

Rheumatic Heart Disease – Systematic Review of Clinical Data and Assessment of Preventative Measures for a Global Solution

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Abstract

A renewed sense of urgency in addressing the global impact of Rheumatic Heart Disease (RHD) is evidenced by the recent adoption of a global resolution by the World Health Organization on Rheumatic Fever and RHD on May 25, 2018. This marks the first time Acute Rheumatic Fever (ARF) and RHD have been recognized on a world-wide stage as a global health priority. The World Heart Federation, is promoting a goal of a 25% reduction in premature deaths from Rheumatic Fever and RHD among individuals aged less than 25 years by 2025. Despite the relative rarity and declining mortality of RHD in high income countries due to adequate access to antibiotics, the disease continues to devastate impoverished countries in Sub-Saharan Africa, South Asia, and Oceania. Rheumatic Heart Disease truly exemplifies rising health inequality in the world today. Therefore, the goal is to provide a systematic review of comprehensive clinical information on the progression of Group A Streptococcus infection to RHD for practicing providers including their epidemiology, pathophysiology, diagnosis, and treatment. An assessment of strategies for a global solution centered on concepts of disease prevention, cost-effective practice, and expansion of resources to those without access will also be of focus.

Keywords: Group A Streptococcus, Acute Rheumatic Fever, Rheumatic Heart Disease, impoverished, health inequality, disease prevention

1. Methods

We conducted a systematic review of current Rheumatic Heart Disease literature acquired from UpToDate and Pubmed. Inclusion criteria were research articles no older than 2015, those that sufficiently detailed current clinical guidelines regarding diagnosis and treatment, and articles that addressed RHD as a global health priority with suggested preventative measures for future progress in RHD elimination. Exclusion criteria were articles that failed to provide succinct disease information that could be utilized in a clinical setting and those that have been reviewed prior to 2015.

2. Pathophysiology

The progression of Streptococcus pyogenes infection to Rheumatic Heart Disease begins with the presentation of the Streptococcus pyogenes surface antigen to T cells. These T cells along with B cells then help to produce IgG and IgM antibodies in preparation to fight the infection (Brimberg, Benhar, Mascaro, 2012). Up to this point, the immune system is working well, as it is taking the appropriate steps to heal itself. Unfortunately, theoretically, the surface antigen occasionally has a similar structure to the proteins found in the heart, joints, and brain and the immune response instead begins attacking these organs. This phenomenon is known as molecular mimicry, which, again, leads to unintended inflammation and damage throughout the body resulting in the progressive symptoms that will be outlined, the heart being the primary victim (Brimberg, Benhar, Mascaro, 2012).

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3.1 Group a Streptococcus: Epidemiology

Before RHD is discussed further, it is important to gain a good grasp of how the disease process begins and the ways that it can be treated early on. With that being said, every person who develops RHD starts off with a streptococcal infection.

Group A Streptococcus also known as Streptococcus Pyogenes is an extremely common bacterial infection with its peak seasons around winter and early spring. The demographic most susceptible to the infection are school aged children between 5 and 15 (Shulman, Bisno, Clegg, 2012). Although there are a notable amount of cases outside this range, especially when the infection is passed between family members and close contacts.

3.2 Group A Streptococcus: Symptoms and Testing

It is important to note that the physical presentation of the infection is often based on an individual's age. Patients over the age of 3 will usually have some assortment of sore throat, enlarged, erythematous tonsils, palatal petechiae, poor oral intake, fever, headache, abdominal pain, nausea, vomiting, anterior cervical lymphadenopathy, and scarlatiniform rash. These symptoms will be abrupt and last around 3-5 days (Shulman, Bisno, Clegg, 2012). Those under the age of 3 will have more atypical symptoms with low grade fever, nasal congestion, rhinorrhea, fussiness, and tender anterior cervical lymph nodes (Nussinovitch, Finkelstein, Amir, Varsano, 1999). Clinically, the Centor Criteria, which comprises the symptoms mentioned above, aid in making the diagnosis. However, given the common ambiguity of these symptoms and difficulty in making a definitive diagnosis simply based on physical exam alone, it is important to get tested to see whether the patient truly has streptococcal pharyngitis or another viral process. The 2 most common testing measures for strep are a Rapid Antigen Detecting Test (RADT) and a throat culture. RADT is the preferred initial test of choice as it can provide results in about 15 minutes (Uhi, Patel, 2016). This allows for a quicker onset of treatment if the patient is positive. However, this test is only 70% sensitive which results in a lot of false negative cases. Therefore, if a patient is negative, it is recommended to send a throat culture as well because cultures are significantly more accurate (90-95% sensitive) even though they take 18-24hrs for results (Shulman, Bisno, Clegg, 2012).

