Rheumatic fever and rheumatic heart disease among children presenting to two referral hospitals in Harare, Zimbabwe

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Background. Acute rheumatic fever (ARF) and rheumatic heart disease (RHD) remain significant causes of morbidity and mortality in resource-limited settings. In Zimbabwe ARF/RHD characteristics have not been systematically documented.
Objectives. To document cases of ARF/RHD among children presenting at referral hospitals in Harare, Zimbabwe, determine their clinical and echocardiographic characteristics, and identify opportunities for improving care.
Methods. A cross-sectional survey was carried out in which consecutive children aged 1 - 12 years presenting with ARF/RHD according to the 2002/3 World Health Organization modified Jones criteria were enrolled.
Results. Out of 2 601 admissions and 1 026 outpatient visits over 10 months, 50 children were recruited, including 31 inpatients with ARF/RHD and 19 outpatients with chronic RHD. Among inpatients, 9 had ARF only, 7 recurrent ARF with RHD, and 15 RHD only. The commonest valve lesions were mitral regurgitation (26/31) and aortic regurgitation (11/31). The commonest reason for admission was cardiac failure (22/31). The proportion of ARF/RHD cases among inpatients aged 1 - 12 years was 11.9/1 000. Of the 22 with RHD, 14 (63.6%) presented *de novo* and 1 had bacterial endocarditis. Among the outpatients, 15 had cardiac failure while echocardiographic findings included mitral regurgitation (18/19) and aortic regurgitation (5/19). At presentation, 18/26 known cases were on oral penicillin prophylaxis and 7 on injectable penicillin. Of those on secondary prophylaxis, 68.0% reported taking it regularly.
Conclusion. ARF/RHD remains a major problem and cause of hospital admissions in Harare, Zimbabwe. Children often present late with established RHD and cardiac failure. With the majority on oral penicillin, secondary prophylaxis was suboptimal in a resource-limited setting unable to offer valve replacement surgery.

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Acute rheumatic fever (ARF) continues to be a significant cause of acquired heart disease in resource-limited settings.[1-3] If recurrent or associated with moderate to severe carditis during the initial episode, ARF may lead to rheumatic heart disease (RHD), resulting in progressive and permanent cardiac valve damage.[4] Primary episodes of ARF occur mainly in children aged 5 - 15 years and are rare in children under 5 years of age.[5] Predisposing factors for ARF and RHD include poor socioeconomic conditions, undernutrition, overcrowding, close person-to-person contact and poorly developed healthcare facilities.[1,6]

Owing to improved standards of living, medical care and use of antimicrobial agents, ARF and RHD are no longer a significant problem in most developed countries except for certain ethnic groups such as the indigenous populations of Australia and New Zealand.[7,8]

Estimates from 2005 showed that most of the 15 - 19 million people affected by RHD worldwide were living in developing countries, and an estimated 233 000 people were dying annually from RHD.[7] Recent estimates based on community-based echocardiographic screening suggest that the burden could be much higher,[9] with estimates from Mozambique showing a prevalence of RHD of 30.4/1 000 among schoolchildren.[2] This is higher than the estimated RHD prevalence of 5.7/1 000 from earlier studies for sub-Saharan Africa (SSA).[7] In a recent review by Zühlke *et al.*,[10] hospital-based estimates showed that RHD remains a significant cause of morbidity in Africa, with 6.6 - 34% of patients hospitalised with cardiovascular diseases or seen in echocardiographic clinics having RHD. Complications of ARF and RHD include valve insufficiency, heart failure, infective endocarditis and death.[11] Surgical repair or replacement of damaged heart valves remains largely unavailable in the developing world,[12] and non-surgical management of ARF and RHD with palliative treatment of heart failure and secondary prophylaxis to slow progression continue to be the primary forms of treatment available in these resource-limited settings.[1,3,12]

SSA has historically been estimated to be the region most affected by RHD,[7] prompting the Pan-African Society of Cardiology to initiate a programme to raise Awareness of the disease, encourage Surveillance of the disease pattern, Advocate for resources and promote Prevention programmes (ASAP), aiming for the control and elimination of ARF/RHD in the region.[13] While sites with register-based RHD control programmes have been set up in some African countries,[14,15] little is known about RHD in Zimbabwe and the country has largely lagged behind in implementing these control programmes. The real burden of ARF and RHD, the clinical and demographic characteristics of these patients, and the adequacy of treatment practices have not been documented systematically. The objectives of the present study were therefore to document cases of ARF and RHD among children presenting at referral hospitals in Harare, to determine their clinical and echocardiographic characteristics, and to identify opportunities for improving care of these patients in Zimbabwe.

