Acute rheumatic fever and rheumatic heart disease

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Abstract

Acute rheumatic fever (ARF) is the result of an autoimmune response to pharyngitis caused by infection with group A *Streptococcus*. The long-term damage to cardiac valves caused by ARF, which can result from a single severe episode or from multiple recurrent episodes of the illness, is known as rheumatic heart disease (RHD) and is a notable cause of morbidity and mortality in resource-poor settings around the world. Although our understanding of disease pathogenesis has advanced in recent years, this has not led to dramatic improvements in diagnostic approaches, which are still reliant on clinical features using the Jones Criteria, or treatment practices. Indeed, penicillin has been the mainstay of treatment for decades and there is no other treatment that has been proven to alter the likelihood or the severity of RHD after an episode of ARF. Recent advances — including the use of echocardiographic diagnosis in those with ARF and in screening for early detection of RHD, progress in developing group A streptococcal vaccines and an

increased focus on the lived experience of those with RHD and the need to improve quality of life — give cause for optimism that progress will be made in coming years against this neglected disease that affects populations around the world, but is a particular issue for those living in poverty.

Acute rheumatic fever (ARF) is the result of an autoimmune response to pharyngitis caused by infection with the sole member of the group A *Streptococcus* (GAS), *Streptococcus pyogenes*. ARF leads to an illness that is characterized by various combinations of joint pain and swelling, cardiac valvular regurgitation with the potential for secondary heart failure, chorea, skin and subcutaneous manifestations and fever. The clinical manifestations of ARF are summarized in the recently updated Jones Criteria for the diagnosis of ARF[1] and the most common clinical presentations are outlined in BOX 1. The acute illness can be severe, with disabling pain from arthritis, breathlessness and oedema from heart failure, high fevers and choreiform movements that impair activities of daily living. ARF is usually best managed in hospital, often for a 2–3 week period, by which time the diagnosis is confirmed and the symptoms are treated. Although most of the clinical features of ARF will resolve during this short hospital stay, the cardiac valvular damage might persist. This chronic valvular damage is known as rheumatic heart disease (RHD) and is the major cause of morbidity and mortality from ARF (BOX 2). ARF can recur as a result of subsequent GAS infections and each recurrence can worsen RHD. Thus, the priority in disease management is to prevent ARF recurrences using long-term penicillin treatment, which is known as secondary prophylaxis.

The major advances in ARF and RHD treatment and control arose during the mid-twentieth century when these diseases were still common in North America. This period was the 'heyday' of ARF and RHD research and confirmed that penicillin treatment of GAS pharyngitis can prevent subsequent ARF (the basis of primary prophylaxis)[2] and resulted in trials confirming the efficacy of benzathine penicillin G for secondary prophylaxis[3]; both of these interventions remain the cornerstones of disease management. As the incidence of ARF and RHD waned in wealthy countries after the 1960s, so too did interest and research[4,5]. As a result, by the end of the 1990s, even the WHO had minimal involvement in reducing the RHD burden. However, during this time, it became increasingly clear that ARF and RHD continued unabated in low-income and middle-income countries.

The twenty-first century has seen a resurgence of interest in ARF and RHD, sparked by a better understanding of the true burden of disease and an emerging group of clinicians and researchers from the countries most affected by the disease, particularly in sub-Saharan Africa, South Asia and Australasia. In this Primer, we outline the current understanding of ARF and RHD pathogenesis and treatment, with a particular focus on heart disease, and we highlight future research priorities.

Epidemiology

Burden of disease

A 2005 systematic review, carefully designed to avoid over-estimating the disease burden of GAS infection, concluded that there were approximately 471,000 cases of ARF each year (336,000 in children aged 5–14 years), 15.6–19.6 million prevalent cases of RHD and approximately 350,000 annual deaths as a result of ARF or RHD; almost all deaths occurred in low-income and middle-income countries[6]. The Global Burden of Disease (GBD) study more recently estimated that there are 33 million prevalent cases of RHD, causing more than 9 million Disability-Adjusted Life Years lost and 275,000 deaths each year[7–9] (FIG. 1).

Risk factors

Age—The incidence of initial cases of ARF is highest in children aged 5–14 years, although first episodes do occur in younger children, with reported cases of ARF in those as young as 2–3 years old[10,11]. Initial episodes can also occur in older adolescents and adults, although cases in people >30 years of age are rare. By contrast, recurrent episodes often affect slightly older children, adolescents and young adults but are rarely observed beyond the age of 35–40 years.

RHD is a chronic disease caused by accumulated heart valve damage from a single severe or, more commonly, multiple recurrent ARF episodes. This means that, although RHD occurs in children, its prevalence peaks in adulthood, usually between the ages of 25 years and 45 years[10].

Sex—In most populations, ARF is equally common in males and females. However, RHD occurs more commonly in females, with a relative risk of 1.6 to 2.0 compared with males. In addition, these sex differences might be stronger in adolescents and adults than in children[10,12]. The reasons for this association are not clear, but intrinsic factors such as greater autoimmune susceptibility, as observed in systemic lupus erythematosus[13], and extrinsic factors such as greater exposure to GAS infection in women than in men as a result of closer involvement in child-rearing might explain this difference. In addition, women and girls might experience reduced access to primary and secondary ARF prophylaxis compared with men and boys, and this could also contribute to differences in RHD rates between females and males. Finally, RHD in pregnancy is becoming increasingly recognized. Indeed, data from South Africa and Senegal suggest that RHD is a leading cause of indirect obstetric death, which in turn accounts for 25% of all maternal deaths in developing countries[14–16]. This effect relates to the worsening of pre-existing disease as a result of haemodynamic changes that occur during pregnancy, rather than any increase in susceptibility to ARF or RHD because of pregnancy[17].

Environmental factors—The vast majority of differences in risk between populations around the world can be explained by environmental factors. The relative contribution of each of these individual risks is difficult to elucidate given that many of them overlap and most are associated with poverty and economic disadvantage[12,18–20]. Household overcrowding is perhaps the best described risk factor and reduced overcrowding has been

cited as one of the most important factors underlying the decline in ARF incidence in wealthy countries during the twentieth century[21]. Recent data clearly show an association of ARF and RHD with household crowding[20,22,23] (see discussion on primordial prevention below).

In most studies, the risk of developing RHD is found to be highest in rural locations. For example, Indigenous Australians who live in remote communities are 3.3 times more likely to develop ARF than Indigenous Australians living in urban centres in the same region[24]. Similar findings have been reported from other regions, although in some studies the risk has been highest of all in urban slums[18,20]. It is likely that these locations are proxy measures of other risk factors such as household crowding — which is greatest in urban slums but often high in poor, rural communities — and access to medical services. There have been several studies, dating back to some carried out in the United States during the 1960s and 1970s, that have shown lower rates of ARF in settings that had improved access to medical care than in communities in which access to care was lower[25]. In several regions, including the French Caribbean and Cuba, a reduction in ARF rates was associated with comprehensive medical programmes that included a range of education and health promotions as well as medical strategies targeting ARF and RHD. As a result, it is difficult to isolate the specific component of access to medical care that contributes to ARF and RHD reduction[26,27].

Other individual associations of environmental factors with ARF and RHD, such as under-nutrition, have been occasionally shown but the evidence linking them to the diseases is not strong[18]. Conversely, there is little doubt that the major associations with ARF and RHD relate to poverty and that these are classic diseases of social injustice[19]. Indeed, recent data from the Central Asian republics highlight how RHD can rapidly emerge in settings of social disruption, which suggests that social instability and wars play a major part in fostering ARF and RHD, probably through displacement, crowding and poor living conditions[28]. Of all of the environmental risk factors, overcrowded housing is the best-described factor that is amenable to improvement.

Mechanisms/pathophysiology

Overview

After GAS infection of the pharynx, neutrophils, macrophages and dendritic cells phagocytose bacteria and present antigen to T cells. Both B and T cells respond to the GAS infection, initially by antibody production (IgM and IgG) and subsequently through T cell activation (mainly CD4^{+} cells). In susceptible individuals, the host response against GAS will trigger autoimmune reactions against host tissues (for example, the heart, brain, joints and/or skin) mediated by both *Streptococcus* spp.-specific antibodies and T cells through a process called molecular mimicry (FIG. 2). Molecular mimicry is the sharing of antibody or T cell epitopes between the host and the microorganism — infections generate antibodies or T cells against the infectious pathogen to clear the infection from the host and these antibodies and T cells also recognize host antigens. In the case of ARF, these host antigens are located in tissues such as the heart and the brain[29–40].

The cross-reactive immune response results in transient migratory polyarthritis as a result of the formation of immune complexes (FIG. 3), leads to Sydenham's chorea as the antibodies bind to basal ganglia and neuronal cells (FIG. 4), causes erythema marginatum and subcutaneous nodules in the skin as antibodies bind to keratin (FIG. 5) and leads to inflammation of both heart valves and the myocardium (FIG. 6). Although the myocardium heals following this inflammation, there can be permanent damage to the valves, which leads to RHD. Diversification of the immune response against an immunodominant epitope leads to its amplification (epitope spreading), which favours the recognition of several self antigens and facilitates tissue damage[41]. In this section, we describe rheumatic carditis (inflammation of the heart) and Sydenham's chorea (inflammation of the basal ganglia). The rarer skin manifestation erythema marginatum might be due to antibodies against group A carbohydrate cross-reacting with keratin[42,43] and the subcutaneous nodules that sometimes form in ARF might be granulomatous lesions that develop in the dermis of the skin as a result of delayed hypersensitivity against GAS antigens. Moreover, the formation of these nodules might be driven by similar mechanisms to Aschoff bodies, which are granulomatous lesions that form in the heart valve.

Genetic susceptibility and group A Streptococcus

Both the features of host susceptibility and the genetic makeup of the streptococcal strain are crucial to the host–streptococcal interactions that result in autoimmunity and in the development of ARF. This has been shown by the changing characteristics of ARF over time. For instance, GAS strains isolated during ARF epidemics of the World War II era were rich in M protein, heavily encapsulated by hyaluronic acid and highly virulent in mice[44]. These strains, notable for their highly mucoid-appearing colonies, primarily infected the throat rather than the skin and were also detected during ARF outbreaks in Utah in the United States towards the end of the twentieth century[45]. GAS strains isolated more recently in tropical climates do not share these characteristics. Indeed, molecular epidemiological studies suggest a greater diversity of GAS strains in tropical regions, with skin-associated strains dominating, raising the possibility that skin-associated strains are also linked to cases of ARF[46–50].

This change in the association of particular strains of GAS with ARF could be due to selective pressures acting on both the host and the organism. The evolution of GAS strains over years of penicillin therapy and prophylaxis might have led to ARF cases that were caused by GAS strains that do not have the same characteristics that were reported in previous ARF outbreaks in the United States many decades ago. In addition, the host might have evolved over this period, as many children who contracted the disease in industrialized countries in the ARF epidemics of the early to mid-twentieth century did not survive or were not physically able to bear offspring. In this context, the most severe genetic predispositions for ARF susceptibility might have been transferred to the next generation at a much lower frequency than they were in non-epidemic settings. These changes over the past 100 years might have changed the bacterium and the host and, together with reduced exposure to GAS as a result of improved living conditions, might have been responsible for the decline in overall rates and the reduction in epidemics of ARF in industrialized countries.

How these factors may have influenced ARF in developing countries is even more uncertain. The extreme rates of RHD seen in the poorest countries have only become evident in recent decades, although high rates of ARF and post-streptococcal glomerulonephritis were well documented in Trinidad as far back as the 1960s[51] and population prevalence rates of RHD between 0.5% and 2.2% were documented in the same period in India, Pakistan and Iran (reviewed in REF. 5). It seems likely that high rates of ARF and RHD have been mainly unreported in developing countries for at least half a century, and the lack of availability of treatment for severe RHD means that premature mortality from RHD is high[52]. Given the ongoing high rates of ARF and RHD in developing countries, any selective pressure on host susceptibility caused by premature mortality seems not to have had a substantial effect in these places. However, it is quite possible that selective pressures on organism factors in developing countries might be affected by those in industrialized nations, given emerging evidence of mobility of GAS strains on a global scale[53].

Genetics of host susceptibility are also important. Studies of families with individuals who were susceptible to ARF found that this susceptibility was heritable and that the associated loci had limited penetrance. In addition, phenotypic concordance among dizygotic twins suggests that susceptibility to ARF has an inherited component but that this inheritance does not follow a classic Mendelian pattern[54]. Polymorphisms in several genes coding for immune-related proteins have been associated with ARF and RHD susceptibility. These proteins include mannose-binding protein C 2 (encoded by *MBL2*), ficolin 2 (encoded by *FCN2*), low-affinity immunoglobulin-γ Fc region receptor IIa (encoded by *FCGR2A*), Toll-like receptor 2 (encoded by *TLR2*), tumour necrosis factor (encoded by *TNF*), interleukin-1 receptor antagonist (encoded by *IL1RN*), transforming growth factor β1 (encoded by *TGFβ1*) and cytotoxic T lymphocyte protein 4 (encoded by *CTLA4*)[55–81] (TABLE 1).

