Acute rheumatic fever

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Acute rheumatic fever (ARF) and its chronic sequela, rheumatic heart disease (RHD), have become rare in most affluent populations, but remain unchecked in developing countries and in some poor, mainly indigenous populations in wealthy countries. More than a century of research, mainly in North America and Europe, has improved our understanding of ARF and RHD. However, whether traditional views need to be updated in view of the epidemiological shift of the past 50 years is still to be established, and improved data from developing countries are needed. Doctors who work in populations with a high incidence of ARF are adapting existing diagnostic guidelines to increase their sensitivity. Group A streptococcal vaccines are still years away from being available and, even if the obstacles of serotype coverage and safety can be overcome, their cost could make them inaccessible to the populations that need them most. New approaches to primary prevention are needed given the limitations of primary prophylaxis as a population-based strategy. The most effective approach for control of ARF and RHD is secondary prophylaxis, which is best delivered as part of a coordinated control programme.

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Acute rheumatic fever (ARF) results from an autoimmune response to infection with group A streptococcus. Although the acute illness causes considerable morbidity and some mortality, the major clinical and public-health effects derive from the long-term damage to heart valves—ie, rheumatic heart disease (RHD). Over the past century, as living conditions have become more hygienic and less crowded, and nutrition and access to medical care have improved, ARF and RHD have become rare in developed countries. The introduction of antibiotics has also helped to reduce the burden of disease, though to a lesser extent than these other factors.[1–4] ARF and RHD are now largely restricted to developing countries and some poor, mainly indigenous populations of wealthy countries. This change in the epidemiology of ARF has not been matched by a proportional expansion of research and public-health activities in developing countries. Whether the principles that underlie ARF and RHD management and control that arose mainly from research in North America and Europe during the early and mid-20th Century remain appropriate for the populations that are now affected needs to be established. In this Seminar, we explore advances in ARF and highlight areas of controversy that need to be researched in a developing world context.[5–8]

Epidemiology

According to WHO,[9] at least 15·6 million people have RHD, 300 000 of about 0·5 million individuals who acquire ARF every year go on to develop RHD, and 233 000 deaths annually are directly attributable to ARF or RHD. However, these estimates are based on conservative assumptions, so the true disease burden is likely to be substantially higher. Furthermore, the overall quality of epidemiological data from developing countries is poor, particularly with respect to research documenting the incidence of ARF.[9]

The incidence of ARF in some developing countries exceeds 50 per 100 000 children. The highest reported rates are in indigenous populations of Australia and New Zealand (table 1).[10–29] For example, the incidence rate in school-age Pacific Islander children in New Zealand is 80–100 per 100 000,[13] and in Aboriginal children of central and northern Australia, rates of 245–351 per 100 000 are documented, though community-based surveillance suggests that the true incidence exceeds 500 per 100 000.[29,30] By contrast, the most recent and representative ARF incidence data for an industrialised country come from the non-indigenous population of New Zealand,[13] for which the incidence is less than ten per 100 000 children. Gordis and colleagues[1] reported similar rates from Baltimore, MD, USA, in the late 1960s, and there have been several outbreaks of ARF in middle-class populations in the intermountain region of the USA since the mid-1980s associated with mucoid strains of group A streptococcus, particularly of M type 18.[31]

The prevalence of RHD in children aged 5–14 years is highest in sub-Saharan Africa (5·7 per 1000), the Pacific and Indigenous populations of Australia and New Zealand (3·5 per 1000), and southcentral Asia (2·2 per 1000),[9] and lowest in developed countries (usually 0·5 per 1000). In many emerging market economies the prevalence is falling.[9]

ARF is a rare disease in the very young; only 5% of first episodes arise in children younger than age 5 years and the disease is almost unheard of in those younger than 2 years.[32] First episodes of ARF are most common just

Search strategy and selection criteria

To ensure that the latest articles were reviewed, we searched our own reference libraries, the Cochrane Library (all dates), and MEDLINE (2000–2004) with the search terms "rheumatic fever" or "rheumatic heart disease". We selected relevant articles published in any language and included several review articles or book chapters because they provide comprehensive overviews that are beyond the scope of this Seminar.

	Country	Year	Population subgroup	Age (years)	ARF incidence (per 100 000 per year)
Cernay et al, 1993[10]	Slovenia	1990–91		0–14	0·7
Lopez, 2000[11]	Cuba	1996		5–14	2·7
Noah, 1994[12]	Barbados	1986–90		0–19	8
Lennon, 2000[13]	New Zealand	1982–97	European descent	5–15	<10
Kermani and Berah, 2001[14]	Algeria	1997–2000		4–19	11·1 (1997) 6·2 (2000)
Eltohami et al, 1997[15]	Qatar	1984–94		4–14	11·2
Eshel et al, 1993[16]	Israel	1980–90		5–15	15·5
Carp, 1999[17]	Romania	1999		5–15	16·5
Baker et al, 2000[18]	New Zealand	1988–97	All	5–14	16·7
Folomeeva and Bennevolenskaia, 1996[19]	Russia	1994		"Children"	18
Omar, 1995[20]	Kuala Lumpur	1981–90		"Children"	21·2
Kechrid, 1997[21]	Tunisia	1990		4–14	30
Hasab, 1997[22]	Oman	1997		6–18	40
Lennon, 2000[13]	New Zealand	1982–97	Maori	5–15	40–80
Kayemba and Dupuis, 1993[23]	Martinique	1987–91		5–14	53
Padmavati, 2001[24]	India	1984–95		5–14	54
Lopez, 2001[25]	Mexico	1994–99		5–20	70
Lennon, 2000[13]	New Zealand	1982–97	Pacific Islanders	5–15	80–100
Australian Institute of Health and Welfare[30]	Australia	1989–2002	Aboriginal	5–14	245–351
Meira, 1995[26]	Brazil	1992		10–20	360
Richmond and Harris, 1998[28]	Australia	1988–92	Aboriginal	5–14	375
Carapetis et al, 2000[29]	Australia	1987–96	Aboriginal	5–14	508

