Suez Canal University Medical Journal Vol. 28 (1), 2025
Pages 8-15

Prevalence of Regular Long-Acting Penicillin Administration as a Prophylaxis against Rheumatic Fever among Ismailia District Students Aged between 5–15 Years

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Abstract

Background: **Acute rheumatic fever (ARF) is a delayed sequela of streptococcal pharyngitis that involves many body systems. Rheumatic heart disease (RHD) is a serious health problem that leads to long-term morbidity and mortality. Intramuscular Long-acting penicillin (LAP) is the most effective antimicrobial agent in secondary prevention of RF, yet the overdiagnosis and unindicated use of LAP puts the children in avoidable hazards.** ***Aim:*** **To assess the non-indicated long-term use of long-acting penicillin as a prophylaxis against rheumatic fever among Ismailia district students.** ***Subjects & Methods:*** **This descriptive survey included 2180 students aged between 6 – 15 years in Ismailia government urban schools between October 2022 and April 2023. The children had comprehensive history taking, and those who reported LAP administration were asked for their previous investigations.** ***Results:*** **Twenty-one students (1%) reported LAP administration as prophylaxis of ARF. Only 7 students had definite ARF based on the Jones criteria. Six students (0.28%) had evidence of chronic RHD. Ten students discontinued the injections, 4 of them were against medical advice.** ***Conclusions:*** **There is a high prevalence of unindicated use of long-acting penicillin among basic education students due to overdiagnosis of ARF. Also, the criteria of diagnosis and regimen of treatment were variable.**

Keywords: Rheumatic Heart Disease, Arthritis, Basic-Education Students, Penicillin G Benzathine.

Introduction

Acute rheumatic fever (ARF) is a delayed sequela of streptococcal pharyngitis during childhood. It begins after about 1 to 5 weeks after group A Streptococcus (GAS) infection due to an autoimmune response; presenting with rheumatologic, cardiac, and neurologic manifestations[1]. Carditis results in long-term valvular affection, rheumatic heart disease (RHD), cardiomegaly, and life-long disability[1,2]. Globally, RHD affected about 30 million people, and caused more than 300000 deaths in 2015[3]. In East African, RHD prevalence in school children was estimated to be 179/1000 child, which decreased to about 117/1000 after 2015[4]. Egypt is one of the countries where RHD persists, especially with the overcrowding, poor hygiene, and other socioeconomic risk factors[3]. In Alexandria, a study including 5465 students

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resulted in an estimated prevalence of 6.2/1000 students[5]. Another study conducted in El-Mahalla RHD center showed that 29.3% of the cases presented with RF sequelae[6]. The diagnosis of ARF should be based on the Jones Criteria, as ARF is a clinical diagnosis[7]. A 2015 revised version of the Jones Criteria endorsed by the American Heart Association (AHA) depends on 3 parts. Part A; for all patients with evidence of preceding GAS infection to have 2 major or 1 major plus 2 minor manifestations to be diagnosed as initial ARF. It also divided the population into low, moderate, and high risk regarding Part B; the major manifestations, and Part C; the minor manifestations[8]. Effective early intervention can prevent premature mortality from RHD[3]. Primary prevention requires proper diagnosis and adequate therapy for GAS pharyngitis[9]. After the first episode of ARF, the secondary prevention aims at reducing the recurrence ARF and the risk of RHD, which requires continuous scheduled antibiotic use[10]. LAP is the most effective for GAS eradication, and is superior to oral penicillin[11]. On the other hand, LAP has many side effects such as pain from the injection up to hypersensitivity and anaphylactic shock[12]. Accordingly, misdiagnosis of RF and the unindicated use of LAP puts the children in an avoidable hazard. In El-Mahalla RHD center, about 37.7% of cases were previously misdiagnosed as ARF and prescribed LAP[6]. An important cause for overdiagnosis is misinterpretation of elevated antistreptolysin O titer (ASOT) by physicians who do not recognize that the normal levels of these antibodies are higher among school-age than among adults[13].

Subjects and Methods

Study setting and Study population: The study was conducted on students from schools in the urban areas of Ismailia government between October 2022 and April 2023. Five primary and six preparatory schools were chosen randomly. All attending students aged between 5 – 15 years were included.

Study design and Sample size: A descriptive survey was conducted on an estimated sample of 2180 students.

