

Clinical characteristics and cardiac outcome of acute rheumatic fever in Italy in the last 15 years

A. Grassi¹, V. Fesslovà³, V. Carnelli¹, E. Boati¹, L. Dell'Era¹, P. Salice²,
M. Bardare¹, F. Corona¹

¹Centre of Pediatric Rheumatology, and ²Pediatric Cardiology Unit, Fondazione IRCCS Policlinico, University of Milan, Milan; ³Centre of Fetal Cardiology, Policlinico San Donato, San Donato, Milan, Italy.

Abstract

Objective

To analyze clinical characteristics, cardiac outcome and response to therapy of an Italian pediatric population affected with acute rheumatic fever (ARF) in the last 15 years.

Methods

135 patients with ARF (aged 2-14.9 years, mean 8.4 ± 2.5 years) diagnosed from 1992 to 2006 at the Pediatric Rheumatology Centre of the University of Milan (Italy) were retrospectively reviewed. All patients underwent physical examination, laboratory evaluation, electrocardiogram and echocardiography. Patients were divided into 2 groups: group 1 – patients with complete adherence to updated Jones criteria (107 patients), and group 2 – exceptions (28 patients). Echocardiographic criteria were used to confirm the presence of carditis and to evaluate severity of mitral (MR) and aortic regurgitation (AR) at diagnosis and after treatment with steroids or acetylsalicylic acid (ASA)/non-steroidal anti-inflammatory drugs (NSAIDs).

Results

We observed a persistence of ARF in the last 15 years (mean 9 new cases/year with a peak of 19 cases in 2000). Carditis and arthritis were the main major criteria observed (102/135 and 71/135 patients respectively), then chorea (29/135), erythema marginatum (8/135) and subcutaneous nodules (1/135). Arthritis and chorea resolved completely with various therapies. At the last follow-up (≥ 5 years) in group 1, loss of MR was observed in 46% steroid-treated (26/56 cases) and in 39% ASA/NSAID-treated (7/18 cases) patients and loss of AR in 59% steroid-treated (22/38) and 2/7 ASA/NSAID-treated patients ($p > 0.05$).

Conclusion

Incidence of ARF is clinically important currently in the area of northern Italy. Non-suppurative complications of streptococcal pharyngitis should be considered when deciding therapy in a pediatric patient that presents with sore throat.

Key words

Rheumatic fever, rheumatic heart disease, child, Italy, streptococcal infections, pharyngitis.

Angela Grassi, MD
 Vlasta Fesslovà, MD
 Fabrizia Corona, MD
 Elena Boati, MD
 Laura Dell'Era, MD
 Patrizia Salice, MD
 Maria Bardare, Professor
 Vittorio Carnelli, Professor

This work is to be attributed to the Centre of Pediatric Rheumatology, University of Milan, Italy.

Please address correspondence and reprint requests to:

*Dr. Angela Grassi,
 Via Caccialepori 35,
 20148 Milan, Italy.
 E-mail: angela.grassi@libero.it*

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Introduction

Resurgence of acute rheumatic fever (ARF) has been observed in the last decades in industrialized countries (1-5). To our knowledge, however, an increased rate of ARF incidence in Italy has not been reported so far, with the exception of a single report of an outbreak in 1986 (1) and our own reported cases in 2000 (6). Rheumatic carditis is the leading cause of permanent disability in ARF patients, being present in 68-70% of the patients (2, 7); the degree of cardiac involvement improves in about two third of them with standard treatment (7). The aim of the study is to assess the clinical importance of ARF and to evaluate cardiac outcome of ARF patients observed retrospectively in the Pediatric Rheumatology Centre of the University of Milan (northern Italy) from 1992 to 2006.

Materials and methods

In the last 15 years (1992-2006) 135 new cases of ARF (69 males, 65 females, age 2-14.9 years, mean age at diagnosis 8.4 ± 2.5 years, median 8.3 years) have been diagnosed according to the updated Jones criteria (8) at the Pediatric Rheumatology Centre of the University of Milan. Patients' clinical and demographic data were extracted from a database on ARF of the Pediatric Rheumatology Centre of Milan.

