Cardiovascular Pharmacology: An Epidemiological Study Rheumatic Heart Disease

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Abstract
Rheumatic fever (RF) and rheumatic heart disease (RHD) continue to be a major health hazard in most developing countries as well as sporadically in developed economies. Despite reservations about the utility, echocardiographic and Doppler (E&D) studies have identified a massive burden of RHD suggesting the inadequacy of the Jones’ criteria updated by the American Heart Association in 1992. Subclinical carditis has been recognized by E&D in patients with acute RF without clinical carditis as well as by follow up of RHD patients presenting as isolated chorea or those without clinical evidence of carditis. Over the years, the medical management of RF has not changed. Paediatric and juvenile mitral stenosis (MS), up to the age of 12 and 20 yr respectively, severe enough to require operative treatment was documented. These negate the belief that patients of RHD become symptomatic ≥20 years after RF as well as the fact that congestive cardiac failure in childhood indicates active carditis and RF. Non-surgical balloon mitral valvotomy for MS has been initiated. Mitral and/or aortic valve replacement during active RF in patients not responding to medical treatment has been found to be lifesaving as well as confirming that congestive heart failure in acute RF is due to an acute haemodynamic overload. Pathogenesis as well as susceptibility to RF continue to be elusive. Prevention of RF morbidity depends on secondary prophylaxis which cannot reduce the burden of diseases. Primary prophylaxis is not feasible in the absence of a suitable vaccine. Attempts to design an antistreptococcal vaccine utilizing the M-protein has not succeeded in the last 40 years. Besides pathogenesis many other questions remain unanswered.

Keywords: Antistreptococcal vaccine, heart disease, myocarditis, rheumatic fever, rheumatic heart disease, streptococcal infections, subclinical carditis.

Introduction
Rheumatic heart disease (RHD) follows rheumatic fever (RF), as a non-suppurative manifestation of group A beta haemolytic streptococcal (GAS) pharyngitis. RF is widely accepted as an immunological disorder following GAS infection. Although the burden has come down in developed countries, RHD continues to be a prominent cause of morbidity and mortality in developing countries of the world. This review highlights the changes that have occurred in the area of RF and RHD in the last 50 years.

Rheumatic heart disease (RHD) is characterised by permanent damage to the valves of the heart that develops as a serious consequence of repeated episodes of acute rheumatic fever (ARF), an autoimmune reaction to a Group A streptococcus (GAS) bacterial infection. Heart failure, atrial fibrillation and stroke are common complications of RHD, resulting in significant premature morbidity and mortality. In HICs RHD is now rare although persisting in at-risk population subgroups. However, the epicentre of RHD has shifted to LMICs, and advances in treatment, research and prevention have moved to these countries [4, 5]. The global focus on RHD is expected to increase as a result of the recommendation made by Executive Board of the World Health Organization in June 2017 for prioritisation of a Rheumatic Fever and Rheumatic Heart Disease Prevention and Control Strategy for adoption at the 2018 World Health Assembly [6]. Yet there remains a lack of clarity about how to implement proven methods of controlling RHD in different settings. Traditionally, approaches have been built around a relatively narrow infectious diseases perspective, based on GAS infection as the root cause of ARF. However, in contemporary endemic settings, improvements in diagnosis and management of RHD require a shift to a broader chronic disease model of care. Therefore, ARF and RHD represent a classic example of how infectious disease and NCD approaches converge.

Problems With Echocardiographic Screening For Rheumatic Heart Disease
However, it is important to remember that RHD screening in its current form with echocardiographic case detection and the institution of secondary prophylaxis aims to prevent ARF recurrences rather than diagnose RHD per se. This explains the rationale for screening children rather than adults as the rate of ARF recurrence in the latter group is very low. Most guidelines support this point of view with recommendations to stop prophylaxis at the age of 18–21 years in individuals with mild valve involvement (and without excessive risk). The ideal timing for screening has to carefully balance picking up more cases (by screening later) with picking up less cases by screening as early as possible to allow maximal time for prophylaxis to make a difference. Unfortunately, the added convenience of screening school children comes at a price as school attendance in poor areas can be <70%.[42] risking underestimating the prevalence of disease in those most likely to be worst affected.

