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# ACUTE RHEUMATIC FEVER: CURRENT DIAGNOSTIC AND THERAPEUTIC CONSIDERATIONS

## Summary

This paper describes the current views on the diagnosis, treatment and prophylaxis of acute rheumatic fever, based on the principles of the latest guidelines of the World Health Organization and other leading scientific societies, including the American Heart Association and the World Heart Federation.

## Keywords

Acute rheumatic fever, revised Jones criteria, Doppler echocardiography, treatment, prophylaxis.

Rheumatic fever is a systemic inflammatory disease of connective tissue with predominant process localization in the cardiovascular system and frequent lesions of several organs and systems, including joints. It usually develops in conjunction with acute infection, caused by group A  $\beta$ -hemolytic Streptococci (GABHS), in individuals with a susceptibility to the disease, mainly in children and adolescents, as a result of autoimmune response to the Streptococcus epitope and cross-reactivity with similar epitopes of human tissues [2, 5, 8-10, 15, 37].

**Epidemiology.** Acute rheumatic fever (ARF) can occur at any age, although it is usually diagnosed in children 5 to 15 years old. Nowadays ARF is fairly rare in developed countries, but in low and middle-income countries and in selected indigenous populations it continues to be a major cause of mortality and morbidity [12, 29, 38]. The general decline in ARF incidence can be attributed to the earlier recognition in ARF, the more widespread use of appropriate antibiotics for GABHS, and improved living conditions [21, 28]. Its incidence rate in 2011 in Ukraine was 1 per 100 thousand, prevalence rate was 3 per 100 thousand children 0-14 years old [3].

**Etiology.** ARF develops after episodes of tonsillitis or pharyngitis caused by «rheumatogenic» strains of GABHS ( $M_1, M_3, M_5, M_6, M_{14}, M_{18}, M_{19}, M_{24}, M_{27}, M_{29}$ ), which are characterized by high contagiousness, and associated with genetically conditioned features of M-protein structure. In patients' families disease occurs three times more often than in a whole population. It was found that specific alloantigen of B-lymphocytes determines genetic susceptibility to the disease [1, 3, 10, 16, 20, 24, 25].

In the **pathogenesis** of ARF the main role belongs to GABHS that produces rheumatic antigens and starts processes of immune inflammation in human

body with disease susceptibility. The role of human leukocyte antigen (HLA) alleles is very important in ARF susceptibility, and HLA-DR7 is the most frequently associated with ARF. Molecular mimicry explains the triggering of ARF, but an intense and sustained inflammation is needed to cause sequels [14, 17, 19, 36].

**Classification** of ARF is presented in Table 1 [6].

**Clinical features.** Typically, ARF starts within 1-3 weeks after streptococcal tonsillitis or pharyngitis. There are 3 periods of the rheumatic process.

*The first period* (1-3 weeks) is usually characterized by asymptomatic course of the disease or slight malaise, arthralgia; nosebleed, pallor of skin, low-grade fever, increased erythrocyte sedimentation rate (ESR) and anti-streptococcal antibodies titres (antistreptolysin O, antistreptokinase, antihyaluronidase, antideoxyribonuclease-B) can be observed, electrocardiographic (ECG) changes may be presented as well.

*The second period* is characterized by polyarthritides or arthralgia, carditis, lesions of several organs and systems, changes in laboratory, biochemical and immunochemical parameters, mucoid swelling or fibroid disorders.

*The third period* is a period of various clinical signs of the recurrent rheumatic fever with latent and continuously recurrent forms of disease [9, 15].

**Table 1. 2004 Ukrainian Association of Rheumatologists clinical classification of ARF**

| Clinical manifestations                                                 |                                                   | Activity of the process                                                        | Consequence                                          | Heart failure                                                               |                                                                         |
|-------------------------------------------------------------------------|---------------------------------------------------|--------------------------------------------------------------------------------|------------------------------------------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Major                                                                   | Minor                                             |                                                                                |                                                      | Stage                                                                       | NYHA functional class                                                   |
| carditis; arthritis; chorea; erythema marginatum; subcutaneous nodules. | fever; arthralgia; abdominal syndrome; serositis. | 3 <sup>rd</sup> (high); 2 <sup>nd</sup> (moderate); 1 <sup>st</sup> (minimal). | without heart defects; with heart defects; recovery. | 1 <sup>st</sup> ; 2 <sup>nd</sup> -A; 2 <sup>nd</sup> -B; 3 <sup>rd</sup> . | 1 <sup>st</sup> ; 2 <sup>nd</sup> ; 3 <sup>rd</sup> ; 4 <sup>th</sup> . |