After collection of the medical history and socio-economic characteristics, all patients underwent physical and cardiological examinations, including electrocardiogram and echocardiography. Echocardiography was performed by two cardiologists (VF, PS), according to the standard criteria (9) and included 2-D, M-Mode, colour Doppler imaging (Acuson 128 XP/10 and Acuson Sequoia 512, Imagegate, Siemens, Erlangen, Germany). Good interobserver agreement was evident when reviewing the videotapes recordings. Probes 3.5 and 5 MHz were used, depending on the patient's height. Echocardiographic measurements were analyzed and compared with normal standard values for pediatric population (10). Valvular regurgitation was diagnosed according to the presence of a newly discovered cardiac murmur of mitral

or aortic regurgitation and the echocardiographic appearance; for mitral regurgitation the regurgitant jet at colour Doppler had to extend at least toward one third of the left atrium, be visible in 2 planes, have a mosaic pattern and be holosystolic at continuous wave or pulsed Doppler, for aortic regurgitation the regurgitant jet had to be holodiastolic, extend to the third of the left ventricle and be visible in 2 planes (11, 12). Published echocardiographic criteria were used to define the severity of the mitral or aortic regurgitation: it was considered mild when the jet extended to the third of the left atrium/left ventricle, moderate when extending to the middle of the left atrium/left ventricle and severe when overpassing it (13-15). Ratio of internal diameter of the left atrium with respect to the aortic root diameter in the parasternal long axis view was also considered to determine the entity of mitral regurgitation. Pericardial effusion was diagnosed by standard echocardiographic criteria.

The evolution of carditis was analyzed after 6 months and then annually. No auscultatory evidence of carditis and absence of mitral/aortic regurgitation at color-flow Doppler examination was considered a successful therapeutic response. Patients included in the cohort underwent an additional examination for this study if they were still receiving secondary prophylaxis with benzathine penicillin G and they were younger than 18-20 years of age (after 18-20 years of age patients are referred to adult rheumatology centres). As per the current guidelines (16), secondary prophylaxis was recommended: a) for 5 years or until 18 years of age (whichever was longer) to patients without cardiac involvement, b) for 10 years to patients with mild or healed carditis, c) lifelong to patients with more severe cardiac damage.

Patients admitted to hospital had throat swab specimen culture onto 5% defibrinated sheep blood agar plates, if throat swab culture had not been performed as an outpatient and antibiotic treatment had not already been started. All cultures were read at 24, 48 and 72 hours. Erythrocyte sedimentation rate (ESR) was analyzed by Westergren method

Competing interests: none declared.

and C-reactive protein (CRP) by quantitative immunoturbidimetric method. Antibody response to streptolysin O (ASO) was determined by immunoturbidimetric assay. An elevated or rising ASO titre was defined as an ASO titre >250 U/L or a two-fold increase in the ASO titre in two consecutive determinations within 2 weeks. The analysis of Streptozyme or antiDNAase B was not routinely measured in our Centre.

According to the updated Jones criteria and their exceptions (8), the patients were divided into two groups:

Group 1: patients with ARF and complete adherence to updated Jones criteria (107 cases: 62 males and 45 females). Patients in this group had evidence of an antecedent Group A beta-haemolytic *Streptococcus* (GABHS) infection (*i.e.* elevated or rising antistreptococcal antibody titres, possibly associated to GABHS-positive throat swab specimen) and presented either two major criteria or one major plus two minor criteria. Patients with carditis showed echocardiographic signs of active inflammation, such as thickening of the valvular leaflets (apart from the regurgitant flow at Doppler).

Group 2: exceptions to updated Jones criteria (28 cases: 8 males and 20 females). Patients in this group presented chorea and/or a newly discovered murmur of mitral and/or aortic regurgitation confirmed by echocardiography. These cases showed a quite settled lesion of the cardiac valves at echocardiography (*i.e.* without evidence of acute inflammatory changes as thickened, highly echodensed valvular leaflets) with normal or mildly elevated acute phase reactants.

Statistical analysis

Data are expressed as a frequency or percentage for the nominal variables. Chi-squared test was used for $r \times 2$ contingency tables and for the linear trend to compare the rate of successful therapeutic response (steroids vs. ASA/NSAIDs) in group 1 for MR and AR (data expressed as percentage of cases normalized at defined time intervals during the follow-up period).

Results

Frequency

A total of 135 new cases of ARF were diagnosed between 1992 and 2006, with a peak of 19 cases in the year 2000 (Fig. 1).

