

Population-Based Study of Incidence and Clinical Characteristics of Rheumatic Fever in Abruzzo, Central Italy, 2000-2009

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Objective To investigate the incidence and describe the characteristics of acute rheumatic fever (ARF) in the pediatric population in a community-based healthcare delivery system of the central Italy region of Abruzzo during 2000-2009.

Study design A retrospective study was conducted in Abruzzo to identify patients aged <18 years with a diagnosis of ARF between January 1, 2000, and December 31, 2009. Each patient's age, sex, date of diagnosis, age at disease presentation, and fulfilled Jones criteria were recorded.

Results A total of 88 patients meeting the Jones criteria for the diagnosis of ARF were identified, with arthritis in 59.1% of the patients, carditis in 48.9%, erythema marginatum in 11.4%, 5.7% with chorea, and 4.6% with subcutaneous nodules. Residual chronic rheumatic heart disease was present in 44.3% of the children. Age at diagnosis ranged from 2.5 to 17 years (average, 8.7 ± 4.0 years). Twelve children (13.6%) were under age 5 years. The overall incidence rate of ARF was 4.1/100 000. The lowest incidence rate was documented in the year 2000 (2.26/100 000), and the highest in 2006 (5.58/100 000).

Conclusion Our data indicate that ARF has not disappeared in industrialized countries and still causes significant residual rheumatic heart disease. Pediatricians should routinely consider the diagnoses of streptococcal pharyngitis and ARF to reduce long-term morbidity and mortality. (*J Pediatr* 2012;160:832-6).

Acute rheumatic fever (ARF) is a nonsuppurative, autoimmune, multisystem response to infection due to group A streptococcus (GAS), usually pharyngitis. Diagnosis is based on the Jones criteria, which include carditis, polyarthritis, erythema marginatum, Sydenham chorea, and subcutaneous nodules, in the setting of a preceding GAS infection.^{1,2} First episodes of ARF most commonly affect children and young adolescents aged 5-14 years and are rare in both children aged <2 years and adults aged >35 years.³

ARF and its sequel, chronic rheumatic heart disease (RHD), continue to contribute significantly to global morbidity and mortality, especially in many developing countries.³⁻⁷ According to the World Health Organization, at least 15.6 million people have RHD; of about 500 000 individuals who acquire ARF every year, 300 000 go on to develop RHD, and 233 000 die from direct effects of ARF or RHD.⁸

The highest incidence of ARF has been reported among the aborigines of Australia, the Maoris of New Zealand, and populations in sub-Saharan Africa.^{3,6,7} Underlying factors related to poverty (ie, overcrowded housing, poor education, and inadequate access to health care) contribute to the high burden of ARF in those countries.^{3,7,9} In contrast, the incidence of ARF has decreased dramatically in most developed countries,^{3,9-11} and the national incidence of ARF has dropped to fewer than 1 case per 100 000 in United States, although a few areas of resurgence were reported in the 1980s.^{12,13}

Little epidemiologic data on the incidence of ARF in Europe are available. Studies conducted in Czechoslovakia (1961-1972) and Sweden (1952-1961) reported incidences of 16 per 100 000 children and 4.5-5 per 100 000 children, respectively.¹⁴⁻¹⁶ Sporadic outbreaks also were reported by Italian authors in the 1980s.^{17,18}

The present study investigated the incidence and characteristics of ARF in the pediatric population of Italian region of Abruzzo between January 1, 2000, and December 31, 2009. The final phase of our program is the reinforcement of primary and secondary prevention strategies for ARF.

Methods

Abruzzo is an industrialized, mountainous region in central Italy with an area of 10 798 km², divided into 4 provinces. According to the Italian National Institute of Statistics records, the total population of the region is nearly 1

ARF	Acute rheumatic fever
GAS	Group A streptococcus
RHD	Rheumatic heart disease

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339 452, 16% of which is aged <18 years, and is mainly of Caucasian origin.¹⁹ Approximately 72% of the population is concentrated in the area of the hills, with the remaining 28% in the mountainous areas.

We performed a retrospective chart review of diagnoses of ARF in children aged 0-18 years between January 1, 2000, and December 31, 2009. We considered 2 independent sources of ascertainment. As a primary source, we queried general practitioners and pediatricians, and as a secondary source, we queried departments of pediatrics, medicine, and rheumatology. The probability of the global ascertainment of the population-based register was estimated using the capture-recapture method (Table I; available at www.jpeds.com). The pooled 2000-2009 global ascertainment of the register was 74.6%.^{20,21}

Approximately 70% of the general practitioners and 90% of the pediatricians in Abruzzo participated in the study. We estimate that at least 90% of the population in the Abruzzo region receive their health care from the physicians who participated in the study. Census-derived regional population figures were taken into account to provide rate denominators.¹⁹ We calculated the incidence rate, expressed as cases per 100 000 population per year. We compared continuous variables using the Student *t*-test, and calculated annual increase rates using a linear regression model. The collected data were stored on a password-protected database. All data analyses were performed using SAS software (SAS Institute, Cary, North Carolina).

