Acute rheumatic fever

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Acute rheumatic fever is caused by an autoimmune response to throat infection with Streptococcus pyogenes. Cardiac involvement during acute rheumatic fever can result in rheumatic heart disease, which can cause heart failure and premature mortality. Poverty and household overcrowding are associated with an increased prevalence of acute rheumatic fever and rheumatic heart disease, both of which remain a public health problem in many low-income countries. Control efforts are hampered by the scarcity of accurate data on disease burden, and effective approaches to diagnosis, prevention, and treatment. The diagnosis of acute rheumatic fever is entirely clinical, without any laboratory gold standard, and no treatments have been shown to reduce progression to rheumatic heart disease. Prevention mainly relies on the prompt recognition and treatment of streptococcal pharyngitis, and avoidance of recurrent infection using long-term antibiotics. But evidence for the effectiveness of either approach is not strong. High-quality research is urgently needed to guide efforts to reduce acute rheumatic fever incidence and prevent progression to rheumatic heart disease.

Introduction

Acute rheumatic fever results from an autoimmune response to infection with the group A streptococcus (GAS)—Streptococcus pyogenes. The illness is characterised by varying degrees of inflammation of the joints and the heart, typically manifesting as polyarthritis and valvular regurgitation. Less commonly, involvement of the basal ganglia during the autoimmune process results in chorea. Except for the valve lesions, all other manifestations of acute rheumatic fever resolve without sequelae. As the acute illness resolves, valvular lesions usually reduce in severity, but can persist or progress, leading to chronic rheumatic heart disease. Although acute rheumatic fever itself is rarely life-threatening, rheumatic heart disease can cause heart failure, stroke, or death. Acute rheumatic fever and rheumatic heart disease are diseases of poverty, and have largely disappeared from affluent parts of the world. However, in low-income countries, and among marginalised sections of society in high-income countries, acute rheumatic fever and rheumatic heart disease remain an important cause of morbidity and mortality. In this Seminar we present our understanding of the epidemiology, pathogenesis, and management of acute rheumatic fever, highlighting knowledge gaps and priorities for research.

Disease burden

Incidence of acute rheumatic fever

The incidence of acute rheumatic fever varies widely, mainly by socioeconomic development.1 Although the disease is no longer a public health problem in high-income countries, occasional outbreaks do occur,2 and the disease continues to persist in some of these countries.3,4 Data from prospective studies suggest that acute rheumatic fever annual incidence ranges between eight and 51 per 100 000 among children and young people.5 More recent reports from two endemic regions indicate annual rates that are lower than 20 per 100 000,6 but incidence remains high in the South Pacific, and among indigenous people in Australia and New Zealand.5,6 However, the true incidence of acute rheumatic fever in large parts of Africa and Asia is unknown, because of the absence of regional data (table I).6,7

Trends in incidence of acute rheumatic fever over time

Few studies have reported acute rheumatic fever incidence over time from the same regions; the available data indicate markedly differing trends, with reductions in some regions,7,8 no change in others (table I),9,10 and possible increases in some others.9 Estimates from the Global Burden of Disease study show a significant reduction in rheumatic heart disease burden over the past 25 years (1990–2015), which could be due to a decline in incidence of acute rheumatic fever.7 However, estimates of global rheumatic heart disease burden need to be interpreted with caution. First, the overall trend obscures the large variations observed between regions (eg, prevalence decrease in east Asia and no change in sub-Saharan Africa), and even within countries.11,12 Second, estimates of global burden rely either on

Search strategy and selection criteria

We searched PubMed up until December, 2017, for English-language articles using the terms “acute rheumatic fever”, “rheumatic fever”, “ARF” alone and in combination with other terms including “incidence”, “Streptococcus pyogenes”, “group A Streptococcus”, “GAS”, “pathogenesis”, “molecular mimicry”, “genomics”, “GWAS”, “proteomics”, “corticosteroids”, “aspirin”, “immunoglobulin”, “rheumatic heart disease”, “RHD”, “primary prevention”, “secondary prophylaxis”, “benzathine penicillin”, and “cost-effectiveness”. We focused on publications in the past 15 years, but did not exclude commonly cited and highly regarded older publications. We also selected relevant publications from the reference lists of the retrieved articles and reviews. We chose to include more recent publications over older ones that illustrated the same point. To provide readers access to more articles, we have included citations to other comprehensive reviews on the subject.
The centre of the figure depicts the three principal stages in the progression to RHD. RHD=rheumatic heart disease.

