



Outcome assessment of spa rehabilitation in ankylosing spondylitis

Procena ishoda banjske rehabilitacije bolesnika sa ankilozirajućim spondilitisom

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Introduction

Ankylosing spondylitis (AS) is a chronic progressive autoimmune inflammatory systemic disease that usually starts at the sacroiliac joints and affects the joints and periarticular structures of the spine and chest. The disease begins at a younger age, and with time it causes postural changes, reduced lung capacity, muscle shortness, joint stiffness, and pain, significantly reducing the quality of life (QoL) and ability to function¹. This illness is more common in men, the exact cause is still unknown, but the genetic marker HLA-B27 is present in more than 95% of patients with AS².

The treatment of patients with AS is very complex and consists of pharmacological, spa physical, and surgical treatment, and an important part of the treatment is also the education of patients. A treatment that would completely stop the progression of the disease has yet to be found. The main goals of AS therapy are reducing disease activity (inflammation), back stiffness, and pain and preserving and improving functional ability, i.e., preventing or at least slowing the progression of irreversible structural changes in the spine and other joints. The treatment of AS should be individually tailored to each patient according to their functional status and comorbidities and should start right after the disease is diagnosed before irreversible functional changes occur. Most people with AS do not need surgery, but they need to have a healthy lifestyle with a Mediterranean diet and follow a regular exercise program. That can help reduce pain, maintain flexibility, and improve their posture^{1,3}.

Rehabilitation in ankylosing spondylitis

Rehabilitation in AS is a lifelong process. According to the definition of the World Health Organization

(WHO), rehabilitation is a complex procedure of (re)training a disabled person after illness and injury for the highest possible physical, mental, social, and professional benefit according to their capabilities. The term disability means that a person has various functional limitations caused by illness, and handicap means a limitation or even inability to participate equally in social life. The development of medical rehabilitation helps people with significant disabilities to live and participate equally in daily life activities. Early and proper medical rehabilitation procedures reduce the number of completely disabled patients with AS from 25% to only 1%. Rehabilitation reduces the incidence of complications and the need for medications and hospitalization and leads to improved QoL in patients with AS⁴.

Multimodal spa treatment

Spa treatment is a very important part of the overall management of AS. Since AS is an autoimmune process with no cure in sight, the treatment is focused on managing functional status, disease activity, and pain. Spa treatment is complex and includes balneotherapy (BT), climatotherapy, thalassotherapy, kinesitherapy, hydrokinesitherapy, sonotherapy, electrotherapy, and other therapeutic modalities according to special needs. It even includes changes in environment and lifestyle which lead to the activation and improvement of body adaptation mechanisms and potentials⁵. Physiotherapy procedures are prescribed by the doctor individually depending on the patient's health condition and possible contraindications. Bearing that in mind, Institute "Dr. Simo Milošević", Igalo, Montenegro has four important natural factors: climate, peloid, seawater, and mineral water, which has enabled it to develop into one of the most modern center for physical medicine and rehabilitation in the region.

Balneotherapy

BT is a combination of natural elements such as mineral waters, peloids, and gases in different world destinations, mostly in health resorts (spas), together with conventional physical therapy (kinesitherapy, sonotherapy, electrotherapy, etc.). Since Roman times, spa therapy has been applied in the treatment of different musculoskeletal conditions⁶. In European countries, BT is provided in health resorts with natural thermal baths (Niška Banja, Vrnjačka Banja, and Banja Koviljača in Serbia, Abano Terme in Italy, Hot Springs of Tiberias in Israel, etc.) or seawater baths (Igalo Spa in Montenegro, Dead Sea in Israel)⁷. For many diseases and injuries, BT is a desirable treatment since there are no serious side effects. BT has direct and indirect effects. Direct action includes the physical effects of water and peloids on the body (hydrostatic pressure, thrust, viscosity, resistance, friction). Balneo treatment also has thermal and chemical effects of substances absorbed through the skin⁸. Indirect effects come as a result of environmental and climate change, exercises, and social and psychological effects⁴.