Data collection tool: The children had comprehensive history taking, and those who reported LAP administration were asked for their previous investigations. The questionnaire included 4 parts; (1) Sociodemographic data and socioeconomic status using the scale by Fahmy et al.[14], (2) Symptoms of ARF, including arthritis and arthralgia (joint symptoms), chest pain, palpitations or dyspnea (carditis), abnormal involuntary movements (Sydenham's chorea), skin lesions (erythema marginatum or subcutaneous nodules), (3) Previous investigations such as throat swab, ASOT, CRP, ESR, TLC, ECG for prolonged PR interval and Echocardiography, (4) Diagnosis and treatment. Parts 3 and 4 were only acquired from the students receiving LAP. Students who reported LAP administration were categorized as definite ARF, probable ARF, possible ARF, or ARF rejected based on the Jones criteria as described in the 2020 Australian guidelines for prevention, diagnosis and management of ARF and RHD; 3.2 edition[9]. Students who fully meet the Jones criteria (have serological evidence of GAS infection with 2 major or 1 major plus 2 minor criteria) are diagnosed as definite ARF. Those who fall short by one major or minor criterion, or do not have serological evidence of GAS infection are further categorized into probable or possible ARF. If clinically ARF is the most likely diagnosis, then the patient is diagnosed as probable ARF. If ARF is considered uncertain but cannot be excluded then the patient is

diagnosed as possible ARF[9]. All the laboratory results and echocardiography findings are considered on a retrospective basis, and none were requested by the researcher.

Results

This study included 2180 students aged 6–15 years; 1125 male and 1055 female. The sample was collected from 5 primary and 6 preparatory schools in the urban areas of Ismailia government, including 1319 and 861 students respectively. The mean age was 11.7 ±1.4 years. Only 21 students - about 1% of the samples studied - reported positive history of LAP injection administration regularly.

a) Sociodemographic Data: The sociodemographic characteristics of the whole sample and the 21 students on LAP are shown in Table 1.

Table 1: Sociodemographic characteristics of the studied students and Students on LAP

Studied Variables	The Studied Students (n=2180) [*n (%)*]	Students on LAP (n=21) [*n (%)*]
Stage of Education		
Primary	*1319 (60.5%)*	*9 (43%)*
Preparatory	*861 (39.5%)*	*12 (57%)*
Gender		
Males	*1125 (51.6%)*	*11 (52%)*
Female	*1055 (48.4%)*	*10 (48%)*
Age		
Less than 10 Years old	*158 (7.2%)*	*2 (10%)*
10 to 12 years old	*1120 (51.4%)*	*8 (38%)*
More than 12 years old	*902 (41.4%)*	*11 (52%)*
Number of young siblings		
No young siblings	*111 (5.1%)*	*1 (5%)*
One young sibling	*467 (21.4%)*	*7 (33%)*
2-3 young siblings	*1330 (61%)*	*11 (52%)*
4 or more young siblings	*272 (12.5%)*	*2 (10%)*
Socioeconomic status (SES)*		
Low SES	*70 (3.2%)*	*3 (14.5%)*
Medium SES	*503 (23.1%)*	*11 (52%)*
High SES	*820 (37.6%)*	*7 (33.5%)*
SES cannot be assessed	*787 (36.1%)*	*0 (0%)*

b) Clinical Picture: The main presentation of students on LAP was arthralgia (81%), yet only 19% reported arthritis (Figure 1). The following symptoms were cardiac symptoms (62%).

c) Investigations: Not all the students had laboratory evidence of GAS infection. Only one student did a throat swab culture and was positive. Also 67% had a high ASOT over 400, yet one child had a negative ASOT and another did not do the titer. Previous investigation results are shown in Figure 2. About 58% did echocardiography (Echo); six of them (29%) had evidence of chronic RHD, ranging from mild MR to moderate and severe multiple valvular affection.

