

Appropriateness and efficacy of Spa therapy for musculoskeletal disorders. A Delphi method consensus initiative among experts in Italy

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Abstract

Objective. The aim of the study was to identify the main aspects concerning appropriateness and efficacy of Spa therapy for musculoskeletal pathologies.

Methods. A committee of 8 experts from Italian universities, public hospitals, territorial services, research institutes and patient associations was set up. Clinicians from Italian medical centers specialized in rheumatology, rehabilitation and thermal medicine took part in a Delphi process aimed at obtaining consensus statements among the participants.

Results. Large consensus was obtained for statements grouped under the following main themes: treatment indications; choice of treatment modality and treatment efficacy.

Conclusions. The experts developed a number of consensus statements which may be used as a practical reference to guide the choice of physicians to treat musculoskeletal diseases with Spa therapy.

Key words

- Spa therapy
- musculoskeletal disease
- balneotherapy
- muds
- peloids
- Delphi studies
- consensus development

INTRODUCTION

The use of natural, thermal water to treat disease is probably as old as mankind. With the term of Spa therapy it is usually intended a multifaceted and multimodal treatment that uses mineral water taken directly from a natural source and delivered rapidly to the point of use by means of showers, baths, pools, and mists. The water can be used itself and can also be combined with various types of clay, and then applied to the skin as muds, peloids or cataplasms. Finally, the mineral water can serve as a vector for massage, as with massage jets [1]. Clinical applications of Spa therapy include, but are not

limited to, musculoskeletal diseases, lymphology, pneumology and dermatology. Despite their long history and popularity, Spa therapy is still a subject of debate and its role in modern medicine is still not clear [2].

Spa therapy for osteoarthritis (OA) has been the object of clinical researches for years [3-6]. In particular, a Cochrane review [7] has established "Silver level" evidence regarding the beneficial effects of mineral baths compared to no treatment in OA. No clear effects have been found as regards all other balneological treatments. However, because of the poor methodological quality of the studies, in particular the lack of adequate

methods of statistical data analysis and presentation of results, the Authors claimed that the “positive results” found had to be viewed with caution [7]. One large multicenter trial conducted in France on 451 patients with knee osteoarthritis, reported positive effects of the bath therapy on pain, stiffness and overall well-being, especially when associated with physical and/or pharmacological therapy, which are maintained over a 6-month follow-up [8]. In a meta-analysis of randomized controlled trials, Pittler and colleagues [9] found that Spa therapy and balneotherapy may be effective for treating patients with low back pain, with beneficial effects on pain when compared to both waiting lists and control groups. They also reported, however, about the need for rigorous large-scale trials to confirm the results of their systematic review.

Spa therapy has also been widely used for rheumatologic conditions. In fibromyalgia patients, Spa therapy is associated with positive effects on pain, general health status and tender-point count [10]. A systematic review founded that Spa therapy may represent a safe and effective complementary treatment to pharmacologic therapy in fibromyalgia, with positive effects on mood and depressive state [11].

A recent Cochrane review assessed the efficacy of Spa therapy in rheumatoid arthritis [12, 13]. According to the Authors, the low-quality of the studies does not allow to take evidences about the efficacy of Spa therapy, nor that some component of Spa therapy can be more effective than others.

Despite a thousand-year use of Spa therapy, therefore, it is evident that the scientific community is not yet able to express a unique opinion about the goodness or otherwise of this type of treatment. Particularly, data about safety, clear clinical indications, as well as about the possible association with other treatments, i.e. rehabilitative treatment, are often lacking. For all these reasons, it is crucial that the clinical issues about indications to Spa therapy be defined on the basis of experiences shared by clinicians who have a high level of expertise in the field of Spa therapy. This would be particularly true in Italy, where there are about 340 certified centers, scattered throughout the country [14].

The Delphi method is a process designed to reach a consensus and develop group decisions in health research [15]. The basic principles of the Delphi method are anonymity (experts work independently of each other), controlled feedback (experts are asked to judge the opinion expressed in previous rounds, presented in statistical form) and a statistical group response leading to a collective view expressed in statistical form [16, 17].