Class II human leukocyte antigen (HLA) molecules are expressed on the surface of antigen-presenting cells (APCs) and are crucial for triggering adaptive immune responses via the T cell receptor. HLA class II alleles have been associated with ARF and RHD around the world; the DR7 allele is the most frequently associated with the conditions[54,82] (TABLE 1). In addition, the class I HLA allele *HLA*B5* is associated with developing ARF and the formation of immune complexes during ARF[83]. These associations indicate that genetic alterations of the Fc receptor (FcR) genes and the potential for failure of clearance of immune complexes might play an important part in disease pathogenesis. Further understanding of genetic susceptibility to ARF is likely to come from large multi-ethnic genome studies rather than studies from a single region.

Humoral immune response

The humoral (antibody-mediated) immune response to GAS is mainly responsible for initiating rheumatic carditis. This carditis is followed by cellular infiltration of the endocardium and valve tissues, which results in further damage that leads to RHD[35,84,85]. The humoral response can also lead to Sydenham's chorea, which involves lymphocytic perivascular cuffing of vessels in the brain and which may occur with or without carditis[86]. Antibodies against *Streptococcus* spp. that cross-react with antigens found in the heart or in the brain have been identified in the sera of patients with ARF and in the sera of rabbits and

mice that had been immunized against streptococcal infection[29–40]. The method for producing monoclonal antibodies (mAbs) enables production and identification of cross-reactive *Streptococcus* spp.-specific mAbs derived from mice and humans with ARF that are heart-specific and brain-specific. These developments facilitated the discovery of the pathogenetic mechanisms that are mediated by autoantibodies produced during ARF, including their effects on proteins in the heart and the brain.

The hypothesis of molecular mimicry occurring between GAS, heart and brain antigens is supported by evidence from studies using human mAbs[35,38], human serum IgG antibodies and both peripheral[33] and intralesional[34] T cell clones from patients with ARF and RHD[32]. A model of ARF affecting both the heart and the brain was developed in Lewis rats and studies using this model have shown that immunization with GAS antigens leads to valvulitis[87] or behaviours similar to those in Sydenham's chorea[30]. The investigation of *Streptococcus* spp.-specific mouse mAbs[40] and human mAbs derived from those with rheumatic carditis[35] and Sydenham's chorea[38] has supported the hypothesis that antibodies against the group A carbohydrate epitope *N*-acetyl-β-D-glucosamine recognize cross-reactive structures on heart valve endothelium and/or endocardium and on neuronal cells, which could cause carditis or Sydenham's chorea, respectively.

Sydenham's chorea—Sydenham's chorea is the neurological manifestation of ARF and is characterized by chorea and neuropsychiatric symptoms[88]. In Sydenham's chorea, neuron-specific antibodies (immunoglobulin G (IgG)) target basal ganglia[36] and cause the release of excess dopamine from neuronal cells in culture[38]. Human mAbs derived from patients with Sydenham's chorea[38] react by molecular mimicry with the group A carbohydrate epitope *N*-acetyl-β-D-glucosamine and a group of antigens found in the basal ganglia including the D1 and D2 dopamine receptors[31], lysoganglioside[38] and tubulin[37]. The cross-reactive neuron-specific antibodies are generated by the response against the group A streptococcal carbohydrate and recognize both host and microbial antigens, which share a structure that is similar enough for the antibody to cross-react. Although the reasons for antibody targeting of the basal ganglia are not well known, specific antibody targeting might be due to the presence of dopamine D2 receptors on dopaminergic neurons in the substantia nigra and ventral tegumental area that project to the striatum[89]. Localization of such targeted neurons was observed when a human Sydenham's chorea-derived mAb was expressed in transgenic mice[31].

A general theme in immunological mimicry by antibodies is the recognition of an intracellular antigen that is a biomarker; by contrast, antigens at the cell surface control disease mechanisms, such as cell signalling or complement-dependent cytotoxicity. Indeed, there is evidence that cross-reactive antibodies generated during ARF can have functional, and potentially pathogenetic, consequences for neuronal cells. Antigens such as lysoganglioside and dopamine receptors in the neuronal cell membrane bind antibody and change cellular biochemistry and signalling through activation of calcium/calmodulin-dependent protein kinase type II (CAMK2), which leads to an increase in tyrosine hydroxylase and dopamine release[31,39,90]. This altered signalling might function as a mechanism in disease[90,91] (FIG. 4). For instance, human mAbs, serum IgG antibodies and/or cerebrospinal fluid from patients with Sydenham's chorea activate CAMK2 (REF.

38) in human neuronal cells and increase ^{3}H-dopamine release from human neuronal cells[39]. CAMK2 activation in neuronal cells was also shown using patient serum, and removal of IgG from the serum abrogated CAMK2 activation[30,38], which indicates that this neuronal signalling is antibody dependent. In addition, a human mAb derived from a patient with Sydenham's chorea induced tyrosine hydroxylase activity in dopaminergic neurons after passive transfer into rat brains[39], which suggests that the neuron-specific antibodies formed in Sydenham's chorea might lead to neuronal changes and manifestations of disease. Furthermore, one study showed that when variable genes encoding a mAb derived from a patient with Sydenham's chorea, mAb 24.3.1, were expressed in transgenic mice, the resulting antibodies targeted dopaminergic tyrosine hydroxylase-expressing neurons in basal ganglia[31] (FIG. 7). In addition, the whole mAb 24.3.1 and the source serum reacted with and signalled through the human dopamine D2 receptor[31]. Other antibodies have been found to react with the human D1 dopamine receptor and the ratio of dopamine D1 receptor-specific to dopamine D2 receptor-specific antibodies in Sydenham's chorea correlates with a measure of symptom severity[29]. Finally, plasmapheresis, in which patients with Sydenham's chorea receive plasma from healthy donors, leads to the improvement of symptoms[92,93]. This finding strongly suggests that disease pathogenesis is antibody-mediated and that patients would, therefore, respond to immunotherapy or corticosteroids, a prediction that has been recently validated in clinical studies[93–98].

Studies using rat[30] and mouse[91] models support conclusions drawn from human studies. Exposure of rats to GAS antigens during immunization with GAS cell walls or plasma membranes leads to behaviours that are characteristic of Sydenham's chorea[30]. Immunized rats could not hold a food pellet or traverse a narrow beam and showed compulsive grooming behaviour[30]. These rats had IgG deposits in striatum, thalamus and frontal cortex with concomitant alterations in dopamine and glutamate levels in cortex and basal ganglia. In addition, sera from *Streptococcus* spp.-immunized rats have been shown to activate CAMK2 in a human neuronal cell line[30], results which are similar to those obtained using sera from patients with Sydenham's chorea[38]. Removal of IgG from sera in these studies greatly diminished the CAMK2 activation in neuronal cells. In a mouse model, immune responses against GAS were also associated with motor and behavioural disturbances[91]. In both models, passive transfer of *Streptococcus* spp.-specific antibodies directly into naive animals led to antibody deposits in the brain and concomitant behavioural changes[90,99]. A study using the rat model has also addressed the effects of antibiotic therapy on behaviour and neurochemical changes. In this study, ampicillin treatment prevented the emergence of the motor symptoms and some of the behavioural alterations that were induced by GAS antigen exposure[100].

Rheumatic carditis—Cross-reactive antibodies have also been implicated in the pathogenesis of rheumatic carditis and recognize a variety of cardiac epitopes. Studies from the 1960s showed antibody deposition in human valve and myocardial tissues from patients who had died as a result of ARF or RHD[84]. These findings were later confirmed using mouse[40,101] and human mAbs[32,35] against GAS that reacted with both myocardial and valvular tissues. The human mAbs targeted striations in the myocardium and the endothelium of the valve, a finding that had been previously reported in studies using sera

from patients with ARF or from animals immunized with GAS antigens[84,102–104]. In support of the molecular mimicry hypothesis[105], the targets of cross-reactive antibodies were cardiac myosin in the myocardium and laminin[35] in the valve endothelium and basement membrane, and these antibodies cross-reacted with the group A carbohydrate or streptococcal M protein[35,40,101].

The cross-reactive antibodies might also recognize glycosylated proteins or carbohydrate epitopes on the valve, which supports previous findings[106] showing an immunological relationship between GAS polysaccharide and the structural glycoproteins of the heart valve[106]. This could help to explain why, in one study, the persistence of elevated group A carbohydrate-specific antibody responses in rheumatic carditis correlated with a poor prognosis of valvular heart disease[107]. Antibodies that target valve surfaces lead to inflammation and cellular infiltration through the valve surface endocardium and/or endothelium[85].

The α-helical protein structures found in streptococcal M proteins, cardiac myosin, keratin and laminin are involved in cross-reactivity with antibodies that react to the group A carbohydrate epitope *N*-acetyl-β-D-glucosamine[42,101]. In addition, mutations in the α-helical M1 protein that stabilize irregularities in its α-helical coiled coil structure diminish its ability to be recognized by *Streptococcus* spp.-specific antibodies that cross-react with M protein and cardiac myosin[108]. This evidence suggests that α-helical protein epitopes and group A carbohydrate epitope *N*-acetyl-β-D-glucosamine are important targets of cross-reactive antibodies in ARF.

Active inflammation in rheumatic carditis is associated with humoral responses against specific epitopes of the S2 fragment of human cardiac myosin heavy chain[109] and these responses can be used to monitor disease progression and the effects of treatment[110]. S2 epitopes are similar among populations in which rheumatic carditis is endemic worldwide[109], regardless of which M protein gene sequence (*emm* type) the GAS in the region carries. Repeated GAS throat (and possibly skin) infections are important in generating molecular mimicry, breaking immune tolerance and inducing epitope spreading, which leads to recognition of more epitopes in cardiac myosin and potentially other heart proteins. For example, epitopes shared among different streptococcal *emm* types in the B or C repeat regions of the streptococcal M proteins might prime the immune system against the heart during repeated streptococcal exposure and might eventually lead to RHD in susceptible individuals[87,111–113]. The A repeat regions of the GAS M proteins that are responsible for the type-specific protection against infection from each serotype are not shared with other M types and are not cross-reactive. Sequences from the A repeat regions of the M protein serotypes have been used in group A streptococcal vaccines that show no evidence of cross-reactivity in animal and human trials[32,114].

Collagen is an important structural protein in the heart valve and autoantibodies against collagen I are produced in ARF[115], but these antibodies are not cross-reactive. They might be produced as a result of immune responses against collagen after aggregation of collagen by certain streptococcal serotypes[116,117]. Alternatively, they might also be due to the release of collagen from damaged valves during RHD[116]. Streptococcal proteins with similarity to

collagen have been reported[118,119], although no immunological cross-reactivity has been observed. This absence of cross-reactivity raises the possibility of an alternative pathogenetic pathway in ARF that produces an antibody-mediated response to collagen in the valve that does not rely on molecular mimicry. As only cardiac myosin and M protein, but not collagen, have been shown to induce valvulitis in animal models[87,120], it is likely that molecular mimicry is important for breaking immune tolerance and for the initiation of rheumatic carditis, whereas the response to collagen probably occurs after this initial damage, as a result of exposure of the immune system to collagen — a process that continues during RHD.

Cellular immune responses in rheumatic carditis

The cellular autoimmune response in rheumatic carditis involves production of autoreactive T cells that infiltrate the valve and the myocardium, the activation of the valvular endothelium and the formation of Aschoff nodules in the valve.

Valvular endothelial activation—IgG antibodies that react with valve endothelium lead to the upregulation of vascular cell adhesion protein 1 (VCAM1) on the endothelial surface, which promotes infiltration of T cells through the activated endothelium into the valve[85,116,121] (FIGS 6,8). This endothelial activation also involves loss of normal endothelial cell arrangement and modifications to valvular collagen, which have been observed using scanning electron microscopy[122]. Both $CD4^+$ and $CD8^+$ T cells infiltrate the valves in ARF[123] but the $CD4^+$ T cell subset predominates in the inflamed rheumatic valve[85] (FIG. 9). Only autoreactive T cells that are continually activated by antigen (that is, valve proteins) survive and remain in the valve to produce inflammatory cytokines and to cause valve injury. In ARF and RHD, lesions called Aschoff nodules or bodies can occur underneath the endocardium near to or at the valve but may also be seen directly in the myocardium, which usually heals in rheumatic carditis. These nodules are sites of granulomatous inflammation that contain both T cells and macrophages and they are formed as a result of an intense inflammatory process that is mainly mediated by $CD4^+$ T cells[124].

VCAM1 also interacts with and upregulates numerous other cell adhesion molecules, chemokines and their receptors. These include integrin $\alpha4\beta1$ (also known as VLA4), intracellular adhesion molecule 1 (ICAM1), P-selectin, CC-chemokine ligand 3 (CCL3; also known as MIP1α), CCL1 (also known as I309) and CXC-chemokine ligand 9 (CXCL9; also known as MIG)[85,113]. The autoimmune reaction in the valves is associated with elevated levels of heart tissue proteins vimentin and lumican and elevated apolipoprotein A1 levels, whereas collagen VI, haptoglobin-related protein, prolargin, biglycan and cartilage oligomeric matrix protein are reduced[125]. This imbalance results in a loss of structural integrity of valve tissue and, consequently, in valve dysfunction.