Methods

Permission to conduct the study was obtained from the Harare Central Hospital Medical Ethics Board and the Joint Research Ethics Council of the College of Health Sciences, University of Zimbabwe, and Parirenyatwa Central Hospital. Written informed consent from caregivers and assent from children aged 8 - 12 years were obtained. A descriptive, cross-sectional survey of children 1 - 12 years of age seen at Harare and Parirenyatwa Central hospitals in Harare, Zimbabwe, was carried out between July 2012 and May 2013. At both hospitals, patients seen in the paediatric units are aged ≤12 years, while those younger than 1 year were excluded from the study because of the rarity of group A streptococcal (GAS) sore throat and ARF below this age.[1,5] The children treated at these two institutions are either referred from the surrounding city, district and provincial health facilities or admitted through the emergency department. Children hospitalised in the paediatric medical wards in both hospitals or seen in the paediatric cardiac clinic based at Parirenyatwa Hospital were screened for possible enrolment in the study. They were enrolled if they showed evidence of congestive cardiac failure (CCF), cardiac murmur, arthritis or chorea and if they satisfied the 2002/3 World Health Organization modified Jones criteria for ARF and RHD.[1] Children were considered to have ARF recurrence in the presence of a documented prior history of ARF or established RHD.[16] Hospitalised patients were followed up to discharge or death during the initial presentation.

The data collected for each patient included demographics, clinical features, history of sore throat in the preceding 4 weeks, echocardiographic features, and select laboratory results as ordered by the attending paediatrician (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), leucocyte count and anti-streptolysin O titre (ASOT)). Reference laboratory values specific to the Zimbabwean population have not been established, so standard laboratory reference values were used. A 12-lead resting electrocardiogram (ECG) and rhythm strip were used to assess for the presence of arrhythmias and a prolonged PR interval according to age-appropriate references.[17] Where available, the patient's most recent chest X-ray was reviewed and the presence of cardiomegaly noted.

A complete two-dimensional paediatric echocardiogram was performed in all the hospitalised eligible patients and in 18 of the outpatients with Doppler and colour flow mapping according to American Society of Echocardiography guidelines.[18] Pulmonary hypertension was defined as an estimated right ventricular systolic pressure >35 mmHg by continuous-wave Doppler.[17] All images were recorded and subsequently reviewed by an independent paediatric cardiologist. Echocardiography was performed using a Sonosite M-turbo USS SN NG020N portable echocardiography machine, with a P21x/5-1 MHz transducer (Sonosite Inc., USA).