Time of presentation, evaluated in the 107 patients of the group 1, has been more frequent during winter (37/107 patients) and spring (41/107 patients). Environmental factors seem to be irrelevant: patients of rural and urban areas were equally affected (53/107 and 54/107 respectively). In our series, a positive family history was reported in 2 cases out of 135.

The follow-up of the patients lasted 2.9 ± 2.7 years (range 0.5-15 years; 9 patients were lost along the study). Two relapses of ARF were observed, after 5.2 and 4.9 years respectively (data excluded from the study); in both cases, the patients were referred to our Centre at the second episode. The first patient, whose parents had decided to discontinue the secondary prophylaxis one year after the onset, presented with arthritis, associated to fever, elevated markers of inflammation, rising antistreptolysin O titre and worsening of the preexisting mitral insufficiency. In the second case, the first episode was misdiagnosed and

the secondary prophylaxis was not suggested; at the time of admission at our Centre the patient presented with fever, arthralgias, elevated markers of inflammation, rising antistreptolysin O titre and newly developed aortic insufficiency.

Clinical characteristics and outcome

Group 1: patients with complete adherence to updated Jones criteria – 107 patients

GABHS infection. Sixty-eight patients (63.6%) presented with sore throat 2 to 4 weeks before the onset of the disease. Pharyngeal culture was performed in 72/107 patients and was positive in 22 cases (31%). Twenty symptomatic patients were treated with antibiotics; in 4 cases (3.7% of 107 patients) the therapy complied with the last guidelines (17).

In all patients of group 1 the antecedent streptococcal pharyngitis was demonstrated by the presence of an elevated ASO titer (104 patients, mean ASO titre 1404 UI/L – median ASO titre 1200 UI/L) or an increasing ASO titre (3 patients), possibly associated to a GABHS-positive throat swab specimen.

Jones criteria. Prevalence of major criteria is indicated in Table I. Ankle and knee were the most frequently affected joints among patients with arthritis (respectively in 43/71=61% and in 32/71=45% of the cases). Polyarticular involvement was prevalent (44/71=62%). In patients with arthritis as single major criterium (24 patients), other causes of arthritis were considered in the differential diagnosis, particularly reactive arthritis; the presence of migratory polyarthritis, involving mainly larger joints, the prompt response to anti-inflammatory therapy and the evidence of an antecedent GABHS infection associated to the presence of two or more minor criteria led to the diagnosis of ARF.

Carditis was characterized by valvulitis, detected usually by auscultation and confirmed by means of echocardiography. Prevalence of mitral (MR) and aortic (AR) regurgitation and their evolution are indicated in Table II.

One patient with moderate AR in the steroid-treated group was affected with

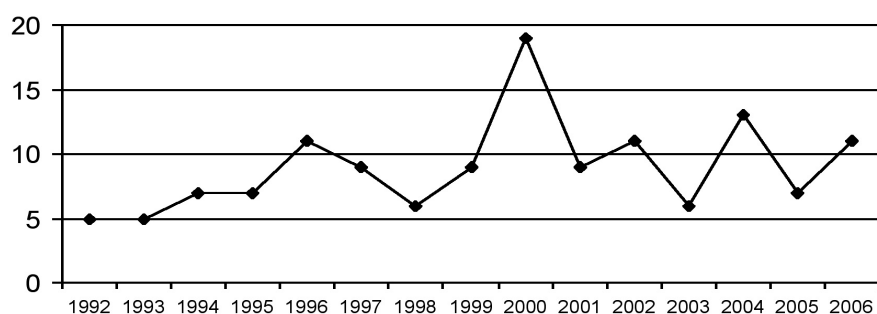


Fig. 1. Cases of ARF diagnosed at the Pediatric Rheumatology Centre of Milan from 1992 to 2006.

congenital bicuspid aortic valve; this patient presented with fever and arthritis, associated to elevated markers of inflammation and a newly developed murmur of aortic insufficiency.

Mild tricuspid regurgitation was present in 5 patients (4.7%), always associated to MR or MR plus AR. In 5 patients a mild pericardial effusion was found at echocardiography in the acute phase (3 with valvulitis); four patients showed left ventricular dilatation, with slightly reduced left ventricular contractile function (two had associated pericarditis).

Among the minor criteria, fever was present in 68/107 (63.6%) of the patients, arthralgias in 22/107 (20.6%), elevated markers of inflammation in almost all patients (106/107 = 99%), prolonged P-R interval in 2/107 (1.9%).