Climatotherapy

The climate is an essential factor that affects human health; it includes temperature, humidity, rainfall, wind, clouds, sunshine, etc. Wet and cold weather can intensify stiffness and pain in people with various rheumatic conditions. Rheumatic patients feel more comfortable in a warm, dry climate. The climate of Igalo is mild, coastal Mediterranean with a large number of sunny days and the air full of scents of diverse subtropical vegetation^{4,8}.

Thalassotherapy

Thalassotherapy factors are coastal climate, seawater, solar radiation, aerosol, sea peloid, sand, and algae. Thalassotherapy is carried out in the warm summer months when its complex effect is most pronounced. It includes sunbathing on the seashore, swimming in seawater, swimming or exercising in seawater pools, but also walking by the sea and inhaling aerosols, or applying sea mud packaging or sand wraps.

In the natural area of the Adriatic Sea, the Igalo peloid (medicinal mud) is formed by mixing and depositing mineral-organic deposits of the river Sutorina and seawater sediment with its mineral and organic planktonic content. Igalo medicinal mud is an inorganic-organic, mostly mineral peloid with good physical and chemical properties. Its basic therapeutic effect is the thermal effect, and mud also has mechanical, biological-chemical, anti-inflammatory, and psychological effects⁴. Peloids can be prescribed as compresses or baths. Contraindications for peloids are rare, but we must emphasize that acutely inflamed joints should not be treated with any form of mud.

Physiotherapy is very important in treating AS, even today when biological drugs are used^{9,10}. In a systematic review, 28 studies were investigated (with a total number of 1,926 patients with AS). It was concluded that the most im-

portant part of the program is exercise (kinesitherapy)¹¹. The main goal of the individually planned exercise program is to reduce pain and morning stiffness, improve spinal mobility, maintain and improve respiratory function, improve the patient's posture, increase muscle strength and endurance, and improve functional status and overall QoL¹². The kinesitherapy program includes strengthening exercises for back and abdominal muscles, hip and knee extensors, stretching exercises (primarily pectoralis muscle, whose fibers shortening occurs due to the characteristic position of the patient), mobilization exercises, or exercises to maintain mobility of the spine and root joints. Breathing exercises with the "chest type" of breathing (inhale through the nose, exhale through the mouth) should be done every morning¹².

The use of hydrokinesitherapy is very common because water contributes to relaxation, and the recommended activities are swimming, mobilization in warm water, and walking in water. Exercise program, both in the gym and a swimming pool, improves functional status in patients with AS^{13,14}. Individual and group exercises are performed in a pool with a seawater temperature of 33–34°C. During the exercises, the beneficial effects of the aquatic environment are as follows: water temperatures, thrust, hydrostatic pressure, and the speed of the body's movement through the water.

Other physical modalities (electrotherapy, sonotherapy, magnetotherapy) are prescribed primarily for the good analgesic effect, to reduce pain and muscle stiffness, and patients are often prescribed manual massages within the spa physiotherapy program. Mineral water "Igaljka", with a temperature of 36–38 °C, is used at the Igalo Institute for pearl baths, mineral baths, and underwater shower massages as part of BT physical treatment. This mineral water is muriatic (sodium chloride) water, where sodium and chloride ions make up 70–80% of the total content of all ions⁴.

Patients in spas often have traditional medicine procedures such as acupuncture, shiatsu, and tai chi; however, pilates and McKenzie and Heckscher exercises should be included¹⁵.

Assessment tools

Leading experts from the Outcomes Measures in Rheumatology Clinical Trials (OMERACT) and Assessment of Spondylo-Arthritis (ASAS) International Society have created a core set to assess the effects of physical therapy. The core set includes several domains: pain, spinal stiffness, axial mobility, physical function, fatigue, and patient's global assessment¹⁴. To get the complete picture of the outcome of spa physical therapy, many studies assess the QoL and ASAS 20 improvement.

Pain should be assessed on the visual analog scale (VAS) or the numerical rating scale (NRS). Pain is a very unpleasant symptom associated with potential tissue damage and the most common reason for visiting a doctor⁴. Even though VAS and NRS scales are psychometric response scales, the double application shall produce objective information about the change in the intensity of pain after spa physical treatment^{14,16}.

