Current Concepts of Rheumatic Fever

G Stollerman

Citation

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Abstract

A half-century ago, students of medicine in the United States learned that rheumatic fever (RF) killed more school-age children than all other diseases combined ([1]). Within the next several decades, acute RF and rheumatic heart disease (RHD) became remarkably rare in the most developed countries of the world ([2]). Yet, in these same countries pharyngitis due to group A streptococci (GAS) continued to account for approximately 20% of sore throats . What explains these remarkable changes in the rheumatogenicity of GAS pharyngitis? Evidence for the marked decline in the virulence of sporadic GAS pharyngitis in developed countries has been accumulating for decades, but the critical importance of GAS strain virulence in the pathogenesis of RF is still not widely appreciated ([3]). Recent studies of the genetic control of the expression of various virulence factors of group A streptococci (GAS) ([3], [4]) are beginning to explain the wide spectrum of group A streptococcal diseases and their striking epidemiological variation . Experimental manipulation of the genome to produce mutants with and without specific virulence factors may soon provide greater insight into their respective roles in the pathogenesis of the various streptococcal diseases.

PATHOGENESIS OF GAS INFECTION

In the log phase of growth, streptococci divide approximately every 20 minutes. Only when they do so are they rapidly killed by penicillin. When phagocyted, they are also readily killed because they are highly susceptible to the antibacterial action of oxygen radicals and other antibacterial substances within phagosomes of white blood cells. Thus, streptococcal infection is principally extracellular, and its virulence relates primarily to resistance to phagocytosis and subsequent invasiveness and toxin production. Strains deficient in both the surface M protein and hyaluronate capsule are killed by phagocytes. Because capsular hyaluronate is virtually non-antigenic whereas M protein is exquisitely type-specific, immunologic protection against virulent strains is primarily dependent upon the action of homologous type anti-M antibodies ([5]). The multiplicity of M types therefore accounts for the repetitive nature of GAS infections and thus for recurrent bouts of RF .Resistance to phagocytosis is further enhanced by several anti-complementary effects of M protein, and by its precipitation of fibrinogen on the bacterial surface. In addition, the hyaluronate capsule itself disrupts connections of epithelial cells and promotes invasion of deeper tissues ([6]). The hyaluronate capsule also resists internalization of the organism by epithelial cells ([7]) or by skin keratinocytes ([8],[9]). Benign, persistent throat carriage may result from epithelial cell internalization of less encapsulated strains where they may grow more slowly and be less readily eradicated by penicillin ([3]).

GAS toxins may contribute to morbidity in several ways. Weight for weight, the cell-surface bound hemolysin, streptolysin S, is one of the most toxic proteins known ([10]). It causes rapid destruction of cell membranes and is very cardiotoxic. Experimentally, the oxygen labile hemolysin, Streptolysin O, is also a powerful cardiac toxin. Streptokinase and desoxyribonuclease liquefy fibrin and nucleic proteins, respectively, accounting for the thin pus of GAS infections. Streptococcal hyaluronidase promotes rapid spread of the organisms through tissues (e.g., cellulitis and lymphangitis). The erythrogenic toxins are responsible for the rash of scarlet fever and are considered an important factor in toxic shock ([11]). Many of these secreted toxins have the properties of superantigens, nonspecifically and powerfully stimulating the host's immune response. M protein also contains moieties that similarly behave as such superantigens, thus further boosting immune responses to virulent strains ([12], [13]) (see "vaccines" below). The way in which these substances interact to produce the various complications of GAS infection is currently a subject of intense investigation.

Genetic control of virulence factors: The recent discovery of the genetic control of the expression of many of the virulence factors of GAS ([4],[14],[15],[16],[17],[18],[19]) has illuminated the basis of strain variation. MGenes of manyore than 40 putative virulence-associated genes of GAS have been

identified so far, and the complete genome sequences of three virulent strains within serotypes M1, M3 and M18 have been described ([20,21,22,23]). By environmental signals or by mutation, or both, de-repression of the genes controlling several virulence factors may lead to the emergence of the GAS clonesmay producing the wide spectrum of GAS diseases. The genes that repress virulence factors may underlie the well-recognized tendency of virulent strains to dissociate rapidly during convalescence from GAS pharyngitis, and during growth of GAS on artificial media ([3]). Furthermore, bacteriophage infection of GAS accounts for production of several of the erythrogenic toxins secreted by GAS that play a role in GAS invasiveness ([22],[[[23a]]]).

Epidemiology of GAS infection in relation to RF: The high attack rate of GAS pharyngitis in families, institutions and military recruits is the result of contact among susceptible persons living closely enough to ensure droplet transmission. In settings where RF has become rare, however, GAS pharyngitis continues to be quite common but is often caused by relatively attenuated strains. These, however, colonize the throat avidly, and often stubbornly ([3]). GAS "skin strains" that cause pyoderma (impetigo) are molecularly distinct from "throat strains" ([24]). Although they may secondarily colonize and infect the throat, pyoderma strains are generally less virulent and are not rheumatogenic ([25, 26,[[[26a]]]). Some skin strains, however, as well as certain throat strains may also cause acute glomerulonephritis (AGN) . In the acute stage, the two diseases very rarely occur simultaneously in the same patient, although each may occur at different times in the same host ([1]). For instance, recurrent epidemics of AGN have been well documented on the island of Trinidad where the prevalence of RF remained constant. Differences in the respective strains associated with each disease have been noted ([27]). However, the precise factors accounting for rheumatogenicity or nephritogenicity remain unclear (see "pathogensis of RF", below).