To the best of our knowledge, a consensus method between experts has not previously been applied to the clinical aspects and management of Spa therapy for musculoskeletal diseases in daily practice.

The aim of the present study was, therefore, to gather, by using the Delphi method, the opinions of a group of Italian clinicians who represent different scientific societies, are involved in the management of patients affected by musculoskeletal diseases and have a high level of expertise in Spa therapies. Our goal was to identify the main aspects involved in patient selection, the

choice of therapeutic agents and the safety profile for muscle-skeletal diseases, to obtain opinion-based recommendations to be used in daily clinical practice.

MATERIALS AND METHODS

The Delphi method was used to conduct this consensus initiative, promoted by the Italian Foundation on Thermal Research (FORST). A committee of 8 experts from Italian universities, public hospitals, territorial services, research institutes and patient associations was set up. A panel composed of a university physiatrist (VS), a physiatrist representing the Italian Society of Physical Medicine and Rehabilitation (SIMFER) (SM), an orthopedist representing the Italian Society of Orthopedics and Traumatology (CR), a geriatrist representing the Italian Society of Gerontology (FR), a general practitioner representing the Italian Society of General Medicine (OB), a representative of the FORST (MV), an expert in pharmaco-economics (NQ), and a representative of a patient association (UV) formed the Consensus Board. The Consensus Board reviewed the literature and, on the basis of the actual indication to Spa therapy in Italy for musculoskeletal disorders, as formulated by the Italian Ministry of Health, developed the first-round questionnaire (Q1). Technical support regarding the questionnaire design, data analysis and interpretation of the results was provided by two public health researchers and three university researchers who attended the meetings held by the Consensus Board.

Q1 was submitted to a group of Italian physicians, experts in Spa therapy for musculoskeletal disorders, who were selected from among the largest Italian medical centers specialized in Spa therapy, by means of a non-probability sampling method. The experts received an email in which the rationale and the aims of the research were explained. The email sent to each physician contained a strictly personal link to Q1 that allowed the questionnaire to be filled in online. Three reminder emails were sent to each expert in the 30-day period within which the Q1 had to be returned.

The Q1 was composed of 32 questions and was divided in two parts: characteristics of the center in which the experts work, professional skills and expertise (part I); treatment of patients affected by musculoskeletal disorders (part II). The Delphi method was only applied to questions in part II, in which a 9-point Likert scale, graded “1” (strongly disagree) to “9” (completely agree), was used to assess the extent to which the experts agreed or disagreed. In order to determine the consensus level, the answers to each question were grouped into three tertiles according to the Likert-scale scores (1-2-3: disagreement; 4-5-6: neutral; 7-8-9: agreement). For the purposes of this study, we considered the consensus level as good (a recommendation can be made), for both “agreement” and “disagreement”, when $\geq 75\%$ of the experts agreed or disagreed. When the neutral answers were $\geq 75\%$, the Consensus Board deemed it impossible to make a specific recommendation on that item. When the consensus level was low (i.e. none of the tertiles attained 60% of answers), the expert opinions were considered to be too dissimilar and a shared recommendation was not made. All the items in which

consensus was weak (i.e. 60-74% of answers) were included again in a second-round questionnaire (Q2) to those physicians who completed Q1. The results yielded by Q2 were analyzed in the same way as those yielded by Q1. The final analysis was followed by a board meeting held to discuss the results and to announce the final recommendations by the Consensus Board (Figure 1).

RESULTS

Q1 was sent to 59 experts, all of whom returned the questionnaire. Sixteen of these experts have declared not to use Spa treatments for musculoskeletal disorders, and were, therefore excluded by the analysis. Both the descriptive and the Delphi analyses were, therefore, conducted on 43 complete questionnaires. Q2 was sent to the 43 responders of the first round. Twenty-nine of 43 questionnaires were filled in and returned (Q2 response rate: 67.4%).

