Toward the Knowledge of the Epidemiological Impact of Acute Rheumatic Fever in Italy

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Background: To estimate the incidence of Acute Rheumatic Fever (ARF) in Tuscany, a region of Central Italy, evaluating the epidemiological impact of the new diagnostic guidelines, and to analyse our outcomes in the context of the Italian overview.

Methods: A multicenter and retrospective study was conducted involving children <18 years old living in Tuscany and diagnosed in the period between 2010 and 2019. Two groups were established based on the new diagnostic criteria: High-Risk (HR) group patients, n = 29 and Low-Risk group patients, n = 96.

Results: ARF annual incidence ranged from 0.91 to 7.33 out of 100,000 children in the analyzed period, with peak of incidence registered in 2019. The application of HR criteria led to an increase of ARF diagnosis of 30%. Among the overall cohort joint involvement was the most represented criteria (68%), followed by carditis (58%). High prevalence of subclinical carditis was observed (59%).

Conclusions: Tuscany should be considered an HR geographic area and HR criteria should be used for ARF diagnosis in this region.

Keywords: acute rheumatic fever, epidemiology, revised Jones criteria, high-risk population, incidence

INTRODUCTION

Acute Rheumatic Fever (ARF) is a multisystemic autoimmune response to infection of the group A streptococcus (GAS). The incidence of ARF is low in high-income countries such as North America (1, 2) and Western Europe (3), but persists high in low-income countries (4, 5), and among marginalized sections of the society of high-income countries (6–8) and in the South Pacific (9–11), becoming an important cause of morbidity and mortality. Jones criteria for ARF diagnosis were first established in 1944, then revised in 1992 (12) and afterward in 2015 (13) by the American Heart Association (AHA), leading to a distinction between moderate to high-risk (HR) and low-risk (LR) populations (incidence cut-off <2 out 100,000 per year), to avoid underdiagnoses in LR populations and overdoses in HR populations. Therefore, these new criteria incorporate three major
changes: the above-mentioned risk stratification based on
disease endemicity, inclusion of polyarthritis or monoarthritis
and monoarthralgia among major and minor criteria of HR
population respectively, and subclinical carditis as a major
manifestation in both LR and HR populations. Consequently, the
knowledge of the incidence of ARF is an essential need for the
application of the new diagnostic criteria in each country.

The incidence of ARF in Italy has been scarcely investigated
and limited to the main regions of Northern and to a single
region of Central Italy. We performed a multicenter retrospective
study to describe the clinical picture of ARF and to estimate
its incidence in Tuscany, a region of the Central Italy, focusing
on the epidemiologic impact of the new diagnostic criteria for
HR populations.

METHODS

Study Design and Data Collection

Demographic data from the Italian National Institute for
Statistics (ISTAT: national and governmental registry that collects
data relating to the permanent census of the population and
housing) were used to define the number of childhood
population at risk of GAS infection living in Tuscany in the 2010–
2019 period. The annual incidence of ARF was estimated using
the number of children at risk for the respective year.

The diagnosis of ARF is based on the criteria of AHA
revised in the 2015 year, which distinguishes the populations
in two groups, HR and LR, respectively, and includes both
major criteria (carditis clinical and/or subclinical, polyarthritis,
erythema marginatum, chorea and subcutaneous nodules, as
well as also monoarthritis and polyarthritis only in HR
populations) and minor criteria such as polyarthritis, fever
(≥38.5°C), erythrocyte sedimentation rate (ESR ≥60 mm/h) in
LR populations, while monoarthritis, fever (≥38°C), ESR ≥30
mm/h in HR populations, and in both populations C-reactive
protein (CRP ≥3.0 mg/dl) and a prolonged PR interval for
age variability.

We included all patients aged <18 years with ARF who were
referred to the three main Pediatric Centers in Tuscany (Pisa,
Florence, Siena) and to the Pediatric Cardiology Unit of the
“Ospedale del Cuore” in Massa in a 10-year period between
January 2010 and December 2019. Additionally, after critically
evaluated, we included the patients from 2010 to 2015 discharged
with related diagnoses such as Sydenham chorea, rheumatic
carditis, post-streptococcal arthritis, undifferentiated arthritis
or undefined polyarthritis that did not meet ARF diagnosis;
therefore, in order to establish the number of children that could
have benefited from an ARF diagnosis, we retrospectively applied
HR criteria in this group.

