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Short Communication

Evaluation of the policy of secondary prevention against rheumatic fever among Egyptian children

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ABSTRACT

Objective: We evaluated the effectiveness of long acting penicillin (LAP) as a 2-weekly regimen in winter and a 3-weekly regimen in summer for prevention of streptococcal colonization and also studied the common complaints of patients during the period of compliance for LAP administration. We also attempted to determine the incidence of relapses or recurrence of rheumatic fever (RF) after the onset of first episode of RF.

Patients & methods: 210 rheumatic patients with good compliance to LAP (for at least one year) were included in the study. Demographic, clinical information, patients' complaints and echocardiographic data of rheumatic patients were collected both retrospectively and prospectively. Anti-streptolysin O titre (ASOT) and throat swab culture were done at the end of the study (on Day 14 in the 2-weekly regimen and on Day 21 in the 3-weekly regimen).

Results: The age of onset of rheumatic fever was mostly between 5 and 15 years and the youngest patient was 2 years old. Subclinical carditis (SCC) was present in 79 (37%) of all the patients in the study population. Only 7 patients (3.3%) had a relapse within 2 years of the acute episode of RF. At the end of the study, ASOT was found to be high only in 11 patients (5.2%) and throat swab cultures were found negative in all patients

Conclusion: LAP regimen is fairly effective in eradicating streptococcal colonization. The incidence of relapse of RF within 2 years of the acute episode of RF is relatively low.

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1. Introduction

Rheumatic fever (RF) and rheumatic heart disease (RHD) cause 40% of all cardiovascular diseases in developing countries.

Disability and death from RHD are mainly caused by recurrent attacks.¹ However, pilot studies conducted during the last five decades in developed and developing countries revealed that the prevention and control of RF and RHD is possible.

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Rheumatic fever is a multisystem, immunologically mediated inflammatory disease, that occurs as a delayed sequel to group A streptococcal (GAS) infection.²

People with a history of RF are at a high risk of recurrent attacks and of developing RHD following streptococcal throat infection. Giving penicillin to these people can prevent recurrent attacks of RF and subsequent RHD. However, there is no agreement on the most effective method of giving penicillin.³

Secondary prophylaxis with benzathine penicillin G (BPG) is the only scientifically proven strategy to control RHD. It is recommended to apply a 2-weekly LAP regimen in the first few years after the acute episode of RF especially in high risk communities. This can then be followed by a 2-weekly LAP regimen in winter and a 3-weekly regimen in summers in the subsequent years. Decisions to stop secondary prophylaxis should be based on regular clinical assessment.

In this study, we aim to evaluate the effectiveness of long acting penicillin (LAP) as a 2-weekly regimen in winter and a 3-weekly regimen in summer for the prevention of streptococcal colonization of the throat. Also, we attempted to assess patients' complaints during the period of compliance for LAP injections administration and to determine if the second rheumatic presentation is related to the initial presentation or not.

2. Patients and methods

It is a cross-sectional observational (retrospective and prospective) study conducted after seeking approval from the local institutional review board and human subjects' protection. Written consent was obtained from patients and their parents.

Our study spanned over one year period and included 210 patients who were diagnosed previously with rheumatic fever according to Jones criteria. All patients reported good compliance to LAP regimen and regularly attended rheumatic fever outpatient clinic for a period of at least one year retrospective to our study. This was confirmed through a specific follow-up card maintained for each patient in Rheumatic Fever Clinic, Cairo University, Children Hospital.

Inclusion criteria:

1. Patients receiving LAP according to their weight (the regimen of secondary prevention of RF was 600,000 units LAP for patients weighing 25 kg or less and 1.2 million units for patients weighing more than 25 kg) every 2 weeks in winter and 3 weeks in summer,⁴ regardless of age
2. Patient exhibiting good compliance with LAP treatment (for at least one year).

Exclusion criteria:

1. Patients who developed penicillin allergy during prophylaxis
2. Patients who refused to continue prophylaxis with LAP
3. Patients on oral penicillin.