The data recorded for each patient included date and place of birth, date of diagnosis, age at disease presentation, sex, ethnicity, presenting Jones criteria met, cardiac involvement at diagnosis and follow-up, laboratory tests results at diagnosis (including throat swab and antistreptolysin O titer), treatments and secondary prophylaxis, any recurrence of disease, and family history of ARF or RHD.

Diagnosis of ARF is based on the Jones criteria, according to the 1992 revision by the American Heart Association, which include both major criteria (ie, carditis, polyarthritides, erythema marginatum, Sydenham chorea, and subcutaneous nodules) and minor criteria (ie, arthralgia, fever above 39° C, elevated acute-phase reactants such as erythrocyte sedimentation rate and C-reactive protein, and a prolonged P-R interval on electrocardiography).¹ Carditis was defined as either a new murmur detected on physical examination and/or valvular regurgitation noted on echocardiography according to the World Health Organization criteria, including the presence of a color jet of >1 cm in length, the presence of this jet in at least 2 imaging planes, a peak velocity of the mosaic jet >2.5 m/s, and a holosystolic Doppler signal for mitral regurgitation or a holodiastolic signal for aortic regurgitation.²² To fulfill the criteria for ARF, a patient must have 2 major manifestations or 1 major and 2 minor manifestations plus laboratory evidence of antecedent GAS infection in the form of elevated or rising streptococcal antibody titer or demonstration of group A streptococci in the throat. A presumptive diagnosis of ARF was made in the absence of the foregoing criteria if isolated chorea was present without

any other manifestation, if long-standing carditis was seen without any other symptom, and if in a patient with a history of ARF or RHD, a single major criterion, or several minor criteria were met.^{1,22} In accordance with World Health Organization guidelines, recurrence of ARF was diagnosed in patients with previous ARF who had a subsequent episode of illness that either strictly met the Jones criteria or had several minor criteria with evidence of streptococcal infection.²² An antistreptolysin O titer >200 Todd units, an anti-DNase B titer \geq 240 Todd units, or a throat culture positive for GAS was considered evidence of streptococcal infection.¹

Results

During the 10 years of this study (2000-2009), 88 patients with ARF (51 males [58%] and 37 females [42%]) aged 0-18 years who met the eligibility criteria were identified. Cases were ascertained by general practitioners and pediatricians alone (*n* = 33), departments of pediatrics, medicine, and rheumatology alone (*n* = 55), and both (*n* = 15). All patients were of Italian origin and from middle class families with ready access to medical care. The overall incidence rate of ARF was 4.1/100 000/year, with a prevalence of 41 of 100 000 children (aged 0-18 years) up to December 31, 2009. The annual number of cases and changes in incidence rates for 2000-2009 are summarized in Table II. The total increase in incidence rate for the years 2000-2009 was 9.56% (*P* = .006). Patient age at diagnosis ranged from 2.5 years to 17 years (average, 8.7 ± 4.0 years). The average age at presentation was 8.8 ± 3.4 years for males and 8.5 ± 3.2 years for females (*P* = .84). Of the 88 patients who met the Jones criteria for ARF, 66 (75%) were aged 5-14 years, 13 were aged <5 years (14%), and 9 (10%) were aged <14 years. Eight patients were excluded because of an incorrect diagnosis of ARF.

The distribution of the Jones criteria in the study patients is presented in Table III. The most prevalent major criteria at diagnosis were arthritis (*n* = 52; 59.1%) and carditis (*n* = 43; 48.9%); the most prevalent minor criteria was an increase in acute-phase reactants (*n* = 73; 82.9%), followed by fever

Table II. Annual number of cases and annual incidence rates of ARF per 100 000 child-years, 2000-2009

Years	No. of cases	Rate, per 100 000	%	Population	Annual increase, %
2000	5	2.26	5.7	221 702	
2001	7	3.20	7.9	218 731	41.90
2002	6	2.80	6.8	216 423	10.87
2003	5	2.30	5.7	215 481	-0.58
2004	11	5.12	12.5	214 732	14.10
2005	11	5.12	12.5	214 992	16.45
2006	12	5.58	13.6	214 905	16.48
2007	10	4.68	11.4	213 473	13.36
2008	11	5.13	12.5	214 233	11.67
2009	10	4.67	11.4	214 257	9.59
2000-09	88	4.10		2 158 929	

% refers to the percentage of all cases diagnosed in that year. Population refers to the population aged 0-18 years in each year considered. % annual increase represents the exponential of the β parameter of the regression model.

