

**FACTORS DETERMINING RHEUMATIC FEVER RECURRENCE AMONG  
RHEUMATIC HEART DISEASE PATIENTS WHO ARE TAKING  
MONTHLY BENZANTHINE G PENICILLIN PROPHYLAXIS  
AT PEDIATRIC CARDIAC CLINIC, TIKUR ANBESSA SPECIALIZED TEACHING HOSPITAL,  
ADDIS ABABA UNIVERSITY, COLLEGE OF HEALTH SCIENCES,  
DEPARTMENT OF PEDIATRICS AND CHILD HEALTH  
ADDIS ABABA, 2014**

**THESIS SUBMITTED TO THE DEPARTMENT OF PEDIATRICS AND CHILD HEALTH, COLLEGE OF  
HEALTH SCIENCES, ADDIS ABABA UNIVERSITY FOR PARTIAL FULFILLMENT OF CERTIFICATE  
OF SPECIALITY IN PEDIATRICS AND CHILD HEALTH**

**Investigator:** Fitsum Dagmawi

**Advisor:** Amha Mekasha, MD, MSc  
Associate professor of pediatrics & child health

## **Acknowledgement**

My deepest gratitude goes to my advisor Dr Amha Mekasha for his generous assistance and valuable and constructive comments throughout the study period.

I am also very grateful to my friends for their unlimited support and encouragement during the preparation of this thesis.

Finally I would like to thank the participants of the study, their parents and the staffs at pediatric cardiac clinic and medical registration for their cooperation during the study.

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## **ACRONYM S**

ARF: Acute Rheumatic Fever  
AR: Aortic Regurgitation  
AS: Aortic Stenosis  
AV: Aortic Valve  
ASO: Antistreptolysin O  
BGP: Benzathine G penicillin  
ETB: Ethiopian Birr  
MR: Mitral Regurgitation  
MS: Mitral Stenosis  
MV: Mitral Valve  
PV: Pulmonary Valve  
RF: Rheumatic fever  
RHD: Rheumatic Heart Disease  
RR: Rheumatic Recurrence  
USD: United States Dollar  
TASH: Tikur Anbessa Specialized Hospital  
TR: Tricuspid regurgitation  
TV: Tricuspid Valve  
WHO: World Health Organization

## **Operational definition**

**Acute rheumatic fever:** is an illness caused by a reaction to a bacterial infection with group A streptococcus, which results in lasting damage to heart valves.

**Rheumatic heart disease:** refers to the major long-term sequel of acute rheumatic fever, which involves the cardiac valves leading to stenosis or regurgitation with resultant hemodynamic disturbance.

**Rheumatic fever recurrence:** refers to subsequent episodes of rheumatic fever in people who have had ARF previously and is diagnosed as recurrent according to standardized World Health Organization criteria .

**Children:** includes those who are 15 years or less old.

**Adherence:** Patients were classified as “adherent” to therapy when they did not skip or delay benzathine penicillin G during interval between appointments. If one or more dose of benzathine penicillin G was delayed or missed during this period, patients were classified as “non-adherent”.

## **ABSTRACT**

### **Introduction:**

Rheumatic fever is a major cause of acquired heart disease in children worldwide, with the disease occurring most frequently in underdeveloped countries. ARF and its chronic sequela RHD remain significant causes of morbidity and mortality in Ethiopia. The main priority of long-term management of ARF or RHD is to ensure secondary prophylaxis is adhered to. Despite its importance, the rate and risk factors of rheumatic fever recurrence is not known in Ethiopian children with ARF/RHD. This study will identify ARF recurrence rates and the extent to which ARF is concentrated in certain populations based on age, sex, education, income, and types of valves involved.

### **Objectives:**

The objective of this study was to identify risk factors for rheumatic recurrence in patients receiving monthly benzathine G penicillin prophylaxis.

### **Method:**

We conducted a retrospective review of medical records of 211 eligible patients with rheumatic heart disease at TASH, pediatric cardiac clinic from April /2014 to Aug. 2014. A descriptive and analytic statistics was used as applicable. Statistically significant associations were set at P-value of <0.05.