During convalescence from GAS pharyngitis, virulent GAS strains strains, rich in M protein and heavily encapsulated, progressively lose these virulence factors ([1],[3]). Attenuated strains of group A streptococci, however, may be transmitted and carried stubbornly for weeks or months ([28, 29]). Throat carriage is often more difficult to eradicate with penicillin (see "treatment"). The rapid dissociation of virulent strains in artificial media also makes maintenance of the virulent phase of the organisms difficult, requiring frequent mouse passage or passage though fresh human blood whereby only

phagocyte-resistant clones survive. These are best preserved for storage or transport by prompt freeze-drying. Strains sent to reference laboratories without careful preservation often attenuate by the time they are studied in the laboratory. Indeed, very few published clinical studies record encapsulation of the strains of GAS isolated, although they may be readily recognized by their mucoid colonies on blood agar ([30]).

PRIMARY PREVENTION OF RHEUMATIC FEVER

RF is a complication solely of GAS pharyngitis. Such prevention therefore depends on either the prevention or proper treatment of GAS pharyngitis. Because of the rarity of RF in some populations, however, the precision with which GAS needs to be diagnosed and the intensity and duration of its treatment has become problematic ([3]). GAS pharyngitis also differs in frequency, severity, and clinical characteristics, depending on the patient's age, the character of the infecting strains, and the circumstances that affect their transmission.

Problems in the clinical diagnosis of streptococcal pharyngitis: However imprecise the clinical diagnosis of GAS pharyngitis may be, some of its features help to differentiate it from much more common viral throat infections. The presence of fever, exudative pharyngitis, tender, enlarged cervical lymph nodes, and the absence of cough, coryza and hoarseness, have, at best, a predictive value no better than 70% ([31]). On the other hand, for non-exudative, sporadic GAS pharyngitis, the clinical diagnosis of GAS is hardly better than an even guess ([32]). To complicate matters, some viral infections, notably infectious mononucleosis and adenovirus, may also produce exudative pharyngitis. Laboratory confirmation is therefore required for precise diagnosis, particularly in settings where RF is still present, and certainly when RF is prevalent.

Laboratory confirmation of the presence or absence of GAS requires throat culture or rapid antigen detection tests (RADTs) . Although in the absence of an immune response, the presence of GAS by either test is only a presumptive diagnosis (approximately 25% or more may be carriers and thus false positives), a negative test by either of these methods is a powerful negative predictor of GAS pharyngitis (>95%). RADTs are currently quite popular with U.S. clinicians because they can be processed from fresh throat swabs and reported within hours ([33, 34]). They are available in convenient commercial kits. Whereas the specificity of some RADTs has been reported to be as high as 95%, their

sensitivity may be considerably less. Therefore, when greater precision of diagnosis is critical and the RADT is negative, a throat culture is still recommended. ([33], [34]). In current clinical practice, the practical value of throat cultures, especially for adults, has become controversial, especially where RF is no longer prevalent ([35,36]).

Throat cultures, however, have the advantage of revealing the presence of mucoid colonies on blood agar to alert clinical laboratories. Early detection of clusters of large mucoid GAS colonies in throat cultures signal danger ([3]). In association with RF, AGN, or invasive disease, such strains should be sent to research or reference laboratories for detailed study if we are to learn more about them. For example, in the 1950's, in throat cultures from naval recruits with epidemic pharyngitis at the Great Lakes Naval Training Center the sudden appearance of a highly encapsulated single M type regularly predicted the onset of an outbreak of ARF ([37]). In contrast, at the same base ARF was not nearly as common among the naval personnel in housed in separate, non-recruit training units. The strains recovered from these epidemics have been an important source of studies of GAS vaccines and other research. More recently, outbreaks of RF in the U.S. have been associated with a single clone belonging to a single M serotype of GAS ([23]). (see below, "RF pathogenesis").

Guidelines by expert committees of the American Academy of Pediatrics ([34]), the Infectious Disease Society of America ([33]), and the American Heart Association ([38]) favor greater precision in diagnosis by the use of throat cultures. In the interest of reducing excessive antibiotic usage that promotes emergence of resistant organisms, the American College of Physicians' published its own guidelines for diagnosis of GAS in adults ([35],[36]). These guidelines eschew throat cultures in favor of RADTs, and suggest that even the latter may be unnecessary in the presence of clearly expressed clinical manifestations of GAS pharyngitis. It is apparent that the threat of rheumatic fever, or other severe complications, and the economic resources available to a given population will influence the practicality of the use of laboratory tests for support of the diagnosis of GAS pharyngitis. Moreover, annual and seasonal variation in the severity of GAS disease may be another factor influencing the local perceived need for precision in the diagnosis of GAS pharyngitis.

ISSUES IN THE TREATMENT OF GAS PHARYNGITIS

Variation in the treatment of GAS pharyngitis should now be considered in relation to the varying prevalence of RF, invasive GAS diseases and AGN in different geographical and social settings. Despite more than a half century of intense clinical use, penicillin resistant GAS strains have not emerged. Group A streptococci are uniformly highly sensitive to the action of penicillin. For rapidly multiplying organisms, penicillin G is bactericidal in a concentration of 0.01 to 0.04 units/mL in a standard broth culture. Thus, sustained low bactericidal blood levels eradicate proliferating group A streptococci as well as high penicillin blood levels.