Table 1: **Incidence of ARF in children and adolescents in studies published since 1990**

before adolescence, wane by the end of the second decade, and are rare in adults older than age 35 years (figure 1).[29,33] Recurrent episodes are especially frequent in adolescence and early adulthood, and occasional cases are seen in people older than age 45 years.[34] RHD usually results from the cumulative damage of recurrent episodes of ARF, although initial attacks can lead directly to RHD.[35,36] The prevalence of RHD increases with age, peaking in adults aged 25–34 years (figure 1), reflecting ARF activity in previous decades.[30] In young patients, mitral valve regurgitation is the predominant cardiac lesion, but mitral stenosis becomes progressively more common with increasing age.[37] This trend, whereby the incidence of ARF peaks in childhood and adolescence, but the prevalence of RHD peaks in adulthood, has been documented in studies done in the USA, in Aboriginal Australians, in India, and in Burma, and is likely to be seen in all populations with high rates of RHD.[36,38,39]

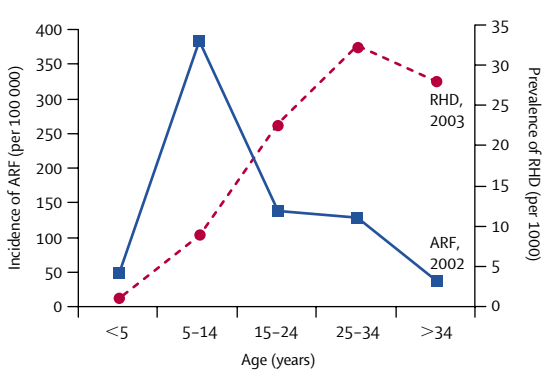

Figure 1: **Incidence of ARF in 2002 and prevalence of RHD in 2003 by age in Aboriginal Australians from the top end of the Northern Territory (personal communcation, Top End RHD Control Program, Department of Health and Community Services, Darwin, Australia)**

In many populations, ARF and RHD are more common in females than males.[40] Whether this trend is a result of innate susceptibility, increased exposure to group A streptococcus because of greater involvement of women in child rearing, or reduced access to preventive medical care for girls and women is unclear.

Although certain ethnic groups have high rates of ARF and RHD—for example Maori and Pacific Island people in New Zealand, Samoan people in Samoa and Hawaii, and Aboriginal people in Australia[13,30,41,42]—an association with ethnic origin has not been identified. There is some evidence that between 3% and 6% of any population is susceptible to ARF.[29]

Pathogenesis

Although the pathogenesis of ARF and RHD remains somewhat elusive, ARF is clearly the result of an exaggerated immune response to specific bacterial epitopes in a susceptible host (figure 2).

The organism

That some strains of group A streptococcus are more likely to cause ARF than others is a widely accepted notion.[43–46] This rheumatogenicity has traditionally been considered a feature only of strains belonging to certain M serotypes. However, some have challenged this theory, arguing instead that rheumatogenicity is not restricted to organisms belonging to only a few serotypes. Classically rheumatogenic M serotypes are,

for instance, infrequently found in several communities with high burdens of ARF and RHD, where newly identified serotypes or those most often associated with skin infections have been linked with disease.[47–49]

Other distinctions between rheumatogenic and non-rheumatogenic strains of group A streptococcus have been sought. In developed countries, strains of group A streptococcus found in the throat and those found on the skin are usually quite different,[50,51] and two antigenic groups (class I and II, respectively) have been identified in vitro.[52] Class II strains bind fibronectin, produce serum opacity factor (SOF), and are associated with poststreptococcal glomerulonephritis. Class I strains, however, are predominantly SOF-negative and are associated with ARF.[53] The arrangement on the group A streptococcus chromosome of *emm* and *emm*-like genes further allows organisms to be classified into one of five groups—groups A–C are associated with throat infections and ARF, group D with skin infections, and group E with infections at either site.[54]

However, results of studies done in tropical and subtropical populations, where rates of ARF and RHD are high, indicate no definitive association between group A streptococcus *emm* sequence type, class, or pattern group, and site of infection or ability to cause disease. In an Australian Aboriginal community, serotyping of group A streptococcus isolates suggested that skin lesions were the principal tissue reservoir for all strains of group A streptococcus irrespective of site of isolation.[55] In Thailand, *emm* sequence typing did not differentiate skin or throat strains associated with ARF or poststreptococcal glomerulonephritis, and there was clear evidence of new sequence types, resulting from genetic recombination between different strains of group A streptococcus.[49] In Aboriginal Australian, Saudi Arabian, and Thai patients, serological responses to class I epitopes did not distinguish patients with ARF or RHD from controls.[56]