### **Results:**

A total of 211 children's medical records were reviewed. Rheumatic fever recurrence occurred in 22 (10.4%) of the 211 patients. Patients with recurrence of RF were less adherent to monthly BGP prophylaxis than patients without recurrence of RF the odds of nonadherent patients was 19.42 (odds ratio= 19.42, CI= (6.885, 54.766) P= 0.000). Non-adherence to BGP prophylaxis at any time during follow up was detected in 10.9% (23 of the 211) of study subjects. Rates of non-adherence were higher in the group of patients that were younger (27.3%, 9.6%, and 7.4% for children less than or equal to 5 year, 6 to 10 year, and 11 to 15 year of age, respectively) than in the group of patients who were older (p=0.046).

### **Conclusion:**

We recommend implementation of a registry, and a system of active search of missing patients in every service responsible for the follow-up of RHD/RF patients. Measures to increase adherence to secondary prophylaxis need to be implemented formally, once non-adherence to secondary prophylaxis is the main cause of RF recurrence.

**Key words:** Rheumatic fever recurrence, rheumatic heart disease.

## INTRODUCTION

Acute rheumatic fever (ARF) is a disease characterized by nonsuppurative inflammatory lesions involving primarily the heart, joints, subcutaneous tissues, and central nervous system (1). It often results in lasting damage to heart valves and thus rheumatic heart disease (RHD). Almost all cases of RHD and associated deaths are preventable (2).

The prevalence of RHD is estimated to be higher in developing than in developed countries, ranging from 24/1,000 to 0.3/1,000, respectively (3, 4, 5). Worldwide, RHD remains the most common form of acquired heart diseases in all age groups, accounting for as much as 50% of all cardiovascular disease and as much as 50% of all cardiac admissions in many developing countries (6). Striking differences are evident in the incidence of ARF and RHD among different ethnic groups within the same country; many, but not all, of these differences appear to be related to differences in socioeconomic status (6). In Ethiopian school children, the prevalence of ARF/RHD is estimated to be in the range of 4.6 to 6.4 per 1000 children (7, 8) and surprisingly enough, not more than 15% of parents of these children know their children had some form of heart disease related with infection and only 22% were on regular prophylaxis showing low knowledge and level of awareness about the disease (7).

Based on conservative estimates, 1.5% of patients with RHD die each year in developing countries. Worldwide, it has been estimated that 233,000 to 492,000 deaths per year occur because of RHD, with 95% of the mortality occurring in developing countries (9).

The severity and prognosis of RHD depends on the extent of cardiac involvement and the frequency of recurrent events (1, 4). The risk of ARF after an untreated group A beta-hemolytic streptococcal (GABHS) infection in healthy children is 0.3% to 3% (4, 10); however, in children with a previous episode of ARF, this risk increases to more than 50%, emphasizing the importance of secondary prophylaxis (11). Secondary prophylaxis, including the use of benzathine penicillin G, is therefore a critical cost-effective intervention for preventing morbidity and mortality related to RF (1, 3, 4, 12, 13).

In its classic form, ARF is acute, febrile, and largely self-limited. However, damage to heart valves may occur, and such damage may be chronic and progressive and lead to severe cardiac failure, total disability, and, not infrequently, death many years after the acute attack. The manifestations of ARF are extremely variable; the disorder remains for the most part a clinical syndrome for which no specific diagnostic test exists. All cases of ARF follow group A streptococcal upper respiratory tract infection, although the exact mechanisms mediating development of the disease remain speculative (1).

In early studies using sulphonamides, 1.5% of treated patients developed ARF recurrences, compared to 20% of untreated patients. Subsequently, penicillin was found to be more efficacious than sulphonamides (2). In the most comprehensive study reported to date, children following this regimen experienced a rheumatic fever recurrence rate of only 0.4 per 100 patient-years of observation (1) while in some areas it still is higher with overall recurrence proportion reaching 4.9% in New Zealand (14) 16.5% in Brazilian children (15) and 37.3% in Alexandria, Egypt (16). In Ethiopia the reported prevalence of rheumatic heart disease in schoolchildren is 4.6 to 6.4 per 1000 population (7, 8, 17) and as to the factors influencing rheumatic fever recurrence in patients taking benzathine prophylaxis, it is not known.

