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Acute Rheumatic Fever: Recent Advances

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Acute rheumatic fever (ARF) is a delayed autoimmune response to streptococcal A infection resulting in a multisystem inflammatory illness. Cardiac involvement in the acute illness can lead to rheumatic heart disease (RHD). Chronic cardiac valve damage can predispose to heart failure, arrhythmia, stroke and early death.¹ Over the past 50 years, the disease has almost disappeared from high-income countries; however, this devastating illness still remains a major cause of morbidity and early mortality in low- and middle-income countries, driven by socioeconomic factors including household crowding.^{1,2} ARF and its long-term sequelae RHD affect >40 million people

worldwide and account for over 300,000 deaths annually, though the true burden of disease is probably underestimated due to missed diagnoses and under reporting.^{1,2} ARF most commonly affects young people with the highest rates in children 5–14 years old, and almost 80% of new cases occur in people under 25 years old.²

High rates of ARF and RHD are reported in low- and middle-income countries and in high-risk populations including First Nations peoples in high-income countries like Australia and New Zealand.^{2,3} RHD prevalence estimates are generally based on echocardiographic screening studies, but the incidence of ARF is not well understood given variable approaches to notification and surveillance, as well as under-recognition of the diagnosis. The high burden of previously undiagnosed RHD identified on screening suggests that many cases of ARF are neither diagnosed nor treated. In Australia, where ARF is notifiable, the incidence of ARF appears to be increasing, which could be due to improved case detection as well as changes in epidemiology. Age-standardized incidence of ARF in First Nations people in Australia was recently estimated at 71.9 per 100,000 per year, with marked geographic variation.³

This brief review summarizes recent progress in diagnostics, management and prevention of ARF, with reference to the need for further research to address barriers to diagnosis and management of ARF and RHD in RLSs, highlighted by an illustrative case from Timor-Leste.

DIAGNOSIS

Echocardiographic screening demonstrates high rates of previously undiagnosed RHD, suggesting missed opportunities for diagnosis of ARF.³ Recognition of ARF provides an important opportunity for secondary prophylaxis to prevent progression of RHD. Improved diagnostic tools for accurately diagnosing ARF are needed. Current approaches rely on clinical diagnosis of ARF based on criteria first described by Jones in 1944. Clinical diagnosis lacks sensitivity and specificity, resulting in both underdiagnosis and overdiagnosis of ARF. Recent modifications to the Jones Criteria include echocardiographic diagnosis of carditis and different criteria based on underlying population risk,⁴ but there have been no other substantive recent changes to diagnostic approach. Individualized national guidelines routinely include modified Jones criteria appropriate to local epidemiology and diagnostic testing capacity, with 4 examples of regional guidelines from the Asia-Pacific region in the past 8 years (New Zealand 2014, Fiji 2015, Australia 2020 and Timor-Leste 2021).

BIOMARKERS

The poor sensitivity and specificity associated with clinical ARF diagnosis has driven research into alternative diagnostic tools, including biomarkers. Erythrocyte sedimentation rate (ESR) and C-Reactive Protein (CRP) are minor diagnostic criteria, but they lack specificity.

Current research is focused on comprehensive search strategies to identify novel

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biomarker profiles associated with ARF.⁵ Untargeted immune phenotyping, transcriptomic, proteomic and metabolomic profiling in patients with ARF is currently underway, using multiple control groups for comparison with the aim to identify a diagnostic test specific to ARF that could foreseeably be translated into a point-of-care test for use in high-burden settings.⁵ Biomarker research may also identify opportunities for immunomodulatory therapies, targeting the inflammatory pathophysiology of ARF.

ECHOCARDIOGRAPHY

Auscultation is less sensitive than echocardiography for the diagnosis of acute carditis or RHD.⁶ Limited access to echocardiography in low-resource settings is a significant barrier decreasing the sensitivity of ARF and RHD diagnosis. Ongoing research aimed at reducing barriers to access is focused on use of less expensive, handheld equipment; brief training for nonexpert health practitioners; and abbreviated echocardiographic protocols. Research has been conducted predominantly in the context of screening studies, diagnosing latent RHD in asymptomatic children. However, the echocardiographic findings of acute carditis are the same as those used to screen for latent RHD (mitral and/or aortic regurgitation). In settings like Timor-Leste where nonexpert practitioners have been trained, and handheld devices and remote support are available, echocardiographic confirmation of the presence of carditis has enabled diagnoses of ARF and RHD even in extremely remote locations.⁶

CASE STUDY FROM TIMOR-LESTE

A 10-year-old male from a rural area in Timor-Leste presented with fever, polyarthralgia and chest pain, with a recent history of pharyngitis that resolved without treatment. Ibuprofen was prescribed with rapid resolution of arthralgia. Examination revealed a holosystolic murmur in the mitral region and left knee arthritis. ECG, ESR and CRP were not performed, and streptococcal serology is not available. Handheld echocardiography can be performed in Timor-Leste with real-time image sharing and review by remote experts, to support diagnosis and management decisions. In this case, echocardiography confirmed moderate mitral regurgitation, and ARF with carditis was diagnosed.

MANAGEMENT

Management of ARF includes streptococcal A eradication and initiation of secondary prophylaxis, symptomatic management of arthropathy, carditis and chorea

and education of the family. New advances in the medical management of ARF are limited, with no convincing evidence for effective disease modifying treatments.

