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# Yersinosis-related reactive arthritis: diagnostic and treatment constraints (individual experience)

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**Abstract.** Reactive arthritis (ReA) remains an important problem in the practice of rheumatology, and is one of the most common types of acute arthritis in young people. The relevance of ReA is due to its high frequency, difficulties of diagnosis, a chronicity with an insufficiently effective treatment. The article discusses current literature data on Yersinia arthritis, features of pathogenesis, diagnosis and treatment. The occurrence of ReA is most often associated with gastrointestinal or urogenital infection, which precedes the development of joint syndrome. Among the ReAs associated with intestinal infection, Yersinia is quite common. Intestinal yersiniosis is severe, has a significant duration with a tendency to chronicity, involvement of various organs and systems in the pathological process. The features of Yersiniosis pathogens in combination with infectious conditions cause a wide variety of clinical manifestations. The disease has a frequent association with HLA-B27 antigen. Among the common clinical symptoms of ReA there are asymmetric arthritis of the lower extremities, sausage-like toe deformity, tendonitis, enthesitis (most commonly heel tendon enthesitis), and asymmetric sacroiliitis. The frequency and severity of extra-articular manifestations may be different: lesions of the eyes, skin, mucous membranes, urogenital or gastrointestinal tract. First-line drugs in the treatment of ReA are NSAIDs. Patients with an active source of infection also require a long-term treatment with antibacterial therapy, sulfosalazine is added in case of a chronic arthritis. The article presents a clinical case of Yersiniosis reactive arthritis, emphasizes the multidisciplinary approach in the management of the patient.

**Keywords:** Yersiniosis arthritis; reactive arthritis

## Introduction

Reactive arthritis (ReA) remains a topical issue of the rheumatologic practice. Within the inflammatory articular condition paradigm, they are ranked third after osteoarthritis and rheumatoid arthritis. The absence of timely diagnostics and adequate treatment result in a long-standing, protracted or recurrent course developing into the chronic forms.

The ReA belong to a group of seronegative spondyloarthritis sharing common features:

— a frequent general inflammation of sacroiliac joints (sacroiliitis) and/or spine (spondylitis);
— a predominating mono- or oligoarthritis;
— enthesopathy /enthesitis;
— HLA-B27 association;
— negative rheumatoid factor (RF);
— extra-articular manifestations: eye afflictions, skin afflictions, mucous membrane afflictions, urogenital or gastrointestinal conditions.

The ReA is an acute non-purulent arthritis following some infections and being closely related to HLA-B27 histocompatibility antigen. The ReA is most often associated with urogenital or gastrointestinal infection. Among the most frequently occurring triggers, there are:

Enterogenous ReA: *Salmonella (of various serotypes), Yersinia enterocolitica, Yersinia pseudotuberculosis, Shigella flexneri, Shigella sonnei, Campylobacter jejuni;*

Urogenous ReA: *Chlamydia trachomatis, Chlamydia pneumoniae, Ureaplasma urealyticum;*

Tonsilogenous ReA: *Streptococcus*, and other ReA types: *Borrelia burgdorferi*, viruses etc.

The ReA diagnostic criteria are presented in the Table.

There is an interesting historical fact that the "reactive arthritis" term was suggested by *P. Ahvonen, K. Sievers* and *K. Aho* in 1969 [2], specifically in order to describe arthritides whose development was associated with Yersiniosis-caused enterocolitis. The intestinal Yersiniosis was caused by Yer-



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sinia enterocolitica, a Gram-negative, bacillus-shaped bacterium, belonging to the family Yersiniaceae. This family includes several types of bacteria, provoking *Y. enterocolitica, Y. pseudotuberculosis, Y. Pestis* in the human body.

Yersinia enterocolitica was first described by *J. Schleifstein* and *B. Coleman* in 1939. The above-mentioned bacterium was named after *A. Yersin*, the French microbiologist who detected the plague bacterium (*Y. pestis*). Yersiniae are environment-resistant, able to replicate within a wide range of temperatures (from 2 to 40° C). The optimal temperature for its growth is 2-5° C (these microorganisms have psychrophilic properties (*Psychrophile* is Greek for 'cold-loving')), which is why they replicate under the conditions of common freezer and winter vegetable storage places. This fact promotes various products, namely vegetables, being contaminated by Yersiniae during their storage. Other possible sources of infection may be sick human subjects, animals or soil. An important burden of infection spread is being carried by rodents [3].