Patients aged 5 years or younger (11 patients) did not show any significant difference in clinical characteristics or cardiac outcome.

Treatment and evolution of arthritis and carditis. Patients affected with arthritis, without carditis, had been treated with non-steroidal anti-inflammatory drugs (NSAIDs), particularly naproxen (15-20 mg/kg/day in two daily doses), with complete resolution of symptoms in a few days.

Patients with carditis had been treated with steroids (prednisone 2 mg/kg/day in 2 daily doses for 4 weeks, then tapered and discontinued in 2 weeks, with concomitant ASA therapy prolonged for 2 weeks after steroid discontinuation) or ASA/NSAIDs; a patient with bivalvular involvement (mild MR plus AR) refused treatment (Table II).

Figure 2 shows the evolution of mitral regurgitation at follow-up after treatment with steroids and ASA/NSAIDs; after 6 months MR was undetectable in 11/56 (20%) and 1/18 (6%) of the patients in the steroid- and ASA/NSAID-group respectively and after 5 years in 26/56 (46%) and 7/18 (39%) of the cases respectively.

One patient in the ASA/NSAID group developed mitral stenosis after 4 years from the onset of ARF.

Figure 3 shows the evolution of aortic regurgitation after treatment with steroids and ASA/NSAIDs, with loss of

Table I. Prevalence of Jones major criteria in 135 ARF patients.

Total	All patients		Group 1 (107 pts)		Group 2 (28 pts)	
	no.	%	no.	%	no.	%
Carditis	102	75.6	81	75.7	21	75
Arthritis	71	52.6	71	66.4	0	0
Chorea	29	21.5	10	7.5	19	67.9
Erythema marginatum	8	5.9	8	7.5	0	0
Subcutaneous nodules	1	0.7	1	0.9	0	0
One major criterium						
Carditis	34	25.2	25	23.4	9	32.1
Arthritis	24	17.8	24	22.4	0	0
Corea	7	5.2	0	0	7	25
Erythema marginatum	1	0.7	1	0.9	0	0
Two (+) major criteria						
Carditis/arthritis	40	29.6	40	37.4	0	0
+ chorea	2	1.5	2	1.9	0	0
+ erythema marg.	2	1.5	2	1.9	0	0
+ subcut. nodules	1	0.7	1	0.9	0	0
+ chorea/eryth.marg.	1	0.7	1	0.9	0	0
Carditis/corea	19	14.1	7	7.5	12	42.9
Carditis/erythema marg.	3	2.2	3	2.8	0	0
Arthritis/erythema marg.	1	0.7	1	0.9	0	0

AR after 5 years in 22/38 (59%) and 2/7 (29%) of the steroid- and ASA/NSAID-treated patients respectively.

At statistical analysis both types of treatment showed a positive trend of loss of MR and AR by Chi squared for the linear trend ($p < 0.001$, $R^2 = 23.63$ for MR treated with steroids and $p < 0.0001$, $R^2 = 34.2$ with ASA/NSAIDs

and $p < 0.002$, $R^2 = 21.5$ for AR treated with steroids and $p < 0.0001$, $R^2 = 33.1$ by ASA/NSAIDs). When tested by Chi squared for 2 contingency tables – the difference between the two therapeutic protocols was not significant both for MR and AR.

Out of a total of 81 patients with valvulitis, bivalvular involvement was

Table II. Description of cardiac involvement of group 1 (107 patients) and group 2 (28 patients) according to the type of treatment.

	Patients with carditis, no.	Treatment			Evolution			
		Steroids	ASA/NSAIDs	None	Same	Improved	No murmur	Worse
All patients	102	68	22	12				
Group 1	81	61	19	1				
Mitral regurgitation	75	56	18	1	18	24	33	...
severe	8	8	—	—	—	6	2	...
moderate	39	30	9	—	9*	18	12	...
mild	28	18	9	1	9	—	19	...
Aortic regurgitation	46	38	7	1	14	7	23	2
moderate	18	17	1	—	6	7 [#]	5	1
mild	28	21	6	1	8	—	18	1 [#]
Group 2	21	7	3	11				
Mitral regurgitation	21	7	3	11	15	5	1	0
severe	—	—	—	—	—	—
moderate	12	6	1	5	8	4
mild	9	1	2	6	7	1	1	...
Aortic regurgitation	4	2	—	2	2	—	2	...
moderate	1	1	—	—	—	—	1	...
mild	3	1	—	2	2	—	1	...