Since World War II, the treatment of GAS pharyngitis has been strongly directed toward the primary prevention of rheumatic fever and suppurative complications. Where rheumatic fever persists in the world, and particularly in undeveloped countries, primary rheumatic fever prevention is still a major consideration in the treatment of group A streptococcal pharyngitis. Such treat.ment should ensure effective penicillin levels for at least 10 days.([39]). Because this result can be achieved by a single intramuscular injection of 1.2 million units of benzathine penicillin G, or 600,000 units for children who weigh less than 27 kg or 60 pounds ([40]), this regimen is a favored one ([38]). Intramuscular injections of repository penicillins, however, produce some local pain and discomfort, and must be administered by physicians or nurses. Injectable .benzathine penicillin G for pharyngitis, therefore, has declined in popularity in developed countries in which ARFrheumatic fever is no longer feared. In such venues, uncertain as compliance with the full 10-day-regimen may be, oral penicillin, usually penicillin V, is currently most popular..

Penicillin V may .be given twice daily in 1.0 g doses and has been shown to be at least as effective as 0.5 g administered four times daily. Greater compliance has been seen with a twice-daily regimen. Oral cephalosporins are also highly effective in the treatment of streptococcal pharyngitis, and some reports show a slightly higher rate of eradication of convalescent carriage than that achieved with penicillin therapy ([41]). Despite these observations, penicillin remains the drug of choice because of its proven efficacy in preventing rheumatic attacks, its low cost, and its relatively narrow antibacterial spectrum. In non-epidemic settings in which rheumatic fever is rare or non-existent, shorter courses of oral penicillin that have been tried may be clinically effective. Based on older studies noted above, however, they are not adequate for prevention of RF when treating GAS pharyngitis due to rheumatogenic strains.

Ideally, treatment of GAS sore throat should be started promptly. However, delay of a few days while awaiting culture results does not interfere with primary prevention of ARF ([39]).

If penicillin allergy is suspected or known to exist, erythromycin may be used in divided doses not exceeding 1 g/d), also for a period of 10 days. Although erythromycin resistance of GAS is not a serious problem in most regions of the United States, this drug has caused GAS resistance with striking frequency when it has been used extensively as the first line drug for treatment of sore throat. Newer macrolides, azithromycin, clarithromycin are also as effective but are much more expensive. Treating streptococcal pharyngitis with bacteriostatic agents like sulfonamides does not prevent rheumatic fever. Sulfonamides are quite effective, however, as preventatives of GAS infection and are therefore used quite effectively as secondary prophylactic agents for rheumatic fever recurrences (see later). Tetracycline-resistant group A streptococci are prevalent in many areas, and therefore this drug is not recommended.

Insistence by some authors that antibiotic regimens produce total eradication of GAS pharyngeal carriage is, at least in my view, unrealistic. It is an outcome virtually impossible to achieve. Preventive antibiotic treatment of rheumatogenic GAS pharyngitis never achieved better than 90-95% GAS eradication rates ([39]). Moreover, from extensive clinical experience, GAS strains persisting following adequate therapy are usually attenuated, so that follow-up cultures and retreatment of asymptomatic patients with persistent throat carriage is not required ([38]). When more efficient eradication of throat carriage is desired, some authors have recommended that clindamycin, which is very effective but quite expensive, be used. Other broad-acting antibiotics (e.g., cepahlosporins, azithromycin, etc.) have been recommended to replace penicillin. In my view, recommendations for treatment with broad-spectrum antibiotics carry greater risk for emergence of resistant pathogenic throat flora, particularly pneumococci and staphylococci, are more expensive, and are unnecessary

"MASS" PRIMARY PROPHYLAXIS OF RF IN EPIDEMICS

When rheumatic sequelae are associated with a focal epidemic of streptococcal pharyngitis, prophylactic treatment of an entire populationcohort may be required (Fig 2) Such events are now rarenow except in military

populations or in closed institutions . A single injection of 1.2 million units of benzathine penicillin G administered to each person in the affected populationcohort affected has promptly terminated such epidemics ([37],[42,43,44]). Alternatively, continuous oral prophylaxis regimens of either penicillin G or V, as recommended for secondary prophylaxis (see below) may be employed for mass prophylaxis but are less effective.

Secondary prevention of RF: For patients who have had RF, protection from recurrences by continuous antibiotic prophylaxis is recommended by health authorities throughout the world ([45]). Upon establishing the diagnosis of acute RF, prophylaxis is initiated with either a single intramuscular injection of 1.2 million units of benzathine penicillin G, or a 10 day course of penicillin V orally. Prevention of recurrences of ARF is most effective by monthly injections of 1.2 million units of intramuscular benzathine penicillin G. ([38],[46,47]). In some parts of the world where rheumatic fever is still quite prevalent, such as Taiwan and Brazil, a few breakthroughs of recurrences have been reported on the monthly benzathine penicillin G regimen. In these reports, injections of the compound every three weeks have been recommended ([48, 49]). One should be sure, however, that the commercial formulation employed contains the full dose of 1.2 million units of benzthine penicillin G and not confusing formulations that contain smaller amounts of benzathine penicillin G mixed with shorter-acting penicillin G compounds. Also, the quality of the vehicle ensuring good suspension of the particles of this poorly soluble penicillin salt is also important to ensure the uniform delivery of a proper dose. Available preparations may not be of uniform quality in all parts of the world.