Table III. Clinical characteristics of 88 patients with ARF

	No. of cases (%)
Distribution of Jones criteria	
Increase in inflammatory markers	73 (82.9)
Fever	70 (79.6)
Arthritis	52 (59.1)
Carditis	43 (48.9)
Arthralgia	42 (47.7)
Erythema marginatum	10 (11.4)
Chorea	5 (5.7)
Prolonged PR interval	5 (5.7)
Subcutaneous nodules	4 (4.6)
Joint involvement	
Knee	41 (46.6)
Ankle	38 (43.1)
Wrist	17 (19.3)
Hip	15 (17.0)
Elbow	13 (14.8)
Foot	8 (9.1)
Shoulder	6 (6.8)
Lumbar spine	2 (2.2)
Thoracic spine	1 (1.1)
Temporo-mandibular articulation	1 (1.1)
Cardiac valvular involvement	
Mitral	37 (42.1)
Aortic	15 (17.1)
Tricuspid	3 (3.4)
Pulmonary	2 (2.2)
Associations of symptoms	
Fever and arthritis	29 (33.0)
Fever and carditis	28 (31.8)
Arthritis and carditis	26 (30.0)
Carditis and arthralgia	15 (17.0)
Arthralgia and erythema marginatum	6 (6.8)
Fever and arthralgia	4 (4.6)
Carditis and erythema marginatum	4 (4.6)
Carditis and chorea	2 (2.2)
Arthritis and erythema marginatum	2 (2.2)

($n = 70$; 79.6%), and arthralgia ($n = 42$; 47.7%). Recurrence was documented in 6 patients (6.8%). One of these 6 patients was receiving secondary prophylaxis with an oral antibiotic; the other 5 patients did not receive secondary prophylaxis.

All of the patients with carditis had a systolic or diastolic murmur that had not been noted previously. No patient had cardiomegaly, congestive cardiac failure, or findings indicative of pericardial effusion. All patients with clinical carditis had pathologic valvular regurgitation at echocardiography. The mitral valve was the most frequently affected valve ($n = 37$; 42.1%), followed by the aortic valve ($n = 15$; 17.1%). Isolated mitral disease was observed in 25 patients, and mitral combined with aortic valve disease was seen in 11 patients. Isolated tricuspid disease was seen in 2 patients, and mitral-associated tricuspid valve disease in 1 patient. Four patients had isolated aortic valve disease (Table III).

Residual valvular damage, defined as permanent damage occurring after cessation of the acute phase, was documented in 39 patients (44.3%). Valvular involvement included mitral regurgitation in 20 patients (22.7%), mitral stenosis in 2 (2.3%), aortic regurgitation in 4 (4.5%), mitral and aortic regurgitation in 8 (9%), tricuspid regurgitation in 2 (2.3%), mitral and tricuspid regurgitation in 1 (1.2%), and pulmonary regurgitation in 2 (2.3%).

The most commonly affected joints were the knees ($n = 41$; 46.6%) and ankles ($n = 38$; 43.1%) (Table III). Five patients (5.7%) had a family history of rheumatic carditis, and 7 (8%) had a history of rheumatic fever. Two patients had undergone prosthetic replacement of the mitral valve because of massive mitral regurgitation. There were no deaths in the study population.

Discussion

Since the 1970s, ARF reportedly has declined worldwide and had almost disappeared in industrialized countries. The overall decline is apparently related to improved hygiene, less crowded living conditions, and improvements in primary prevention (ie, treatment of streptococcal pharyngitis), including access to health care and use of antibiotics. Nevertheless, an unexplained, geographically limited resurgence of ARF occurred in the United States during the last 2 decades of the twentieth century.^{13,23,24} Outbreaks of ARF also were reported in various hospitals in northern Italy between 1986 and 2010.^{17,18,25-27} No population-based study of ARF epidemiology in Italy has been published previously, however.

The present retrospective, population-based study of pediatric ARF in a well-defined population in central Italy identified 88 patients with an established diagnosis of ARF. The estimated overall incidence rate of ARF was 4.1/100 000/year, and the prevalence in January 1, 2010 was 41/100 000 children aged 0-18 years.

Our findings are in accordance with previous studies of the incidence of ARF among European children performed in Sweden in 1955-1964 and 1952-1961 and in Czechoslovakia in 1961-1972, which reported annual incidence rates of 4.5/100 000, 5/100 000, and 16/100 000, respectively.¹⁴⁻¹⁶ The only authors who documented a decline of ARF in Europe were Cernay et al,²⁸ who in 1993 reported a low incidence rate in Slovakia (0.7/100 000), and Giannoulia-Karantana et al,²⁹ who reported an incidence of 1.1/100 000 in Greece in 2001. Unfortunately, epidemiologic data on ARF from Europe and Italy for the last 50 years are scarce. Recently, Pastore et al²⁷ reported 13 cases of ARF in Trieste, northern Italy, between January 2007 and December 2008 and calculated an annual incidence rate of new cases as high as 23-27/100 000. Data from the literature suggest that the epidemiology of ARF in Italy and in Europe has not changed in the last 50 years. In light of these data, we need to consider whether the incidence of ARF in Europe has actually decreased, or whether we are seeing a resurgence of the disease.