Our study had both retrospective and prospective components.

2.1. Retrospective component

It was taken through an organized filing system for each patient in rheumatic fever clinic and it includes: complaint at initial attack, history of relapses or recurrence, investigations done at initial attack (ESR, CRP, ASOT and Echocardiography) and echocardiography follow up every 3 months. All cases of relapses were diagnosed in rheumatic fever clinic. The patients were admitted immediately to Cairo University, Children Hospital and were subsequently investigated by one of the eminent professor of pediatric cardiology who performed an echocardiography to document the echocardiographic criteria of relapses. According to the protocol of rheumatic fever clinic any case of relapse has to be admitted to Cairo University, Children Hospital in order to be fully investigated (full labs and echocardiographic imaging).

2.2. Prospective component

Any recent complaint and extensively present medical history. Anti-streptolysin O titer (ASO Latex test): The plasmatic ASO Latex test kit for qualitative and semi-quantitative estimation of anti-streptolysin O antibody in human serum was used. Throat swab culture was done to isolate and identify group A β hemolytic streptococci. ASOT and throat swab culture were done at the end of the study (on day 14 in the 2-weekly regimen and on day 21 in the 3-weekly regimen prior to receiving the LAP injection) and sensitivity test was also done for positive culture.

2.3. Echocardiography

Imaging echocardiogram was performed every 3 months and at the end of the study using standardized protocol with M-mode, 2-dimensional and pulsed, continuous-wave using general electric medical echocardiographic machine-model: lived 7 Pro, GE Vingmed ultrasound AS-N190, Horton–Norway equipped with 3 & 7 MHz transducers.

2.4. Statistical methods

Statistical analysis was conducted using Statistical Package for Social Science (SPSS) program version 15 (Chicago, Illinois, USA). Data was summarized as number and percentage.

3. Results

Our study included 210 patients with a history of RF (120 on 2-weekly regimen and 90 patient on 3-weekly regimen). It included 100 males and 110 females with male to female ratio of 1:1.1. In our patient cohort, the mean age of onset of RF was 8.0 ± 2.4 years (2–15 years) and the mean patient age was 11.5 ± 2.8 years (4–19 years). **Table 1** shows the age of onset of rheumatic fever of the patients under study. Presenting clinical symptoms of RF included-polyarthritis in 143 patients (68%), Carditis (clinical and subclinical carditis diagnosed by echocardiography) in 130 patients (61%), chorea in 14 patients (6.6%), and Erythema marginatum and subcutaneous nodules in 1 patient (0.5%) each. 102 out of 210 (48.5%) patients were

Table 1 – Age of onset of rheumatic fever.

Age groups	n	%
<5 yrs	17	8.1
5–10 yrs	131	62.6
10–15 yrs	60	28.4
15–20 yrs	2	0.9

anemic (Hb% < 11.5 g/dl) at presentation, 19% patients had cardiomegaly, 19.9% had thrill and 58.8% had apical systolic/basal diastolic murmur. 54 (25.7%) patients complaint of sore throat but on examination, only 19 cases (9%) were found to have pharyngitis. 46.4% patients complaint of arthralgia but on examination only 0.5% had arthritis. Rheumatic arthritis in the first attack was found in 68% of the studies patients. Systems affected during the period of the study are shown in Table 2. Echocardiographic finding of rheumatic patients at the end of the study is shown in Table 3.

In our study, 7 patients (3.3%) had relapse within the first 2 years after acute episode of RF. 4 patients (75%) had relapse in the form of arthritis, 1 patient (14.2%) had carditis and 2 patients (28.5%) had chorea. Demographic and clinical data of patients with relapses are shown in Table 4. ASOT of rheumatic patients at the end of the study was >200 todd U/ml in 11 (5.2%) patients. Throat swab cultures of all patients were negative.