Oral prophylactic regimens are also effective but are less reliable. They are recommended when the risk of rheumatic recurrences is relatively low. Penicillin V orally is recommended in doses of 250 mg bid. Sulfadiazine is also about as effective for secondary prevention and is inexpensive. The recommended dose of oral sulfadiazine is 0.5 g once daily for patients who weigh less than 27 kg (60 pounds) and 1 g daily for heavier persons. For the rare patient who is sensitive to both penicillin and sulfonamides, erythromycin may be substituted in a dose of 250 mg twice daily.

Duration of secondary prophylaxis for rheumatic subjects (Table 1) depends on a number of variables that influence the rate of recurrences ([50]). . Such variables include the

presence or absence of rheumatic heart disease, the time elapsed from the previous attack, the number of previous attacks, and the severity of the antecedent infection (Table 2). To these should now be added variation in the local prevalence of rheumatogenic streptococci. In areas of the world where rheumatic fever is still rampant, patients with rheumatic heart disease who are exposed to children may have to be maintained on prophylaxis indefinitely. On the other hand, prophylaxis has been safely suspended after several years of treatment when rheumatogenic streptococci have been shown to have disappeared from a community ([51], [52]). For patients without rheumatic heart disease, the duration of prophylaxis may be shortened to approximately five years, depending again on the risk of exposure to GAS pharyngitis in cohorts and to the prevailing epidemiology of RF. The risks of travel to so-called "undeveloped countries" should be considered, particularly for patients with rheumatic heart disease.

Figure 1

Table 1: Duration of Secondary Rheumatic Fever Prophylaxis: Special Statement by the Committee on Treatment of Acute Streptococcal Pharyngitis and Prevention of Rheumatic Fever.*

Category	Duration
RF with carditis and residual heart disease (persistent valvular disease)	At least 10 y since last episode at least until age 40 yrs; or lifelong if indicated.
RF with carditis but no residual heart disease (no valvular disease)	10 yrs or well into adulthood, whichever is longer
RF without carditis	5 y or until age 21 y, whichever is longer

*Adapted from American Heart Association, 1995 (7567345)

Table 2. Ratio of Rheumatic Recurrences to Streptococcal Infections in patients Stratified for Heart Disease and for ASO Rise[1]

ASO rise*	Heart Disease	No heart disease
0-1	3/24 (13%)	1/72 (1%)
2	10/36 (28%)	2/46 (4%)
3	6/16 (37%)	4/32 (13%)
4	9/14 (65%)	9/25 (36%)

*Tube dilutions

[1] Taranta A, et al, Rheumatic fever in children and adolescents. Along-term epidemiological study of subsequent prophylaxis, streptococcal infections, and clinical sequelae IV. Relation of the rheumatic fever recurrence rate per streptococcal infectrion to the titers of streptococcal antibodies. Ann Intern Med 1964 60(Suppl 5) 5;47.

PROBLEMS WITH THE DIAGNOSIS OF RF

A clear diagnosis of RF, and particularly rheumatic carditis, is important since it commits an individual to prolonged prophylactic antibiotic therapy. As RF becomes rare in developed countries, its familiarity to younger physicians also wanes. Moreover, the diagnosis of RF may be particularly difficult when it presents as an isolated major manifestation. Unfortunately, RF remains a clinical syndrome without a single pathognomic feature. In the 1940s, T. Duckett Jones adopted the constellation of major manifestations of RF that were first recognized as a single disease at the end of the 19th century by William Cheadle ([53]). The Jones criteria ([54]) became particularly useful in clinical investigation to ensure admission to clinical studies of a uniform cohort of clear-cut cases of ARF. Thus, these guidelines avoid overdiagnosis but do not always capture the more subtle manifestations of the disease. The major manifestations are polyarthritis, carditis, and chorea, and less frequently, but no less characteristically, subcutaneous nodules and erythema marginatum.

In the 1960s, when antistreptolysin O and other GAS antibody titers generally became available to clinical laboratories a committee of the American Heart Association revised the Jones criteria suggesting that, particularly those of polyarthritis, could be strengthened by including evidence of antecedent GAS infection ([55]). Some limitations were emphasized; circumstances in which a diagnosis of ARF may be made without strict adherence to the Jones criteria ([56]). For example, in contrast to arthritis, chorea, the latest-appearing of the major manifestations following the antecedent infection, may present without any other major or minor features of ARF - so-called "pure chorea" (see below). Also, isolated acute carditis may first come to medical attention several months into or after the rheumatic attack. By then, antibody titers may have declined to normal levels and the minor manifestations of systemic inflammation (fever, ESR, C-reactive protein, etc) may have abated.