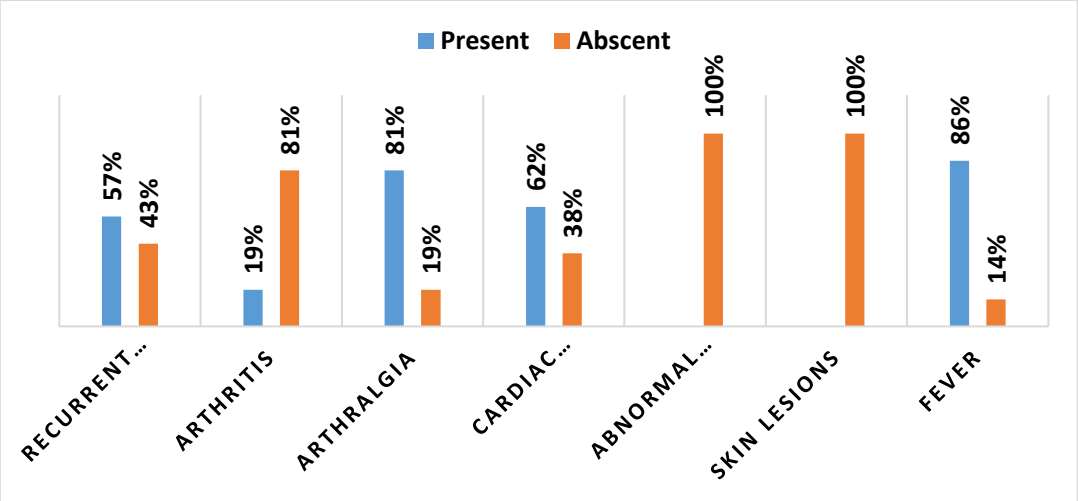

Figure 1: Clinical picture of students receiving LAP

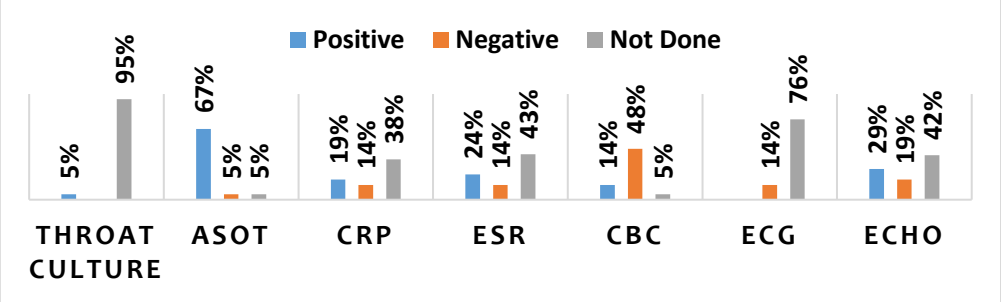

Figure 2: Investigations of the students receiving LAP

d) Diagnosis: When revising the Jones criteria with the symptoms, laboratory, and radiological findings, only 33% of the students on LAP – 7 students - had definite ARF, and one student did the required investigations but did not fulfill the criteria (ARF rejected). 62% did not do all the investigations needed, thus they were suspected to have ARF (Figure 3). Among those with missing laboratory data, 10% fulfilled the criteria except for the evidence of GAS infection (2 students), 19% were missing one major or minor criterion (4 students), these two groups were diagnosed as probable ARF. In 33% of the students the diagnosis of ARF was unlikely (possible ARF), either they were missing both the evidence of GAS infection and one criterion (5 students) or had elevated ASOT with only fever without any other manifestations (2 students).

e) Treatment: All the students were prescribed IM benzathine penicillin by a physician. The mean age at which the students started the LAP was 9.8 ± 2.7 years old (Table 2).

Table 2: Descriptive analysis of students on LAP according to different parameters

Studied Variable	Descriptive Data			
	Min. – Max.	Mean ± SD	Median	Mode
Age at time of data collection (years)	7 - 15	12.5 ± 2.2	13	15
Age at the time of diagnosis (years)	3-14	9.8 ± 2.7	10	10
Duration of treatment (months)	1-60	12.2 ± 14.6	6	6

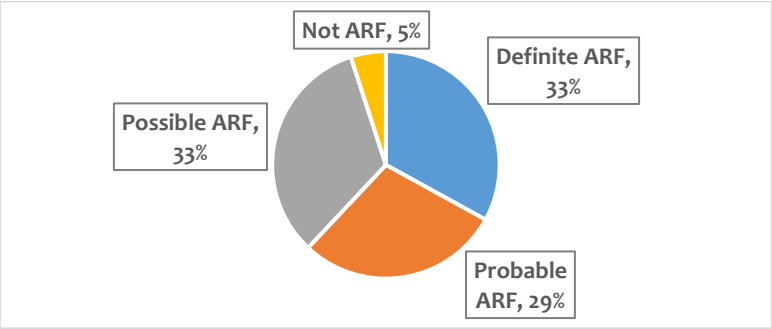

Figure 3: Students' diagnosis as definite, probable, possible, or not ARF

One student reported being prescribed LAP at the age of 3 and receiving it for a year and stopped after tonsillectomy. The longest duration of LAP administration was 5 years reported by 2 students (10%), yet most of the students (57%) were on LAP for 1 year or less. Regarding the frequency of the injections, nine students (42%) had LAP every 15 days, eight every 3 weeks, and only one student every 4 weeks. Three students changed the regimen according to the seasons or the level of the ASOT. Among the 21 students, only 11 were compliant on the LAP. Four patients (19%) stopped the treatment without medical advice; three of them due to the pain, and one stopped after 5 years because the symptoms improved. All the students had skin test before having the LAP for the first time, but only 52% did the skin test with every following dose. Regarding the complications of LAP, only 2 students reported skin allergy after the skin test, and 6 reported pain as a side effect to the injections.