That the distinction between rheumatogenic and non-rheumatogenic strains of group A streptococcus, and between those with trophism for the skin or the throat, is blurred in places with high rates of superficial infection with group A streptococcus is not surprising. In such settings, multiple genetically-different strains of group A streptococcus circulate at the same time, often within small populations. Different strains are sometimes even isolated from individual impetigo lesions.[57–59] Multilocus sequence typing identified substantial genetic recombination between so-called skin and throat strains of group A streptococcus[60] and various new combinations of *emm* and housekeeping genes in a small community with high rates of ARF and group A streptococcus impetigo.[61] The virulence of group A streptococcus might be enhanced in settings that favour rapid person-to-person transmission.[62] Furthermore, horizontal transfer of genetic information between strains of group A streptococcus complicates the search for the factors that cause ARF.

The host

In the 19th century, familial clustering suggested that ARF and RHD were hereditary,[63] possibly transmitted in autosomal recessive fashion with limited penetrance.[64] Results of studies in twins indicated a stronger genetic link for chorea than for arthritis and carditis.[65,66]

Numerous studies have linked specific genetic markers with ARF and RHD. The lack of consistent findings of HLA associations with ARF and RHD in older studies has been attributed to the use of serological rather than molecular typing and the heterogeneity of clinical patterns of ARF and RHD analysed.[67] Use of molecular techniques has led to identification of associations between disease and HLA class II alleles, though the particular alleles associated with apparent susceptibility or protection differ between populations.[67–71] Associations have also been described with high concentrations of circulating mannose-binding lectin[72] and polymorphisms of transforming growth factor-b 1[73] and immunoglobulin genes.[74]

A potentially important advance has been the identification of specific B-cell alloantigens associated with susceptibility to ARF and RHD. When mouse monoclonal antibodies were prepared against B cells from patients with RHD, one (D8/17) reacted with significantly higher numbers of B cells from patients with ARF or RHD than controls.[75] D8/17 was expressed in a high proportion of B cells in patients with ARF or a

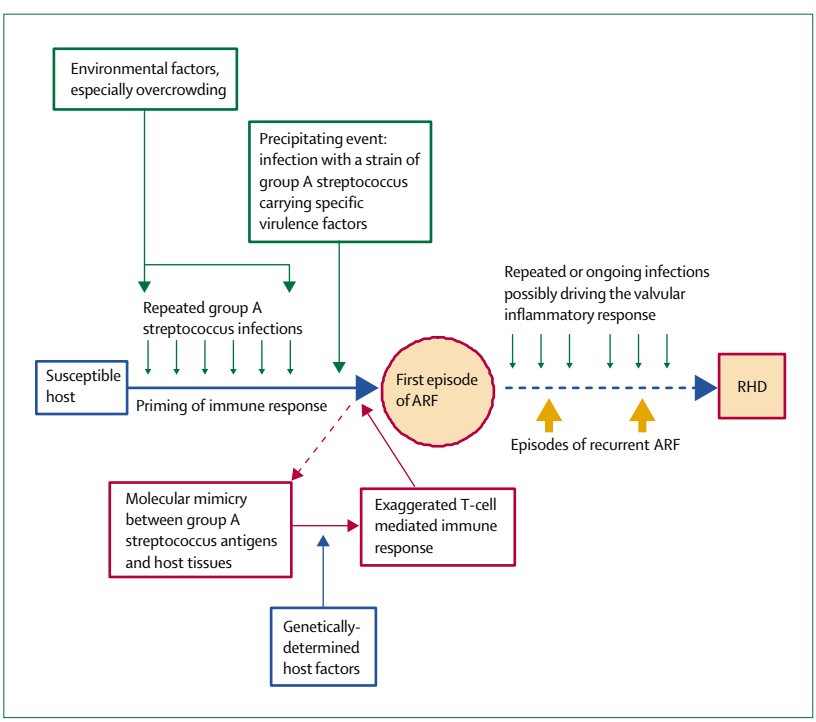

Figure 2: **Pathogenetic pathway for ARF and RHD**

history of ARF and in a moderate proportion of B cells in first-degree family members, suggesting that the marker is an indicator of inherited susceptibility.[75] The D8/17 antibody binds to a non-HLA protein on the surface of B cells and cross-reacts with human cardiac, skeletal, and smooth muscle, and with recombinant streptococcal M protein, suggesting that D8/17 antigen acts as a binding site for group A streptococcus on B cells.[76]

A strong association between the expression of D8/17 and ARF and RHD exists in several populations worldwide, including North America, the Caribbean, Israel, Russia, Mexico, and Chile.[75,77–81] There are notable exceptions. One US group found no association between the proportion of B cells expressing the D8/17 alloantigen and ARF.[82] In India, different monoclonal antibodies (PG-12A, PG-13A, and PG-20A) raised against B cells from Indian patients with RHD were better than D8/17 at distinguishing those with ARF or RHD from controls.[83,84] Further investigation is needed before B-cell alloantigen markers can be used to identify individuals with, or at risk for, ARF or RHD.

