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ACUTE RHEUMATIC FEVER AND COMPLICATIONS WITH COST EFFECTIVE TREAMENT

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ABSTRACT
Rheumatic fever is still posing challenge for the third world countries. Exception to this somehow remains in New Zealand. Rheumatic fever is still a cause of cardiac disease which has to be challenge seriously. This is becoming a headache for heavy financial burden in poor countries. So, in suspected patients' streptococcal infection is detected from the tonsils, staphylococcus aureus can be detected by taking swab from the nose, it can be diagnosed by taking blood sample for vitamin D, ferritin and hair of the head. The main diagnostic web is clinical and ECG on the other hand sever case require medical and surgical intervention. In this context we are focusing on the diagnosis and heart valve lesions the standard treatment of these patient is single short of benzathine penicillin given intramuscular and dose is 1.2 million units AST. After three weeks again they above dose is repeated. all the other drugs except azithromycin have a long half-life and other good points which make it as alternative to penicillin for these patients. Though penicillin has been used decade together but know azithromycin is posing as an effective contender. so, this drug should be used as an alternative to penicillin because for a long-time azithromycin has proved itself as an effective at relatively affordable price. In our study, oral azithromycin (AZT) 500 mg once weekly was compared to oral penicillin (phenoxy methyl penicillin 250 mg twice daily). Fifty-two consecutive patients with established RHD (54 percent males, mean age 21 years) were randomly assigned to one of two groups: AZT or oral penicillin. Patients were evaluated clinically, serologically, and by throat swab culture taken at randomization, 1 month, 3 months, and 6 months. The absence of streptococcal colonization, infection, or fever at the end of 6 months was the end point. During the study, four patients (15.4 percent) in the AZT group developed sore throat and fever, as well as a positive throat culture and serology indicating streptococcal infection. None of the group of patients spelled positive while taking azithromycin. In the oral penicillin group again, none showed sterilization from streptococcal infection. So, there was no demarcation as far as superiority is considered.

KEYWORDS: rheumatic heart disease rheumatic fever, penicillin, developing countries, disease outbreaks, scarlet fever, streptococcus morbidity, mortality, upper respiratory infections.

INTRODUCTION
Rheumatic fever is very lethal as it is an autoimmune response to throat caused by infection with A *Streptococcus* (GAS), *Streptococcus pyogenes*. It is dangerous as it affects joints, brain, heart and almost tall essential organs of the body. The OPD presentation of ARF are briefed in the recently presented Jones Criteria for the diagnosis of ARF[1] and the most common clinical presentations are outlined. The acute illness can handicap as a result of joint pain, dyspnea and oedema from heart failure, high fevers and choreiform ataxia make the living tough. ARF is to admit the patent for at least a month onwards. Here the patient is made to undergo various investigations and evaluated for the treatment to make the cost of treatment bearable. All the features suffered by the patient subside except the cardiac issues. Involvement of various valves in which mitral valve is of prime importance. There is always a fear of getting infected frequently, so we must endeavor to block the possibility to make the disease treated frequently. It can pass easily from close contacts via. Upper Respiratory attacks person to person like other infections ordinarily. In some people, repeated strep infections stress the immune system to react against the tissues of the body affecting heart valves, CHF & fever. In majority cases mitral valve stenosis is the commonest caused by various related infections to *Streptococcus and Staphylococcus as already explained.* Rheumatic fever mostly affects children and adolescents in low- and middle-income countries, especially where poverty is widespread and access to health services is limited. overcrowded of population and poverty are at major risk factors. Disease is endemic in cases Where fever and heart disease are the principal heart disease seen in pregnant women, thus

making it so lethal. Pregnancy where rheumatic fever, heart arrythmias and heart failure due to effect on the heart valves. Rheumatic fever can follow a throat infection from a group A streptococcus. Group A streptococcus infections of the throat cause strep throat or, less commonly, scarlet fever. Group A streptococcus infections of the skin or other parts of the body rarely trigger rheumatic fever. The link between strep infection and rheumatic fever isn't clear. It appears that the bacteria trick the immune system into attacking otherwise healthy tissue. The body's immune system typically targets infection-causing bacteria. In rheumatic fever, the immune system mistakenly attacks healthy tissue, particularly in the heart, joints, skin and central nervous system. This faulty immune system reaction results in swelling of the tissues (inflammation). There's little chance of developing rheumatic fever when a strep throat infection is promptly treated with antibiotics and all the medication is taken as prescribed. If a child has one or more episodes of strep throat or scarlet fever that aren't properly treated, rheumatic fever may occur. Environmental Things that may increase the risk of rheumatic fever include: Genes. Some people have one or more genes that might make them more likely to develop rheumatic fever, Specific type of strep bacteria. Certain strains of strep bacteria are more likely to contribute to rheumatic fever than are other strains. Environmental factors. A greater risk of rheumatic fever is associated with overcrowding, poor sanitation and other conditions that can cause strep bacteria to easily spread among many people.

