus, and leukemic anemia; thrombocytopenia of lupus or leukemia; thrombocytosis of acute inflammatory disorders such as Kawasaki disease and systemic juvenile rheumatoid arthritis.

The urinalysis screens for lupus nephritis and the pyuria of urethritis.

TABLE 4. Laboratory Evaluation of Suspected Rheumatic Disease: Suggested Initial Screening Tests

White blood cell count, differential
Hemoglobin, hematocrit, mean corpuscular volume
Platelet count
ESR
Urinalysis
ANA
Rheumatoid factor
Chemistry screen (renal and liver function tests, at least)
Quantitative immunoglobulins
CH50 and/or C3 and C4

The ESR is an excellent screening test for the presence of inflammatory disease. However, a normal ESR does not rule out rheumatic disease. Children with dermatomyositis and scleroderma typically have normal ESRs. The ESR may be normal in children with juvenile rheumatoid arthritis, enthesopathy syndromes, and lupus.

Chemistry screening tests serve primarily to determine renal and liver status. An elevated SGOT value, and even SGPT, should also trigger throughts of inflammatory myopathy. Quantitative immunoglobulins (IgM, IgG, and IgA) screen for immunodeficiency-related arthropathy and the high levels of immunoglobulins seen in certain chronic inflammatory states.

The C3, C4, and CH50 screen for acquired hypocomplementemia, as in lupus. The CH50 also screens for rheumatic disease syndromes associated with rare congenital complement deficiency states, such as C1 or C2 deficiency.

The rheumatoid factor test is much less helpful in pediatric rheumatology than it is in adult rheumatology. Only 7% of patients with juvenile rheumatoid arthritis will be rheumatoid factor positive when first tested.

The ANA test is valuable. For example, 34% of patients with pauci- and polyarticular onset juvenile rheumatoid arthritis will be ANA positive when first tested. The ANA is not a good screening test, however, for systemic onset juvenile rheumatoid arthritis, because only 2% of such patients are positive when first tested. The ANA test screens for presence of abnormally large quantities of any of a variety of antibodies to nuclear components of cells. So far, antibodies to at least 30 different nuclear antigens have been identified and characterized. To determine which specific antibody(s) is responsible for a given positive ANA test result, it is possible to test for antibodies against many of these specific nuclear antigens. Suggested additional tests to be done if an ANA test is positive and lupus is a consideration are listed in Table 5.

An ANA test is more productive than a rheumatoid factor test in screening for childhood rheumatic disease.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

The initial drug of choice for most rheumatic conditions is one of the nonsteroidal anti-inflammatory drugs. The ones most commonly used for children are listed in Table 6. Of the nonsalicylate nonsteroidal anti-inflammatory drugs, tolmetin and naproxen are approved by the Food and Drug Administration for treatment of juvenile rheumatoid arthritis.

TABLE 5. Additional Suggested Tests If Antinuclear Antibody Is Positive and Lupus Is a Consideration

Antibodies to specific nuclear antigens:
Anti-ds DNA (double-stranded DNA)
Anti-RNP (Ribonucleoprotein)
Anti-Sm (Smith antigen)
Anti-SSA (Sjogren syndrome A)
Anti-SSB (Sjogren syndrome B)
Anti-histone and anti-ssDNA (if drug-induced Lupus is a consideration)
CH50 and/or C3, C4
VDRL
Coombs
Prothrombin time
Partial thromboplastin time
Anticardiolipin antibodies

The therapeutic and toxic effects of nonsteroidal anti-inflammatory drugs appear to be due to their ability to inhibit prostaglandins. They inhibit the enzyme cyclooxygenase (Figure). Cyclooxygenase initiates conversion of arachidonic acid to thromboxane A2, prostacyclin (PGI2), and other prostaglandins (PGE2, PGD2, PGF2). These prostaglandins are believed to play a major role in the inflammatory process, but other roles include maintenance of the health of gastroduodenal mucosa and maintenance of appropriate renal blood flow. Inhibition of prostaglandin synthesis, therefore, suppresses undesirable inflammation but may adversely affect gastroduodenal mucosa and renal blood flow.

