Rheumatic heart disease

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Rheumatic heart disease, often neglected by media and policy makers, is a major burden in developing countries where it causes most of the cardiovascular morbidity and mortality in young people, leading to about 250 000 deaths per year worldwide. The disease results from an abnormal autoimmune response to a group A streptococcal infection in a genetically susceptible host. Acute rheumatic fever—the precursor to rheumatic heart disease—can affect different organs and lead to irreversible valve damage and heart failure. Although penicillin is effective in the prevention of the disease, treatment of advanced stages uses up a vast amount of resources, which makes disease management especially challenging in emerging nations. Guidelines have therefore emphasised antibiotic prophylaxis against recurrent episodes of acute rheumatic fever, which seems feasible and cost effective. Early detection and targeted treatment might be possible if populations at risk for rheumatic heart disease in endemic areas are screened. In this setting, active surveillance with echocardiography-based screening might become very important.

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Introduction

Rheumatic heart disease is the result of valvular damage caused by an abnormal immune response to group A streptococcal infection, usually during childhood.[1] Although this disease—associated with poverty—has almost disappeared from wealthy countries, its burden remains a major challenge in developing nations.[2,3]

Preventive measures, based mainly on penicillin use and associated with economic and social development, are very efficient and have nearly eradicated rheumatic heart disease in developed countries. However, according to the 2008 Population Reference Bureau, about 80–85% of children younger than 15 years (around 2 billion) live in areas where rheumatic heart disease is endemic.[4] Worldwide, this disease is the leading cause of heart failure in children and young adults, resulting in disability and premature death and severely affecting the workforce in emerging nations.[3] Demographic trends in the developing world, including poor access to birth control and rural exodus, will probably contribute to the substantial rise in the number of people at risk for rheumatic heart disease in the next 20 years.[4] The disease receives little attention from the medical community, as shown by the low number of publications and congress presentations on this subject, and consequently is poorly covered by the media.

Acute rheumatic fever usually occurs 3 weeks after group A streptococcal pharyngitis and can affect the joints, skin, brain, and heart.[5] Around half of patients with acute rheumatic fever present with cardiac inflammation mainly involving the valvular endocardium.[6–11] Although the initial attack can lead to severe valvular disease, rheumatic heart disease most often results from cumulative valve damage due to recurrent paucisymptomatic episodes of acute rheumatic fever, which suggests that it might be insidious at onset.[3,5,12] Because secondary prevention can prevent adverse outcomes, early echocardiography-based identification of silent rheumatic heart disease (showing no clinical signs) with minimal valve lesions by active surveillance programmes might be of major importance.[13–15]

In this Seminar we discuss epidemiology, pathophysiology, available preventive strategies, the rationale for and first experiences with echocardiography-based screening, and treatments for rheumatic heart disease.

Epidemiology

Improved living conditions, nutrition, access to medical care, and penicillin use have substantially changed the epidemiology of acute rheumatic fever and rheumatic heart disease.[3] Nevertheless, both prevail in developing nations and some underprivileged, mainly indigenous, populations in affluent countries.[16,17] Carapetis and colleagues[3,18] have reviewed the worldwide burden of these diseases, but prevalence is difficult to estimate, mainly because of the scarcity of comprehensive disease registries, the use of passive survey systems, and underreporting of acute and chronic cases.[16,19]

Rheumatic heart disease causes at least 200 000–250 000 premature deaths every year,[3] and is the major cause of cardiovascular death in children and young adults in developing countries.[3,20] Epidemiological data for Africa are scarce, despite local efforts to raise awareness and to launch prevention programmes such as those outlined in the Drakensberg declaration.[21,22] In areas of poor or no medical attention, the natural course of the disease prevails because patients have no access to treatment. Mortality

Search strategy and selection criteria

We searched PubMed for publications in English with the terms "rheumatic heart disease and epidemiology", "rheumatic heart disease and pathophysiology", "rheumatic heart disease and diagnosis", "rheumatic heart disease and screening", "rheumatic heart disease and echocardiography", "rheumatic heart disease and therapy", "rheumatic heart disease and prevention", and "rheumatic fever". We focused on, but did not restrict the search to, publications from the past 5 years. We selected relevant articles published in any language and have referenced several review articles and book chapters, particularly on pathophysiology, because they provided comprehensive overviews that are beyond the scope of this Seminar. We also searched the Cochrane database with the term "rheumatic heart disease", and our own database of references and those of linked articles in the searched journals. When more than one article referred to the same point, the most representative article was chosen. Regarding the acute phase of rheumatic heart disease (acute rheumatic fever), we describe only the most classic forms of presentation.

rates in these areas can be as high as 20% at 6-year follow-up according to a Nigerian paediatric cohort study,[23] or 12·5% every year, as documented in rural Ethiopia.[24]

Additionally, rheumatic heart disease causes substantial morbidity in children[25] and adults, and can affect quality of life[26] and economic growth. According to a 2004 WHO report, the number of disability-adjusted life-years lost to the disease was as high as 5·2 million per year, worldwide.[20]

The global incidence of acute rheumatic fever in children aged 5–14 years is roughly 300 000–350 000 per year, although incidence varies substantially by region.[3,5,27] The yearly incidence of a first attack of acute rheumatic fever ranges from 5 to 51 per 100 000 population in Indigenous New Zealand communities, and can reach 80–254 per 100 000 in Indigenous Australian communities.[28,29] Identified modifiable risk factors for acute rheumatic fever include poverty, overcrowding, malnutrition, and maternal educational level and employment.[6,30–33] Virulence of streptococcal strains and genetic susceptibility might partly account for the reported variations in acute rheumatic fever incidences worldwide.[34,35]