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The first attack of rheumatic fever starts with increase in body temperature to sub-febrile or febrile (38-40 °C), chills and sharp pain in joints. Due to arthritis patient can be immobilized. Dyspnea appears as a result of heart involvement [27, 39].

**Rheumatic polyarthritis** is characterized by migration of inflammatory joints lesions, often symmetrical involvement of joints and complete regression of inflammatory changes in joints during 2-3 weeks or several days after nonsteroidal anti-inflammatory drugs (NSAIDs) administration [5, 7, 37, 41].

*Clinical features of rheumatic arthritis:*

- chronological relationship with acute streptococcal infection;
- develops more often in the case of primary rheumatic fever than recurrent disease;
- mainly large joint are affected;
- multiple joint lesions;
- migrating arthritis;
- acute or subacute inflammation;
- immediate effect after NSAIDs administration (during 3-5 days).

The most common **skin lesions** are erythema marginatum (4-5% among all age groups) and rheumatic nodules (0,5-1%).

*Erythema marginatum* (Fig.) is the pink annular elements which are located mostly on the inner area of upper and lower extremities, on the abdomen, neck and trunk, not accompanied by itching, not rising upon skin, paling after pressure, not living after it pigmentation, exfoliation, atrophic changes.

*Subcutaneous nodules* are tight, slow-movable, painless formation, sized from millet grain to beans that are located on the extensor surface of the elbow, knee, metacarpophalangeal joints, in the area of ankle, spinous process of the vertebrae, occiput, etc. Rheumatic nodules are observed only in children



**Fig. Erythema marginatum in patient with ARF**

(1-3%), usually during the first attack of ARF and disappear after 2-4 weeks after disease onset [4, 10].

All layers of **heart** (myocardium, endocardium, and pericardium) may be involved in pathological process. Patients complain of shortness of breath during exercise and at rest, palpitations, chest pain. During physical examination tachycardia is observed that does not match the body temperature, moderate hypotension, a significant expansion of percussion border of the heart to the left or in all directions. Auscultation reveals a significant suppression of heart sounds, weakening of the 1<sup>st</sup> tone, pathological 3<sup>rd</sup> and 4<sup>th</sup> tones with development of gallop rhythm. On the ECG there is dysfunction of excitability and repolarization processes, slowing of atrioventricular conduction, extension of electrical systole and changing of atrial complex.

The main criterion of rheumatic carditis is *valvulitis*, reliable signs of which are new murmurs in normal sized heart, or change of typical existing sound. Valve apparatus is involved in the pathological process, that leads to the heart defects development, often mitral. Heart defect after first attack of ARF forms in 30% of patients. It is usually forming during 3-12 months after ARF onset. Mitral regurgitation may develop in 3,5 months, aortic — 4,5 months [4, 34, 40].

If severe rheumatic carditis is present, it is possible to auscultate pericardial fremitus, to find expanding borders and signs of pericarditis on X-ray.

*Recurrent rheumatic carditis* usually occurs in adults (90-93%) and adolescents, rarely in children with secondary ARF on the background of cardio-sclerosis and heart defects. That is why secondary rheumatic carditis leads to the complication of heart defects or to the formation of allied and combined heart defects.

Among **vascular lesions** the most common are vasculitis due to the increase of vascular permeability and the deposition of immune complexes in the walls of capillaries and arterioles. Rheumatic arteritis of internal organs lead to the development of rheumatic visceritis (nephritis, meningitis, encephalitis, etc.).

**Rheumatic chorea** develops in 12-15% of children, it is more frequent among adolescents (25%), mostly among girls, and is caused by involving of various brain structures into the pathological process. For chorea pentad of symptoms is typical: hyperkinesia, muscular dystonia, disorders in statics and coordination, vascular dystonia, psychiatric disorders. These symptoms become more severe during disturbance and stop during sleep [7, 9].

