Primary Prevention for Rheumatic Fever

Progress, Obstacles, and Opportunities

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ABSTRACT

Acute rheumatic fever and rheumatic heart disease are noninfectious sequelae of group A streptococcal pharyngeal infection. These diseases represent a huge public health burden in developing countries with significant mortality and morbidity. Early diagnosis and appropriate antibiotic treatment with group A streptococcal pharyngitis provides an opportunity for prevention of acute rheumatic fever and rheumatic heart disease. The use of locally adapted clinical algorithms for diagnosing group A streptococcal pharyngitis has great potential in resource-poor settings for earlier diagnosis and early treatment. Intramuscular penicillin is the drug of choice in developing country settings. Recent work has demonstrated the cost-effectiveness of a treat-all strategy with intramuscular penicillin, whereas incorporating a clinical decision rule remains the preferred strategy. We strongly support the adoption of a comprehensive prevention and control program for acute rheumatic fever and rheumatic heart disease, incorporating primary prevention, as critical to underpinning the efforts in many parts of the world to stem the tide of this devastating disease.

Acute rheumatic fever (ARF) and rheumatic heart disease (RHD) continue to kill children, adolescents, and young adults living in poverty. Yet, a cheap and effective preventative agent to these sequelae of group A streptococcal (GAS) infection has existed for decades in the form of penicillin. Despite strong evidence of penicillin's efficacy in primary prevention of ARF, debate still rages on regarding the appropriate role for primary prevention within RHD prevention and control strategies. Some of the arguments against the incorporation of primary prevention into RF/RHD control strategies are based on the expense and logistics of delivery, but as has been discussed elsewhere [1], these need not be limiting factors. Conversely, a recent publication has demonstrated the cost-effectiveness of such a strategy [2]. More importantly, these arguments serve, unwittingly, to undermine the role of primary prevention in the control of RHD.

BURDEN OF DISEASE

Group A streptococcal disease

GAS has been studied for decades and is a well-known pathogen. It is responsible for over 600 million infections annually, ranging from self-limiting pharyngitis to invasive and life-threatening toxic shock syndrome and necrotizing fasciitis [3]. The global burden of severe GAS infections has been estimated to be as high as 18.1 million cases with 1.78 million new cases a year and over 500,000 deaths each year [4]. This predominantly occurs in developing countries and poor subpopulations within middle- and high-income countries (such as the indigenous populations of Australia and New Zealand). Although long ignored as a disease of the developing world, the recent resurgence of invasive disease in developed countries [5], coupled with evidence of hypervirulent strains has resulted in increased academic interest and activities relating to vaccine development. This has also highlighted the many unknowns relating to this organism, especially in terms of pathogenicity, distribution of isolates, and virulence factors.

Acute rheumatic fever and rheumatic heart disease

ARF is the systemic noninfectious sequel to the often self-limiting pharyngitis caused by rheumatogenic strains of GAS. The only permanent and devastating sequel to ARF is RHD, for which no proven treatment exists to alter the natural history of the disease. ARF has shown a dramatic decrease in incidence in developed countries, with increasing standards of living and access to health care being the major determinants of this change [6]. In developing countries, this pattern is following a similar though markedly attenuated trend. A systematic review [7] of studies reporting incidence of ARF conducted in 2008 still demonstrated a high incidence (>10 per 100,000) in poorer regions of Eastern Europe, Middle East (highest), Asia, and Australasia, while no data could be included for Africa. A more recent review was able to include data from Sub-Saharan Africa and recorded the highest incidence in the Western Pacific and Asia [8]. Mortality due to ARF relates strongly to differences in health care with higher case fatality rates in developing as opposed to developed countries.

