

## **Primary Prevention of Rheumatic Fever in India: The Reality**

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About 100 years back Rheumatic fever (RF) and rheumatic heart disease (RHD) were believed to be diseases of "temperate climate", and with improved hygiene there has been a dramatic decrease in incidence of the disease in developed nations. But still it continues to be a major health problem in most developing countries. There are 2.4 million affected children between five and fourteen years of age in developing countries [1]. Addition of subclinical carditis by echocardiographic criteria increases the prevalence of the disease 10 to 20 times because of detection of clinically "silent" RHD in the same age group [2]. Up to 1% of school children in Africa, Asia, the Eastern Mediterranean region and Latin America show signs of RHD [3]. However concern is that there has been a resurgence of the disease in the developed countries as well. The last epidemic of RF in Utah area in USA occurred in well to do middle class families in absence of overcrowding and with access to good medical care [4]. In Russia, also there had been a dramatic increase in new cases of RHD in the last decade of 20th century [5]. Aboriginal people in the Kimberley region of north-west Western Australia suffer from unacceptably high rates of acute rheumatic fever (ARF) and rheumatic heart disease (RHD), with an estimated prevalence of at least 1.3% [6].

The endemicity of RHD has been related to low socio-economic status which contributes to unhygienic living conditions, overcrowding and malnutrition. Overcrowding and unhygienic living conditions lead to persistent and repeated GAS infection while malnutrition leads to decreased immune response.

Prevention strategy of RF consists of three components: primordial prevention, primary prevention and secondary prevention. Primordial prevention includes socio economic improvement, public awareness, prevention of overcrowding and availability of prompt medical care. The controversy remains as Utah epidemic occurred in well to do middle class families in the absence of overcrowding and with access to good medical care. Primary prevention can be defined as 'action taken prior to the onset of disease, which removes the possibility that a disease will ever occur'. The basic reality of primary prevention in rheumatic fever lies in identification of sore throat and treatment by injectable penicillin and vaccination. For detection of GAS infections, we can use clinical evidence, culture sensitivity or rapid antigen detection test. Treatment should be started within 9 days of infection to prevent rheumatic fever. But the Utah epidemic revealed that 78% of GAS sore throats may be asymptomatic and the unanswered question remains how to target the asymptomatic patients with sore throat [4].

Thus, for effective prevention of rheumatic fever, all patients of sore throat need to be treated with penicillin. This also seems impractical considering the resources. For example, 10,000 sore throats need to be treated to prevent rheumatic fever in only one to six children as can be shown by a mathematical calculation. If there are 10,000 sore throats, approximately 300 - 2000 will have GAS infection (3 - 20%). Of theses one to six children will have RF (0.3%) and 90% of these children with rheumatic fever will develop RHD. Hence giving penicillin to all is an impractical approach.

Partial solution to the problem lies in best utilization of available antibiotics. The problem continues when we see that RF occurred in 15 - 48% of children treated with oral penicillin for 10 days in the Utah epidemic [4]. This also raised the question of compliance of 10 days oral therapy. The present recommendation for primary prevention is one injection of 1.2 MU of benzathine penicillin. But this may not be enough to eradicate GAS infection especially in endemic areas [7]. The other alternative remains use of procaine penicillin (400,000 units twice daily for ten days). Limitations are being painful injection and compliance.

The other oral drugs recommended are amoxicillin, cephalosporin and erythromycin [8]. It has been reported that Azithromycin administered at a dosage of 60 mg/kg in children or administered for 3 days at a dosage of 500 mg/day in adults is more effective than oral penicillin [9,10].

Thus, the reality of prevention lies in proper anti-streptococcal vaccine. Till now majority of the work had been on M protein based vaccine assuming the fact that M protein is responsible for rheumatic fever due to structural similarity with cardiac tropomyosin. A potential barriers to M protein based vaccine are that there are > 200 emm types of GAS, its heterogenous distribution and frequent mutation of the emm gene within a few weeks [11]. Moreover, M protein considered to be the virulent factor, is not expressed in toxic shock syndrome, necrotizing fasciitis or acute glomerulonephritis. A 26-valent (strain specific) vaccine so far developed may not be useful in developing countries. Other non-M protein based vaccines, such as the streptococcal C5a peptidase (ScpA), the IL-8 serine protease (SpyCEP) and fibronectin-binding proteins are in the process of development [12,13]. Combined vaccine is also in the process of development to prevent all types of GAS infections.

Thus, the primary prevention of rheumatic fever is a myth rather than reality and answer lies solely on primordial prevention and possibly effective vaccination.

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