Autoreactive T cells—Autoreactive T cells that infiltrate the myocardium and valves recognize myocardium-derived and valve-derived proteins and have an oligoclonal profile — they are derived from only a few individual T cell clones — in patients with both acute carditis and chronic RHD[126]. These autoreactive T cells taken from rheumatic valves proliferate and express TNF and interferon-γ (IFNγ) (T_H1 subsets), whereas only a few T

cells taken from rheumatic valves secrete the regulatory cytokine IL-4, which might explain the progression of valvular lesions in some cases[127]. The granulomatous T_H1 cell response and the presence of IFNγ have been reported in rheumatic valves[127]. Although less is known about T_H17 cell responses in RHD, T_H17 cells are important in GAS infections and have been identified in nasopharyngeal and tonsillar lymphoid tissues in streptococcal infection animal models[128–130]. In ARF and RHD, elevated numbers of T_H17 cells, high IL-17A levels and decreased T regulatory cells were reported in peripheral blood[131]. IL-17 triggers effective immune responses against extracellular bacteria, such as promoting neutrophil responses[132,133].

The cross-reactive T cells taken from ARF and RHD heart valves mainly recognize three regions (residues 1–25, 81–103 and 163–177) of the amino-terminal region of M protein, several valve-derived proteins[134] and peptides of the β-chain of human cardiac light meromyosin region, which is the smaller of two subunits produced by tryptic digestion of human cardiac myosin[33,34]. Peripheral blood and valve-infiltrating[34] human T cells react strongly against peptides of streptococcal M protein and human cardiac myosin. In animal models of RHD, the intact streptococcal M protein and peptides from A, B and C repeat regions of streptococcal M protein have been investigated for their potential to cause valvular heart disease. For instance, rat T cell lines that are specific for streptococcal M5 protein epitopes such as DKLKQQRDTLSTQKET[134] passively transfer valvulitis and upregulation of VCAM1 (REF. 135) to uninfected rats.

Pathological consequences of inflammation

The inflammatory cascade in ARF has structural and functional effects on various parts of the heart valves that can lead to acute inflammatory damage and ultimately to RHD. This includes dilation of valve annuli — rings that surround the valve and that help close leaflets during systole — and elongation of chordae tendinae, which connect leaflets of the mitral and tricuspid valves to the left and right ventricles, respectively. Together these changes result in inadequate coaptation (that is, meeting) of the valve leaflets, which in turn causes regurgitation (that is, backwards leakage of blood through the valve when it closes)[136]. Further inflammation leads to fibrinous vegetations in the rough zone of the anterior leaflet and scarring of leaflets, which might ultimately lead to valvular stenosis, in which the valve becomes narrowed, stationary and is unable to fully open (FIG. 6).

Diagnosis, screening and prevention

Diagnosis

The diagnosis of ARF is made using clinical criteria (the Jones Criteria) and by excluding other differential diagnoses. The Jones Criteria were first established in 1944 (REF. 137) and since then have undergone multiple modifications, revisions and updates, most recently in 2015 (REFS 1,138–141). The criteria are divided into major and minor manifestations (TABLE 2). The diagnosis of ARF is made when the patient presents with two major manifestations or one major manifestation and at least two minor[1] manifestations. In addition, evidence of preceding infection with GAS must be shown, which is usually done using streptococcal serology. The exceptions to these criteria are patients who present with

chorea or indolent carditis because these manifestations might only become apparent months after the causative streptococcal infection and, therefore, additional manifestations might not be present and streptococcal serology testing might be normal[88].

The most common presenting features of ARF are arthritis (75% of patients) and fever (>90% of patients). The arthritis of ARF is the most difficult diagnostic challenge because of the large number of differential diagnoses, especially in patients who present with an initial monoarthritis. In patients presenting with a single inflamed joint, it is important to exclude septic arthritis[142]. The arthritis of ARF is highly responsive to anti-inflammatory drugs (aspirin and NSAIDs) and if the patient does not respond within 48–72 hours alternate diagnoses should be considered. Subcutaneous nodules are small (0.5–2 cm in diameter), painless and round nodules that develop over bony prominences or extensor tendons, and erythema marginatum are bright pink, blanching macules or papules that spread outwards in a circular pattern, usually on the trunk and proximal limbs. Both are infrequent manifestations of ARF, occurring in less than 10% of patients[24,50]. Carditis occurs in >50% of patients with ARF and is predominantly characterized by valvulitis of the mitral valve (mitral regurgitation) and, less frequently, of the aortic valve (aortic regurgitation)[143–145]. Cardiomegaly occurs when there is moderate or severe valvular regurgitation. Since publication of the previous Jones Criteria in 1992, new data have been published on the use of Doppler echocardiography in diagnosing cardiac involvement in ARF[145–149]. On the basis of these results, echocardiographic evaluation for all patients who are suspected of having ARF is a new recommendation that has been included in the 2015 Jones Criteria. Both clinical and subclinical carditis fulfil a major criterion, even in the absence of classical auscultatory findings[1] (FIGS 10,11).

Chorea occurs in up to 30% of those who have ARF. It is characterized by involuntary and purposeless movements of the trunk, limbs and face. Chorea may also present on its own without other features of ARF and without evidence of a recent streptococcal infection. In this scenario, it is important to exclude other potential causes of chorea including drug reactions, systemic lupus erythematosus, Wilson disease and other diseases, and to carry out an echocardiogram because chorea is strongly associated with carditis.

The 2015 revision of the Jones Criteria was undertaken by the American Heart Association in response to emerging data regarding differences in presentation of ARF between low- and moderate–high-risk cohorts. Moderate–high risk is defined as coming from a population with an ARF incidence of >2 per 100,000 school-aged children per year or an all age RHD prevalence of >1 per 1,000 people per year. In moderate–high risk populations, monoarthritis in addition to the more classic polyarthritis can fulfil a major manifestation[1]. This change is meant to increase the sensitivity of the criteria in areas where ARF remains endemic[24,150,151] and to maintain high specificity in low-risk areas. These modifications were previously reflected in the Australian and New Zealand guidelines, which allow for less-stringent findings among those at greatest risk[152,153]. In many high-risk tropical areas, acute onset arthritis and fever can be caused by arboviral infections such as dengue, chikungunya and Ross River fever. These infections are important and common differential diagnoses for ARF. The risk of overdiagnosis of ARF can be reduced by testing for these and other arboviral infections if possible, ensuring that streptococcal serology is positive

when making a diagnosis of ARF (preferably by comparing acute and convalescent titres) and by completing a full work-up for ARF that includes an echocardiogram.

Patients might present with established RHD rather than ARF. This is very common in resource-poor settings in which patients frequently present with late-stage RHD. For example, in a cohort of 309 patients with RHD in Uganda, none had a previous history of ARF[154]. The presentation with *de novo* RHD is most often associated with symptoms of cardiac failure, although patients might also present with embolic stroke, infective endocarditis or arrhythmia (atrial fibrillation). There is evidence that RHD contributes to sudden cardiac death, probably as a result of cardiac arrhythmia[155]. RHD might also be diagnosed when a heart murmur is detected as part of routine care. Diagnosis of RHD in pregnant women is of particular importance because these patients present challenging issues in their management.

Prevention

Primordial prevention—Primordial prevention involves prophylactic strategies to avoid GAS infection. ARF is triggered by GAS pharyngitis and the GAS transmission is facilitated by close contact between people. Thus, living conditions, knowledge regarding the importance of a sore throat caused by GAS and an understanding of the mechanisms of transmission are integral, both for the lay public and for health professionals, to the control of ARF. Studies carried out in Baltimore in a low-resource inner city area outlined how the alleviation of household crowding could reduce the incidence of ARF independent of ethnic group[156]. Older ecological studies in the British army showed that bed spacing in crowded barracks was crucial to the control of ARF[157]. More recent studies lack analysis of the relative importance of primordial factors. However, in New Zealand, a developed country in which ARF clusters in poorer sections of the population, there is a clear association between ARF and socioeconomic deprivation. This association is shown using the New Zealand Deprivation Index, which combines 9 variables from the most recent national census including income, education, employment, accommodation and access to car and/or telephone[158].

Primary prevention—Primary prevention aims to stop a GAS infection from causing ARF. ARF is preventable with appropriate healthcare by treating the preceding GAS pharyngitis with antibiotics (primary prophylaxis). As many cases of GAS pharyngitis might be asymptomatic or cause only a mild sore throat, primary prophylaxis is only possible when a patient has symptoms of a sore throat that are sufficient to lead them to seek medical attention[2]. This presentation relies on access to healthcare with the knowledge, both on the part of the general population and the healthcare professionals, that treating a sore throat is important for ARF prevention. High-quality studies on the control of ARF through healthcare interventions such as use of long-acting depot penicillin, which is a slow-release formulation of penicillin delivered by injection, were carried out soon after penicillin became available in the United States armed forces, in which ARF was occurring at very high rates[2]. Community-based studies are, by their nature, less rigorous and have suggested that widespread sore throat diagnosis and treatment might be effective in reducing ARF incidence in developing and developed countries, although it has yet to be definitively

determined that primary prophylaxis alone will significantly reduce the incidence of ARF[114,159,160]. A randomized controlled trial (RCT) in New Zealand of a school-based sore throat intervention involving approximately 22,000 students determined the efficacy of active sore throat surveillance accompanied by throat swab confirmation and antibiotic treatment of GAS-positive cases. Although this trial found a 28% reduction in ARF incidence in schools in which intervention had taken place, this result failed to reach statistical significance ($P = 0.27$)[161]. A large-scale effectiveness evaluation of this intervention is underway in New Zealand and might provide definitive evidence of the potential for primary prophylaxis to reduce ARF incidence at a population level.

In the vast majority of published studies on primary prevention interventions, throat swabbing was not used to separate GAS pharyngitis from the more common viral pharyngitis. Rather, most of those who presented at clinics were treated with injectable long-acting penicillin. Clinical algorithms for better precision to avoid unnecessary antibiotic treatment for a viral pharyngitis have poor prediction[162]. Thus, culture of a throat swab, when it is possible to do so, is the best way to accurately diagnose GAS pharyngitis and to target antibiotic treatment to patients whose sore throat is caused by a GAS infection in order to prevent ARF.

The persistence of a pharyngeal GAS is an important risk factor for the development of ARF following an acute pharyngitis episode[163]. Early studies found that eradication of the microorganism can be achieved using injectable benzathine penicillin and subsequent studies have showed that satisfactory rates of eradication can also be achieved using 10 days of oral penicillin twice a day or 10 days of oral amoxicillin once a day[164–166]. In order to reduce the risk of development of ARF, treatment of GAS pharyngitis must be initiated within 9 days of onset of a sore throat[2,156]. There are different reasons for choosing one of each of these three modalities. Use of other antimicrobial drugs is not supported; broad-spectrum antibiotics are more expensive and, in the face of increasing resistance, not indicated for the majority of presentations. In some tropical areas where ARF is common, GAS carriage and GAS pharyngitis seem to be less common than in temperate areas, but impetigo (a superficial skin infection that results in sores and crusting) caused by GAS occurs at very high levels[167]. In New Zealand, the GAS isolates associated with ARF come from classically skin-associated *emm* types and *emm* cluster types[168,169]. These observations, and other data, have led to the hypothesis that GAS impetigo might contribute to the pathogenesis of ARF[46,167], but no definitive link has been found between the two conditions and no studies on the treatment of GAS impetigo for primary prevention of ARF have been carried out.

Secondary prevention—The importance of secondary penicillin prophylaxis for prevention of recurrent ARF and progressive RHD cannot be overemphasized. This strategy has been proven in RCTs to prevent recurrence of ARF[170] and remains the single most important step of management of ARF. Intramuscular benzathine penicillin (BPG) is superior to oral penicillin. There is strong evidence that secondary prophylaxis reduces the severity of RHD by preventing disease progression[171,172]. Studies carried out in the mid-twentieth century showed that 40–60% of patients with ARF progress to RHD[173–175] and that the rate of regression of mitral regurgitation increased from 20% to 70% after penicillin

was introduced[173]. More recently, Lawrence and colleagues[10] studied 1,149 children with ARF (27.5% these children presented with carditis) in the Northern Territory, Australia, and reported that 35% of children with ARF developed RHD by 1 year and 61% had evidence of RHD by 10 years[10]. Of children that progressed to RHD, 14% showed heart failure at 1 year and 27% had heart failure at 5 years. In a multivariate analysis, the only factor found to be strongly associated with RHD incidence was age at first ARF episode (risk decreased by 2% per year of age). There was a suggestion that the risk of developing RHD after an ARF diagnosis was higher for Indigenous than for non-Indigenous people and for female than for male patients, but the confidence intervals for both hazard ratios included 1.0, which implies that there was no definitive evidence of difference in RHD risk between the groups.

