

Acute rheumatic fever prophylaxis in high-income countries: clinical observations from an Italian multicentre retrospective study

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Abstract Objective

The aim of the study is to evaluate the compliance rate to secondary prophylaxis and the presence of rheumatic heart disease (RHD) in a cohort of Italian patients with acute rheumatic fever (ARF).

Methods

This is a multicentre retrospective study. The patients were divided into two groups by the presence or absence at last follow-up of RHD. Clinical features, ARF recurrences and the rate of compliance to secondary prophylaxis were evaluated.

Results

Two-hundred and ninety patients were enrolled (137 females; 153 males). Carditis at onset was present in 244 patients (84.7%). At the end of follow-up, 173 patients manifested RHD. Adherence to secondary prophylaxis was low in 26% of patients. The presence of RHD at follow-up was associated with the presence of carditis and its severity at onset ($p=0.001$), but it was not related to secondary prophylaxis adherence ($p=NS$). No association between prophylaxis adherence and ARF recurrence was found ($p=NS$) nor between ARF recurrence and RHD at the end of follow-up ($p=NS$).

Conclusion

Poor adherence to secondary prophylaxis does not seem to be associated with increased risk of RHD in developed countries. Further studies are needed to confirm our data in a larger population.

Key words

acute rheumatic fever, compliance, carditis, prophylaxis, rheumatic heart disease

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Received on April 10, 2019; accepted in
 revised form on October 18, 2019.

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 EXPERIMENTAL RHEUMATOLOGY 2020.

Introduction

Acute rheumatic fever (ARF) is a systemic, inflammatory disease induced by Group A *Streptococcus* (GAS) sore throat infections. The clinical criteria for ARF diagnosis have been recently modified in the updated Jones Criteria (1). Except for heart involvement, the majority of ARF clinical manifestations, such as chorea, arthritis and skin involvement, are benign and resolves with no sequelae within some weeks or few months from its appearance. Carditis is characterised by acute inflammation of mitral and/or aortic valves, which results in regurgitation and it is not associated with GAS-associated myocarditis (2). ARF recurrences may lead to permanent heart valvular damage, also known as Rheumatic Heart Disease (RHD), which is almost disappeared in high-income countries but represents the most common cause of acquired cardiovascular morbidity and mortality in developing countries (3). The management of active rheumatic carditis is based on anti-inflammatory drugs, nonetheless the fact that aspirin and steroids could prevent valvular damage (4). In this clinical setting, recurrence prevention by secondary prophylaxis in those patients is crucial (5); however, the compliance to prophylaxis is not always appropriate, in particular in those areas in which ARF incidence is higher (6). No data exist about prophylaxis adherence and RHD rate among high-income countries. Our study aimed to evaluate the secondary prophylaxis compliance and the heart outcome in an Italian population of ARF patients.

Materials and methods

Patients selection

This is a retrospective, multicentre, cohort study. Since it is a retrospective study, IRB approval is not required by Italian law. The records of patients who met 1992 Jones Criteria (7) were reviewed. All patients, who were first seen between January 1st, 2000 and December 31st, 2015 and who had the last follow-up between January 1st, 2016 and December 31st, 2016, were included. Five tertiary care centres participated in the study: (1) Institute for Ma-

ternal and Child Health - IRCCS Burlo Garofolo, Trieste, Italy; (2) Department of Paediatrics, University of Chieti, Italy; (3) University Department Pro. Sa.M.I. G. D'Alessandro, University of Palermo, Italy; (4) Rheumatology Unit-Paediatric Section, NEUROFARBA Department, Anna Meyer Children's Hospital, University of Florence, Italy and (5) Rheumatology Unit, Bambino Gesù Children's Hospital, Rome, Italy.