**OBJECTIVES:**

**General objectives:** To determine the factors associated with rheumatic fever recurrence in RHD patients taking monthly benzathine G penicillin prophylaxis.

**Specific objectives:**

- To determine the association between sociodemographic status and rheumatic fever recurrence
- To determine the association between adherence to monthly benzathine G penicillin prophylaxis and rheumatic fever recurrence
- To determine the association between duration of benzathine G penicillin prophylaxis and rheumatic fever recurrence
- To describe the association between type of valve lesions and rheumatic fever recurrence
- To describe the association between parental educational status with the development of rheumatic recurrence.

**MATERIALS & METHODS:**

**SETTING:** The study was done at Addis Ababa University, college of health sciences, Tikur Anbessa Specialized Teaching Hospital, Department of Pediatrics and child Health, pediatric cardiac clinic, in Addis Ababa, Ethiopia. The department has seven major wings with a total of 202 beds: Casualty and emergency admission unit, neonatal ICU, Pediatric ICU, under five year medical admission unit, above five year medical admission unit, hemato-oncology unit, and pediatric surgical admission unit. Patients of all categories of diseases are admitted and treated.

Cardiac patients are admitted to the casualty & emergency admission unit, and medical admission units (under five or above five years medical admission units). The department also has pediatric cardiac clinic throughout the week days – 9:00am to 12:00pm where all cardiac patients /congenital and acquired heart disease / are followed. As per the hospital's protocol, patients who are 15 years of age and above are followed at adult cardiac clinic. The clinic is attended by pediatric cardiologist and residents with an average of 150 patients per week.

**SOURCE POPULATION:** All pediatric cardiac patients with rheumatic heart disease on follow up at Tikur Anbessa Specialized Teaching Hospital, pediatric cardiac clinic.

**STUDY POPULATION:** Children below the age of 15 years with documented rheumatic heart disease or acute rheumatic fever and who were on monthly benzathine G penicillin prophylaxis.

**STUDY DESIGN:** A retrospective cross sectional review of medical records of 229 children with RHD or ARF was conducted (figure 1) using a structured data collection sheet.

**EXCLUSION CRITERIA**

- ARF / RHD patients who are newly diagnosed and/or those with less than six months of follow up.

### **SAMPLE SIZE:**

A simple random sampling technique will be used to select the required sample size. The sample size calculation was done on the basis of the following assumptions:

1. The proportion of rheumatic recurrence in rheumatic heart disease patients taking BGP is estimated to be 37.3% (16)
2. The level of significance is taken as 5% (95% confidence interval)
3. The desired margin of error /d/ is estimated to be 5%

$$n = \frac{z_{1-\alpha}^2 P(1-P)}{d^2} = 1.962 \times 0.373(1-0.373) / (0.05)^2 = 184 + 10\%$$

$$n = 203$$

### **DATA ANALYSIS**

The data were entered in Statistical package for social science /SPSS/ data base; after cleaning, descriptive and analytic analysis were done as applicable.

Statistical significance was set at P-value of 0.05. Binary logistic regression was used to produce a summary of statistics of proportions including crude odds ratio and 95% confidence intervals.

Screening of predictors of recurrence of RF was done using binary logistic regression for each variable one at a time. Then, those variables with a P-value <0.05 were collected and entered into logistic regression to control possible confounders. Only covariates that were associated with the outcome (P<0.05), after controlling potential confounders, were retained. Recurrence of RF was set as the dependent variable and tested for association with socio-demographic and child factors.