According to traditional diagnostic criteria, 15·6–19·6 million people worldwide have rheumatic heart disease.[3] These data mainly originate from surveys of school children in whom diagnosis is made by clinical assessment.[20,32,36,37] Prevalence is highest in adults aged 20–50 years.[3,5,12] Distribution of rheumatic heart disease varies between continents, and sub-Saharan Africans and Indigenous Australians seem to have the highest prevalence.[3,27,38,39] In Pacific Islanders and Indigenous Australians, the prevalence is 5–10 per 1000 school children, and roughly 30 per 1000 adults aged 35–44 years.[17,37] In Asia, rheumatic heart disease prevalence varies,[18]—eg, in rural Pakistan it has a prevalence in the community as high as 12 per 1000 people.[40] In South and Central America, rheumatic heart disease has a lower reported prevalence (1·3 per 1000 school children).[3]

The recent use of echocardiography-based screening and the subsequent detection of silent cases is challenging these traditional epidemiological data.[13,14,41,42]

Pathophysiology

The pathogenesis of rheumatic heart disease results from an immune response consisting of humoral and cellular components after exposure to *Streptococcus pyogenes* (classified as a group A streptococcus by the Lancefield system), usually after a throat infection. The precise pathophysiology is obscure but several advances have now been reviewed.[34,43] Antigenic mimicry in association with an abnormal host immune response is the cornerstone of pathophysiology, based on the triad of rheumatogenic group A streptococcal strain, genetically susceptible host, and aberrant host immune response.[44,45]

Some strains are more likely to cause acute rheumatic fever than are others.[5] *S pyogenes* contains M, T, and R surface proteins, which are all associated with bacterial adherence to throat epithelial cells. The rheumatogenicity of some streptococcus families has traditionally been considered a feature of strains belonging to specific M serotypes. However, data show that rheumatogenic M serotypes were infrequently identified in communities with high burdens of acute rheumatic fever and rheumatic heart disease. These results question the potential importance of other disease-causing serotypes, especially those that cause streptococcal skin infections, which might be implicated in cases of acute rheumatic fever.[46–48]

In 1889, Cheadle noted that the chance of an individual with a family history of acute rheumatic fever acquiring the disease is "nearly five times as great as that of an individual who has no such hereditary taint".[49] Generally, HLA class II molecules (which participate in antigen presentation to T-cell receptors) seem to be more closely associated with an increased risk of acute rheumatic fever or rheumatic heart disease than are class I molecules, although no single HLA haplotype or combination has been consistently associated with disease susceptibility.[34] The exact molecular mechanism by which HLA class II molecules confer susceptibility to autoimmune diseases is unknown.

The role of autoimmune reactions in the pathogenesis of acute rheumatic fever was substantiated when antibodies against group A streptococcus reacted with human heart preparations.[50,51] After binding to the antigenic peptide, the particular HLA complexes can initiate inappropriate T-cell activation.[52] Molecular mimicry takes place between streptococcal M protein and several cardiac proteins (cardiac myosin, tropomyosin, keratin, laminin, and vimentin), and different patterns of T-cell antigen cross-recognition have been identified.[53,54] Mannose binding lectin (MBL) is an acute-phase inflammatory protein that functions as a soluble pathogen recognition receptor. MBL binds to a wide range of sugars on the surface of pathogens and plays a major part in innate immunity because of its ability to opsonise pathogens, enhancing their phagocytosis and activating the complement cascade via the lectin pathway.[55] One study reported that genotypes that correlated with high concentrations of MBL were associated with rheumatic heart disease.[56] Cytokines (interleukins 1 and 6, and tumour necrosis factor α [TNFα]) are thought to play a part in acute rheumatic fever, and the *TNFα* gene maps close to the MHC region; however, whether this association is related to other possible risk-associated genes is unclear.[57]

Case-control association studies using a fine-resolution genome-wide approach should help to identify genetic variants affecting individual susceptibility to rheumatic heart disease.[35]

Natural history and presentation

Acute rheumatic fever

The disorder manifests as a combination of fever, polyarthritis, carditis, chorea, erythema marginatum, and subcutaneous nodules in patients about 3 weeks after

they have had pharyngitis (most often paucisymptomatic or asymptomatic) caused by a group A streptococcal infection (diagnosed by a positive throat swab culture or a high or rising streptococcal antibody titre), and most often affects children, adolescents, and young adults.[5,58] The clinical presentation of acute rheumatic fever varies and can be affected by delayed consultation or the use of over-the-counter treatments such as anti-inflammatory drugs. In 1944, Jones described the main clinical features of the disease, which have since been modified and revised to become more stringent.[59] Other criteria have been put forward to increase sensitivity and encourage investigators to standardise patients' characteristics under the auspices of WHO and the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand.[5,60,61]

The peak incidence of acute rheumatic fever is in children aged 5–14 years. Arthritis is usually the earliest feature of the disease, present in 60–80% of patients, and is often very painful and migratory, affecting medium and large joints.[5] Sydenham's chorea presents later, usually between 1 and 6 months after the initial exposure to group A streptococcus, and manifests as involuntary, irregular movements, including fibrillatory tongue movements, and spooning with external rotation of the hands. The proportion of patients with chorea varies considerably, from 7% to 28% in different settings.[58,62] Cutaneous manifestations are rare and sometimes difficult to diagnose.