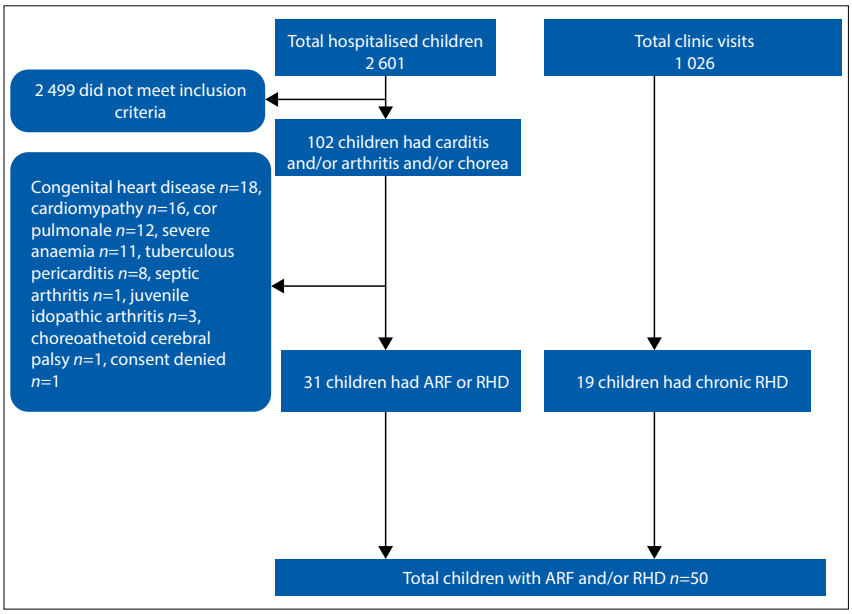

Fig. 1. Flow diagram of patient enrolment.

Statistical analysis

Data were collected, verified and checked for completeness and missing data retrieved from admission and laboratory records. This was then entered into a REDCap (Research Electronic Data Capture) database hosted at the University of Zimbabwe.[19] The data were first exported to Microsoft Excel (Microsoft Corporation, USA) for quality assessment, then imported into Stata, version 10.1 (StataCorp, USA) for descriptive analysis. Descriptive statistics between patient groups were compared using the χ^2 test. A p-value of <0.05 was considered significant.

Results

Patient screening and enrolment are summarised in Fig. 1. A total of 2 601 children aged 1 - 12 years were admitted to the paediatric medical units over the study period. One hundred and two children (3.9%) presented with a cardiac murmur, CCF, arthritis or chorea. Of the 2 601 children hospitalised during the study period, 31 had ARF and/or RHD, giving an overall case rate of 11.9/1 000 hospitalised children. Only two of the children were aged <5 years, and both had ARF only. Chronic RHD was present in 22 of 85 children hospitalised with cardiovascular-related conditions, giving a case rate of RHD among such children of 25.9%. There were a total of 1 026 outpatient visits by children aged 1 - 12 years, from which 19 children were seen with chronic RHD.

Demographic characteristics

Of the 50 children seen with ARF and/or RHD, 32 (64.0%) were female. The median age was 9.5 years (interquartile range 7.5 - 10.5 years). All of the children were black Africans. A reported family history of RHD was present in 3/50 children (6.0%). Most of the children seen were from either a rural or farming area of residence (54.0%) or an urban high-density area (30.0%).

Clinical presentation

Table 1 summarises the clinical features of enrolled subjects. Among the 16 children with ARF, 9 (56.3%) presented with an initial episode of ARF, while ARF recurrence with established RHD was present in 7 children (43.8%), of whom 2 had a documented history of prior ARF; both had established RHD.

Overall, 15/41 (36.6%) of children with chronic RHD presented *de novo* with no prior documented history of ARF or RHD. The proportion of patients presenting with RHD in the absence of prior documented ARF was higher among hospitalised children (14/22, 63.6%). The most common clinical feature at hospitalisation was carditis, which was present in 25/31 (80.6%) children, of whom 22/25 (88.0%) had CCF. Acute cardiac failure was present in 20/22 (90.9%) children

Table 1. Description of the children seen with ARF and/or RHD, including clinical features

	All (*N*=50) *n* (%)	Hospitalised patients (*n*=31)			Outpatients (RHD only) (*N*=19) *n* (%)
		ARF only (*N*=9) *n* (%)	ARF + RHD (*N*=7) *n* (%)	RHD only (*N*=15) *n* (%)	
Prior history of RHD					
Prior history	26 (52.0)	-	2 (28.6)	6 (40.0)	18 (94.7)
De novo RHD	15 (30.0)	-	5 (71.4)	9 (60.0)	1 (5.3)
Clinical features					
Arthritis	-	4 (44.4)	1 (14.3)	1 (6.7)	-
Carditis	-	4 (44.4)	6 (85.7)	15 (100.0)	19 (100.0)
Cardiomegaly on chest X-ray, when available	-	1/6	6/6	11/11	6/6
Chorea	-	3 (33.3)	2 (28.6)	-	-
Subcutaneous nodules	-	-	1 (14.3)	-	-
Fever	-	6 (66.7)	5 (71.4)	4 (26.7)	-
Polyarthralgia	-	3 (33.3)	3 (42.9)	3 (20.0)	-
Elevated acute phase reactants	-	8 (88.9)	5 (71.4)	5 (33.3)	-
Elevated ESR	-	4 (44.4)	4 (57.1)	2 (13.3)	-
Elevated CRP	-	4 (44.4)	3 (42.9)	2 (13.3)	-
Leucocytosis	-	3 (33.3)	4 (57.1)	4 (26.7)	-
Elevated ASOT	-	7 (77.8)	5 (71.4)	1 (6.7)	-
A recent history of sore throat	-	5 (55.6)	4 (57.1)	5 (33.3)	-
Prolonged PR interval for age	-	2 (22.2)	-	3 (20.0)	-
Clinical pulmonary hypertension	25 (50.0%)	-	2 (28.6)	14 (93.3)	9 (47.4)

