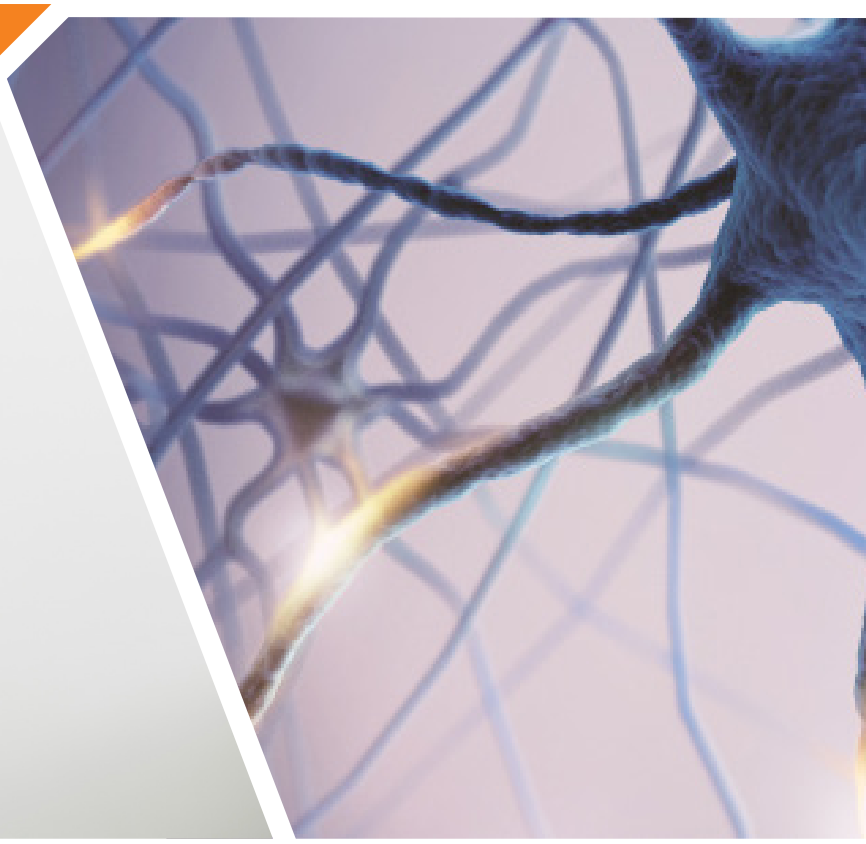
Micro-immunotherapy
International Medical Experience

Leaky Gut Syndrome:
The Micro-immunotherapy Approach



This brochure is for doctors and other health professionals only

Summary

Increased gut permeability (Leaky Gut Syndrome) can trigger uncontrolled inflammatory processes with consequences on various systems. This “silent” inflammation can over time lead to various diseases such as allergies, autoimmune diseases or neuropsychiatric and/or neurodegenerative disorders (e.g. depression). By regulating inflammation and dampening it to a healthy, protective level, micro-immunotherapy, an immunomodulatory approach, contributes to bringing the affected systems back to balance and thus provides a long-term benefit to patients with gut-derived systemic inflammation and associated diseases.

Introduction

The gut and its associated systems (enteric nervous system, immune system, endocrine system, microbiome) represent a closely interconnected network. In addition to the assimilation of food and the induction of oral tolerance, it protects the human body from harmful substances and environmental influences. When the intestinal barrier is functioning properly, it is able to selectively introduce important nutrients into the bloodstream, including vitamins, electrolytes and trace elements, and to protect the body from the presence of foreign elements and pathogens, all in close collaboration with gut symbionts.

In contrast, in Leaky Gut Syndrome, the protective function of the intestinal barrier is limited. Leaky Gut Syndrome is related to several factors, such as insufficient intake of foods with enzymatic capacity, fermentation and decomposition processes (ammonia), as well as heavy metals, microbial neurotoxins and microorganisms. These factors keep the immune barrier in a state of alarm that promotes inflammation. Initially, the barrier emits local, intestinal but also extra-intestinal warning signals, gradually triggering ever-increasing inflammatory processes, which are ultimately responsible for abdominal pain. It is now known that these processes in turn can trigger associated diseases. Examples include allergies, autoimmune tendencies or neuropsychiatric disorders associated with chronic inflammation such as depression[7,11,14].