Carditis occurs a few weeks after the initial infection in about 50% of patients with acute rheumatic fever, and presents as valvulitis, sometimes combined with pericarditis or (more contentiously) myocarditis.[8,63] Patients are examined for various hallmarks of acute carditis, such as sinus tachycardia (particularly its persistence at night) and a diminished first heart sound caused by a frequent, extended PR interval, verified by electrocardiography.[59,64] A soft, blowing, pansystolic murmur is characteristic of mitral regurgitation and strongly suggests rheumatic valvulitis. Pericarditis is common in acute rheumatic fever, and is characterised by chest pain and a transient pericardial friction rub accompanied by a small pericardial effusion on echocardiogram. A very large effusion causing cardiac tamponade is rare. Signs of poorly tolerated valvular regurgitation include a prominent left ventricular impulse due to dilatation, and signs of left or right heart failure. A chest radiograph might show cardiac enlargement or signs of congestive heart failure.

Minich and colleagues[65] were among the first to describe subclinical carditis in children. In their cohort, several patients with no murmur had echocardiographic findings consistent with pathological mitral regurgitation,[65] a result supported by many others.[7,11]

Rheumatic heart disease

Patients might be diagnosed with rheumatic heart disease after a known acute rheumatic fever attack; however, the disease is often diagnosed in patients who were previously asymptomatic or who do not recall acute rheumatic fever symptoms or episodes. Most patients present after the onset of shortness of breath at ages 20–50 years.[12] Although controversy exists about the female predominance of acute rheumatic fever,[29] women of childbearing age do have a higher prevalence of established rheumatic heart disease than do men.[12,40] Researchers have not fully addressed the reasons for this female predominance, but some have proposed that social factors (such as child rearing, which might result in repeated exposure to group A streptococcus), access to health care (especially preventive medicine), and genetically-mediated immunological factors that predispose women to autoimmune diseases might be associated.

Clinical diagnosis is based on pathological valvular heart murmur detected during auscultation. Mitral valve incompetence is the most common valvular lesion in patients with rheumatic heart disease, particularly in the early stages.[8,66] Mitral stenosis usually develops later as a result of persistent or recurrent valvulitis with bicommissural fusion,[67] although mitral stenosis has been described in adolescents.[66,68] Patients with mitral incompetence can remain asymptomatic for up to 10 years as a result of compensatory left atrial and left ventricular dilatation before the onset of left ventricular systolic dysfunction. Aortic regurgitation is most often associated with some degree of mitral regurgitation, but can be isolated and severe. Tricuspid regurgitation is often functional, mainly caused by mitral stenosis with high pulmonary pressures and consequent right ventricular dilatation.[69] Isolated pulmonary or tricuspid regurgitation are not classic features of rheumatic heart disease. The disease might also present after a complication such as atrial arrhythmia, an embolic event, acute heart failure, or infective endocarditis.

Echocardiography is used to link murmurs detected during auscultation to their cause. Typically, morphological changes of the mitral valve include leaflet thickening, subvalvular apparatus thickening, shortened chordae tendineae, commissural fusion, calcification, and restricted leaflet motion (figure 1). Some degree of commissural fusion is always present in rheumatic mitral stenosis (figure 2).[67] The aortic valve might have thickened cusps with rolled edges.

The natural course of severe valvular disease leads to severe heart failure in the absence of appropriate intervention. In very advanced stages of the disease, surgery might become contraindicated when myocardial dilatation and dysfunction prevail.[70] Unfortunately, many patients present too late, especially in remote areas.

Preventive strategies

Prevention strategies are the most appealing option for sustainable disease control in developing nations. Medical intervention is based on the eradication of group A streptococcus with penicillin, which prevents the initial

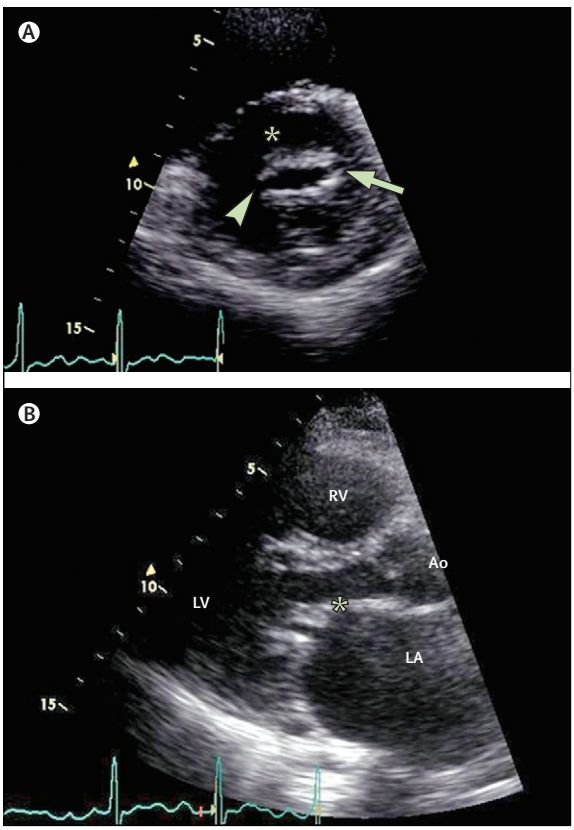

Figure 1: **Transthoracic echocardiography of symptomatic rheumatic mitral stenosis**
(A) Parasternal short axis view showing thickened anterior mitral leaflet (asterisk), bicommissural fusion (arrows), and restricted mitral leaflet motion, which are all features of mitral stenosis. (B) Parasternal long axis view with anterior (asterisk) and posterior mitral leaflet thickening, subvalvular apparatus fusion and shortening, restricted bileaflet motion with classic dog-leg deformity of the anterior mitral leaflet, and left atrium dilatation. Ao=aorta. LA=left atrium. LV=left ventricle. RV=right ventricle.

