

Update on acute rheumatic fever

It still exists in remote communities

Sharen Madden MD CCFP FCFP Len Kelly MD MClInSc CCFP FCFP

Acute rheumatic fever (ARF) remains a disease of First Nations residents of northwest Ontario, despite a declining incidence in developed economies. This review article was prompted by 5 unrelated cases seen over 36 months in our regional community hospital. We hope that it will remind physicians working in remote areas of Canada that ARF remains a part of our clinical vocabulary.

Quality of evidence

A literature review was undertaken; we searched MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews from 1996 to 2007 using MeSH terms *rheumatic fever* and *rheumatic heart disease* for articles focusing on prevention, epidemiology, or disease management. The abstracts of 600 papers were read, and 60 key articles (either comprehensive reviews or from established journals) were read in full. Most were reviews, outbreak descriptions, treatment descriptions, or secondary prevention program descriptions (levels II and III evidence). There were no recent randomized controlled trials owing to the known virulence of the illness, and the only level I articles were a meta-analysis and a systematic review. Case series data from medical records at the Sioux Lookout Meno Ya Win Health Centre in Ontario were also used. Ethics approval for the case series was obtained from the Sioux Lookout Meno Ya Win Health Centre Research Review Committee.

Main message

Literature review. Two distinct schools of literature exist for ARF: studies and commentaries from North America and Europe that view rheumatic fever as a rare disease and discuss the limited efficacy of screening for streptococcal sore throat, ARF's presumed precursor; and literature from the developing world and international aboriginal literature that documents a robust discussion of the presentations, epidemiology, and control of rheumatic fever and its sequela, rheumatic heart disease (RHD), which is of ongoing relevance.

In a meta-analysis of antibiotics for the primary prevention of ARF in patients with documented pharyngitis (N=7665), Robertson et al found a protective effect (relative risk 0.32, 95% confidence interval 0.21 to 0.48) for a reduction in risk of almost 70% (level I evidence).¹ Interestingly, inclusion of randomized controlled studies done in the 1950s by the US Army might make such overviews less informative, as they were done in an era of endemic group A streptococcus (GAS) and ARF.¹

This article has been peer reviewed.

Cet article a fait l'objet d'une révision par des pairs.

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Abstract

OBJECTIVE To remind physicians who work with aboriginal populations of the ongoing prevalence of acute rheumatic fever and to review the recent evidence on presentation, treatment, and secondary prophylaxis.

SOURCES OF INFORMATION The Cochrane Database of Systematic Reviews, MEDLINE, and EMBASE were searched from 1996 to 2007 with a focus on prevention, epidemiology, and disease management. Case series data from medical records at the Sioux Lookout Meno Ya Win Health Centre in Ontario were also used.

MAIN MESSAGE Acute rheumatic fever is still a clinical entity in aboriginal communities in northwest Ontario. Identification, treatment, and secondary prophylaxis are necessary.

CONCLUSION Acute rheumatic fever is not a forgotten disease and still exists in remote areas of Canada.

Résumé

OBJECTIF Rappeler au médecin qui travaille avec les populations autochtones que le rhumatisme articulaire aigu est toujours présent, et revoir les données récentes sur son tableau clinique, son traitement et la prophylaxie secondaire.

SOURCES DE L'INFORMATION On a consulté la Cochrane Database of Systematic Reviews, MEDLINE et EMBASE entre 1996 et 2007, en ciblant surtout la prévention, l'épidémiologie et le traitement de cette maladie. On a aussi utilisé les données d'une série de cas du centre de santé Sioux Lookout Meno Ya Win en Ontario.

PRINCIPAL MESSAGE Le rhumatisme articulaire aigu est toujours présent dans les communautés autochtones du nord-ouest de l'Ontario. Détection, traitement et prophylaxie secondaire sont nécessaires.

CONCLUSION Le rhumatisme articulaire aigu n'est pas une maladie oubliée et il existe toujours dans les régions reculées du Canada.