In all patients the previous streptococcal tonsillar infection
was demonstrated by the evidence of elevated or rising ASO
titer or by the throat swab or culture positive for GAS. An

Abbreviations:

Anti-DNase B, Anti-Deoxyribonuclease B; ARF, Acute
Rheumatic Fever; ASO, Antistreptolysin-O; CRP, C-reactive protein; ECG,
Electrocardiography; ESR, Erythrocyte sedimentation rate; GAS, Group A
Streptococcus; HR, High-Risk; LR, Low-Risk; RHD, Rheumatic Heart Disease.
patients (1.4:1). No significant differences were observed for age (HR median age = 9.5 95%CI = 7.4–10.2, LR median age = 9.4 95%CI = 8.1–9.7, P = 0.91) and gender (Chi squared with Yates correction χ² = 0.001, P = 0.98) between group HR and LR patients (Table 1).

The median range time between the streptococcal infection and the onset of ARF symptoms was 12 days (IQR 17). ASO and Anti-DNase B titres of both groups did not differ significantly and the onset of ARF symptoms was 12 days (IQR 17). ASO and Anti-DNase B titres of both groups did not differ significantly (HR median ASO = 1,378 95%CI = 1,270–1,610, LR median ASO = 1,385 95%CI = 1,270–1,463, P = 0.58; HR median anti-DNase B = 1,385 95%CI = 1,385–2,200, LR median anti-DNase B = 927 95%CI = 730–1,218, P = 0.24) (Table 1).

Most of the cases were diagnosed during spring (42% of total cases) with the peak of incidence in March (18% of total cases) and a late peak in June (15% of total cases) (Figure 1). ARF cases presented with chorea showed a delayed peak in June.

**TABLE 1 | Main characteristics of LR and HR patients.**

|                         | LR Group | HR Group | Total |
|-------------------------|----------|----------|-------|
| Number of patients, n (%) | 96 (77)  | 29 (23)  | 125 (100) |
| Median age, years (IQR)  | 9.36 (3.96) | 9.52 (3.89) | 9.41 (3.65) |
| Sex, n (%)               | Male 56 (58) | Male 17 (59) | Male 73 (58) |
|                         | Female 40 (42) | Female 12 (41) | Female 52 (42) |
| Children aged <5 years, n (%) | 5 (5) | 1 (3) | 6 (5) |
| Children aged 5 to 10 years, n (%) | 60 (63) | 17 (59) | 77 (62) |
| Children aged 10 to 15 years, n (%) | 27 (28) | 10 (35) | 37 (29) |
| Children ≥ 15 years, n (%) | 4 (4) | 1 (3) | 5 (4) |
| ASO titer, median (IQR) | 1,375 (1,045) | 1,270 (896) | 1,360 (981) |
| Anti-DNase B, median (IQR) | 926 (1,216) | 1,384 (1,468) | 1,109 (1,449) |
| Number of days between GAS infection and ARF onset, median (IQR) | 11 (17) | 13 (20) | 12 (17) |

IQR, interquartile range; ASO, anti-streptolysin antibody; Anti-DNase B, Anti-Deoxyribonuclease B; GAS, Group A Streptococcus; ARF, acute rheumatic fever.

In the group HR patients post-2015 the number of ARF diagnoses per year varied over the years 2015 and 2019 and increased of 58 and 26%, respectively, by using diagnostic criteria for HR population. Similarly, in the HR group patients pre-2015 the use of HR criteria would have led to an increase in ARF diagnoses of 9% in 2014, 67% in 2013 and of 30% in 2012. Notably, 40% of ARF patients would have been diagnosed in 2013.

When the epidemiologic impact on total ARF diagnoses was calculated by using HR criteria, an increase of 30% was estimated (Table 2).

**Clinical Presentation: Major Criteria**

Exploring major criteria in the overall cohort, joint involvement was the most common (68%) followed by carditis (58%) and Sydenham chorea (19%). Only nine patients (7%) showed erythema marginatum. No patients were found with subcutaneous nodules.

Among LR group patients, carditis was the most common criteria (72%), while 58% had polyarthritis and 46% polyarthralgia.

Among HR group patients joint involvement was always documented, the most common being the knee (27%), representing the most inclusive criterion for ARF diagnosis: 72% had monoarthritis (being the only major criterion in 17 patients), 41% polyarthritis (being the only criterion in four). The most non-articular major criterion was carditis (14%), whereas chorea was found in only one patient (Table 3).