The antigen properties allow us to select 9 biotypes and 76 serotypes of the causative agent. *Y. enterocolitica* has a somatic O-antigen; some strains have a virulence-associated V-antigen locater on the outer membrane. While incubating at the temperature under 30° C, the flagellar H-antigen is selected. *Y. enterocolitica* has pathogenic properties: adhesion, colonization on the intestinal epithelium surface, enterotoxigeneity, invasiveness and cytotoxicity. *Y. enterocolitica* is characterized by a significant pathogenicity, reflected to a different extent in various serotypes and agent strains; the latter account for a magnitude of intestinal Yersiniosis clinical forms. The most pathogenic serovars for human beings are O:1,2,3; O:3; O:9; O:13; O:20; O:21 [4].

For the most part, Yersiniosis occurs in the countries with a cool climate: the Northern and Western Europe, the UK, Japan, the USA, Canada. In the USA and Western Europe, the intestinal Yersiniosis ranks 7$^{th}$ among the acute intestinal infections and 3$^{rd}$ among the bacterial agents after salmonellosis and campylobacteriosis. According to the reference sources, various Ukrainian oblasts rarely witness the epidemic outbursts of Yersiniosis; more often the physicians deal with sporadic cases [3].

The intestinal Yersiniosis is severe, long-running, has a chronization tendency; it involves various organs and systems in the pathological process. At the same time, the features of Yersiniosis agents in conjunction with contaminating conditions account for the multitude of clinical manifestations. The disease may be limited to such acute intestinal infection signs as vomiting, diarrhea etc., or have more common forms, involving the affliction of mesenteric lymph nodes, terminal ileitis, mesadenitis or even sepsis. In some cases, the course of infection resembles an acute appendicitis. Sometimes a respiratory syndrome develops, along with throat ache, reddening of the back throat, palatal swelling, coughing and stuffed nose. With intestinal Yersiniosis, the infection may turn into a chronic form [5, 6].

After *Y. enterocolitica* exposure, there may be systemic manifestations. The pathological process often involves kidneys, liver, pancreas, cardiovascular and nervous system. Quite often, such patients, especially facing the chronic course, suffer from the reactive arthritis, uveitis, iritis, conjunctivitis, glomerulonephritis, Erythema nodosum. According to the reference sources, these manifestations are more often registered among the HLA-B27 positive Yersiniosis patients. There is a confirmed close correlation between the ReA development and HLA-B27 antigen. According to the reference sources, among the patients who develop the ReA following the Yersiniosis 80% cases are HLA-B27 positive. For some intestinal bacteria (*Yersinia, Salmonella*), the present HLA-B27 is a factor considerably alleviating the microorganisms invading the synovial membrane cells [7]. The HLA-B27 antigen is an antigen-presenting molecule, able to deliver the arthritogenic peptides to cytotoxic CD8 T-lymphocytes [8]. In this case, chondrocytes located both in the cartilage tissue and inflammation-afflicted enthesis are subject to lysis. The developing post-Yersiniosis arthropathies are promoted by the homology between the HLA-B27 leucocyte antigens and Yad-adhesin of Yersiniae: adhesion molecules are using HLA-B27 as a ligand affecting the articular synovial lining cells. When stimulated by the bacterial lipopolysaccharides (LPS), the HLA-B27 positive lymphocytes produce an increased number of anti-inflammatory factors [10, 10].

The greatest number of antibodies occurs at the second week of disease, as a causative agent has a lot of antigens and stimulates an active immune response. The IgA antibodies are synthesized in the initial days of disease, and after the recovery they are circulating in the blood for several months; with chronic intestinal Yersiniosis, for a much longer time.

## Clinical case

The patient H., born in 1989, was hospitalized at the first rheumatologic department of "Oleksandrivska Clinical Hospital of Kyiv" (communal non-commercial institution) due to complains of pain and edema of left foot, left ankle joint, sporadic pain at the buttocks site, edema, reddening of right eye.