The Intestinal Barrier: An Interface

In the small intestine, the intestinal mucosa consists of an epithelial lining with specialised ciliated cells with microvilli, enterocytes, goblet cells, M-cells and Paneth cells, which adhere to the lumen of the intestine. The highly prismatic epithelial cells are attached to each other by tight junctions. Beneath the epithelial layer lies the lamina propria, a connective tissue membrane with numerous immunocompetent cells. This structure enables the intestinal immune system (Fig. 1) to recognise antigens in the intestinal lumen and tolerate them if they pose no danger to the organism, or to initiate an adaptive immune reaction if unwanted intruders/pathogens are detected. Among these immunocompetent cells are:

- **Dendritic cells** with the ability to uptake antigens present in the intestinal lumen and present/activate both T cells and B cells which reside in the lamina propria.
- **M cells in Peyer’s patches:** Enterocytes specialised in antigen uptake and transfer to the lamina propria.
- **Resident epithelial cells and macrophages:** Antigen-presenting cells which can activate the production of cytokines and antimicrobial substances, stimulate the differentiation and development of epithelial cells and maintain tight junctions[13].
- **Intraepithelial lymphocytes:** Lymphoid cells resident in the intestinal epithelium with immunoregulatory capacity which preserve barrier integrity and possess cytotoxic activity.

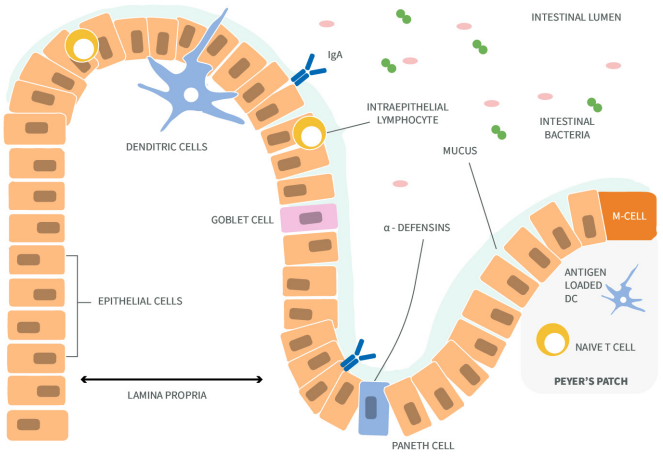


Fig. 1: Overview of the intestinal wall, immune cells and the microbiome

The information collected by these cells activates T lymphocytes in the lymph nodes, which then differentiate into different subtypes of effector T lymphocytes, and B cells which differentiate into antibody-producing plasma cells. Via systemic circulation, these activated cells return to the intestinal mucosa, where they produce specific cytokines and synthesise protective IgA (sIgA).

The gut microbiota is also an essential component of the barrier. It contains more than 10^{14} bacteria and is strongly influenced by genetics, lifestyle, diet and the intake of certain medications (e.g. antibiotics). The microbial ecosystem is of crucial importance for immune function. A healthy, highly diverse gut microbiota curbs the overgrowth and activity of harmful bacteria, fungi, parasites and viruses and trains the immune system throughout life to maintain physiological oral tolerance[1].

Disorders Of The Intestinal Barrier

In Leaky Gut Syndrome, the protective mechanisms of the gastrointestinal tract are impaired. On the one hand, dysbiosis can lead to inhibition of the renewal of the mucous layer, which is essential for preventing microbial adhesion to the epithelial layer as it contains antimicrobial substances. In dysbiosis and Leaky Gut Syndrome, the mucus layer thins down and less protective IgA is produced. On the other hand, tight junction dysfunction is associated with increased intestinal permeability and the penetration of harmful substances such as putrefactive substances, fermentation products and toxins into the body.