Discussion

In our study, the prevalence of LAP injection administration was 10/1000 students (21 students). In agreement with our results, a study in Dakahlia, Egypt (2020) done by Deraz et al. on 5000 students showed that 7/1000 were on LAP, and they mostly started the treatment before confirming the diagnosis[15]. On the other hand, a study in Mansoura District (2022) done on 4847 students aged 5-18 years by Arafa *et al.* showed that 145/1000 students received LAP at least once before[16]. which is very high compared to our results. Regarding the 21 students receiving LAP, we found that only 33% of them met the Jones criteria as definite ARF based on their old laboratory and echocardiography findings. This shows the overdiagnosis of ARF and LAP misuse for only arthralgia or elevated ASOT without other manifestations. This was also shown by Ghamrawy *et al.* in El-Mahalla RHD center between 2006-2018 as 37.7% of the total sample were previously misdiagnosed as ARF[6]. The mean age at which the students started the LAP was 9.8 ± 2.7 years, yet one student reported being prescribed LAP at the age of 3 based clinically on recurrent tonsilitis and fever, their parents did not remember the investigations, as they stopped the treatment 10 years ago. A case report by Miller et al. of a 3-year-old child with ARF was reported in the UK who developed moderate to severe MR, trivial AR and mild TR that progressed to acute left ventricular failure[17]. Even though the child in our study did not fulfill the criteria, it is important to put ARF in mind even with patients aged 2 and 3 years old with suspicious symptoms. In our study, joint symptoms were the main presenting symptoms, with 81% of LAP re-

ceivers were complaining of arthralgia and 19% reported a history of arthritis. Our result goes in line with previous results in Dakahlia by Deraz et al. as 63% of students on LAP had arthralgia, and by Ghamrawy et al who found that 14.9% the cases attending El-Mahalla RHD center presented with rheumatic arthritis, compared to only 10.8% with carditis[15,6]. This also applies to other high-risk populations in the world including some areas in Australia as mentioned in the Australian guidelines 2020 who emphasized that arthralgia could be the only presenting manifestation mainly in developing countries[9]. On the other hand, a study in the United States by de Loizaga et al. showed that the most common major manifestation was carditis (49%) followed by polyarthritis (30%), while 19.2% had arthralgia[18]. None of the students experienced Sydenham chorea, erythema nodosum nor subcutaneous nodules. In Elmahalla, Ghamrawy et al. found that only 0.05% of patients presented with Sydenham chorea[6]. In our study, the leading cause of LAP prescription was elevated ASOT as 67% of the patients had ASOT over 400. Yet, 14% of them did not have other major manifestations and 19% had only arthralgia without evidence of carditis. A study done by Kotby et al. concluded that these elevated levels of ASOT alone do not indicate further investigations or treatment as long as the child is normal and has no complaints, as the ULN of ASOT in normal children with history of repeated tonsillitis while being free of streptococcal infection was as high as 1600 IU/mL[13]. Even for students who had some symptoms suggesting ARF, whether major like polyarthralgia or minor like fever, the majority - about 67% of the students on LAP - were not told to do some important investigations necessary to verify the diagnosis, either CRP, ESR or echocardiography. The issue of incomplete investigation was addressed in the 2020 Australian guideline; they mentioned that ESR and/or CRP testing was absent for 19% of 151 children with ARF identified during a national study of ARF in children, and diagnosis was unable to be confirmed for another 8 children in whom timely streptococcal serology was not done[9]. Accordingly, patients who fall under the category "probable" ARF need secondary prophylaxis with LAP and follow-up echocardiogram[9]. In our study, only 58% of the students receiving LAP did echocardiography; six of them had RHD, resembling about 2.7/1000 student out of the whole sample. This prevalence rate of RHD was higher than the previous study by Deraz et al. where the prevalence was 1/1000[15]. Yet, again, our result was much lower than the prevalence of RHD found by Arafa et al. which was 9/1000[16]. The relatively high ratio in our study is probably a result of depending on the previous echocardiography reports, thus the doppler criteria for pathological rheumatic valvulitis could not be assessed by the researcher, which may lead to over- or underestimating the prevalence of RHD. Also, the results by Arafa et al. included students aged up to 18 years old, which would contribute to the higher prevalence. Regarding the patients who are no longer on LAP, 29% were medically advised to stop the injections; 9.5% of them after tonsillectomy and 9.5% after the ASOT normalized. Putting aside the fact that none of them fulfilled the criteria of ARF, yet the level of ASOT should not be the parameter on which the decision of stopping LAP is made.

Conclusion

There is a high prevalence of long-acting penicillin use among basic education students because of misdiagnosis as acute

rheumatic fever. There was also a considerable variability in the criteria of diagnosis and treatment regimen followed by the physicians.

Recommendations

A regional referral RHD center should be established, which would be responsible for the screening, assessment and diagnosis of all suspected patients, and the treatment and follow up of those who are diagnosed. Such centers would also provide data for larger studies which would help establish national guidelines for ARF diagnosis and treatment.

Limitations

This study is a descriptive survey. The presence of carditis/RHD was not assessed by the researcher using echocardiography.

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