The infection

Results of studies done during the first half of the 20th Century established the tenet that only pharyngeal infection with group A streptococcus causes ARF.[6,85] This notion is supported by strong epidemiological and laboratory evidence.[86] ARF did not follow group A streptococcus skin infection and documented outbreaks of impetigo caused glomerulonephritis but not ARF.[87] The role of group A streptococcus infection is complex, however, and repeated infection is necessary to prime the immune response, quantitatively and qualitatively, before the first episode of ARF occurs.[88] We have hypothesised that, in tropical countries with a high prevalence of both pyoderma and RHD, skin infections caused by group A streptococcus have a priming role or even cause ARF, either directly or by subsequent infection of the throat.[89] Another hypothesis is that group C or G streptococci play a pathogenic part.[90] These organisms are more commonly isolated than group A streptococcus from the throat in tropical settings and can acquire virulence factors by horizontal transmission from group A streptococcus.[91,92]

The immune response

The autoimmune response that causes ARF might be triggered by molecular mimicry between epitopes on the pathogen (group A streptococcus) and specific human tissues.[88,93,94] The structural and immunological similarities between streptococcal M protein and myosin —both alpha-helical, coiled-coil molecules—seem essential to the development of rheumatic carditis. Lewis rats immunised with streptococcal M protein or selected M protein fragments developed myocarditis and valvulitis.[95,96] T cells from immunised rats proliferate in response to both the group A streptococcus M protein and cardiac myosin, but not to skeletal muscle myosin, whereas lymphocytes from control rats do not proliferate in response to any of the three antigens.[97] CD4+ T cells from patients with RHD proliferate in response to group A streptococcus M protein and heart tissue antigens with a degenerative antigen recognition pattern.[98] Normal cardiac cell turnover might result in the sensitisation of host T cells to the host's own cardiac myosin, which is usually intracellular and thus sequestered from the immune response.[97,99] These T cells might then be recalled by subsequent exposure to cross-reactive streptococcal M protein epitopes. The immunological response could be accentuated by raised cytokine concentrations, leading to the idea that streptococcal superantigens help to drive the process.[100,101]

However, valvular disease, rather than acute myocarditis, is responsible for most of the cardiac morbidity and mortality of ARF.[102–105] Myosin is not present in cardiac valves, so how can an immune response against myosin induce valvulitis? The initial damage to the valve might be due to the presence of laminin, another alpha-helical coiled-coil molecule present in the valvular basement membrane and around endothelium, and which is recognised by T cells against myosin and M protein.[106] There is also evidence that antibodies to cardiac valve tissues cross-react with N-acetyl glucosamine in group A carbohydrate.[94,107] An exaggerated antibody response to group A carbohydrate was noted in patients with ARF, and titres remained raised in individuals with residual mitral valve disease, providing further support for the notion that these antibodies cause valve damage.[108] Whether the initial valvular insult is due to antibody or cell-mediated immunological damage is uncertain, but the subsequent damage seems to be caused by T-cell and macrophage infiltration.[94,109,110]

Clinical features and diagnosis

The main clinical features of ARF are outlined in the Jones Criteria,[111] which were established in 1944 and then modified,[112] revised twice,[113,114] and updated (panel)[115] by the American Heart Association. Every revision increased the specificity but decreased the sensitivity of the criteria,[8,116,117] largely in response to the steadily declining incidence of ARF in developed countries. In regions of the world where ARF is endemic or epidemic, however, and where the risk associated with missed diagnoses—lack of provision of secondary prophylaxis to prevent recurrent ARF and worsening RHD—might outweigh the consequences of over-diagnosis, the 1992 Jones criteria might not now be sufficiently sensitive. As such, the 2002–03 WHO criteria[8] which, among other things, specified less stringent requirements for the diagnosis of recurrent ARF in patients with established RHD should probably be adopted (panel). The Jones and the WHO criteria are only diagnostic guidelines,

however, and should be adapted in certain circumstances, for example to increase sensitivity of diagnosis in populations at high risk of ARF.

Arthritis and arthralgia

In some regions, for example, patients with aseptic monoarthritis or migratory polyarthralgia, and those with classic migratory polyarthritis, are diagnosed with a major joint manifestation of ARF. Many patients with ARF who live in India and Australia have less severe joint involvement,[118,119] possibly as a result of early administration of anti-inflammatory medication, often self-prescribed or given before ARF is considered or confirmed.[8] It is noteworthy that the original Jones criteria included arthralgia as a major manifestation.[111]

Patients with arthritis not typical of ARF, but who have recently had a streptococcal infection, are said to have post-streptococcal reactive arthritis (PSRA). This form of arthritis generally affects the small joints of the hand, is less responsive to anti-inflammatory treatment, and does not carry a risk of accompanying carditis.[120] However, some patients do go on to develop ARF, suggesting that they originally had ARF rather than PSRA.[120,121] Because of the lack of a clear distinction between PSRA and ARF, we recommend that a diagnosis of PSRA is not made in patients from populations with a high incidence of ARF. If such a diagnosis is made, patients should receive secondary prophylaxis for at least 5 years, compared with the 1-year prophylactic course given to patients with PSRA from low-risk populations.[120]

Carditis

Use of echocardiography to diagnose ARF is controversial, especially when there is clinically inaudible mitral or aortic regurgitation.[122,123] The Jones criteria[115] state that so-called subclinical carditis (valvular damage detected only by echocardiography) cannot lead to a diagnosis of ARF unless one or more of the other major manifestations of the disease are also present. The report[8] from the WHO expert committee recognises the usefulness of echocardiography in providing supporting evidence for the diagnosis of rheumatic carditis in the presence of an equivocally pathological murmur or in patients with polyarthritis and equivocal minor manifestations. They agree that echocardiography can be used to diagnose subclinical acute rheumatic carditis and silent indolent rheumatic carditis, which they recommend be managed as RHD until proven otherwise. However, the committee did not suggest that echocardiographically-diagnosed subclinical carditis be added to the Jones criteria in the acute setting.