Table 2. Description of the echocardiographic features in children presenting with ARF/RHD

	All (*N*=49) *n* (%)	Hospitalised patients (*n*=31)			Outpatients, RHD only (*n*=18) *n* (%)
		ARF only (*n*=9) *n* (%)	ARF + RHD (*n*=7) *n* (%)	RHD only (*n*=15) *n* (%)	
MR	44 (89.8)	4 (44.4)	7 (100)	15 (100)	18 (100)
MR + MS	2 (4.1)	0 (0.0)	1 (14.3)	1 (6.7)	-
MR + AR	16 (32.7)	0 (0.0)	2 (28.6)	9 (60.0)	5 (27.8)
Left ventricular systolic dysfunction	21 (42.9)	3 (33.3)	4 (57.1)	7 (46.7)	7 (38.9)
Pulmonary hypertension	17 (34.7)	1 (11.1)	1 (14.3)	11 (73.3%)	4 (22.2)

hospitalised with RHD and in 2/9 (22.2%) children hospitalised with ARF only.

Among the 16 children with ARF, one major Jones criterion was present in 11 (68.8%) and two major criteria in 5 (31.3%), specifically carditis plus chorea in 3, carditis plus arthritis in 1 and carditis plus subcutaneous nodules in 1. No child had more than two major Jones criteria. Carditis was the most common major Jones criterion, present in 10 children (62.5%), followed by chorea in 5 (31.3%) and arthritis also in 5 (31.3%). Subcutaneous nodules were uncommon and seen in only 1 child (6.3%), while none had erythema marginatum. The most common minor Jones criteria were fever in 11 (68.8%), elevated acute-phase reactants in 13 (81.3%) (being leucocytosis in 7 (43.8%)), elevated ESR in 8 (50.0%) and elevated CRP in 7 (43.8%). Polyarthralgia was present in 6 children (37.5%) and first-degree heart block in 2 (12.5%). Elevated ASOT was present in 12 children (75.0%) with ARF, while there was a history of sore throat within the preceding 4 weeks in 9 (56.3%).

Comorbid illnesses were present in 12/31 hospitalised children (38.7%), including pneumonia in 5, tonsillitis in 2, ascites in 2, severe anaemia in 1, post-streptococcal glomerulonephritis in 1 and cerebrovascular accident in 1. Among the 19 children seen as outpatients, 15 (78.9%) had chronic cardiac failure and 18 (94.7%) a cardiac murmur.

Echocardiographic findings

Among the hospitalised children, the most common valve lesion was mitral regurgitation (MR), present in 26/31 (83.9%) and in 11/16 (68.8%) of the children with ARF (Table 2). Aortic regurgitation (AR) and mitral regurgitation were present concurrently in 11/22 children (50.0%) with ARF and/or RHD. Mitral stenosis (MS) was present in 2 patients aged 9 and 12 years, and no patient had aortic stenosis or isolated AR. Left ventricular systolic dysfunction was present in 14/31 hospitalised children (45.2%) and pulmonary hypertension in 13 (41.9%). Among outpatients, MR was present in all of the 18 children (100%) who underwent echocardiography at presentation, AR in 5 (27.8%) and pulmonary hypertension in 4 (22.2%).