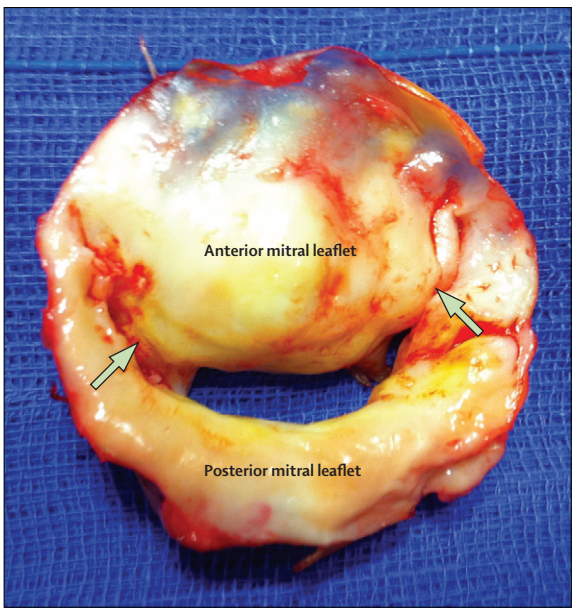

Figure 2: **Macroscopic view of a rheumatic mitral valve**
Typical features of advanced rheumatic valve disease such as bicommissural fusion (arrow) and retraction of the anterior mitral leaflet are shown. Image courtesy of Stéphane Aubert, Clinique Ambroise Paré, Neuilly-sur-Seine, France.

acute rheumatic fever attack (primary prophylaxis) or disease recurrences (secondary prophylaxis). The efficacy and safety of antibiotic prophylaxis are well established, and should lead to near complete eradication of advanced rheumatic heart disease when combined with broader changes such as improved living conditions, education, and awareness.[71–73]

Community-based prevention

Primordial prevention—ie, elimination of risk factors within the community at the earliest stage—is linked to socioeconomic development, which directly affects hygiene, access to medical care, and living conditions. In developed nations, the decrease in acute rheumatic fever incidence started before the antibiotic era and has been attributed to better living conditions in the USA and western Europe.[74] Although some countries have achieved major economic development, access to hygiene and public health measures are often inequitable across populations.[75] In any case, economic improvement does not provide complete protection against acute rheumatic fever and rheumatic heart disease, as shown by disease outbreaks in middle-class children in the USA in the 1990s and in northern Italy more recently.[58,76]

Primary prevention

Ideally, prophylaxis should prevent the first acute rheumatic fever attack, particularly if given shortly after a sore throat.[2,77] Primary prevention relies on the eradication of group A streptococcal carriage through active sore throat screening and by treatment of pharyngitis by oral antibiotics (phenoxymethylpenicillin 250 mg two or three times daily for patients weighing ≤27 kg, phenoxymethylpenicillin 500 mg two or three times daily for patients weighing >27 kg; or amoxicillin 50 mg/kg per day for 10 days) or intramuscular antibiotics (benzathine benzylpenicillin 600 000 IU [one injection] for patients weighing ≤27 kg, or 1 200 000 IU [one injection] for patients weighing >27 kg).[78] So far, primary prevention alone as a large-scale strategy has often been neglected in developing countries.[79] Programmes that target subpopulations with a high prevalence of rheumatic heart disease might be more efficient than present practices.[80] A systematic review of primary prevention showed an overall benefit, with one case of acute rheumatic fever prevented for 53 sore throats treated;[81] this finding was supported by a meta-analysis by Lennon and colleagues.[82] However, these results are somewhat controversial because a randomised controlled trial from New Zealand of 24 000 children did not show a decrease in acute rheumatic fever incidence after implementation of this

strategy.[83] The diagnosis of group A streptococcal pharyngitis is difficult on clinical grounds alone and needs microbiological confirmation.[78] However, laboratory analysis is rarely available in developing countries. Two other fundamental limitations of primary prevention strategies are the existence of asymptomatic throat infection complicated by an inflammatory response, and the possibility of other sites of pathogenic infection (such as skin).[84,85]

Another possibility for primary prevention is vaccine development. Research initially focused on targeting the variable region of the M protein.[86] Investigators have completed phase 2 trials of a multivalent M-type-specific vaccine in adults, and have reported evidence of safety and immunogenicity.[87] However, most vaccine developments have targeted strains prevalent in low-risk areas such as North America. Ubiquitous vaccines using highly conserved antigens would be the ideal solution. Although research remains active, vaccines are not scheduled to be introduced to the market in the foreseeable future.[88]

Secondary prevention

Secondary prevention attempts to reduce the acquisition of new group A streptococcal strains that might induce repeated or chronic acute rheumatic fever attacks, and is a major determinant of cardiac outcome.[89,90] Some researchers recommend one intramuscular injection of benzathine benzylpenicillin in patients every 3–4 weeks after an acute rheumatic fever attack, rather than oral treatment, because of its proven efficacy and compliance (table).[92] The duration of secondary prophylaxis depends on the patients' age, the date of their last attack, and most importantly the presence and severity of rheumatic heart disease. In some highly endemic regions, risk of recurrence is high, and some institutions have recommended long-term or lifelong prophylaxis for patients with severe rheumatic heart disease or previous valvular surgery.[2,60,78,91]