In contrast, the prevalence of RHD appears to be increasing. Seckeler et al. [8] were able to show this trend through almost all the World Health Organization regions of the world except for Europe. Given the decreasing incidence of ARF, this is most likely due to advances in

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medical and surgical treatments for RHD and the resultant increased survival. Most importantly, the diagnosis of RHD has also become more rigorous with the use of echocardiography. The increased sensitivity of echocardiography has resulted in rates that are 10-fold that of RHD diagnosed by auscultation alone [9]. Vital registration data have determined that mortality rates from RHD follow the same pattern as that for ARF: highest in developing countries, although high-quality mortality data are lacking from Sub-Saharan Africa [10]. The highest case fatality rate for RHD was recorded in Pakistan at 3.7 per 100,000 [10]. Clearly, it is irrefutable that the highest burden of disease for both ARF and RHD lies in developing countries with concomitant high mortality rates. What is also clear is that in the absence of a cure for RHD, and being cognizant of the limited health resources of developing countries, our focus should turn toward effective prevention.

RATIONALE FOR PRIMARY PREVENTION

Pharyngitis is a common childhood illness with up to 26% of these infections being caused by GAS [11]. ARF is thought to occur in 0.3% to 3% of individuals infected with GAS as an autoimmune response to the initial infection. Controversy remains regarding the role of GAS infections other than pharyngitis [12]. There is anecdotal evidence for the potential role of skin infections, particularly in the Australian Aboriginal population, yet this remains circumstantial and as yet unproven in other populations [13–15]. What is clear is that GAS infection is causally related to the development of ARF, as is evidenced by outbreaks of GAS pharyngitis followed by outbreaks of ARF and the increased antistreptococcal antibodies found in patients with ARF [16]. Primary prevention strategies focus on the early diagnosis and timely treatment of GAS pharyngitis with antibiotics to prevent the autoimmune consequences resulting from the infection in susceptible individuals. It is thought that antibiotic therapy initiated within 9 days of onset of pharyngitis is effective in preventing ARF [17].

EVIDENCE FOR PRIMARY PREVENTION

The value of primary prevention has been known as early as the 1950s when randomized control trials demonstrated that ARF could be prevented by treating GAS pharyngitis with penicillin. Research conducted among army personnel demonstrated proof of effectiveness of primary antibiotic prophylaxis as a strategy for high-risk populations [18]. This was followed by successful programs such as the Baltimore-based program that demonstrated a 50-fold drop in ARF incidence 15 years after instituting a comprehensive prevention program focusing on the diagnosis and treatment of streptococcal sore throats in inner-city children [19]. A report from the House of the Good Samaritan, Boston, noted that although mortality due to rheumatic carditis had been steadily declining in the United States since about 1921, a 4-fold acceleration of the decline occurred after 1945, the approximate time when penicillin began to be widely used for streptococcal pharyngitis [20].

A systematic review of hospital-based primary intervention strategies evaluated the effectiveness of antibiotics in preventing ARF and was able to determine a substantial protective effect using pooled meta-analysis of randomized and quasi-randomized trials. In patients with a sore throat and symptoms suggestive of GAS infection, antibiotic treatment reduced the risk of ARF by 70% and by 80% when intramuscular penicillin was used [21]. The subgroup analysis, focusing on the group treated with intramuscular penicillin, yielded a number needed to treat of 60.

IMPORTANT CASE STUDIES

Like the hospital-based programs, community efforts such as those in Cuba, Costa Rica, and Martinique have also shown remarkable success and have resulted in the virtual elimination of ARF using comprehensive, integrated programs targeting primary and secondary prevention [22,23]. These 10-year programs were able to demonstrate a reduction in ARF in Martinique and Guadeloupe of 78% and 72%, respectively and from 18.6 per 100,000 to 2.5 per 100,000 in Cuba. These were both comprehensive community interventions, consisting of awareness campaigns, establishment of registries and medical training with particular emphasis on primary and secondary prevention. Both these programs resulted in dramatic declines in direct costs (86% in both Cuba and Martinique). Although it is difficult to tease out which specific component was primarily responsible for the rapid decrease in incidence of ARF, it does provide convincing evidence that a strategy that includes primary prevention can be markedly effective.

