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IMMUNO-MEDIATED DISEASES OF THE GI TRACT: WHERE DO WE STAND?
Symposium 238 | Florence | November 8–9, 2024
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Listening to and learning from each other

It's a rare opportunity when high-ranking experts on 4 vastly different yet related topics such as eosinophilic esophagitis (EoE), celiac disease, inflammatory bowel disease (IBD), and microscopic colitis (MC) get together for intensive discussions. The meeting in Florence offered participants the opportunity to get an overall impression of their own research discipline as well as that of other fields.

Scientific organizers:
Flavio Caprioli, Nicola de Bortoli, Axel Dignass, Iris Dotan, Edoardo V. Savarino

This was exactly what the organizers had intended when they came up with the innovative strategy for the meeting. Rather than focusing each individual session on a single disease, in this format each session was built around a specific topic, including epidemiology, pathophysiology, monitoring algorithms, existing and future treatment options, dietary strategies, and patient preferences. This allowed the many participants – many themselves seasoned gastroenterologists – to dive deeper into specific aspects across each of the four featured indications.

With the focus on these topics, it was encouraging to see how much knowledge about IBD has already been gathered and fascinating to observe how microscopic colitis remains relatively unexplored and underestimated. When it comes to therapy, huge differences also came to light. While with IBD, a whole arsenal of biologics is available, patients with celiac disease have to make do with the only "magic bullet" available to them: the gluten-free diet, which is challenging to adhere to and expensive.

The latest findings on EoE were also very encouraging. Knowledge about EoE is increasing, and we are making progress. At the same time, it's difficult to keep patients motivated. Compliance rates of just 40% mean that we have to come up with a new strategy. It's a Herculean task to empower patients to take action for their disease themselves.

All 4 conditions were discussed at each session. Experts on celiac disease were able to learn from microscopic colitis specialists. The concerns of the speakers on EoE could be shared with IBD experts. This all led to a lively and energetic discussion.

A number of young scientists presented their own research projects in the form of poster presentations that attendees could visit during the breaks. Three posters on innovative topics were honored with awards. The significance of research was obvious during nearly every session, since there is still a shortage of biomarkers and conclusive monitoring concepts. The search for still more effective and safe options for therapy will most likely never stop. Creativity is called for.

This also applies to the dietary approach. Not every condition requires a special diet. A healthy, varied diet that is predominantly plant-based (Mediterranean) can be highly effective. New technologies, apps, and artificial intelligence can make diets more individualized. But no matter what, in Florence it became evident that the only truly effective therapy is one developed not just for the patients, but in collaboration with them.

EoE: Successful Therapy Thanks to Shared Decision-making

The pathophysiology and monitoring of eosinophilic esophagitis (EoE) is complex and presents significant challenges for GI specialists. Managing the condition is further complicated by the demanding nature of the therapy and frequent patient noncompliance. To make progress and prevent emergencies caused by food obstruction, close collaboration and coordination with patients is essential.

Among the immune-mediated GI tract disorders, EoE is a relatively recent focus of medical attention, having emerged as a distinct condition only in the early 21st century. Diagnostic and therapeutic guidelines for EoE were not introduced until 2007.The condition predominantly affects boys and men in industrialized countries, with a worldwide incidence of 5.3 cases per 100,000 patient years. However, there are significant regional differences. For example, EoE is more frequently diagnosed in southern Spain than in the north of the country. However, according to **Dr. Christopher Ma**, Calgary (Canada), the incidence of EoE has been rising. The increase in diagnoses cannot be attributed to the higher number of biopsies, however. While the number of biopsies doubled between 1997 and 2012, the incidence of EoE has increased 25-fold since then. According to Ma, this is due to the introduction of a formal definition for EoE, which contributed to a 20-fold increase in the incidence of the disease. Ma thus suggested that increased awareness of EoE is responsible for the rising incidence.

The average global prevalence of EoE currently stands at 40 cases per 100,000 inhabitants. As the incidence continues to rise slightly and EoE is a chronic disease, the prevalence of EoE is expected to increase for several years until a plateau has been reached, Ma said. Given the progressive and chronic nature of EoE, as the number of cases grows, Ma predicts that the number of patients with esophageal fibrosis will also increase, in turn leading to a rise in the number of obstruction-related emergencies. The past 10 years have seen a dramatic increase in the number of such complications. This means that the increase in number of serious complications will outpace the linear trend observed thus far. Ma expects that the Western industrialized nations could reach a phase of prevalence equilibrium starting from around 2050 (Fig. 1).