Complications: Are caused as, Inflammation caused by rheumatic fever can last a few weeks to several months. For some people, the inflammation causes long-term complications, One complication of rheumatic fever is permanent damage to the heart (rheumatic heart disease). Rheumatic heart disease usually occurs years to decades after the original illness. However, severe rheumatic fever can start to damage the heart valves while your child still has symptoms of the infection. Damage is most common with the valve between the two left chambers of the heart (mitral valve), but the other valves can be affected. Rheumatic fever can cause the following types of heart damage.

- Narrowing of a heart valve (valve stenosis). This decreases blood flow.
- Leaky heart valve (valve regurgitation). Blood flows backward across the valve.
- Damage to heart muscle. The inflammation associated with rheumatic fever can weaken the heart muscle, affecting its ability to pump. Damage to the heart valves or other heart tissues can lead to irregular, chaotic heartbeats (atrial fibrillation) or heart failure later in life.

Prevention

The only way to prevent rheumatic fever is to treat strep throat infections or scarlet fever promptly and completely with a full course of appropriate antibiotics.

MATERIAL AND METHODS

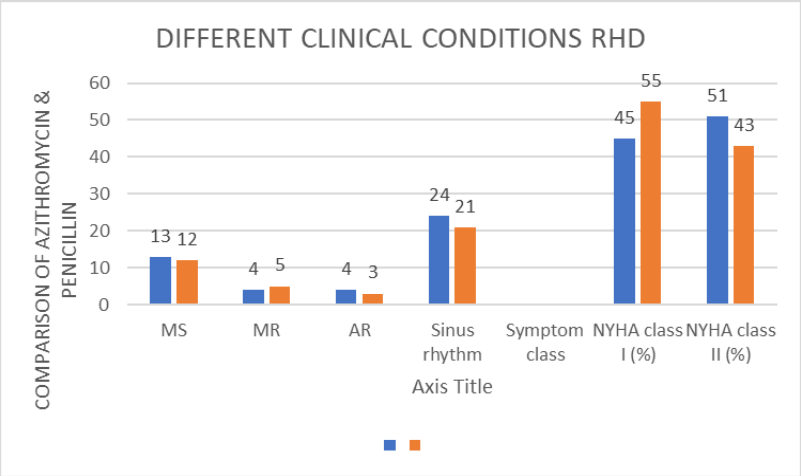
Consecutive patients attending the RHD clinic of SCTIMST, who were initiated on oral rheumatic prophylaxis for the first time, and willing to be followed up as per protocol, not allergic to penicillin and AZT were randomized to receive either weekly 500 mg AZT orally or phenoxy methyl penicillin 250 mg twice daily were included in this open label study. Patients who were changed over from injectable benzathine penicillin to oral penicillin for many reasons (e.g., non-availability) were also included. All patients gave a formal informed consent. The study was approved by the departmental ethics committee.

Cure of group A beta hemolytic streptococcus (GABHS) infection was defined as negative throat culture at the end of 10 days of antibiotic treatment. Further evaluation for rheumatic fever recurrence was done at 3 weeks. Every attempt was made to prevent rheumatic reactivation following a throat infection during the study period. All patients were instructed to report immediately if they developed sore throat for evaluation and 'sledgehammer treatment' as per WHO recommendation4 was initiated at the earliest, to eradicate the nidus of infection. It was planned to cross over the groups if recurrence of throat infection occurred. A third recurrence was taken as an indication to change over to benzathine penicillin. Patients were evaluated at randomization, at 1 month, 3 months and 6 months, clinically and by ASO and throat swab culture. End points were absence of streptococcal colonization, infection or fever at the end of 6 months.