Globally, 73 out of 125 (58%) patients of the overall cohort showed a cardiac involvement which resulted significantly higher in LR group patients when compared to HR group patients, as shown in Table 3 (P < 0.001). Furthermore, among LR group patients, 29% presented moderate-severe mitral insufficiency. Moderate-severe aortic insufficiency was always associated with moderate-severe mitral insufficiency. Among HR group patients mild mitral valve damage was mainly recorded (75%) and no
TABLE 2 | ARF annual incidence rates expressed as cases per 100,000 population according to LR and HR criteria by year.

| Year | School-age population* | Incidence with LR criteria | Incidence with HR criteria | Diagnosis with LR criteria (%) | Diagnosis with HR criteria (%) | HR impact (%) |
|------|------------------------|-----------------------------|-----------------------------|-------------------------------|-------------------------------|---------------|
| 2010 | 328,525                | 1.52                        | 1.52                        | 100                           | 0                             | 0             |
| 2011 | 329,234                | 0.91                        | 0.91                        | 100                           | 0                             | 0             |
| 2012 | 329,626                | 3.03                        | 3.94                        | 77                            | 23                            | 30            |
| 2013 | 330,341                | 1.82                        | 3.03                        | 60                            | 40                            | 67            |
| 2014 | 331,182                | 3.32                        | 3.62                        | 92                            | 8                             | 9             |
| 2015 | 331,848                | 3.62                        | 5.73                        | 63                            | 37                            | 58            |
| 2016 | 331,719                | 1.51                        | 1.51                        | 100                           | 0                             | 0             |
| 2017 | 331,140                | 4.23                        | 6.04                        | 70                            | 30                            | 43            |
| 2018 | 330,020                | 3.33                        | 4.24                        | 79                            | 21                            | 27            |
| 2019 | 327,293                | 5.81                        | 7.33                        | 79                            | 21                            | 26            |

*Population at risk data derived by ISTAT census.
cases of aortic valve injury or combined lesions of both valves were found (Table 4).

Our outcomes showed a prevalence of subclinical carditis (34%) on the overall population (Table 3). Of note, the number of patients with subclinical carditis was significantly higher in LH group than in HR patients ($\chi^2 = 8.4; P = 0.004$). No patient presented valve stenosis as well as cardiovascular complications such as ventricular dysfunction at the time of diagnosis, except for one patient with mild pericardial effusion. Of note, two patients with carditis developed sequelae, one transient ischemic attack, and one dilation of the right ventricle.

Chorea showed a prevalence of 19% in our cohort and females were predominantly affected (14 out of 24). Among HR group patients chorea was not associated simultaneously with carditis, while within the LR group 22 out of 23 patients with chorea additionally presented cardiac involvement (two-sided Fisher exact test, $P = 0.002$), particularly mitral valve regurgitation.

### Clinical Presentation: Minor Criteria

Most of the patients selected in our study were admitted with fever (74%) and elevation of ESR and/or CRP (86%). No difference was found between HR and LR groups concerning the prevalence of these criteria. LR group patients showed high prevalence of polyarthritis (46%).

Among the overall population, 10% showed prolonged PR interval for age and 10 out of 13 patients had cardiologic involvement. The median values of the PR interval among LR and HR groups were 140 ms ($n = 10$, IQR = 78) and 240 ms ($n = 3$, IQR = 120), respectively (Table 3). Moreover, other ECG abnormalities were found only in three patients of LR group: second-degree atrioventricular block (Mobitz type 1 and type 2) in two and an episode of supraventricular tachycardia in one.
TABLE 3 | Main clinical manifestations of patients.

|                          | LR Group | HR Group | Total | P-value |
|--------------------------|----------|----------|-------|---------|
| Carditis, n (%)          | 69 (72)  | 4 (14)   | 73 (58) | <0.001 |
| Subclinical carditis, n (%) | 40 (42)  | 3 (10)   | 43 (34) | 0.004   |
| Chorea, n (%)            | 23 (24)  | 1 (3)    | 24 (19) | 0.01    |
| Erythema marginatum, n (%) | 9 (9)    | 0        | 9 (7)   | 0.11    |
| Subcutaneous nodules, n (%) | 0        | 0        | 0 –    | –       |
| Polyarthritis, n (%)     | 56 (58)  | 0        | 56 (45) | –       |
| Monoarthritis, n (%)     | 0        | 21 (72)  | 21 (17) | –       |
| Polyarthralgia, n (%)    | 44 (46)  | 12 (41)  | 56 (45) | 0.83    |
| Monoarthralgia, n (%)    | 0        | 0        | 0 –    | –       |
| First-degree atrioventricular block, n (%) | 10 (10) | 3 (10) | 13 (10) | 0.76    |

–, not applicable.