Secondary prophylaxis is more efficiently delivered within community-based registry programmes than in areas that have no registry.[93] Poor compliance with secondary prophylaxis (as low as 50% in some campaigns[94,95]) has been an issue in several programmes, mainly because of the mobility of the target population, understaffing, and remote settings.[96] Education, use of health workers with strong local community links, and integration into existing primary-care networks are paramount to improve the efficiency of community-based secondary prevention programmes.[97,98]

Cost-effectiveness and global results

Assessment of the cost-effectiveness of preventive strategies is difficult and data can seldom be translated from one region or timeframe to another. Analyses have shown several primary prophylaxis campaigns to be cost effective in developed countries, although the campaigns do use a substantial amount of resources.[99,100] In South Africa, the cost per prevented episode of acute rheumatic fever has been estimated at US$46.[81,101]

Secondary prophylaxis is thought to be the most cost-effective intervention.[102,103] In a large multicentre programme of secondary prophylaxis undertaken by WHO, cost-effectiveness was assessed by the number of hospital days averted. The penicillin cost was considerably outweighed by the reduction in the number of hospital days that patients needed.[94] In New Zealand, the cost of an efficient secondary prevention programme

	Intramuscular benzathine benzylpenicillin dose by patient weight	Interval of benzathine benzylpenicillin injections	Oral alternative treatments (dose)	Duration
WHO, 2001[2]	<30 kg: 600 000 IU; ≥30 kg: 1 200 000 IU	21 days if high risk; 28 days if low risk	Phenoxymethylpenicillin (250 mg twice a day); sulphonamide (<30 kg: 500 mg daily; ≥30 kg: 1000 mg daily); erythromycin (250 mg twice a day)	No carditis: for 5 years or until 18 years of age*; resolved carditis†: for 10 years or until at least 25 years of age*; moderate to severe RHD or surgery: lifelong
Australia, 2006[60]	<20 kg: 600 000 IU; ≥20 kg: 1 200 000 IU	28 days; 21 days if high risk‡	Phenoxymethylpenicillin (250 mg twice a day); erythromycin (250 mg twice a day)	No carditis: for 10 years or until 21 years of age*; resolved carditis or mild RHD: for 10 years or until 21 years of age*; moderate RHD: until 35 years of age; severe RHD or surgery: until at least 40 years of age
India, 2008[91]	<27 kg: 600 000 IU; ≥27 kg: 1 200 000 IU	15 days if <27 kg; 21 days if ≥27 kg	Phenoxymethylpenicillin (250 mg twice a day in children; 500 mg twice a day in adults); erythromycin (20 mg/kg; maximum dose 500 mg)	No carditis: for 5 years or until 18 years of age*; mild to moderate carditis or healed carditis: for 10 years or until 25 years of age*; severe RHD or postintervention: lifelong or until 40 years of age
USA, 2009[78]	<27 kg: 600 000 IU; ≥27 kg: 1 200 000 IU	28 days; 21 days if having recurrent attacks	Phenoxymethylpenicillin (250 mg twice a day); sulphonamide (<27 kg: 500 mg daily; ≥27 kg 1000 mg daily); macrolide (dose variable)	No carditis: for 5 years or until 21 years of age*; resolved carditis: for 10 years or until 21 years of age*; RHD: for 10 years or until 40 years of age*; consider lifelong if high risk

Benzathine benzylpenicillin is the preferred antibiotic according to all guidelines. RHD=rheumatic heart disease. *Whichever is longer. †Healed carditis or mild mitral regurgitation. ‡For moderate to severe carditis, valve surgery is recommended if the patient has good adherence to monthly treatment, or after recurrence despite monthly injections.

Table: **International recommendations for secondary prophylaxis of acute rheumatic fever**

accounted for only 13% of the total budget allocated to acute rheumatic fever.[104]

The campaign against rheumatic heart disease needs a strong political will, driven by the awareness and lobbying capacity of health carers. The principles that underlie control of this disease in highly resourced nations might not apply to developing countries. Where health-care finances are very scarce and health is often provided by non-governmental organisations (NGOs), rheumatic heart disease might not be perceived as a priority. Three successful approaches originating from Central America and the Caribbean, in different economic and political contexts, showed the efficiency of combined strategies consisting of education and primary and secondary prophylaxis (figure 3).[30,72,73]

Surveillance in rheumatic heart disease

The aims of surveillance (either passive or active) are to provide accurate estimates of disease burden and to allow initiation of preventative therapy for as many affected people as possible.