The 43 experts who responded to Q1 comprised 20

(46.5%) thermal medicine specialists, 8 (18.6%) physiatrists, 5 (11.6%) rheumatologists, and 10 (23.2%) categorized as "other", including 1 cardiologist, 1 geriatricist, 1 pharmacologist, 1 pulmonologist and 6 who did not list any post-graduate qualification. Thirty-one (72.1%) experts had more than 10 years of experience in musculoskeletal disorders treatment, and 20 of them (64.5%) stated that they directly followed at least 50 patients each month. More than one quarter of the responders reported that in 2015 they had prescribed Spa therapies to 400 to 2000 patients.

By analyzing data from both questionnaires, the Board identified those statements that attained a wide consensus (more than 75%), which led to the definition of the recommendations (Tables 1 and 2).

DISCUSSION

Thermal therapies, also called Spa therapies, are widely used in the field of musculoskeletal pathologies

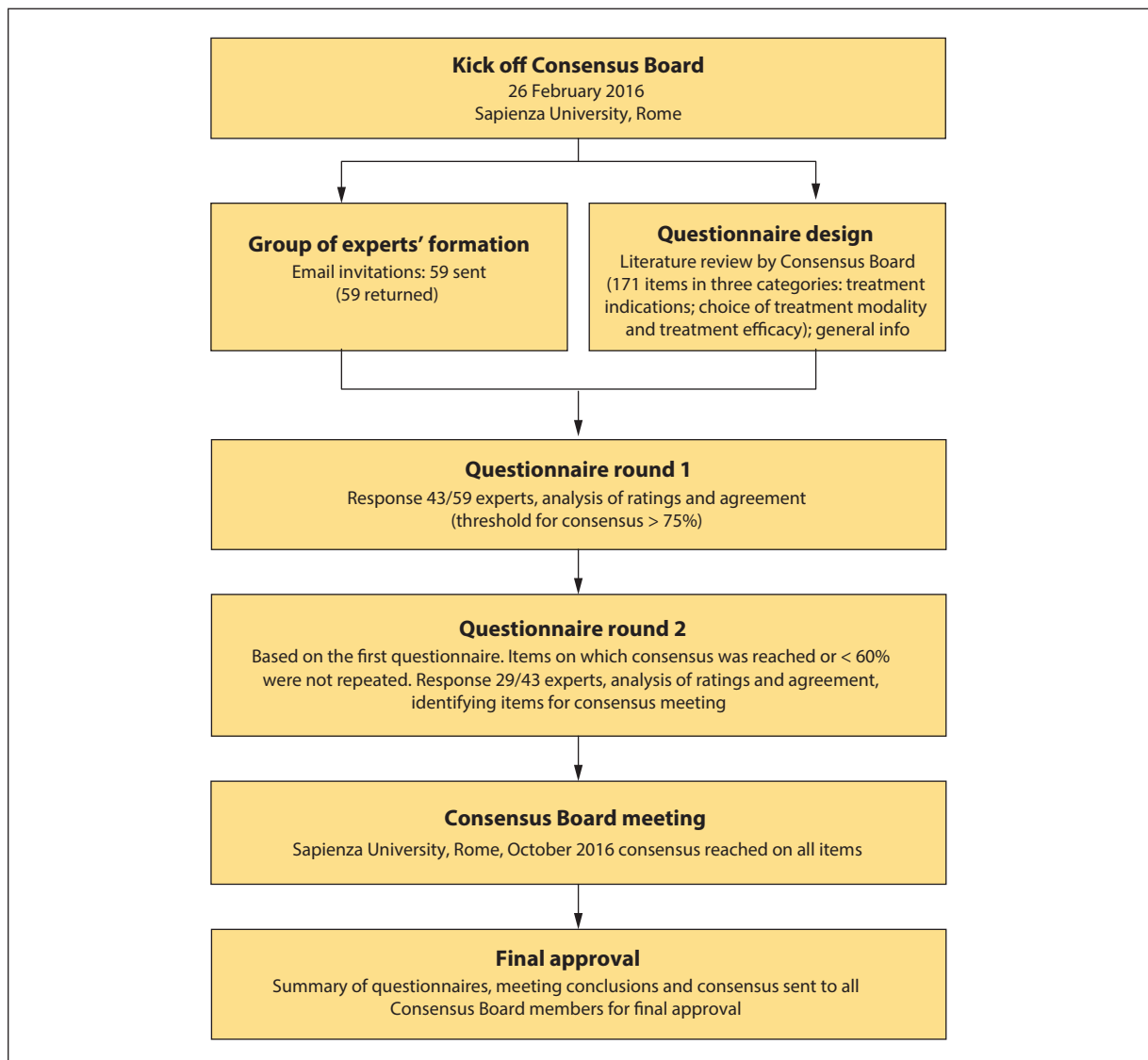


Figure 1
Flow chart of the consensus process.

Table 1
Summary of recommendations in which a consensus was reached for agreement

Recommendations	(%)
Spa therapies are useful in patients with hip OA	84
Spa therapies are useful in patients with knee OA	88
Spa therapies are useful in patients with shoulder OA	75
Spa therapies are useful in patients with ankle OA	81
Spa therapies are useful in patients with spine OA	84
Spa therapies are useful in the rehabilitation after orthopedic surgery of the shoulder	82
Spa therapies are useful in the rehabilitation after orthopedic surgery of the knee	81
Spa therapies are useful in the rehabilitation after orthopedic surgery of the hip	79
Spa therapies are useful in the rehabilitation after orthopedic surgery of the ankle	77
Spa therapies are useful in the rehabilitation after orthopedic surgery of the spine*	76
Spa therapies are useful in patients with overuse pathologies of the knee	75
Hydrotherapy in thermal water is useful for OA	93
Hydrotherapy in thermal water is useful for rheumatologic diseases with articular involvement	89
Hydrotherapy in thermal water is useful in the rehabilitation after orthopedic surgery	86
Hydrotherapy in thermal water is useful in patients with degenerative/overuse peri-articular pathologies (tendinopathies, bursitis)	79