*1 patient with mitral stenosis; [#]1 patient with aortic valve replacement.

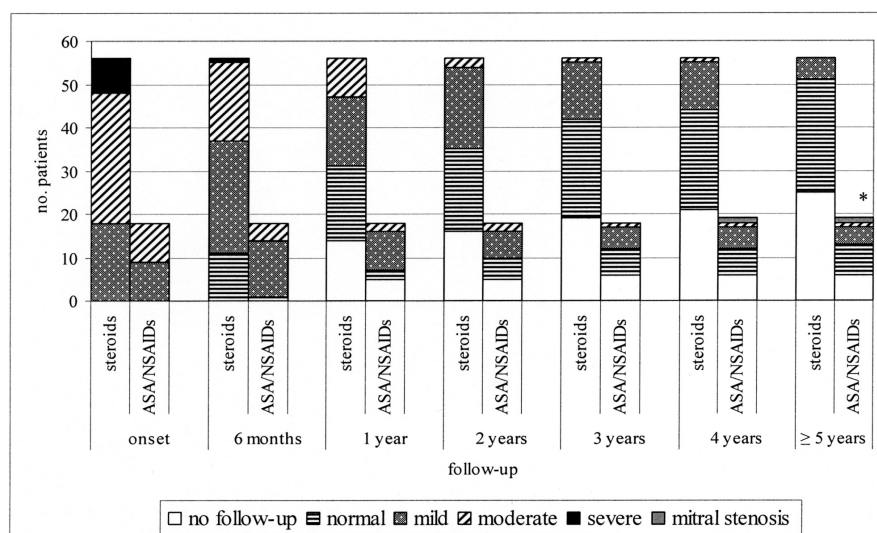


Fig. 2. Evolution of carditis in Group 1 patients with mitral regurgitation according to treatment.
*no. of patients with normal echocardiographic findings in patients treated with steroids and ASA/NSAIDs = $p > 0.05$.

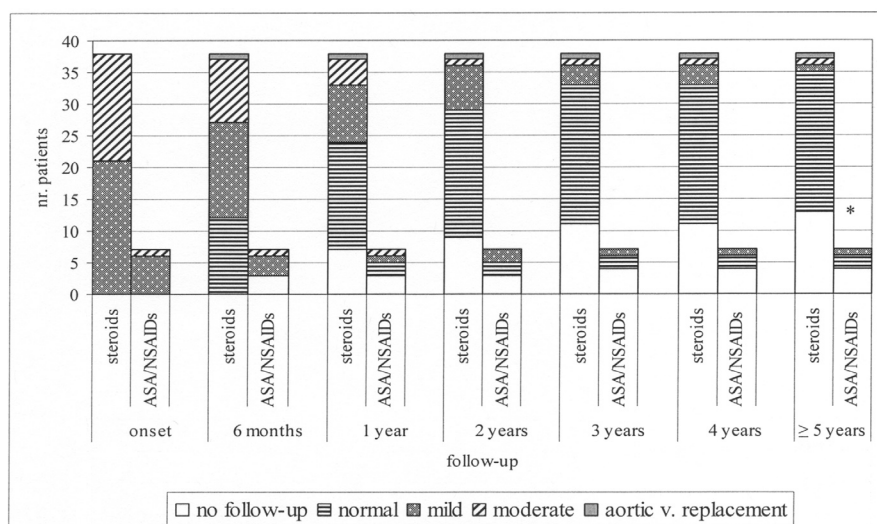


Fig. 3. Evolution of carditis in Group 1 patients with aortic regurgitation according to treatment.
*no. of patients with normal echocardiographic findings in patients treated with steroids and ASA/NSAIDs = $p > 0.05$.

present in 40 patients. The evolution of 33 patients treated with steroids is shown in Figure 4. Six patients with bivalvular involvement were treated with ASA/NSAIDs; 3 of them had mild MR and AR, 2 patients moderate MR and mild AR, 1 patient had moderate AR and mild MR. After 5 years of follow-up, 1 patient had normal echocardiographic findings, 1 patient showed mild MR and 1 patient mild AR (3 patients being lost at follow-up). One patient with mild MR and AR refused treatment. The patient with congenital bicuspid aortic valve and moderate AR, treated with steroids, and the patient

who refused treatment required aortic valve replacement because of the progressive worsening of regurgitation and the left ventricular function.