Passive surveys rely on identification of cases of diagnosed rheumatic heart disease in a predefined population, and can be done retrospectively. Hospital and primary-care facilities should both be surveyed to detect the largest number of cases, and accurate demographic data are needed. Case ascertainment might be improved if there are existing registers, although under-reporting usually occurs.[19]

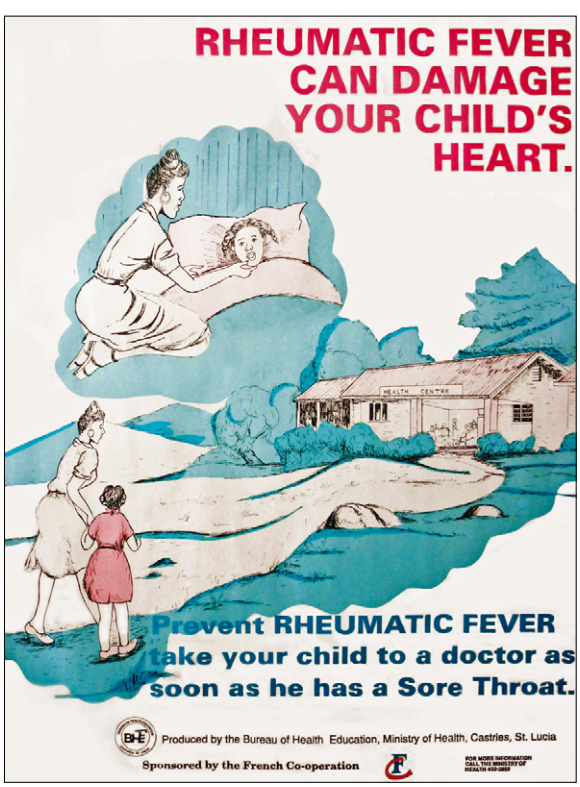

Figure 3: **Poster to raise awareness of rheumatic fever in the low-income Caribbean island of Santa Lucia**
Health authorities achieved success by redistributing part of the budget for rheumatic heart disease, taking some away from cardiac surgery and putting it towards a control programme for acute rheumatic fever and rheumatic heart disease, which included primary and secondary prophylaxis. Image courtesy of Xavier Jouven, Hôpital Européen Georges Pompidou.

Active screening has important methodological advantages because it consists of cross-sectional surveys to detect previously unknown cases, avoiding bias induced by asymptomatic cases or poor access to health services, and usually leading to higher prevalence or incidence estimates than with passive screening.[27] The rationale for active surveillance is not only to provide the most accurate epidemiological data of the disease but also to offer early treatment to those affected, especially the large proportion of asymptomatic patients who might subsequently develop advanced disease.

The Council of Europe and WHO recommend screening programmes for preventable diseases.[105,106] In 1984, WHO initiated a programme that screened about 15 million children for rheumatic heart disease across 16 countries.[107] Unfortunately, the outbreak of HIV and its devastating results might have diverted local priorities in many developing nations and led to discontinuation of funding for many rheumatic heart disease programmes.

The first large active surveillance surveys of rheumatic heart disease were based on clinical examination.[20,94,108] However, cardiac auscultation can have low sensitivity. Small regurgitant volumes, especially mitral posteriorly directed jets, might not be audible to the human ear. Cardiac examination needs a quiet environment and is time-consuming, and to distinguish functional from organic murmurs is far more challenging in clinical practice than in theory.[109] Functional murmurs are very common in children, especially in the presence of fever or anaemia—eg, during malaria or sickle-cell disease. An assessment of a three-step screening programme undertaken in Tonga compared medical students' and local paediatricians' auscultation skills and reported that even though the paediatricians detected more pathological murmurs than did the students, at least half the cases of rheumatic heart disease were missed by auscultation alone.[14] In addition to the intrinsic limitations of auscultation for the detection of valvular disease, results of cardiac examination can be normal just a few weeks after clinical carditis in some patients, which suggests that disease in some children cannot be detected by the classical clinical approach.[6,66,110]

School screening programmes and community-based surveys have both advantages and limitations. Community-based surveys might prove to be more accurate than school screening at estimation of disease burden because they include adults, in whom rheumatic heart disease prevalence is highest.[3,12,40] As for children, community screening has the advantage of avoiding the drawback of low attendance at schools, although it can be more difficult to do. School-based surveys could be improved by targeting a specific age range, preferably the

earliest age when the prevalence starts to peak in pilot studies (around 12 years of age in some regions).[13,14]

Valvular lesions, detected with echocardiography, might emerge in the future as a surrogate marker of rheumatic heart disease. In our large comparative survey of school-aged children in Cambodia and Mozambique, we noted that the case detection rate when we used echocardiography-based screening was about ten times greater than that achieved by careful clinical examination alone. Echocardiographic criteria included doppler and morphological features identified by three independent and skilled readers, with good reproducibility (figure 4).[111] Similar results were noted by other groups with slightly different echocardiographic criteria for subclinical rheumatic heart disease (figure 5).[13,14,41,42,112–114]

A short on-site echocardiography protocol is needed when screening for valvular lesions, ideally followed by confirmation of suspected cases in a medical centre. A simplified 5–10 min protocol per child could be easily implemented.[14,114] Training of health workers as nurses or technicians to obtain cardiac ultrasound images and detect obvious abnormalities might take less time than the teaching of auscultation skills. Since the first echocardiography-screening study,[115] further technological improvements have been achieved for field echocardiography equipment, including miniaturisation of technology and longlasting portable batteries.

A prevention programme using echocardiography to screen for rheumatic heart disease has not yet been formally assessed; however, the programme would include a coordinated approach between local health, social, and education workers, and potentially international institutions that could provide training and technology. Mid-term to long-term funding would need to be obtained.