### **ETHICAL CLEARANCE**

The study was conducted after obtaining ethical clearance from the Institutional Review Board of College of Health Sciences, Addis Ababa University. Verbal and/or written consent was obtained from the respondents (parents/caregivers). Detailed description of the purpose of the study was explained to the participants before they enrolled and agree to participate.

## RESULTS

A total of 229 medical records of children with RHD were approached (fig. 1), of whom 18 were excluded from the study (11 were newly diagnosed cases of RHD, 5 did not return to the clinic after their first visit and 2 were not reachable). Medical records of the 211 children's below 15 years of age (44.1% male and 55.9% female) were reviewed thoroughly. Hundred thirty five (64%) were between the ages of 6 and 10 year, while children 11 to 15 years of age were 54 (25.6%) and those aged 5 or less accounted for 22 (10.4 %) of the study population. Ninety eight (46.4%) of children were from Oromia region. The youngest age at diagnosis of RHD was 29 months. Minimum duration of follow up among the study population was 7 months and maximum was 126 months. Combined mitral, aortic, and tricuspid valve lesions were the most common accounting for 46.9% (99) of patients followed by combined mitral and tricuspid valve and isolated mitral valve lesions, 23.2% (49) and 11.8% (25) patients, respectively (fig. 2). Forty seven (22.3%) of patients were having mitral stenosis on their first presentation of whom 24 (11.4%) were severe. Hundred eighty eight (89.1%) of study subjects had reported complete adherence to BGP prophylaxis.

Rheumatic fever recurrence occurred in 22 (10.4%) of 211 patients while on BGP/ follow up. Of patients who developed recurrence of RF twelve (54.5%) occurred during the first 12 months, and nineteen (86.3%) occurred in the first 24 months of follow up. Thirteen (59.1%) of those who developed recurrence of RF were males. Children aged five year or less, 6 to 10 year and 11 to 15 year accounted for 4 (18.2%), 15 (68.2%), and 3 (13.6%) of recurrence cases, respectively, from each group.

While testing for association patients with rheumatic fever recurrence were less adherent to BGP prophylaxis and the odds of nonadherent patients was 19.42 (odds ratio= 19.42, CI= (6.885, 54.766) P= 0.000). There was not a significant difference between patients who did and did not have recurrence in relation to gender, age, parental/caregiver educational status, monthly income of the family, frequency and duration of follow up. The type and severity of valve lesions involved at the time of diagnosis of RHD also failed to show significant association with the development of recurrent episode of rheumatic fever. Of the 211 children 32(15.2%) had had rheumatic fever recurrence on their first presentation (at the time of diagnosis of RHD) and there was not a significant difference between patients who did and did not develop recurrence of RF in relation to the presence of recurrence of RF at the time of diagnosis (table 1).

Non-adherence to BGP prophylaxis at any time during follow up was detected in 10.9% (23 of the 211) of patients. Within patients who had a recurrence, 52.2% were non-adherent to BGP prophylaxis while the rest of patients who had recurrences reported adherence to BGP prophylaxis. Non-adherence to BGP prophylaxis had a significant association with the recurrence of rheumatic fever (p = 0.000). Rates of non-adherence were higher in the group of patients that were younger (27.3%, 9.6%, and 7.4% for children less than or equal to 5 year, 6 to 10 year, and 11 to 15 year of age, respectively) than in the group of patients who were older (fig. 3). This was statistically significant (P-value of 0.046). There was not a significant difference between male and female patients; 88.2% of males and 89.8% of females were adherent to their BGP prophylaxis (P= 0.531). There also was not a significant difference between patients who were and were not adherent in relation to parental/caregiver's education, total size of the family, frequency of follow up, and duration of follow up. For complete access of tables, figures and annexes look at the original document which is available at the department. Living in Addis Ababa and out of Addis Ababa were not associated with significant difference in adherence or non-adherence (0.368) and with the development of recurrence of RF (p=0.48).