The therapeutic, as well as toxic, effects of nonsteroidal anti-inflammatory drugs appear to be due to inhibition of prostaglandin synthesis.

Nonsteroidal anti-inflammatory drugs have little effect on lipoxygenase, the enzyme that initiates conversion of arachidonic acid to leukotrienes. However, inhibition of cyclooxygenase by nonsteroidal anti-inflammatory drugs may "shunt" arachidonic acid metabolism into the lipoxygenase pathway, thereby causing overproduction of leukotrienes. Increased leukotriene levels may then accentuate nonsteroidal anti-inflammatory drug toxicity, including gastrointestinal effects.

Nonsteroidal anti-inflammatory drug-induced gastropathy (gastritis, esophagitis) represents a major concern. It is unclear whether children are at less risk for such gastropathy than are adults. It is also unclear whether patients receiving nonsteroidal anti-inflammatory drugs should be treated prophylactically with drugs such as H_2-receptor antagonists and sucralfate.

Probably by suppressing the vasodilatory role of renal prostaglandins, nonsteroidal anti-inflammatory drugs may decrease creatinine clearance and increase serum creatinine levels. This is primarily relevant for patients

TABLE 6. Nonsteroidal Anti-Inflammatory Drugs

Generic Name	Dosage (mg/kg/d)	Doses/d
Tolmetin sodium	25–30	4
Naproxen*	10–20	4
Ibuprofen	30–40	4
Aspirin	80–100	4
Choline magnesium trisalicylate*	50–75	2–4

* Available in liquid form.

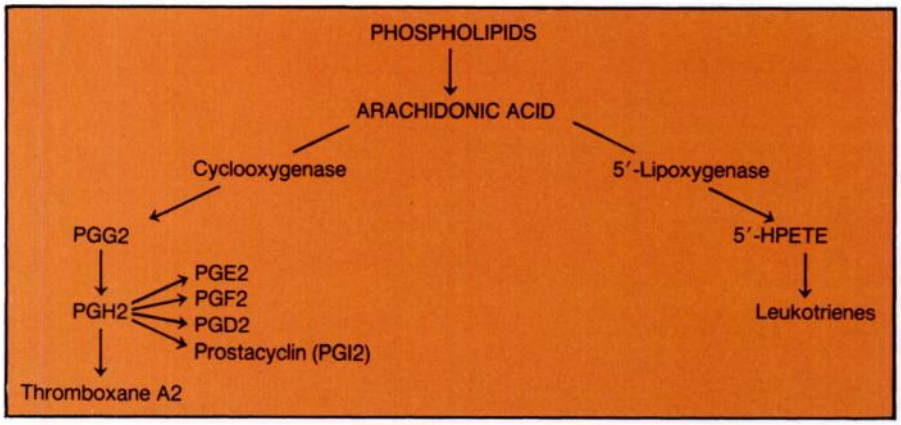

Figure. Biosynthesis of thromboxane A_2, prostaglandins, and leukotrienes. HPETE, hydroxyperoxyeicosatetraenoic acid.

with hypovolemia and impaired renal function. Interstitial nephritis and nephrotic syndrome may rarely occur with a number of nonsteroidal anti-inflammatory drugs.

By inhibiting cyclooxygenase within platelets, most nonsteroidal anti-inflammatory drugs decrease platelet aggregation. Aspirin, in dosages as low as 80 mg daily, irreversibly acetylates cyclooxygenase and decreases platelet aggregation for the rest of the life of the platelet. After aspirin is discontinued, this platelet effect persists for ten to 12 days. Other cyclooxygenase-inhibiting nonsteroidal anti-inflammatory drugs also decrease platelet aggregation, but their inhibition is reversible, so that the platelet effect disappears as soon as the drug is completely excreted (within 24 hours, eg, with tolmetin and ibuprofen.) The nonacetylated salicylates (eg, choline magnesium trisalicylate) are poor inhibitors of cyclooxygenase and have little or no effect on platelets.