Table 1: Incidence of acute rheumatic fever

<table>
<thead>
<tr>
<th>Country or territory</th>
<th>Population at risk (age)</th>
<th>Annual incidence (per 100,000)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steer et al (2009)²⁷</td>
<td>Fiji 5-14 years</td>
<td>15.2</td>
<td>Prospective surveillance of hospital admissions for acute rheumatic fever in a tertiary care hospital; annual incidence rates suggest a decline from the annual rate of 144 per 100,000 estimated in 1965-66</td>
</tr>
<tr>
<td>Vinker et al (2010)³⁰</td>
<td>Israel 5-14 years</td>
<td>7.5</td>
<td>Retrospective survey of community clinics and hospital records</td>
</tr>
<tr>
<td>Breda et al (2012)¹⁴</td>
<td>Italy 2.5-17 years</td>
<td>4.1</td>
<td>Retrospective community-based survey of practitioners and health records</td>
</tr>
<tr>
<td>Milne et al (2012)¹⁴</td>
<td>New Zealand 5-14 years</td>
<td>17.2</td>
<td>Data obtained from National Medical Statistics; annual incidence rates varied widely by ethnicity—Maori people 40-2 per 100,000, Pacific islanders 81.2 per 100,000, and others 2.1 per 100,000</td>
</tr>
<tr>
<td>Lawrence et al (2013)²⁰</td>
<td>Australia 5-14 years</td>
<td>194</td>
<td>Data obtained from the Northern Territory, Australia, acute rheumatic fever and rheumatic heart disease register; annual incidence was recorded in Aboriginal children</td>
</tr>
<tr>
<td>Kumar et al (2014)²⁰</td>
<td>India 5-14 years</td>
<td>8.7</td>
<td>Prospective, active surveillance of a single district of 1.1 million individuals over 8 years</td>
</tr>
<tr>
<td>Beaudoin et al (2015)⁴</td>
<td>American Samoa &lt;18 years</td>
<td>150</td>
<td>Retrospective review of hospital records at the only hospital in the country</td>
</tr>
<tr>
<td>Faucher et al (2015)¹⁵</td>
<td>French South Pacific Island</td>
<td>112</td>
<td>Retrospective review of medical records</td>
</tr>
<tr>
<td>Corsenac et al (2016)¹⁵</td>
<td>New Caledonia 9-10 years</td>
<td>131</td>
<td>Retrospective review of the acute rheumatic fever and rheumatic heart disease register (we calculated the crude rate from data in the paper)</td>
</tr>
<tr>
<td>Kočevar et al (2017)¹⁵</td>
<td>Slovenia 3-14 years</td>
<td>1.25</td>
<td>Retrospective review of hospital records at a single tertiary referral hospital</td>
</tr>
</tbody>
</table>

This table presents the most recent data on acute rheumatic fever incidence reported in the literature. Data published before 2010 have been reviewed previously.⁶,⁹ Note that most data are from retrospective studies, and there was a single study from Asia and no studies from Africa.

Subclinical rheumatic heart disease as a surrogate for acute rheumatic fever incidence

Systematic and active surveillance of children and young people in the community is needed to establish the true incidence of acute rheumatic fever. But, active disease-specific surveillance is costly, and is not feasible in low-income countries. Therefore, other methods might be needed to estimate acute rheumatic fever burden. Subclinical rheumatic heart disease detected by echocardiographic screening⁶ could represent an intermediate stage before the development of clinical disease (figure 1; panel 1 after the index acute rheumatic fever event. Subclinical rheumatic heart disease prevalence correlates closely with acute rheumatic fever incidence. A study from Australia showed that the prevalence of echocardiographically confirmed rheumatic heart disease was higher among indigenous children who are at high risk of acute rheumatic fever (annual incidence 194 per 100,000),³ than in a low-risk (annual incidence <10 per 100,000) population (definite rheumatic heart disease prevalence 8-6 per 1000 vs 0 per 1000)³⁰. Similarly, another study in a low-risk US paediatric population could not identify any cases with definite rheumatic heart disease in the 500 echocardiograms that were screened.²⁷ Definite subclinical rheumatic heart disease prevalence can derive the lower and upper limits of all-age burden from the number of school-age children with rheumatic heart disease.²³⁻²⁶ However, this formula is likely to overestimate burden in countries with a young population (most endemic countries), because the all-age burden is extrapolated from the school-age numbers (appendix). A modified formula (also based on data used for the original derivation),²³⁻²⁶ which uses actual numbers from census data and a different set of multiplication factors could produce more conservative estimates (figure 1; appendix).

See Online for appendix

modelling⁷ or on extrapolations from estimates of prevalence in school children.⁹ Either approach has potential for error. In the absence of data from all regions of the world,¹⁰ modelling-based approaches are susceptible to errors in estimation, simply because of the influence of model variables that are strongly associated with disease prevalence. Likewise, extrapolation of school-age burden to estimate all-age rheumatic heart disease burden is prone to large errors. A widely used formula uses multiplication factors of 5-5 and 7-7 to derive the lower and upper limits of all-age burden from the number of school-age children with rheumatic heart disease.²³⁻²⁶ However, this formula is likely to overestimate burden in countries with a young population (most endemic countries), because the all-age burden is extrapolated from the school-age numbers (appendix). A modified formula (also based on data used for the original derivation),²³⁻²⁶ which uses actual numbers from census data and a different set of multiplication factors could produce more conservative estimates (figure 1; appendix).
therefore serve as a surrogate measure of acute rheumatic fever incidence. The use of subclinical rheumatic heart disease as an alternative metric to estimate acute rheumatic fever incidence has several potential advantages. First, this method is less costly and more feasible than active surveillance for acute rheumatic fever. Second, the method is repeatable and can yield information on time trends in acute rheumatic fever incidence. Third, since a wide variation exists in acute rheumatic fever incidence even within countries, screening can be used to obtain locally representative data. Finally, this information can be used for targeted implementation of prevention programmes. However, the prognosis and treatment of patients with subclinical disease is unknown at present, and children identified to have subclinical rheumatic heart disease could be exposed to anxiety and unnecessary treatment. More research is needed to validate this approach.

Pathogenesis

The pathogenesis of acute rheumatic fever remains incompletely understood. Evidence supports the view that acute rheumatic fever is the result of an autoimmune response to pharyngeal infection with GAS in genetically predisposed individuals, which is mediated through molecular mimicry. About 0.3–3% of people with GAS pharyngitis develop acute rheumatic fever, depending on genetic predisposition and the virulence of the infecting strain. Although some genetic and epidemiological evidence exists for skin infection as the event that leads to acute rheumatic fever, pharyngeal infection is considered to be the trigger in most cases. Streptococcal antigens activate humoral and cell-mediated immune pathways leading to the production of antibodies against streptococcal components, which cross-react with human proteins. This results in immune-mediated inflammation and injury (figure 2).

