Prevention of rheumatic fever
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Introduction
Rheumatic fever is an inflammatory disease that occurs as a delayed nonsuppurative sequel to group A streptococcal infection of the pharynx. It involves the heart, joints, central nervous system, skin, and subcutaneous tissues with varying frequency. Its clinical manifestations include migratory polyarthritis, fever, carditis, and less frequently Sydenham’s chorea, subcutaneous nodules, and erythema marginatum. Rheumatic fever is a clinical syndrome for which no specific diagnostic test exists. No symptom, sign, or laboratory test result is pathognomonic. Although several combination of them are diagnostic. Its importance relates to involvement of the heart, which, though rarely fatal during the acute stage, may lead to rheumatic valvular disease, a chronic and progressive condition that causes cardiac disability or death many years after the initial event.

Antecedent infection of the upper respiratory tract with the group A streptococcus is necessary for the development of rheumatic fever. Cutaneous streptococcal infection may lead to acute glomerulonephritis but has never been demonstrated to cause rheumatic fever. The evidence establishing the group A streptococcus as the etiologic agent of rheumatic fever is only indirect, because the organism cannot be recovered from the lesions and there is no experimental animal model. Never the less, the evidence from clinical, immunologic and epidemiologic studies is overwhelming. At least one third of patients deny previous sore throat, and cultures of the pharynx are often negative for group A streptococci at the onset of rheumatic fever. However, an antibody response to streptococcal extracellular products can be demonstrated in all most all cases, and the attack rate of acute rheumatic fever is strongly correlated with the magnitude of the antibody response. A clear sequential relationship between outbreaks of streptococcal pharyngitis or scarlet fever and rheumatic fever has been demonstrated in epidemiologic studies of military recruit camps, and such outbreaks can be eradicated when streptococcal infection is controlled by chemotherapy. Prompt and effective penicillin therapy of streptococcal pharyngitis prevents the initial attack of rheumatic fever (So called primary prevention), and continuous chemoprophylaxis against streptococcal infection (Secondary prophylaxis) prevents its recurrences.

Rheumatic fever (RF) and rheumatic heart disease (RHD) continue to be serious health hazards in most developing countries including Bangladesh. RHD has always been considered to be a preventable disease. The three strategies for prevention consist of (i) primordial prevention (ii) primary prevention and (iii) secondary prevention.

Primordial prevention
Primordial prevention requires, preventing the development of “risk factors” in the community to prevent the disease in the population and thus protect individuals. Measures for primordial prevention in relation to RF and RHD consist of: (i) Improvement in socio-economic status (ii) Prevention of overcrowding (iii) Prevention of under nutrition & malnutrition (iv) Availability of prompt medical care and (v) Public education regarding the risk of RF...
from sore throat specially below the age of 15 years. The last one, that is, public education is the most important component for primordial prevention. Unless parents know that a sore throat can cause RF and RHD, it is most unlikely to be seen by a physician and treated. It is necessary to point out that the recent resurgence of RF in United States of America (USA) occurred in well off families, without any overcrowding and with good quality medical facilities being readily available. As such, improvement in socio-economic status and preventing overcrowding cannot be relied upon to reduce the burden of RHD. Improvement in socio-economic status is also not under medical control and it is not possible to wait for it to happen.

Primary prevention
Primary prevention of RF is theoretically feasible but practically almost impossible to achieve at the community level. However, it can be practiced on an individual basis. Primary prevention requires identification of group-A beta hemolytic streptococcal (GABHS) sore throat and use of penicillin to eradicate the streptococci. Measures for primary prevention consist of: (i) Public awareness regarding danger of RF from sore throat (ii) Identification of sore throat as being streptococcal, and (iii) Use of injectable penicillin to cure the streptococcal infection.

It is important to know that oral penicillin may not be effective in preventing RF. RF occurred in 15% to 48% children given oral penicillin for 10 days in the recent epidemic in USA. It is, therefore, essential that injectable penicillin is used in order to prevent RF. The recommended dose of penicillin is 400,000 units of procaine penicillin twice daily for 10 days. Although recommended, one injection of 1.2 mega units of benzathine penicillin may not be enough to eradicate GABHS infection.

The inability to utilize primary prevention at the community level is due to the large number of sore throats required to be treated to prevent RF. Community level management requires a sledge hammer approach, that is, treating each sore throat. Bacteriological facilities required to diagnose streptococcal sore throat at the community level for the whole country, at present, do not exist and are not likely in the near future. Hence, each sore throat will need to be treated. This is logistically not feasible for the whole country. Anywhere from 3% to 20% of sore throats can be streptococcal, the rest being viral infections which do not require treatment. About 0.3% of streptococcal sore throats result in RF. Recent data suggests that almost 90% of those who get RF develop RHD. Hence if 10,000 sore throats are treated by the sledge hammer approach, anywhere between 300 to 2000 streptococcal sore throats would be required to be treated (assuming that 3-20% of these are streptococcal). This would result in preventing RF in 1 to 6 children (0.3% streptococcal sore throats cause RF), and RHD in 5 or 6 children. Thus community level primary prevention is not feasible although it may be possible for select individual patients.

Another problem with sledge hammer approach is the identification of sore throat and its treatment. The data related to resurgence of RF in USA indicates that up to 78% of streptococcal sore throats may be asymptomatic. The 10-day oral penicillin treatment was not followed even by well educated families and up to 48% of those given oral penicillin still developed RF. Unless a sore throat is symptomatic, it would not be treated and can result in RF. This makes primary prevention, based on the diagnosis of streptococcal sore throat and use of oral penicillin, inadequate to reduce the burden of RHD in the country.

