MANY clinicians presently believe that the attack rate of acute rheumatic fever (ARF) in children has decreased sharply in recent years, and that there exists a marked geographic difference in the severity of the disease from one part of the world to another. A closer appraisal of the available data, however, does not support this contention. On the contrary, a resurgence of ARF has been reported from several areas for the past few years. Likewise, a comparison of prospective studies from different parts of the world documents that the clinical profile of ARF among children does not show a true geographic difference. The purpose of the present communication is to discuss the following aspects of ARF during childhood: (1) diagnosis, (2) management, (3) prognosis, and (4) prevention.

**Diagnosis**

An accurate diagnosis of ARF has been problematic ever since Hippocrates first described arthritis in man in 4000 BC. Throughout the Galenic era of medicine, all forms of joint involvement were lumped together as gout. Baillou was the first person who introduced the term *rheumatismus* to differentiate joint involvement of rheumatic origin from that due to gout. His work was published posthumously in 1642. Over the next 250 years, various manifestations of ARF such as arthritis, carditis, chorea, and subcutaneous nodules were described. However, not one person during this period recognized that all these diverse manifestations represented the spectrum of one common underlying disease, namely, acute rheumatic fever. The credit for bringing these manifestations to postulate a unitary concept of the disease goes entirely to Cheadle. At the same time, the disease was also described independently by Botkin.

Following these brilliant descriptions, "Cheadle cycle" or acute rheumatic fever, as we call it today, became a common diagnosis. However, lack of well-defined criteria soon led to a diagnostic chaos with the result that the disease was either over-diagnosed or under-diagnosed. This prompted Jones to propose a set of diagnostic criteria that he termed "major" and "minor". Since the original description, Jones diagnostic criteria for ARF have been modified several times. According to the most recent recommendations (Table 1), the presence of one major and two minor, or two major criteria plus an unequivocal evidence of a preceding sore throat due to group A beta-hemolytic streptococcus are mandatory for establishing the diagnosis of ARF.

*Is There a Need to Modify the Revised Jones Diagnostic Criteria?*

These recommendations, however, present certain problems. As pointed out by Roy, in some parts of the world, arthralgia may be as common a manifestation of ARF as arthritis. Cherian compared the clinical profile of ARF in a group of patients with arthralgia to that in another group with arthritis and found no substantial difference in terms of other manifestations of ARF or antistreptolysin 0 (ASLO) titers. Accordingly, he suggested that arthralgia, supported by evidence of a preceding sore throat of group A betahemolytic streptococcal origin, should be consi
dered as a major diagnostic criteria for ARF. Observations by Lue et al and others support this contention.

It seems, therefore, that strict adherence to modify Jones diagnostic criteria for ARF as recommended by the American Heart Association may lead to an under-diagnosis of ARF in certain areas of the world, and thereby, deny effective antistreptococcal chemoprophylaxis to a substantial number of children from geographical areas where ARF and its long-term sequelae, rheumatic heart disease (RHD), continue to be major causes of morbidity and mortality. Therefore, it seems prudent to consider arthralgia as a major diagnostic criteria of ARF among children from such areas, provided that (1) other causes of joint involvement are ruled out and (2) there is evidence for sore throat of group A beta-hemolytic streptococcal origin preceding the onset of joint involvement.

Table 1. Revised Jones diagnostic criteria for ARF:

<table>
<thead>
<tr>
<th>Diagnostic Criteria</th>
<th>Major</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Clinical</td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td></td>
<td>Fever</td>
</tr>
<tr>
<td>Carditis</td>
<td></td>
<td>Arthralgia</td>
</tr>
<tr>
<td>Chorea</td>
<td>History of previous ARF</td>
<td>or RHD</td>
</tr>
<tr>
<td>Subcutaneous nodules</td>
<td>Laboratory Data</td>
<td></td>
</tr>
<tr>
<td>Erythema marginatum</td>
<td>Acute phase reactants:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Erythrocyte sedimentation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rate (ESR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- C-reactive protein (CRP)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PR interval prolongation</td>
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</tbody>
</table>

Supporting evidence of a preceding streptococcal infection due to group A beta-hemolytic streptococcus (an increase in ASLO or other streptococcal antibody titers); throat culture positive for group A beta-hemolytic streptococci; recent scarlet fever.