Digoxin treatment was indicated in a total of 3 patients with moderate-severe valvulitis and/or left ventricular dilatation (all treated with steroids).

Treatment and evolution of chorea (appeared in acute phase). Eight out of 10 patients (all with carditis) were treated with steroids, associated with diazepam (0.2-0.3 mg/kg/day) in 1 case, and 2 patients received haloperidol (0.25-0.5 mg/day in 2-3 divided daily doses).

Resolution of chorea, *i.e.* absence of the typical fast, clonic, involuntary movements, was variable (1 month to 1 year, mean 4 months).

Secondary prophylaxis was started with benzathine penicillin G (1.200.000 UI i.m. if weight ≥ 27 kg, 600.000 IU i.m. if ≤ 26 kg, every 21 days); duration of treatment was determined by the presence and the entity of cardiac involvement (16).

Group 2: Exceptions to updated Jones criteria (28 patients)

Nineteen patients out of 28 (Table I) presented with chorea. At the time of admission, a murmur of MR or AR was detected in 12/19 patients (4 with bivalvular involvement).

Nine patients were referred to our Centre as outpatients due to an occasional finding of a holosystolic murmur suggestive for MR or of a diastolic murmur suggestive for AR, which led, after a confirmatory echocardiography, to the diagnosis of indolent carditis.

Treatment and evolution. Six out of 19 patients with chorea received haloperidol, associated with steroids in 3 cases and ASA in 1 case. Three patients received tiapride hydrochloride (5-10 mg/kg/day in 2-3 daily doses), two patients prednisone, 2 patients valproate sodium (15 mg/kg/day in 3 daily doses), 1 patient diazepam. Five cases were not treated at all. As in group 1, resolution of chorea was variable (1 months to 3 years, mean 9 months, median 4.5 months). Characteristics, treatment and outcome of patients with carditis are indicated in Table II.

Secondary prophylaxis with benzathine penicillin G was recommended to every patient, according to the current guidelines (16).

Discussion

The high incidence of ARF in the developing countries has been attributed to low-socio economic status, associated to genetic increased susceptibility of some ethnic groups, particularly Australian aboriginal groups (18). In western countries, therefore, the achievement of higher quality standard of life and the availability of medical care led to hypothesize the gradual disappearance of ARF and rheumatic heart disease (RHD).

Our experience, however, shows that ARF still represents in Italy a relevant clinical issue. The Pediatric Rheumatology Centre of Milan is a primary and tertiary care unit. The patients, who came to our observation, lived in the area of Milan or were referred to our Centre on suspicion of a rheumatologic disease by pediatricians working in the hinterland of Milan. The real incidence of ARF in this area, therefore, could be misrepresented by the high number of patients referring to our Centre by other hospitals. Nevertheless, giving the fact that the number of admissions and visits had remained unchanged during the whole period of the present study, a persistence of ARF has been reported in the last decade, as described also by authors from Europe and the United States (2, 3, 7, 19).

A crucial role in the insurgence of ARF seems to be played by a lacking recognition and adequate treatment of the triggering pharyngeal GABHS infection, as all the patients of our cohort belonged to middle-class families and had prompt access to medical care. The reason could be related to the high prevalence of asymptomatic patients and to inadequate antibiotic treatment mainly due to poor therapeutic compliance. A full therapeutic course of antibiotic therapy was verified in only 4 patients; according to the most recent guidelines (17) the treatment should have been adequate to prevent ARF. Nevertheless, it is possible that antibiotic resistance in macrolide-treated patients or internalization of GABHS in penicillin-treated patients developed in these cases.

Recently, the Cochrane Library faced the problem of primary prevention of ARF (20). In their meta-analysis, the lack of new cases of ARF among patients treated with antibiotics and controls (2484 patients enrolled after 1990) led to the assumption that antibiotic treatment for sore throat should not be prescribed in order to prevent ARF, except in subpopulations at high risk. Vice versa, the reports of outbreaks of ARF in many different countries, including Italy, and of the persistence of mucoid strains among more developed populations (4) should make us consider more thoroughly the indications for the antimicrobial therapy.