**Rheumatic polyserositis** is a damage of serous membranes observed in the case of severe ARF. It manifests as pericarditis, pleuritis and peritonitis.

*Rheumatic pericarditis* occurs on the background of damage of other heart membranes (pancarditis). It has a favorable course and due to antirheumatic therapy exudate quickly resolves. Possible result of

rheumatic pericarditis could be minor adhesions between pericardial leaves, however complete their merger, development of adherent pericarditis, heart rupture does not occur. This feature distinguishes rheumatic pericarditis from bacterial one and tuberculosis [2, 15, 33].

**Rheumatic pleuritis** (it is more often bilateral) is characterized by rapid reverse course after antirheumatic therapy.

**Rheumatic peritonitis (abdominal syndrome)** is rare manifestation, observed mostly in childhood, in the case of severe rheumatic attack. Its characteristic feature is diffuse migratory abdominal pain. Typically, abdominal syndrome is combined with other signs of rheumatic fever.

**Lung manifestations** of ARF are rheumatic pneumonia and lung vasculitis. Rheumatic lung lesion develops mainly among children with pancarditis, is characterized by its resistance to the antibacterial therapy and positive effect of antirheumatic treatment [41].

Usually in the case of **kidney involvement** reverse nephritis develops. It is characterized by insignificant protein- and hematuria. Chronic glomerulonephritis or nephrotic syndrome among patients with ARF is rare.

**Diagnosis.** Criteria for the diagnosis of ARF are listed in Table 2 [32].

**Table 2. Revised Jones Criteria (AHA, 2015)**

| A. For all patient populations with evidence of preceding GABHS infection                                                                                                                                               |                                                                                                                                                                                                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Diagnosis: initial ARF                                                                                                                                                                                                  | 2 major<br>or<br>1 major + 2 minor                                                                                                                                                                    |
| Diagnosis: recurrent ARF                                                                                                                                                                                                | 2 major<br>or<br>1 major + 2 minor<br>or<br>3 minor                                                                                                                                                   |
| B. Major criteria                                                                                                                                                                                                       |                                                                                                                                                                                                       |
| Low-risk populations*                                                                                                                                                                                                   | Moderate- and high-risk populations                                                                                                                                                                   |
| carditis (clinical and/or subclinical);<br>arthritis (polyarthritis only);<br>chorea;<br>erythema marginatum;<br>subcutaneous nodules.                                                                                  | carditis (clinical and/or subclinical);<br>arthritis (monoarthritis or polyarthritis);<br>polyarthralgia;<br>chorea;<br>erythema marginatum;<br>subcutaneous nodules.                                 |
| C. Minor criteria                                                                                                                                                                                                       |                                                                                                                                                                                                       |
| Low-risk populations*                                                                                                                                                                                                   | Moderate- and high-risk populations                                                                                                                                                                   |
| polyarthralgia;<br>fever ( $>38,5^{\circ}\text{C}$ );<br>ESR $>60$ mm in the first hour and/or CRP $>3,0$ mg/dL;<br>prolonged PR interval, after accounting for age variability (unless carditis is a major criterion). | monoarthralgia;<br>fever ( $>38^{\circ}\text{C}$ );<br>ESR $>30$ mm/h and/or CRP $>3,0$ mg/dL;<br>prolonged PR interval, after accounting for age variability (unless carditis is a major criterion). |

\* Low-risk populations are those with ARF incidence  $<2$  per 100000 school-aged children (usually 5-14 years old) or all-age rheumatic heart disease prevalence of  $<1$  per 1000 population per year.

**Laboratory tests.** In the case of acute onset of disease since the first days increase in ESR, high levels of fibrinogen and C-reactive protein (CRP) are observed that often takes place over a long time after the disappearance of clinical signs of ARF. Study of protein spectrum of blood serum reveals  $\alpha_2$ -hyperglobulinemia, but in the case of chronization of the process it reveals  $\gamma$ -hyperglobulinemia as well [2-5, 18, 33, 41].