Evidence from numerous small candidate-gene studies, and more recently, two genome-wide association studies, suggests that genetic susceptibility could be conferred by polymorphisms of genes involved both in the innate and adaptive immune pathways (panel 2). The genetic susceptibility to acute rheumatic fever is heritable, as shown by the higher risk of concordance among monozygotic twins than dizygotic twins (44% vs 12%). Inheritance is non-Mendelian and polygenic, with variable and incomplete penetrance. Ongoing large genome-wide association studies will provide further insights.

There are several reasons why molecular mimicry is believed to be the most likely mechanism underlying the development of autoimmunity in acute rheumatic fever. First, the GAS M protein and the carbohydrate epitopes with human cardiac myosin and laminin on heart valves. Second, monoclonal antibodies against these antigens, derived from tonsillar and peripheral blood lymphocytes of patients with acute rheumatic fever, cross-react in vitro with human myosin and valvular endothelium. Finally, immunisation with recombinant streptococcal M protein induces autoantibody formation and valvulitis in Lewis rats. Structural similarity between the myosin epitopes and heart valve proteins, such as laminin and vimentin, could be the basis of antibody-mediated damage to valve structures. Although a wide variety of GAS emm types can induce carditis, a mechanism common to all of them could be the targeting of epitopes in the S2 subregion of human cardiac myosin by autoantibodies. Molecular mimicry also underlies the cell-mediated immune inflammation that occurs in acute rheumatic fever. T-cell clones derived from rheumatic lesions react with myosin and vimentin, and release inflammatory cytokines upon exposure to these antigens in vitro.

Valve damage in acute rheumatic fever occurs as a result of both humoral and cellular immune responses against valve proteins. Binding of cross-reactive antibodies at the valve surface induces the upregulation of vascular cell adhesion molecule 1, which facilitates the adherence and infiltration of activated CD4 T cells and B lymphocytes. Local tissue damage is mediated predominantly through a T helper cell 1 response, leading to production of inflammatory cytokines such as interferon γ and tumour necrosis factor α, with decreased concentrations of interleukins 4 and 10 (figure 2). Local epitope spreading results in the identification of other self-antigens (vimentin and collagen), which causes amplification of
Mechanisms other than molecular mimicry have also been proposed to explain the pathogenesis of acute rheumatic fever. Streptococcal M protein binding to basement membrane collagen type 4 epitopes can induce autoimmunity to collagen, resulting in inflammation and scarring of valve leaflets. However, antibodies against collagen do not induce valvulitis in animal models. Therefore, molecular mimicry is probably essential for induction of autoimmunity and initiation of valve damage during acute rheumatic fever, and antibodies against collagen could contribute to disease progression.

### Risk factors and diagnosis

Poverty and social disadvantage are among the strongest predisposing factors for developing acute rheumatic fever, acting possibly through household overcrowding, which facilitates easy transmission of GAS. Ethnicity could be another predisposing factor, but the increased susceptibility in some ethnic groups might be explained by the higher prevalence of poverty and overcrowding in these groups, rather than genetic susceptibility.

The incidence of acute rheumatic fever is highest among children aged 10–14 years, followed by those aged 5–9 years. Children younger than 5 years rarely develop acute rheumatic fever, and a first episode is rare beyond age 30 years. Recurrences can occur at older ages but are rare beyond 40 years. Males and females are equally likely to have acute rheumatic fever, although rheumatic heart disease is more common in females.

### Diagnosis of acute rheumatic fever: the Jones criteria

No single laboratory test or clinical feature is diagnostic of acute rheumatic fever. Most patients with acute rheumatic fever present with a combination of fever, joint manifestations, and cardiac involvement. A smaller proportion have chorea, and skin manifestations are infrequent. In children, fever and joint symptoms are common, can have many causes, and are by themselves not sufficient to diagnose acute rheumatic fever. Chorea and the skin manifestations are specific to acute rheumatic fever. The Jones criteria provide a framework for allocating weights to individual clinical features (ie, major and minor criteria) to make a syndromic diagnosis. With the decline of acute rheumatic fever in the USA, the original criteria were revised periodically to improve their specificity (at the cost of sensitivity). Acute rheumatic fever incidence varies considerably around the world, and clinical manifestations can vary by acute rheumatic fever endemcity. Therefore, the need for modification of the criteria and their nuanced application to different populations was recognised, and the most recent revision of...
the Jones criteria incorporated several modifications. The three major changes in the revision were: risk stratification based on disease endemicity, different implications of joint manifestations for different populations, and acceptance of echocardiographic evidence of carditis (subclinical carditis) as a major manifestation. The revision also provides guidance on diagnosing recurrent acute rheumatic fever (panel 3).

