Health resort medicine and human immune response

How balneology can protect and improve our health

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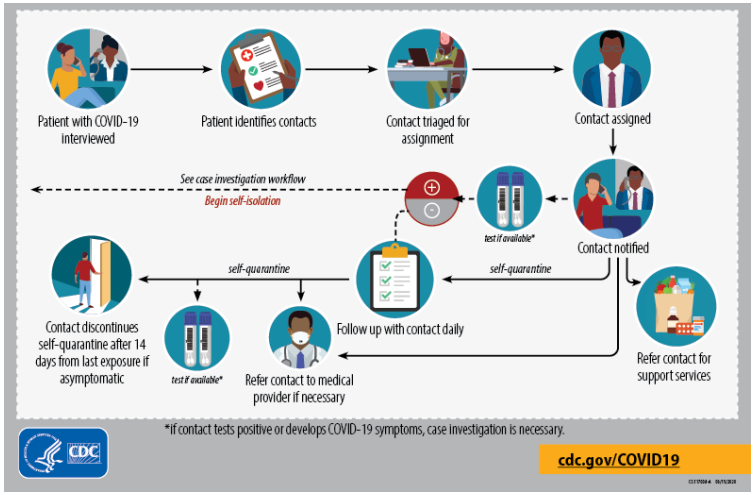
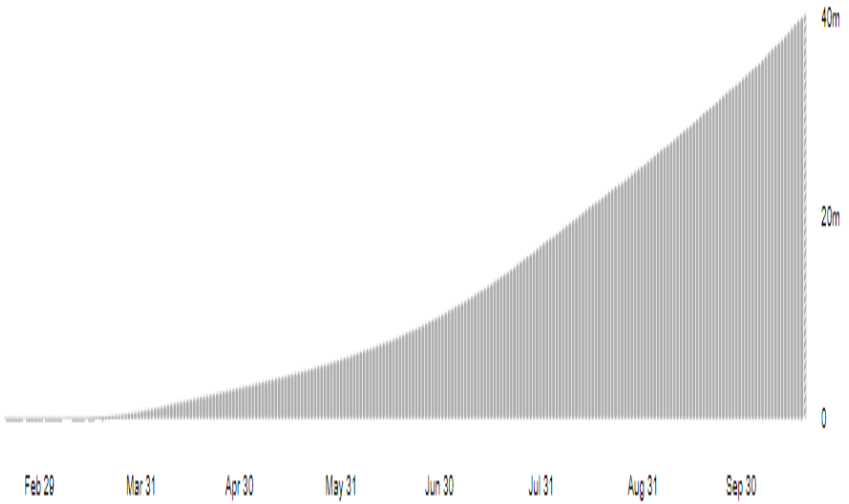
COVID-19 monitoring - Report of October

- Globally, there have been **40.665.438 confirmed cases** of COVID-19.
- In the last months an increase in new cases has been reported.
- New cases are found thanks to intensive screening and the costant monitoring of close contacts.





Source: World Health Organization

Background

- One of the aspects that have emerged in the prevention, therapy and rehabilitation from COVID-19 infection is the **important role played by the immune system.**
- Reduction of CD4+ T cells, CD8+ T cells, and natural killer cells is reported in severely ill patients.
- Increase in T-helper 17 cells is partly responsible for the severe immune injury in the lungs.
- Patients admitted to the intensive care unit (ICU) have higher plasma concentrations of IL-2, IL-6, IL-7, IL-10, and TNF compared to those not admitted to the ICU.


The immunology of COVID-19: is immune modulation an option for treatment?