Complications of ARF/RHD

Congestive cardiac failure (22/31, 71.0%) and pulmonary hypertension (13/31, 41.9%) on echocardiography were the commonest complications of ARF/RHD in hospitalised children. On 12-lead ECG, no patient was found to have cardiac arrhythmias. One hospitalised child had suffered a cerebrovascular accident secondary to infective endocarditis. Two (6.5%) of the 31 hospitalised children died, one from severe heart failure and the other from infective endocarditis.

Treatment and secondary prophylaxis

Medical therapy for complications was the main form of treatment available for children with ARF/RHD, with no open heart surgical facilities available locally. One child who was hospitalised for evaluation had undergone mitral valve replacement in another country.

Of the 26 patients known to have ARF/RHD, 25 (96.2%) were on secondary penicillin prophylaxis at presentation (Table 3). The majority (18/25, 72.0%) of the children were on oral penicillin, while 7/25 (28.0%) were on long-acting intramuscular penicillin prophylaxis. One child, a known case of ARF who was not on antibiotic prophylaxis at presentation, had been hospitalised with recurrent ARF and RHD. Almost a third (8/25, 32.0%) of the known cases self-reported forgetting to take secondary penicillin prophylaxis regularly. There was no significant association between the type of penicillin prophylaxis and a reported history of missing antibiotic prophylaxis (p=0.15).

Table 3. Secondary prophylaxis

	n/*N* (%)
Penicillin prophylaxis at presentation	25/26 (96.2)
Oral penicillin	18/25 (72.0)
Injectable penicillin	7/25 (28.0)
Reported history of missing antibiotic prophylaxis	8/25 (32.0)

Discussion

This study showed that ARF remains common and is a major cause of hospitalisation among children presenting to referral hospitals in Harare. A number of children presented *de novo* with established RHD and cardiac failure, and secondary antibiotic prophylaxis for children with ARF/RHD was suboptimal. It was significant that 63.6% of the children who were hospitalised with established RHD presented without a prior history of ARF, showing that even patients <12 years of age tended to present late. This was a higher proportion compared with the 8.6% of patients with *de novo* presentation of RHD seen in the Heart of Soweto study[20] and the 38% in a Fijian study,[16] although those studies included older patients who may have had different healthcare-seeking behaviour compared with younger children. However, in a longitudinal study in Australia, it was noted that the risk of developing RHD following initial diagnosis of ARF decreased with older age and time from diagnosis.[21]

The overall case rate of ARF/RHD among hospitalised children aged 1 - 12 years was high at 11.9/1 000, with 25.9% of the children hospitalised with cardiovascular-related conditions having established RHD. In a recent review by Zühlke *et al.*,[10] 6.6 - 34% of children hospitalised or seen in echocardiographic clinics in Africa had RHD.

While no significant association between gender and ARF has been described in the literature, in this study there were more females than males with ARF/RHD, with 64.0% being female. A positive family history of RHD was found in 6.0% of the patients in this small study, which is consistent with previous work that showed a genetic association, with a positive family history being present in 2 - 14% of patients with ARF.[22-25]

Clinical and echocardiographic features among children with ARF were comparable to findings from similar settings, with carditis being the commonest major Jones criterion.[24,26] The rate of migratory polyarthritis in this cohort was relatively low at 31.3%. A recent worldwide review described a higher frequency of arthritis, almost equal in frequency to carditis (59.3% v. 59.5%).[25] The frequency of chorea (31.3%) was similar to findings from other hospital-based studies in low-resource settings, where this ranged from 18.8% in India[22] to 27.5% in Brazil.[24] Subcutaneous nodules were rare (6.3%), and no child presented with erythema marginatum. In studies from other low-resource settings these major criteria ranged in frequency from 0% to 5.9%,[22-25] while in Montreal, Canada, a developed country with a predominantly Caucasian population, Carceller *et al.*[27] found a higher proportion with erythema marginatum of 23.5%.