Lue and colleagues[176] reported that patients receiving penicillin every fourth week, compared with those who received it every third week, were more likely to have undetectable serum penicillin levels between doses and were fivefold more likely to have prophylaxis failure[176]. However, contemporary data from New Zealand showed that ARF recurrences were rare among people who were fully adherent to a 4-weekly BPG regimen — the rate of ARF recurrence in fully adherent individuals on a 28-day regimen was 0.07 cases per 100 patient years. Failure on the prophylaxis programme (that is, recurrence of ARF, including in those who were less than fully adherent) was 1.4 cases per 100 patient years[177]. Patients without auscultation evidence of carditis are still at considerable risk of developing RHD. In one study, the prevalence of subclinical carditis following the first episode of ARF was 18% and half of the patients had persistence or deterioration of disease 2–23 months later[178]. Studies by Araujo and colleagues[179] and Pekpak and colleagues[180] reported that the proportion of patients with subclinical ARF who had persistence of carditis at least 1 year later was 72% and 55%, respectively.

Efforts to optimize compliance with penicillin and to ensure a safe and adequate supply of the drug are crucial components of secondary prophylaxis[181]. Non-adherence to penicillin was strongly associated with recurrent ARF in a 2010 Brazilian study[182]. Many patients with RHD who live in developing countries seek medical attention too late to benefit from secondary prevention. For instance, one study found that Ugandan patients with RHD (n = 309) had a mean age of 30 years (range 15–60 years) and 85% had cardiovascular symptoms at initial presentation[154]. In addition, half of these patients had severe complications including heart failure, atrial flutter and/or fibrillation, pulmonary hypertension and stroke. None had ever been diagnosed with ARF or taken penicillin. Mitral stenosis is also more common at initial presentation in the developing world[183].

The appropriate duration of secondary prophylaxis depends on several factors. These include the time elapsed since the last episode of ARF (ARF recurrences occur more commonly in the first 5 years since the last episode)[177], age (ARF recurrence is less common after the age of 25 years and uncommon after the age of 30 years)[177], the presence or absence of carditis at presentation and the severity of RHD at follow-up, and the environment (particularly the likelihood of ongoing exposure to GAS such as having young children in the household). On the basis of these factors, the recommended duration of secondary prophylaxis is usually for a minimum of 10 years after the most recent episode of ARF or until age 18–21 years (whichever is longer)[184]. Recent guidelines recommend that those with moderate RHD

continue prophylaxis until age 30–35 and those with severe RHD continue until age 40 (REFS 184,185).

Screening for RHD

Developing an effective screening strategy that could bridge the gap between the large number of patients with RHD who would benefit from secondary prophylaxis and the relatively small proportion of those who have a known ARF history has the potential to result in significant reduction of disease morbidity and mortality. Portable echocardiography machines have made large-scale field echocardiography screening possible, even in remote settings. Multiple studies of school-aged children have shown a significant (fivefold to fiftyfold) increase in detection of RHD by echocardiography screening compared with auscultation[186–195]. The prevalence of RHD in these studies ranged from 8–57 out of 1,000 children screened; if all of these cases represented true RHD, the disease might affect 62–78 million people worldwide and cause up to 1.4 million annual deaths[196]. Beaton and colleagues[192] found associations between lower socioeconomic status and older age with higher RHD prevalence. No patients with screening-detected RHD recalled a history of ARF, underscoring the importance of screening as perhaps the only tool for early case detection in settings in which ARF is uncommonly diagnosed and RHD presentations occur late in the illness. The World Heart Federation (WHF) published standardized screening guidelines in 2012 for the use of echocardiography without auscultation[197]. Using the WHF criteria, no definite RHD cases were found in a low-risk group of Australian children and borderline RHD was more common in high-risk than in low-risk children, suggesting that definite RHD is likely to represent true disease and borderline RHD includes many children with true RHD[198].

Smartphone-size hand-held echocardiography (HHE) offers hope for more efficient, mobile and cost-effective screening. Beaton and colleagues[199] reported that HHE was highly sensitive and specific for distinguishing between healthy individuals and those with RHD in a retrospective study of 125 Ugandan patients[199]. Moreover, HHE had good sensitivity (79%) and specificity (87%) for RHD detection, being most sensitive for definite RHD (97.9%) in a large prospective study of 1420 children in four schools in Gulu, Uganda[200].

Although few would argue against putting those with definite RHD on prophylaxis, management of borderline patients is unclear, given the risks associated with penicillin and the stigma of being labelled with a chronic disease[201]. The population of patients with borderline RHD is heterogeneous and includes patients who are likely to have physiological mitral regurgitation and patients who are likely to develop progressive carditis[202]. There are no long-term follow-up data regarding this patient population. In four studies looking at short-term follow-up, 331 patients with subclinical RHD were followed for 4–27 months[186,188,203,204]. Approximately two-thirds of patients had no change and one-third had improvement or resolution. One study found disease progression in 10% of cases[188]. There was insufficient data on secondary prophylaxis or recurrence but one study that used prophylaxis for all patients found no disease progression[204].

Training frontline medical personnel is necessary for better access to screening. In Fiji, echocardiographic screening by two nurses had good sensitivity and specificity in detecting

mitral regurgitation[205]. Screening children who do not attend school, older children and young adults[206], and pregnant woman[14] might yield an even higher burden of disease. Studies are needed to determine if echocardiography screening can be cost effective[196]. A study using a Markov model found that echocardiography screening and secondary prophylaxis for patients with early evidence of RHD might be more cost effective than primary prophylaxis[207].

A public health approach that combines multiple modalities could result in a highly sensitive and specific screen that is affordable and could greatly affect resource allocation for prevention of ARF. The addition of biomarkers to echocardiography screening programmes, such as B-type natriuretic peptides and antibodies against *Streptococcus* spp., that are specific for cardiac involvement and immunological assays might result in more specific and sensitive screening programmes.

Management

ARF

High suspicion in geographic areas where ARF is endemic is vital. In any child or young person with an acutely painful and swollen joint, ARF should be considered in addition to septic arthritis and injury as well as rarer causes of their symptoms. Use of NSAIDs might mask the usual progression from this initial disease stage to polyarthritis, which is a hallmark of ARF. The major priority in the first few days after presentation with ARF is confirmation of the diagnosis. Ideally, all patients with suspected ARF should be hospitalized, primarily for an echocardiogram and other investigations as needed, such as a needle aspiration of the joint if septic arthritis is a possibility, inflammatory markers and a search for a preceding streptococcal throat infection (preferably by measuring streptococcal titres). A search for other causes of polyarthritis that are dependent on the geographic area, for example arboviral infections in the tropics, might be helpful if the echocardiogram remains normal for 3 weeks or more after the initial presentation. Hospitalization also provides an ideal opportunity for education about ARF, especially the need for secondary prophylaxis. The priorities in management of ARF relate to eradication of GAS from the throat, symptomatic treatment of arthritis and/or arthralgia and management of carditis and/or heart failure (BOX 3).

To reliably eradicate GAS[208], intramuscular BPG as a single dose or a full 10 days of oral penicillin or amoxicillin should be given. The first dose of intramuscular BPG should also be given in hospital in association with education about the importance of secondary prophylaxis, as the majority of patients are children[209]. Controlled studies have failed to show that treating ARF with penicillin affects the outcome of rheumatic valvular lesions 1 year later[210,211].

In the pre-penicillin era, prolonged bed rest in those with rheumatic carditis was associated with shorter duration of carditis, fewer relapses and less cardiomegaly[212]. In the absence of contemporary studies, ambulation should be gradual and as tolerated in patients with severe acute valve disease, especially during the first 4 weeks, or until the serum C-reactive protein level has normalized and the erythrocyte sedimentation rate has normalized or significantly

reduced. Those with milder or no carditis should only remain in bed as long as necessary to manage arthritis and other symptoms[153].

Carditis—Long-term morbidity and mortality from ARF are mainly due to RHD, which in turn is mostly a function of the extent of acute cardiac involvement of ARF and the incidence of subsequent episodes of recurrent ARF. Corticosteroids reduce the inflammatory markers of ARF, especially fever and elevated acute phase reactants and are widely used in severe acute carditis with heart failure, even though there is little objective data to prove that they augment the usual strategies such as bed rest, fluid restriction and cardiac medications[213,214]. There is no evidence that corticosteroid use alters the severity of chronic valvular heart disease 1 year after ARF[213,214]. However, previous studies of corticosteroid therapy for the treatment of ARF were mainly carried out in the 1950s and 1960s, before the advent of echocardiography[213–215]. Valvular outcomes, which were primarily based on the presence of an apical systolic murmur, at 12-month follow-up were not significantly improved and inflammation tended to rebound once steroid therapy was withdrawn. Despite this, corticosteroids are frequently used to treat severe carditis around the world[215,216]. Intravenous immunoglobulin has been used in a RCT treatment study of ARF but no benefit was shown[216]. There are no reliable data to support the use of other inflammatory modulators.

There is a strong argument for the need to carry out a multicentre RCT of corticosteroids versus placebo for ARF using echocardiographic end points for acute carditis (at 6 weeks) and chronic valvular disease (at 6 months to 1 year)[214]. Such a study would need to be powered to account for the natural improvement of carditis after the acute phase[216] but would provide an evidence-based approach to corticosteroid therapy for active rheumatic carditis. Similar multicentre studies of other immunomodulators, informed by an expanded understanding of ARF immunopathogenesis, could eventually be considered but there is no role for small, underpowered studies[217].

Heart failure—An urgent echocardiogram and cardiology assessment are recommended for all patients with heart failure. Diuretics and fluid restriction are the mainstay of treatment. Angiotensin-converting enzyme (ACE) inhibitors are recommended for some patients with aortic regurgitation[209]. ACE inhibitors improve haemodynamics by increasing cardiac output in patients with aortic regurgitation. They are indicated if there are symptoms or if there is left ventricular dysfunction, but should not be a substitute for surgery[218].

Cardiac surgery is usually deferred until the acute inflammation has subsided so that the repair is technically easier and a more durable repair can be achieved. Rarely, chordae tendinae rupture leads to a flail leaflet, by which the unsecured section of the valve results in severe regurgitation and acute pulmonary oedema owing to a rapid rise in left atrial pressure. This condition is often misdiagnosed as pneumonia as the pulmonary venous congestion is often unilateral. Such cases require emergency life-saving surgery to repair the flail leaflet[219]. Even in the absence of a flail leaflet, urgent surgery might be indicated owing to torrential mitral or aortic regurgitation or both. The philosophy for cardiac surgery in the young should always be to repair rather than to replace the mitral valve[220]. A recent retrospective report of 81 patients aged 3–19 years showed not only lower morbidity (less

endocarditis and no thromboembolism) for repairs but also that the need for reoperation was not increased compared with the mitral valve replacement group[197].

Sydenham's chorea—Sydenham's chorea can be self-limiting with resolution within weeks to months but some case series report the persistence of symptoms beyond 2 years[221]. Mild or moderate chorea does not require any specific treatment, aside from rest and a calm environment.

As chorea is often benign and self-limiting and medications against chorea medications are potentially toxic, treatment should only be considered if the movements interfere substantially with normal activities, place the person at risk of injury or are extremely distressing to the patient, their family and their friends[209]. Aspirin therapy has no significant effect on rheumatic chorea[212]. Valproic acid and carbamazepine are now preferred to haloperidol, which was previously considered to be the first-line medical treatment for chorea[222,223]. Valproic acid enhances neurotransmitters and stabilizes mood, and carbamazepine is a benzodiazepine anticonvulsant and analgesic. A small, prospective comparison of these three agents concluded that valproic acid was the most effective[224]. However, because of the small potential for liver toxicity with valproic acid, it is recommended that carbamazepine be used initially for severe chorea requiring treatment and that valproic acid be considered for refractory cases[209]. Recent evidence from case series, a retrospective analysis and a single RCT suggest that corticosteroids can reduce symptom intensity and the time to remission in chorea, therefore short courses of prednisolone treatment can be considered for severe or refractory cases[93–98]. The onset of chorea during pregnancy (chorea gravidarum) can be caused by ARF but there are many other causes of chorea that begin in pregnancy.

Arthritis—The pain of mild arthritis or arthralgia and fever might respond to paracetamol alone, which should be used if the diagnosis is not confirmed (as early use of NSAIDs might mask the evolution of the typical migratory polyarthritis). This is particularly important in areas in which echocardiography is unavailable, as the typical evolution of migratory polyarthritis is a hallmark of ARF. Aspirin has been the mainstay of treatment for decades, although published evidence also supports naproxen as an alternative for control of the arthritis of ARF. There is no similar published evidence for the use of other NSAIDs, although expert opinion supports the use of ibuprofen and this, as well as other NSAIDs and paracetamol, are recommended in guidelines for first-line treatment of arthritis pain[209]. Naproxen has similar analgesic potency as aspirin but, unlike aspirin[225,226], does not have the risk of the rare complication of Reye's syndrome, which is associated with multiorgan failure when aspirin is used to treat in viral infections in children. Aspirin and NSAIDs quickly control joint symptoms so they should be stopped as quickly as possible — while acknowledging that there is sometimes a need to prolong treatment somewhat to avoid 'rebound' joint symptoms on weaning — as there is no evidence that they have an influence on carditis.