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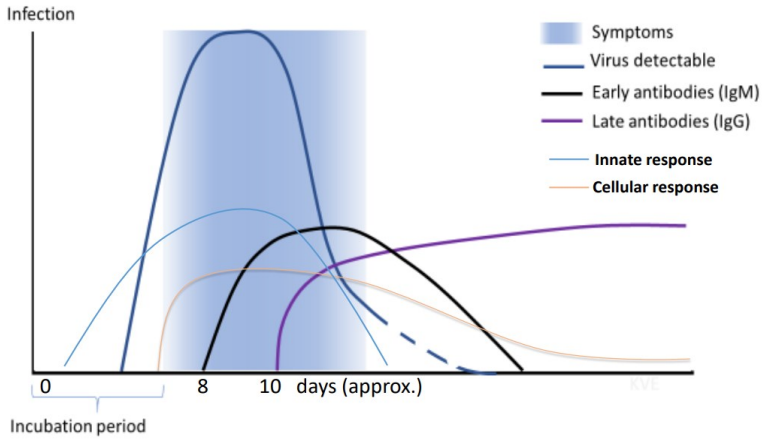
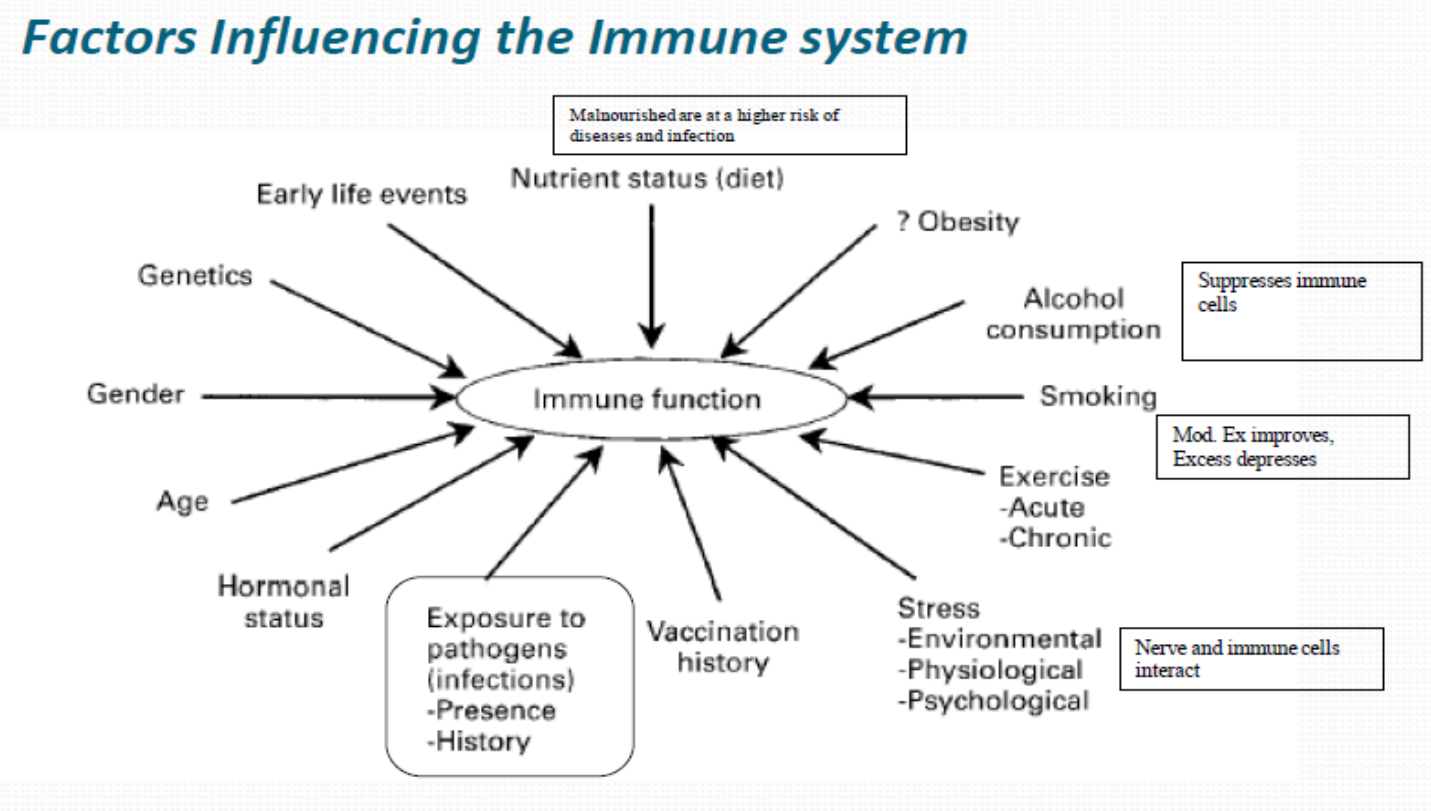
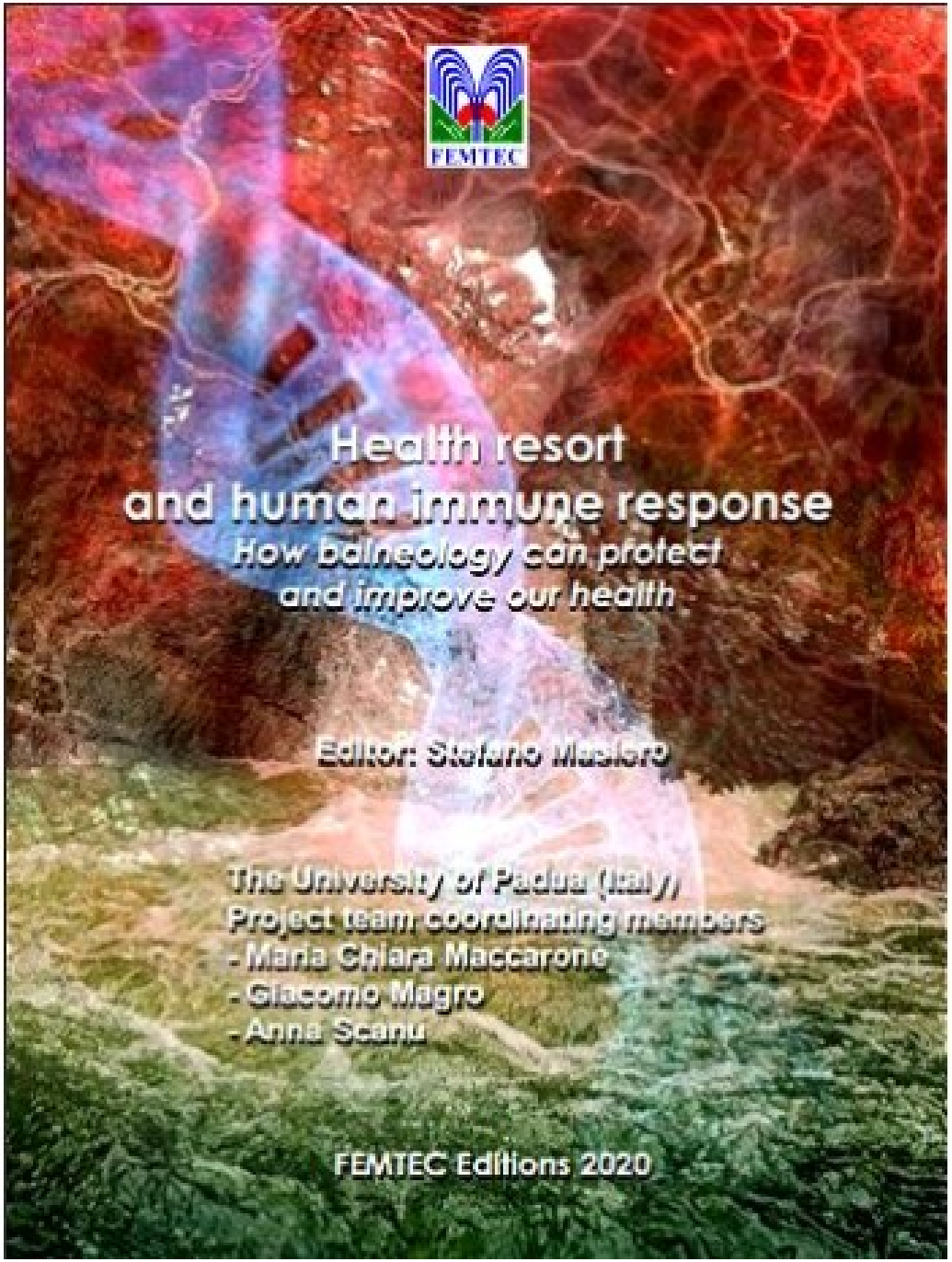