* The presence of two major criteria or one major and two minor criteria suggest the possibility of ARF. Evidence of a preceding streptococcal evidence supports very strongly the diagnosis of ARF. Absence of evidence for preceding streptococcal infection makes the diagnosis of ARF suspect EXCEPT in children who present with Sydenham's chorea.

**Genetic Markers for Diagnosis of ARF**

There is a subset of patients with ARF who present further diagnostic dilemma. These are children with a recent history that strongly suggests ARF. However, clinical examination shows no evidence of carditis, chorea, arthralgia, or arthritis. The antibody titers against group A beta-hemolytic streptococci are within normal limits.

Recently, Zabriskie reported data regarding the use of monoclonal antibodies in identifying individuals with ARF. However, these studies require highly sophisticated laboratory facilities that are limited to very few medical centers. In this respect, the observations by Sanyal et al are of particular interest. A comparison of dermatoglyphic characteristics in 75 children with ARF to those of 46 first-degree relatives and 1,310 normal subjects showed an ulnar deviation of the axial tri radius in 75% of children with ARF; in approximately 40%, the ulnar deviation was associated with a concomitant distal displacement of the axial triradius, resulting in a significantly lower ab and tid ridge counts. Whether these dermatoglyphic alterations can be used as diagnostic criteria of ARF or to identify an individual with a genetic predisposition to develop ARF, a careful evaluation of dermatoglyphic profile in a large number of children with ARF or RHD is required.

**Management**

The basic principles regarding management of an attack of ARF include eradication of group A beta-hemolytic streptococci, bed rest, and antiinflammatory therapy.

**Eradication of Group A Beta-Hemolytic Streptococcus**

To eradicate group A beta-hemolytic streptococci, penicillin is the anti-microbial agent of choice, provided the patient is not allergic to the drug. A number of preparations and therapeutic regimes are available. The most effective procedure is a single intramuscular injection of longacting benzathine penicillin, 600,00 to 900,000 units for younger children (5 to 11 years) and 1.2 million units for adolescents. Besides ensuring an adequate bactericidal level, a single injection of benzathine penicillin minimizes the problems of non-compliance. In patients who are allergic to
penicillin, erythromycin is the drug of choice. A
dose of 125 to 250 mg, 4 times daily for 10 days,
is effective. Tetracycline or sulfonamides have no
place in the eradication of group A beta-
hemolytic streptococci.

Bed Rest

Bed rest and restriction of physical activity until
the rheumatic process has become quiescent
are the best methods in the management of ARF.
However, there are no objective criteria to deter-
mine precisely the optimum duration of bed rest
for these patients. Several factors which determine
the rapidity of ambulation, albeit arbitrarily,
include age of the patient, nature and severity of
clinical manifestations, rapidity of response, gen-
eral appearance, laboratory data, and the
number of previous attacks of ARF.

In general, prolonged bed rest is not neces-
sary when joint involvement is the only
manifestation of the disease. Presence of carditis
warns more caution (Table 2). These patients
require a much longer period of bed rest and the
duration is determined by the severity of
Carditis: mild (no cardiomegaly), moderate
(progressive cardiomegaly), and severe
(congestive heart failure and/or pericarditis).

Anti-Inflammatory Therapy

Salicylates and steroids are the two most commonly
used anti-inflammatory drugs in the management of
ARF. Both are extremely effective in controlling
fever and joint manifestations, and both agents
suppress the acute phase reactants, such as
erythocyte sedimentation rate (ESR) and C-
reactive protein (CRP). Although clinical
observations suggest that steroids are more effective as
anti-inflammatory agents and may be life-saving in
acutely ill patients, neither salicylates nor steroids
prevent cardiac damage or long-term residual heart
disease. 35-37

There is general agreement that salicylate is
the drug of choice for patients in whom joint
involvement is the sole manifestation, including
those who have mild carditis. On the other hand,
patients with moderate or severe carditis, charac-
terized by progressive cardiomegaly, congestive heart failure or pericarditis,
steroids offer the most effective therapeutic choice.

The dosage and duration of treatment with
anti-inflammatory agents are determined basi
cally by the clinical manifestations of the disease
(Table 3). Of the several steroid preparations,
prednisone is preferred because it causes few elec-
trolyte imbalance. Once the acute manifestations

Table 2. Guidelines for bed rest and ambulation for children with
ARF.