Among the minor Jones criteria, the frequency of fever (68.8%), and polyarthralgia (37.5%) was not significantly different from previous findings by other workers.[16,24-26] Elevated CRP was present in 43.8%, comparable to 42% seen in Sydney, Australia.[26] In contrast, the frequency of elevated ESR (50.0%) was lower than 94% observed in Saudi Arabia.[28] One child in the present study was noted to have concurrent ARF and post-streptococcal glomerulonephritis, an unusual occurrence that is thought to be due to some GAS strains being both nephritogenic and rheumatogenic.[29]

Among the children with ARF, mitral regurgitation was the predominant valve lesion on echocardiography. Mitral valve regurgitation has been found to be the most frequent cardiac lesion in patients with ARF with documented frequencies varying from 21.6% in India[22] to 77% in Australia,[26] and has also been associated with recurrent episodes of ARF.

All 15 children hospitalised with RHD alone had chronic CCF, a very high proportion compared with Fiji, where CCF was the reason for admission in 51% of children.[16] Only one child (6.7%) was admitted with infective endocarditis in the present study, which is lower than findings reported in the Fiji (10.6%),[16] Canadian (16.3%)[27] and Indian (36.5%)[22] studies. These differences may be explained in part by age; in the present study the oldest patient was 12 years old, whereas the other investigators included older patients. However, despite the relatively young age of children in the present study there was still a high frequency of CCF, which may be due to late presentation with severe forms of the disease.

MR was also the predominant valve lesion in children with RHD only, being present in all of the children, followed by AR in 42.4%. This is comparable to previous observations in Fiji, where 91% of the patients had mitral valve involvement,[16] but was higher than in India, where MR was present in 39.5% and AR in 3.9%,[22] probably owing to late presentation in this setting with more advanced disease. MS was rare, as expected given the age limit of 12 years in the patients seen. No arrhythmias were documented, which is not surprising given the young population that was studied in this series.

Treatment of patients with complications of RHD was primarily supportive, with no facilities for surgical repair. Only one patient had mitral valve replacement done while her family was living in another country. Open-heart surgery is currently not available in Zimbabwe.

Optimising secondary antibiotic prophylaxis is necessary to improve ARF and RHD outcomes, especially in settings where surgical options are not available. In this study secondary antibiotic prophylaxis was mainly with oral penicillin, which is suboptimal,

consistent with other studies.[22,30] Secondary prophylaxis has been shown to be effective only when there is a high level of compliance, with an increased risk of recurrence and more severe RHD among patients defaulting treatment.[31-33] While the majority (96.2%) of children previously diagnosed with ARF/RHD were on penicillin prophylaxis at presentation, only 68.0% reported taking the prophylaxis regularly. This lack of adherence to penicillin prophylaxis has also been reported in a study from 16 developing countries between 1986 and 1990, when adherence was reported to be 63.2%.[30] Although 68.0% were said to be adherent to secondary prophylaxis, 76.0% of patients in this series were on oral penicillin. Several previous studies have shown parenteral penicillin to be more efficacious than oral penicillin.[34-36]

Study limitations

This was a hospital-based study with the usual limitations. The wards were visited daily to screen all hospitalised children. Hospitalised children tend to reflect only the severe cases, and minor cases may be missed. Community rates of ARF and RHD cannot be directly inferred from this hospital-based data. Other study variables such as regular use of penicillin prophylaxis were based on history only and could have been affected by recall bias. The relatively small sample size also reduced the statistical power of the study.

Conclusions

ARF remains a significant problem and cause of hospital admissions among children presenting at referral hospitals in Harare, Zimbabwe, many of whom present with *de novo* advanced RHD. Clinical and echocardiographic features of patients with ARF and RHD in Zimbabwe were comparable to findings from other studies done in resource-limited settings. Adherence to secondary penicillin prophylaxis among patients with ARF and RHD in this setting was suboptimal, and many patients were using oral penicillin for secondary prophylaxis instead of the preferred parenteral form. These findings suggest that there is a need to raise awareness among patients, healthcare workers and policy makers on the importance of improving management of ARF and RHD patients, including best treatment practices to enable optimal utilisation of the available resources and consideration of establishing cardiac surgery programmes.

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