Most patients with recurrent ARF also fulfill the Jones criteria, but in some the diagnosis of a recurrence is less obvious. For example, when rheumatic valvular disease preexists, clear recognition of a new bout of carditis requires evidence of fresh cardiac injury such as pericarditis, acute cardiac enlargement and/or congestive heart failure, or a newly detected murmur from a valve not previously affected. The Jones Criteria, therefore, apply more readily to initial attacks, and more diagnostic latitude is sometimes needed to interpret recurrent carditis in patients with pre-

existing rheumatic heart disease. The steps in the evolution of the modification of the Jones Criteria have been reviewed recently in detail ([57]).

Isolated polyarthritis: the diagnosis of isolated polyarthritis is problematic because of the large differential diagnosis ([1],[3]). However, polyarthitis appears early in the rheumatic attack when streptococcal antibodies are at peak elevation. Therefore, the absence of significantly increased GAS antibodies at the onset of polyarthritis, is a useful negative predictor of the diagnosis of ARF and suggests a reactive arthritis due to another infection, such as rubella, Lyme disease, the enteric organisms causing Reiters disease, ankylosing spondylitis, etc. When GAS antibodies are increased, however, the diagnosis of ARF in isolated cases of polyarthritis remains presumptive, requiring months of close observation because such elevations may have been only coincidental GAS infections not causally related.

Chronicity of the arthritis, and particularly its recurrence in the absence of a new GAS pharyngeal infection, the appearance of joint deformity, or the presence of rheumatoid factor or DNA antibodies may eventually reveal a different disease, (e.g. rheumatoid arthritis, systemic lupus, polyarteritis, etc.). Although typically migratory, many authorities have observed patients with the polyarthritis of ARF that was not initially "migratory", but rather, "additive", persisting in many joints at once, and furthermore stubbornly "rebounding" once or twice after six week courses of anti-rheumatic therapy (more often with corticosteroids than NSAIDs ([1], [58]). In prospective studies of acute rheumatic attacks that occur in the absence of a new GAS infection, relapses of ARF have been noted as late as 5 weeks after completion of six weeks of antirheumatic therapy ([1]). And some patients do not respond brilliantly to salicylates, requiring supplemental corticosteroids. Nonetheless, these cases finally heal without deformity. In a few patients, rheumatic heart disease has been noted years later ([3]).

"Post-streptococcal reactive arthritis" (PSRA): At issue is whether to recognize PSRA as a separate disease from the polyarthritis clearly associated with ARF ([59],[60],[61],[62]). The characteristics of PSRA that are not typical of ARF are: persistence of arthritis for several months, non- migratory polyarthritis, poor response to NSAIDs, and, in adults, an apparent predilection for females. Thus, some authors claim that PSRA does not meet published Jones criteria and should therefore be excluded ([60]). Brief, textbook descriptions of the typical polyarthritis of ARF, however, such as those described in the Jones guidelines as "almost always migratory" and "lasting 4 weeks", are helpful guidelines but only an arbitrary and not necessarily a mandatory requirement for the diagnosis of ARF ([3]). Indeed, Jones criteria have been "required" only in rigorous clinical trials to assure homogeneity of patient cohorts.

Although a different etiology of polyarthritis may be inadvertently included, we prefer to retain so-called PSRA patients within the framework of the diagnosis of RF and administer antibiotic prophylaxis to them, but perhaps for a modified duration, the exact time dependent on other variables, particularly the prevalence of ARF in the community. Moreover, some PSRA patients apparently have developed rheumatic valvular disease after several years of follow-up, indeed, reported in some children to be as high as 7% of PSRA ([60]). Although the numbers of the reported cases of so-called PSRA are still rather few, and not always similarly defined, they deserve further study ([61],[62]). Whether or not PSRA is part of RF, it is generally agreed that secondary prophylaxis to prevent recurrences and possible heart disease is prudent.

ISOLATED CHOREA AND POST-INFECTIOUS AUTOIMMUNE NEUROLOGICAL DISEASES (PANDAS)

Sydenham's chorea may also occur as an isolated manifestion, and frequently recurs following new streptococcal pharyngitis ([1]). After puberty, Sydenham's chorea is almost entirely limited to women . Like polyarthritis, it is most often evanescent, over in a few weeks, but occasionally it may be stubborn, persisting for many months. The pathogenesis of chorea, (similar to that of the synovitis of polyarthritis), seems to be associated with immune complex disease produced by non-destructive antoantibodies localized to the basal ganglia and striatal system of the brain ([63],[64],[65],[66]). Severe chorea seems to respond sometimes to treatment with intravenous IgG ([67]) . It also seems to be closely related in pathogenesis to the so-called PANDAs (post-infectious autoimmune neurological diseases ([64], [65], [68]). These include tics, Tourettes syndrome, and obsessive-compulsive behavior, all of which have been observed in some patients during or after an attack of rheumatic chorea. PANDA cases that did not express choreiform movement and were not previously referred to rheumatic fever centers were more often referred to pediatric neurologists. Pandas are often associated with antecedent GAS infection ([69]) and some cases have clearly been shown

to be associated with deposition of streptococcal antigens in the basal ganglia ([65]).