Spinal stiffness – patients should answer questions about how long they have been feeling stiffness in their back (in min, or VAS, NRS). When it is done twice (on admission and discharge), objective information about the change in the intensity of spinal stiffness is obtained after spa treatment^{4,16}.

Spinal mobility – the range of motion in the spine in segments is assessed (occiput-to-wall distance, Otto's test, modified Schober index) or overall axial mobility with the Bath Ankylosing Spondylitis Metrology Index (BASMI) index. Occiput-to-wall distance shows whether the mobility of the cervical spine is reduced: if the distance is more than 0 cm, neck movements are reduced. Otto's test shows the mobility of the thoracic spine – normal values are 8 cm or more, and in advanced AS, it is significantly reduced. The modified Schober index shows the mobility of the lumbar spine, which is reduced if the result is less than 5 cm. BASMI shows the overall axial status of the patient with AS. The total BASMI score is obtained by measuring cervical rotation (in degrees), intermalleolar distance (in cm), lumbar flexion (modified Schober test, in cm), lateral lumbar flexion (in cm), and tragus-wall distance (in cm)¹⁷. Measured values are translated, using an algorithm, into values between 0–10, where a higher score shows more reduction in mobility of the spine^{4,9}. Spinal mobility measures correlate well with physical function, emotional role, mental health, and general health domains in the Medical Outcomes Study 36-item Short Form Health Survey (SF-36) questionnaire¹⁸. Impaired spinal mobility is associated with restricted pulmonary function¹⁹.

Physical function – ASAS group experts suggest that physical function can be monitored using different questionnaires: Bath Ankylosing Spondylitis Functional Index (BASFI), The Dougados Functional Index (DFI), or Health Assessment Questionnaire for Spondyloarthropathies (HAQ-S)⁹. BASFI shows functional disability, it has 10 questions, eight of which concern activities referring to the functional anatomy (bending, changing position, standing, reaching, turning, and climbing steps), and two questions assess the patient's ability to cope with everyday life. BASFI uses a VAS scale with descriptors “easy” and “not possible”, and a higher score means more functional disability^{4,14,16}. BASFI strongly correlates with fatigue and global patient assessment in AS²⁰. DFI consists of 20 questions about functional issues. A more recent version of DFI uses a 5-point Likert scale. BASFI is more sensitive to changes than DFI regarding functional status in patients with milder disease²¹. HAQ-S consists of 25 items, where 20 questions are from the original Health Assessment Disability Index (HAQ-DI) for arthritis patients, and the additional 5 questions are more specific to the issues of physical functioning and impairment specific to AS. A higher score means that the patient has more functional problems⁹.

Fatigue often occurs in inflammatory rheumatic diseases and is associated with increased disease activity. It is determined on the 10 cm long VAS scale (or NRS), marked with “no fatigue” on the left and “maximum fatigue” on the right^{4,16}. Fatigue is increased by sleep disorders and depression. Functional Assessment of Chronic Illness Therapy –

Fatigue (FACIT-F) is a short questionnaire covering thirteen questions on the level of fatigue that occurs when performing various activities during the previous seven days. FACIT-F uses a 4-point Likert scale. It was originally developed for assessing fatigue in people with anemia, but it is now widely used for different conditions, including AS²².

The patient's global assessment refers to the current health condition of the respondents and is registered on the VAS or NRS scale. The Bath Ankylosing Spondylitis Global Score (BAS-G) is also a commonly used index. It assesses the general health of AS patients over a given time period. BAS-G contains two items on the VAS scale; a higher score means worst general health condition^{9,23}.

QoL assessment – Ankylosing Spondylitis Quality of Life (AS-QoL) is the most frequently used disease-specific questionnaire. It is developed to assess the QoL in AS. This questionnaire shows the impact of disease on sleep, mood, motivation, independence, coping, activities of daily living, relationships, and social life. No/Yes answers are offered as responses, scored as 0/1. The final score is 0–18, where the highest score means the worst QoL. Still, a “golden standard” in QoL assessment in different diseases is the SF-36 questionnaire. SF-36 and EuroQol (EQ-5D) are generic questionnaires. SF-36 includes eight domains of QoL: Physical Function, Physical Role, Bodily Pain, Vitality, General Health, Social Function, Emotional Role and Mental Health. All scores are coded and transformed into eight 0–100 scales, where a higher value means better QoL. The use of these generic questionnaires allows comparison of QoL of patients with different diseases²⁴.