A Cochrane review by Del Mar et al looked at the benefit of antibiotics for sore throats (N=2835) and found that they reduced ARF by more than two-thirds (relative risk 0.22, 95% confidence interval 0.02 to 2.08), although in developed societies most patients would derive no benefit given the low incidence of ARF (level I evidence).²

Natural history. Repeated GAS infections are thought to occur and prime the immune response before the first episode of ARF.³ Symptoms of arthritis, carditis, erythema marginatum, subcutaneous nodules, or chorea usually present 1 to 3 weeks after GAS pharyngitis (level II evidence).⁴ In recent outbreaks in the United States, affected patients reported only mild pharyngitis, for which only a few sought medical attention (level II evidence).^{4,5} The subsequent outcome, RHD, might be the first presentation: 46% of RHD patients in the Northern Territory of Australia, for example, had no known prior diagnosis of ARF (level II evidence).⁶

Risk factors are poorly understood but likely include host factors such as susceptibility to the immune response to GAS (limited to 3% to 6% of the population); housing and overcrowding remain important considerations (level III evidence).^{2,7} The Jones criteria, established in 1944, were revised in 1965 and 1984, then updated in 1992 and 2002 to provide diagnostic guidelines for clinical diagnosis.⁸⁻¹⁰ They require 2 major or 1 major and 2 minor criteria and evidence of prior streptococcal infection (throat culture positive for the bacteria, positive rapid antigen detection test results, or elevated antistreptolysin O titre [ASOT]). Major and minor criteria are outlined in **Box 1**. Echocardiogram is not part of the criteria but is often part of the cardiac workup.

Disease frequency. In Canada ARF is not a reportable disease. Available data place Canadian, American, and Western European incidences at 0.1 to 2 cases per 100 000 persons (level II evidence).^{11,12} Isolated cases can occur anywhere from time to time. A series of 3 cases in Nova Scotia was reported in 1998 (level II evidence).^{13,14} Another 3 cases were reported in a UK teaching centre during a 6-month period in 2000 (level II evidence).¹⁵

Acute rheumatic fever is now generally seen as a disease of “emerging economies,” indigenous communities,

Box 1. Jones criteria for diagnosing acute rheumatic fever: *Diagnosis requires 2 major, or 1 major and 2 minor, criteria and evidence of streptococcal infection or chorea alone.*

Major criteria

- Carditis—tissue inflammation or new changing murmur
- Polyarthritis—migratory pain in limb joints
- Chorea—abrupt, purposeless movements with or without emotional changes
- Erythema marginatum—nonpruritic rash, spares face
- Subcutaneous nodules—painless, firm, on bones or tendons

Minor criteria

- Fever
- Arthralgia
- Previous acute rheumatic fever or rheumatic heart disease
- Acute-phase reactants—erythrocyte sedimentation rate, C-reactive protein, leukocytosis
- Electrocardiogram—prolonged PR interval

Evidence of streptococcal infection

- Throat culture positive for the bacteria
- Positive rapid antigen detection test results
- Elevated antistreptolysin O titre
- Scarlet fever

and tropical regions, with incidences in these settings of 10 to 20 cases per 100 000 persons (level II evidence).¹² Hot spots, such as Northern Australia, have rates of more than 50 cases per 100 000 persons (level II evidence).¹⁶ According to W. De Groote, MD, among aboriginal children presenting to a Winnipeg, Man, referral centre serving northwest Ontario and Manitoba, ARF remains the most common underlying cause of cardiac murmurs (level III evidence) (written communication, March 2008). Despite this, no association with ethnicity has been identified in the literature (level III evidence).³

Changing epidemiology of GAS infections. Only rheumatogenic strains of GAS result in ARF (level II evidence).¹⁷ The endemic strains seen during World War II had particularly high ARF rates (3%).¹⁷ By the 1970s those streptococcus M antigen serotypes (which confer resistance to phagocytosis) had virtually disappeared in North America, although there was little change in the rate of endemic streptococcal sore throat (level II evidence).⁴ Lower incidence of ARF had more to do with changes in virulence and improvement in socioeconomic conditions than with use of antibiotics (level II evidence).⁴

By the 1980s a resurgence of the streptococcus M antigen subtype 5M occurred, along with outbreak reports in Utah and Colorado identifying more than 30 cases annually (level II evidence).⁵ The epidemiology of ARF in aboriginal communities in Australia challenges the historical belief that streptococcal skin infections cannot cause the disease. In these communities pyoderma is the most common manifestation of GAS, and