The 2015 revision adopted a Bayesian approach to diagnosis by categorising patients from regions with an acute rheumatic fever annual incidence of less than 2 per 100 000, or an all-age rheumatic heart disease prevalence of less than or equal to 1 per 1000, as having a low-risk of disease, and all other patients as having a moderate or high risk. Polyarthralgia and aseptic monoarthritis are considered to be major manifestations, and monoarthralgia a minor manifestation of the disease in individuals who are at moderate or high risk of acute rheumatic fever. This classification is based on data indicating that polyarthralgia and monoarthralgia are common manifestations of acute rheumatic fever in endemic regions. Migratory polyarthritis, the classic description of the type polyarthralgia and monoarthritis are common manifestations of less than or equal to 1 per 1000, as having a low-risk of rheumatic fever (panel 3). The decision to include subclinical carditis as a major manifestation is timely, and is supported by good data. Echocardiography identifies patients with cardiac involvement more reliably than clinical examination alone. A systematic review showed that echocardiography performed within 3 months of an episode of acute rheumatic fever identified subclinical carditis (mitral regurgitation as diagnosed by WHO criteria) in about 18% of patients. About 45% of these patients had persistent or worsening valve lesions over 2 years, highlighting the non-trivial nature of subclinical carditis. Echocardiography is also better at establishing the severity of lesions than clinical examination. Since severity of the index episode of carditis is one of the best predictors of rheumatic heart disease on follow-up, echocardiography could provide better prognostic information. In a retrospective analysis of patients with acute rheumatic fever followed up for about 9 years, only 4% of patients with a normal echocardiogram progressed to rheumatic heart disease, compared with 25% of patients who had no clinical carditis. Likewise, a smaller proportion of patients with mild lesions on echocardiography progressed than did those who had mild clinical carditis. These results highlight the potential for misclassification of moderate carditis as mild, and mild lesions as normal, by clinical examination. These data suggest that for every 1000 patients with acute rheumatic fever, echocardiography would identify 124 additional patients with subclinical carditis, most of whom would progress to rheumatic heart disease.

<table>
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<tr>
<th>Panel 2: Mediators of genetic susceptibility to acute rheumatic fever</th>
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<tr>
<td>Several genes confer susceptibility to acute rheumatic fever and rheumatic heart disease, through alleles that code for proteins involved in both the innate and adaptive immune response to GAS infection.</td>
</tr>
<tr>
<td>- Innate immunity: TLR2, FCN2, MASP2, MBL2, MIF, and FCGR2A</td>
</tr>
<tr>
<td>- Adaptive immunity: HLA class II alleles and IGHV4-61*02</td>
</tr>
<tr>
<td>- Both innate and adaptive immunity: IL1RA, TNF, TGFBI, IL10, and CTLA4</td>
</tr>
<tr>
<td>TLR2 and FCN2 are involved in pathogen recognition and elimination of bacteria. MASP2, MBL2, MIF, and FCGR2A are involved in clearing immune complexes. Several HLA DR alleles are located in the short arm of chromosome 6 in the DRB1 gene, of which HLA-DR7 is the most commonly associated with acute rheumatic fever. GWAS data suggest that variation at the HLA-DQA1 and DQB1 loci could confer increased risk of developing acute rheumatic fever in Indigenous Australians. An allele of the IGHV gene segment (IGHV4-61*02) was shown to be associated with rheumatic heart disease in another GWAS. The genes that control the production of inflammatory mediators are IL1RA and TNF, and TGFBI regulates cell proliferation, differentiation, and migration into the tissues. Interleukin 10 induces anti-inflammatory cytokines, and CTLA4 interferes with the T-cell immune response.</td>
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Simplifying the diagnosis of acute rheumatic fever in moderate and high-risk populations

In endemic regions in low-income countries, less emphasis should be placed on obtaining evidence of preceding streptococcal infection, because bacteriological diagnosis is seldom sought, and anti-streptolysin O titres alone might not be sufficiently sensitive or specific. Similarly, temperature records during fever might not be available, and fever could be masked by the use of over-the-counter antipyretics. Despite these barriers to the strict application of the Jones criteria, correctly identifying patients who will develop chronic rheumatic heart disease is imperative. Cardiac involvement at baseline, detected by echocardiography, is the best predictor of developing rheumatic heart disease in the future. Because 70–90% of patients with acute rheumatic fever have echocardiographic carditis, all patients with a high probability of acute rheumatic fever based on clinical symptoms should undergo echocardiography. Although in developed countries acute rheumatic fever as a cause of joint symptoms is rare both in the community and in hospital settings, the small amount of data available from developing countries indicate a high likelihood of acute rheumatic fever among patients presenting with joint symptoms. In hospital-based studies, the proportion of patients with arthritis who had acute rheumatic fever was 15% in the West Indies and 41% in India. Therefore, we suggest that all children and adolescents in endemic regions who have joint manifestations (polyarthritis, polyarthralgia, or monoarthritis), with evidence of elevated erythrocyte sedimentation rate (ESR) or C-reactive protein, with or without fever, should have echocardiography for the detection of carditis. Carditis should be diagnosed...
Panel 3: Common clinical features of acute rheumatic fever

The clinical features of acute rheumatic fever are accompanied by evidence of inflammation in the form of elevated C-reactive protein (CRP; >3 mg/dl) and erythrocyte sedimentation rate (ESR; >60 mm in the first hour in low-risk populations, and >30 mm in high-risk populations). A prolonged PR interval (after adjustment for age) is considered a minor manifestation (in the absence of carditis), along with raised ESR and CRP, and monoarthritis (polyarthritis in low-risk populations).

A first or recurrent episode of acute rheumatic fever can be diagnosed in the presence of two major and one minor criteria, or one major and two minor criteria. A recurrent episode can also be diagnosed if three minor criteria are present.

**Fever**

Seen in more than 90% of patients; a low temperature cutoff of 38°C has been suggested for diagnosing fever in endemic regions. In low-resource settings, a clear history of fever can be more important than the temperature at the time of examination.