4. Discussion

In our study, age of onset of rheumatic fever was between 5 and 15 years for 91% of the patients and between 5 and 10 years for 62.6% patients. This agreed with the study done by Omokhodion et al and Mahmudi et al, who reported that 70% of patients had age at onset of RF between 5 and 15 years.^{5,6} This age distribution coincides with the peak incidence of streptococcal infection in children.⁷

Table 2 – Systems affected during the period of the study of patients included in the study.

Variables	n	%
Articular affection		
Arthralgia	98	46.7
Arthritis	1	0.5
Cardiac affection		
Chest pain	37	17.6
Dyspnea	52	24.8
Exercise intolerance	105	50.0
Neuropsychiatric manifestation		
Abnormal movements during regimen	7	3.3
Emotional lability during regimen	5	2.4
Respiratory manifestation		
Pharyngitis	19	9
Nares excoriatum	42	20.0
Wheezes	14	6.7
Crepitations	64	30.5
Gastrointestinal		
Hepatomegaly	3	1.4
Urological manifestation		
Loin tenderness	20	9.5

Table 3 – Echocardiographic findings of rheumatic patients included in the study.

Variables	n	%
Mitral valve thickness	160	76
Mitral regurgitation	168	80
Mitral stenosis	6	2.8
Aortic valve thickness	6	2.9
Aortic regurgitation	56	27
Aortic stenosis	2	1
Pericardial effusion	1	0.5
Pulmonary artery pressure		
Normal	110	52.1
Elevated	87	41.2
Undetermined	14	6.6

Seventeen of our patients (8.1%) had age of onset of RF below 5 years (the youngest was 2 years old). This agreed with the study done by Yee et al, who reported rheumatic carditis in the first year of life.⁸ Also, Seckeler et al, found that age at diagnosis of RF ranged from 2.9 to 17.1 years (median 10.6 years).⁹

In our study, initial presentation of RF was in the form of: 143 patients (68%) had polyarthritis, 130 patients (61%) had carditis (clinical and subclinical diagnosed by echocardiography), 14 patients (6.6%) had chorea, 1 patient (0.5%) had erythema marginatum and 1 patient (0.5%) had subcutaneous nodules. This coincides with Seckeler et al, who reported that fever and carditis were the most common presenting findings.⁹

Rheumatic fever (RF) is usually preceded by Group A β hemolytic streptococci (GA β HS) of the upper respiratory tract. A history of earlier sore throat (32%) was reported by Mahmoud et al,¹⁰ while in Omran and Mourad¹¹ the percentage was little lower (29.3%). In our study, 54 patients (25.7%) complained of sore throat while on examination pharyngitis was detected only in 19 cases (9%). This is also confirmed by Carapetis et al,¹² who noted that the symptoms of acute pharyngitis are more often caused by viruses (adenoviruses, enteroviruses and influenza viruses) than by Group A Streptococcal (GAS). Differentiation of GAS pharyngitis from viral pharyngitis based on history and clinical findings is difficult. Even experienced clinicians are unable to differentiate streptococcal pharyngitis from pharyngitis caused by other pathogens.¹²

In our study population, the most common articular manifestation during the compliance period of LAP injections was in the form of arthralgia, which presented in 46.7% patients. However, only 0.5% of the patients had clinical signs of arthritis on examination. This small incidence of clinical arthritis may be due to the other causes of arthritis such as post-streptococcal reactive arthritis associated with streptococcal infections. Because of difficulties in differentiating this kind of arthritis from that of acute rheumatic fever (ARF), this condition should rarely, if ever, be diagnosed in high risk populations.¹² Carapetis et al,¹² suggested that in recurrent attack of ARF in high risk groups, polyarthritis or aseptic monoarthritis or polyarthralgia should form a major criterion for diagnosis. Rayamajhi et al also proposed that arthralgia should be changed from a minor to a major criterion.¹³

Similarly, the common cardiac symptoms during the period of our study included chest pain in 37 (17.6%) patients,

Table 4 – Demographic and clinical data of patients with relapses.