Hydrotherapy in thermal water is useful in sub-acute/chronic post-traumatic rehabilitation	79
Hydrotherapy in thermal water is useful for extra-articular rheumatologic diseases*	76
Mud-bath therapy is useful for OA	91
Mud-bath therapy is useful for rheumatologic diseases with articular involvement	79
Bath therapy is useful for OA	84
Bath therapy is useful in the rehabilitation after orthopedic surgery*	76
Peloid-therapy are useful for OA	
The high safety profile is an important factor for the choice of Spa therapies	96
Long term results are important factors for the choice of Spa therapies	84
Possibility of integration with pharmacological/ non pharmacological is an important factor for the choice of Spa therapies	81
EBM is an important factor for the choice of Spa therapies	77
Costs determine the lack of use of Spa therapies*	83
Poor knowledge by medical doctors determines the lack of use of Spa therapies	79
Spa therapies are effective on symptoms relief (pain; quality of life) in patients with musculoskeletal diseases	93
Spa therapies are effective to control objective signs (range of motion; radiological, immunological and inflammatory parameters) in patients with musculoskeletal diseases	79
Spa therapies are effective to reduce systemic NSAIDs/analgesic drugs consumption	86
Association between rehabilitation and Spa therapies in the same setting is considered useful	77
Rehabilitation performed in a Spa environment is helpful to reduce the physiological consequences of disease and relative treatment	89

*Recommendations derived from Q2. OA: Osteoarthritis; NSAIDs: Non-steroidal anti-inflammatory drugs.

Table 2
Summary of recommendations in which a consensus was reached for disagreement

Recommendations	(%)
Spa therapies are useful in patients with acute rheumatoid arthritis	93
Spa therapies are useful in patients with acute crystal deposits arthritis	84

and pain management [4, 18, 19]. However, methodological issues, as well as the fact that Spa therapies are multifaceted and multimodal, has led to unclear recommendations in clinical practice. The present Delphi survey, therefore, has been designed in order to collect the opinion of Italian clinicians expert in the field of thermal medicine and musculoskeletal disorders.