Laboratory studies

Lab personnel were blinded with regard to the treatment arms. Throat culture, antibiotic sensitivity and serology were done by standard methods. Throat swab was obtained and immediate plating was done in blood agar. Gram-stain was done after 48 hours of culture and sub-culture was done whenever necessary. Anti-streptolysin-O titre was estimated using latex agglutination in serial dilutions.

Table 1: Baseline characteristics.



*P = not significant. AR: aortic regurgitation, MR: mitral regurgitation, MS: mitral stenosis, NYHA: New York Heart Association, RHD: rheumatic heart disease.

Table 2: Data on first attack of rheumatic fever (n = 25).

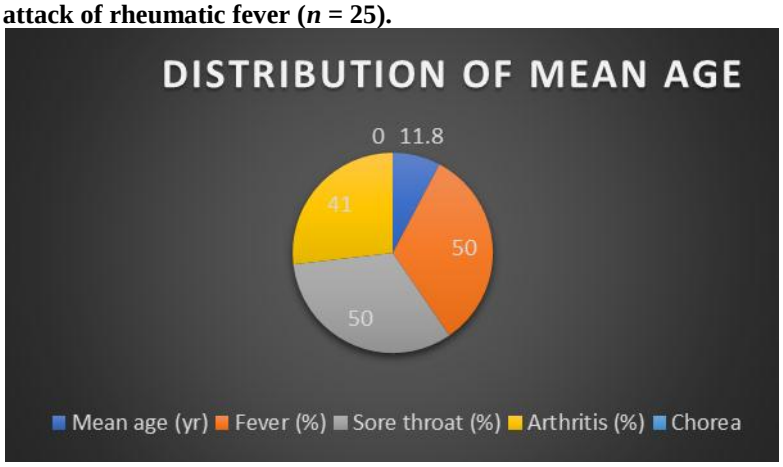
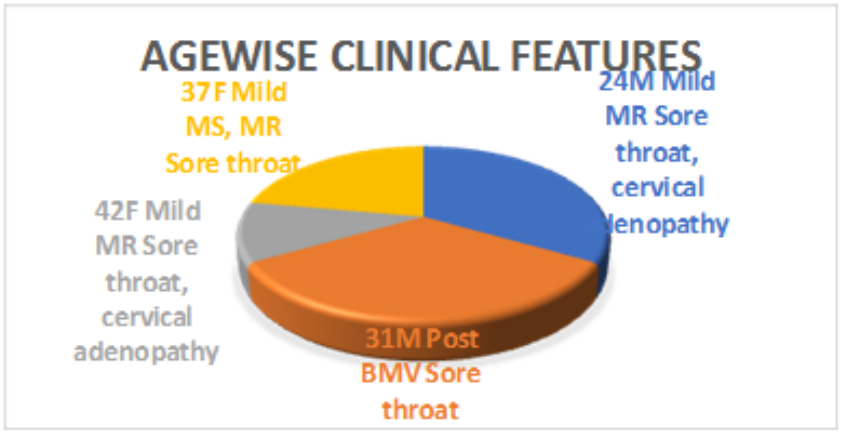


Table 3: Features Of Patient Who Had Sore Throat While On Azithromycin Prophylaxis.



BMV: Balloon Mitral Valvotomy, Mr: Mitral Regurgitation, Ms: Mitral Stenosis, Ses: Socio-Economic Status.

DISCUSSION

Rheumatic fever and its sequelae, RHD is still an important public health problem in developing countries.[1-4] The compliance to different prophylactic regimens is relatively poor.[9,10] Azithromycin, with a long half-life, which can be administered once weekly was thought to improve the compliance.[14] So we decided to study the effectiveness of AZT in the secondary prophylaxis of rheumatic fever. Females predominated (58%) in our study population in contrast to the male predominance in a usual cohort of RHD patients.[14] This was because there is a referral bias for