If studies in progress reveal at least some of these neurological manifestations to be preventable by antistreptococcal prophylaxis, they might well be included, like PSRA, as variable features of the syndrome of ARF. This is notwithstanding the fact that, as in Sydenham's chorea, other autoimmune disease (e.g.,systemic lupus erythematosus) may occasionally cause them, just as SLE may also cause endocarditis. A possible association of PANDAS with rheumatic heart disease, such as seen in long-term follow-up of patients with chorea, should also be carefully studied. Currently, the role of GAS pharyngitis as a cause of recurrent episodes of obsessive-compulsive disorders in children without chorea or other PANDA manifestations is being evaluated.([69], [[[69a]]]). The relation of recurrences of all of the manifestions of the PANDAs could be assessed by continuous antistreptococcal prophylaxis, preferably with monthly benzathine penicillin G to insure compliance.

Eventually, the immunologic and host factors deciding the development of the major manifestations of ARF, their severity, and their chronicity may warrant separate etiological classifications other than their coexistence, as noted by T. Duckett Jones , "with a frequency exceeding chance". Meanwhile, in my opinion they still warrant the same prophylactic management currently advised for RF patients.

Isolated carditis: Isolated myocarditis or pericarditis without valvulitis is rarely, if ever, due to ARF ([1]). So, the finding of valvular involvement is critical to the diagnosis of rheumatic carditis and is much aided by non-invasive imaging methods.

Echocardiography (EC) and Doppler methods: Most cases of rheumatic carditis are not severe enough to be symptomatic and for the most part the diagnosis of isolated carditis has previously depended on auscultation alone. Approximately 80% or more of the cases of mitral regurgitation detected by EC are also readily diagnosed by the auscultation of experienced clinicians. The remaining so-called subauscultatory cases are usually those with the mildest degree of mitral or aortic regurgitation ([70]). More than 80% of these valvular lesions are likely to heal without scarring (see Treatment, below). To avoid overdiagnosis, experience with the echocardiographic features of the minimal lesions of rheumatic valvulitis is important in order to differentiate

functional degrees of valvular regurgitation ([70],[71,72]) especially in children and other, thin, active individuals with highly elastic valve rings, leaflets and chordae tendinae.

Although EC, particularly accompanied by Doppler studies, offers greater sensitivity and specificity for the assessment of valvular regurgitation it need not be considered essential for the diagnosis of RF by experienced primary care physicians in settings where the disease is common and medical resources limited ([56]). Nonetheless, cardiologists proficient in echo-Doppler technology now use this method routinely to detect abnormal valve structure and function more sensitively and accurately than can be achieved by auscultation alone. Despite the relatively good prognosis of "silent" rheumatic mitral regurgitation, EC can, indeed, provide a more accurate assessment of the presence and severity of valvulitis, especially in an era when cardiac auscultation has been taught less extensively and is used with less confidence by young clinicians. In any case, it is doubtful that such a powerful diagnostic tool as EC will be neglected in the assessment of valvular disease wherever the instrument is available, and certainly where its expense may not be too great a concern as in developed countries. It is now important to extend recent long term studies ([75]), to establish more precisely the natural history of the subauscultatory valvular rheumatic valvular regurgitation as diagnosed by echocardiography. Such information will further influence the choice and duration of secondary prophylaxis.

RIGHT VENTRICULAR ENDOMYOCARDIAL BIOPSY

When the characteristic murmurs of rheumatic carditis are detected early in the course of a rheumatic attack and are associated with other major and minor manifestations of ARF, such as arthritis and fever, the yield of useful additional clinical information from endomyocardial biopsy (EB) has been low. Its diagnostic sensitivity in one relatively large study was only 27% ([77]). EB has, however, confirmed the presence of underlying carditis in unexplained congestive heart failure of acute onset in some patients with preexisting rheumatic heart disease and elevated antistreptolysin titers, suggesting a rheumatic recurrence. In patients with chronic rheumatic heart disease, however, EB does not appear to provide additional diagnostic information. In my opinion, in patients with rheumatic carditis endomyocardial biopsy should be limited to clinical investigation.

Troponin 1 levels in rheumatic carditis are low (except when underlying a severe pericarditis, arguing against extensive myocardial muscle necrosis as a significant feature of rheumatic myocarditis ([78,79]). Earlier studies found that serum glutamic-oxalacetic transaminase (SGOT) levels are not elevated in acute carditis in the absence of toxic doses of salicylates ([80, 81]), supporting our view that rheumatic myocarditis is principally interstitial rather than severe cardiac muscle damage ([1]). The heart failure associated with acute rheumatic carditis is considered to be due primarily to severe valvular insufficiency, although severe interstitial myocardial inflammation causing myoicardial dysfunction has not been entirely excluded as a contributing factor.

TREATMENT OF RF

In a recent well-controlled trial of 59 patients with acute rheumatic fever, of whom 39 had carditis, intravenous gamma globulin did not affect the course of the illness. No detectable differences in the clinical, laboratory or echocardiographic parameters of the disease process were found between treated and control patients during the subsequent 12 months ([82]).