Other diseases may closely resemble ARF, that's why laboratory evidence of antecedent GABHS infection is needed whenever possible, and the diagnosis is in doubt when such evidence is not available. Any one of the following can serve as evidence of preceding infection:

- increased or rising streptococcal antibodies titer (a rise in titer is better evidence than a single titer result);
- a positive throat culture for GABHS;
- a positive rapid group A streptococcal carbohydrate antigen test in a child whose clinical presentation suggests a high pretest probability of streptococcal pharyngitis [30].

Urinalysis sometimes allows defining minimal proteinuria or microhematuria.

**ECG** is used to clarify the nature of heart rhythm and conduction disorders.

**Echocardiography** (EchoCG) is a tool to diagnose cardiac involvement in ARF. A lot of studies have reported EchoCG/Doppler evidence (Table 3) of mitral or aortic valve regurgitation in patients with ARF despite the absence of classic auscultatory findings [22, 23, 31, 32, 35, 43].

2015 Scientific Statement from the American Heart Association (AHA) concludes that EchoCG with

**Table 3. EchoCG/Doppler findings in rheumatic valvulitis**

| Morphological findings on EchoCG in rheumatic valvulitis |                                                           |                                                                                                                                                                                                                                |
|----------------------------------------------------------|-----------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1.                                                       | Acute mitral valve changes                                | annular dilation;<br>chordal elongation;<br>chordal rupture resulting in flail leaflet with severe mitral regurgitation;<br>anterior (or less commonly posterior) leaflet tip prolapse;<br>beading/nodularity of leaflet tips. |
| 2.                                                       | Chronic mitral valve changes (not seen in acute carditis) | leaflet thickening;<br>chordal thickening and fusion;<br>restricted leaflet motion;<br>calcification.                                                                                                                          |
| 3.                                                       | Aortic valve changes in either acute or chronic carditis  | irregular or focal leaflet thickening;<br>coaptation defect;<br>restricted leaflet motion;<br>leaflet prolapse.                                                                                                                |
| Doppler findings in rheumatic valvulitis                 |                                                           |                                                                                                                                                                                                                                |
| 1.                                                       | Pathological mitral regurgitation (all 4 criteria met)    | seen in at least 2 views;<br>jet length $\geq 2$ cm in at least 1 view;<br>peak velocity $>3$ m/s;<br>pansystolic jet in at least 1 envelope.                                                                                  |
| 2.                                                       | Pathological aortic regurgitation (all 4 criteria met)    | seen in at least 2 views;<br>jet length $\geq 1$ cm in at least 1 view;<br>peak velocity $>3$ m/s;<br>pandistolic jet in at least 1 envelope.                                                                                  |

Doppler should be performed in all cases of confirmed and suspected ARF; in any patient with diagnosed or suspected ARF even if documented carditis is not present on diagnosis; to assess whether carditis is present in the absence of auscultatory findings, particularly in moderate- to high-risk populations and when ARF is considered likely [32].

**Chest radiography** is useful in assessing cardiac size. Pericarditis, pulmonary oedema and increased pulmonary vascularity are other findings which may be seen.

**Radionuclide imaging** has been used successfully to identify rheumatic carditis by non-invasive means, but there is not enough experience with such methods to allow them to be used for the routine diagnosis of ARF.

**Endomyocardial biopsy.** On histologic examination, the only pathognomonic feature of rheumatic carditis is the Aschoff nodule. A series evaluating the utility of endomyocardial biopsy found Aschoff nodules in only 27% of the patients with clinically documented carditis according to the revised Jones criteria. Nonspecific myocyte or interstitial alterations may occur in most patients with clinically definite rheumatic carditis and be absent in those with clinically inactive disease. On the basis of these data, routine endomyocardial biopsy for the diagnosis of rheumatic carditis cannot be recommended [40].

**Differential diagnosis.** It is important to have a differential diagnosis when considering each of the major criteria in the diagnosis of rheumatic fever. Alternative diagnoses we should consider in the evaluation of patients with arthritis (septic arthritis, connective tissue and other autoimmune diseases, viral arthropathy, Lyme disease, gout, reactive arthritis, etc.), carditis (physiological mitral regurgitation, mitral valve prolapse, fibroelastoma, congenital mitral or aortic valve disease, infective endocarditis, viral or idiopathic myocarditis, Kawasaki disease, etc.) or chorea (drug intoxication, Wilson disease, encephalitis, familial chorea, intracranial tumor, Lyme disease, antiphospholipid antibody syndrome, systemic lupus erythematosus, systemic vasculitis, etc.) [4, 9, 32].