Serial no of relapse	Age of onset of RF (yrs)	Age of patients (yrs)	Time from 1st attack till relapse (yrs)	Form of 1st attack	Form of relapse	Duration of regimen at relapse (WK)	Recent ASOT Todd U/ml
1	8	9	1	Polyarthritis	Monoarthritis	3	<200
2	5	12	2	Polyarthritis	Chorea	3	400
3	9	13	2	Polyarthritis	Carditis	2	<200
4	4.5	6.5	1	Polyarthritis	Polyarthritis	2	<200
5	11.5	17	1.5	Polyarthritis	Polyarthritis	3	<200
6	10	13	2	Polyarthritis	Polyarthritis	3	<200
7	9	12.5	1.5	Polyarthritis	Chorea, carditis	3	<200

dyspnea in 52 (24.8%) patients and exercise intolerance in 105 (50.0%) patients. Dyspnea and exercise intolerance may be due to the fact that 102 of the studied patients (48.5%) were anemic (HB% <11.5 g/dl). Regarding cardiac signs, on clinical examination 19% patients had cardiomegaly, 19.9% had thrill and 58.8% had apical systolic/basal diastolic murmur. In our study, rheumatic carditis (evident clinically and sub-clinically as diagnosed by echocardiography) was detected in a total of 130 (61%) out of 210 studied cases. Evident clinical carditis at 1st presentation was detected in 51 (24.3%) of all studied patients while subclinical carditis (clinical examination is normal but echocardiogram is abnormal) was found in 79 (37%) of all studied patients.¹⁴

In a study by Figuerora et al, to determine the frequency of occurrence and long term evolution of subclinical carditis in patients with ARF, it was found that during an episode of RF and also during follow up, Doppler echocardiography detected more valvular lesions than clinical examination. In this study, 25 of 35 rheumatic patients (71% of studied patients) had echocardiographic evidence of valvular (mitral or aortic) incompetence at the time of entry into study. On the other hand, in 10 out of 35 patients (30% of all the RF patients entering the study), no auscultatory or clinical findings suggestive of acute rheumatic carditis could be found despite repeated examinations. These 10 individuals constituted the group of rheumatic fever patients with subclinical carditis.¹⁵

Khriesat and Najada, found four cases (25%) with silent carditis which were established after echocardiography.¹⁶ This finding shows it is important to repeat echocardiography over the period of next 3–4 weeks because the valvular involvement which was absent in the beginning may appear later. This validates that echocardiography results are the major criterion for diagnosis of ARF. The diagnosis of silent carditis was established only after echocardiography. These findings highlight the importance of repeating echocardiography over the next 3–4 weeks, as valvular involvement which was absent initially, may appear later, supporting the view, that echocardiographic findings should be considered as a major criterion for diagnosis of ARF.¹⁵ According to Carapetis et al, echocardiography results showing subclinical valve damage will help skilled clinicians to diagnose ARF and confirm the presence of carditis in cases of ARF without a clear pathological heart murmur. Therefore, it is important to include diagnosis of echocardiographically suggested valve damage as the major manifestation in patients with ARF/RHD. Echocardiographic diagnosis of subclinical valve damage can help experienced clinicians in making the diagnosis of ARF, or

in confirming the presence of carditis in cases of ARF without an obviously pathological heart murmur. Therefore, they recommended that echocardiographically suggested valve damage (subclinical or otherwise), diagnosed by a clinician with experience in echocardiography of patients with ARF/RHD, be included as a major manifestation.¹²

Mitral regurgitation (MR) was found to be the most common valve affection in our study and was diagnosed by echocardiography at the end of the study. MR was evident in 80% of cases, a figure close to findings by Mahmudi et al,⁶ from Iran, who reported that mitral regurgitation was present in 75% of rheumatic patients. Another study revealed that MR was the most common lesion in the first and second decades of life.¹⁷ Pereira et al also noticed that MR was the most commonly occurring lesion in ARF.¹⁸ The rates of mitral valve repair for RHD are currently greater than 90% in the children's cardiac unit but remain low in adult cardiac units in New Zealand.¹⁹ In our study, Aortic regurgitation (AR) was the second most often affected cardiac valve. It was evident in 27% of cases, a finding similar to that of Biter et al from Lebanon, who found the incidence of AR among rheumatic patients to be close to 35%. However, this finding was in contrast to that of Omran et al who reported the incidence of AR in rheumatic patients to be 52%.²⁰