<table>
<thead>
<tr>
<th>Arthritis (Alone)</th>
<th>Carditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild a + b</td>
<td>Mild Carditis (A)</td>
</tr>
<tr>
<td>Moderate a + b + c</td>
<td>Moderate Carditis</td>
</tr>
<tr>
<td>Severe a + b + c</td>
<td>Severe Carditis</td>
</tr>
</tbody>
</table>

The characteristics of carditis are:

(a) elevation in sleeping pulse rate; (b) heart murmur-apical
pansystolic and/or decrescendo diastolic murmur at III left
intercostal space, parasternally; (c) progressive cardiomegaly; and
(d) congestive heart failure and/or pericarditis.

Table 3. Recommended anti-inflammatory agents and their
dose schedules for ARF.

<table>
<thead>
<tr>
<th>Arthritis (Alone)</th>
<th>Definite Carditis (No Cardiomegaly) (CHF/Pericarditis; Cardiomegaly)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Salicylates 100mg/kg/day</td>
<td>(1) Prednisone 2mg/kg/day for 4 weeks</td>
</tr>
<tr>
<td>(2) After, week, reduce to 60 mg per kg/day for 1 week</td>
<td>(2) Begin salicylates in the third week while tapering prednisone</td>
</tr>
<tr>
<td>(3) Continue for 3-4 weeks</td>
<td>(3) Continue salicylates for 6-8 weeks</td>
</tr>
<tr>
<td>(4) Change salicylates to prednisone if cardio megaly develops</td>
<td></td>
</tr>
</tbody>
</table>

The dosage and duration of treatment with
anti-inflammatory agents are determined basi
of rheumatic fever subside (2 to 4 weeks), the dose of the steroids should be tapered gradually. It is important to add salicylates to the regime while the steroid is being tapered and to continue salicylate therapy for a period of 2 to 3 months on the basis of serial evaluation of the clinical condition of the patient, acute phase reactants (ESR and CRP), and other pertinent laboratory data. The initiation of salicylate therapy while steroids are being tapered and its continuation thereafter, represent an important step towards minimizing the rebound phenomenon.

Side Effects

Patients who are receiving anti-inflammatory agents should be observed closely for any possible adverse effects. For patients who are receiving salicylates, salicylate intoxication as characterized by tinnitus, nausea, vomiting, or an increase in respiratory rate, is a major concern. Recently, Hamdan et al reported salicylate-induced hepatitis in 5 of 34 children with ARF. Salicylate intoxication or salicylate-induced hepatic dysfunction is common in patients whose serum salicylate level exceeds the therapeutic range of 1.4 to 1.8 mmol/L. Therefore, liver function tests and serum salicylate level should be monitored periodically during the course of therapy. In the event of adverse effects, the therapy should be discontinued for a day or two and then restarted at a reduced level.

In certain geographic locations, such as the Eastern Province of Saudi Arabia, glucose-6-phosphate-dehydrogenase (G6PD) deficiency may be endemic and may occur together with ARF. Observations by Sanyal et al suggest that aspirin in recommended doses does not induce hemolysis in such patients.

A short course of steroid therapy is usually well-tolerated. Serious side effects, such as gastric ulcer or compression fracture of the spine are extremely rare when the therapy is limited to a few weeks. In patients with congestive heart failure who are taking steroids, their fluid and salt intake, urine output, daily weight, and blood pressure should be monitored closely.

Rebound Phenomenon

With tapering off or after discontinuation of anti-inflammatory therapy, clinical or laboratory evidence of rheumatic activity may reappear. Such rebounds may be mild or severe, depending upon the severity of the attack and the point during the course of the rheumatic process when the therapy is reduced or discontinued. The severity of the disease during the rebound may equal or exceed the severity at the beginning of the treatment. In addition to clinical manifestations, the laboratory evidence for rheumatic activity reappears; ESR is elevated and C-reactive protein becomes positive.

Mild rebounds usually subside spontaneously in a few days and rarely require medication. In patients with severe rebound, it may be necessary to re-institute anti-inflammatory therapy. Whenever possible, salicylates should be used for this purpose, since a subsequent rebound is less likely to occur after salicylates than after steroids. As mentioned earlier, the occurrence of the rebound phenomenon can be minimized by giving salicylates concurrently with the tapering off of the steroid therapy and by continuing salicylates for several weeks, thereafter, on the basis of clinical status and laboratory data.