TABLE 4 | Echocardiographic findings of patients with cardiac involvement.

|                     | Mild     | Moderate | Severe | Aortic regurgitation |
|---------------------|----------|----------|--------|----------------------|
| Mitral regurgitation|          |          |        |                      |
| LR group, n (%)     | 36 (52)  | 18 (26)  | 2 (3)  | 23 (33)              |
| HR group, n (%)     | 3 (75)   | 1 (25)   | 0      | 0                    |
| Total, n (%)        | 39 (53)  | 19 (26)  | 2 (3)  | 23 (32)              |

DISCUSSION

Our results highlight that the annual incidence of ARF in Tuscany was above the cut-off (<2 out 100,000 per year), when calculated in a period of 10 years (2010-2019), with an increasing trend from 2012 to 2019. The mean incidence was over the limit for most of the years considered in the selected period. Interestingly, it remained above the threshold value either after or before the application of HR criteria leading to an increase of 30% on total ARF diagnoses. Therefore, Tuscany should be considered an HR geographic area and, according to the latest guidelines, the criteria for HR populations should be used in this region.

Investigations on the incidence of ARF along the Italian country are few and limited to the Northern Italy. Recently, Licciardi et al. (15) estimated that ARF incidence in children living in the Province of Turin (Northern Italy) in the period between the years 2007–2016 ranged from 3.8 to 12.7/100,000, when calculated using LR and HR criteria respectively. Moreover, the study concluded that the application of HR criteria led to a 20.7% increase in the ARF diagnosis. In the period between the years 2014 and 2016 the Province of Turin showed an ARF rate incidence higher than Lombardy in the Northern Italy (4.24/100,000) (16). Other investigations performed along the territory of the North of Italy were conducted in Emilia Romagna in the period between 2000 and 2014 (before the publications of the AHA guidelines), showing that the ARF annual incidence in children presented with and without carditis were 0.8–2.4/100,000 and 1.5–3.8/100,000/year, respectively (17). Recently, a retrospective analysis of the childhood population living in the province of Bologna (Emilia Romagna) in the period between 2012 and 2017 showed ARF annual incidence of above two out of 100,000 (18). The unique report about the ARF incidence in the Central Italy refers to the Breda's study which evidenced in the period 2002–2009 an ARF incidence of 4.1/100,000 (19). Comparing the above-mentioned Italian studies we observed the same overall ARF rate incidence with regional variations in the same periods analyzed. In particular, Tuscany represented the unique region in which the incidence, calculated with HR criteria, was under the limit in 2016, reaching value over the limit in the next years. This indicates that the use of HR criteria is mandatory to avoid ARF underdiagnoses. Indeed, the ARF incidence in 2017 would have changed from 6.04 to 4.23/100,000, with the loss of six cases out of 20 if the use of HR criteria had not been continued. In an attempt to explain the inter-regional differences in the ARF rate incidence, we focused on the strains of GAS-causing infections. GAS M types have been highlighted as an important determinant to clarify the distribution and development of ARF outbreaks. Genetic variation in the \textit{emm} gene, which encodes the M protein, has been correlated with varying ARF incidence, particularly the occurrence of GAS serotype M18 isolates (20–22). The association of several outbreaks of ARF with the circulation of mucoid GAS strains in the community has been reported (23). Therefore, we might argue that the variability of ARF incidence observed in the same periods in our country could be related to the heterogeneity and resurgence of rheumatogenic strains and to the different distribution of M types, due to the mobility of GAS strains on a global scale (24).

Concerning the peak of incidence observed in our cohort in 2019, an increase in throat GAS infections untreated or not correctly treated could be the explanation. Recently Di Muzio et al. reported knowledge gaps of GAS pharyngitis diagnosis and low adherence rates to the treatment in our country,
resulting in difficulties to reduce the incidence of ARF (25). This observation strongly indicates the need to improve the pediatrician’s approach to diagnosis and management of GAS infection, as the decline in the incidence of ARF in developed countries in previous decades, has reduced the attention to either diagnosis or treatment of streptococcal pharyngitis.