ASAS improvement criteria are commonly used to monitor the outcome of drug treatment or physiotherapy. ASAS improvement is calculated only once when the program is finished, and the final score is calculated in percentage. Five areas relevant to disease outcome are covered: patient global, back pain, functional impairment, morning stiffness, and the fifth one examines whether there is further deterioration in any given area. ASAS 40, ASAS 50, or even ASAS 70 can be achieved often in therapy with biologics⁴.

Assessment of multimodal spa treatment

Despite the differences in clinical manifestations, multimodal spa rehabilitation is applied in different chronic inflammatory and degenerative arthritis^{6, 24–28}. BT, together with climatic factors and other physical modalities, significantly reduces disease activity and improves functional status and QoL in rheumatoid arthritis^{25, 29}. Rehabilitation in AS patients is a lifelong process. It should solve their overall life situation, i.e., their somatic, psychological, family, professional, and social problems. It represents a continuous process by which the patient maximizes their functional abilities. A multimodal spa treatment is a very important part of overall treatment in AS patients^{1, 4, 20, 24, 30}. The program should be individually tailored based on clinical signs and symptoms, disease activity, functional status, deformities, posture, general health status, comorbidities, and patient preferences.

Since we cannot completely stop disease progression, treatments often focus on the management of symptoms, such as stiffness, pain, and mobility. BT improves the clinical course and slows the progression of the disease in patients with predominant axial involvement³¹.

The consensus of the experts of the international ASAS group is that the optimal treatment requires a combination of drugs and non-pharmacological treatment measures and that they are of equal importance in rehabilitation³². A meta-analysis showed that all interventions in patients with AS and axial spondyloarthritis, both nonpharmacological and pharmacological significantly reduce pain and fatigue and improve physical function, spinal mobility, and patient global status when compared to control group¹⁶. Biologics are effective in AS; those patients already receiving biologics may also benefit from targeted physical therapy (improvement regarding pain, BASFI, BASDAI, chest expansion, modified Schober index)³³. Still, approximately 20–40% of those receiving tumor necrosis factor inhibitor do not respond well to therapy³⁴. Spa physical therapy reduces pain and the need to take analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs)³⁵. Contrary to BT, there are still many open questions regarding optimized treatment strategies and individual drug selection³⁶. A Dutch AS patient study showed 40 weeks of prolonged benefits (measured with BASFI and EQ-5D) after 3 weeks of spa physical therapy compared to those with just regular exercises³⁷.

Dagfrund et al.¹² summarized data about the effects of different types of physical therapy. The conclusion is that the best care is provided when AS patients follow individually prescribed complex spa physical treatment with specific exercises program in a group. Patient education, active involvement, and motivation are of importance in AS¹¹. Natural factors of the Niška Banja Spa increase axial mobility and decrease disease activity in AS³⁸. A complex spa rehabilitation program that includes BT leads to a significant reduction of disease activity (BASDAI, ASDAS-CRP) and functional status (BASFI); it significantly improves the general index ASAS 20^{4, 39, 40}.

Yurtkuran et al.⁴¹ divided AS patients into three groups, the first had BT, the second BT and NSAIDs, and the third one had only NSAIDs for three weeks. Patients also had kinesitherapy – postural exercises and breathing exercises. Results were significantly better in groups with BT – they had less pain, less morning stiffness, and a better BASFI score.

Altan et al.⁴² showed that three weeks of BT procedures together with exercises leads to significantly better health status (physical pain, patient's assessment of health status, functional status, disease activity) when compared to a group that had only exercises.

Conclusion

The treatment of AS is very complex and includes early diagnosis and initiation of adequate pharmacological therapy and application of multimodal spa physical treatment. Three or four weeks of a complex spa rehabilitation program showed favorable cost-effectiveness and cost-utility ratios compared with standard exercise treatment alone.