**Treatment.** Nowadays in Ukraine we use the staged scheme of treatment: the 1<sup>st</sup> stage lasts for 4-6 weeks of in-patient treatment in active phase; the 2<sup>nd</sup> stage is a sanatorium or sanatorium-resort treatment after in-patient treatment, the 3<sup>rd</sup> stage is a dispensary observation in out-patient clinics [2].

During the first 3 weeks bed rest should be recommended, because carditis, if not already present, may appear during this period. Patients with polyarthritis only, are usually asymptomatic by the 2<sup>nd</sup> or 3<sup>rd</sup> week of salicylate therapy and may then be gradually ambulated while continuing treatment.

**Diet.** Pevsner diet table № 10 should be recommended. Food must contain proteins not less than 1 g/kg of weight, salt — up to 3-6 g daily, including great amount of fruits and vegetables with vitamin C.

**Pharmacological treatment.** Antibiotics with sensitivity to GABHS, NSAIDs, glucocorticoids, aminoquinoline should be recommended. Choice of optimal doses of drugs depends on patient's condition, level of activity and clinical features of ARF [7, 18].

**Antimicrobial therapy** is used for liquidation of the focus of streptococcal infection from the nasal pharynx. Therapy should be started from the course of benzathine benzylpenicillin at 1,2 mln U daily in intramuscular injections. In absence of risk factors it is possible to use oral penicillins for 10 days (phenoxymethylpenicillin — 0,5 g twice daily, amoxicillin — 1,0 g daily), cephalosporins of the 1<sup>st</sup> or the 2<sup>nd</sup> generations.

In the case of intolerance to the penicillins macrolides should be recommended for usage *per os* (eg, azithromycin (first day — 0,5 g, further — 0,25 g daily during 5 days)) (Table 4) [2, 5, 7, 27, 30, 33].

**Table 4. Initial treatment of GABHS pharyngitis (AHA, 2009)**

| Antibiotic                     | Dose                                 | Mode of administration | Frequency   | Duration     |
|--------------------------------|--------------------------------------|------------------------|-------------|--------------|
| Benzathine benzylpenicillin    | 1,2 mln U                            | Intramuscular          | One time    | Acutely only |
| Penicillin V                   | 500 mg                               | Oral                   | Twice daily | 10 days      |
| Amoxicillin                    | 1000 mg                              | Oral                   | Daily       | 10 days      |
| Penicillin Allergic            |                                      |                        |             |              |
| Narrow-spectrum cephalosporins | Varies by drug                       |                        |             | 10 days      |
| Clindamycin                    | 300 mg                               | Oral                   | Twice daily | 10 days      |
| Azithromycin                   | 500 mg (day 1),<br>250 mg (days 2-5) | Oral                   | Daily       | 5 days       |
| Clarithromycin                 | 250 mg                               | Oral                   | Twice daily | 10 days      |

**NSAIDs** are prescribed in the case of rheumatic arthritis, chorea and carditis of mild and moderate severity, minimal and moderate activity, subacute, lingering and latent courses. Total duration of anti-inflammatory therapy should be 9-12 weeks [13].

**Glucocorticoids** are used in severe cases, when carditis is life-dangerous, in maximal, sometimes in moderate degree of process activity. Usually prednisone is used, but in the case of rheumatic carditis with heart defect triamcinolone should be prescribed. Prednisone is administered at an initial dose of 0,7-0,8 mg/kg (max — 1 mg/kg), usually not more than 20-30 mg daily. Therapeutic dose is recommended for 2 weeks, then it should be reduced by 2,5 mg in 5-7 days to the dechallenge [2, 5, 8].

**Aminoquinolines** are used in the case of lingering, continuously relapsing course of rheumatic fever. Chloroquine is administered at a dose of 0,25 g twice daily, hydroxychloroquine — 0,2 twice daily for 1 month, then 1 tablet at night for 6-12 months, sometimes for 2 years [26].