**Joint manifestations**

Seen in more than 75% of patients; the classic description is that of a migratory polyarthritis involving the large joints (knees, ankles, elbows, and wrists) that responds well to salicylates. Axial and small joint involvement is rare. Usually these joint manifestations are self-limiting and subside with or without treatment by 4 weeks. Polyarthritis and aseptic monoarthritis are commonly seen in endemic regions and are considered major manifestations for diagnosis in moderate-to-high risk populations in the 2015 Jones criteria. Monoarthritis is considered a minor manifestation.

**Carditis**

Classically described as a pan-carditis—ie, carditis is associated with involvement of the pericardium, myocardium, and endocardium. Pericarditis resolves without sequelae. Only some regions of the myocardium are involved, which might not cause systolic dysfunction. Endocardial involvement in the form of valvulitis presents as regurgitation of the mitral valve and, less commonly, of the aortic valve. Clinical manifestations can include palpitations, dyspnea, and heart failure (when regurgitation is severe due to leaflet prolapse or chordal rupture). The holosystolic murmur of mitral regurgitation and, uncommonly, the mid-diastolic Carey Coombs murmur can be audible. Carditis is diagnosed clinically in 50–70% of cases. Subclinical carditis is diagnosed in an additional 12–21% of cases. Carditis, either clinical or subclinical, is now considered a major manifestation.

**Chorea**

Chorea involves involuntary, purposeless movements of the extremities and trunk. Chorea usually follows the index episode of acute rheumatic fever by 1–3 months, and can occur as an isolated manifestation. Seen in 10–30% of cases of acute rheumatic fever, chorea is considered a major manifestation for diagnosis. Evidence of preceding streptococcal infection can be absent because of the long delay to manifestation. Cardiac involvement is common in patients with chorea. Up to 90% of patients have carditis when subclinical involvement is also considered. When chorea is the only manifestation, other causes such as drug toxicity and Wilson’s disease should be ruled out.

**Skin manifestations**

Erythema marginatum is a non-pruritic pink maculopapular rash that blanches on pressure, and occurs mainly on the trunk and proximal extremities. The rash is transient and difficult to identify in patients with dark skin. Subcutaneous nodules seen in acute rheumatic fever are small, painless, and palpated over the bony prominences on the extensor surfaces of the limbs, and along the spinous processes of the vertebrae. Skin manifestations are uncommon (0–10%), but are specific for acute rheumatic fever and are considered major manifestations for diagnosis.

using the modified World Heart Federation criteria suggested by Gewitz and colleagues. The presence of carditis should be sufficient to make a diagnosis of acute rheumatic fever (figure 3). A normal echocardiogram documented during the index illness rules out carditis. If facilities for echocardiography are not available locally (as can often be the case), patients should be referred to an equipped centre for evaluation within 12 weeks of the onset of symptoms. This flexibility in the timing to obtain an echocardiogram can ensure feasibility in most situations. Patients who have a normal echocardiogram can be further assessed for acute rheumatic fever (without carditis) based on the 2015 Jones criteria. The implications of incorrect diagnosis in the absence of carditis are small, because cardiac involvement is unlikely during recurrences because of its mimetic nature. The suggested approach is very similar to that used for the diagnosis of acute rheumatic fever in patients presenting with chorea, and will improve sensitivity in moderate and high-risk populations.

**Treatment of acute rheumatic fever**

The treatment of acute rheumatic fever has three primary goals: elimination of the inciting GAS infection; supportive treatment for arthritis, carditis, and chorea; and treatment directed at reducing progression to chronic rheumatic heart disease. However, many of the treatments that are in use are not based on strong evidence.

**Treatment of the GAS infection**

The goal of treatment with penicillin in acute rheumatic fever is to eradicate GAS infection. Eradication is achieved with either a single dose of intramuscular benzathine benzylpenicillin, or a 10-day course of oral phenoxymethylpenicillin. Although resistance of GAS...
strains to penicillin has not been reported, tolerance is well recognised, but its clinical significance is unknown. Oral amoxicillin (35–40 mg/kg per day for 10 days), oral cephalosporins, and high-dose azithromycin, all result in higher cure rates than oral penicillin. But resistance to macrolide antibiotics is common, and treatment failures have been reported. The antibiotic regimen with the lowest likelihood of treatment failure should be chosen while also taking into account availability and cost constraints. In practice, a single dose of benzathine benzylpenicillin is often used, because it is cheap, eliminates the potential for non-compliance associated with oral agents, and serves as an introduction to secondary prophylaxis. In patients who have known minor hypersensitivity to penicillin, cephalosporins could be the best option. Patients with a history of angio-oedema, hypotension, or anaphylaxis following penicillin administration should receive macrolide antibiotics.

### Symptomatic and supportive care

#### Arthralgia and arthritis

Joint manifestations respond within 1–3 days to treatment with high-dose aspirin (80–100 mg/kg per day in three or four divided doses). Treatment is usually required for 1–4 weeks, but can be given for up to 12 weeks. Aspirin commonly causes gastrointestinal side-effects, and proton pump inhibitors are often co-prescribed. Tinnitus can occur with aspirin, but subsides after cessation of treatment. Data on the efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) other than aspirin in the treatment of acute rheumatic fever are scarce. In a small, open-label, randomised controlled trial (RCT), naproxen (15–20 mg/kg/day in two divided doses) showed comparable symptom relief to aspirin. Other NSAIDs such as ibuprofen could plausibly also be effective, but this assumption is based on anecdotal data. Steroid therapy results in a more rapid fall in ESR than treatment with aspirin, but can be associated with a greater likelihood of rebound ESR increase on cessation of therapy than aspirin. Fever is rarely high grade and responds well to either paracetamol or aspirin.