Treatment remains supportive. There is no longer significant doubt that corticosteroids, however symptomatically beneficial, do not prevent valvular damage ([83, 84]). For mild rheumatic carditis, lingering doubt in the minds of some investigators about the possible long-term benefit of corticosteroids over salicylates was based upon the results of but a few studies suggesting favorable outcomes of such treatment of minimal rheumatic mitral regurgitation ([84]). These minimal mitral murmurs are most difficult to standardize (perhaps EC will help) but spontaneous healing occurs in 80% or more of patients with minimal mitral regurgitation from acute RF (Table 3), so that the putative advantages of corticosteroids for mild cases of carditis are not likely to be resolved. For the present, most physicians choose to use corticosteroids over salicylates in rheumatic carditis simply because adrenalcortical hormones are more potent anti-inflammatory agents. Many authorities do not endorse this practice except for patients with severe carditis especially if with congestive heart failure. In such patients the powerful suppression of inflammation may at times make management easier by suppressing fever and reducing toxicity and anemia ([1], [85]). The new COX-2 inhibiting NSAIDs, though currently expensive, presumably may reduce the adverse gastrointestinal effects of large doses of aspirin, although for four to six-week therapeutic courses, such side effects have not been a great problem, especially in children. The use of the Cox-2 inhibitors might be limited to patients with as history of peptic ulcer. Because valvular scarring is suspected to be the result of cytotoxic cellular autoimmunity, anti-TNF drugs that delay or reduce joint destruction in rheumatoid synovitis may deserve a trial in severe acute rheumatic carditis to determine whether they might similarly reduce valvular injury and scarring.

Figure 2

Table 3. Prognosis in relation to cardiac status at the start of treatment*

Cardiac status at start of treatment	5 -year follow-up No. of cases	5 -year follow-up Percent with no murmur	10 year follow-up No. of cases	10 year follow-up Percent with no murmur
Carditis			80	94
None	71	96		
Questionable	32	84		
Murmurs				
Apical systolic				
Grade 1	39	82	27	70
Grade 11 and 111	60	68	50	74
+ middiastolic	44	48	38	63
Basal diastolic	45	53	45	60
CHF, or pericarditis,a	33	30	28	32
or both				
Preexisting RHD, CHF, or pericarditis,° or both		,		
Absent	80	30	60	40
Present	22	0	19	11

°RHD: rheumatic heart disease; CHF: congestive heart failure
* United Kingdom and United States Joint Report.: The natural history of rheumatic fever and rheumatic heart disease: Ten-year report of a cooperative clinical trial of ACTH, cortisone and aspirin. Circulation 1965;32:457-76.

CURRENT RESEARCH OF RF PATHOGENESIS

The agent: Frustratingly, the precise pathogenesis of the various manifestations of RF still eludes us even so many decades after the group A streptococcus was established as the sole etiologic agent of the disease. Some pathogenetic facts are clear, however: The antecedent infection must be pharyngeal and caused by the markedly virulent strains that since 1968 I have referred to as "rheumatogenic" ([26], [26a], [86,87]). This viewpoint is based on my personal study of GAS strains freshly isolated from patients with and without RF, and particularly strains clearly causing extensive military epidemics of RF ([3]). These strains have all been heavily encapsulated, possess large M protein molecules, are highly mouse virulent, extremely resistant to phagocytosis, do not produce serum opacity factor (OF) and are have so far been found within a limited number of M protein serotypes. They are primarily pharyngeal and do not primarily infect skin but they may cause invasive GAS infections secondarily by infecting wounds.. Much strain variation occurs within a given M protein serotype and therefore not all strains within

the M serotypes associated with RF are either highly virulent or rheumatogenic. That the latter tend to be clonal, is best illustrated by recent studies that revealed several outbreaks of RF in the Rocky Mountain areas of the U.S.A. to be caused by a single clone of M18. It was identifiable from other M18 strains by its unique, bacteriophage-induced erythrogenic toxin ([22], [23], [23a]).

As noted above, the entire genome of three M serotypes, M1, M3 and M18 have already been determined, ([20], [21], [22], [23]). Such analysis may help to establish the clonal nature of the strains that cause either RF, AGN or invasive streptococcal infections as well. Bacteriophage infection of the GAS genome is common and such genomic transformation by this agent as well as other causes of mutations may help account for the sudden appearance and focal outbreaks of RF and invasive disease. The tendency of such virulent strains to spread to contacts has been well demonstrated in nosocomial invasive GAS infections ([88]). What remains at issue is whether a rheumatogenic strain requires some unique toxin or antigen, or whether a number of highly virulent GAS strains can initiate the various manifestations of the rheumatic process in predisposed hosts.

The immune response: The immune response to every GAS antigen that has been studied is exaggerated in the RF patient when compared with patients recovering from GAS pharyngitis who do not develop RF. The rheumatic host, however, responds normally to challenge with non-streptococcal antigens ([89]). A plausible explanation for the exaggerated GAS immune response in RF is that the antecedent streptococcal infection causing RF was associated with the pharyngeal delivery of a particularly large load of antigen, enhanced by the superantigenic properties of M protein ([12]) and the various streptococcal toxins ([13]). Whether or not rheumatogenic strains require a unique antigen to initiate the disease, or whether intense antigenic stimulation alone may trigger a variety of immune responses to various antigens that then produce various manifestations of RF is not yet clear. Mimetic autoimmunity is a very attractive pathogenetic hypothesis ([63]) but evidence for its relevance is still indirect.

Immune complexes containing host antigens identical to some streptococcal epitopes have been identified in synovia, heart and brain ([63], [65], [66], [90]). These may cause the non-destructive, reversible rheumatic inflammation seen in joints, skin and brain (polyarthritis, nodules/ erythema, chorea and PANDAs .Cytotoxic autoimmunity, on the other hand, has

been hypothesized to cause destruction of heart valves ([91],[92],[93]). But how is such putative autoimmune intolerance be initiated? Do large amounts of group A streptococcal antigens swallowed and absorbed in the course of GAS pharyngitis result in an intense immunologic stress that breaks immune tolerance to certain antigens in susceptible hosts? Knowledge of the immunophysiology of the immune system of the gut is still evolving, particularly with regard to its role in immune tolerance and autoimmunity.