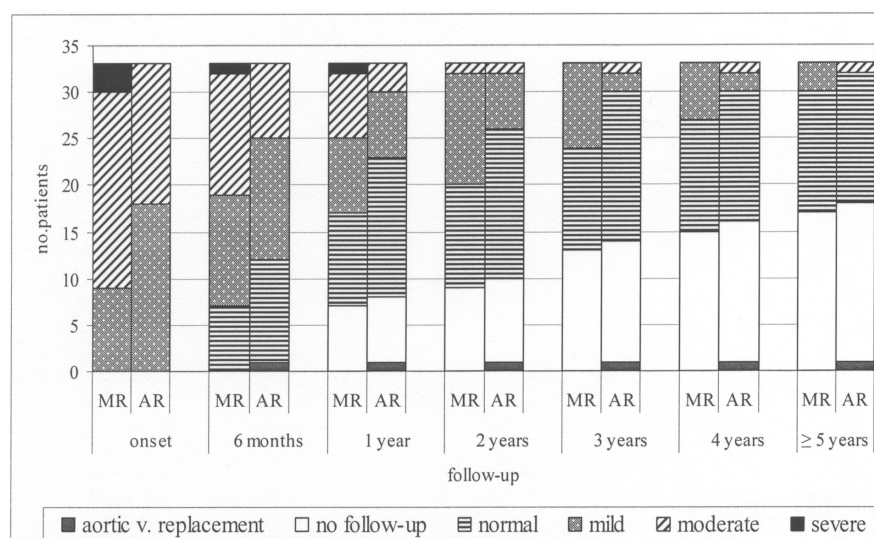


Fig. 4. Evolution of bivalvular lesions of mitral and aortic regurgitation in steroid treated Group 1 patients (33 patients).

MR: mitral regurgitation; AR: aortic regurgitation.

Carditis prevailed as the major criterium of ARF, while in most series from the United States and Europe arthritis is the main major criterium (2, 7, 21). Prevalence of chorea is very different among various settings, ranging from 4.5% (2) to 36% (7). We observed a prevalence of 21.5% (29/135 patients), with a rather unusual early presentation in 6 cases, in acute phase of ARF, associated in all to carditis. Erythema marginatum and subcutaneous nodules are rare manifestations also in our study, the former being detected in 5.9%, the latter in a single case.

We can confirm from our experience the usefulness of echocardiography and mainly of the echo-Doppler in the evaluation of patients with suspected carditis. These techniques can provide supporting evidence of rheumatic carditis in presence of a murmur, albeit it should not be used as a single criterium in patients with "silent" mitral or aortic regurgitation (8). The use of echocardiographic criteria helps the physicians in differentiating pathological from innocent murmurs and congenital heart lesions, particularly in less developed countries (22).

As to the efficacy of different therapeutic protocols, arthritis showed a prompt regression after ASA/NSAIDs as well as after the steroid treatment. We preferred to use NSAIDs in patients who had arthritis as a single major criterium,

in agreement with the current opinion (23).

The evolution of carditis showed a positive trend: we observed an improvement of the degree of rheumatic carditis in 75.7% and 66.7% of the patients with mitral and aortic regurgitation, respectively. As for the treatment of carditis, we did not find any significant difference in cardiac outcome between the two therapeutical regimens, even if patients receiving steroids were faster to recover, in agreement with the conclusion of the Cochrane Library meta-analysis on this issue (24).

We have to recognize the limits of a retrospective study: severe cases and generally the majority of the patients with carditis in our cohort received by choice steroids instead of NSAIDs, because of their high tolerability and negligible side effects when used for a short period. The assessment of evolutivity in the patients is further complicated by the natural improvement of rheumatic carditis reported in some studies (20), albeit in most patients with RHD of our series cardiac damage remained unchanged, with no differences with regard to the treatment administered.

We have to underline in any case the usefulness of a specific treatment of carditis, with the knowledge that a possible worsening of the lesions occurred in the only patient whose parents

refused treatment. We observed in our series another patient in whom the pattern of AR worsened despite treatment with steroids. However, this patient had a congenital aortic valve anomaly complicated by ARF. Evolution toward mitral stenosis did not occur in the steroid-treated patients, but only in one patient treated with NSAIDs.

Secondary prophylaxis remains a mainstay in the management of ARF patients: both patients who experienced relapses of ARF were not receiving secondary prophylaxis.

Strategies of interventions in order to identify subjects with GABHS pharyngitis should be mandatory in particular settings, where ARF incidence is high and generally associated with less availability of medical care. Our series, although limited, joins the reports of other authors on the persistence of ARF in western countries, this being an entity of which young clinicians should be aware.

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