Levels of evidence

Level I: At least one properly conducted randomized controlled trial, systematic review, or meta-analysis

Level II: Other comparison trials, non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than one study

Level III: Expert opinion or consensus statements

typical rheumatic strains are not present (level II evidence).¹⁸ Researchers postulate that even non-GAS infections (eg, group C and G streptococci) might play a role in these high-incidence settings and note that the high rates seen among Australian aboriginal children parallel overcrowding and poor living conditions.¹⁹

Changing presentation of ARF. Acute rheumatic fever is a clinical diagnosis for which presentations are highly variable (level III evidence).²⁰ Rheumatic carditis is associated with the murmurs of valvulitis and is more common in children; arthritis predominates in adults (level II evidence).²¹ In the Utah outbreak of the 1980s, carditis was seen in 80% of patients, arthritis in 70% of patients, and chorea in 28% of patients (level II evidence).²² The arthritis is migratory, with pain often worse than physical findings would suggest; any one site might resolve within 2 to 5 days (level II evidence).²³ Chorea occurring alone meets the Jones criteria and typically presents 2 to 6 months after the initial infection as purposeless movements of the extremities, dysphonia, and possible emotional lability.²⁰

Disease-related murmurs are most often caused by mitral insufficiency; aortic insufficiency is the second most common disease-related cause (level II evidence).¹⁵ Silent carditis is sometimes found during echocardiography (7% to 47% of cases).¹⁵ Mitral stenosis is a delayed complication with increasing age (level II evidence).⁷ There is a natural improvement of the carditis over several years, in the absence of ARF recurrences, with more than 65% of patients demonstrating resolution or improvement (level II evidence).⁵ Disease recurrence, however, increases long-term risk and the degree of valvular damage.⁵ Erythema marginatum and subcutaneous nodules are both infrequent, occurring in less than 5% of presentations (level II evidence).⁷

Investigations. Investigations are useful mainly to confirm the existence of prior streptococcal infection by elevated ASOT, to check for ongoing pharyngeal GAS infection, and to assess erythrocyte sedimentation rate. Echocardiography is not part of the diagnostic criteria, but is generally done as part of the initial workup to clarify cardiac involvement.

Prevention, treatment, and prophylaxis. Most cases of ARF can be prevented by antibiotic treatment received within 9 days of GAS pharyngitis (level II evidence).²⁴ After onset of ARF there is no effective treatment for the immune reaction. Salicylates and antibiotics for any current GAS infection remain the cornerstone for treating most cases (level II evidence).²⁵ Salicylates give relief from fever and arthritis. They have no role in the treatment of carditis, which is addressed with bed rest (level II evidence).¹ Prednisone is not useful for arthritis but it is the drug of choice for those patients who experience chorea (level II evidence)¹ (Box 2).

Box 2. Treatment of acute rheumatic fever

Bed rest—for carditis

Anti-inflammatories—acetylsalicylic acid for fever and joint pain and inflammation; steroids for chorea

Antibiotics—penicillin; erythromycin for patients allergic to penicillin

Secondary prophylaxis for prevention of new GAS pharyngitis is warranted for all patients, as there is an 8% to 10% recurrence rate of ARF within 5 years—with an attendant increase in cardiac involvement (level II evidence).¹⁵ Oral regimens can be used, but the treatment of choice remains intramuscular benzathine penicillin injections given monthly for 5 years, until adulthood, or for longer, depending on the severity of RHD or the existence of frequent ARF in the community.²⁶

No vaccine currently exists, although development of a multivalent streptococcal M antigen vaccine is under way.⁴

Disease in northwest Ontario. Our observation of 5 unrelated ARF cases out of 60 000 patient-years gives an incidence rate of 8.33 cases per 100 000 persons. This is a much higher rate than generally reported for developed countries (0.1 to 2 cases per 100 000), but lower than rates seen in some indigenous communities of Australia. Our rate of cultures positive for streptococcus was in keeping with other general population studies (about 25%), and there was a correlation between the peak months of streptococcal throat infections and the timing of ARF presentations (level I evidence).²⁷

Presentations were generally similar to those reported in the literature. We saw arthritis in 40% of cases and joint symptoms in 60% overall (literature shows up to 80%). Chorea was prominent as a presenting symptom, seen in 2 of 5 of cases (40%); both patients were female. The literature documents the increasing presence of chorea and a nonclassic oligoarthritis that does not respond to acetylsalicylic acid (level II evidence).^{7,24,26} Each of the rare manifestations (erythema marginatum and subcutaneous nodules) was found in at least 1 patient.