Other host factors: Rheumatic recurrences are an obviously unique host response but one that may be either genetic or acquired, or both. RF is rare in very young children, and reaches its peak incidence between 6 to 15 years of age after repeated group A streptococcal pharyngeal infections. The importance of genetic predisposition is still unclear. ARF is less concordant in identical twins (about 20%) than it is in twins with other immunologic diseases such as atopic allergy and hyperthyroidism, or in infections such as tuberculosis or poliomyelitis ([94]). No clear association of class I human leukocyte antigens (HLAs) with rheumatic fever has been found. The trend toward an asso..ciation of HLA B5 may be related to an increased response to streptococcal antigens produced by these persons. HLA DR2, 3, and 4 have been detected with increased frequency in black, white, and Indian patients, respectively, notably those with rheumatic heart disease. HLA DR1 and DRw6 were observed with increased frequency in South African black persons.([96],[97]). Recent analyses indicate that certain class II alleles/haplotypes are associated with risk or protection from rheumatic heart disease and that these associations are stronger and more consistent when analyzed in patients with relatively more homogeneous clinical manifestations ([98]).

In contrast to the lack of a definitive association with specific HLA DR antigens, a strong relationship has been detected with a non HLA B cell antigen originally designated 883 and detected in widely distributed populations from New York to Bogota, Colombia, and New Mexico to India ([97], [99]). Studies with a series of monoclonal antibodies directed against B cells from rheumatic fever patients have identified another B cell alloantigen labeled D8/17.([99]). It is present in a relatively large percentage of the total B cells of rheumatic fever probands: 33.5% compared with 14.6% and 13%, respectively, of the B cells of unaffected siblings and parents. Two sets of identical twins were included in these studies. The proband with rheumatic fever had 43% positive B cells, whereas the unaffected twin

had only 15%. In the other set of unaffected twins, 20% and 10%, respectively, had D8/17 B cells. Thus, this B cell alloantigen is not unique to rheumatic hosts but is expressed more vigorously in those who have had rheumatic fever. Thus, it may be an acquired feature of the GAS exaggerated immune response. At any rate, perhaps a predisposing host factor, present to some degree in all persons, is more expressible in rheumatic hosts who are stimulated by antigens, and perhaps, as recently shown ([100]), by the varied host responses to superantigens contained in virulent pharyngeal strains of GAS (see below).

PROSPECTS FOR A VACCINE AGAINST RHEUMATIC FEVER

Because immunity to GAS is type specific and dependent on antibodies to M protein, attempts at vaccine production have focused primarily on M protein purification. Since the extraction of M protein by Rebecca Lancefield ([101]), its further purification has led to its molecular definition ([102,103]). A clean separation of the type-specific N-acetyl terminal peptide (the type specific antigenic determinant) from the proximal part of the M molecule has been achieved freeing it from the more proximal region of the M molecule that contains the epitopes cross-reactive with heart, brain, skin and synovial tissue antigens . The terminal type-specific M epitope is antigenic in humans without raising host-tissue cross reactions and it is non-toxic in human skin ([104]). An effective vaccine against rheumatic fever may not require the inclusion of all known M protein serotypes, but rather those identified most clearly as containing rheumatogenic strains. In fact, a recombinant, multivalent vaccine containing the type-specific epitopes of some 26 M serotypes associated the great majority of serious GAS infections is currently under field trial ([105]). Newly identified M types containing dangerous strains could be added subsequently as necessary. The potential for the production of IgA antibodies to M proteins by employing such preparations for oral human immunization is suggested by recent experimental studies ([106]). The protective role of mucosal Iga and its production by oral streptococcal vaccines is under vigorous current investigation.

SUMMARY AND CONCLUSIONS

Rheumatogenic strains of GAS still infest the majority of the world's population. Jet travel may at any time spread such strains from high to low-risk regions of the globe. Dangerous GAS strains may emerge in any location by mutation, transduction, or by other as yet unknown environmental factors. Adverse social conditions causing crowding affect

their spread. Therefore, in my opinion the appearance of but one case of RF in any community should be greeted with alarm and all infected contacts among cohorts identified and properly treated in the same fashion as the contacts of the recently reported nosocomial septic infections caused by clones of invasive strains ([107]). Vaccines are under trial that may afford protection against the most virulent and dangerous of known GAS strains. If we learn how to identify and immunize safely susceptible hosts, prevention will be greatly simplified. Meanwhile, even those privileged to live in affluent surroundings must continue to diagnose and treat GAS pharyngitis effectively, remain alert to the threat of ARF , and continue to strive toward the eradication of RF from the human race.

CORRESPONDENCE TO

Gene H. Stollerman, M.D. Professor of Medicine & Public Health Boston University #21 The Courtyard Hanover, New Hampshire 03755 Email: gstollerman@valley.net Tel/Fax 603-643-3336

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Author Information

Gene H. Stollerman, MD

Professor of Medicine & Public Health, Boston University