#### Carditis

Most patients with carditis during an acute episode of acute rheumatic fever have mild or moderate mitral regurgitation. These patients are usually treated with angiotensin-converting enzyme inhibitors, although these drugs have not been studied in acute rheumatic fever. Diuretics are used for symptom relief. About 10–30% of patients have severe mitral regurgitation, and have pulmonary oedema often benefit from intravenous vasodilators such as sodium nitroprusside, although there are no data in patients with acute rheumatic fever. Nevertheless, since the annular and ventricular dilatation causing severe mitral regurgitation are likely to reverse once inflammation subsides, aggressive vasodilator therapy might be useful in the acute phase of the illness. Rarely, chordal rupture and severe mitral valve prolapse can cause fulminant mitral regurgitation, requiring urgent surgery. The cause of heart failure in patients with acute rheumatic fever has been attributed solely to the rapid onset of valvular regurgitation. Left ventricular dysfunction is thought not to occur in rheumatic carditis, because myocardial involvement is patchy and does not fulfill the criteria for diagnosis of myocarditis, and echocardiographic indices of ventricular function are normal in patients with heart failure. However, data showing elevated cardiac troponin concentrations during carditis suggest that myocardial injury can occur. Furthermore, cardiac MRI in some patients with carditis shows features suggestive of myocarditis. If ventricular dysfunction is documented, patients should receive guideline-based therapy for heart failure.

#### Chorea

Chorea generally develops weeks to months after the GAS infection, and therefore patients can present without the other features of acute rheumatic fever. Spontaneous resolution occurs in most patients between 1 and 6 months. Numerous reports of symptomatic improvement with dopamine antagonists, such as haloperidol, pimozide, and chlorpromazine, have been published, but controlled trials have not been done with any of these agents. Moreover, these agents, especially haloperidol, are associated with extrapyramidal side-effects that limit patients’ daily activities. The antiepileptic drugs carbamazepine and sodium valproate provide symptomatic relief with fewer side-effects, and might be preferable over dopamine antagonists. Oral prednisolone (2 mg/kg per day for 4 weeks) reduced the intensity of chorea and the time to complete remission in a randomised trial. However, clinically significant side-effects (such as weight gain) occurred with steroid treatment. Low-quality evidence

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**Figure 3**: A simplified algorithm for the diagnosis of a first episode of acute rheumatic fever in moderate and high-risk populations

<table>
<thead>
<tr>
<th>Event</th>
<th>Action</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint manifestations and elevated CRP and ESR, with or without fever</td>
<td>Diagnose ARF if 2015 Jones criteria fulfilled</td>
<td>Diagnose acute rheumatic fever</td>
</tr>
<tr>
<td>Echocardiography within 12 weeks</td>
<td>Pathological mitral or aortic regurgitation, with or without morphological changes suggestive of acute carditis</td>
<td>No cardiac involvement on echocardiogram performed within 12 weeks of the index illness</td>
</tr>
<tr>
<td>CRP=acute rheumatic fever, ESR=acute rheumatic fever, ARF=acute rheumatic fever</td>
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CRP=C-reactive protein. ESR=erythrocyte sedimentation rate. ARF=acute rheumatic fever.
**Panel 4: Acute rheumatic fever: critical research needs**

Although several questions relating to acute rheumatic fever remain unanswered and merit focused research, there are only a small number of dedicated acute rheumatic fever and rheumatic heart disease researchers, and the funding available for acute rheumatic fever research is small compared with other neglected diseases. Therefore, consolidating international research efforts might be wise, as is prioritising the research agenda to focus on key areas. Efforts in this direction include the Addis Ababa Communiqué and the recent resolution on rheumatic heart disease passed at the 71st World Health Assembly.

**Obtain locally relevant data on the burden and time trends of acute rheumatic fever**
Collecting these data might require the use of surrogate measures, such as subclinical rheumatic heart disease in vulnerable populations. This approach will help with efficient resource allocation, and focus preventive efforts to communities with the greatest need. Interventions such as school-based sore-throat screening and treatment programmes, which have been shown to work in wealthy countries, could be too resource intensive for low-income countries to implement as fully fledged national programmes, but could be feasible in selected communities at high risk of acute rheumatic fever.

**Randomised trials of secondary prophylaxis to prevent acute rheumatic fever recurrence**
Rigorous evaluation of secondary antibiotic prophylaxis in subclinical rheumatic heart disease, using contemporary research methods and assessment tools, will provide much needed evidence for the use of secondary prophylaxis in general. One trial (NCT03346525) is underway, and more are needed to assess the efficacy of prophylaxis.

**Reducing progression to rheumatic heart disease**
Anti-inflammatory therapy for acute rheumatic fever has long been considered to have the greatest potential for reducing the risk of progression to rheumatic heart disease. Eight RCTs (n=996) have compared various steroid preparations with aspirin, placebo, or no treatment. Overall, steroid therapy did not result in lower rates of valve disease at 1 year (relative risk 0·87, 95% CI 0·66–1·15). The results were similar in the subgroup of patients with severe carditis. However, these results cannot be considered conclusive because of serious limitations of the data. The risk of bias was high, and there was significant heterogeneity between studies, which could only partly be explained by the different agents that were used (oral prednisone, corticoterop, hydrocortisone, and intravenous immunoglobulin). Moreover, echocardiography was used for diagnosing carditis and assessing outcomes in only one of the studies. Therefore, although the available evidence does not support the use of anti-inflammatory therapy in acute rheumatic fever with carditis, adequately powered RCTs of anti-inflammatory therapy are clearly needed. Such studies should evaluate contemporary immunosuppressive regimens, such as pulse methylprednisolone, and use echocardiography for diagnosing carditis and assessing progression (panel 4).