The spa rehabilitation program should be strictly individualized, primarily according to the stage and disease activity, previous treatment, and the patient's general condition. The best results are achieved in those treated with optimal pharmacological therapy before a spa treatment. BT procedures should be applied patiently, with discipline, and accurately at the right time, respecting the principles of chronotropism. Patients should not take baths right after the application of peloids because they can lose the positive chemical effect of mud. Exercises in the gym and pool have a central place in the rehabilitation of AS patients. Prolonged rest leads to muscle weakness, increased morning stiffness, decreased range of motion, reduced respiratory index, accelerated ankyloses, or contractures. Different analgesic procedures (heat, ice, interfering currents, ultrasound, transcutaneous electrical nerve stimulation – TENS) are often prescribed. Massage relaxes muscles and has a whole-body relaxing effect. The goals of multimodal spa physical therapy are numerous – to reduce pain, inflammation, stiffness in joints, and muscle spasm, accelerate the resorption of edemas and exudates, prevent contractures and ankyloses, strengthen muscles, preserve posture, and improve functional ability, health, and mood.

A recommended core set to assess complex spa physical therapy includes several domains: pain, axial stiffness, spinal mobility, physical function, fatigue, and patient's global assessment. Many studies use QoL questionnaires and ASAS 20 improvement, which leads us to believe that the proposed core set can be extended with these instruments. All the instruments are standardized and easy to use, and their application has reduced the potential bias of the interviewers to the smallest possible extent since most of the questionnaires are filled out independently. The BASMI index contains objective parameters (occiput-wall distance, lateral flexion, modified Schober index, etc.), so the bias of the interviewers cannot be entirely eliminated. Survey for patients may show their health condition better than it really is, but this is practically eliminated in tests as they are done two or more times. In the future, large studies with a low risk of bias are needed.

Natural factors are complex; they act simultaneously and should not be separated. However, when applied together, they lead to positive effects on AS patients that persist for several months after the end of the spa program, as shown by “cost-benefit” studies.

REFERENCES

1. *Van der Linden S, Brown M, Gensler LS, Kenna T, Maksymowych WP, Taylor WJ.* Ankylosing spondylitis and other forms of axial spondyloarthritis. In: *Firestein GS, Budd RC, Gabriel SE, Kozrtzky GA, McInnes IB, O'Dell JR*, editors. *Firestein & Kelly's Textbook of Rheumatology*. 11th ed. Philadelphia, PA: Elsevier; 2021. p. 1319–43.
2. *Hanson A, Brown MA.* Genetics and the Causes of Ankylosing Spondylitis. *Rheum Dis Clin North Am* 2017; 43(3): 401–14.