COST OF PRIMARY PREVENTION

In the resource-limited areas where ARF and RHD are most rife, the importance of cost analyses cannot be overestimated. The cost of chronic RHD treatment has been estimated at US$319 per patient per year, whereas an open heart operation would cost anywhere from US$35,000 to US$50,000 [24]. In Brazil, it was estimated in 2001 that the chronic care costs for a patient with ARF could constitute as much as 1.3% of annual family income. As ARF and RHD are intimately related to poverty, this economic burden is unsustainable for the countries and people involved. Yet the cost of the prevention program in Martinique was a fraction of the cost of cardiac surgery: US$44,500 per year for the program compared with US$654,000 for open-heart surgery [23]. This is also the case in more recent comprehensive RHD control programs, which have been run for only a fraction of the cost of performing heart valve surgery on severe RHD patients [25]. Until recently, the costs of a focused primary prevention strategy were thought to be prohibitive [26]. However, Irlam et al. [2] described a cost-effective analysis of various strategies for the primary prevention of ARF in

an urban primary healthcare clinic. Using a Markov model, they were able to determine that a treat-all strategy using intramuscular penicillin was the least costly, whereas the strategy of incorporating a clinical decision rule is overall the preferred strategy. This landmark study reinforced the belief that culturing all children with pharyngitis was prohibitively expensive in developing country settings [2].

OBSTACLES TO EFFECTIVE PRIMARY PREVENTION

Taranta and Gordis [27] described prevention for RHD, in the face of no cure, as "not only desirable but essential." They did acknowledge, though, the inherent difficulties associated with the accurate diagnosis and treatment of streptococcal pharyngitis in the general population. Significant barriers to the adequate diagnosis and treatment of streptococcal pharyngitis and thus primary prevention remain namely: 1) the diagnosis of GAS pharyngitis; 2) treatment options and concerns; 3) patient and physician awareness; and 4) the positioning of primary prevention within a control program.

Diagnosis of GAS pharyngitis

The gold standard confirmatory test for streptococcal pharyngitis is largely accepted to be a pharyngeal swab culture that is positive for GAS [28]. Office pediatricians in developed countries make use of rapid strep tests to make this diagnosis. However, there are very few countries in highly affected regions of the world utilizing routine rapid antigen or microbiological testing due to the cost involved. Furthermore, the delay involved in awaiting results of culture before a diagnosis can be made will result in missed diagnoses and tragic consequences. Finally, rapid antigen detection tests, although demonstrating positive results [29], should be tested within the local setting prior to advocating their use. The use of a locally adapted, risk stratified, clinical prediction rules such as those used in New Zealand and Cuba [22,30,31] offers a different approach to detect GAS pharyngitis. A recent pragmatic scoring system tested in Brazil was able to demonstrate a receiver-operator characteristic curve of 0.66 (95% confidence interval: 0.62 to 0.71) and allowed for significant (35% to 55%) sparing of antibiotic prescriptions while still maintaining an 88% specificity [32]. This is in stark contrast with the World Health Organization prediction rule, which missed up to 96% of children with positive cultures when applied to children in poorer settings [33]. Clinical prediction rules thus do run the risk of over- or underdiagnosis. However, this risk is substantially decreased when algorithms incorporating local ARF pre-test risk factors are applied. This will improve correct diagnosis of GAS sore throat while keeping unnecessary antibiotic usage to a minimum.

Treatment options and concerns

The current treatment guidelines for GAS pharyngitis were revised in 2009 and are detailed in Table 1 [17]. The American Heart Association has recommended penicillin V or amoxicillin as first-choice antibiotics, followed by benzathine penicillin. Evidence for recommending oral penicillin as first-line treatment is scant. Given that the few trials testing the efficacy of penicillin for preventing ARF were limited to intramuscular (as opposed to oral) penicillin [34,35], our recommendation is that intramuscular penicillin should be the first choice in keeping with the evidence. This will also result in better compliance [21]. However, there are problems with both the consistency of supply and quality of benzathine penicillin G around the world. There are a number of studies documenting that different batches from suppliers may have variable pharmacokinetic properties, and the batches may vary physically, resulting in unreliable serum penicillin levels [36–40]. Benzathine penicillin G is on the Core List of Essential Medicines for developing countries, so it is critical that we find a solution to this problem. Patients treated with oral penicillin are advised to complete a 10-day course and pediatric solutions need to be kept refrigerated. This clearly is highly problematic in the countries in question and has resulted in lack of concordance with treatment regimes. In addition, reluctance on behalf of patients due to the associated pain from an intramuscular injection and practitioners relating to concerns regarding anaphylaxis must be taken into consideration. The use of intramuscular penicillin must be balanced against the risk of incomplete oral regimes for GAS pharyngitis and local quality and supply of intramuscular penicillin.