Although echocardiography might prove valuable in the detection of cases at an early stage, two fundamental issues remain: the absence of gold-standard echocardiographic criteria to diagnose subclinical rheumatic heart disease, and the need for a clear optimum management strategy for patients with clinically silent and mild valvular abnormalities.[15]

Differences between echocardiographic criteria considerably affect the apparent prevalence of rheumatic heart disease in screening surveys, and emphasise the difficulties in the diagnosis of subclinical disease.[111] Some might argue that there is a wide range of definitions of normality and that echocardiography screening might lead to overdiagnosis. Although controversial, evidence supports a link between mild valvular lesions, detected by echocardiography, and rheumatic heart disease, particularly the substantially higher case detection rates of such lesions in populations at risk for acute rheumatic fever.[116] Experts

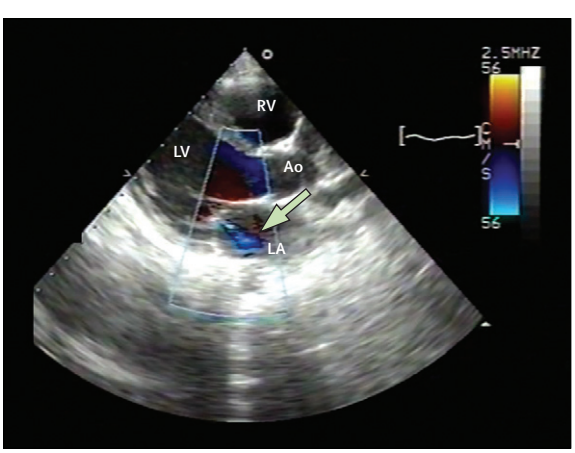

***Figure 4*: Transthoracic echocardiogram of patient with subclinical rheumatic heart disease**
Parasternal long-axis view with colour doppler. Note mildly thickened mitral valve leaflets with mild posteriorly directed mitral regurgitant jet (arrow). Ao=aorta. LA=left atrium. LV=left ventricle. RV=right ventricle. Reproduced from Marijon and colleagues,[111] by permission of Wolters Kluwer Health.

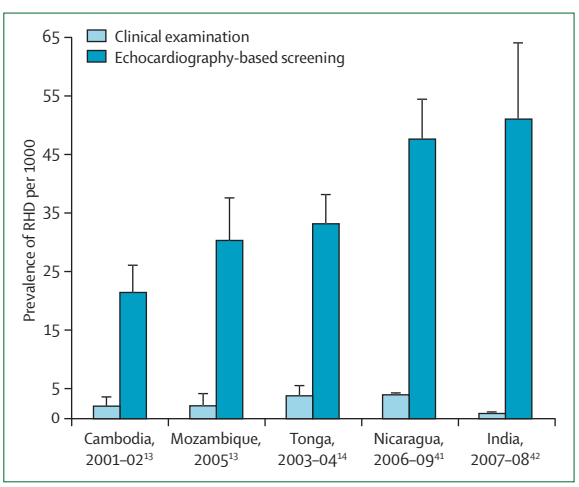

***Figure 5*: Rheumatic heart disease (RHD) prevalence rates in children: echocardiography-based screening versus clinical examination**
Results of the first four studies to investigate differences in RHD detection methods are shown (subsequent findings have since been reported[112–114]). In Cambodia and Mozambique, echocardiography-based RHD was defined as regurgitant jet seen in at least two planes and morphological features suggestive of the disease, such as restricted leaflet mobility, focal or generalised valvular thickening, and abnormal subvalvular thickening.[13] In Tonga, echocardiography-based RHD was defined by a combination of WHO criteria (regurgitant jet >1 cm in length in at least two planes, mosaic colour jet with a peak velocity >2·5 m/s, persistence of jet throughout systole [mitral valve] and diastole [aortic valve], and morphological criteria such as valvular thickening and elbow deformity of the anterior mitral valve leaflet). If only mitral regurgitation with no morphological changes was seen, the case was considered as definite only if mitral regurgitation was graded at least as mild. Mitral or aortic stenoses were a sign of definite RHD, defined by a transmitral mean pressure gradient greater than 4 mm Hg and a transaortic peak velocity greater than 2 m/s, respectively. If only very mild mitral regurgitation and no morphological changes were seen, the child was classified as having borderline RHD (not reported here).[14] In Nicaragua, echocardiography-based RHD including possible cases was defined by morphological mitral changes (thickened mitral valve leaflets or dog-leg deformity of the anterior mitral valve leaflet or both), and substantial left-side regurgitation (holosystolic mitral regurgitation jet ≥2 cm and ≥1 cm for aortic regurgitation, in two planes, of high velocity).[41] In India, echocardiography-based RHD was defined by regurgitant jet greater than 1 cm in length in at least two planes, mosaic colour jet with a peak velocity greater than 2·5 m/s, and persistence of jet throughout systole (mitral valve) and diastole (aortic valve). Prevalence would only be 14·1 per 1000 with more stringent criteria combining doppler echocardiography and pronounced mitral valve thickening (>6 mm).[42]

from around the world, chaired by Australia and New Zealand and supported by the World Heart Federation, have recently revisited the definition of subclinical rheumatic heart disease, and guidelines based on their conclusions suggest that a combination of semiquantitative doppler and morphological features is the consensus choice.[117] The standardised criteria might be more or less stringent than what has been used in previous studies. The proportion of definite rheumatic heart disease cases will probably diminish as the proportion of borderline patterns increases. The criteria are based on the available evidence; however, their complexity might make them difficult to implement because of the possible scarcity of expertise in areas where rheumatic heart disease is endemic.

Management of subclinical cases detected by echocardiography is a challenge.[118] No evidence exists to support systematic treatment of all subclinical cases, so long-term follow-up and randomised controlled clinical trials are urgently needed to assess whether population-wide subclinical rheumatic heart disease screening programmes should be recommended.