3.3 Group a Streptococcus: Treatment

If found to be positive by the RADT or the throat culture, the patient should be started on antibiotic treatment. Penicillin is considered 1st line treatment and is especially beneficial because it is cheap, effective, has a narrow spectrum of action, and safe to use in children (Spinks, 2013). However, medication like amoxicillin is often used due to its similar profile and better taste. Those with penicillin allergies are recommended to use a cephalosporin, macrolide or clindamycin instead (Tack, Henry, Gooch, 1998)(Gooch Pichichero, 1994).

4.1 Acute Rheumatic Fever: Epidemiology

Ensuring that patients see a physician whenever they start having streptococcal pharyngitis like symptoms is important because it allows them to get tested and treated in a timely manner. Although the infection is self-limited to around 5 days, getting proper care prior to resolution of symptoms will help to reduce their infectivity rate toward others and reduce their risk of complications (Brink, Rammelkamp, Denny, Wannamaker, 1951). In the 1990s around 3% of untreated strep infections escalated to Acute Rheumatic Fever (ARF), yet with better education and a greater availability of antibiotics nowadays only about 1% progress. It is estimated that there are 33 million people world-wide who have had ARF at least once in their lives with 470,000 new cases every year. These numbers are very rare in developed countries with only 2 cases out of every 100,000 people. However, in more endemic regions around the world, the incidence is much higher at 380 cases for every 100,000 people (Carapetis, Steer, Mulholland, Weber, 2005)(Zühlke, Steer, 2013).

4.2 Acute Rheumatic Fever: Symptoms and Diagnosis

How to determine whether or not a person has ARF is based on 2 categories: major and minor symptoms along with a history or lack of previous history of ARF. The major symptoms include Carditis / Valvulitis (50-70%), Arthritis (35-66%), Central Nervous System Involvement – chorea (10-30%), Subcutaneous Nodules (0-10%), and Erythema Migrans (<6%) with heart related complications being the most severe and the most common (Gewitz MH, Baltimore, Tani, 2015). The minor symptoms include Arthralgia, Fever (101.3°F), ESR \geq 60 mm/hour and CRP \geq 3 mg/dL, and a Prolonged PR interval $>$ 0.2 sec (Gewitz MH, Baltimore, Tani, 2015). The Jones Criteria helps to clarify if a person can be diagnosed with ARF. According to the criteria, those with at least 1 previous episode of ARF are considered positive if they have a preceding strep infection (generally 2-3 weeks prior) with either 2 major symptoms or 1 major + 2 minor symptoms.

Those with no previous history of ARF require 2 major symptoms, 1 major + 2 minor symptoms, or 3 minor symptoms to be considered positive (Gewitz, Baltimore, Tani 2015) (Ferrieri, 2002).

4.3 Acute Rheumatic Fever: Treatment

Once a diagnosis of ARF is made, prompt antibiotic treatment, such as the one stated earlier for strep throat should be implemented in order to eradicate any lingering infection. This will help to mitigate symptoms and reduce the amount of damage done. Fortunately, resistance to antibiotic treatment has been fairly insignificant in regards to strep over the last 50 years (Pichichero, 2018). Therefore, it remains an effective option for treatment throughout life. However, other medication that seem helpful intuitively such as glucocorticoid steroids, aspirin, and IVIG have shown little to no benefits in reducing carditis. Once any acute infections have resolved, prophylactic antibiotic treatment needs to be initiated. Those with an asymptomatic history of ARF will require continuous prophylactic antibiotic treatment for the next 10 years or till age 21. And those who remain symptomatic will need continuous prophylactic antibiotic treatment for life (Gerber, Baltimore, Eaton, 2009) (Berrios, Campo, Guzman, Bisno, 1993). Doing so will help to reduce the progression of the disease by reducing the likelihood of future attacks.