Background



Can health resort medicine play a role in modulating the human immune response?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Aim of the study

- In recent years, there has been an increased interest in the use of preclinical models to investigate the effects of Balneotherapy (BT) on inflammation and immunity.
- Recently, also clinical trials and RCTs have been developed to study the effects of BT on human immune system.
- The biological mechanisms are still not completely understood.

We aim to summarize the current available information about the effects of thermal mineral waters or of their organic and inorganic components on the immune response.

Materials and Methods

Studies were found by screening PubMed and Google Scholar database **from 1997 up to June 2020.**

Keywords: spa therapy, health resort medicine, balneotherapy, mud therapy, immune response, immunity, immune system.

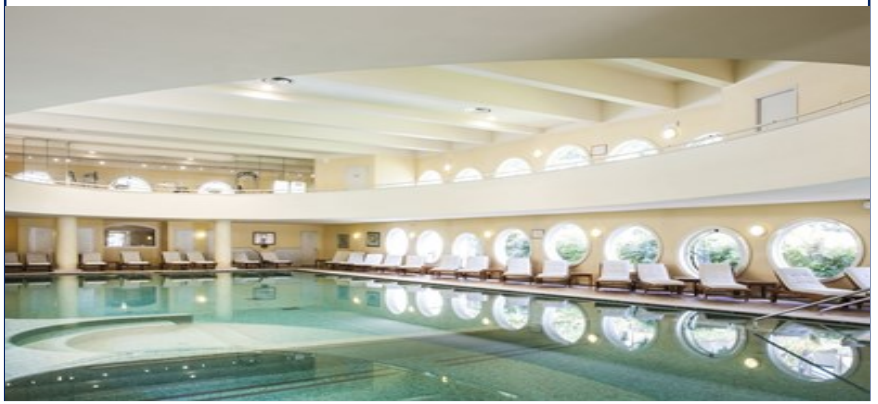
Eligible studies: in vitro research on human or animal samples, randomized controlled trials (RCTs) or clinical trials with health resort medicine as the intervention under study.

Status of health resort medicine and immune system evidence

Effects of BT on immune response in skin diseases

- **In vitro:**
  - **Psoriasis →** ↓ IL-6, IL-8, IL- 17, IL-22, TNF-α, VEGF-A
  - **Rosacea →** ↓ IL-1α, TNF-α, VEGF
  - **Skin diseases →** ↓ IL-6, IL-8, differentiation of CD4+ T cells in Th1, Th2, Th17

- **Clinical trials:**
  - **Psoriasis →**
    - reduction in circulating Th17 after only one week of treatment, reduction in IL-23R and IL17/IL-22 secretion, in T cells producing IL-17 and IL-22, and in Th1 phenotype.