In addition to uncertainties relating to the prognostic and therapeutic implications of abnormal findings, cost-effectiveness is another issue to be addressed. Therefore, until further data are available, clinicians should tailor their screening procedure to the available resources, taking other health issues into consideration in policy making. Echocardiography-based screening needs to be introduced into pre-existing primary and secondary prevention programmes that have proven to be effective.

Treatment

Acute rheumatic fever

Penicillin is the cornerstone of acute rheumatic fever and rheumatic heart disease treatment. Its safety has been widely acknowledged[71,73] and its price has substantially decreased to the extent that even the most poorly resourced countries should not be deterred from introducing prophylaxis and treatment.

Penicillin injection at the acute phase of rheumatic fever should clear group A streptococcal infection which can induce chronic or relapsing autoimmune reactions. It should provide a unique opportunity to educate the patient about the importance of secondary prophylaxis, which might improve compliance.[119] Most classic treatments have not been tested and their use is based on common sense and proven safety. A meta-analysis of eight studies that were undertaken in the 1950s and 1960s showed that salicylates, steroids, or immunoglobulins did not improve cardiac outcomes.[120] One randomised controlled trial assessed the efficacy of immunoglobulin therapy during a first attack of acute rheumatic fever and showed no significant improvement in cardiac outcomes.[121] Salicylates (aspirin 80–100 mg/kg per day)[60] are mainly a symptomatic treatment aimed at fever and joint pain and do not affect the prevalence of clinical valve sequelae.[122] Corticosteroids are often prescribed but no evidence exists that supports their effect on cardiac outcomes. Bed rest was historically recommended for patients with acute rheumatic fever in the preantibiotic era, but nowadays gradual mobilisation is advised once the initial symptoms resolve.[5] Patients and parents should be taught to initiate secondary prophylaxis at an early stage, while they are most receptive.

Urgent surgery is mandatory for uncontrolled heart failure secondary to acute rheumatic mitral regurgitation, preferably with valve repair.[123,124] However, surgery can be avoided when congestive signs are easily controlled with medical treatment, and the indication should be reassessed after the acute phase because the severity of valvular regurgitation might decrease.[7,10]

Rheumatic heart disease

At present, no specific treatment for rheumatic heart disease exists other than for its complications, including heart failure, atrial fibrillation, ischaemic embolic events, and infective endocarditis. Medical treatment (other than antibiotic prophylaxis) has shown little evidence of slowing the progression of the disease. Medical heart-failure treatment is given when patients become symptomatic, and includes mainly β blockers, angiotensin-converting-enzyme inhibitor therapies, or a combination of both, as tolerated, and symptomatic treatments such as diuretics. Patients with atrial fibrillation need rate or rhythm control and anticoagulation with warfarin if at high risk of embolic complications. Rheumatic heart disease is a major cause of infective endocarditis in African countries.[125] North American and European guidelines have considerably reduced the number of heart disorders needing antibiotic prophylaxis to prevent infective endocarditis.[126,127] Whether guidelines issued from developed regions can be safely applied to developing countries is debatable, and further studies are warranted.

Pregnancy in patients with rheumatic heart disease is a challenge, and is associated with high morbidity and mortality.[128,129] Antenatal consultation with support from cardiology and obstetrics clinics should be done to provide contraception, counselling, treatment planning before start of pregnancy, and planning for patients with moderate to severe disease who are already pregnant (eg, caesarean section).[130]

Interventional treatment (surgery and cardiac catheterism) is warranted when patients with severe valvular lesions become symptomatic.[131] Mitral valve repair yields better outcomes than does mitral valve replacement in rheumatic mitral regurgitation and should be undertaken whenever possible.[132] However, long-term results vary and depend mainly on the degree of active carditis and on the skill of local physicians.[124,133] The choice of prosthesis (either mechanical or bio-prosthetic) for valve replacement has to be carefully considered, taking into account the patient's age, potential pregnancy, and likelihood of adherence to anticoagulant treatment, especially in remote and

socially underprivileged areas.[134] Investigators with detailed experience of rheumatic heart disease in remote areas have recommended tissue valves in Indigenous Australian and New Zealand populations because of poor anticoagulation control,[135] which differs from clinical practice in more affluent settings.[136,137] In very advanced stages of the disease, surgery might be contraindicated when myocardial dilatation and dysfunction coexist.

In cases of substantial mitral stenosis, percutaneous mitral balloon commissurotomy has replaced surgical commissurotomy and yields excellent early outcomes, with a 50–60% event-free outcome at 10-year follow-up.[138] Patient selection through predictive score might ensure the intervention is successful and avoid acute severe mitral regurgitation.[139] Clinical presentation of mitral stenosis varies with time and region, with younger patients in Africa having more severe mitral stenosis and raised pulmonary artery pressures than do patients from developed countries.[140,141] However, these differences do not seem to affect immediate and mid-term results of percutaneous mitral balloon commissurotomy.[141]

In low-income countries, most invasive procedures are either done abroad, at great expense for the individual, or locally by visiting NGOs, which have focused on the initiation of programmes and the training of local staff to ensure continuity. Unfortunately, medical and surgical care for people with severe rheumatic heart disease is the least cost-effective intervention and consumes almost all funds available for this disease.

Contributors

All authors contributed to the concept, reference search, and writing of this Seminar under the coordination of the corresponding author. Figure design was managed by EM and MM.

Conflicts of interest

We declare that we have no conflicts of interest.

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