**Prophylaxis.** The World Health Organization (WHO) experts conclude that a proper primary and secondary prevention programs are both cost effective.

tive and inexpensive and hence reduce the burden of disease.

**Primary prophylaxis** is nonspecific and includes general healthy events for increasing of natural immunity (training, organization of healthy living conditions, physical activity); sanitary-and-hygienic events aimed to the prophylaxis of streptococcal infection, especially in children; adequate treatment of acute respiratory diseases (tonsillitis and pharyngitis) caused by GABHS.

When pharmacotherapy is non-effective, tonsillectomy is performed in sub-acute period, not earlier than in 2-2,5 months after the onset of disease. Vaccination containing M-protein epitopes of rheumatogenic GABHS and not participating in the cross-reactions with antigens tissues of the organism might be an effective measure for primary prophylaxis (especially among patients with genetic markers of susceptibility to ARF) [33].

**Secondary prophylaxis** is aimed to the prevention of relapses in patients with episodes of ARF by regular usage of antibiotics listed in Table 5 [30, 33].

Penicillin prophylaxis for recurrent attacks of ARF must be continued also during pregnancy. There is no evidence of teratogenicity associated with benzathine benzylpenicillin. The sulfa drugs are not recommended because of the potential risk to the fetus [33, 42].

**Table 5. Secondary prophylaxis regimen for patients with documented ARF (WHO, 2004; AHA, 2009)**

| Antibiotic                  | Dose      | Mode of administration | Frequency          |
|-----------------------------|-----------|------------------------|--------------------|
| Benzathine benzylpenicillin | 1,2 mln U | Intramuscular          | Every 3 to 4 weeks |
| Penicillin V                | 250 mg    | Oral                   | Twice daily        |
| Erythromycin                | 250 mg    | Oral                   | Twice daily        |
| Sulfadiazine                | 1 g       | Oral                   | Daily              |
| Sulfisoxazole               | 1 g       | Oral                   | Daily              |

Duration of secondary prophylaxis should be recommended with individual approach to each patient (Table 6) [11, 30].

**Current prophylaxis** must be performed in all patients that had an episode of ARF and have undercurrent infectious diseases and small operations (tooth extractions, abortion, tonsillectomy etc.) for 10 days and should include administering of antibacterial drugs to which streptococci are sensitive [39].

**Prognosis** in ARF depends on severity of rheumatic carditis and its susceptibility to recurrence, adequate treatment, regularity of prophylaxis.

Direct threat to life due to ARF is absent (except very rare cases of pancarditis in childhood). Mainly prognosis is determined by heart condition (presence and severity of heart defect, stage of heart failure).

Typically, adults die from heart failure after formed heart defects, rarely — due to the thrombotic complications. Death in acute period occurs very rare (mostly among children, from diffuse myocarditis or acute meningoencephalitis).

Prognosis becomes worse in the case of early onset of ARF. If person get sick in the age after 25 years old, heart disease is less severe, heart defects are forming rare, course of ARF is more favorable [2, 9, 41].

**Table 6. Duration of ARF secondary prophylaxis (AHA, 2009; AHA/ACC, 2014)**

| Category of patients                                                                   | Duration of after last attack                                                           |
|----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| Rheumatic fever without carditis                                                       | 5 years or until 21 years of age (whichever is longer)                                  |
| Rheumatic fever with carditis but no residual heart disease (no valvular disease)      | 10 years or until 21 years of age (whichever is longer)                                 |
| Rheumatic fever with carditis and residual heart disease (persistent valvular disease) | 10 years or until 40 years of age (whichever is longer), sometimes lifelong prophylaxis |

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## ГОСТРА РЕВМАТИЧНА ЛИХОМАНКА: СУЧАСНІ ПОГЛЯДИ НА ДІАГНОСТИКУ ТА ЛІКУВАННЯ А.С. Свінціцький

### Резюме

У статті наведено сучасні погляди на питання діагностики, лікування і профілактики гострої ревматичної лихоманки, які базуються на положеннях останніх настанов Всесвітньої організації охорони здоров'я та інших провідних наукових товариств, зокрема Американської асоціації серця та Всесвітньої федерації серця.

**Ключові слова:** гостра ревматична лихоманка, переглянуті критерії Джонса, еходоплеркардіографія, лікування, профілактика.