patients with mitral valve disease who were referred to our hospital for percutaneous and surgical interventions. We could enroll only patients with established RHD, since ours is a tertiary care Centre. No patient at entry into the study had isolation of GABHS in throat culture or had features of acute rheumatic fever. Median age of the study population was 30 years. This is because of the referral bias of our Centre, which primarily caters to those patients requiring valvular interventions. We included older patients who changed over from benzathine penicillin to oral penicillin in the study population. Past history of rheumatic fever was present in 50% of our patients. This is in concordance with the studies reporting prevalence of this history in patients with established RHD.[15,16] Incidence of arthritis in our population was 41%, though in the literature it is 75%. It is reported that arthralgia predominates in the Indian population rather than arthritis.[17] None of the patients in the penicillin group had treatment failure, i.e., either GAS throat infection or colonisation. But the reported streptococcal throat infection rate in patients under 'good' oral penicillin prophylaxis is 7.3–16.2 per 100 patient years.[18,19] A significant number of patients (15.4%) in AZT group in our study had GABHS throat infection as evidenced by clinical pharyngitis, positive throat culture, and elevated ASO titre. However, none had recurrence of rheumatic fever as per the modified Jones criteria. After curative treatment, when the treatment was changed over to penicillin, no recurrence was noted. There are no data in the literature on the use of AZT in the secondary prophylaxis of rheumatic fever. But there are reports of the successful use of once weekly AZT in preventing colonisation and recurrences of streptococcal throat fections.[11,12]

Gray et al.[12] reported superiority of weekly oral AZT in the prevention of upper respiratory infection over penicillin when used as prophylaxis in 1016 US marine trainees at high-risk of respiratory disease. Azithromycin group reported less side-effects, respiratory symptoms and serological evidence for streptococcal, mycoplasmal, and chlamydial infections. However, there is a report by Ghirga[20] on the occurrence of rheumatic fever after a successful treatment of GAS throat infection by AZT. Our study showed a recurrence of infection as high as 15.4%. This is definitely high for this small cohort of patients. It is possible that these patients with established RHD constitute a high-risk group. Why AZT failed to prevent GAS infection in 15.4% of patients is not very clear. One possibility is that drug dosage was too widely spaced. Though AZT has a long half-life, drug concentration might not have been adequate in this high-risk population at the end of the dosage interval.

Treatment with a 3-day, once daily 10 mg/kg AZT for GABHS pharyngitis is associated with similarly high levels of clinical efficacy, but lower levels of bacteriologic eradication, than with 10-day 100,000 IU/kg/day penicillin V.[21]

Casey et al.[22] in a meta-analysis has reported that in children, AZT administered at 60 mg/kg per course was superior to the 10-day course of penicillin, with treatment failure occurring 5 times more often in patients receiving penicillin. Azithromycin administered at 30 mg/kg per course was inferior to the 10-day courses of penicillin, with bacterial failure occurring 3 times more frequently in patients receiving AZT. Three-day AZT regimens were inferior to 5-day regimens. So, AZT treatment may be required in higher doses and for a more prolonged duration to be effective in preventing recurrences of GABHS throat infection. Azithromycin treatment was cost-effective in the regimen which we used in this study. If we increase the dosage or the frequency, it may not be cost-effective. Other possibilities of failure of AZT might include poor patient compliance, failure of the drug to reach adequate concentration in the mucosa, microbial tolerance to AZT, recurrent exposure of patients to virulent strains of GAS, suppression of natural immunity and disturbance of normal flora of throat. Azithromycin inhibits growth of alpha streptococci that are normal defenders of pharyngeal mucosa against pathogens at lower MIC.[23] Intracellular accumulation of macrolides have been shown in leucocytes but not in epithelial cells, which are probably the principal cells targeted by GABHS. In leucocytes AZT accumulates predominantly in lysosomes, whereas intracellular GABHS is found in phagosomes and cytosol.[24]

Recently single 2.0-g dose of AZT microspheres has become available and found to be as effective and well tolerated as a 7-day course of extended-release clarithromycin in the treatment of adults with mild-to-moderate community acquired pneumonia.[25] A further advantage of single-dose therapy is the potential for use as directly-observed therapy, which may be useful in prophylaxis of rheumatic fever.[26]

IN CONCLUSION, weekly 500 mg of AZT is not effective in prevention of streptococcal throat infection compared to oral penicillin therapy in adult patients with established RHD. It is worthwhile evaluating newer long-acting preparations of AZT as the compliance rate of the available regimens are very poor.

LIMITATIONS

1. Age of the study population, well above the usual age of rheumatic fever, 5–15 years.
2. Small number of patients.
3. All patients were having established RHD.
4. Microbiological studies to assess the rheumatogenicity of streptococcal strains were not undertaken.

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