As regards neuropsychiatric manifestations, 4.3% patients complained of abnormal movement and 3.8% of behavior abnormalities during the period of our study. On examination 3.3% patients had abnormal movements and 2.4% had emotional disability during their period of compliance with LAP injections. Chockalingam et al found chorea in only 4% of their total study population of acute rheumatic patients.²¹ This small number of such cases may be due to other causes of chorea, because pediatric autoimmune neuropsychiatric disorders are also associated with streptococcal infections. However, due to the difficulties in differentiating chorea from ARF, this condition should not be suspected, especially in low-risk populations.¹²

In our study, 7 patients (3.5%) had relapses – 3 patients had polyarthritis, 1 patient had monoarthritis, 1 patient had carditis and 2 patients had chorea. Four of these seven patients, who had relapse in form of arthritis, also had arthritis as their initial presentation. The remaining 3 patients had different form of relapse from their original manifestation. Oran et al reported that, the recurrences were associated with more severe damage to organs, particularly the heart, which may have been injured during the initial attack.²² Relapse occurs within the first 2 years of the acute episode of RF (3 patients

after 2 years, 2 patients after 1.5 years, and 2 patients after 1 year).

American Heart Association (AHA) recommended 3-weekly regimen of LAP in countries where incidence of rheumatic fever is particularly high. However, some authors have recommended 2-weekly regimen. These recommendations are in agreement with findings from our study-out of the 7 patients who had relapse, 5 were on the 3-weekly regimen of LAP, while 2 were on the 2-weekly regimen of LAP. This indicates the effectiveness of LAP in prevention of repeated attacks of RF. Oran et al suggested that the interval between injections should be 15 days during the first 2 years after the acute episode of RF and 21 days during the subsequent years.²²

Manyemba and Mayosi reported that penicillin reduces the risk of recurrence of RF by 55% and that of streptococcal throat infections by 16%.³ On the contrary, Seckeler et al reported the recurrence rate of RF in penicillin treated group as 38%.⁹

An individual who had already suffered an attack of RF is more prone to develop a recurrence following GAS pharyngitis. To prevent such recurrences, these people must be administered continuous antimicrobial prophylaxis. The duration of prophylaxis is determined based on the number of previous attacks; time elapsed since the last attack, age of the patient, any cardiac involvement and risk of exposure to GAS infections. Penicillin is the drug of choice for secondary prophylaxis among such cases, but in penicillin-sensitive patient sulfadiazine, macrolide or azalide may also be considered.⁴

A rather low incidence of relapse in our study reflects the effectiveness of giving LAP as a 2-weekly regimen in winter and a 3-weekly regimen in summer. This finding also corroborates with a recent systematic review which compared 2-3 weekly LAP treatment with 4-weekly IM penicillin in patients with earlier attacks of RF. One trial was done, showing that the 2 or 3 weekly injections were more effective than 4-weekly injections in preventing RF recurrences. Evidence of the trial shows 2-weekly injections results in almost 50% reduction in RF recurrences and 40% decrease in streptococcal throat infections as compared to 4-weekly injections. However, the evidence for 3-weekly injections is comparatively less stronger if the systematic error by inadequate randomization in the study is taken into account.^{3,12}