**Randomised trials of anti-inflammatory therapy in acute rheumatic fever**
No treatment is known to reduce or delay progression to rheumatic heart disease. International randomised trials are needed to rigorously assess the efficacy of immunosuppressive regimens in reducing disease progression in patients with acute rheumatic fever.

**Genomics and proteomics to unravel susceptibility and pathogenesis**
Contemporary genomic and proteomic approaches could help unravel new pathophysiological pathways of immune damage and disease progression in acute rheumatic fever, some of which might be amenable to therapeutic intervention. Several genome-wide association studies are underway, two of which have already reported their primary results. Early plasma and tissue proteomic data provide support for current hypotheses of acute rheumatic fever pathogenesis.

**Vaccine development**
This approach potentially offers the most efficient method to reduce disease burden. Although a large proportion of the funding for acute rheumatic fever and rheumatic heart disease research goes to vaccine development, the quantum of funding available is only a fraction of that available for other vaccines in development, and a viable vaccine is still several stages away from clinical use. Aiming for a vaccine that prevents sore throat and invasive group A streptococcus infection could avoid the market failure that has been associated with the development of a dedicated vaccine for acute rheumatic fever prevention.

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**Prevention of acute rheumatic fever**
The decline in mortality due to acute rheumatic fever and rheumatic heart disease in developed countries preceded the discovery of penicillin by a few decades, and is attributable mainly to the improved living conditions that followed economic prosperity. Rising incomes plausibly lead to better housing and reduced household overcrowding. Primordial prevention measures such as improved housing are likely to yield the greatest reduction from two small randomised trials (with a total of 14 children treated) suggests that intravenous immunoglobulin can result in faster recovery than symptomatic treatment alone. Small case series have also reported the successful use of plasmapheresis. Given its self-limited course, however, mild isolated chorea often does not need treatment. Carbamazepine or sodium valproate could be the best choices when drug therapy is needed.
in acute rheumatic fever incidence. Prevention and treatment of GAS infection (primary prevention), and prevention of recurrent GAS infections with long-term antibiotics (secondary prevention) are other approaches to reduce acute rheumatic fever and rheumatic heart disease burden. Although we discuss these individually, we emphasise that countries that have managed to reduce disease burden have done so by implementing comprehensive control programmes, which included both primary and secondary prophylaxis, complemented by education of people and health-care workers in the community.109–111

**Primary prevention: GAS vaccine**

Prevention of GAS infection using a vaccine could be the most efficient method for preventing acute rheumatic fever. The GAS M protein, encoded by the *emm* gene, is the primary target for vaccine development. The main challenges to the development of a viable vaccine candidate are the diversity of the *emm* types and the wide variation in their global distribution.112 Researchers have adopted two strategies to overcome these challenges. First, recombinant vaccines based on multivalent polypeptides, comprising the most common rheumatogenic M protein epitopes, have been developed. A 30-valent vaccine shows promising efficacy in preclinical testing,113 and a 26-valent vaccine has already completed early clinical evaluation.114 Despite the small number of *emm* types covered by these vaccines, cross-opsonisation has recently been shown between several *emm* types (so-called *emm* clusters), raising the possibility that these might be more broadly protective than previously believed.115,116 The second approach is to target the conserved regions of the M protein on the C terminal, exemplified by two candidate vaccines.117 One is based on a minimal B-cell epitope on the conserved region of the M protein known as J8, and has been shown to induce protective antibodies in mouse models.118,119 A C-repeat epitope-based vaccine has been shown to induce high titres of opsonic, neutralising, and protective antibodies, and will also shortly enter clinical trials.120,121 Despite substantial advances in knowledge and technology, progress in vaccine development has been slow. A shift in strategy, towards a vaccine to prevent GAS pharyngitis and invasive infections (which might have greater global utility than a vaccine solely for preventing acute rheumatic fever), has been advocated to avoid the potential for market failure.122 Whether this strategy will accelerate vaccine development remains to be seen.

**Primary prevention: treatment of GAS pharyngitis**

Primary antibiotic prophylaxis aims to eradicate the GAS infection before it can trigger the immune response leading to acute rheumatic fever. Moderate quality evidence exists for the concept from several randomised and quasi-randomised hospital-based studies, which were done with patients drawn from closed communities (such as army barracks).123 The magnitude of effect of any antibiotic therapy compared with a placebo in preventing acute rheumatic fever is large (RR 0·32, 95% CI 0·21–0·48), with most of the studies using intramuscular penicillin (RR 0·20, 0·11–0·36).124 Model-based analyses also suggest that, in endemic areas, treating all patients presenting to a clinic with a sore throat, even without bacteriological confirmation of GAS infection, might be cost-effective.125

However, implementation of primary prevention in the wider population presents numerous challenges.126 Poor health-seeking behaviour, low awareness among patients and caregivers about the importance of prompt treatment, and lack of resources for bacteriological confirmation of GAS infection are some of these challenges. Additionally, many sore throats that lead to acute rheumatic fever can remain asymptomatic.127 One approach to implementation of primary prevention in the community is a school-based sore-throat identification and treatment programme. In a cluster-randomised trial, such a programme was associated with a (non-statistically significant) 28% reduction in the number of acute rheumatic fever cases when compared with usual care.128 Analysis of pooled data from all the available randomised and before–after studies indicated a nearly 60% reduction in the number of acute rheumatic fever cases.129 In a subsequent national school-based sore-throat screening and treatment programme in New Zealand, a statistically significant 26% decline in notifications of first acute rheumatic fever episodes was reported among children aged 5–12 years in all the ten District Health Boards covered by the programme.130 However, the decline in the number of acute rheumatic fever cases cannot be definitively attributed to the programme, because a significant reduction in the number of cases was also observed among older children who were not covered by school-based screening.131 Moreover, the programme was cost-effective only in a region where both the incidence of acute rheumatic fever and programme effectiveness were high (annual incidence of acute rheumatic fever was 87 per 100,000, and reduction by 30%).132 Therefore, despite the potential for benefit, the practicability and cost-effectiveness of such resource-intensive efforts in low-income countries is debatable. Integrating primary prevention into the existing health-care infrastructure could be more feasible and less expensive.