It is known that first episodes of ARF can rarely occur in children younger than 5 years, the highest incidence being reported among children aged between 10 and 14 years, followed by those ones aged between 5 and 9 years (4, 6, 26, 27), with episodic occurrence in adolescence. Furthermore, our population showed equal distribution.

According to previous studies (15), ARF diagnosis in our cohort showed a typical seasonal distribution pattern, time between the triggered infection and the onset of clinical manifestations being after about 2–3 weeks, predominantly in March, except for chorea which developed after about 40 days from the infection, compatible with a greater latency on developing symptoms.

Arthritis was the most frequent major criterion found in our cohort. Interestingly, in LR group it presented as polyarthritis without being the more relevant, while it is always found in HR group, mainly as monoarthritis, proving to be the most inclusive sign for ARF diagnosis. This observation agrees with a previous study which underlies the clinical relevance of monoarthritis in high incidence population (28), confirming its value as major criteria only in HR population.

Clinical carditis and arthritis in our cohort showed a frequency similar to that reported in studies from the other regions of Northern Italy (15, 29).

After arthritis, carditis was the second represented Jones's criterion in our cohort. It was present in more than half of the overall cohort, significantly predominant in LR patients and mainly involving mitral valve. Similarly, subclinical carditis showed a prevalence in both groups with significant predominance in LR group. This outcome indicated a higher frequency of silent carditis (without a reduction in the frequency of total carditis) in our region than in the regions previously investigated (15, 29). Indeed, in most of the patients of our cohort the presence of polyarthralgia and monoarthritis, as first signs, oriented to a suspicious of ARF, leading to discover a silent carditis. It is known that ARF clinical features can resolve completely in weeks or months, while valvular lesions may persist and lead to RHD (30–32). The evolution of the silent carditis has not been completely clarified; however, a prospective study demonstrated that subclinical lesions can persist and sometimes even worsen (33). Since it has been observed that subclinical RHD prevalence correlates closely with ARF incidence, being considered as its surrogate measure in HR population (34), we highlight the relevance of the echocardiographic evaluation to estimate ARF incidence in HR populations.

Chorea was the third represented criterion in our cohort, females being more affected, as described in other reports (35). As opposed to our results and previous investigations (29), Pastore et al. (30) reported a higher prevalence of chorea (54%). Interestingly, we enlightened a higher frequency of carditis among patients with chorea either at presentation or during the follow-up; of note, chorea was usually associated with mild cardiac involvement, confirming that patients with chorea hardly develop severe carditis (36, 37). Therefore, we emphasize that echocardiographic assessment should be routinely performed in each patient with suspected or confirmed chorea in order to identify the presence of valvulitis (even subclinical) at the time of diagnosis or developing later.

Among minor criteria, the prolongation of PR interval [occurring in over 2% of the normal population (38)] was detected in a limited number of our cases without a positive correlation with carditis or with other major criteria.

The present study has some limitations because of its retrospective design and a prospective study will be necessary to confirm our findings. Due to the lack of nationwide epidemiological data, especially in the unexplored South of Italy, an Italian registry of all cases of ARF may be a relevant aim. Finally, we point out the need of a critical approach in the application of the new ARF criteria in children presenting with fever, polyarthralgia and increase of ESR and/or CRP, particularly in HR population.

CONCLUSION

The epidemiological impact of HR criteria is relevant in Tuscany, where their application led to an increase in ARF diagnoses of 30%. Thus, Tuscany should be considered an HR area and the new criteria for HR populations should be used in this region. Moreover, if the observed trend were confirmed, it would represent an inversion with respect to the past century, when a decline in the incidence of ARF in developed countries has been described as consequence of improved public hygiene and widespread use of antibiotics.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

AMQA conceptualized and designed the study, designed the data collection instruments, contributed to collect the clinical data, conducted the final database, and drafted the manuscript. FP conducted the final database, performed the statistical analyses, and drafted the initial manuscript. ADG designed the data collection instruments, performed the statistical analyses, contributed to interpretation of data, and drafted the initial manuscript. SC, GB, SA-R, AB, and AO contributed to collect the clinical data, carried out the initial analyses, and critically reviewed the manuscript for important intellectual content. DP, NA, CG, and GS conceptualized and designed the study, supervised data collection, contributed to interpretation of data, and critically reviewed the manuscript for important intellectual content. RC conceptualized and designed the study, coordinated and supervised data collection, contributed to interpretation of data, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.
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