As of today, there are no markers which can be utilized to identify susceptibility to RF. Susceptibility to RF in the form of studies of HLA and the B-lymphocyte antigen, D8/17 have not given results which can be utilized to identify the susceptible people in the population to practice primary prevention.
However, primary prevention is feasible if an antistreptococcal vaccine becomes available.

Secondary prevention
Secondary prevention requires identification of those who have had RF or have RHD. Once identified, the patient needs injections of benzathine penicillin, given once in two to three weeks, depending on age, body size and muscle mass. Benzathine penicillin is painful, and may result in fever and very rarely (one in a million injections in children) in anaphylactic reactions.

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<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Mode</th>
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<tbody>
<tr>
<td>Benzathine penicillin G</td>
<td>1200000 U every four weeks* or</td>
<td>Intramuscular</td>
</tr>
<tr>
<td>Penicillin V</td>
<td>250mg twice daily for patient</td>
<td>Oral</td>
</tr>
<tr>
<td>Sulfadiazine</td>
<td>0.5g once daily for patients = 27 kg(60 lb)1.0g once daily for patients &gt; 27kg(60 lb)</td>
<td>Oral</td>
</tr>
<tr>
<td>For individuals allergic to penicillin and sulfadiazine Erythromycin 250 mg twice daily</td>
<td>Oral</td>
<td></td>
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* In high-risk situation, administration every three weeks is justified and recommended.

<table>
<thead>
<tr>
<th>Category</th>
<th>Duration</th>
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<tr>
<td>Rheumatic fever with carditis and residual heart disease (persistent valvular disease*)</td>
<td>At least 10 years since last episode and at least until age 40 years, sometimes lifelong prophylaxis</td>
</tr>
<tr>
<td>Rheumatic fever with carditis but no residual heart disease (no valvular disease*)</td>
<td>10 years or well into adulthood, whichever is longer.</td>
</tr>
<tr>
<td>Rheumatic fever without carditis</td>
<td>5 years or until age 21 years, whichever is longer.</td>
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*Clinical or Echocardiographic

Table 1: Secondary prevention of rheumatic fever

Table 2: Duration of secondary rheumatic fever prophylaxis

Most physicians are very reluctant to give benzathine penicillin injections. Penicillin prophylaxis is considered necessary because RF has a tendency of recurrence in those who have had RF in the past. Each new attack causes further damage to the valvular tissue making the disease worse than before\(^\text{11}\).

Secondary prevention can reduce the chance of recurrence but cannot prevent the initial damage. While it is ethically mandatory to prevent recurrences, secondary prevention cannot reduce the burden of RHD.

Anti-streptococcal vaccine
Availability of an anti-streptococcal vaccine which could prevent streptococcal infection is essential for primary prevention of RF. It is at present not available. Several GABHS protein components and the polysaccharide have been considered for utilization in developing a vaccine\(^\text{13}\). Most work has been done in relation with the M-protein, considered to be the virulence factor of the GABHS. M-protein has been found to be strain specific, that is, each strain has its specific characteristics and will protect against only that particular strain. Since more than hundred different strains have been identified it becomes essential that the vaccine must be polyvalent, that is, it should incorporate all those strains which are present in the community. The problem associated with M-protein is that the GABHS has a strong tendency for mutation which can occur rapidly\(^\text{14}\). A vaccine made from the locally dominant strains of GABHS may not be effective if the infection is due to a mutant organism. M-protein has a conserved C-region component which is common to most strains and variable A and B regions which differ from strain to strain. Attempts to use the preserved C-region component of M-protein have not succeeded as yet.

More recently GABHS has been found not to express M-protein\(^\text{15}\). If fatal infection can occur from GABHS which does not have M-protein, it is difficult to accept that M-protein is the main virulence factor of GABHS. Vaccine based on M-protein is unlikely to
succeed because: (i) M-protein cross-reacts with myocardium and may not be safe (ii) M-protein is strain-specific, hence the anti-GABHS vaccine has to include all the strains in the community (iii) since GABHS strains vary from place to place, vaccine based on M-protein made in one country may not be effective in another country (iv) GABHS mutation alters the emm gene sequence of the M-protein. Mutation can occur in a few weeks, making the vaccine ineffective even in a very short time and (v) virulent GABHS is now known not to express M-protein. Hence, M-protein cannot be the chief virulence factor of GABHS.

Other components of GABHS which are being tried for preparing a vaccine are GABHS C5a peptidase, a major surface virulence factor; fibronectin binding protein sfb1, and the chimeric peptide J8 from the conserved region of the M-protein.

Streptococcus pneumonia (pneumococcus) is another variety of streptococcus species causing disease in humans. A vaccine against pneumococcal infection is already available and is being used though it is, as yet, not as effective as one would like it to be. The vaccine has been prepared using the polysaccharide conjugated with proteins to make it stable and have a longer duration of effectiveness. The GABHS polysaccharide has been shown to be immunologically active and reactive with cardiac valvular tissue. Since the polysaccharide component of GABHS is uniformly identical, it is surprising that it is not being utilized to prepare an anti-GABHS vaccine as has been done for the anti-pneumococcal vaccine.

Conclusion
We are fortunate in our country that the health of the child generally remains a priority and responsibility of the parents even when the child becomes an adult. Hence, prevention of RF and RHD is possible to a large extent if we can provide the message, in local languages, to the population (parents) that sore throats should not be neglected; that sore throats should be shown to a doctor for treatment to prevent RF and RHD. All medias are the means available for reaching each and every corner of the country and should be utilized for this purpose. If education can be made compulsory till the age of 15 years, school health care facilities can be utilized to control RF. Primary prevention will have to wait till a safe and effective GABHS vaccine becomes available.

References