5.1 Rheumatic Heart Disease: Epidemiology

Rheumatic Heart Disease (RHD) is the final stage of a progressive autoimmune disorder that causes worsening, permanent damage to a person's heart tissue. Repeated inflammatory episodes by the immune system can cause fibrosis to the endocardium which lead to regurgitation/stenosis of the heart valves, necrosis of the myocardium which lead to heart failure, and friction rub of the pericardium which leads to angina (Marcus, Sareli, Pocock, 1989) (WHO, 2001). Many of those who reach this stage will live with debilitating heart complications and increased risk of mortality. Back in 2015, there were approximately 33.4 million cases of RHD and 320,000 deaths. Fortunately, these numbers have dropped by around 50% since the 1990s (Watkins, Johnson, Colquhoun, 2005). This dramatic improvement is primarily seen in the western world as it has benefited most from the increased prevalence of antibiotics with only 3.4 cases for every 100,000 people. However, there are still many endemic regions around the world including Oceania, Sub-Saharan Africa, and South Asia who are greatly affected. In those areas, the incidence is around 444 cases for every 100,000 people, a stark contrast to those seen in more medically resourced regions (Watkins DA, Johnson CO, Colquhoun, 2005). The over hundred-fold difference between the two regions and the devastating consequences of not getting proper treatment is a sobering reality. By bringing greater awareness to this disease and offering solutions for those most affected, it is possible for millions of lives to be protected and thousands of lives to be saved.

Yet in many endemic regions around the world, strep infections are left to resolve on their own and ARF is not properly handled either. This often leads to recurrent episodes of acute rheumatic fever and as a result, multiple insults to the heart tissue. Each progressive episode adds further damage and around 10% of individuals with a history of ARF eventually progress to Chronic Rheumatic Heart Disease (Remenyi B, ElGuindy A, Smith SC Jr, et al., 2016). Some develop chronic heart disease over a few decades while others manifest within a few years. This is why ARF and RHD is the leading cause of cardiovascular death in the first 5 decades of life (Carapetis, Steer, Mulholland, Weber, 2005).

5.2 Rheumatic Heart Disease: Symptoms and Diagnosis

Symptoms of chronic Rheumatic Heart Disease include pericarditis which causes angina, myocarditis which causes myocardial infarcts, and endocarditis which causes fibrosis to the valves and chordae tendineae. Of these symptoms, endocarditis and damage to the mitral valve are the most common. Fibrosis of the mitral valves often lead to prolapse, heart failure, and rupture of the chordae tendineae all of which significantly increase mortality (Remenyi B, ElGuindy A, Smith SC Jr, et al., 2016). Yet in order to make an accurate diagnosis an echocardiogram needs to be performed to help visualize the structure, activity, and flow of blood through the heart. Patients who do not have a history of ARF are still considered positive if they have pathologic mitral regurgitation (MR) and at least two morphologic MV features of RHD, MS mean gradient ≥ 4 mmHg, pathologic aortic regurgitation (AR) and at least two morphologic features of the MV, borderline disease of both the aortic valve and MV in individuals ≤ 20 years old, or pathologic AR and at least two morphologic features of the aortic valve in individuals < 35 years old (Remenyi, Wilson, Steer, 2012). If they do have a history of ARF, then they simply need MV changes, aortic Valve changes, or pathological valve regurgitation to be considered positive (Remenyi, Wilson, Steer, 2012).

5.3 Rheumatic Heart Disease: Treatment

In regards to treatment, antibiotic regimens as seen used for strep and ARF are recommended to treat any underlying infections and prevent reoccurrence. Routine echocardiograms are then added to help providers observe the progression of the heart over time.