Various causes for the resurgence of ARF have been proposed. Most investigators support the possibility of "rheumatogenic" strains of GAS responsible for localized outbreaks of the disease. In a 1985 outbreak in Salt Lake City, Utah, Veasy et al¹³ isolated specific mucoid strains of GAS (notably M3, M5, and M18) considered particularly virulent. The role of host factors in ARF is another possible explanation for our findings. Different clinical outcomes have

been reported during outbreaks of single rheumatogenic strains of GAS, suggesting a strong genetic component in the susceptibility to ARF.³⁰ Another possible explanation might be that the historical decline in the incidence of ARF has reduced the surveillance of the disease, leading to failures of primary and secondary prevention.

Primary prevention of ARF has focused on antibiotic treatment of symptomatic GAS pharyngitis. A course of 10 days of oral penicillin V or a single injection of benzathine penicillin, started within 9 days of the onset of streptococcus pharyngitis, prevents most cases of ARF.³¹⁻³³ A systematic review of the literature concluded that giving antibiotics to patients with a sore throat and symptoms suggesting streptococcal infection reduced the risk of ARF by 70%, and administration of intramuscular penicillin reduced the risk by 80%.³³

Secondary prophylaxis involving monthly penicillin injections for children with evidence of ARF/RHD has been shown to be the most efficient and cost-effective strategy for reducing the RHD burden.^{3,34,35} The recommended regimen for patients in the United States and in other countries with a low incidence of ARF consists of a single injection of 1 200 000 U of benzathine penicillin G every 4 weeks. In populations with a particularly high incidence of ARF, the administration of benzathine penicillin G every 3 weeks is recommended.³¹ Successful prophylaxis depends primarily on patient adherence to prescribed regimens; most failures of prophylaxis are due to poor adherence. Patients need to be regularly reminded about the importance of continuing prophylaxis and given thorough instructions. The majority of our patients received intramuscular injections of penicillin for prophylaxis; only 2 received oral penicillin. Fourteen patients (15.9%) did not receive any secondary prophylaxis; of these, surprisingly, only 2 demonstrated residual cardiopathy. The risk of recurrent ARF is greater in individuals receiving oral prophylaxis than in those receiving intramuscular benzathine penicillin.^{31,36} Indeed, in the present study, the 2 patients receiving oral prophylaxis developed RHD.

A surprising finding of this study is the relatively large number of children under 5 years of age (14%) compared with previous studies that included only ~5% of children aged <5 years at the diagnosis of ARF.³⁷ In this group of younger children, arthritis and carditis were the principal symptoms; only 1 child had erythema marginatum. As reported previously, no patient aged <5 years had chorea.³⁷

Arthritis was present in 59.1% of our patients, in line with rates reported in previous studies.^{4,27} Carditis was present in 48.9% of our patients, close to previously reported prevalences of 30%-45%.⁴ However, 44.3% of our patients with ARF developed residual cardiopathy, a marginally lower percentage than that reported by others.⁴ Moreover, we found a lower incidence of chorea compared with other studies.^{4,13,27}

This study has some limitations, including its retrospective design and relatively small number of patients. As is common for a retrospective study, clinical follow-up data were incomplete, especially for the patients with chronic heart disease. In addition, information on the pharyngeal rheumatogenic strains was not available.

In conclusion, ARF is far from eradicated, even in developed Western countries. Surveillance is necessary to reinforce current control strategies and to aid in the development of primary and secondary prevention strategies. An accurate and up-to-date register of persons with known previous ARF and RHD is critical for the efficient delivery of prophylactic therapy and monitoring of this delivery. ■

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Table 1. Combined ascertainment probabilities from 2 sources*

Year	Source 1	Source 2	Both	Total cases	Estimated total cases	Ascertainment probability, %
2000	3	2	1	5	5.0	100.1
2001	4	3	1	7	9.0	77.8
2002	2	4	1	6	6.5	92.3
2003	2	3	1	5	5.0	100.1
2004	5	6	2	11	13.0	84.6
2005	4	7	2	11	12.3	89.4
2006	4	8	2	12	14.0	85.7
2007	2	8	1	10	12.5	80.0
2008	3	8	2	11	11.0	100.1
2009	4	6	2	10	10.7	93.4
Pooled (2000-09)	33	55	15	88	118.0	74.6

*Primary sources: General Practitioners and Pediatricians. Secondary sources: Departments of Pediatrics, Medicine, and Rheumatology.