Various factors can negatively influence the gut microbiome, damage the protective mucosa and reduce the production of IgA, thus triggering a Leaky Gut Syndrome. These include today's very unbalanced and widespread Western diet, characterised by industrial foods and the intake of cereal products rich in gluten and casein[12]. Alcohol, uncritical use of antibiotics, chronic stress[10], nutrient deficiencies, as well as infections of the digestive tract are further factors which contribute to impairing the protective function of the intestinal barrier.

From Leaky Gut To Autoimmune Diseases And Depression Through Inflammation

If the intestinal microbiota is damaged, harmful bacteria, toxins and heavy metals can accumulate in the intestinal mucosa. If harmful substances enter the bloodstream, inflammatory processes are initiated, mainly controlled by pro-inflammatory cytokines such as interleukin 1 (IL-1), interleukin 6 (IL-6) and tumour necrosis factor alpha (TNF-α).

This gradually increasing silent inflammation, characterised by an overexpression of the TH1 response and a reduction in anti-inflammatory TH2 and TH3 cytokines, can lead to intestinal or extraintestinal symptomatology with indeterminate complaints, often resulting in misdiagnosis. This inflammatory state can spread through the blood, the lymphatic and the nervous system to other organs, and even lead to the recognition of one's own molecules and structures as foreign, favouring the onset of autoimmune diseases (e.g. CIDs, Hashimoto's, autoimmune hepatitis, type 1 diabetes, multiple sclerosis, endometriosis, lupus)[6,7]. (Fig. 2)

In addition, the gut is in active exchange with the brain (gut-brain axis) via nerve pathways (especially the enteric nervous system and the vagus nerve), messenger substances and microbial metabolic products, constantly influencing each other. Over time, gut-derived systemic inflammation can lead to the disruption of epithelial tight junctions in the blood-brain barrier, further exacerbating the inflammatory response and increasing the risk of neuroinflammation and associated psychological disorders such as depression[2,5]. (Fig. 3)

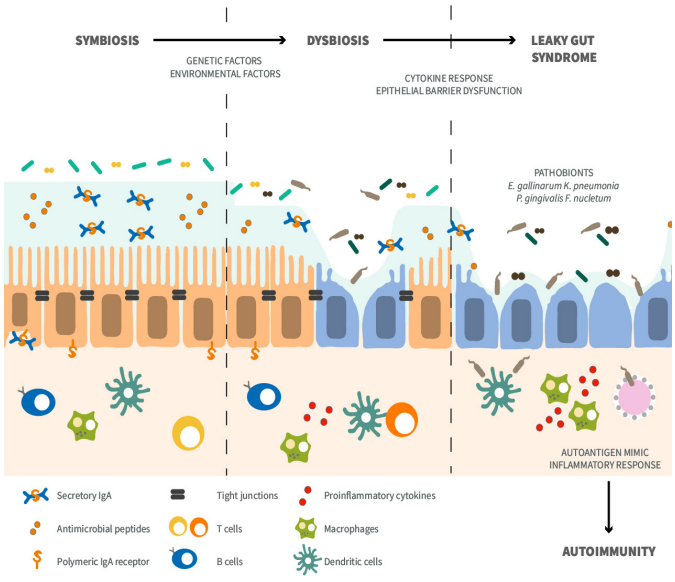


Fig. 2: Autoimmune responses induced by dysbiosis and Leaky Gut Syndrome.

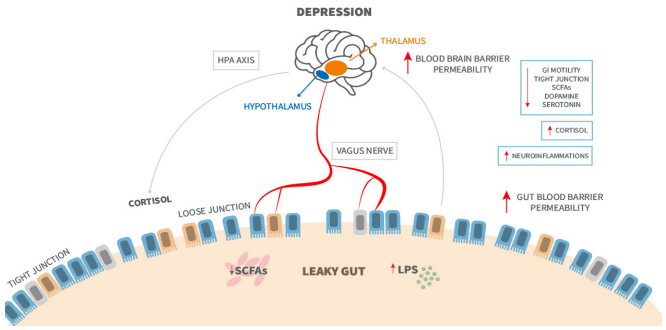


Fig. 3: Connection between Leaky Gut Syndrome and neuroinflammation.

