Title: OUTCOMES OF POSSIBLE AND PROBABLE RHEUMATIC FEVER: A COHORT STUDY USING NORTHERN AUSTRALIAN REGISTER DATA, 2013-2019

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Background & Aims: Acute rheumatic fever (ARF) presentations are highly variable in clinical phenotype, severity and clinical outcome. Some presentations appear to be ARF but do not fulfill diagnostic criteria. The practice in Australia is to categorize ARF diagnoses as ‘definite’, ‘probable’ or ‘possible’. The ‘possible’ category was introduced in 2013 to provide a safety net for children likely to benefit from penicillin prophylaxis but not meeting ‘probable’ or ‘definite’ criteria. Our aim was to understand how these categories are being applied, and to compare longitudinal outcomes after a diagnosis of definite, probable or possible ARF.

Methods: We extracted data from the Northern Territory Rheumatic Heart Disease Register (RHD) for Indigenous Australians with an initial diagnosis of definite, probable or possible ARF during a 5.5-year period (01/01/2013 - 30/06/2019). Descriptive statistics were used to describe the demographic and clinical characteristics at initial ARF diagnosis. Kaplan-Meier curves were used to assess the probability of survival free of disease progression. Cumulative incidence risk at each year since initial diagnosis was calculated. Cox proportional hazards regression was used to determine whether time to disease progression differed according to ARF diagnosis and whether progression was associated with specific predictors at diagnosis. A multinomial logistic regression model was performed to assess whether ARF diagnosis was associated with RHD outcome and to assess associations between ARF diagnosis and clinical manifestations. A generalised linear mixed model was developed to assess differences in antibiotic adherence between ARF diagnosis categories and to examine longitudinal trends in antibiotic adherence.

Results: There were 913 initial ARF cases, 732 with normal baseline echocardiography. Of these, 92 (13%) experienced disease progression: definite ARF 61/348 (18%); probable ARF 20/181 (11%); possible ARF 11/203 (5%). The proportion of ARF diagnoses that were uncertain (i.e. possible or probable) increased over time, from 22/78 (28%) in 2013 to 98/193 (51%) in 2018. Cumulative incidence risk of any disease progression at 5.5 years was 33.6 (23.6-46.2) for definite ARF, 13.5 (8.8-20.6) for probable and 11.4% (95% CI 6.0-21.3) for possible ARF. The probability of disease-free survival was lowest for definite ARF and highest for possible ARF (p=0.004). Cox proportional hazards regression indicated that disease progression was 2.19 times more likely in those with definite ARF than those with possible ARF (p=0.026). Progression to RHD was reported in 37/348 (11%) definite ARF, 10/181 (6%) probable ARF, and 5/203 (2%) possible ARF. The multinomial logistic regression model demonstrated a significantly higher risk of progression from no RHD to RHD if the initial diagnosis was definite compared to possible ARF (p<0.001 for both mild and moderate-severe RHD outcomes). The generalised linear mixed model estimated that patients with definite ARF had a significantly higher adherence to antibiotic prophylaxis compared with possible ARF (p=0.024).

Conclusions: These data indicate that the ARF diagnostic categories are being applied appropriately, are capturing more uncertain cases over time, provide a useful way to stratify risk and guide prognosis, and can help inform practice. Possible ARF is not entirely benign; some cases progress to RHD.