Data collection

The patients were divided into two groups by the presence or absence at last follow-up of RHD according to the fulfillment of World Heart Federation criteria for echocardiographic diagnosis of RHD (8). The severity of RHD, described as mild, moderate and severe was assessed accordingly to the American College of Cardiology/American Heart Association (ACC/AHA) recommendations (9). The following parameters were also recorded for each patient at the time of diagnosis: age, sex, clinical characteristics, treatment and prophylaxis scheme recommended. Echocardiographic findings at onset were also evaluated and heart involvement classified as mild, moderate and severe following the New Zealand guidelines for ARF (10), where possible. Improvement or worsening of heart involvement at the end of follow-up was evaluated comparing the severity of RHD with carditis at onset. ARF recurrences were also recorded. The participants were also asked to determine the total number of prophylactic penicillin injections per year evaluating then their adherence to secondary prophylaxis as follows: low (<12 injections per year or prophylaxis withdrawal at least six months earlier than expected) and high adherence (≥12 injections per year).

Statistical analysis

All the data have been saved in an Excel database. Statistical analysis was carried out with Stata/IC 14.0 statistical software (StataCorp, College Station, Texas). Descriptive statistics were used for clinical and laboratory parameters. We realised first a univariate analysis, testing the effects of each collected explanatory variable (independ-

Competing interests: none declared.

Table I. Association between prophylaxis adherence and outcomes. Presence of RHD was evaluated at last follow-up.

	High adherence	Low adherence	<i>p</i> -value
Presence RHD, nr (%)	133/213 (62%)	39/75 (52%)	NS
Presence RHD among patients with carditis at onset, n. (%)	131/178 (74%)	38/66 (58%)	0.019
Presence RHD among patients without carditis at onset, n. (%)	3/35 (8,6%)	0/7 (0%)	1
Heart involvement worsening at last follow-up, n. (%)	5/157 (3%)	7/38 (18%)	0.006
Heart involvement improvement at last follow-up, n. (%)	81/178 (46%)	41/66 (62%)	0.03
ARF recurrence	6/216 (3%)	6/75 (8%)	0.085

ARF: acute rheumatic fever; RHD: rheumatic heart disease.

Table II. Comparison between the two population groups (high and low compliance) of age of diagnosis, mean time follow-up and severity of carditis at onset.

	High adherence (215 patients)	Low adherence (75 patients)	<i>p</i> -value
Age of diagnosis (years)	9 (IQR: 7-11)	8 (IQR: 6-11)	0.37
Mean time follow-up (years)	4 (IQR: 2-6)	5 (2-11)	0.22
Severity of carditis at onset (no carditis / mild / moderate-severe)	37/122/56	7/38/28	0.245

ent variables) on the main outcome variable (dependent variable). Pearson χ^2 testing or Fisher's exact two-tailed test were used to compare categorical and ordinal data, and Student's *t*-tests or Mann-Whitney rank-sum tests were used to analyse continuous data in two different groups, as appropriate. Explanatory variables significantly associated with dependent variables at univariate analysis with a *p*-value <0.05 were entered into a logistic regression model, to identify variables with strong and independent association with the main outcome variables.

This study does include human participants but it is a retrospective one and according to the Italian law ethical approval is not mandatory.

Results

The cohort consisted of 290 patients (139 females and 151 males) with a median age of 9 years (IQR: 7–11) at diagnosis. The median time of follow-up was four years (IQR: 2–7) and the median age at follow-up was 14 years (IQR: 10–16). At onset, 85% (244/288) of patients presented carditis, 47% (135/288) arthritis, 22% (53/288) chorea, 3.5% (10/288) erythema marginatum and 0.4% (1/288) subcutaneous nodules. Among patients with carditis, 66% (160 out of 244 patients) presented mild carditis, while 34% (84/244) presented a moderate or se-