Patient and community awareness

In a study from Dar Es Salaam, Tanzania, the following barriers to the diagnosis and treatment of GAS pharyngitis were identified: 1) that patients do not present for treatment of sore throat; and 2) that there is little patient and community knowledge regarding the importance of treating a sore throat. In addition, the concomitant lack of awareness of primary prevention had resulted in a lack of prioritization of GAS screening and treatment [41].

Even RHD patients themselves uniformly stated that they would not take their children with a sore throat to professional healthcare providers. Cost and travel to a district-level clinic was a major factor in their decision making, a factor that was also in a report from Jimma, Ethiopia [42]. A concerningly high level of ignorance around the causality of ARF and RHD was encountered in this and other papers, with few of the respondents with RHD questioned in a paper from South Africa knowing the cause of ARF [43]. Patients had poor knowledge of the connection between pharyngitis and RHD and preferred local remedies or simple pain medication. Physicians in these 3 studies were of the overwhelming opinion that patients and their families were not aware about the consequences of untreated GAS infection. Patients reported little prior knowledge of ARF before their diagnosis, an indication of the lack of community awareness of the disease. Physician awareness of the importance of sore throat management was generally good, although respondents indicated that screening patients with GAS might be seen

TABLE 1. Primary prevention of rheumatic fever (treatment of streptococcal tonsillopharyngitis)

Agent*	Dose	Mode	Duration
Penicillin			
• Penicillin V	Children: 250 mg 3 times daily for <27 kg Adolescents and adults: 500 mg 2 to 3 times daily	Oral	10 days
• Amoxicillin	50 mg/kg once daily (maximum 1 g)	Oral	10 days
• Benzathine penicillin G	600,000 IU for patients≤ 27kg 1,200,000 IU for patients >27 kg	Intramuscular	Once
Allergic to penicillin			
• Narrow-spectrum cephalosporin	Variable	Oral	10 days
• Clindamycin	20 mg/kg per day divided in 3 doses (maximum 1.8g/d)	Oral	10 days
• Azithromycin	12 mg/kg once daily (maximum 500 mg)	Oral	5 days
• Clarithromycin	15 mg/kg per day divided into 2 doses (maximum 250 mg twice daily)	Oral	10 days

IU, international units.

*The following antibiotics are not acceptable: sulphonamides; trimethoprim; tetracyclines; and fluoroquinolones.

Adapted from Gerber MA et al. [17].

as interfering with other priority diseases such as the human immunodeficiency virus and malaria.

Positioning of primary prevention within a control program

There is international disagreement regarding the way in which primary prophylaxis should be incorporated into control strategies [1,44–46]. Everyone seems to be in agreement that promotion of sore throat diagnosis and treatment within existing primary healthcare systems is important, although it is not clear how this should be done. The particular role of systematic sore throat screening and treatment programs in schools or communities is also contentious. The debate revolves around the role of sore throat screening and treatment programs in schools, with one side claiming that there is sufficient evidence to promote this approach and the other claiming that the evidence of efficacy, effectiveness, and cost-effectiveness is insufficient to recommend it [31,47]. We believe that the existing evidence is insufficient, that a more definitive study would be logistically difficult and expensive, and, furthermore, that even if it were proven to be effective, such a strategy would be difficult to implement and unaffordable in low-income countries [48]. Unlike the school-based model, the community models from Cuba, Costa Rica, and the islands of Martinique and Guadeloupe represent the best evidence for integration. Here a comprehensive strategy involving syndromic treatment of suspected GAS pharyngitis with penicillin was introduced and maintained for over 10 years. This was within a concerted educational campaign that attempted to involve and target the public, social, and educational professionals, as well as healthcare workers at every level, in particular those at primary care facilities. A media education campaign involving radio, television, and pamphlets together with workshops and symposia for healthcare workers ran throughout the period of the program and stressed the benign presentation of sore throat and contrasted it with the severity of heart disease [22,23].