Another study was done in Brazil to evaluate penicillin concentrations in sera at 1, 10, 14, and 21 days after IM injections of benzathine penicillin G (BPG) 40,000 IU/kg. The minimum recommended serum penicillin concentrations in order to prevent recurrence of RF is 0.02 mg/ml. This study revealed that the mean serum penicillin concentration after 1, 10, 14 and 21 days of drug administration was 0.08, 0.03, 0.02 and 0.01 micro gm/ml respectively. This means that in a majority of children, by week 3 of administration, serum penicillin concentration becomes inadequate for prevention of RF in a majority of children.²³ According to pharmacokinetic studies, the concentration of penicillin in serum remains above the minimum inhibitory levels when penicillin injections are given every 2 weeks. So, the above results support a 2-weekly regimen.³

In our study, at the time of relapse, one relapsed patient had ASOT equal 400 todd U/ml, while the remaining 6 patients had recent ASOT less than 200 todd U/ml. The results of all

throat swab cultures of the studied patients were negative. This proves the effectiveness of a 2-weekly regimen in winter and a 3-weekly regimen in summer for eradicating streptococcal colonization in the throat. However, this raises an important question – why did 7 patients had relapse, while all of them had negative throat cultures? This can partly be explained by the fact that the throat cultures in our study were only done for Group A streptococcal infections and not for other groups such as C, G, F and B. Many other researchers have had similar findings in the past. In 2001, researchers studied the streptococcal carriage rate in throat among the public school children in Nigeria and found the carriage rate to be 13.3%. Another study found the streptococcal carriage rate of 9.78% without any Lance field group A isolates. However, the incidence of streptococcal groups C, G, F and B carriers was found to be 38%, 36%, 20%, and 7% respectively.

Non-group A streptococci are more dominant in tropical and subtropical countries, therefore its very likely that a larger no of patients develop RF secondary to non-group A β hemolytic streptococci. In fact, scientists have suggested a stronger role of groups C and G β hemolytic streptococci in humans with non-suppurative sequelae in the tropical and subtropical countries, where the prevalence of RF/RHD is high.⁵ Dinkla et al also suggested that the streptococcal strains causing ARF form an auto antigenic complex with human collagen IV. Pharyngeal carriage of group C and G streptococci prevails in some geographical regions witnessing high incidence of ARF. M-like surface proteins that bind to human collagen have been identified on the surface of group C and G streptococci. Therefore, it advisable to eradicate streptococci that possess collage binding proteins to prevent recurrent of RF.²⁴

On the other hand, we found that only 11/210 (5.2%) patients had recent ASOT >200 todd U/ml after compliance LAP regimens at least for one year. This reflects the effectiveness of LAP regimen in lowering ASOT value and prevention of streptococcal colonization of the throat. This raises the question about why 11 patients still has high ASOT in our study while all throat cultures were negative. This can be explained by the fact that there are other causes that raises ASOT, as in certain related diseases such as rheumatoid arthritis, familial Mediterranean fever, Takayasu's arteritis and streptococcal impetigo.²⁵

Limitation of the study:

1. Longer term follow-up study is difficult to do.
2. Serum level of penicillin was not evaluated due to unavailability of the kits in our country.
3. No control group was included due to refusal of non-compliant patients for follow up.

We concluded that age of onset of rheumatic fever was mostly between 5 and 15 years and the youngest age was 2 years. Polyarthritis was the most common presentation of RF followed by carditis. Subclinical carditis was present in 79 patients (37%) of all studied patients. MR was the most common lesion followed by aortic regurgitation. Rate of relapse of RF is low and it happens within 2 years after the acute episode of RF. LAP is effective for eradication of streptococcal colonization in the throat. Secondary prophylaxis with LAP is shown to be the only effective RHD control strategy.

We recommend applying the 2-weekly LAP regimen in the first few years after the acute episode of RF especially in high risk communities. Then, during the subsequent years, a 2-weekly LAP regimen in winter and a 3-weekly regimen in summer, appeared to be very effective. We also advise monthly cardiac follow up and routine serial echocardiography for the early detection and management of complications. Aggressive follow up also helps make timely decisions regarding withdrawal of secondary prophylaxis.

Conflicts of interest

All authors have none to declare.

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