Treatment indications

According to our results, Spa therapy is considered useful in a wide range of pathologies. Particularly, the panel of experts agreed that Spa therapy is a good therapeutic option for patients with OA of hip, knee, shoulder, ankle and spine.

OA represents the most frequent arthropathy. Studies showed that Spa therapy may be useful in generalized OA [20, 21], which can be probably considered as the most common form of OA. Despite patients may refer to health services for single-joint symptoms, in fact, the common observation is that the OA is usually observable also in the other joints. From this point of view, it is relevant how the perception of effectiveness of Spa therapies for OA has been high for all the joints usually affected by OA. We might speculate that a patient with generalized OA, therefore, could have benefit from Spa therapies which are usually systemic.

Despite the exact mechanism by which Spa therapy acts on musculoskeletal diseases is still not fully understood, recent evidences suggest that a possible role might be found in the reduction of serum levels of adiponectin and resistin [22], two cytokines secreted by adipose cells, that play a role in the pathophysiology of OA.

Furthermore, the effect of temperature of thermal baths should also be considered [23], as well as an increase in serum levels of corticosteroids and catecholamines [24] and a reduction in circulation levels of TNF- α and IL-1 β [25].

Spa therapy is also considered as useful in the rehabilitation after orthopedic surgery of several districts, including hip, knee, ankle, shoulder and spine. This point is of particular importance, because it introduces a relative new model of care for those conditions determining a transient disability, including aftereffects of orthopedic surgery, that need, therefore, for a period of more or less prolonged hospital stay. Obviously, it could only mean that the same physical and rehabilitation therapies delivered in a “non-thermal” context, might be delivered in a Spa resort, thereby providing a combination effect of the two approaches.

It is interesting that the experts agreed that rehabilitation performed in a Spa environment can be helpful to reduce the physiological consequences of disease and relative treatment. After orthopedic trauma and/or surgery, in fact, patients commonly experience a series of disorders interfering with functional gains, including post-traumatic stress syndrome, depression, and anxiety [26]. Rehabilitation performed in a more “ecologic” and “pleasant” setting, like Spa environment, can help trauma patients navigate their short-term recovery, promoting holistic approaches, coping skills, mindfulness, peer visitation, and educational resources. Indeed,

Spa therapy has been considered a helpful measure for treating the symptoms of a different stressful condition, like occupational burnout [27].

The fact that Spa resorts can be viewed more extensively than in the past in the modern era of health promotion can also be viewed considering recent experiences in the framework of the European Innovation Partnership on Active and Healthy Ageing (EIP on AHA), like the Balaruc-MACVIA-LR® approach, which promote a combination of balneotherapy, education and physical therapies in a Spa environment, as a health promotion strategy for active and healthy ageing [28].

The experts of the present survey agreed that in patients with acute rheumatoid arthritis and acute crystal deposits arthritis Spa therapies should not be indicated, reflecting the general consideration not to treat rheumatologic condition in the acute inflammatory phase of disease.

Choice of treatment modality

According to our experts, several factors can contribute to the choice of Spa therapies for musculoskeletal disorders. In keeping with the percentage of answers, the high safety profile of Spa therapies seems to be the most important factor. It should be noted that Spa therapies are generally considered safe. Among adverse events reported, respiratory tract infections were the most common (8%), followed by mild neurological disorders (6%), pain exacerbation (5%), skin diseases (2%), falls (1%) urinary tract infections (< 1%), cardiovascular disorders, and erysipelas (0.005%) [1].

As the most part of musculoskeletal disorders that refers to Spa therapies are chronic, maintaining clinical results in the long term is important, as well as the possibility of integration with other pharmacological and non-pharmacological therapies.