The patient considers the disease to last for about 6 months, when the initial pain occurred in the left foot, followed by edema. During the recent month, the patient is suffering from a severe pain in hip joints. Three months ago,

***Table. IV International Workshop on Reactive Arthritis: Working classification of ReA diagnoses [1]***

| ReA diagnostic criteria |
|---|
| **Principal:**<br>• arthritis (asymmetrical, mono-, oligoarthritis, lower limb joint afflictions);<br>• clinical manifestations of infection (enteritis precedes arthritis by 6 weeks, urethritis, cervicitis – usually by 8 weeks) |
| **Supporting:**<br>• direct agent detection;<br>• serological assay with type-specific antisera, detection of agent substrate by means of polymerase chain reaction (PCR) test |

an acute iridocyclitis of left eye occurred. During the recent month, the reddening of right eye is observed. The patient reports a periodical stool loosening, pain in the left iliac region.

During the out-patient examination, the patient was diagnosed with "Spondyloarthritis, peripheral form with systemic manifestations". Taking into account the high extent of activity and duration of articular syndrome, the patient was prescribed the 8 mg dose of Methylprednisolone and referred for hospitalization.

Being admitted at the department, the patient was in a moderately severe condition. The cutaneous lining and mucous membranes were pale, no rash was present, and the tongue was moist and somewhat furred with a whitish film. The tonsils are not enlarged, uncovered with film. The peripheral lymph nodes are not enlarged. The blood rate is 82 beats per min., it is rhythmic and of satisfactory quality. The heart activity is rhythmic, its tones are rather hushed, and there are no murmurs. The pulmonary auscultation registered a vesicular breathing, the crackling is absent. The abdominal palpation registered softness, in the left iliac region the superficial and deep palpation produces a certain discomfort. The liver is located at the level of costal arch; its edge is regular, elastic. The spleen is not detected at palpation; however, the percutaneous analysis demonstrates that its size is within normal ranges. The costovertebral angle (CVA) tenderness is absent bilaterally. The urine is of a regular color. There is a tendency of stool loosening. There is no edema present.

The articular state: normosthenic body composition, accentuated thoracic kyphosis, flattened lumbar lordosis. While walking, the patient is limping, favoring the left leg. The spinal movement range is sufficient. There is an edema, pain and restricted range of movement in the left talocrural joint, II-IV metatarsophalangeal joints, dactylitis of the second toe of the left foot; the movement and palpation of joints are painful, the movement range is restricted (Fig. 1). The clinical manifestation of sacroiliitis (Kushelevsky's symptom, Patrick's test) is negative.

Results of the general clinical *examination*. Complete blood count (CBC): hemoglobin – 117 g/l, erythrocytes – $4.67x10^{12}$/l, leucocytes – $5.7x10^{9}$/l, ESR – 40 mm/hour, platelets - $240x10^{9}$/l, hematocrit – 34.3 %, stab cells - 5%, segments – 61 %, monocytes – 24 %, lymphocytes – 8%, eosinophils – 2 %. Biochemical blood test: cholesterol – 3.92 mmol/l, bilirubin (BR) – 11.9 umol/l, creatinine – 61 μmol/l, ALT - 21 IU/ml, AST – 18 IU/ml, glucose – 4.5 mmol/l, CRP – 39.2 g/ml, RF< 12 IU/ml. Urinalisys: no changes of clinical importance. HBsAg – undetected, Anti-HCV total – undetected. Blood sample of HIV antibodies: no antibodies detected. In order to rule out the reactive arthritis of urogenous type, urogenital scraping was performed: ureaplasma, mycoplasma, and chlamydia – negative result. Immunogenetic test of HLA-B27 – positive result.

Results of the general clinical *instrumental examination*. EKG – sinus rhythm, regular, signs of an early ventricular repolarization; ECHO-CG - mitral valve prolapse with I stage regurgitation; ultrasound study of abdominal cavity – signs of right hepatic lobe hemangioma, gallbladder congestion. Considering the pain in the buttocks region, one performed the magnetic resonance imaging (MRI) study of sacroiliac joints to detect changes: signs of degenerative changes, no results supporting sacroiliitis, inflammatory changes of Iliolumbar ligament.

The patient underwent ophthalmologist consultation. Among the reported results: fibrinous (plastic) iridocyclitis of the right eye. Considering the periodical stool loosening and pain at the left iliac site, the patient was referred to a gastroenterologist, and at his recommendation was subject to: fibrogastroduodenoscopy (conclusion: a moderate reflux gastritis, superficial bulbitis); colonoscopy with biopsy (conclusion: erosive colitis). According to the findings and results of a follow-up gastroenterologist's consultation, there are no data of inflammatory intestinal diseases (Crohn' s disease or ulcerative colitis).