3. Ward MM, Deodhar A, Gensler LS, Dubreuil M, Yu D, Khan MA, et al. 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. *Arthritis Rheumatol* 2019; 71(10): 1599–613.
4. Mustur D. Effects of balneo-climatological physical treatment on the health status of patients with ankylosing spondylitis. [dissertation]. Belgrade: Faculty of Medicine, University of Belgrade; 2010. (Serbian)
5. Falagas ME, Zarkadoulia E, Rafailidis PI. The therapeutic effect of balneotherapy: evaluation of the evidence from randomised controlled trials. *Int J Clin Pract* 2009; 63(7): 1068–84.
6. Verbagen AP, Bierma-Zeinstra SM, Boers M, Cardoso JR, Lambeck J, de Bie RA, et al. Balneotherapy for osteoarthritis. *Cochrane Database Syst Rev* 2007; (4): CD006864.
7. Gutenbrunner C, Bender T, Cantista P, Karagülle Z. A proposal for a worldwide definition of health resort medicine, balneology, medical hydrology and climatology. *Int J Biometeorol* 2010; 54(5): 495–507.
8. Maraver F, Armijo F, Fernandez-Toran MA, Armijo O, Ejeda JM, Vazquez I, et al. Peloids as Therapeutic Agents. *Int J Environ Res Public Health* 2021; 18(4): 1965.
9. Zochling J. Measures of symptoms and disease status in ankylosing spondylitis: Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), and Health Assessment Questionnaire for the Spondylarthropathies (HAQ-S). *Arthritis Care Res (Hoboken)* 2011; 63(Suppl 11): S47–58.
10. Nghiem FT, Donohue JP. Rehabilitation in ankylosing spondylitis. *Curr Opin Rheumatol* 2008; 20(2): 203–7.
11. Sharan D, Rajkumar JS. Physiotherapy for Ankylosing Spondylitis: Systematic Review and a Proposed Rehabilitation Protocol. *Curr Rheumatol Rev* 2017; 13(2): 121–5.
12. Dagfinrud H, Kvien TK, Hagen KB. Physiotherapy interventions for ankylosing spondylitis. *Cochrane Database Syst Rev* 2008 23(1): CD002822.
13. Pécourneau V, Degboé Y, Barnette T, Cantagrel A, Constantin A, Ruyssen-Witrand A. Effectiveness of Exercise Programs in Ankylosing Spondylitis: A Meta-Analysis of Randomized Controlled Trials. *Arch Phys Med Rehabil* 2018; 99(2): 383–9. e1.
14. Liang Z, Fu C, Zhang Q, Xiong F, Peng L, Chen L, et al. Effects of water therapy on disease activity, functional capacity, spinal mobility and severity of pain in patients with ankylosing spondylitis: a systematic review and meta-analysis. *Disabil Rehabil* 2021; 43(7): 895–902.
15. Roşu MO, Ţopa I, Chiriac R, Ancuta C. Effects of Pilates, McKenzie and Heckscher training on disease activity, spinal motility and pulmonary function in patients with ankylosing spondylitis: a randomized controlled trial. *Rheumatol Int* 2014; 34(3): 367–72.
16. Andreasen RA, Kristensen LE, Baraliakos X, Strand V, Mease PJ, de Wit M, et al. Assessing the effect of interventions for axial spondyloarthritis according to the endorsed ASAS/OMERACT core outcome set: a meta-research study of trials included in Cochrane reviews. *Arthritis Res Ther* 2020; 22(1): 177.
17. van der Heijde D, Landewé R, Feldtkeller E. Proposal of a linear definition of the Bath Ankylosing Spondylitis Metrology Index (BASMI) and comparison with the 2-step and 10-step definitions. *Ann Rheum Dis* 2008; 67(4): 489–93.
18. Vesović-Potić V, Mustur D, Stanislavljević D, Ille T, Ille M. Relationship between spinal mobility measures and quality of life in patients with ankylosing spondylitis. *Rheumatol Int* 2009; 29(8): 879–84.
19. Berdal G, Halvorsen S, van der Heijde D, Mowse M, Dagfinrud H. Restrictive pulmonary function is more prevalent in patients with ankylosing spondylitis than in matched population controls and is associated with impaired spinal mobility: a comparative study. *Arthritis Res Ther* 2012; 14(1): R19.
20. Mustur D, Vesović-Potić V, Ille T, Stanislavljević D, Ille M. Assessment of health-related quality of life of patients with chronic arthritis. *Srp Arh Celok Lek* 2009; 137(11–12): 684–9. (Serbian)
21. Ruof J, Stucki G. Comparison of the Dougados Functional Index and the Bath Ankylosing Spondylitis Functional Index. A literature review. *J Rheumatol* 1999; 26(4): 955–60.
22. Butt Z, Lai JS, Rao D, Heinemann AW, Bill A, Cella D. Measurement of fatigue in cancer, stroke, and HIV using the Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) scale. *J Psychosom Res* 2013; 74(1): 64–8.
23. Jones SD, Steiner A, Garrett SL, Calin A. The Bath Ankylosing Spondylitis Patient Global Score (BAS-G). *Br J Rheumatol* 1996; 35(1): 66–71.
24. Mustur D, Vujsinović-Stupar N, Ille T. Influence of physical treatment on disease activity and health status of patients with chronic arthritis. *Srp Arh Celok Lek* 2008; 136(3-4): 104–9. (Serbian)
25. Mustur D, Vesović-Potić V, Vujsinović-Stupar N, Ille T. Beneficial effects of spa treatment on functional status and quality of life of patients with rheumatoid arthritis. *Srp Arh Celok Lek* 2008; 136(7–8): 391–6. (Serbian)
26. Mustur D. Influence of balneoclimatological physical treatment on functional status in patients with knee osteoarthritis. *Balneoclimatologia* 2021; 45(2): 270–7. (Serbian)
27. Mustur D, Vujsinović-Stupar N. The impact of physical therapy on the quality of life of patients with rheumatoid and psoriatic arthritis. *Med Pregl* 2007; 60(5–6): 241–6. (Serbian)
28. Karagülle M, Kardeş S, Karagülle MZ. Real-life effectiveness of spa therapy in rheumatic and musculoskeletal diseases: a retrospective study of 819 patients. *Int J Biometeorol* 2017; 61(11): 1945–56.
29. Karagülle M, Kardeş S, Dişçi R, Karagülle MZ. Spa therapy adjunct to pharmacotherapy is beneficial in rheumatoid arthritis: a crossover randomized controlled trial. *Int J Biometeorol* 2018; 62(2): 195–205.
30. Gravaldi LP, Bonetti F, Lezzerini S, De Maio F. Effectiveness of Physiotherapy in Patients with Ankylosing Spondylitis: A Systematic Review and Meta-Analysis. *Healthcare (Basel)* 2022; 10(1): 132.
31. Coşşu F, Ciprian L, Carrara M, Galozzi P, Zanatta E, Scannu A, et al. Balneotherapy in chronic inflammatory rheumatic diseases—a narrative review. *Int J Biometeorol* 2018; 62(12): 2065–71.
32. Zochling J, van der Heijde D, Dougados M, Braun J. Current evidence for the management of ankylosing spondylitis: a systematic literature review for the ASAS/EULAR management recommendations in ankylosing spondylitis. *Ann Rheum Dis* 2006; 65(4): 423–32.
33. Gyürsik Z, Bodnár N, Szekaneck Z, Szántó S. Treatment of ankylosing spondylitis with biologics and targeted physical therapy: positive effect on chest pain, diminished chest mobility, and respiratory function. *Z Rheumatol* 2013; 72(10): 997–1004.
34. Tabir H. Therapies in ankylosing spondylitis—from clinical trials to clinical practice. *Rheumatology (Oxford)* 2018; 57(Suppl 6): vi23–vi28.
35. Mustur D. Influence of spa physical therapy on pain and analgesics intake in patients with ankylosing spondylitis. *Balneoclimatologia* 2021; 45(2): 232–8. (Serbian)