Subclinical valvular damage in ARF has been noted worldwide.[83,124–137] One report[138] from India, however, describing 28 patients with polyarthritis or chorea did not note its presence. Clear criteria exist to help experienced echocardiographers in ARF-endemic areas distinguish pathological from physiological regurgitation.[8,126] Although clinical examination remains the mainstay of diagnosis of rheumatic carditis, and many areas of the developing world do not have access to colour flow doppler echocardiography or experienced echocardiographers, doctors who work in hospitals where these resources are available are using echocardiography to help make and confirm diagnoses of ARF. Echocardiography also avoids over-diagnosis of ARF, by excluding flow murmurs and congenital heart disease in up to 20% of suspected cases.[135,139]

Whether subclinical rheumatic valvular damage has a different prognosis to clinical carditis is unknown. Results of three studies[130,133,140] indicate persistence of valve lesions in small numbers of patients with subclinical rheumatic carditis after 6 months to about 8 years. However, larger studies with longer follow-up times are needed. Preliminary data from New Zealand suggest that the inclusion of subclinical carditis as a major manifestation in the Jones criteria would affect

Panel: **Diagnosis of ARF[8,115]**

Jones criteria (1992)[115]

Two major or one major and two minor manifestations must be present, plus evidence of antecedent group A streptococcus infection

Chorea and indolent carditis do not require evidence of antecedent group A streptococcus infection

Recurrent episode requires only one major or several minor manifestations, plus evidence of antecedent group A streptococcus infection

Major manifestations

Carditis

Polyarthritis

Chorea

Erythema marginatum

Subcutaneous nodules

Minor manifestations

Arthralgia

Fever

Raised erythrocyte sedimentation rate or C-reactive protein concentrations

Prolonged PR interval on electrocardiogram

Evidence of antecedent group A streptococcus infection

Positive throat culture or rapid antigen test for group A streptococcus

Raised or rising streptococcal antibody titre

WHO criteria (2002–03)[8]

Chorea and indolent carditis do not require evidence of antecedent group A streptococcus infection

First episode

As per Jones criteria[115]

Recurrent episode

In a patient without established RHD: as per first episode

In a patient with established RHD: requires two minor manifestations, plus evidence of antecedent group A streptococcus infection. Evidence of antecedent group A streptococcus infection as per Jones criteria, but with addition of recent scarlet fever

the diagnosis of ARF in only about 10% of cases (NJW, unpublished data). In our opinion, where the risk of recurrence of ARF is high, subclinical carditis should be considered as part of the spectrum of RHD.

Fever

Fever associated with ARF is generally defined as an oral or tympanic temperature of 38°C or higher.[101] Some doctors, however, extend this definition to include a history of fever with the current illness, which allows febrile patients who have received anti-inflammatory medication before a temperature is documented—a fairly common situation in remote settings—to satisfy this minor manifestation.

Recurrent ARF

The latest version of the Jones criteria,[115] specifies that the criteria apply only to first episodes of ARF, and that recurrences should be diagnosed on the basis of the presence of one major or several minor manifestations. This change recognises that patients with a history of ARF have a relatively high risk of further episodes compared with the wider community. Since recurrences are the major cause of worsening heart damage, greater sensitivity rather than specificity of diagnosis is warranted. Furthermore, recurrences sometimes cause only subtle clinical manifestations.[115,141,142] The WHO criteria[8] allow for the diagnosis of recurrent ARF in a patient with RHD to be based only on minor manifestations, which is a welcome advance. We do not apply different diagnostic criteria to patients in high-risk populations who do and do not have established RHD, since we consider them all at risk of developing cardiac damage in the event of recurrences. For example, we have shown[143] that more than half of patients who have no evidence of carditis during episodes of Sydenham's chorea subsequently develop RHD. However, we also believe that, in the absence of major manifestations, a recurrence should only be diagnosed in the presence of a joint manifestation—eg, polyarthralgia—or when there is evidence of cardiac involvement—eg, a prolonged PR interval on electrocardiogram (panel).

The need to be discerning in the diagnosis of recurrences is especially important in populations with endemic group A streptococcus-associated skin infections. In these settings, most children might have serological evidence of recent group A streptococcus infection, so that the diagnosis of ARF relies almost entirely on the clinical features. For example, in Aboriginal children in three remote communities of northern Australia,[144] the median titres of antibodies against streptolysin and DNase B were 256 IU and 3172 IU, respectively. One-off streptococcal serology is difficult to interpret in this population. Relying on rising titres in paired sera might not always be appropriate in these circumstances because titres might already be at or near to their peak at the time of presentation with ARF (because of the latent period between infection with group A streptococcus and ARF onset).[145] Additionally, identification of a four-fold rise in titre when the baseline titre is very high is difficult.