Erythema marginatum and subcutaneous nodules—Erythema marginatum and subcutaneous nodules are painless and transient manifestations. There is no specific

treatment for either but local treatment might be required for ulceration that might rarely occur when the skin overlying the nodules is damaged.

RHD

Best practice RHD care involves secondary prevention with penicillin prophylaxis, timely reviews by a specialist experienced in RHD management, access to echocardiography to serially assess left ventricular function and valve function, adequate monitoring of anticoagulation therapy in patients with atrial fibrillation and/or mechanical prosthetic valves, access to oral healthcare and timely referral for heart surgery[209].

The fundamental goals of long-term management of RHD are to prevent ARF recurrences (which lead to the progression of valve disease) and to monitor left ventricular size and function. In many patients with mild or moderate RHD, in which the left ventricle is not at risk of failing, resolution of RHD is observed over time[227–229]. By contrast, in those with severe RHD, disease might progress owing to the irreversible damage of the valves. This damage leads to impaired left ventricular function as a result of longstanding left ventricular overload, even without recurrences of ARF. Echocardiography has become an essential tool for grading the severity of valvular disease and for assessing left ventricular size and systolic function. Mitral stenosis usually occurs many years after the initial episode of ARF. The pathogenesis and progression of stenosis with valvular, subvalular fibrosis and calcification is often associated with silent ARF recurrences causing symptoms before the age of 20 years[230].

Pregnancy and childbirth—Ideally, women with known RHD should have a complete cardiac assessment before pregnancy[142]. In women who are already symptomatic with considerable RHD, consideration should be given to cardiac surgery before pregnancy to avoid severe morbidity or even mortality as a result of the physiological changes of pregnancy on cardiac work. Mitral stenosis is particularly hazardous. Percutaneous balloon mitral valvotomy may be considered in women with anything more than mild mitral stenosis.

Women with moderate and severe RHD are at risk of obstetric complications such as preterm delivery and fetal complications such as fetal growth restriction. Cardiac complications can be compounded if pregnancy disorders such as pre-eclampsia or obstetric haemorrhage develop. Pregnant women with RHD should ideally be under the care of a multidisciplinary team with an obstetrician in collaboration with a cardiologist and/or an obstetric physician. Women with severe RHD should have their delivery at a referral centre that has onsite cardiology and intensive-care facilities.

Anticoagulation—Warfarin, a vitamin K antagonist, is the drug of choice for anticoagulation for patients with prosthetic heart valves, including those with both RHD and non-rheumatic valve disease. As the absorption of warfarin is affected by diet, the international normalized ratio must be measured on a regular basis with adjustments of the dose as required. Newer anticoagulants have been developed that dose-dependently inhibit thrombin or activated factor X (such as dabigatran), but the efficacy and the safety of these newer agents are still being studied in patients with prosthetic valves and these agents are

currently not recommended for use in this situation[209]. Anticoagulation is also indicated for those who develop atrial fibrillation.

Infective endocarditis—Although the American Heart Association guidelines no longer list RHD as an indication for antibiotic prophylaxis to prevent infective endocarditis, in other regions of the world where RHD and endocarditis are common, it is recommended that persons with established RHD or prosthetic valves should receive antibiotic prophylaxis before procedures expected to produce bacteraemia, especially for *Viridans streptocci*[142,209,231]. Individuals who have a history of ARF but no valvular damage do not require antibiotic prophylaxis[209].

Indications for cardiac surgery—Referral for cardiac surgery is indicated in adults with severe mitral regurgitation, severe aortic regurgitation or severe mitral stenosis[218]. Specific indications are evidence-based[218]; valve regurgitation is assessed on the basis of symptoms and left ventricular size, and mitral stenosis is assessed on the basis of symptoms and valve gradient. Concomitant valve surgery for tricuspid regurgitation might be required. The body of evidence for the threshold for cardiac surgery in children is minimal compared with the adult literature and is mainly based on published experience from New Zealand[220,232–235]. If the valve is judged to have a high likelihood of repair, surgery can be recommended for moderate to severe mitral regurgitation with normal left ventricular size and function.

Mitral valve repair is the operation of choice for mitral regurgitation because of lower mortality and morbidity[236]. In adults, mitral valve repair has a higher reoperation rate than replacement[237]. When it is considered feasible to offer further surgery in the future, repair avoids the potentially fatal consequences of thromboembolism with a prosthetic valve[238]. If the mitral valve is not suitable for repair, the option is valve replacement with either a mechanical valve prosthesis or a bioprosthetic valve. Women of childbearing age who are planning a pregnancy should be offered a bioprosthetic valve rather than a prosthetic valve, even though the reoperation rate will be higher, because the risk of warfarin to the fetus and the risk of heparin regimens to the patient remain high[239].

In most cases, referral for cardiac surgery or valvuloplasty is indicated for severe disease with symptoms and increasingly for asymptomatic disease with evidence of moderate to severe disease (TABLE 3). An exercise test can help to define if 'asymptomatic' patients do in fact have restricted capacity. Early referral should be considered in younger patients as they have a better chance of successful mitral valvuloplasty than older patients. Combined severe mitral regurgitation and severe aortic regurgitation are the most deleterious to long-term ventricular function[233].

Quality of life

The WHO has defined quality of life as "individuals' perception of their position in life in the context of the culture and values systems in which they live and in relation to their goals, expectations, standards and concerns" (REF. 240). However, health-related quality of life (HRQOL) is a function of a wide range of social and cultural factors making measurement and evaluation of HRQOL difficult. A small number of quantitative (using standardized

scoring tools) and qualitative approaches have been applied to understand the effect of RHD on HRQOL.

In Sao Paulo, Brazil, a Portuguese translation of the Pediatric Quality of Life Inventory core and cardiac module was used to investigate the quality of life of 109 young people with RHD and their parents[241]. Results indicated global impairment of quality of life in physical, emotional, social, school and psychosocial domains. Similarly, in Egypt, a sample of 400 parents of children with heart disease (32.5% with RHD) was compared with 400 parents of children with minor illness with an Arabic version of a standardized quality of life questionnaire (SF-36)[242]. The parents of children with heart disease reported that their children had significantly ($P < 0.001$) different HRQOL with a reduction in general health and physical functioning and with role limitations as a result of physical, emotional and social problems. Factors determining HRQOL included age, severity of illness and the financial situation of families. An Arabic version of the Pediatric Quality of Life Inventory was also used to investigate the quality of life of 100 school-aged Egyptian children with ARF. The majority of children recorded a neutral HRQOL and these results correlated well with maternal reports[243]. In Queensland, Australia, the parent-reported CHQ-PF28 tool was used to score the quality of life outcomes of an RHD echocardiography screening programme[244]. The study identified an adverse effect on quality of life in children with an abnormal screening result in the domains of 'general health perception' and 'parental impact — emotional'. Further work to use the PedsQL approach for young people identified with asymptomatic RHD in Nepal is underway[245].

A small number of qualitative studies support quantitative HRQOL data. Anxiety about the medical, social, marital and financial outcomes of people living with RHD is a prominent theme worldwide[246,247]. Studies investigating determinants of adherence to secondary prophylaxis have identified a range of logistical, relational and educational factors with the potential to influence both HRQOL and health-seeking behaviour[248,249]. Strong themes expressed by patients in these studies are lack of empowerment, social and integrative challenges and poor coping mechanisms that are exacerbated by ill health.

The paucity of HRQOL data suggests that the non-medical effect of RHD has been underexplored relative to the severity and the burden of disease worldwide. One of the greatest challenges in the control of RHD is supporting people living with the disease to engage with ongoing prophylactic and therapeutic intervention. Greater attention to the lived experience of children, adults and communities with RHD has recently been prioritized by the RHD clinical and research community[250]. Priorities for further research are outlined in BOX 4. Improving the depth and the breadth of QOL studies is a crucial manifestation of this commitment and ultimately an opportunity to optimize clinical care for people living with RHD.

Outlook

With a few exceptions[227], research into RHD has not received the backing of researchers from high-resource countries who are supported by dedicated funding and contemporary methodological and technological tools. However, there has recently been a sustained

increase in the focus on RHD among researchers in RHD-endemic countries[251–253]. We believe that these efforts will contribute to a reduction in ARF and/or RHD burden if they can be coordinated around three broad themes: effective implementation of known, evidence-based interventions, generation of new knowledge and interventions for RHD prevention and treatment, and advocacy of RHD control efforts (BOX 5). Although these represent distinct areas of focus, there is much overlap between these strategies and their integration into one concerted effort will be crucial to the success of ARF and/or RHD control.

Implementation of evidence-based interventions

It is now well known that there is poor use of established preventive and control strategies in populations with RHD. As an example, recent data indicate that just more than half of eligible patients were receiving secondary antibiotic prophylaxis[52], an intervention proven to reduce the recurrence of ARF[170]. The barriers to uptake of simple, inexpensive treatments such as penicillin are numerous but mainly reflect the lack of systems to identify and to track patients with RHD in the community. Establishment of ARF and RHD registers for this purpose has been advocated as an important step towards disease control. However, there are currently only two countries (Australia and New Zealand) that have widespread register-based RHD control programmes, perhaps reflecting the barriers to establishing disease-specific vertical control programmes in resource-poor countries. Integration of ARF and RHD control efforts into existing disease prevention and control programmes is likely to be a more feasible option in these countries. Case-finding, referral and treatment monitoring as part of school health or other child health programmes is possible with education of providers and little additional funding. For example, RHD is one of the many diseases earmarked for screening and referral under a national child health-focused programme in India (the Rashtriya Bal Swathya Karyakram initiative)[254]. It might be possible to include the provision and the monitoring of secondary prophylaxis, and perhaps even sore throat detection and treatment, under this and similar schemes.

Generation of new knowledge and interventions

This is the most resource-intensive of the three outlined strategies and until recently has been the purview of researchers in high-resource countries. In general, funding for neglected diseases is poor (<2%[218,255] of healthcare research and development spending) and ARF and RHD research receives a mere 0.7% of these funds, the bulk of which (>90%) comes from public and philanthropic donors[256]. Thus, an essential first step in generating new knowledge is to convince funders (including the philanthropic arms of industry) to increase allocation to ARF and RHD research.

We believe that there are six key areas of research that will advance ARF and RHD control. First, contemporary descriptions of the epidemiology of ARF and RHD are needed to identify demographic predispositions, to determine the rates of disease progression and adverse outcomes and to identify shortfalls and barriers to effective care. Such efforts are already underway[52,253]. Second, there are little data on the place of tools, such as screening echocardiography and rapid streptococcal antigen tests, and strategies, such as blanket treatment of sore throats[160], in diagnosis and management algorithms. Formal assessment of

these health technologies and practices, and their economic evaluation, are urgently needed for efficient resource allocation. Third, the development of a safe and effective vaccine against GAS will revolutionize the primary prevention of ARF and RHD. Efforts to accelerate the development of candidate vaccines are ongoing but will need greater coordination and funding[257]. Polyvalent vaccines based on type-specific M protein antigens and some vaccines based on the conserved regions of the GAS M protein seem promising[257,258]. Fourth, the strong genetic predisposition to the development of RHD[259] has led investigators to design large genome-wide association studies to identify potential genetic markers. At least three large studies are underway and are likely to contribute to our understanding of the genetics of ARF and RHD. Fifth, the use of contemporary tissue and plasma proteomic techniques might enhance our understanding of the development and the progression of RHD and might help to identify pathophysiological pathways that are amenable to therapeutic modification[260,261]. Finally, development of longer acting formulations of penicillin might improve adherence to secondary prophylaxis. Awareness of this need has stimulated partnerships between academic researchers, industry and government, which are likely to lead to the development of marketable products in the near future.

Advocacy of ARF and RHD control efforts

Advocacy is of crucial importance in the case of ARF and RHD. RHD predominantly affects the poor and underprivileged in society, the very people whose voices are unlikely to be heard in the absence of strong advocates of their cause. Furthermore, in many RHD-endemic countries, there is an increasingly common perception that ARF and RHD are on the decline. This perception might be based on incomplete and often skewed data[262] and might potentially damage control efforts by understating the public health importance of the disease to policy makers. Accurate data on the burden of the disease in the community and its effects on quality of life and loss of productivity are needed to make advocacy more credible and effective. Advocacy should therefore also place equal emphasis on raising awareness about the need for establishing systems for reliable assessment of disease burden. Finally, the highly successful advocacy campaigns directed at the 'big three' diseases (HIV, tuberculosis and malaria) involved a large number of people and organizations beyond those in the healthcare profession. By contrast, advocacy for ARF and RHD control is mainly done by the few healthcare professionals working on the disease. Broader societal engagement in advocacy efforts, with the involvement of citizens' groups and nongovernmental organizations, is needed for the success of the ARF and RHD control agenda.