Status of health resort medicine and immune system evidence

Effects of BT on immune response in musculoskeletal diseases

- **In vitro:**
  - **Rheumatoid Arthritis and Osteoarthritis →** ↓ IL-6, TNF-α, NO production, COX-2 and NF-kB activation, Inflammatory processes
  - **Osteoarthritis →** ↓ MMP-2 and MMP14
  - **Osteoporosis →** ↓ osteoclast differentiation, intracellular ROS; ↑ antioxidant gene expression

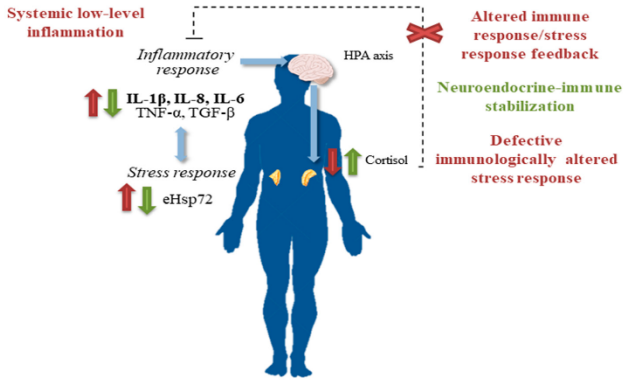
On murine samples:

•**Osteoporosis →** Increases cell proliferation, ALP and SOD activities; decreases apoptosis, NO release, NADPH oxidase activity, and p38/ERK1/2/MAPKs activation.

Status of health resort medicine and immune system evidence

Effects of BT on immune response in musculoskeletal diseases

- **Clinical trials:**
  - **Knee OA →**
    - proinflammatory cytokines IL1β, TNF-α, IL8, IL-6 ↓
    - CD4 CD25 FOXP3 Treg cells, Increase CD8 CD28 Treg cell. ↓ ↑
    - cortisol ↑
    - percentage and phagocytic activity of neutrophils ↑
  - **Ankylosing Spondylitis →**
    - TNFα, IL-1β, and IL-6 ↓
    - TGF-β ↑
  - **Fibromyalgia Syndrome →**
    - PGE2 level, IL1 and LTB4 ↓



Status of health resort medicine and immune system evidence

Effects of BT on immune response in inflammatory diseases

- **In vitro:**
  - **Inflammatory processes →**
    - Decreases proliferation of lymphocyte subsets, CD8+ T and NK cells, IL-2 production and ROS
    - Accelerates the resolution of inflammatory processes
  - **Inflammatory processes of respiratory tract →**
    - Increases short-term survival of neutrophils
    - Reduces caspase-3 cleavage and p38/MAPK phosphorylation in neutrophils
    - Inhibites elastase release
    - Accelerates the resolution of inflammator y processe
  - **Inflammatory processes of systemic lupus erythematosus →**
    - Increases cell proliferation
    - Reduces systemic Lupus erythematosus
- **On murine sample:**
  - **Inflammatory processes of bowel diseases** → Enhances T cell activation, and IL-2 expression; Increases cystathionine γ-lyase and cystathionine β-synthase expression; Reduces inflammatory processes.

Status of health resort medicine and immune system evidence

Effects of BT on immune response in healthy subjects

- Bellometti et al. (1998): **mud pack therapy** → pain relief by reducing the inflammatory reaction
  - 31 subjects
  - mud pack therapy
  - blood samples before and after the therapy to assay serum levels of prostaglandin (PGE2) and leukotriene (LTB4)
  - The study showed a decrease in PGE2 and LTB4 serum levels in all the samples after mud pack therapy.

- Yamaoka et al. (2004): **radon hot spring**
  - white blood cell differentiation antigen (CD8/CD4) assay
  - The study showed that radon therapy
    - enhanced the percentage of CD4 positive cells, which is the marker of helper T cells, and decreased the percentage of CD8 positive cells, which is the common marker of killer T cells and suppressor T cells
    - enhanced the antioxidation functions, such as the activities of superoxide dismutase (SOD) and catalase
    - increased the levels of alpha atrial natriuretic polypeptide, beta endorphin, adrenocorticotropic hormone (ACTH), insulin and glucose-6-phosphate dehydrogenase (G-6-PDH), and decreased the vasopression level.

Status of health resort medicine and immune system evidence

Effects of BT on immune response depending on different kind of waters

Skin diseases

Sulfurous waters → reduce IL- 6, IL-8, IL-17, IL-22; reduce inflammation events typical of psoriatic lesions; reduce MAPK/ERK signaling phosphorylation

Waters rich in sodium, calcium and bicarbonate → reduce VEGF-A expression and secretion and chemotactit effects, reduce IL-6, IL-8, TNF-α.