Management of Chorea

The management of chorea is not clear. None of the therapeutic regimes that have been tried are uniformly effective. Certain guidelines, however, have emerged over the years. Once the diagnosis of chorea is established, the child should preferably be taken out of the school. Strict bed rest is also indicated for the majority of the patients and care must be taken to prevent patients from falling out of the bed. This may necessitate some type of restraint. For patients who cannot feed themselves due to involuntary movements, maintenance of fluid and calorie intake should be closely monitored.

The observation that choreiform movements disappear during sleep and are aggravated by stress, provides the rationale for the use of sedatives. Phenobarbital is the drug of choice. A recommended dose schedule is 15 to 30 mg given orally every 6 to 8 hours. The dose then is increased by increments of 15 mg/day until involuntary movements are reduced. This schedule is maintained for 2 to 3 weeks and then reduced gradually over a 1-to-2-week period. In some patients, phenobarbital may cause further aggravation, or the dose required may be too large and cause incapacitating insomnolence; in some
other patients phenobarbital may fail altogether to suppress the involuntary movements. A tranquilizing agent, such as chlorpromazine, should be tried in such patients. The efficacy of steroids in the management of chorea remains controversial. The eradication of the streptococcal organisms and the application of long-term antistreptococcal chemoprophylaxis are mandatory for every child who has chorea.

Supportive Therapy

Five percent to 10 percent of children with first attack of ARF may develop congestive heart failure during the course of illness. These children should have complete bed rest and should not receive oral feeding until the acute stage of congestive heart failure is under control. Acute left ventricular failure is usually associated with hypoxemia of moderate to severe degree, and in some patients the respiratory insufficiency may subsequently progress to respiratory failure. Acid-base and blood gas profile should be monitored closely. Patients with hypoxemia should be placed in a moist, cool oxygen tent in a semi-reclining position (45°), and oxygen therapy should be monitored on the basis of serial evaluation of acid-base and blood gas profile. In the event of respiratory failure, ventilatory support should be started. In addition, fluid and sodium intake is reduced and the daily weight of the patient, fluid intake, and urine output should be recorded meticulously. Most patients with acute congestive heart failure are anxious and irritable and may benefit from sedation. Steroids should be the anti-inflammatory agents of choice for these patients. In addition, congestive heart failure should be treated with digitalis and diuretics to enhance myocardial contractility and to decrease the pre-load, respectively. For inotropy, digoxin is the digitalis preparation of choice. The initial total oral digitalizing dose (TDD) for children is 0.03 to 0.04 mg/kg of body weight per day. Patients with carditis may be sensitive to digitalis, hence, lower dose is preferable. Since the patients are acutely ill, the intravenous route for digitalization is preferred. When used intravenously, two-thirds (75%) of the total oral digitalizing dose are used to digitalize the patient. Digitalization is begun by giving half of TDD and the remaining half is administered in two equally divided doses, at 6 to 8 hours interval. After completing the TDD, maintenance therapy should begin 8 to 12 hours later. The daily maintenance dose is calculated as 25 percent of the TDD and is given in two equally divided doses, 12 hours apart.

A baseline 12 lead electrocardiogram (ECG) is obtained before starting digitalization. Pulse rate is counted before each dose of digitalis. If the heart rate is below 80 to 85 beats per minute, digoxin is withheld. An ECG is then taken and the serum digoxin level is checked in order to ensure that the level does not exceed the upper limits of the normal (2.5 nmol/L). Among the diuretics, furosemide is preferred during the initial stages of acute illness. Hydrochlorothiazide and spironolactone are preferred for subsequent long-term management. Potassium supplementation should be given to patients who are receiving diuretic therapy and serum electrolytes should be checked periodically.

Prognosis: Long-Term Sequelae

Of the various manifestations of ARF, only carditis and chorea are apt to produce long-term sequelae in terms of residual heart disease. However, all children with carditis do not develop RHD. In the absence of recurrence of ARF, heart murmur disappears in 30% to 35% of children who present with carditis during the initial attack. Of these children who subsequently develop residual RHD, mitral regurgitation is the most common valvular lesion and is present in 85% to 90%. Contrary to earlier reports, mitral stenosis is not very common, provided recurrence of ARF is prevented. Some children with chorea may develop mitral stenosis in spite of receiving continuous antistreptococcal chemoprophylaxis and in the absence of clinically documented recurrence.

Besides recurrence, the cardiac status during the initial attack of ARF is the other major determinant regarding development of long-term sequelae. Carditis, cardiomegaly, severity of mitral insufficiency, and congestive heart failure increase significantly (P<0.001) the risk of subsequent RHD. These data establish that the evolution, spectrum, and prevalence rate of RHD, following the initial attack of ARF, are very similar in different parts of the world and that recurrence of ARF is
prevented by strict adherence to continuous antistreptococcal prophylaxis.