Other side effects of nonsteroidal anti-inflammatory drugs include hepatotoxicity, diarrhea, headache, tinnitus, skin rash, fluid retention, and rarely bone marrow suppression. The potential side effects should not be minimized, and the risk to benefit considerations should be discussed thoroughly with the family. A complete blood cell count, urinalysis, and chemistry profile ideally should be obtained every 6 months to screen for toxicity.

To date it is difficult to state with certainty whether one nonsteroidal anti-inflammatory drug is more effective or, on balance, any less toxic than another. Aspirin appears to cause more gastrointestinal toxicity and a greater incidence of hepatotoxicity than the newer drugs. There is some evidence that aspirin may predispose to Reye syndrome. There is no evidence to date that non-aspirin nonsteroidal anti-inflammatory drugs predispose to Reye syndrome. Nonacetylated salicylates may create less gastrointestinal disease than other nonsteroidal anti-inflammatory drugs. Sulindac and nonacetylated nonsteroidal anti-inflammatory drugs may suppress renal prostaglandins to a lesser degree. There is no evidence that combination nonsteroidal anti-inflammatory drug therapy is more effective than use of a single agent. A major factor in determining preference for one drug over another is ease of administration. Several of the newer agents may be administered once or twice daily. Several are also available in liquid form.

Although beneficial effects may become apparent in a few days, it may take 2 to 6 weeks of sustained therapy before maximum benefits occur. Therefore a 2- to 6-week trial is wise before abandoning a given nonsteroidal anti-inflammatory drug, unless adverse side effects develop.

SUGGESTED READING

Aho K, Leirisalo-Repo M, Repo H: Reactive arthritis. Clinics in Rheumatic Diseases 1985;11:25–38

Calin A: *Spondylarthropathies*. Orlando, FL, Grune & Stratton, Inc, 1984

Kunnamo I, Kallio P, Pelkonen P, et al: Serum-sickness-like disease is a common cause of acute arthritis in children. *Acta Paediatr Scand* 1986;75:964–969

Rennebohm RM, Correll JK: Comprehensive management of juvenile rheumatoid arthritis. *Nurs Clin North Am* 1984;19:647–662

Robinson DR: Lipid mediators of inflammation. *Rheum Dis Clin North Am* 1987;13:385–400

Rosenberg AM, Petty RE: A syndrome of seronegative enthesopathy and arthropathy in children. *Arthritis Rheum* 1982;25: 1041–1047

Steere AC, Malawista SE, Hardin JA, et al: Erythema chronicum migrans and Lyme arthritis. *Annal Intern Med* 1977;86:685–698

Stollerman GH: Rheumatic fever, in Kelly WN et al: *Textbook of Rheumatology*. Philadelphia, WB Saunders, 1985, pp 1277–1293

ACKNOWLEDGMENTS

The author thanks Drs Richard Kern and Cheryl Cook for their suggestions.

Self-Evaluation Quiz

11. Most patients with juvenile rheumatoid arthritis (JRA) have or are characterized by each of the following *except*:

A. Acute onset of the arthritis.
B. Morning stiffness.
C. Both joint pain and joint swelling.
D. Pauciarticular onset.
E. Female gender.

12. Enthesopathy syndromes (classical spondyloarthropathies) include each of the following *except*:

A. Ankylosing spondylitis.
B. Acute transient synovitis of the hip.
C. Reiter syndrome.
D. Psoriatic spondyloarthropathy.
E. Spondyloarthropathy associated with inflammatory bowel disease.

13. A 13-year-old boy has persistent pain and swelling in his right knee. Each of the following associated findings would be typical of juvenile ankylosing spondylitis *except*:

A. Chronic low back pain.
B. Limited back mobility.
C. Enthesopathy of heels.
D. HLA B27 negativity.
E. Episodic acute iritis.

14. True statements pertaining to erythema chronicum migrans include each of the following *except*:

A. It is associated with Lyme disease.
B. It develops at the site of a recent tick bite.
C. Any associated arthropathy typically occurs at the time of onset of the rash.
D. It is a slowly expanding circular rash with a maculopapular border.
E. It usually fades within 3 to 4 weeks.