Until a definitive diagnostic test is available for ARF, there will be debate about how to balance the sensitivity and specificity of different clinical criteria for the diagnosis of a disease for which the manifestations are shared by many other diseases (table 2).[8,146] The American Heart Association has not embraced the notion of more sensitive criteria for populations with high incidences of ARF. As such, doctors who work in these settings should use their own judgment in patients in whom ARF is the most likely diagnosis.

Treatment

Not all treatments for ARF have been tested in randomised controlled trials. Some are based on anecdotal evidence, common sense, and proven safety. For example, penicillin is considered mandatory for the eradication of possibly persistent group A streptococcus infection of the upper respiratory tract, though this treatment has not been shown to alter the cardiac

	Presentation		
	Polyarthritis and fever	Carditis	Chorea
Differential diagnoses	Septic arthritis (including gonococcal)	Innocent murmur	Systemic lupus erythematosus
	Connective tissue and other autoimmune disease*	Mitral valve prolapse	Drug intoxication
	Viral arthropathy†	Congenital heart disease	Wilson's disease
	Reactive arthropathy†	Infective endocarditis	Tic disorder‡
	Lyme disease	Hypertrophic cardiomyopathy	Choreoathetoid cerebral palsy
	Sickle cell anaemia	Myocarditis—viral or idiopathic	Encephalitis
	Infective endocarditis	Pericarditis—viral or idiopathic	Familial chorea (including Huntington's disease)
	Leukaemia or lymphoma		Intracranial tumour
	Gout and pseudogout		Lyme disease
			Hormonal§

*Includes rheumatoid arthritis, juveline chronic arthritis, inflammatory bowel disease, systemic lupus erythematosus, systemic vasculitis, sarcoidosis. †Mycoplasma, cytomegalovirus, Epstein-Barr virus, parvovirus, hepatitis, rubella vaccination, and Yersinia spp and other gastrointestinal pathogens. ‡Possibly including PANDAS (paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection). §Includes oral contraceptives, pregnancy (chorea gravidarum), hyperthyroidism, hypoparathyroidism

Table 2: **Differential diagnoses of common presentations of ARF**[8,146]

outcome after 1 year in controlled studies.[147,148] Similarly, long-term bed rest accelerated recovery from carditis and reduced the incidence of relapse before penicillin was available,[149] but since its emergence no randomised studies have been done. Although most patients with ARF need bed rest early in their illness, we recommend gradual mobilisation once the initial symptoms have begun to resolve.

Salicylates lead to rapid resolution of fever, arthritis, and arthralgia.[150] Naproxen has also been used successfully in small case series and in one small randomised trial.[151,152] However, the available evidence suggests that salicylates should not be used for the treatment of carditis, and results of comparisons of salicylates with no treatment or bed rest alone[150,153] suggest that they do not decrease the incidence of residual RHD. Results of a randomised controlled trial[154] showed that patients treated with aspirin for 12 weeks had a similar prevalence of murmurs 1 year later as did untreated controls. Findings of meta-analyses[155,156] indicate no benefit of salicylates over corticosteroids or vice-versa in reducing the subsequent development of RHD. We restrict the use of these medications to the symptomatic treatment of fever, arthritis, and arthralgia.

Corticosteroids greatly reduce the inflammatory response of ARF, especially fever and raised concentrations of acute phase reactants.[37,150] Many doctors believe they lead to more rapid resolution of cardiac compromise than other drugs and can be life-saving in severe cases of acute carditis, though there is little objective evidence.[156,157] Results of randomised trials done before echocardiography became available and those of subsequent meta-analyses have not shown a benefit of corticosteroids over placebo or salicylates in the prevalence of residual RHD in the 1–10 years after ARF.[37,155,156] However, all of the studies included in the meta-analyses were done more than 40 years ago, before echocardiography, and most did not test corticosteroids that are in common use today.

In a placebo-controlled, randomised trial,[124] intravenous immunoglobulin administered to patients with ARF early after presentation did not alter the clinical course or lead to reduction in echocardiographic evidence of acute valvular disease or chronic cardiac damage at 1 year.

Large, probably multicentre, randomised controlled trials are needed that use modern echocardiographic techniques to assess the potential benefits of corticosteroids and other newer anti-inflammatory agents on acute rheumatic carditis and longer-term cardiac outcome. However, most interventions to alter the outcome of ARF will be hampered by the inherent delays in making the diagnosis associated with the 1–5-week interval between infection with group A streptococcus and the onset of symptoms,[158] and delays between onset of symptoms and seeking medical attention and between seeing a doctor and confirmation of the diagnosis.

Further complicating the assessment of new treatments is the natural improvement of rheumatic carditis that occurs in the absence of recurrences. Findings of studies[37,159] done before availability of echocardiography showed that, with few or no recurrences, more than 60% of rheumatic valve lesions had regressed about 10 years after the initial attack of ARF. With echocardiography, results of a follow-up study[129] 6 months to 7 years after the first episode of ARF indicated that 64% of patients with carditis had evidence of improvement, and that murmurs disappeared at follow-up in 41% of those with mild carditis, 36% with moderate carditis, and 24% with severe carditis initially. Often this improvement arises in the short term; results of a study published in 2001,[124] showed that in 27% of patients with ARF who had initial carditis and were treated with placebo carditis resolved without sequelae after 1 year, and that 41% of regurgitant aortic or mitral valves were no longer regurgitant after only 6 months.