Our cases differed in that cardiac presentations were seen in 4 of 5 cases (literature suggests 40%). Echocardiography documented valvular cardiac involvement in 3 cases and an innocent murmur in a fourth case. The ASOT was positive in all cases, and the erythrocyte sedimentation rate was elevated in 4 of 5 cases, consistent with literature rates of 80% or higher.

Conclusion

A low but substantial rate of ARF is present in the First Nations population of northwest Ontario. A Cochrane review recognizes its presence in “emerging economies,” implicating socioeconomic factors. Physicians would

be well served to consider ARF when arthritic, cardiac, choreiform, or other Jones criteria symptoms occur and to assess for possible history of GAS infection by measuring ASOT.

The rationale for disease identification and secondary prophylaxis is 2-fold. Valvular damage from an acute attack can be minimized, and those with 1 episode of ARF have an increased susceptibility to recurrence, which is associated with greater cardiac involvement. ✱

Dr Madden is an Assistant Professor and Dr Kelly is an Associate Professor in the Division of Clinical Sciences at the Northern Ontario School of Medicine in Sioux Lookout, Ont.

Contributors

Dr Madden and Kelly contributed to the literature review, selection and review of studies, and preparation of the manuscript for publication.

Competing interests

None declared

Correspondence

Dr S. Madden, Northern Ontario School of Medicine, Box 489, Sioux Lookout, ON P8T 1A8; e-mail smadden@slmh.on.ca

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EDITOR'S KEY POINTS

- Although acute rheumatic fever (ARF) is relatively rare in developed economies, it is much more common in the developing world and among aboriginal populations. Higher rates of ARF might be related to overcrowded and poor living conditions.
- Diagnosis requires 2 major, or 1 major and 2 minor, Jones criteria, as well as evidence of previous streptococcal infection. Major criteria include carditis, polyarthritits, chorea, erythema marginatum, and subcutaneous nodules; minor criteria include fever, arthralgia, previous ARF or rheumatic heart disease, acute-phase reactants, and prolonged PR interval on electrocardiogram.
- Most cases of ARF can be prevented with antibiotic treatment received within 9 days of group A streptococcal pharyngitis. After onset of ARF there is no effective treatment for the immune reaction. Salicylates provide relief from fever and arthritis, prednisone can be used for patients who experience chorea, and carditis is addressed with bed rest. Secondary prophylaxis to prevent recurrence is warranted for all patients.

POINTS DE REPÈRE DU RÉDACTEUR

- Même si rhumatisme articulaire aigu (RAA) est relativement rare dans les économies développées, il est beaucoup plus fréquent dans les régions en voie de développement et chez les populations autochtones. Des taux plus élevés de RAA pourraient être reliés à la promiscuité et aux mauvaises conditions de vie.
- Le diagnostic requiert 2 critères de Jones majeurs ou 1 majeur et 2 mineurs, en plus d'une preuve d'infection antérieure au streptocoque. Les critères majeurs incluent: cardite, polyarthrite, chorée, érythème marginé et nodules sous-cutanés; les critères mineurs comprennent: fièvre, arthralgie, RAA ou cardite rhumatismale antérieurs, réactants de phase aiguë et prolongation de l'espace PR à l'électrocardiogramme.
- La plupart des cas de RAA peuvent être prévenus par un traitement antibiotique administré moins de 9 jours après une pharyngite à streptocoque du groupe A. Une fois le RAA installé, il n'y a pas de traitement efficace contre la réaction immunitaire. Les salicylates procurent un soulagement de la fièvre et de l'arthrite, la prednisone peut être utilisée chez les patients qui présentent une chorée, et la cardite se traite par le repos au lit. La prophylaxie secondaire pour prévenir les récurrences est indiquée pour tous les patients.

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