According to the experts, the lack of use of Spa therapy in musculoskeletal disorders is mainly due to two factors: costs and poor knowledge by medical doctors. As for the costs, it should be noted that a survey conducted in 297 certified Italian Spa centers demonstrated the health promoting value of Spa therapies in several clinical condition, including but not limited to musculoskeletal diseases, pointing out how disease-appropriate Spa treatments were followed by a reduction in the need of subsequent health interventions [14]. This would further confirm previous data about the cost-effectiveness of Spa therapy in OA patients [29]. The level of scientific evidence about Spa therapy represents another issue to consider, on the basis of the results of the present survey. This statement reinforces the need for good quality randomized controlled trials, to demonstrate the effectiveness of Spa therapies in the treatment of musculoskeletal disorders

Treatment efficacy

Experts are in agreement that the Spa therapies are effective in controlling the symptoms and objective signs of disease in patients with musculoskeletal disorders, as well as in ensuring a decrease in the recruitment of NSAIDs and analgesics.

Spa therapy comprises multiple modalities, which can differently act on pathologic status of patients. For this reason, it was interesting in the present survey, to try to differentiate the general treatment effects to those of any single modality.

According to our experts, hydrotherapy in thermal water is considered useful for the following conditions: OA, articular and extra-articular rheumatologic diseases, degenerative/overuse periarticular pathologies (tendinopathies, bursitis), as well as in the rehabilitation after orthopedic surgery and in sub-acute/chronic post-traumatic rehabilitation.

A part from the role of mineral water in the treatment of OA [5], a recent systematic review found that aquatic exercise have small, short-term, and clinically relevant effects on patient-reported pain, disability, and quality of life in people with knee and hip OA [30]. From this point of view, it can be viewed positively the association between a typical thermal medicine modality and a rehabilitation treatment.

Further indications on the role of Spa therapies for OA come from the agreement about the usefulness of mud-bath therapy and peloids-therapy in this condition.

CONCLUSIONS AND LIMITS

The present results are based on a Delphi method-based survey, and thus reflect the current opinion of a sample of doctors with a high level of expertise who work in the field of Spa therapies for musculoskeletal diseases in Italy. However, in order to be rigorous in the interpretation of our results, we decided to put a high cut-off for both agreement and disagreement (75% of answers). Delphi method has strengths and limitations,

anyway, that should be considered when interpreting results. A major strength of this method is that the people taking part bring a wide range of expertise and experience to the decision-making process. One limitation is the choice of an appropriate panel of physicians, which should ideally include a wide range of experiences relevant to the question being addressed. From this point of view, we cannot exclude, for example, that some disagreement may have resulted from lack of specific knowledge/ experience.

In conclusion, this Delphi method-based survey has highlighted several consensus statements that may prove useful as a reference for the management of patients with musculoskeletal diseases by means of Spa therapies.

Author's contribution statement

MP, AB, DC, AN, AF: design of the study, analysis and interpretation of data, drafting the manuscript.

OB, SM, NQ, FR, CR, UV, MV: conception and design of the study, interpretation of data, revising the manuscript. They formed together with VS the Consensus Board

VS: conception and design of the study, analysis and interpretation of data, drafting and revising the manuscript. He is guarantor for the accuracy and honesty of the report and the morality of the study.

Conflict of interest statement

None.