Most cases of mild Sydenham's chorea need no treatment. The condition is usually benign and self-limited (rarely, cases can last 2–3 years[143,160]), and many of the drugs are potentially toxic. Treatment should, therefore, be reserved for individuals with moderate-to-severe chorea refractory to conservative management—eg, reassurance and moving of the patient to a quiet and calm environment—or if movements are distressing to the patient or their family. Findings of a small study[161] concluded that valproic acid was more effective than carbamazepine or haloperidol. When needed, we recommend that either carbamazepine or valproic acid be used,[162,163] and that doctors avoid the temptation to try multiple different medications in the same patient. Findings of another small study[164] suggested that intravenous immunoglobulin might hasten recovery from chorea, though this work needs to be repeated. It is noteworthy that intravenous immunoglobulin seems to have no effect on cardiac outcome in ARF,[124] so until further data are available we do not recommend this option except for severe cases refractory to other treatments. Similarly, corticosteroids, used by some doctors for chorea, have not been studied for this indication and cannot therefore be recommended.

Prevention

The overall lack of effective treatments for ARF means that any reduction of the burden of ARF and RHD will most likely come from new initiatives in prevention. Primary prevention of ARF has focused on antibiotic treatment of symptomatic pharyngitis caused by group A streptococcus. A course of antibiotics started within 9 days of the onset of a sore throat caused by group A streptococcus prevents most subsequent cases of ARF.[165–168] Table 3 lists the most frequently-used antibiotic regimens for primary prophylaxis.[8,13,169–177] Additional regimens that have been studied include once-daily dosing with amoxicillin, which seems

	Dose	Frequency	Duration
Primary prophylaxis (treatment of group A streptococcal pharyngitis)			
Benzathine penicillin G	1·2 million units intramuscularly (600 000 units if bodyweight <27 kg)	Single dose	Single dose
Phenoxymethylpenicillin (penicillin V) or amoxicillin	Children: 250 mg orally Adolescents and adults: 500 mg orally	Two to three times daily	10 days
First generation cephalosporins or erythromycin (only if allergic to penicillin*)	Orally: dose varies with drug and formulation	Varies with agent and formulation	10 days
Secondary prophylaxis (long-term preventive therapy in patients with a history of ARF or RHD)			
Benzathine penicillin G	1·2 million units intramuscularly (600 000 units if bodyweight <20 kg)	Every 3–4 weeks	5 years since last episode or age 18 years (whichever is longer) 10 years since last episode or age 25 years (whichever is longer) if mild or healed carditis Lifelong if more severe carditis or valve surgery†
Phenoxymethylpenicillin (penicillin V)	250 mg orally	Twice daily	
Erythromycin	250 mg orally	Twice daily	

*Small proportion of patients with penicillin allergy also allergic to cephalosporin. Erythromycin should not be used in regions with high rates of group A streptococcus macrolide resistance. †WHO recommendation.[8] See text for discussion of alternatives.

Table 3: **Recommended antibiotic regimens for primary and secondary prophylaxis of ARF[8]**

effective[169,170] by contrast with once-daily dosing with penicillin V, which is less effective than more frequent dosing.[171] Cure rates might be higher with high-dose amoxicillin (2 g per day) in adults.[172] Neither once-daily high-dose amoxicillin is recommended by US authorities.[173,174] Several other antibiotics—eg, azithromycin and newer cephalosporins delivered for 3–5 days have been studied,[175] but none is presently recommended as first-line treatment by US authorities.[173,174]

However, whether or not primary prophylaxis is effective on a wide scale in populations at high risk for ARF is difficult to prove unless accompanied by a comprehensive health-care programme and general improvement in health-services delivery; highly sensitive and specific clinical diagnostic algorithms for group A streptococcus pharyngitis are not available, microbiological diagnosis is expensive and not feasible in primary-care settings in most developing countries, and little is known about health-seeking behaviour for sore throat in these populations.[178,179] Even in optimum circumstances, the effectiveness of primary prophylaxis is limited by the fact that up to two-thirds of patients with ARF do not get a sore throat and do not therefore seek medical attention.[129]

From the 1950s to the 1970s, there were numerous intensive, school-based sore throat screening and treatment programmes initiated in the USA. Among these was a 2-year programme in Casper, WY, USA.[180] In this example, greater reductions in acquisition and transmission of pharyngitis associated with group A streptococcus and in ARF incidence were seen in the school district involved than in a neighbouring school district that had no primary prevention programme. Findings of a 4-year programme[181] among Navajo schoolchildren, which included treatment of carriers of group A streptococcus as well as children with group A streptococcus culture-positive sore throat, showed a possible reduction in ARF incidence of 21% (from 12·6 to 10·0 per 100 000 per year), though at a cost of US$12 per child per year, or $65 000 per ARF case prevented in 1965 dollars. Results of another programme[182] in Alaskan Eskimo schoolchildren also showed a possible reduction in ARF incidence, at a cost of $21·50 per child per year in 1971 currency. A subsequent programme[183] in Hawaii found no effect on ARF incidence. None of these programmes, however, had an adequate control group, so any effect on ARF incidence remains uncertain.