15. Each of the following is a true statement *except*:

A. An ANA test is more productive than a rheumatoid factor test in screening for childhood rheumatic disease.
B. JRA is characterized by constant joint swelling which is present daily for at least 6 weeks.
C. Lyme disease can cause recurrent, migratory, or chronic types of arthralgias or arthritis.
D. The therapeutic, as well as the toxic, effects of nonsteroidal anti-inflammatory drugs appear to be due to stimulation of prostaglandin synthesis.
E. Entheses are sites of attachment of ligaments, tendons, and fasciae to bone.

U.S. Postal Service

STATEMENT OF OWNERSHIP, MANAGEMENT AND CIRCULATION

Required by 39 U.S.C. 3685)

1A. Title of Publication	1B. PUBLICATION NO.	2. Date of Filing
Pediatrics in Review	0 1 9 1 9 6 0 1	October 1988
3. Frequency of Issue	**3A. No. of Issues Published Annually**	**3B. Annual Subscription Price**
Monthly July through April	10	$80.00

4. Complete Mailing Address of Known Office of Publication *(Street, City, County, State and ZIP+4 Code) (Not printers)*

141 Northwest Point Blvd. Elk Grove Village, IL 60007

5. Complete Mailing Address of the Headquarters of General Business Offices of the Publisher *(Not printer)*

American Academy of Pediatrics
141 Northwest Point Blvd. Elk Grove Village, IL 60007

6. Full Names and Complete Mailing Address of Publisher, Editor, and Managing Editor *(This item MUST NOT be blank)*

Publisher *(Name and Complete Mailing Address)*
American Academy of Pediatrics
141 Northwest Point Blvd. Elk Grove Village, IL 60007

Editor *(Name and Complete Mailing Address)*
Robert J. Haggerty, MD
New York Hospital, Cornell Medical Center, New york NY 10022

Managing Editor *(Name and Complete Mailing Address)*
Jean Dow
American Academy of Pediatrics, Elk Grove Village, IL 60007

7. Owner *(If owned by a corporation, its name and address must be stated and also immediately thereunder the names and addresses of stockholders owning or holding 1 percent or more of total amount of stock. If not owned by a corporation, the names and addresses of the individual owners must be given. If owned by a partnership or other unincorporated firm, its name and address, as well as that of each individual must be given. If the publication is published by a nonprofit organization, its name and address must be stated.) (Item must be completed.)*

Full Name	Complete Mailing Address
American Academy of Pediatrics	141 Northwest Point Blvd.
	Elk Grove Village, IL 60007
(non-profit organization under	
section 501 C (3) of the Internal	
Revenue Code)	

8. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages or Other Securities *(If there are none, so state)*

Full Name	Complete Mailing Address

9. For Completion by Nonprofit Organizations Authorized To Mail at Special Rates *(DMM Section 423.12 only)*
The purpose, function, and nonprofit status of this organization and the exempt status for Federal income tax purposes *(Check one)*

(1) [X] Has Not Changed During Preceding 12 Months
(2) [ ] Has Changed During Preceding 12 Months
(If changed, publisher must submit explanation of change with this statement.)

10. Extent and Nature of Circulation *(See instructions on reverse side)*	Average No. Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
A. Total No. Copies *(Net Press Run)*	30,318	30,529
B. Paid and/or Requested Circulation 1. Sales through dealers and carriers, street vendors and counter sales	0	0
2. Mail Subscription *(Paid and/or requested)*	19,780	23,126
C. Total Paid and/or Requested Circulation *(Sum of 10B1 and 10B2)*	19,780	23,126
D. Free Distribution by Mail, Carrier or Other Means Samples, Complimentary, and Other Free Copies	0	0
E. Total Distribution *(Sum of C and D)*	19,780	23,126
F. Copies Not Distributed 1. Office use, left over, unaccounted, spoiled after printing	10,538	7,403
2. Return from News Agents	0	0
G. TOTAL *(Sum of E, F1 and 2—should equal net press run shown in A)*	30,318	30,529

11. I certify that the statements made by me above are correct and complete

Signature and Title of Editor, Publisher, Business Manager, or Owner
Jean Dow Managing Editor

PS Form 3526, Dec. 1987 *(See instructions on reverse)*