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RESEARCH LETTER

Refining Risk Stratification Among Children With Latent Rheumatic Heart Disease

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The GOAL trial (Determining the Impact of Penicillin in Latent RHD; URL: https://www.clinicaltrials.gov; Unique identifier: NCT03346525) was a randomized controlled trial of secondary antibiotic prophylaxis (SAP) compared with no prophylaxis among Ugandan children with latent, or screen-detected, rheumatic heart disease (RHD).[1,2] SAP resulted in a significant reduction in RHD progression (worsening of diagnostic category) versus no prophylaxis (0.8% versus 8.3%; $P<0.001$), whereas nearly half of the children, regardless of SAP administration, regressed (improvement in diagnostic category) over 2 years.[2] Understanding risk factors for progression and regression of latent RHD at the time of screening echocardiogram could refine approaches to SAP in RHD, which would have both individual and health system benefit.

Here, the association between sociodemographic and echocardiographic features at GOAL trial entry and risk of progression and regression was examined. All study procedures were approved by local institutional review boards and participants gave informed consent or assent.[3] The data, methods, and materials used to conduct the research are available by author request.[2]

In brief, school-based echocardiographic screening was used to identify children ages 5 to 17 years with latent RHD. Participants were randomized to receive SAP with benzathine benzylpenicillin G every 28 days for 2 years or no SAP. At study completion, side-by-side enrollment and 2-year echocardiograms were presented to a blinded expert panel who determined progression, regression, or no change.[1,2] Logistic regression models, adjusted for the randomized treatment arm and the stratification variable (definite or borderline RHD), were used to generate odds ratios with 95% CIs by risk factor.

A total of 799 participants (799/818 [97.7%]) reached GOAL trial completion (399 SAP). Sociodemographic and clinical features were similar between groups. Approximately 80% of participants in both groups had borderline RHD (2012 World Heart Federation Criteria[4]), 60% were older than 12 years, 55% were female, and 19% lived in permanent housing as compared with semi-permanent housing. Water, Assets, Maternal Education, and Income (WAMI) Index[5] was low (0.3) but did not differ between groups.

Progression of RHD was observed in 36 of 799 participants (4.5%). The most common forms of progression were worsening grade of existing mitral or aortic regurgitation (16/36 [44.4%]) and new development of abnormal mitral or aortic valve morphology (18/36 [50.0%]). Among those who progressed, 19 (52.8%) were classified as moderate or severe RHD at trial completion.

Regression was observed among 386 participants (48.3%). The most common forms of regression were disappearance or decreased grade of mitral or aortic regurgitation (374 [96.9%]); resolution of abnormal morphology was much less common (25 [6.5%]). Among those who regressed, 363 (94%) were classified as normal at trial completion.

Key Words: child ■ rheumatic heart disease ■ risk

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Several sociodemographic factors were associated with higher risk of progression and increased likelihood of regression. Female participants had 2.6 times higher odds of progression (95% CI, 1.19 to 5.68; *P*=0.016). Those with a higher WAMI index were less likely to progress; the odds of progressing for every 10-point increase in WAMI index was 0.48 (95% CI, 0.38 to 0.88; *P*=0.01). Whereas age was not a factor in progression, children were more likely to regress if they were older at time of diagnosis (OR, 1.05 [95% CI, 1.00 to 1.10]; *P*=0.046). Additional sociodemographic factors including type of school (boarding or day) and family history of RHD were not associated with differential odds of progression or regression (data not shown).

Children with isolated pathologic mitral regurgitation had the lowest odds of progression of all subcategories of latent RHD (OR, 0.07 [95% CI 0.1 to 0.48]; *P*=0.006; Table). The major category of RHD (borderline versus definite) was not associated with progression. However, a diagnosis of definite RHD at study entry was associated with lower odds of regression (OR, 0.63 [95% CI, 0.44 to 0.91]; *P*=0.014).

The results of these subanalyses of the GOAL trial data demonstrated that female participants and those living in less advantaged conditions were at risk for progression of latent RHD. Furthermore, those with isolated pathologic aortic regurgitation and those with both abnormal mitral valve morphology and pathologic mitral regurgitation were more likely to progress. In contrast, participants were more likely to regress if they were older at diagnosis and if they had borderline RHD, as compared with definite RHD.

This study has several limitations. First, the overall low incidence of progression (36 of 799) limits multivariate modeling. Second, the cohort size has limited power to determine differences in progression and regression among subgroups. The risk for conditions with few participants, such as aortic regurgitation, cannot be reliably assessed.

Table. Echocardiographic Risk Factors for Progression and Regression Adjusted for Treatment Arm and Borderline or Definite Disease at Study Entry

Echocardiographic risk factors	Percentage		Odds ratio (95% CI)	*P* value
	With risk factor	Without risk factor		
Progression				
Category of RHD (borderline/definite): ref = definite	6.8	4.0	1.995 (0.92–4.32)	0.080
Subcategory of RHD				
Borderline				
B: Pathologic MR	3.8	18.2	0.07 (0.01–0.48)	0.006
C: Pathologic AI	3.4		0.08 (0.009–0.66)	0.019
Definite				
A: MV morphology and pathologic MR	4.9		0.11 (0.02–0.82)	0.032
C: AV morphology and pathologic AI	25		0.82 (0.07–10.4)	0.879
D. Borderline disease of MV and AV	11		0.30 (0.03–3.18)	0.315
Regression				
Category of RHD (borderline/definite): ref = definite	39.2	50.3	0.63 (0.44–0.91)	0.014
Subcategory of RHD				
Borderline				
B: Pathologic MR	50.6	45.5	1.25 (0.38–4.16)	0.714
C. Pathologic AI	49.4		1.19 (0.34–4.17)	0.791
Definite				
A: MV morphology and pathologic MR	39.3		0.79 (0.23–2.73)	0.706
C: AV morphology and pathologic AI	12.5		0.17 (0.02–1.93)	0.155
D. Borderline disease of MV and AV	50		1.21 (0.27–5.47)	0.801

AI indicates aortic insufficiency; AV, aortic valve; MR, mitral regurgitation; MV, mitral valve; and RHD, rheumatic heart disease.

Improved risk stratification of children at the time of echocardiographic screening could inform SAP strategies at scale. These data begin to unravel level of risk of RHD progression, with both sociodemographic and echocardiographic risk factors incorporated into the analyses. Further work is needed to validate these risk factors across contexts.

ARTICLE INFORMATION

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Disclosures

None.

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