Prevention

It is now well-accepted that ARF and its recurrence represent a potentially preventable complication of infection due to group A beta-hemolytic streptococcal microbial agents. Prevention of group A beta-hemolytic streptococcal infection should therefore provide an ideal mean. There are two types of prevention. Primary prevention is the prevention of the initial attack of ARF, and secondary prevention is the prevention of the recurrence of the disease. Historically, measures for secondary prevention preceded those for primary prevention.

Secondary Prevention

The demonstration by Coburn and Moore55 and later by Thomas and France56 showed that the regular use of small doses of sulfonamide reduced the recurrence of ARF substantially; this finding heralded a whole new era in the prevention of ARF.57-60 Introduction of penicillin added another dimension to the secondary control of the disease.61-67 Subsequently, Wood et al68 compared the effectiveness of different prophylactic regimes to prevent streptococcal infection and established that a monthly injection of long-acting benzathine penicillin offered the most effective means for long-term continuous antistreptococcal chemoprophylaxis. For those children who are allergic to penicillin, sulfadiazine provides an alternative means for prophylaxis. It is presently accepted worldwide that continuous antistreptococcal prophylaxis is mandatory for every child with ARF or RHD and that prophylaxis must begin as soon as the diagnosis is established.69-72 Recently, it has been reported by Lue et al73 that prophylaxis given once every three weeks is more effective than when given once every month. The optimum duration of prophylaxis remains controversial.50,74 Several factors merit careful consideration when making this decision. These include the prevalence of ARF in the community, the anticipated rate of recurrence per injection, age of the patient, and environmental factors such as overcrowding, low socioeconomic status, and the number of school-age children in the family. Another factor concerns situations where there is an increased risk for exposure to group A beta-hemolytic streptococcal infection, such as parents of young school-age children, school teachers, physicians, nurses, allied health personnel, and young military recruits.

It has been suggested that for children who present initially with isolated arthritis as the manifestation of ARF, prophylaxis should be discontinued after 5 years.50 Such recommendation is based on observations that recurrence of ARF tends to decline after 5 years and that recurrences are mimetic. However, as emphasized by Sanyal et al,74 recurrences do occur after 5 years, especially in those patients whose prophylaxis has been stopped,75-77 and children without carditis during the initial attack may present with carditis during subsequent recurrence.

We therefore believe that for rheumatic subjects, antistreptococcal chemoprophylaxis should be continuous and life-long, particularly in overcrowded Third World countries where a large, young population is at risk and where ARF and RHD continue to be the major causes for morbidity and mortality among children, adolescents, and young adults. Life-long continuous prophylaxis, in the form of monthly injection poses a major problem in terms of compliance.

Primary Prevention

Likewise, primary prevention of infections due to group A beta-hemolytic streptococcus presents problems.75-80 Firstly, it requires an accurate diagnosis and an optimal antibiotic therapy against pharyngitis due to group A beta-hemolytic streptococcus. However, one-third of the patients may have a subclinical form of infection and may not seek medical care. Another one-third, although symptomatic, may not seek the help of a physician. There are still others who are symptomatic, seek medical advice, and still develop ARF despite appropriate antibiotic therapy.

These limitations of primary and secondary prevention of ARF and its sequelae have prompted several investigators to pursue the development of a streptococcal vaccine. The feasibility of the production of a vaccine against the causative organisms for ARF has been greatly enhanced by various recent developments.81-85 Firstly, the concept that group A beta-hemolytic
streptococcal organisms cause two types of pharyngitis, rheumatogenic and nephritogenic, and that each has distinctive characteristics.85-87 Secondly, the rheumatogenic strains which are prevalent in a community are limited in number and this makes it feasible to prepare a polyvalent vaccine.88-90 Another factor involves the successful isolation and purification of M protein antigen from rheumatogenic strains that is pure, immunogenic and produces type-specific antibodies, does not cross-react with the sarcolemmic membrane of the cardiac tissue, and is safe for human use.91-93 It appears that successful immunization with streptococcal vaccine may become a reality in the near future.94 The development of a streptococcal vaccine will fulfill the ultimate aim of primary prevention of streptococcal infection and will mark the beginning of an era with a true universal decline of ARF and its long-term sequelae.95

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