36. *Poddubnyy D, Sieper J.* Treatment of Axial Spondyloarthritis: What Does the Future Hold? *Curr Rheumatol Rep* 2020; 22(9): 47.
37. *Van Tubergen A, Boonen A, Landewé R, Ruttén-Van Mölken M, Van Der Heijde D, Hidding A,* et al. Cost effectiveness of combined spa-exercise therapy in ankylosing spondylitis: a randomized controlled trial. *Arthritis Rheum* 2002; 47(5): 459–67.
38. *Nedović J, Stamenković B, Stojanović S, Stanković A, Dimić A.* Effects of natural factors of Niska Banja spa on indexes of mobility of vertebral column in patients with ankylosing spondylitis. *Srp Arh Celok Lek* 2009; 137(3–4): 175–8. (Serbian)
39. *Stamenković B, Stanković A, Nedović J, Stojanović S, Dimić A, Djordjević D,* et al. Effects of balneotherapy on the reactants of acute inflammation phase in ankylosing spondylitis. *Srp Arh Celok Lek* 2009; 137(5–6): 255–8. (Serbian)
40. *Mustur D.* Positive Effects of a Four-Week Rehabilitation Spa Program on Quality of Life in Patients with Ankylosing Spondylitis. *Acta Fac Medicae Naiss* 2021; 38(4): 343–50.
41. *Yurtkuran M, Ay A, Karakoç Y.* Improvement of the clinical outcome in Ankylosing spondylitis by balneotherapy. *Joint Bone Spine* 2005; 72(4): 303–8.
42. *Altan L, Bingöl U, Aslan M, Yurtkuran M.* The effect of balneotherapy on patients with ankylosing spondylitis. *Scand J Rheumatol* 2006; 35(4): 283–9.

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