After the infectionist's consultation, and upon his recommendation, the following studies were prescribed in order to rule out the infectious gastrointestinal diseases: helminth and worm egg counts in stool did not reveal any; stool bacterial inoculation did not reveal any pathogenic flora. Test of the specific intestinal infections: *Brucella ab.* – negative findings, *Shigella fl.* – negative findings, *Yersinia enterocolitica*, IgA antibodies – 3.39 (positive), *Yersinia enterocolitica*, IgG antibodies – 6.11 (positive), *Yersinia pseudotuberculosis* – negative findings.

Considering the above-mentioned findings, there was a follow-up infectionist's consultation. As a result, the patient was diagnosed with "Yersiniosis, secondary focal form with systemic manifestations".

The previous diagnosis was thus revised. Considering the character of articular syndrome (asymmetrical oligoarthritis involving the joints of the lower extremities, dactylitis), its duration over 6 months, (ophthalmologist-confirmed) iridocyclitis, increased ESR and CRP rate, MRI-detected enthesitis though undetected sacroiliitis and spondylitis,

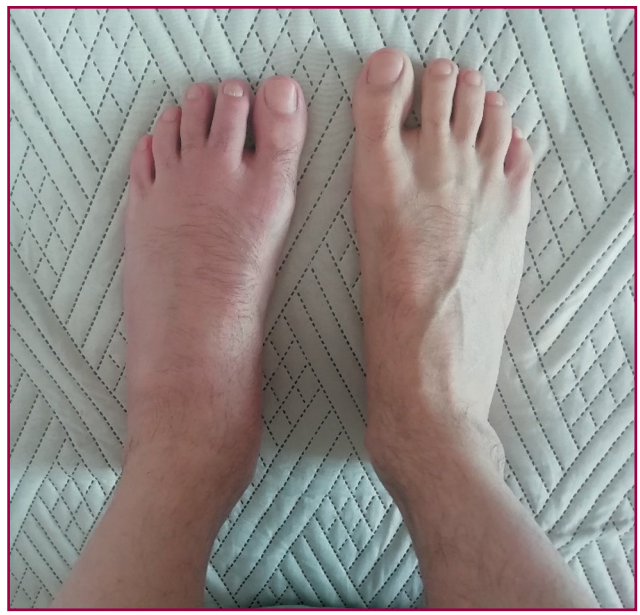

***Fig. 1. Edema of the left talocrural joint, II-IV metatarsophalangeal joints, dactylitis of the second toe of the left foot***

HLA-B27 positive status, *Yersinia enterocolitica* detection, and infectionist's conclusion, the following conclusive diagnosis was made: "Reactive enterogenous (Yersinia) arthritis, chronic course, moderate activity, affliction of ankle joint, metatarsophalangeal joints of the left foot, dactylitis of the left foot's 2nd toe, X-ray stage I, functional articular insufficiency of II stage, fibrinous (plastic) iridocyclitis of the right eye. HLA-B27 positive. Yersiniosis, secondary focal form".

The patient was prescribed the following treatment: 500 mg Ciprofloxacin twice a day during 14 days, 90 mg Etoricoxib during 14 days, 1 g Sulfasalazine (SSZ) twice a day for a long time, 20 mg Omeprazole per day during 14 days. The ophthalmologist recommended: Broksinak, Deksapol, Atropine by the regimen, Methylprednisolone – regularly discontinued.

During the two weeks of treatment, all symptoms gradually receded; the patient was discharged in a satisfactory condition. While observing the patient dynamically, we detected no relapses. The patient was recommended to continue taking Sulfasalazine (SSZ) up to 6 months.

## Conclusions

To sum up, the articular syndrome in combination with intestinal disorders requires a thorough observation, involving specialists from adjunct fields, in order to verify the final diagnosis. One should remember that Yersiniosis is characterized by a long duration, tendency of chronization, involvement of various organs and systems (namely, joints, eyes, skin). The above-mentioned clinical case also demonstrates that in certain cases rheumatologists should perform differential diagnostics among the group of conditions sharing clinical features, as the treatment of these nosological forms is different.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are "first-line" drugs to treat ReA. In case of a resistant articular syndrome, one may use localized glucocorticoid injections only once. One should sanitize the infectious nidus with etiotropic antibacterial drugs. In case of a chronic course, recurrent character or extraarticular manifestations, one should prescribe basic therapy of Sulfasalazine (SSZ).