Acknowledgments

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Box 1 | Most common clinical presentations of ARF*

- Large joint arthritis and/or arthralgia, usually with fever, and sometimes with pansystolic murmur of mitral regurgitation

- Acute fever, tiredness and breathlessness from cardiac failure, with or without other manifestations (most commonly joint pain and/or swelling) and pansystolic murmur of mitral regurgitation

- Choreiform movements, commonly with behavioural disturbance but often without other manifestations

- Gradual onset of tiredness and breathlessness, which is indicative of cardiac failure, without fever or other manifestations, and pansystolic murmur of mitral regurgitation, which indicates the insidious onset of carditis

*Skin manifestations (erythema marginatum and subcutaneous nodules) are less commonly observed in acute rheumatic fever (ARF).

Box 2 | Key terms

Acute rheumatic fever

An acute illness caused by an autoimmune response to infection with group A *Streptococcus*, leading to a range of possible symptoms and signs affecting any or all of heart, joints, brain, skin and subcutaneous tissues. Acute rheumatic fever is diagnosed according to the Revised Jones Criteria and has a tendency to recur with subsequent group A streptococcal infections.

Rheumatic carditis

Active inflammation of the heart tissues, most importantly the mitral and/or the aortic valves, caused by acute rheumatic fever. Rheumatic carditis can lead to chronic damage that remains after the acute inflammatory episode has resolved.

Rheumatic heart disease

The persistent damage to heart valves resulting in mitral and/or aortic regurgitation, or in long-standing cases stenosis, that remains as a result of acute rheumatic fever with rheumatic carditis. Complications of rheumatic heart disease include heart failure, embolic stroke, endocarditis and atrial fibrillation.

Box 3 | Priorities in management of ARF

Key management priorities in acute rheumatic fever (ARF) and the main actions used to address them include:

Diagnosis

- Hospitalization for assessment and investigations, including echocardiography, acute phase reactants, streptococcal serology and tests for other differential diagnoses

Eradication of group A *Streptococcus* from the throat

- Single dose benzathine penicillin G

Symptomatic treatment of joint involvement and fever

- Nonsteroidal anti-inflammatory drugs (paracetamol may be used until diagnosis has been confirmed)

Management of heart failure

- Bed rest, fluid restriction and cardiac medications

- Corticosteroids may be considered for severe heart failure

- Deferral of surgery, if possible, until acute inflammation has subsided

Management of chorea

- Rest and calm environment

- For severe or refractory cases, administration of valproic acid, carbamazepine or corticosteroids may be considered

Commencement of long-term care

- Education and registration for long-term care

- First dose of benzathine penicillin G (to eradicate group A *Streptococcus* from the throat)

Box 4 | Research priorities on quality of life in RHD

- Understanding the social, cultural and economic effect of rheumatic heart disease (RHD) on communities with an endemic burden of disease

- Investigating the effect of therapeutic interventions — including echocardiography screening, secondary prophylaxis and cardiac surgery — on people living with RHD using comprehensive quality of life assessments

- Investigating the acceptability and quality of life influence of new RHD interventions, including reformulated antibiotics for secondary prophylaxis and potential group A streptococcal vaccines

Box 5 | Potential strategies for ARF and RHD control

Effective implementation of known evidence-based treatments

- Integration of acute rheumatic fever (ARF) and rheumatic heart disease (RHD) control efforts into existing child-health programmes

- Disease-specific and register-based case finding, treatment and tracking (where feasible)

Generation of new knowledge and interventions

- Contemporary data on disease characteristics and outcomes

- Health technology assessment and economic evaluation

- Vaccine development

- Genetic studies

- Plasma and tissue proteomic studies

- Development of longer acting penicillin formulations

Advocacy

- Reliable data on disease burden and effects on populations

- Adaptation of elements from advocacy models of the 'big three' diseases
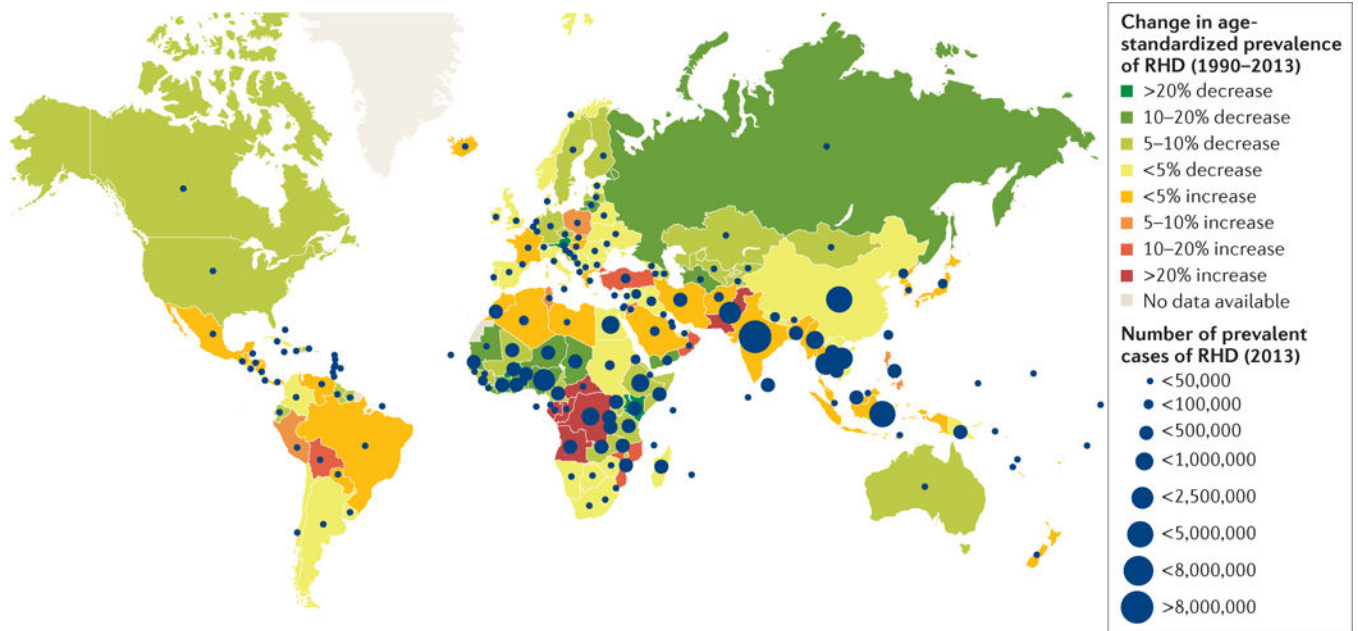
Figure 1. The global burden of RHD

Number of prevalent cases of rheumatic heart disease (RHD) in 2013 by country, as well as the change in age-standardized RHD prevalence from 1990 to 2013. Data from REF. 9. Image courtesy of R. Seth, Telethon Kids Institute, Perth, Australia.
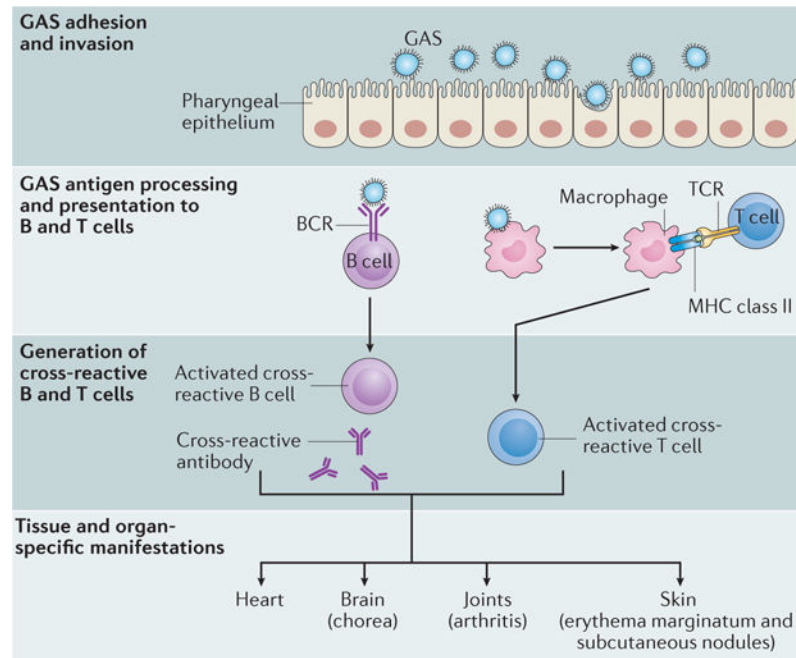
Figure 2. Generation of a cross-reactive immune response in ARF

Following group A *Streptococcus* (GAS) adhesion to and invasion of the pharyngeal epithelium, GAS antigens activate both B and T cells. Molecular mimicry between GAS group A carbohydrate or serotype-specific M protein and the host heart, brain or joint tissues can lead to an autoimmune response, which causes the major manifestations of acute rheumatic fever (ARF). BCR, B cell receptor; TCR, T cell receptor.
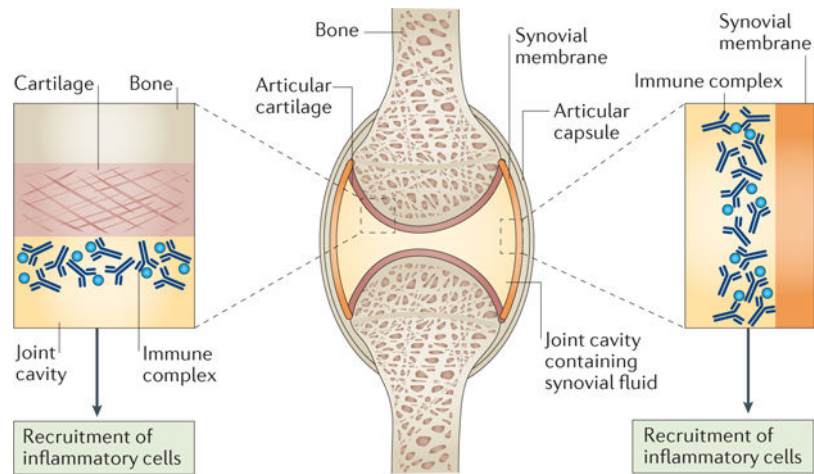
Figure 3. Manifestations of ARF in the joints

Arthritis might be a result of the formation of immune complexes that bind to the synovial membrane and/or collagen in joints, which leads to recruitment of inflammatory cells. ARF, acute rheumatic fever.
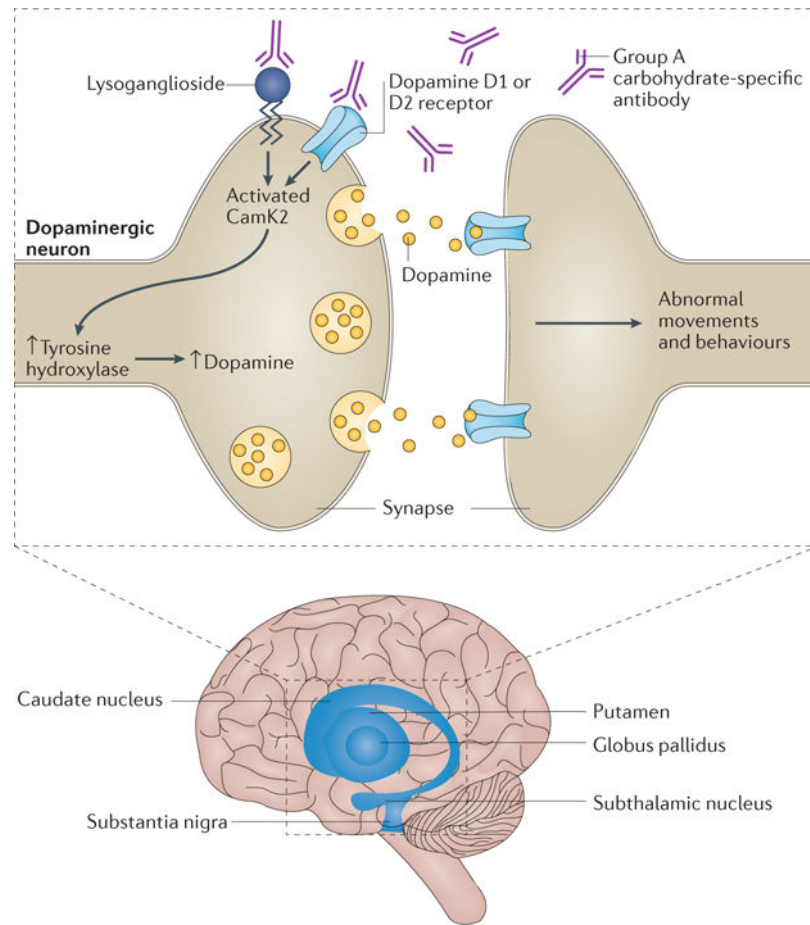
Figure 4. Molecular and cellular basis of Sydenham's chorea