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REFERENCES

- Forestier R, Erol-Forestier FB, Francon A. Current role for spa therapy in rheumatology. *Joint Bone Spine* 2016;6.pii: S1297-319X(16)30068-9. DOI: 10.1016/j.jbspin.2016.05.003
- Guidelli GM, Tenti S, De Nobili E, Fioravanti A. Fibromyalgia syndrome and spa therapy: myth or reality? *Clin Med Insights Arthritis Musculoskelet Disord* 2012;5:19-26. DOI: 10.4137/CMAMD.S8797
- Karagulle M, Kardes S, Disci R, Gurdal H, Karagulle MZ. Spa therapy for elderly: a retrospective study of 239 older patients with osteoarthritis. *Int J Biometeorol* 2016;60(10):1481-91. DOI: 10.1007/s00484-016-1138-7
- Branco M, Rego NN, Silva PH, Archanjo IE, Ribeiro MC, Trevisani VF. Bath thermal waters in the treatment of knee osteoarthritis: a randomized controlled clinical trial. *Eur J Phys Rehabil Med* 2016;52(4):422-30.
- Forestier R, Erol Forestier FB, Francon A. Spa therapy and knee osteoarthritis: A systematic review. *Ann Phys Rehabil Med* 2016;59(3):216-26. DOI: 10.1016/j.rehab.2016.01.010
- Fortunati NA, Fioravanti A, Seri G, Cinelli S, Tenti S. May spa therapy be a valid opportunity to treat hand osteoarthritis? A review of clinical trials and mechanisms of action. *Int J Biometeorol* 2016;60(1):1-8. DOI: 10.1007/s00484-015-1030-x
- Verhagen AP, Bierma-Zeinstra SM, Boers M, Cardoso JR, Lambeck J, de Bie RA, de Vet HC. Balneotherapy for osteoarthritis. *Cochrane Database Syst Rev* 2007(4):CD006864. DOI: 10.1002/14651858.CD006864
- Forestier R, Desfour H, Tessier JM, Francon A, Foote AM, Genty C, Rolland C, Roques CF, Bosson JL. Spa therapy in the treatment of knee osteoarthritis: a large randomised multicentre trial. *Ann Rheum Dis* 2010;69(4):660-5. DOI: 10.1136/ard.2009.113209
- Pittler MH, Karagulle MZ, Karagulle M, Ernst E. Spa therapy and balneotherapy for treating low back pain: meta-analysis of randomized trials. *Rheumatology (Oxford)* 2006;45(7):880-4. DOI: 10.1093/rheumatology/kel018
- McVeigh JG, McGaughey H, Hall M, Kane P. The effectiveness of hydrotherapy in the management of fibromyalgia syndrome: a systematic review. *Rheumatol Int* 2008;29(2):119-30. DOI: 10.1007/s00296-008-0674-9
- Fraioli A, Grassi M, Mennuni G, Geraci A, Petracchia L, Fontana M, Conte S, Serio A. Clinical researches on the efficacy of spa therapy in fibromyalgia. A systematic review. *Ann Ist Super Sanità* 2013;49(2):219-29. DOI: 10.4415/ANN_13_02_13
- Verhagen AP, Bierma-Zeinstra SM, Boers M, Cardoso JR, Lambeck J, De Bie R, De Vet HC. Balneotherapy (or spa therapy) for rheumatoid arthritis. An abridged version of Cochrane Systematic Review. *Eur J Phys Rehabil Med* 2015;51(6):833-47.