The Micro-immunotherapy Approach

The treatment of Leaky Gut Syndrome is crucial in the prevention and treatment of various diseases associated with gut-derived systemic inflammation. In this context, micro-immunotherapy (low-dose immunotherapy) is aimed at regulating uncontrolled inflammatory processes in order to reestablish an appropriate immune response, thus contributing to intestinal health and overall balance in the organism.

The proinflammatory immune response is an extremely important and powerful protective function of the body. If the immune system detects the threat of a pathogen, proinflammatory TH1 type cytokines are released to deal with microorganisms. However, this reaction needs to be precisely coordinated and regulated so that, after successful elimination of the pathogen, it can be resolved smoothly, allowing for the re-establishment of homeostasis. If this is not the case, as in leaky gut syndrome, chronic inflammation (silent inflammation) and the so-called TH1 switch may damage cells and tissue systems.

The aim of micro-immunotherapy in these cases is to break this vicious circle of inflammation and to bring about a physiological normalisation of the immune response. Low and ultra-low doses of cytokines and other immune messenger substances are administered sequentially to modulate the immune system in a gentle way and thus train it back to a balanced response. Micro-immunotherapy uses these immune mediators in concentrations equal or below the physiological concentrations at which they naturally circulate in the organism, and is therefore well-tolerated.

The administration of the active substances in varying concentrations allows for the functions of the immune system to be stimulated, modulated or inhibited depending on each specific clinical condition. The fine-tuned action of micro-immunotherapy draws from the principle of hormesis[3,4] and the clinical experience of health professionals applying micro-immunotherapy in their daily practice[9].

Study

The anti-inflammatory effect of specific micro-immunotherapy formulas

Special Focus on the Cellular Anti-Inflammatory Effects of Several Micro-Immunotherapy Formulations: Considerations Regarding Intestinal-, Immune-Axis-Related- and Neuronal-Inflammation Contexts

Micro-immunotherapy offers specific formulas aimed at dampening inflammation and that can be integrated into a multimodal treatment strategy to prevent or treat disorders associated with increased intestinal permeability and systemic inflammation*:

Formula **MICI**

Fields of application

- Inflammatory bowel diseases (irritable bowel syndrome, Crohn's disease, ulcerative colitis)

Immunoregulatory objectives

- Reestablish the balance between the signalling pathways involved in the development or persistence of inflammatory processes.
- Limit the TH1 response by downregulating the activity of cytokines such as IL-1 and TNF-α.
- Favour the activity of TH2 and TH3 anti-inflammatory cytokines (IL-4, IL-10).

Dosage

1 per day

- **Maintenance therapy**

Formula **INFLAM**

Fields of application

- Acute, subacute and chronic (low-grade) inflammation and associated diseases.
- Soft tissue, systemic and metabolic inflammation.

Immunoregulatory objectives

- Inhibit proinflammatory pathways by downregulating TH1 cytokines
- Stimulate anti-inflammatory pathways by upregulating TH3 cytokines and maintaining the activity of TH2 cytokines.
- Counteract harmful metabolic effects of chronic processes.

Dosage

3-4 per day

- **Acute Inflammation:** Until symptoms improve

↓ Afterwards dose reduction.

1 per day

- **Maintenance therapy** Until symptoms disappear or even longer (3-6 months), depending on the clinica condition.

Formula **DEP**

Fields of application

- Depressive mood
- Mild depression
- Burnout
- Inflammatory fatigue / Sickness behaviour syndrome

Immunoregulatory objectives

- Balance dysregulations of the HPA axis.
- Reestablish the TH1/TH2/TH3 balance, dampen inflammation and regulate the kynurenine metabolism
- Promote neuroregeneration and neuroplasticity.