In Sydenham's chorea, neurons in the basal ganglia are attacked by antibodies against the group A carbohydrate of *Streptococcus* spp. that react with the surface of the neuron. This reaction activates signalling through calcium/calmodulin-dependent protein kinase type II (CAMK2), which involves an increase in tyrosine hydroxylase in dopaminergic neurons. Receptors, such as the D1 and D2 dopamine receptors, and lysoganglioside might be autoantibody targets on the neuronal cell. This targeting could lead to altered cell signalling and increased levels of dopamine, in turn leading to abnormal movements and behaviours.
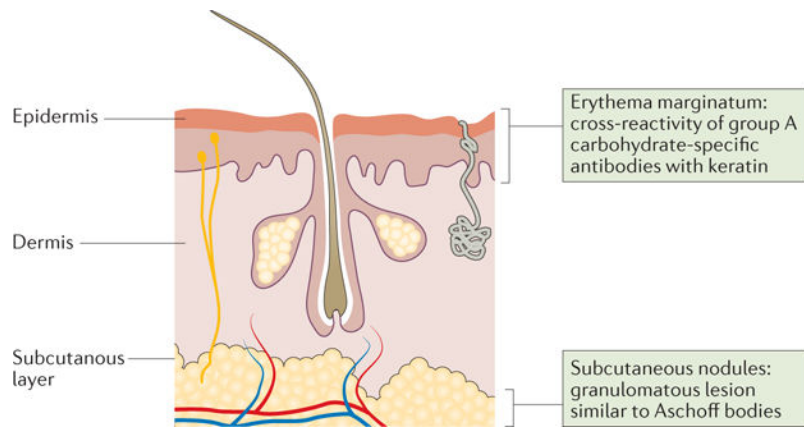
Figure 5. Skin manifestations of ARF

Erythema marginatum might be due to antibodies against group A carbohydrates cross-reacting with keratin and subcutaneous nodules might be caused by delayed hypersensitivity against group A streptococcal antigens.
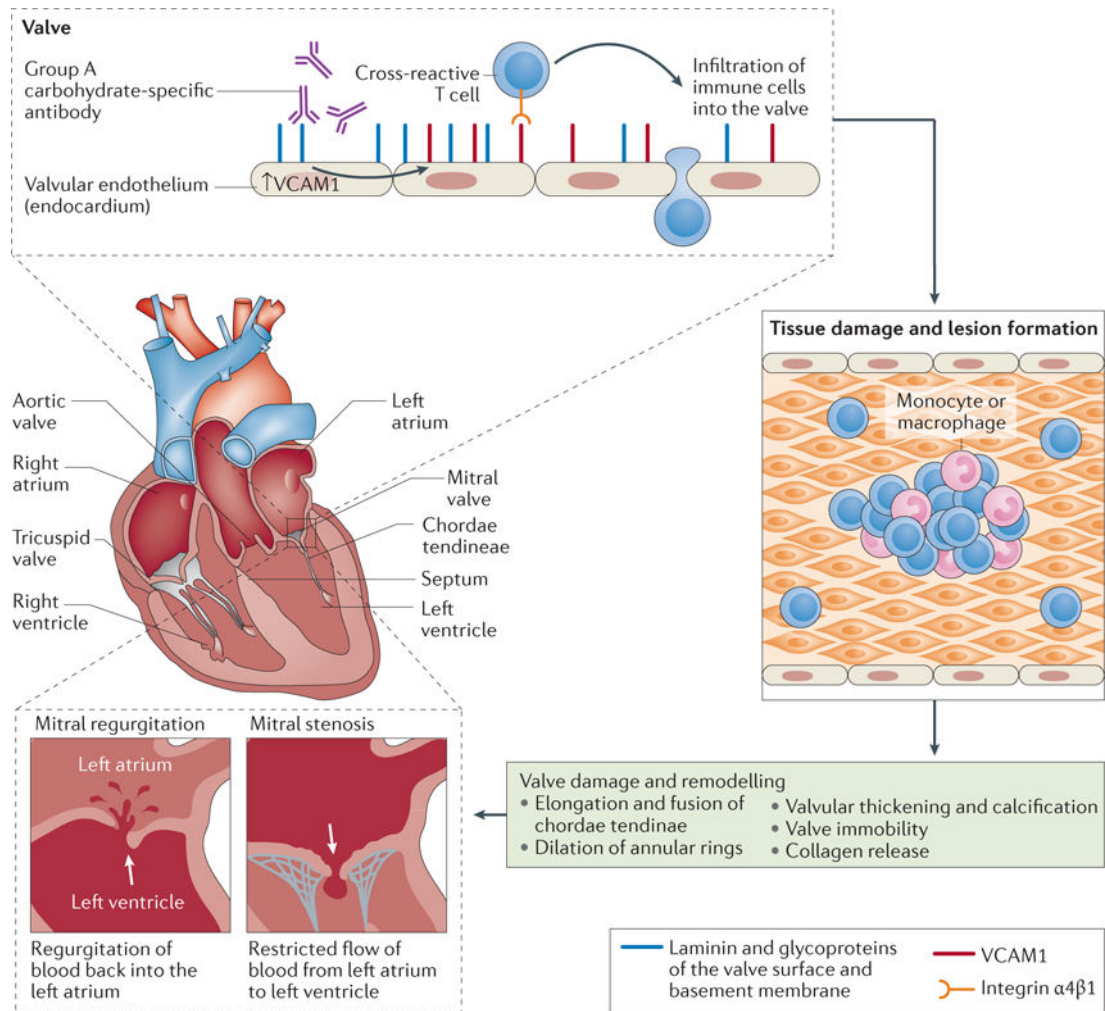
Figure 6. The GAS cross-reactive immune response in the heart

The heart is affected by antibodies (generated by B cells) against the group A carbohydrate binding to the surface of the valve and upregulating vascular cell adhesion molecule 1 (VCAM1) on the surface of the valve endothelium. The upregulation of VCAM1 allows T cells expressing integrin α4β1 (also known as VLA4) to adhere to the endothelium and to extravasate into the valve. The inner valve becomes infiltrated by T cells, primarily CD4+ T cells, and Aschoff bodies or granulomatous lesions form underneath the endocardium. Damage to the endothelium and infiltration of T cells into the valve remodels the valve structure, including the chordae tendineae, with malformation of the valve leading to regurgitation or stenosis of the valve. Breakdown of the valve releases collagen and results in further immune-mediated damage to the valve.
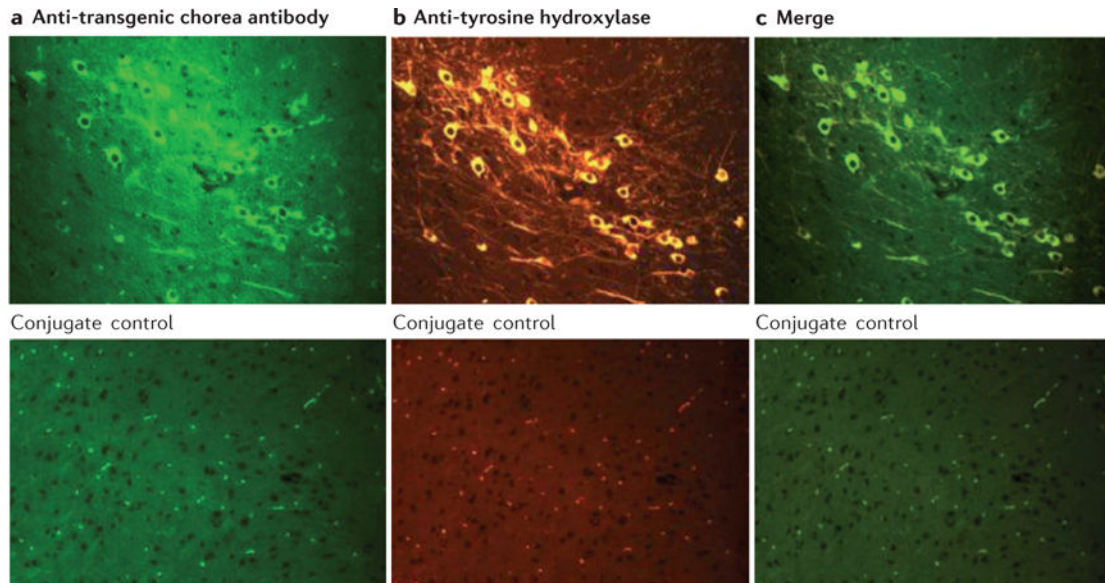
Figure 7. Localization of Sydenham's chorea-derived antibodies and tyrosine hydroxylase in the brains of transgenic mice

Transgenic mice are shown in which genes encoding variable segments of a human monoclonal antibody derived from a patient with Sydenham's chorea are expressed. The resulting antibodies target the dopaminergic neurons in these mice, showing that these antibodies cross the blood–brain–barrier to target the neurons. **a** | Antibody penetration of basal ganglia and neurons in the substantia nigra or ventral tegumental area. Neurons are stained in green with an antibody specific for the transgenic chorea IgG1a antibody. **b** | Dopaminergic neurons are labelled in red using a tyrosine hydroxylase-specific antibody. **c** | Merged frames show the transgenic chorea antibodies target cells that express tyrosine hydroxylase. Magnification 20×. Images are reproduced, with permission, from REF. 32 © (2014) Taylor & Francis.
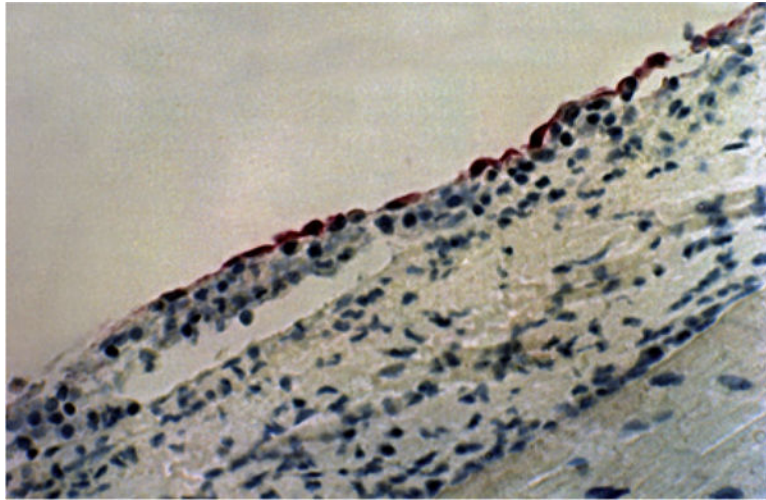
Figure 8. Expression of VCAM1 by the valvular endothelium
Immunohistochemistry of the valvular endothelium in the context of acute rheumatic fever and valvulitis is shown. Vascular cell adhesion protein 1 (VCAM1) has been labelled with an VCAM1-specific monoclonal antibody (mAb) (red). The VCAM1-specifc mAb reacted with the rheumatic valvular endothelium but not with the normal valve (not shown). That is, the antibody to anti-VCAM1 is conjugated to alkaline phosphatase and developed with fast red indicated binding of the antibody to VCAM1. Original magnification 400×. Image is modified, with permission, from REF. 85 © (2001) Oxford Journals.
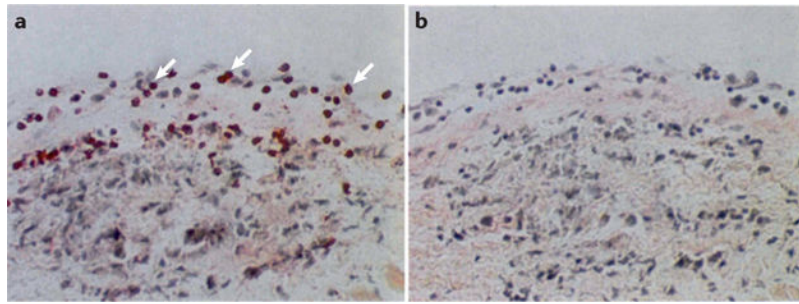
Figure 9. Immunohistochemistry of infiltration of CD4+ T cells into the valve of the left atrium in ARF

