Rheumatic Heart Disease
The Unfinished Global Agenda

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KEYWORDS

• Rheumatic heart disease • Rheumatic fever • Global health • Noncommunicable disease

KEY POINTS

- Rheumatic heart disease (RHD) is a neglected chronic disease of poverty.
- RHD affects an estimated 33 million people worldwide and causes 275,000 deaths annually.
- Although RHD has been eradicated from high-income countries, endemic regions of low-income and middle-income countries continue to struggle with preventive, diagnostic, and management strategies.
- Further research is needed to better understand RHD pathophysiology, epidemiology, and health system responses.

INTRODUCTION

Rheumatic heart disease (RHD) is a neglected chronic disease primarily affecting the poorest people worldwide and is the most common form of acquired heart disease among children and young adults in low-income and middle-income countries. RHD affects an estimated 33 million people worldwide by Global Burden of Disease study estimates.[1] However, up to 80 million people may have asymptomatic RHD.[2] Annually, RHD accounts for approximately 275,000 deaths, and is a major cause of premature mortality and morbidity among children and young adults in low-income and middle-income countries.[1,3]

RHD was a prioritized subject of active investigation in developed countries in the first half of the twentieth century; however, RHD was largely eradicated in developed countries by mid-century, and subsequent research endeavors investigating RHD diminished. Thus, most of our current knowledge of RHD pathophysiology and treatment is largely based on decades-old studies that lack the modern investigative standards of today. Over the past 2 decades, there has been renewed interest in RHD in a global health context given its predominance as a major cause of cardiovascular morbidity and mortality in low-income and middle-income countries. Recently, an emerging global health equity movement has increased the awareness among global health practitioners, researchers, and policy makers to the disparity in RHD care. A growing body of new clinical research has emerged from endemic countries, to inform evidence-based interventions for RHD diagnosis and management.

This review provides an overview of the current diagnosis and treatment gaps for RHD as embedded within a historical context. First, we look back at the history of RHD as a subject of study in medicine and public health. Then, we review the evolution of RHD diagnosis as new technologies have emerged. Third, we will review the current epidemiologic data on RHD at a global level and its limitations. We next discuss current

The authors have nothing to disclose.

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Cardiol Clin 35 (2017) 165–180
http://dx.doi.org/10.1016/j.ccl.2016.08.006

management principles and gaps in knowledge. Finally, we survey current advocacy efforts to improve RHD awareness and care.

HISTORICAL OVERVIEW: WHERE WE LEFT OFF

A century ago, acute rheumatic fever (ARF) was the leading cause of death among school-age children in the United States, and was second to tuberculosis among young adults aged 20 to 30 years.[4] In New England, half of adult heart disease was caused by childhood rheumatic disease, and 8% of autopsies from New York's Presbyterian Hospital in 1938 showed evidence of "rheumatism."[5,6]

In 1927, a special research unit was established at the House of Good Samaritan in Boston where Dr T. Duckett Jones began a lifelong study of ARF. He ultimately published the first set of "Jones criteria" in 1944, systematizing the diagnosis of ARF based on the presence of discrete clinical signs.[7] In his seminal paper, Jones described ARF as "one of the important soluble medical problems of our day."[7] Indeed, such a common source of morbidity among young adults had significant social repercussions, especially in a wartime setting. During World War II it was estimated that approximately 100,000 men were rejected from military service because of RHD.[8] Crowded air bases provided an ideal setting for ARF outbreaks, with up to 25 to 100 per 1000 troops reported ARF at some bases.[9]

The high prevalence of the ARF among armed forces personnel served as an impetus for increased national attention to the disease. Experiments involving antimicrobial therapy were conducted among army recruits with good results.[5] Health service–based studies in the early penicillin era targeting high-prevalence populations showed the important role that improvements in health care access can play in diminishing disparities in ARF care.[10]

Although tempting to credit the increased access to antibiotics for the decline of RHD in the United States, it is notable that the start of the decline of ARF and RHD well preceded the antibiotic era by several decades. In addition, researchers noted that only a small percentage (<3%) of those with streptococcal infections went on to develop ARF, suggesting that other host factors played an important role in pathogenesis.[10] The decline of RHD at a societal level has been linked broadly to "primordial" factors related to the environment and host, such as living conditions, sanitation, and hygiene. Even today, RHD is more common in poor communities, and among children attending lower socioeconomic schools, those who have low formal education, lack formal employment, or live in crowded conditions.[11–15] For example, RHD is 60 times more common among poor indigenous people of Australia than nonindigenous.[16]

By the 1950s, there was waning public interest in RHD given its decline in the civilian population and the end of World War II. Further investigation into the complex determinants of ARF and RHD were not continued.[10] Speaking in 1985 when RHD had all but disappeared from the medical consciousness, the renowned epidemiologist Leon Gordis[10] ominously reminded his audience of the persistently high prevalence among children and young adults in developing countries and called urgently for renewed research on biological, host, and social determinants of disease. His call remained essentially unheeded until several decades later when increasing awareness of neglected disease among the global poor and the rise of a global health equity platform would begin to revive and reprioritize the disease.

PATHOPHYSIOLOGY AND GAPS IN SCIENCE

The pathophysiology of RHD remains incompletely understood, with host, bacterial, environmental, and genetic factors all implicated in its pathogenesis. Although Group A β-hemolytic Streptococcus (GAS) infection is undoubtedly involved, the disease has strong heritability and significant variation in natural history and severity according to host factors and geography.

Classically, ARF usually occurs 2 to 6 weeks after an episode of untreated GAS pharyngitis in approximately 0.4% to 3.0% of patients.[17,18] In patients with an active episode of ARF, the throat culture may be negative for GAS and antibody titers for streptococcal enzymes, such as streptolysin O and DNase, should be elevated. Rheumatic carditis is classically described as a pancarditis, involving the pericardium, myocardium, and endocardium.[19] Histopathologically, rheumatic myocarditis is characterized by the presence of focal perivascular inflammation, termed Aschoff bodies.[20,21]

The development of RHD occurs in some patients with ARF as a result of valvular damage from an immune-mediated process after one or repeated infections. Among Brazilian children with ARF, 72% developed chronic valvular disease and 16% developed severe mitral and/or aortic disease.[22] A prevailing theory is that cross-reactivity between moieties in the GAS strain and cardiac antigens are responsible for immunologic activation and eventual tissue destruction.[17] The