The best available data for the effectiveness of intensive school-based sore throat diagnosis and treatment come from a study[183] done in a high-ARF incidence region of Auckland, New Zealand, in which schools were randomly assigned intervention or no intervention. Results of an initial analysis indicate no reduction in ARF incidence (odds ratio 0·76, 95% CI 0·41–1·44). Hence, even the most intensive programme of sore throat diagnosis and treatment might not lead to substantial reductions in ARF incidence. Although primary prophylaxis should be promoted to health staff and to patients with sore throats, coordinated programmes are unlikely to be practical, affordable, or cost-effective in developing countries.

In view of the hypothesis that skin infections play a part in ARF pathogenesis,[89] community-based skin sore and scabies control programmes[58,184,185] could provide an approach to primary prevention of ARF. The association should, however, first be proven.

Several potential group A streptococcus vaccines are in development, including a multivalent, M-serotype specific construct that is in phase II trials in North America.[186,187] The diversity of M serotypes (and *emm* genotypes) in many tropical countries could limit the efficacy of this vaccine.[4,188] Although a serotype-specific vaccine could be designed to target the prevalent strains

in a particular tropical area, this option is not likely to be practical or affordable. Furthermore, the rapid turnover of group A streptococcus serotypes in endemic regions would probably make such a vaccine less effective over time.[49,61,189] Various alternative vaccines based on antigens common to all or most strains of group A streptococcus, using either the conserved region of the M protein or antigens against non-M protein antigens, are in pre-clinical development.[190,191] An effective vaccine is unlikely to be available before 2015 though, and even then the issue of cost will have to be addressed if the vaccine is to be delivered to the populations most in need.

At present, therefore, no practical and affordable strategy exists for the primary prevention of ARF in developing countries.[178,192] The only proven cost-effective intervention is secondary prophylaxis: the long-term administration of antibiotics to people with a history of ARF or RHD, to prevent ARF recurrences and the development or deterioration of RHD. The best drug for this purpose is intramuscular benzathine penicillin G administered once every 3 or 4 weeks, which in head-to-head studies proved more efficacious than oral penicillin or sulfadiazine.[193–196] We recommend 4-weekly injections for most patients, and consider three-weekly injections only in a small number of highly motivated patients who have severe cardiac lesions and have shown good adherence to 4-weekly injections. The most comprehensive economic analysis of ARF and RHD control undertaken to date[197] concluded that secondary prophylaxis was the most cost-effective option (US$142 per DALY gained and $5520 per death averted) and that primary prophylaxis the least cost-effective ($1049 per DALY gained and $40 920 per death averted).

The recommended antibiotic regimens for secondary prophylaxis are listed in table 3. WHO guidelines suggest 600 000 units of benzathine penicillin G for those who weigh less than 27 kg,[8] but results of pharmacokinetic studies indicate that this dose is insufficient for some children.[176,177] The recommendation in table 3 for lower dosing to those weighing less than 20 kg is based on the New Zealand experience,[13] where this regimen is associated with an ARF recurrence rate of only 0·6 per 100 patient-years. Techniques used to reduce the pain of benzathine penicillin injections include use of small gauge needles, increased injection volumes,[198] and addition of 1% lignocaine or procaine penicillin.[199,200] We find that the simple measures of applying direct pressure to the injection site, warming the medication to room temperature, ensuring that skin swabbed with alcohol is dry before injecting, distracting the patient with conversation, and delivering the injection slowly (preferably over 3 min) ensure that the injection is well tolerated even by young children. Decisions about the duration of secondary prophylaxis relate to the balance between the risk of recurrent ARF (reduced with older age, longer duration since last ARF episode, and in low-incidence populations) and the risk to the patient should a recurrence occur (higher with increasingly severe heart disease). Therefore, local guidelines might vary from the WHO suggested duration, which is specified in table 3.[8]

Secondary prophylaxis is best delivered in the context of a formal, register-based ARF and RHD control programme. These have been especially successful in New Zealand and India, where they have led to reduced rates of ARF recurrences and high degrees of adherence to and awareness of secondary prophylaxis, maintained over many years.[13,201–203] Control programmes have added benefits beyond improving adherence to secondary prophylaxis, such as ensuring good clinical follow-up of patients with ARF and RHD, providing a means to undertake educational and health promotion activities, and providing accurate epidemiological data for monitoring and research purposes. The desirable elements of an ARF and RHD control programme have been summarised previously,[8,204] and include a central register of patients, a dedicated coordinator, an advisory committee, guaranteed funding, guaranteed supply of benzathine penicillin G, and mechanisms for finding new patients, facilitating communication between health providers in hospitals and communities, and providing education for health staff and the wider community.

Conclusion

ARF has fallen off the radar of many doctors in developed countries, yet remains a daily challenge to doctors who work in developing countries. In this Seminar, we have attempted to present clinical aspects of ARF from the perspective of those who work with populations that bear the brunt of this disease. Further advances in our knowledge of ARF will, by necessity, come from developing countries. We hope that the next generation of researchers, teachers, and experts will also come from these countries.

Conflict of interest statement

J R Carapetis and M McDonald receive research funding from the Australian National Health and Medical Research Council and the National Heart Foundation of Australia. J R Carapetis has undertaken consultancy work related to rheumatic fever for WHO, is a grant recipient and has acted as an adviser for the US National Institutes of Health, and has received funding from various other Australian funding bodies (none of which has a vested interest in rheumatic fever-related topics). All other authors declare that they have no conflict of interest.

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