vere involvement. Among minor clinical criteria, fever was present in 81% (234/288) of patients, arthralgia in 57% (164/288), ESR or CRP elevation in 34% (97/288), prolonged P-R interval on ECG in 36% (104/288) of patients, while 9% (25/288) of patients presented a past history of ARF. At diagnosis, all patients were treated with antibiotics, and all patients were then recommended to follow a secondary prophylaxis scheme. RHD was present at the end of follow-up in 60% (172/288) of patients, 82% (141/172) presented a mild RHD, while 18% (31/172) presented moderate/severe heart involvement. Twelve patients out of 290 (4.1%) experienced an ARF recurrence during follow-up. Adherence to secondary prophylaxis was low in 26% (75/290) and high in 74% (215/290) of patients. Among patients with low prophylaxis, 17 of them never did their prophylaxis, 19 received <8 injections/year, while 39 patients between 9 and 11 injections per year.

The presence of RHD at follow-up was associated with the presence of carditis at onset (169/244 vs. 3/42, *p*=0.001); RHD severity was associated with carditis severity at onset as well (22/84 vs. 9/160, *p*=0.0001), but it was not associated with secondary prophylaxis adherence (133/213 vs. 39/75, *p*=NS). Multivariate analysis confirms these data showing that, if corrected with prophylaxis

adherence, the severity of carditis at onset is an independent predictor of RHD (*p*<0.001). Among patients with carditis at onset, higher prophylaxis adherence was associated with higher RHD rates at the end of the follow-up (131/178 vs. 38/66, *p*=0.019). Among patients with no cardiac involvement at onset, there was no difference in RHD whether prophylaxis adherence was high or low (3/35 vs. 0/7, *p*=NS). Lower prophylaxis adherence was associated with both improvement (41/66 vs. 81/178, *p*=0.03) and worsening (7/38 vs. 5/157, *p*=0.06) of heart involvement at the end of follow-up if compared with carditis onset. No association between prophylaxis adherence and ARF recurrence was found (6/75 vs. 6/215, *p*=NS) nor between ARF recurrence and RHD at the end of follow-up (7/115 vs. 5/173, *p*=NS). The results are summarised in Table I. No difference between low adherence and high adherence subgroup of patients was found regarding the age of diagnosis, carditis severity at onset and median time of follow-up (Table II).

Discussion

To our knowledge, this is the first report about RHD rate among ARF patients in high-income countries. The frequency of major manifestations of ARF in our population is substantially congruent with literature data (11). All

patients received antibiotic treatment, and all patients were advised to follow the secondary prophylaxis scheme (5). At the end of follow-up, a significant percentage of patients (18%) presented a moderate or severe RHD.

The adherence to secondary prophylaxis was low in 26% of patients and it is surprising to notice the 6% of patients who stated that they never got any penicillin injection. It is also interesting to underline that 16% (29/172) of patients stopped the prophylaxis regimen earlier than expected. All these data underline the difficulties that patients' families experience in respecting the American Heart Association about secondary prophylaxis. There are no data in the literature about secondary prophylaxis adherence in developed countries. However, the rate of adherence varies between 35% (12) to 93% (13) in developing countries, suggesting that the prophylactic regimen can be problematic with regard to patient compliance, even in those regions with a higher ARF incidence where the prophylactic regimen is considered crucial in preventing RHD.

Our data did not show any significant association between prophylaxis adherence and RHD. This is the first time such a result has been reported. In the literature, low or no-adherence on secondary prophylaxis regimen has been associated with higher risk to develop or to worsen RHD but these data derive from studies conducted in developing countries or among a native indigenous population of New Zealand and Australia where the ARF incidence is still very high (>100/100.000) (14) compared with western countries (15). However, the recommendations about secondary prophylaxis are the same in higher income countries. This evidence comes from three randomised controlled trials that were published on this topic (16-18) more than 40 years ago, when ARF incidence was as high as it currently is in developing countries (19).

On the other hand, the presence of carditis, and its severity, at onset seems to be the most relevant factor predicting RHD at the end of follow-up. This is not surprising, and it has already been

described in the past; in fact Araujo *et al.* and Yilmazer *et al.* showed how initial severe carditis was an important factor in the long-term prognosis of chronic RHD (20; 21).