Patients who have mitral regurgitation with moderate symptoms should have an echocardiogram once per year and every 6-12 months in severe cases. Patients with mild mitral regurgitation should be tested every 3-5 years, every 1-2 years in moderate cases, and annually if severe (Carapetis, Brown, Maguire, 2012). In Mitral Stenosis individuals are more prone to atrial fibrillation and thromboembolism, therefore anticoagulant therapy is often used to reduce their risk (Cupido, Zühlke, 2019). But in regards to treatment outside antibiotics, echocardiograms, and anticoagulants, which are limited in their efficacy, there are only a few options available that greatly decrease mortality and they are not without risk. For younger patients, valve repair is the preferred choice over valve replacement because it reduces the risk of bleeding, thromboembolism, and negates the need for anticoagulation especially in those who wish to be pregnant (Cupido, Zühlke, 2019). However, the drawback of valve repair is that they undergo restenosis over time, which would require subsequent repairs or valve replacement all together. If that route became necessary, then individuals would need to understand the risks of the surgery and commit to taking anticoagulants for life. In either case, correction of the afflicted valves through surgical intervention is directly related to decreased mortality rates and better long-term outcomes at this point (Oliveira, Antunes, 2006)

5.4 Rheumatic Heart Disease: Global Impact

However, an echocardiographic study that was done in back 2012 has put into question whether or not the number of people actually affected by RHD is accurate. As stated earlier in this essay, 33 million people were believed to have RHD based on the Global Burden of Disease study done in 2015 (Watkins DA, Johnson CO, Colquhoun SM, et al., 2017). This is a significant proportion of the world's population given the high mortality rate and debilitating consequences of the disease. Yet this new study, shows evidence that the findings in 2015 may be incorrect and far lower than what is truly indicated. The study took into account individuals between 5 and 16 years age in Sub-Saharan African countries which represent 6-7% of total RHD burden and calculated that 2.7 for every 1000 people with a 95% confidence interval (CI 1.6-4.4) had actual clinical manifestations of RHD whereas 21.1 per 1000 people with a 95% confidence interval (CI 14.1-31.4) were clinically silent (Rothenbühler, O'Sullivan, Stortecky, 2014) (Weinberg J, Beaton A, Aliku T, Lwabi P, Sable C, 2016). The dramatic difference between those who showed symptoms of RHD and those who did not is quite astounding. Based on the numbers, there were around 7-8x as many people who were asymptomatic as compared to those who are. If this is true, then the amount of people affected by RHD would be closer to 50-80 million people rather than 33 million with upper wards of 47 million people completely unaccounted (Weinberg J, Beaton A, Aliku, 2016). This is a huge global concern because 10s of millions of children with clinically silent RHD wouldn't be receiving the care that they need or taking any measures to reduce their risk.

The children and their parents won't know to seek prophylactic antibiotic treatment, anticoagulant therapy, and are not seeking evaluations to see if they are candidates for valve replacement or repair because they don't have any symptoms to suggest otherwise. As a result, these people over time are transitioning from having clinically silent features that are only detectable on an echocardiogram to having true obvious clinical manifestation. And by that point, it is too late. They will have permanent heart related complications, more severe symptoms, and have higher rates of mortality, a problem for which could have been stabilized earlier if the appropriate steps were taken. Another problem is the risk they pose to the people around them. Individuals with RHD have had multiple episodes of strep in the past and can easily spread the infection to others in their family and in their community. This may be why many regions that are overcrowded, impoverished, and under medically resourced have the highest rates of RHD and early onset death due complications of the disease. The solution, therefore, begins with primordial prevention.

6. Primordial Prevention

Often overlooked are the social determinants that significantly impact the spread of Group A Streptococcal (GAS) infection. Due to GAS pharyngitis being spread through direct person to person transmission via saliva or nasal secretions, a sanitary environment is essential to prevent disease spread (Coffey et al., 2018). Globally, ARF and RHD are almost exclusively seen in developing nations or among disadvantaged populations within developed nations. Among populations safeguarded by high standards of living, RHD rates are virtually zero. This dramatic contrast highlights the true influence of environmental, economic, social and behavioral conditions on risk of GAS infection and progression to ARF and RHD (Coffey et al., 2018).