Table 1.1: Frequency distribution of characteristics, pediatric cardiac clinic of Tikur Anbessa Specialized Teaching Hospital, Addis Ababa, Ethiopia, 2014

Characteristics	Frequency (%) N=211	RR during follow up (%)		P – value
		No (%)	Yes (%)	
<b>Age</b>				
≤ 5 years	22 (10.4%)	18 (81.8%)	4 (18.2%)	0.093
6 - 10 years	135 (64%)	120 (88.9%)	15 (11.1%)	
11 -15 years	54 (25.6%)	51 (94.4%)	3 (5.6%)	
<b>Gender</b>				
Male	93 (44.1%)	80 (86%)	13 (14%)	0.135
Female	118 (55.9%)	109 (92.4%)	9 (7.6%)	
<b>Parental education</b>				
Illiterate	59 (27.9%)	52 (88.1%)	7 (11.9%)	0.667
Read & write	39 (18.5%)	35 (89.7%)	4 (10.3%)	
Elementary school	70 (33.2%)	63 (90%)	7 (10%)	
High school	39 (18.5%)	35 (89.7%)	4 (10.3%)	
Higher education	4 (1.9%)	4 (100%)	0	
<b>Family Size</b>				
≤4	28 (13.3%)	23 (82.1%)	5 (17.9%)	0.718
5 – 6	86 (40.8%)	80 (93%)	6 (7%)	
7 – 10	87 (41.2%)	77 (88.5%)	10 (11.5%)	
>10	10 (4.7%)	9 (90%)	1 (10%)	
<b>Monthly income of the family ETB (USD)</b>				
<750 (38)	78 (37.0%)	67 (85.9%)	11 (14.1%)	0.357
750 (38)–2350 (118)	118 (55.9%)	109 (92.4%)	9 (7.6%)	
2350 (118)-3550(178)	13 (6.2%)	11 (84.6%)	2 (15.4%)	
3550(178)- 5000 (251)	2 (0.9%)	2 (100%)	0	
<b>Duration of monthly BGP prophylaxis /follow up</b>				
6 – 12 months	36 (17.1%)	35 (97.2%)	1 (2.8%)	0.156

13 - 24 months	52 (24.6%)	44 (84.6%)	8 (15.4%)	
25 – 36 months	47 (22.3%)	45 (95.7%)	2 (4.3%)	
37 -48 months	32 (15.2%)	27 (84.4%)	5 (15.6%)	
49 – 60 months	14 (6.6%)	13 (92.9%)	1 (7.1%)	
61 -72 months	11 (5.2%)	10 (90.9%)	1 (9.1%)	
>72 months	19 (9.0%)	15 (78.9%)	4 (21.1%)	
<b>Adherence to monthly BGP prophylaxis</b>				
Adherent	188 (89.1%)	178 (94.7%)	10 (5.3%)	<0.001
Nonadherent	23 (10.9%)	11 (47.8%)	12 (52.2%)	
<b>Missed doses of BGP during the follow up period (adherence)</b>				
Completely adherent	188 (89.1%)	178 (94.7%)	10 (5.3%)	0.005
1 dose missed	4 (1.9%)	3 (75%)	1 (25%)	
2 doses missed	4 (1.4%)	2 (50%)	2 (50%)	
3 doses missed	3 (1.4%)	1 (33.3%)	2 (66.7%)	
≥4 doses missed	12 (5.7%)	5 (41.7%)	7(58.3%)	
<b>Frequency of follow up</b>				
q 1 – 3 months	130 (61.6%)	115(88.5%)	15 (11.5%)	0.611
q 4 – 6 months	73 (34.6%)	67 ((91.8%)	6 (8.2%)	
>6 months	8 (3.8%)	7 (87.5%)	1 (12.5%)	
<b>Valves involved at diagnosis of RHD</b>				
Isolated mitral valve	25 (11.8%)	23 (92%)	2 (8%)	0.182
Mitral + Aortic valves	22 (10.4%)	21 (95.5%)	1 (4.5%)	
Mitral + Tricuspid Valves	49 (23.2%)	44 (89.8%)	5 (10.2%)	
Mitral +aortic+ tricuspid valves	99 (46.9%)	88 (88.9%)	11 (11.1%)	
All four valves	12 (5.7%)	10 (83.3%)	2 (16.7%)	
MV + TV +PV	4 (1.9%)	3 (75%)	1 (25%)	

## DISCUSSION

In our study, of the 211 study subjects females outnumber males (55.9% and 44.1%, respectively), which also was seen in a previous study done among school children in central Ethiopian rural town, Butajira(17).