Dosage

2 per day

↓ Reduction of dose once symptoms improve.

1 per day

- 3-6 months

Note:
Hidden infections may be among the factors contributing to systemic inflammation by overburdening the immune system. Depending on the clinic of the patient, it may be advisable to rule out microbial burdens diagnostically. Should a burden be confirmed, micro-immunotherapy formulas aimed at supporting the immune response in “silent” infections can be added to treatment (e.g. Formulas EBV, CMV, CHLA, TOXO)

According to the clinical experience of doctors of the International Micro-immunotherapy Associations (AEMI, IFMi, MeGeMIT). The choice of formulas will depend on the patient’s clinical picture, the criteria of the health professional, the individual risk factors of the patient and laboratory test results. It is recommended to ensure adherence to treatment by first addressing the factors that are most directly related to the patient’s clinic.

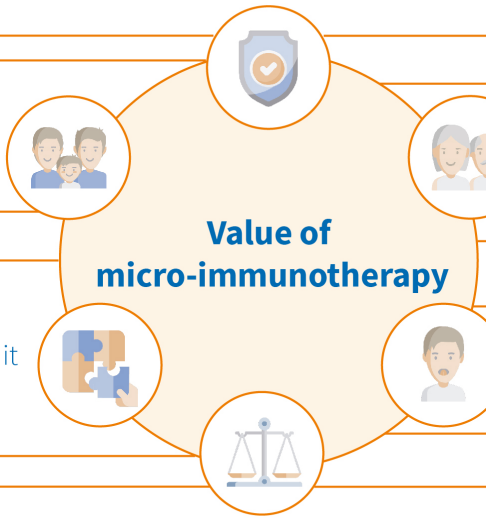
Clinical Benefit Of Micro-Immunotherapy In Leaky Gut Syndrome

In Leaky Gut Syndrome and associated conditions, micro-immunotherapy represents a valuable treatment option with various clinical benefits:

Given the sequential administration of low doses of cytokines and other immune messenger substances, micro-immunotherapy communicates with the immune system in a gentle and non-invasive way, allowing to **sustainably readjust the inflammatory response** to a protective level without producing undesired side-effects, while at the same time preventing medication overload.

It can be recommended to **patients of all age groups,** as it has **a good safety profile** and is **well-tolerated.**

It is of special interest as an immune supportive treatment in **elderly and/or polymedicated patients.**



It can be synergistically combined with other treatment approaches (e.g. medication, supplements) as it uses low and ultra-low doses of immune mediators.

It is **easily taken sublingually,** thus ensuring adherence to treatment.

It downregulates the proinflammatory response by **readjusting the dysregulated immune signalling pathways** in gut-derived systemic inflammation, thus **addressing the root mechanisms** that underlie leaky gut syndrome and associated conditions.

Synergies With Other Therapeutic Approaches

Prevention and treatment of diseases related to intestinal inflammation should be based on a multilevel, synergistic approach that considers the individual factors contributing to systemic imbalances in affected patients. These factors (immune stressors) include chronic stress, silent infections or virus reactivations, diet or lack of exercise. Checking for micronutrient deficiencies and analysing the gut microbiome are also key diagnostic steps prior to applying therapeutic measures aimed at regenerating the intestinal wall.

Given the key role of the intestinal immune system in the body's overall regulatory mechanisms, regulating immune signalling pathways towards balance is essential in disorders associated with intestinal inflammation. In this context, micro-immunotherapy's immunoregulatory action may be combined with the following therapeutic measures to reestablish intestinal and overall balance in the organism:

- Regular exercise
- Stress management
- Sufficient sleep
- Dietary changes: avoiding industrial foods, gluten and alcohol
- Balancing the gut microbiome through probiotics and prebiotics (from a mainly plant-based diet, with fresh foods, and/or supplementation if needed)
- Regenerating the intestinal mucosa
- Balance micronutrient deficiencies (e.g. vitamin D, vitamin B3, B6, B12, zinc, magnesium)

Conclusion

The gastrointestinal tract, and particularly the gut as a major immune organ, is one of the main pillars of health. It has a predominant influence on the integrity, tolerance and functions of the human immune system and associated systems. Based on current scientific knowledge, it should in future be the focus of attention for disease prevention, health promotion and become central to therapeutic measures.