Nonsteroidal Anti-inflammatory Drugs

High-dose aspirin has been widely used to treat arthritis in ARF; however, the potential for toxicity in children has caused concern and recent guidelines have recommended other nonsteroidal anti-inflammatory agents. Naproxen and ibuprofen have been compared against aspirin in retrospective studies, demonstrating similar time to resolution of symptoms and normalization of inflammatory markers, but with fewer side effects compared with aspirin.⁷

Corticosteroids and Intravenous Immunoglobulin

Corticosteroids are often used for treatment of severe carditis or chorea, but with limited evidence. A meta-analysis including 8 randomized controlled trials found no evidence of benefit from administering steroids; however, there was significant heterogeneity between studies and outcomes were predominantly based on auscultatory findings.⁸ Until further scientific evidence becomes available, expert consensus supports the use of corticosteroids for severe acute or life threatening carditis, particularly where surgical intervention is not indicated or not available.

Intravenous immunoglobulin has been evaluated for the treatment of carditis but did not demonstrate benefit in improving cardiac disease after 1 year of treatment⁸ and is not recommended.

Sydenham Chorea

Sydenham chorea has a broad clinical phenotype ranging from subtle symptoms to chorea paralytica. Pharmacotherapy is indicated for children with a functional impairment, though the evidence to guide this is limited, with no placebo-controlled trials. Valproic acid and carbamazepine have similar efficacy without significant side effects. Successful use of levetiracetam, olanzapine and risperidone has been documented in case reports; however, they require further investigation.⁹ Corticosteroids have also been used in the treatment of severe sydenham chorea. Multiple studies have demonstrated a reduction in the time to remission; however, all are limited by small sample sizes and inconsistent reporting mechanisms. More research is required to determine the benefit of steroids in this population.

Hydroxychloroquine

A small case series including 10 cases of ARF showed that streptococcal A infection

activates persistent interleukin 1 β and granulocyte-macrophage colony-stimulating factor (GM-CSF) production in peripheral mononuclear cells; an effect which may be suppressed by hydroxychloroquine.¹⁰ In 2020, a case series described the use of hydroxychloroquine in 2 cases of ARF with severe carditis who were treated with both corticosteroids and hydroxychloroquine, with effective suppression of inflammatory markers and clinical stabilization, though the specific effect of hydroxychloroquine is unknown.¹⁰ Further research is underway.

Penicillin

Secondary prophylaxis using regular penicillin is essential for prevention of streptococcal A infections and associated ARF recurrence and RHD progression. Recent evidence has demonstrated the effectiveness of secondary prophylaxis for screening-detected latent RHD (borderline and mild definite cases) in addition to its proven role in people who have had ARF.¹¹

However, intermittent BPG injections are painful and poor adherence to treatment risks further streptococcal A infections and recurrent ARF.² There is increased recognition of the need to engage meaningfully with patients, families and communities around improving adherence, but implementation of strategies is complex and challenging.¹²

Occasionally, recurrences can occur despite adherence to 4-weekly prophylaxis,² most likely due to streptococcal A exposure occurring when serum penicillin levels are below 0.02 mg/L. Recent studies have shown that the median duration of adequate penicillin concentration following BPG administration is <14 days, with lower levels observed in obese patients.¹³ Pharmacokinetic studies have observed a longer half-life of BPG if administered subcutaneously rather than intramuscularly.¹⁴ While safety and tolerability data are currently limited, the potential for slow-release subcutaneous delivery of penicillin will be explored further.

PREVENTION

Current strategies for prevention of ARF focus on primary prevention, with prompt antibiotic treatment of streptococcal A pharyngitis and impetigo; and ongoing efforts to effect primordial prevention by addressing underlying social determinants of health, including poverty and household crowding.²

Vaccine Development

Studies searching for a streptococcal A vaccine began in the 1920s; however, the first vaccines were highly reactogenic and did not prevent disease. In the 1960s, newer vaccines were tested; however, safety

concerns related to higher rates of ARF in those vaccinated led to an almost 30-year hiatus in vaccine development.¹ Since 2006, vaccine candidates have included multivalent M protein-based vaccines, M protein vaccines containing conserved repeat epitopes, cell wall carbohydrate vaccines and non-M protein multicomponent vaccines.¹ In 2018, the World Health Organisation published the Group A Streptococcal Vaccine Research and Development Roadmap, and in 2019, a Strep A Vaccine Consortium was formed. There are currently a small number of vaccine candidates under development; however, only one has reached phase II trial.¹ The recent establishment of a streptococcal A pharyngitis human challenge infection model aims to contribute to vaccine development by aiding understanding of streptococcal A pathogenesis and providing a platform for vaccine efficacy studies.¹⁵

CONCLUSION

Elimination of ARF as a public health problem is achievable, but requires community leadership and multisectoral collaboration across health, research, government and nongovernment organizations.² Improved recognition and diagnosis can facilitate access to treatment and secondary prevention. Diagnostic accuracy has been improved by the inclusion of echocardiography to diagnose carditis, and the global use of this is increasing.

Improved penicillin delivery strategies may be on the horizon. Prevention is better than cure, and while an effective vaccine would have a huge impact, addressing underlying socioeconomic risk factors in partnership with affected communities is essential.

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