13. Verhagen AP, Bierma-Zeinstra SM, Boers M, Cardoso JR, Lambeck J, de Bie R, de Vet HC. Balneotherapy (or spa therapy) for rheumatoid arthritis. *Cochrane Database Syst Rev* 2015;(4):CD000518. DOI: 10.1002/14651858.CD000518.pub2
14. Coccheri S, Gasbarrini G, Valenti M, Nappi G, Di Orio F. Has time come for a re-assessment of spa therapy? The NAIADE survey in Italy. *Int J Biometeorol* 2008;52(3):231-7. DOI: 10.1007/s00484-007-0117-4
15. Jones J, Hunter D. Consensus methods for medical and health services research. *BMJ* 1995;311(7001):376-380.
16. Capra R, Battaglia MA, Gaudio A, Lopes L, Paolicelli D, Paoloni M, Pozzilli C, Santilli V, Solaro C, Trojano M. The MoSt Project--more steps in multiple sclerosis: a Delphi method consensus initiative for the evaluation of mobility management of MS patients in Italy. *J Neurol* 2014;261(3):526-32. DOI: 10.1007/s00415-013-7230-6
17. Paoloni M, Bernetti A, Bellelli A, Brignoli O, Buoso S, Caputi AP, Catani F, Coclite D, Fini M, Mantovani L et al. Appropriateness of clinical and organizational criteria for intra-articular injection therapies in osteoarthritis. A Delphi method consensus initiative among experts in Italy. *Ann Ist Super Sanità* 2015;51(2):131-8. DOI: 10.4415/ANN_15_02_11
18. Routh HB, Bhowmik KR, Parish LC, Witkowski JA. Balneology, mineral water, and spas in historical perspective. *Clin Dermatol* 1996;14(6):551-4.
19. Bender T, Karagulle Z, Balint GP, Gutenbrunner C, Balint PV, Sukenik S. Hydrotherapy, balneotherapy, and spa treatment in pain management. *Rheumatol Int* 2005;25(3):220-4. DOI: 10.1007/s00296-004-0487-4
20. Forestier R, Genty C, Waller B, Francon A, Desfour H, Rolland C, Roques CF, Bosson JL. Crenobalneotherapy (spa therapy) in patients with knee and generalized osteoarthritis: a post-hoc subgroup analysis of a large multicentre randomized trial. *Ann Phys Rehabil Med* 2014;57(4):213-27. DOI: 10.1016/j.rehab.2014.03.001
21. Erol FB, Forestier RJ, Guneri FD, Karagulle MZ, Erdogan N. Spa therapy for generalized osteoarthritis: an open, observational, preliminary study. *Therapie* 2015;70(3):273-81. DOI: 10.2515/therapie/2014213
22. Fioravanti A, Giannitti C, Cheleschi S, Simpatico A, Pascarelli NA, Galeazzi M. Circulating levels of adiponectin, resistin, and visfatin after mud-bath therapy in patients with bilateral knee osteoarthritis. *Int J Biometeorol* 2015;59(11):1691-700. DOI: 10.1007/s00484-015-0977-y
23. Sramek P, Simeckova M, Jansky L, Savlikova J, Vybiral S. Human physiological responses to immersion into water of different temperatures. *Eur J Appl Physiol* 2000;81(5):436-42. DOI: 10.1007/s004210050065
24. Laatikainen T, Salminen K, Kohvakka A, Pettersson J. Response of plasma endorphins, prolactin and catecholamines in women to intense heat in a sauna. *Eur J Appl Physiol Occup Physiol* 1988;57(1):98-102.
25. Bellometti S, Galzigna L, Richelmi P, Gregotti C, Berte F. Both serum receptors of tumor necrosis factor are influenced by mud pack treatment in osteoarthrotic patients. *Int J Tissue React* 2002;24(2):57-64.
26. Vincent HK, Horodyski M, Vincent KR, Brisbane ST, Sadasivan KK. Psychological distress after orthopedic trauma: prevalence in patients and implications for rehabilitation. *PMR* 2015;7(9):978-89. DOI: 10.1016/j.pmrj.2015.03.007
27. Blasche G, Leibetseder V, Marktl W. Association of spa therapy with improvement of psychological symptoms of occupational burnout: a pilot study. *Forsch Komplement-med* 2010;17(3):132-6. DOI: 10.1159/000315301
28. Blain H, Bernard PL, Canovas G, Raffort N, Desfour H, Soriteau L, Nogues M, Camuzat T, Mercier J, Dupeyron A et al. Combining balneotherapy and health promotion to promote active and healthy ageing: the Balaruc-MACVIA-LR® approach. *Aging Clin Exp Res* 2016;28(6):1061-5. DOI: 10.1007/s40520-016-0596-4
29. Fioravanti A, Valenti M, Altobelli E, Di Orio F, Nappi G, Crisanti A, Cantarini L, Marcolongo R. Clinical efficacy and cost-effectiveness evidence of spa therapy in osteoarthritis. The results of "Naiade" Italian Project. *Painminerva Med* 2003;45(3):211-7.
30. Bartels EM, Juhl CB, Christensen R, Hagen KB, Daneskiold-Samsøe B, Dagfinrud H, Lund H. Aquatic exercise for the treatment of knee and hip osteoarthritis. *Cochrane Database Syst Rev* 2016;3:CD005523. DOI: 10.1002/14651858.CD005523.pub3