Primordial prevention aspires to establish and maintain conditions to minimize hazards to health (Coffey et al., 2018). Among the conditions that have been studied and are proposed to influence the spread of GAS infection include household crowding, educational attainment, employment, income, nutrition, and overall socioeconomic status (Coffey et al., 2018).

The most statistically significant factor, based on studies, is overcrowding, which can be measured by persons per household, number of children or siblings, dwelling space, and sleeping space per person (Coffey et al., 2018). Reducing crowding in developing nations, therefore, is a practical target for preventative, primordial action against ARF and RHD (Coffey et al., 2018).

7. Primary Prevention

Primary prevention of RHD deals with treatment of streptococcal pharyngitis to decrease the risk of ARF. Once diagnosis of pharyngitis has been established, treatment within nine days of infection is recommended (Leal et al., 2019). This duration among studies has been shown to prevent the development of ARF in the majority of susceptible individuals, in addition to avoiding spread between contacts (Leal et al., 2019). Intramuscular benzathine penicillin G remains the most widely used antibiotic for treatment, and studies are ongoing on a vaccination against *Streptococcus pyogenes*, but several barriers remain that must be addressed for improvement in primary prevention (Leal et al., 2019). Poor education and health-seeking literacy and lack of awareness have proven to be barriers of successful primary prevention and represent significant areas of improvement (Leal et al., 2019).

8. Secondary Prevention

Once a diagnosis of ARF or RHD is established, secondary prophylaxis is critical to prevent disease progression. The appropriate duration of secondary prophylaxis, involving continuous antimicrobial prophylaxis, is controversial, and dependent on several factors, including time elapsed since last episode of ARF, age, presence of carditis, and severity of RHD at follow-up (Leal et al., 2019). Based off of these factors, the recommended duration is a minimum of 10 years after the most recent episode of ARF or until age 18-21 years. Patients with moderate RHD continue prophylaxis until age 30-35 and those with severe RHD until 40 (Leal et al., 2019). Treatment being this long introduces several challenges involving patient adherence, satisfactory access to continual health care, and cost for the prolonged treatment regimen (Leal et al., 2019).

9. Solutions

To begin making progress in the world with RHD, a humbling reminder of the many obstacles must be delivered. Inadequate data on the disease burden, challenges in effective advocacy to international foundations, ongoing inequality and poverty, and weak health systems in endemic regions all threaten the chance of this preventable disease ever being eliminated (Dougherty et al., 2018). The first solution, addressing the obstacle of inadequate data on the disease burden, would be to establish an ARF and RHD registry for high quality data collection. However, in addition, there also must be a better way to detect RHD if high quality data is to exist, which can be completed by introducing more portable echocardiographic screening into endemic areas as well as continue to recognize the clinical significance of asymptomatic RHD (Dougherty et al., 2018). With regards to ineffective advocacy on the global stage, it is a wonder that so much advocacy has not proven beneficial in gaining traction with government and funding agencies. Surprisingly, one of the most critical barriers to gaining RHD support is figuring out how to present the disease in a clear, concise manner as opposed to the complex, multifactorial disease it is (Dougherty et al., 2018). A second challenge is the difficulty in correctly framing the disease into the established funding priorities already in place on a global health scale (Dougherty et al., 2018). Historically, the international health community has focused on infectious diseases, such as HIV/AIDS, tuberculosis, and malaria. In order for RHD to gain any ground, Group A *Streptococcus* infection must have a clear presentation to funding agencies and be seen in the same category as these infectious diseases so a reassessment of the international budget could be entertained (Dougherty et al., 2018). Third, fixing poverty and inequality certainly seems like an impossible task. This should not, however, keep the world from seeking strategies for improvement. Reasons for disparity in impoverished areas include a long distance to health clinics, a lack of healthcare availability, and a significantly less quality of care (Dougherty et al., 2018). To make matters even more complicated, RHD has proven to require a strong health system, adequate infrastructure, and a multi-tiered workforce for primary, secondary, and tertiary services, which is an exorbitant amount of money (Dougherty et al., 2018). The only plausible solution is engaging in policy dialogue to encourage developed countries to invest health care resources in areas that are most impacted. This truly would take an international effort, but the reward of eliminating RHD may well be worth it.

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