It is critical to be reminded that even in the most optimal circumstances, as many as 60% of patients subsequently diagnosed with ARF cannot recall a previous episode of sore throat [49]. Therefore, it is crucial that the patients who do present with sore throats, provide us with an important opportunity for intervention that should not be missed.

OPPORTUNITIES FOR PRIMARY PREVENTION

We are currently witnessing a surge in ARF and RHD control activity largely driven from parts of the world where ARF/RHD mostly occurs. Research, as well as public health programs and political advocacy, are now centered in developing countries and those subpopulations within middle- and high-income countries where high burdens of disease still exist. A real opportunity exists for dramatic progress to occur toward the goal of "eradicating ARF and RHD in our lifetime" [50,51].

Following up on the excellent work carried out in Cuba, Costa Rica, and other countries, similar programs have now evolved in several other sites, a world-leading program of RHD control in Pacific Island nations has individuals from Tonga, Fiji, and Samoa at the helm, whereas the ASAP (Advocacy, Surveillance, Awareness, and Prevention) program, under the auspices of the Pan-African Society of Cardiology has galvanized efforts in Africa to combat this disease [52]. These programs all feature a comprehensive approach combining education, awareness, and primary care management as key components [26,53–55]. Collaborations between developing countries, such as India, Brazil, and

South Africa, promise to yield important insights into understanding of the GAS antigenic processes and RF pathogenesis and inform vaccine development [56].

These efforts have been met with renewed support from global organizations such as the World Heart Federation, which has made a major commitment to leading the charge on RHD control, supporting programs in the Pacific and Africa, establishing an international web-based resource in ARF/RHD, and, in their most recent strategic plan, committing to "eliminating rheumatic fever and minimizing the burden of rheumatic heart disease." The World Heart Federation also hosted the Postgraduate Course on Rheumatic Heart Disease: Challenges and Opportunities at the Seventh Global Forum on Humanitarian Medicine in Cardiology and Cardiac Surgery in Geneva, Switzerland. Not only will this raise the profile of ARF and RHD within the medical community, but also the community at large, through their partners and global alliances [57].

A major limitation of an integrated primary prevention strategy relates to existing healthcare infrastructure, which is grossly under-resourced and poorly serviced in the very populations in which RF/RHD is rampant. The ever-increasing need for skilled healthcare workers has led to the formation of cadres of assistant medical officers and task shifting [58]. Using community health workers in integrated primary health care, human immunodeficiency virus management has achieved much success in resource-limited countries such as Haiti and Rwanda [59,60]. By integrating treatment of sore throat into other programs, and the innovative use of community health workers to strengthen the program, in terms of treatment as well as education, similar successes could be achieved.

SUMMARY

Rheumatic heart disease is unique among chronic cardiovascular diseases in several ways. It is entirely preventable. It is among the few chronic cardiovascular diseases of childhood, adolescence, and young adulthood, and it straddles the silos of infectious and noncommunicable diseases and, therefore, represents perfectly the needs of developing countries in the 21st century, now dealing increasingly with this double burden [61]. The potential economic burden of chronic cardiovascular disease in the developing world is overwhelming, and any opportunity to prevent chronic disease should be embraced and strongly advocated at the highest levels. We have presented the progress made in primary prevention of acute rheumatic fever, as well as listing some of the obstacles and opportunities in this field. Primary prevention is the cornerstone of any RHD program and integration into existing primary care systems should be a priority.

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