**Conflicts of interests.** Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

**Information on the individual contributions.** O.I. Ivashkivskyi – concept and design of the study, analysis and generalization of patient data, T.A. Karasevska – analysis of national and foreign references, writing the article, M.B. Dzhus - design of the study, editing the article, H. L. Novytska – working with patient (collection of anamnesis, data of instrumental and laboratory studies), description of findings and data of a clinical case.

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# Ієрсиніозний реактивний артрит: труднощі діагностики та лікування (власний досвід)

**Резюме.** Реактивний артрит (РеА) залишається важливою проблемою в практиці ревматолога і є одним із найбільш поширених видів гострого артриту в осіб молодого віку. Актуальність РеА пов'язана з його високою частотою, труднощами діагностики, досить частою хронізацією при недостатньо ефективному лікуванні. У статті обговорюються сучасні дані літератури щодо ієрсиніозного артриту, особливості патогенезу, діагностики та лікування. Виникнення РеА найчастіше асоційоване із шлунково-кишковою або урогенітальною інфекцією, що передує розвитку суглобового синдрому. Серед РеА, пов'язаних із кишковою інфекцією, ієрсиніозний зустрічається досить часто. Кишковий ієрсиніоз відрізняється тяжкістю, значною тривалістю перебігу з тенденцією до хронізації, залученням у патологічний процес різних органів і систем. При цьому особливості збудників ієрсиніозу в поєднанні з умовами зараження зумовлюють різноманітність клінічних проявів. Хвороба має високу асоціацію з антигеном HLA-B27. Загальними клінічними симптомами РеА є асиметричний артрит, найчастіше суглобів нижніх кінцівок, сосископодібна дефігурація пальця стопи, тендиніт, ентезит (найбільш характерним є ентезит п'яткового сухожилля), асиметричний сакроілеїт. Частота та вираженість позасуглобових проявів може бути різною: ураження очей, шкіри, слизових оболонок, урогенітального або шлунково-кишкового тракту. Препаратами першої лінії для лікування РеА є нестероїдні протизапальні засоби. Пацієнти з активним вогнищем інфекції також потребують тривалого лікування із застосуванням антибактеріальної терапії, а при хронізації артриту до терапії додають сульфасалазин. У статті наведений клінічний випадок ієрсиніозного реактивного артриту з акцентом на мультидисциплінарному підході у веденні хворого.

**Ключові слова:** ієрсиніозний артрит; реактивний артрит

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# Иерсиниозный реактивный артрит: трудности диагностики и лечения (собственный опыт)

**Резюме.** Реактивный артрит (РеА) остается важной проблемой в практике ревматолога и является одним из самых распространенных видов острого артрита у лиц молодого возраста. Актуальность РеА связана с его высокой частотой, трудностями диагностики, достаточно частой хронизацией при недостаточно эффективном лечении. В статье обсуждаются современные данные литературы об иерсиниозном артрите, особенностях патогенеза, диагностики и лечения. Возникновение РеА чаще всего ассоциировано с желудочно-кишечной или урогенитальной инфекцией, которая предшествует развитию суставного синдрома. Среди РеА, связанных с кишечной инфекцией, иерсиниозный артрит встречается достаточно часто. Кишечный иерсиниоз отличается тяжестью, значительной длительностью течения с тенденцией к хронизации, вовлечением в патологический процесс различных органов и систем. При этом особенности возбудителей иерсиниоза в сочетании с условиями заражения обусловливают разнообразие клинических проявлений. Болезнь имеет высокую ассоциацию с антигеном HLA-B27. Общими клиническими симптомами РеА являются асимметричный артрит, чаще суставов нижних конечностей, сосископодобная дефигурация пальца стопы, тендинит, энтезит (наиболее характерен энтезит пяточного сухожилия), асимметричный сакроилеит. Частота и выраженность внесуставных проявлений могут быть различными: поражение глаз, кожи, слизистых оболочек, урогенитального или желудочно-кишечного тракта. Препаратами первой линии в лечении РеА являются нестероидные противовоспалительные средства. Пациенты с активным очагом инфекции также требуют длительного лечения с применением антибактериальной терапии, а при хронизации артрита к терапии добавляют сульфасалазин. В статье изложен клинический случай иерсиниозного реактивного артрита с акцентом на мультидисциплинарном подходе в ведении больного.

**Ключевые слова:** иерсиниозный артрит; реактивный артрит