Cost-effectiveness of RHD screening
It remains to be determined if echocardiography screening is cost-effective.[5,43,44] A study by Manji et al.[43] using Markov modeling suggested that primary prophylaxis may be less cost-effective than echocardiographic screening and treatment of early RHD using secondary prophylaxis. The decisions regarding how and where limited resources should be focused in developing countries is an important ethical question[45] and the decision regarding whether to invest in echocardiographic RHD screening programs at the expense of other, possibly more robust evidence-based interventions for other conditions, warrants due consideration.

Understanding the natural history of borderline RHD in particular is crucial because screening studies tend to uncover a burden of disease that is double (or more) that of definite RHD[42,70].
If borderline RHD is indeed confirmed to be associated with an increased risk for ARF recurrences or progression to definite RHD, then this may more than triple the number of individuals who might benefit from secondary prophylaxis and screening programs.[32] Notwithstanding these considerations, however, we do know that patients with mild, clinically evident RHD have an excellent long-term prognosis (even without regular penicillin prophylaxis)[71] and it should follow then that subclinical disease detected by echocardiography might have a potentially even better outcome[45].

Methods
It then examines the application of vertical, horizontal and diagonal control programs. Lessons that can be drawn from both infectious and chronic disease models of care are provided, and how these may be applied in the health system context.

Results
RHD: Disease development and progression
RHD begins with a GAS infection of the pharynx, or potentially the skin [12, 13] with ARF developing in a small minority of susceptible cases resulting from an abnormal immune response to GAS infection. Risk of developing ARF is a function of bacterial, genetic and environmental factors. The importance of GAS strain type remains relatively poorly understood [14, 15]. Understanding the genetic susceptibility to ARF/RHD is the subject of active research [16, 17] with estimates of ARF heritability estimated to be as high as 60% in a meta-analysis of twin studies [18].

RHD epidemiology
RHD affects 33.4 million people globally and causes 347,000 deaths annually [28]; 80% of ARF cases occur in LMIC [29]. The REMEDY study [4] conducted in 14 LMICs highlighted the high burden of RHD on young people (particularly women) where access to quality secondary and tertiary prevention services is poor. Indigenous populations of high income countries like Australia [30], New Zealand [31] and Canada [32] have some of the highest documented rates.

The decline of cases in resource-rich settings was associated with reduced crowding, improved socioeconomic environments, access to health care and the widespread availability of penicillin [33]. RHD prevention and treatment approaches were developed and implemented in the 1940s–1960s by clinical researchers in the United States and Europe [34, 35], providing a template for RHD control programs and clinical care worldwide. This foundation has been built on by ongoing basic science studies, implementation research and RHD control programs [34].

Levels of disease prevention
The aetiological pathway of RHD provides scope for a broad range of disease control strategies. These can be considered within the four levels of the prevention framework: primordial - addressing the environmental, socio-economic [36, 37], behavioural and cultural factors underpinning disease incidence; primary - preventing disease acquisition; secondary - interrupting the disease process or preventing complications arising from established disease; and tertiary - managing disease to limit consequences. This framework [7, 38] provides a structure for comparing the management strategies relevant to both infectious disease and NCD. The infectious origins of RHD place it between the communicable and NCD ends of the spectrum, providing a novel lens to explore lessons from both sectors.

Conclusion
While the body of ARF/RHD literature is now growing rapidly, such that there are increasing RHD-specific data available to guide program development, the cross-fertilisation of ideas from the comparative domains which we describe here can provide an important means of accelerating progress. There is a need to develop and further refine innovative, location-specific systems-level interventions to allow successful implementation of treatments that have been known to work since the 1950s.

Specifically, policies to adopt the CCM framework for the secondary and tertiary prevention of RHD in settings with limited resources, in conjunction with strengthening of systems through integration/linkages with other well-performing and resource-rich services has the potential to significantly reduce the burden of RHD globally. More funding for implementation research into different models of care in LMIC settings is required to provide a strong evidence base for RHD policy and practice.

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