In acute rheumatic fever (ARF), CD4+ T cells cross the valvular endothelium and infiltrate into the subendocardium, where they are involved in the formation of Aschoff's bodies. **a** | An Aschoff body, with CD4+ T cells in the valve (red, indicated with arrows) labelled with a primary monoclonal antibody against CD4, secondary antibody against human IgG and fast red. **b** | An IgG1 isotype control did not react with the rheumatic valve. CD4+ T cells are stained with the CD4-specific mAb, a secondary antibody conjugated to alkaline phosphatase and development with fast red to detect antibody binding to CD4+ T cells. Magnification 200×. Image is modified, with permission, from REF. 87 © (2001) American Society for Microbiology.
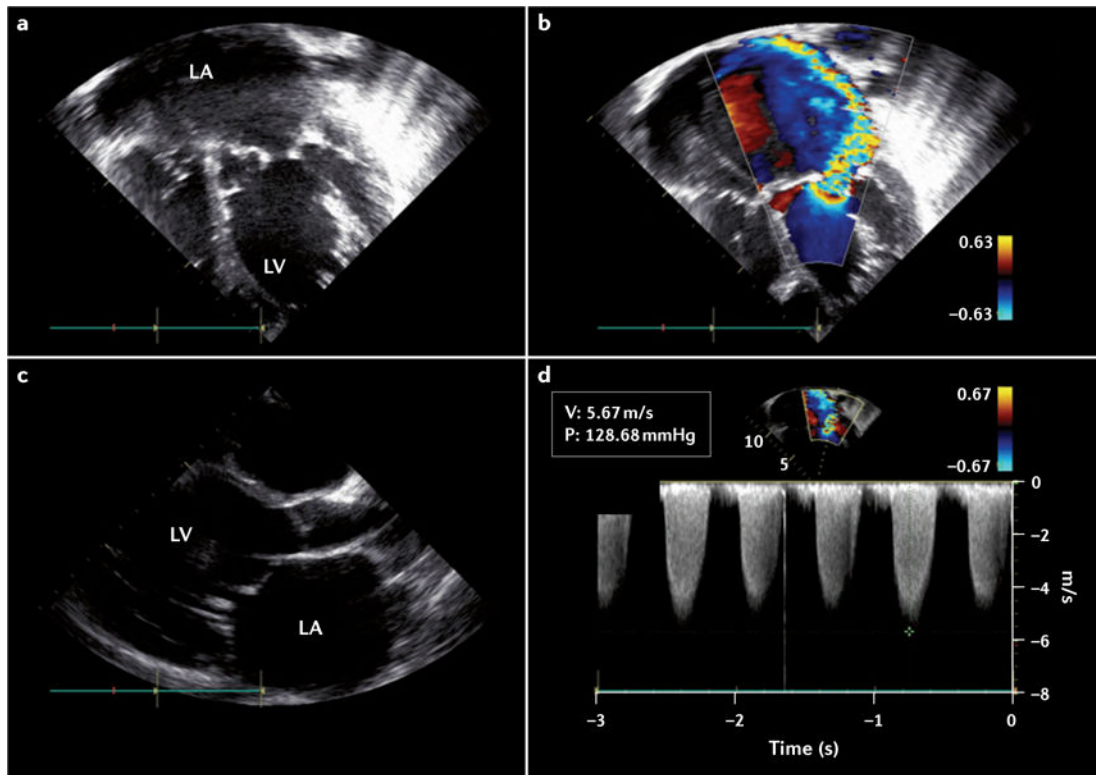
Figure 10. Echocardiogram from child with severe mitral regurgitation

This echocardiogram was produced as part of an echocardiography screening programme. **a** | Apical four-chamber view in black and white Doppler. **b** | Apical four-chamber view in colour Doppler. The colour jet extends to the back of the left atrium. **c** | A parasternal long-axis view. The mitral valve is thickened with excessive leaflet tip motion and lack of coaptation. The left atrium is severely dilated and the left ventricle is moderately dilated. **d** | Pan-systolic spectral Doppler of mitral regurgitation. LA, left atrium; LV, left ventricle; P, pressure; V, volume.
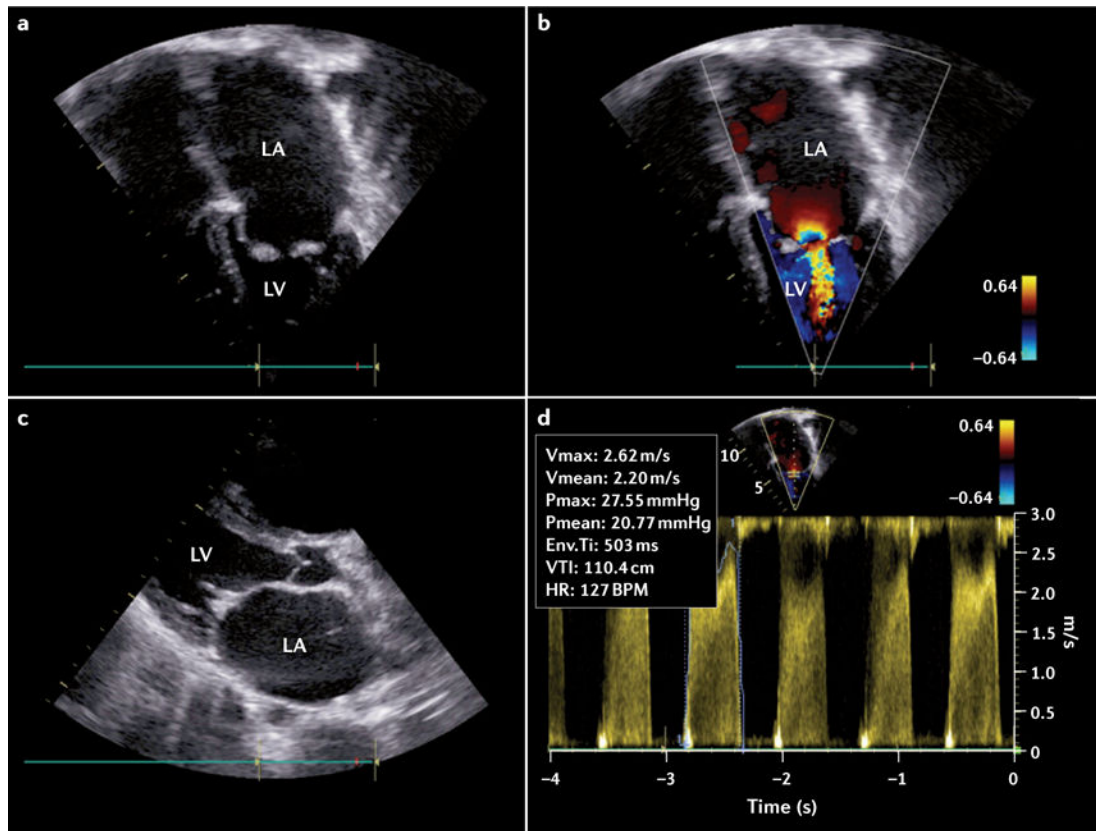
Figure 11. Echocardiogram from child with severe mitral stenosis
This echocardiogram was produced as part of an echocardiography screening programme. **a** | Apical four-chamber view in black and white Doppler. **b** | Apical four-chamber view in colour Doppler. The colour jet reveals turbulence in diastole. **c** | A parasternal long-axis view. The mitral valve is thickened with limited motion and the chordae are thickened and fused. The left atrium is severely dilated. **d** | Pan-diastolic spectral Doppler of with severe mitral stenosis mean gradient (mean 21 mmHg). Env. Ti, envelope time; HR, heart rate; LA, left atrium; LV, left ventricle; Pmax, maximum pressure gradient; Pmean, mean pressure gradient; Vmax, maximum velocity; VTI, velocity time integral.

Table 1

Genetic polymorphisms of immune response-related genes associated with ARF and RHD

Gene	Polymorphism	Effect of polymorphism	Population	Refs
MBL2	−221 X,Y (promoter, exon 1) A (52C, 54G, 57G), O (52T, 54A, 57A)	High production of mannose-binding protein	Brazilian	55
	A (52C, 54G, 57G), O (52T, 54A, 57A)	Low level of *MBL2* in sera	Brazilian	56
FCN2	−986G>A, −602G>A, −G>A (promoter)	Low levels of *FCN2*	Brazilian	57
TLR2	2258A>G (exon 3), resulting in 753 Arg>Gln	Low level of pathogen recognition	Turkish	58
FCGR2A	494A>G (exon 4), resulting in 131 His>Arg	Low ability of receptor to bind human IgG2	Turkish	59
IL1RN	Variable number of tandem repeats A1, A2 A3, A4 (intron 2)	Low level of receptor expression	Egyptian and Brazilian	60,61
TNF	−308G>A (promoter)	T_H1 and T_H2 imbalance	Mexican, Egyptian and Brazilian	60,62,63
	−238G>A (promoter)	High production of TNF	Turkish, Mexican and Brazilian	63,64
TGFB1	−509C>T (promoter)	T_H1 and T_H2 imbalance	Egyptian	65
	−509C>T (promoter)	Protection from developing RHD	Chinese	66
	869T>C (exon 1), resulting in 10 Leu>Pro	Association with elevated serum TGFβ1	Egyptian	65
IL10	−1082G>A (promoter)	T_H1 and T_H2 imbalance	Egyptian	60
CTLA4	49A>G (exon 1)	Transmits an inhibitory signal to T cells	Turkish	67
HLA class II	Diverse HLA-DR alleles located at short arm of chromosome six at *DRB1* gene, including DR1, DR2, DR3, DR4, DR5, DR6, DR7 and DR9	Antigen recognition and antigen presentation to T cells; activation of humoral and cellular immune responses	Several ethnic populations	68–81

AFR, acute rheumatic fever; *CTLA4*, cytotoxic T lymphocyte-associated protein 4; *FCGR2A*, Fc fragment of IgG low-affinity IIa receptor; *FCN2*, ficolin 2; HLA, human leukocyte antigen; *IL10*, interleukin-10; *IL1RN*, interleukin-1 receptor antagonist; *MBL2*, mannose-binding lectin protein C 2; RHD, rheumatic heart disease; *TGFB1*, transforming growth factor β1; T_H, T helper; *TLR2*, Toll-like receptor 2; *TNF*, tumor necrosis factor.

Table 2

The Jones Criteria 2015 for the diagnosis of rheumatic fever

Criteria	Patient population[*]	Manifestations
Major	Low risk[‡]	• Carditis[§] (clinical and/or subclinical[§]) • Arthritis (polyarthritis only) • Chorea • Erythema marginatum • Subcutaneous nodules
	Moderate and high risk	• Carditis (clinical and/or subclinical) • Arthritis (including monoarthritis, polyarthritis or polyarthralgia[‖]) • Chorea • Erythema marginatum • Subcutaneous nodules
Minor	Low risk[‡]	• Polyarthralgia • Fever (38.5 °C) • An ESR of 60 mm per hour and/or CRP of 3.0 mg per dL[¶] • Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)
	Moderate and high risk	• Monoarthralgia • Fever (38 °C) • An ESR of 30 mm per hr and/or CRP of 3.0 mg per dL[¶] • Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)

As in the past Jones Criteria versions, it should be recalled that erythema marginatum and subcutaneous nodules are rarely 'stand alone' major criteria. In addition, joint manifestations can only be considered in either the major or minor categories but not both in the same patient. ARF, acute rheumatic fever; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RHD, rheumatic heart disease.

[*] For all patient populations with evidence of preceding group A *Streptococcus* infection, diagnosis of initial ARF requires two major manifestations or one major plus two minor manifestations. Diagnosis of recurrent ARF requires either two major manifestations, one major and two minor manifestations or three minor manifestations.

[‡] Annual ARF incidence of 2 per 100,000 school-aged children or all age RHD prevalence of 1 per 1,000 people per year.

[§] Defined as echocardiographic valvulitis.

[‖] Polyarthralgia should only be considered as a major manifestation in moderate and high risk populations after exclusion of other causes.

[¶] CRP value must be greater than the normal laboratory upper limit. In addition, as the ESR might evolve during the course of ARF, peak ESR values should be used.

Table 3

Indications for cardiac surgery in RHD

Condition	Patient group	Criteria
Severe mitral regurgitation	Adults	• Severe mitral regurgitation with symptoms (NYHA class 2–4) and an LVEF of >30% • Asymptomatic mitral regurgitation and one of the following: LVESD of 40 mm, impaired left ventricular function with an LVEF of >30% and <60%, pulmonary hypertension of >50 mmHg or new onset atrial fibrillation • Moderate to severe mitral regurgitation with an LVEF of >60% and an LVESD of <40 mm, and only if the valve is judged to have a high likelihood of repair
	Children	• Severe mitral regurgitation with symptoms of breathlessness • Asymptomatic mitral regurgitation and one of the following: impaired left ventricular function of <60%, an LVESD z-score of 2.5 mm or pulmonary hypertension of >50 mmHg
Mitral stenosis *	Adults and children	• Severe mitral stenosis with symptoms (NYHA class 2–4) • Asymptomatic severe mitral stenosis and one of the following: paroxysmal atrial fibrillation, a mitral valve area of <1.5 cm^2, pulmonary hypertension of >50 mmHg or thromboembolism
Severe aortic regurgitation	Adults	• Symptoms NYHA class 2–4 • Asymptomatic severe aortic regurgitation and one of the following: an LVESD of 50 mm, impaired left ventricular function with an LVEF of <50% or a LVEDD of >65 mm
	Children	• Symptoms • Asymptomatic severe aortic regurgitation with an LVESV z-score of >4 and impaired left ventricular function with an LVEF of <50%

LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association; RHD, rheumatic heart disease.

*Mitral valvuloplasty or cardiac surgery is recommended.