Among patients with carditis at onset, low prophylaxis adherence seemed to be associated with both RHD improvement and worsening at the end of follow-up. It is very hard to explain how high adherence to secondary prophylaxis could worsen heart outcome; we think that this is probably because only 12 patients showed a cardiac worsening at the end of follow-up. However, these data again suggest that heart outcome may evolve independently of prophylaxis adherence.

Although the presence of arthritis has been previously considered a protective factor for heart involvement (20), 3 out of 44 patients who did not present cardiac involvement at onset developed RHD at the end of follow-up, even if these data do not reach statistical significance. All of them referred good adherence to secondary prophylaxis.

Finally, even if ARF recurrence seemed to be more frequent among the population with lower prophylaxis adherence, it did not reach statistical significance, and ARF recurrence was not associated with RHD outcome.

Our data show that the rate of secondary prophylaxis adherence in a developed country is low and do not seem to correlate with RHD frequency and severity nor with ARF recurrence.

Secondary prophylaxis with penicillin is still considered the milestone to prevent ARF recurrences and RHD. However, it is important to underline that the burden of ARF among high-income countries has dramatically reduced in the past century especially due to the improvement in living standards and the better availability of health care (22), rather than to antibiotic discovery; in fact, if penicillin has accelerated the ARF decline, it certainly did not initiate it (23). Thus, the number of subjects that have to be treated with penicillin prophylaxis to prevent a single case of ARF could hardly be measurable in high income countries. Indeed, it has been recently demonstrated that, among French patients with acute tonsillitis, the cost

to prevent a putative case of ARF is €2196000 per ARF case and 180000 cases of acute tonsillitis need to be treated to prevent one case of ARF (24).

In contrast, the over-representation of ARF in developing countries probably reflects a combination of overcrowded living conditions, socio-economic deprivation and low access to health care (25). In these settings there is enough evidence that penicillin prophylaxis is cost effective to prevent RHD.

A Cochrane review recently focused on the role of penicillin for secondary prevention of rheumatic fever. Only three studies, for a total of 1301 patients, were included in the analysis comparing oral or intramuscular penicillin *versus* control. The results from all three studies showed that penicillin reduced the risk of ARF recurrence, but the data were statistically significant only for one trial. No association with all cause of mortality and/or progression of heart failure was found (26). The authors also stated that the population of the studies was not properly randomised, resulting in a possible bias of treatment allocation and underlined that this evidence is based on poor quality of trials.

Finally, some recent data would suggest that ARF and carditis could be facilitated or prevented by some specific genetic backgrounds. It has been demonstrated, for example, that some FCN2 gene polymorphisms could be considered a protective factor in the development of ARF and carditis (27).

Moreover, Engel *et al.* have demonstrated that the risk of ARF in a monozygotic twin with a history of ARF in the co-twin is increased by more than six times compared to that of dizygotic twins, suggesting that there are some susceptibility genetic loci for ARF (28). These data suggest that, at least in developed countries, the genetic background could play a major role for ARF and carditis development. In consideration of the low disease incidence, a genetic risk prediction tool would be helpful in order to select the subgroup of population with a higher risk to develop carditis and who could benefit more from antibiotic prophylaxis.

Our study has several limitations. It is a retrospective study and all the clinical

and heart ultrasonography examinations were reviewed on medical charts. Moreover, the secondary prophylaxis adherence was checked via a questionnaire, and an overestimation of prophylaxis adherence is possible.

It is important to underline that our data do not lead to any firm conclusion and do not suggest modifying the secondary prophylaxis scheme for ARF.

Although our data do not seem to prove its efficacy, we strongly recommend that all patients follow the secondary prophylaxis correctly. We perfectly recognise that the present success in disease prevention is currently due to prophylaxis rather than to socio-health-economic improvement, and prophylaxis schedules might be modified only if further prospective studies confirmed our data in a larger population.

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