Muscoloskeletal diseases

Sulfurous waters → reduce cell death and oxidant-induced mitochondrial dysfunction, reduce IL- 6, IL-8, TNF-α, MMP-3 and MMP-13 production, COX-2, osteoclast differentiation, and intracellular ROS levels. Increase osteoblast mineralization. Reduction of the Increased serum PGE2 level, in IL-1 and LTB4 in FM patients.

Acidic sulfate waters, rich in calcium, magnesium and iron → reduce NO levels, iNOS expressions, and apoptosis in OA chondrocytes.

Radon hot spring waters → Decrease levels of TNF-α, IL-1β, and IL-6 in AS patients.

Status of health resort medicine and immune system evidence

Effects of BT on immune response depending on different kind of waters

Inflammatory diseases

Sulfurous waters → increase short-term survival of neutrophils delaying the onset of apoptosis, accelerate the resolution of inflammatory processes, decrease proliferation of CD8+ T and NK cells, and reduced IL-2 production. Reduce ROS, inhibite elastase release. Increase Foxp3 mRNA levels in CD4+ T cells cultured under Treg-polarizing conditions and RORγT mRNA levels in CD4+ T cells under Th17 polarizing conditions. Increase cystathionine γ-lyase and cystathionine β-synthase expression.

Waters rich in sodium chloride, bromine and iodine → reduce TNF-α, IL-1β, IL-6, IL-12, CXCL8, CCL5 production, ROS formation and antioxidant enzymes.

Healthy subjects

Radon hot spring → enhance the percentage of CD4 positive cells and decrease the percentage of CD8 positive cells; enhance the antioxidation functions.

Status of health resort medicine and immune system evidence

Effects of mudpack on immune response depending on different kind of waters

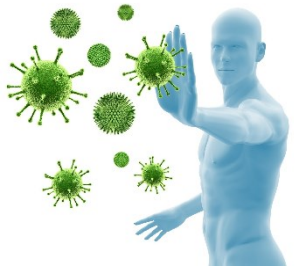
Musculoskeletal diseases

OA → decreases serum concentrations of the pro-inflammatory cytokines IL-1β, TNF-α, IL-8. Reducted percentage of CD4 CD25 FOXP3 Treg cells, increased CD8þ CD28– Treg cell. Increase in the systemic levels of cortisol.

Healthy subjects

Decreased PGE2 and LTB4 serum levels.

Conclusion



- On human in vitro samples, sulphur compounds contained in thermal waters have been shown to exert an **anti-inflammatory action on psoriatic lesions, on arthrosic chondrocytes and on inflammatory processes.**
- In **patients suffering from osteoarthritis**, balneotherapy has demonstrated to have **anti-inflammatory efficacy**, modulating the cytokinic response and modifying the percentage of regulatory T-cells in circulation. After balneotherapy and mud therapy, a reduction in serum levels of pro-inflammatory molecules such as TNF-α, IL-1β, PGE2, LTB4 and C-reactive protein, and an increase in anti-inflammatory molecules such as the IGF-1 growth factor have been shown.
- In patients with **fibromyalgia or ankylosing spondylitis balneotherapy can influence the inflammatory mediators.**
- Balneotherapy should have also an **anti-inflammatory role on healthy subjects**.

CORRESPONDENCE

Health resort medicine can be a suitable setting to recover disabilities in patients tested negative for COVID-19 discharged from hospital? A challenge for the future

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- The **positive social atmosphere** of health resort medicine may also play a therapeutic role on the immune system.

In the future…

- These effects on the immune system can be seen as an opportunity, exploiting it for example for preventive treatments and therapeutic paradigm that can address the COVID-19 infection outcomes.

Fioravanti et al. 2011
Masiero et al. 2020

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