Recurrences of RF are directly related to morbidity, mortality and disease progression (18). Twenty two (10.4%) of patients in our study had a recurrence of RF while on monthly BGP prophylaxis, however elsewhere recurrence was 0.4% in a study involving 16 developing countries (19). Other studies detected rates of 16.5% in Brazil (15) and in Alexandria (Egypt), in 1998, RF recurrence was found to be 37.3% and the risk factors implied were: living in rural and semi-urban areas, and lack of adherence to secondary prophylaxis [16].

Our study detected that nonadherence to GBP prophylaxis was strongly associated with the development of recurrence of rheumatic fever; these was also demonstrated in a study among Brazilian children (15). In contrast to our results, increase in age and aortic regurgitation were identified as a predictor of RF recurrence in a cross-sectional study in Nepal (20) and also male sex was detected as a predictor of recurrence of RF in a study done in Brazilian children (15).

In our study population, nonadherence to BGP prophylaxis was 10.9% in the study subjects and recurrence was associated to nonadherence to BGP prophylaxis in 52.2% of cases. In other studies nonadherence rate varies from 10% to 65.7% (11, 15, 16, 21, 23, 24, 25) in Australia, Brazilian children, Alexandria (Egypt), Cuba, Lifou (New Caledonia) and Iran. Our study demonstrated that younger age was related to lack of adherence and parental/caregiver education, income of the family, family size, address, and gender were not associated with nonadherence. Whereas in a study done elsewhere, factors related to the lack of adherence were: lower education of the parents, living in rural or semi-urban areas, low parental knowledge about the disease and dissatisfaction of the family with care (16). In a study from Lifou, New Caledonia, household with more than five people, a previous medical history of symptomatic ARF and an adequate healthcare coverage were protective against poor adherence (24).

To guarantee higher adherence to prophylaxis, implementation of education and awareness strategies for patients and families may be a solution. According to the KAP (knowledge, attitude, practice) model of promotion of health, knowledge is necessary in order to change individuals' behaviors [26, 27]. Counseling about the relevance of adherence to therapy, how to organize administration of medication, remembering notes about appointments, rewards to the efforts of patients in following the prescribed regimen, and stimulus of the support of family and friends are effective interventions to long course treatments [11]. These interventions might represent hard work, but they are cost-effective [28, 29]. They have been associated to enhancement in adherence to long course treatments in 50%; and among those, 44.5% had improvement of prognosis [29]. Training of health personnel, healthcare education, community involvement, and epidemiological surveillance were part of the Cuban project that significantly reduced first and recurrent attacks of RF, severity of RHD, and direct costs of managing the disease, as well as increased compliance with secondary prophylaxis [21].

## LIMITATIONS OF THE STUDY

The limitation of our study was that as it was a retrospective review of medical records, reasons for nonadherence to BGP prophylaxis were difficult to assess.

## CONCLUSION AND RECOMMENDATION

Our study supports the need to concentrate on optimizing adherence to BGP prophylaxis and to assure medical staff and patients of the long-term benefits of benzathine G penicillin administration to prevent recurrent RF. Based on the rates of non-adherence to secondary prophylaxis, which lead to recurrent episodes of RF, we recommend implementation of a registry, and a system of active search of missing patients in every service responsible for the follow-up of RF patients. Measures to increase adherence to secondary prophylaxis involving patients and families need to be implemented formally, once non-adherence to secondary prophylaxis is the main cause of RF recurrence, still an issue in many parts of the world. Detection of irregularity in secondary prophylaxis should be an alert for closer observation. Further prospective studies are recommended to identify the factors associated with nonadherence.

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