**Secondary antibiotic prophylaxis**

Disease progression after the index acute rheumatic fever episode is believed to be due to incremental valve damage sustained during recurrences of acute rheumatic fever. Long-term antibiotic prophylaxis, usually with benzathine benzylpenicillin, is widely advocated to prevent GAS infections that could lead to recurrences.133,134 Although this approach has a strong biological plausibility, good evidence of efficacy and effectiveness is lacking. The efficacy of routine secondary prophylaxis in preventing disease...
progression has primarily been assumed from comparisons between acute rheumatic fever recurrence and disease progression rates in the pre-penicillin era\[10\] with those from several decades later in the penicillin era.\[129-131\] Such comparisons ignore the temporal decline in acute rheumatic fever rates during this period. A systematic review of penicillin prophylaxis in rheumatic heart disease\[132\] identified only three randomised or quasi-randomised trials (n=1301) of poor methodological quality comparing antibiotic therapy with a control.\[133-135\] Of these trials, the only study that showed a reduction in acute rheumatic fever recurrences lost over a quarter of patients during follow-up.\[136\] The best support for secondary prophylaxis comes from studies comparing intramuscular benzathine benzylpenicillin with oral penicillin preparations. Although these studies were also of poor methodological quality, they showed large reductions (87–96%) in the risk of recurrent acute rheumatic fever.\[136-139\] Despite reducing acute rheumatic fever recurrence, no randomised trial evidence supports secondary prophylaxis to prevent disease progression.

Despite the scarcity of data on efficacy, long-term benzathine benzylpenicillin is widely used in practice. However, the delivery of benzathine benzylpenicillin to the community has numerous challenges. Poor patient adherence because of low awareness, the pain of intramuscular injections, inconsistent availability and quality of benzathine benzylpenicillin, and the fear of anaphylaxis all contribute to poor compliance.\[144\] Perhaps owing partly to suboptimal delivery, observational studies have not shown the effectiveness of benzathine benzylpenicillin in preventing recurrences or disease progression. Penicillin prophylaxis did not independently predict acute rheumatic fever recurrence or disease progression in the Northern Territory of Australia.\[31\] In a 2-year prospective study of patients with established valve disease, measures of the severity of valve disease, and not secondary prophylaxis, were associated with clinical outcomes.\[145\] A similar absence of effect of secondary prophylaxis on acute rheumatic fever recurrence and clinical events has been noted in other observational studies.\[146\] Secondary prophylaxis could potentially be more useful in patients with mild valve disease. In the cooperative clinical trial of corticotropin,\[147\] cortisone, and aspirin, the risk of a murmur detected 10 years after enrolment in the trial increased with acute rheumatic fever recurrences, mainly among patients who had mild disease at enrolment (grade 1 apical systolic murmur; appendix). By extrapolation, secondary prophylaxis could be most useful in patients with subclinical rheumatic heart disease, but little evidence supports long-term treatment with benzathine benzylpenicillin in such patients.\[148-150\]

Therefore, considering all the available evidence, a short duration of antibiotic prophylaxis (10 years, or up to age 40 years after the index acute rheumatic fever or rheumatic heart disease diagnosis, whichever is later) could be appropriate. This recommendation is based on the biological plausibility of the value of secondary prophylaxis, and data showing near-zero acute rheumatic fever recurrence rates beyond this period.\[7,35\] Contrary to guidelines (which tailor duration on the basis of disease severity),\[132,151\] the duration of prophylaxis should be the same for all patients with carditis detected during the first acute rheumatic fever episode, with the recognition that patients with milder disease could potentially derive the greatest benefit from preventing recurrent acute rheumatic fever. In patients with clinically significant disease, the management of valve disease and heart failure, which have major prognostic implications, should be prioritised.\[152\] Patients who are allergic to penicillin should receive oral erythromycin (250 mg, twice per day). Less frequent dosing regimens of macrolides should not be used.\[153\]

**Conclusion**

For a disease that has afflicted humans for over a century, our understanding of acute rheumatic fever remains incomplete. Accurate data on disease burden from endemic countries are scarce, and there are gaps in our understanding of disease pathogenesis. Treatments for the disease are all based on low-quality evidence. Nevertheless, the global burden of acute rheumatic fever and rheumatic heart disease has decreased over the past few decades, probably more as a result of socioeconomic development than control efforts. Further acceleration of this decline will require concerted, international effort (panel 4) to bridge the gaps in knowledge.

**Contributors**

GK wrote the first draft of all sections, and all subsequent revisions. LG contributed to the sections on pathogenesis and vaccine development.

**Declaration of interests**

GK is a member of the rheumatic heart disease expert panel of the Global Burden of Disease study group, and is chair of the Global Advisory Board of Rheumatic Heart Disease, Evidence, Advocacy, Communication, Hope. LG holds a patent for a group A streptococcal vaccine that is due to enter clinical trials.

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Seminar


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