In this respect, micro-immunotherapy's immunoregulatory action can be of great help as part of an integrated treatment plan that seeks to sustainably reestablish homeostasis in patients suffering from diseases associated with increased intestinal permeability and gut-derived inflammation. Addressing individual stressors (e.g. "silent infections", chronic stress, diet), regenerating the intestinal wall and rebalancing inflammatory signalling pathways are key therapeutic measures to target the underlying causes of disease and sustainably reestablish balance in the organism.

Literature

1. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell. 2014 Mar 27;157(1):121-41.
2. Beurel E, Toups M, Nemeroff CB. The Bidirectional Relationship of Depression and Inflammation: Double Trouble. Neuron. 2020 Jul 22;107(2):234-256.
3. Calabrese EJ, Mattson MP. How does hormesis impact biology, toxicology, and medicine? NPJ Aging Mech Dis. 2017 Sep 15;3:13.
4. Calabrese EJ. Hormesis: a fundamental concept in biology. Microb Cell. 2014 Apr 23;1(5):145-149.
5. Clapp M, Aurora N, Herrera L, Bhatia M, Wilen E, Wakefield S. Gut microbiota's effect on mental health: The gut-brain axis. Clin Pract. 2017 Sep 15;7(4):987.
6. Fasano A. All disease begins in the (leaky) gut: role of zonulin-mediated gut permeability in the pathogenesis of some chronic inflammatory diseases. F1000Res. 2020 Jan 31;9:F1000 Faculty Rev-69.
7. Fasano A, Shea-Donohue T. Mechanisms of disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases. Nat Clin Pract Gastroenterol Hepatol. 2005 Sep;2(9):416-22.
8. Ganal-Vonarburg SC, Duerr CU. The interaction of intestinal microbiota and innate lymphoid cells in health and disease throughout life. Immunology. 2020 Jan;159(1):39-51. doi: 10.1111/imm.13138. Epub 2019 Nov 27.
9. Jacques C, Floris I. Special Focus on the Cellular Anti-Inflammatory Effects of Several Micro-Immunotherapy Formulations: Considerations Regarding Intestinal-, Immune-Axis-Related- and Neuronal-Inflammation Contexts. J Inflamm Res. 2022 Dec 13;15:6695-6717.
10. Madison A, Kiecolt-Glaser JK. Stress, depression, diet, and the gut microbiota: human-bacteria interactions at the core of psychoneuroimmunology and nutrition. Curr Opin Behav Sci. 2019 Aug;28:105-110.
11. Mu Q, Kirby J, Reilly CM, Luo XM. Leaky Gut As a Danger Signal for Autoimmune Diseases. Front Immunol. 2017 May 23;8:598.
12. Obrenovich MEM. Leaky Gut, Leaky Brain? Microorganisms. 2018 Oct 18;6(4):107. doi: 10.3390/microorganisms6040107. PMID: 30340384; PMCID: PMC6313445.
13. Peterson LW, Artis D. Intestinal epithelial cells: regulators of barrier function and immune homeostasis. Nat Rev Immunol. 2014 Mar;14(3):141-53.
14. Sonali S, Ray B, Ahmed Tousif H, Rathipriya AG, Sunanda T, Mahalakshmi AM, Rungratanawanich W, Essa MM, Qoronfleh MW, Chidambaram SB, Song BJ. Mechanistic Insights into the Link between Gut Dysbiosis and Major Depression: An Extensive Review. Cells. 2022 Apr 16;11(8):1362.

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Contact us / visit our website:

mi@micro-immunotherapy.com

www.micro-immunotherapy.com