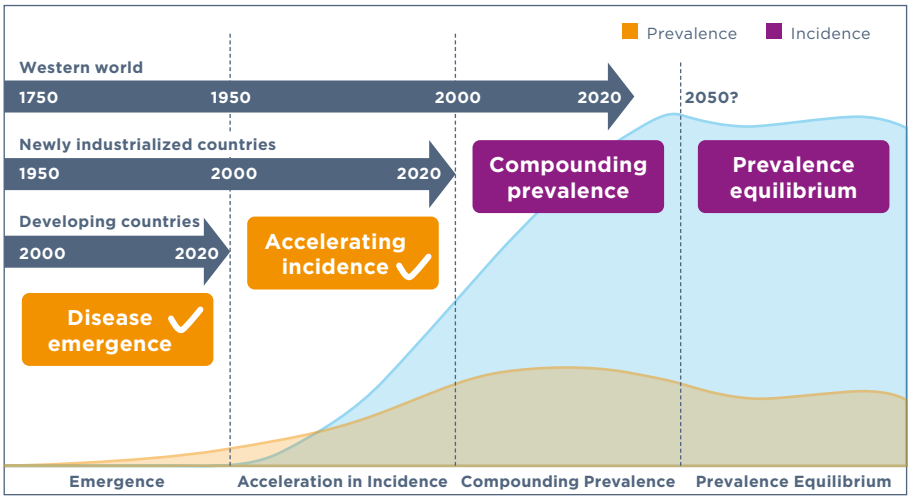


Fig. 1. Development of the incidence and prevalence of EoE worldwide. The Western industrialized countries are currently in a phase of increasing prevalence (modified after Kaplan GG, Windsor JW. The four epidemiological stages in the global evolution of inflammatory bowel disease. Nat Rev Gastroenterol Hepatol. 2021 Jan;18(1):56-66. doi: 10.1038/s41575-020-00360-x.)

Driven by Food Allergies – Type 2 Inflammation

Being aware of the pathophysiology of EoE is an important prerequisite for developing suitable therapies, **Dr. Marc E. Rothenberg**, Cincinnati, Ohio (USA), explained. He reported on a study with a drug (benralizumab) that was able to reduce the number of eosinophils in the blood but was unable to improve the signs and symptoms of the disease, as measured with the 4-item Dysphagia Symptom Questionnaire (DSQ) (Fig. 2).

Rothenberg reported that there appears to be an important genetic disposition for EoE. Monozygotic twins have a considerably higher incidence of developing the immune-mediated disorder than dizygotic twins. However, it is notable that dizygotic twins are affected more frequently than normal siblings. The microbiome in the esophagus may play a role, since it develops simultaneously in twins. The esophagus has its own microbiome that is dominated by Firmicutes species and can be reconstituted by means of a fecal microbiota transplant (FMT). The microbiome regulates the development of the epithelium. It is also known that dysbiosis, triggered for example by antibiotic therapy, can predispose patients to an allergic response and increased immunoglobulin E (IgE) levels. Genetics and the microbiome thus both play a role in EoE.

Genetic variants that promote EoE have been known for around 15 years. An overlap with genetic

Question	Response options	Score
1. Since you woke up this morning, did you eat solid food?[b]	No	–
	Yes	–
2. Since you woke up this morning, has food gone down slowly or been stuck in your throat?	No	0
	Yes	2
3. For the most difficult time you had swallowing food today (during the past 24 hours), did you have to do anything to make the food go down or to get relief?	No, it got better or cleared up on its own	0
	Yes, I had to drink liquid to get relief	1
	Yes, I had to cough and/or gag to get relief	2
	Yes, I had to vomit to get relief	3
	Yes, I had to seek medical attention to get relief	4
4. The following question concerns the amount of pain you have experienced when swallowing food. What was the worst pain you had while swallowing food over the past 24 hours?[c]	None, I had no pain	0
	Mild	1
	Moderate	2
	Severe	3
	Very Severe	4

DSQ Dysphagia Symptom Questionnaire
[a]The scoring algorithm was constructed from responses to questions 2 and 3, to ensure that the final DSQ score was driven by the frequency and severity of dysphagia
[b]Responses to question 1 were unscored
[c]Responses to question 4 were not included as part of the psychometric analysis; question 4 is a standalone item on the DSQ

The Dysphagia Symptom Questionnaire (version 4.3) and score for each response option a

Fig. 2. Using the DSQ, the severity of EoE signs and symptoms can be quickly assessed (Source:https://www.researchgate.net/figure/The-Dysphagia-Symptom-Questionnaire-version-40-and-score-for-each-response-option-a_tbl1_319651726. Hudgens S, Evans C, Phillips E, Hill M. Psychometric validation of the Dysphagia Symptom Questionnaire in patients with eosinophilic esophagitis treated with budesonide oral suspension. J Patient Rep Outcomes. 2017;1(1):3. doi: 10.1186/s41687-017-0006-5. http://creativecommons.org/licenses/by/4.0/)

alterations in atopic disorders is striking. The desmosome-regulatory 2p23 gene has been identified as the gene being particularly responsible for EoE, which leads to higher susceptibility to CAPN14-mediated degradation of the desmosomes and, in turn, to increased permeability of the epithelium. In patients with EoE, the 5q22 gene is also often genetically altered. Certain food allergies, such as allergies to milk, egg, legumes, or fish, can then lead to increased expression of thymic stromal lymphopoietin (TSLP). This cytokine activates the innate and adaptive immune response, leads to the delivery of interleukin-4 (IL-4) by dendritic cells and plays a role in the differentiation of native T cells to T_H2 cells, which drive the type 2 inflammation. However, they do this by means of increased secretion of IL-4, IL-13, and IL-5. IL-4 and IL-13 activate the mast cells to a great extent. The mast cells too continue to drive the process further, as Rothenberg explained. It is now believed that the pathogenesis is driven by an IL-13 mediated transcriptome of the epithelial cells with the involvement of eotaxin-3. IL-13 appears to be a central driver of pathogenesis, and Rothenberg considers therapy targeting this mechanism to be highly promising.

The receptors of the cytokine IL-13 include the subunit IL-4Rα, which is targeted by the biologic dupliumab. Studies have shown that the efficacy of this biologic, in terms of achieving histological remission and improving signs and symptoms, is observed only when it is administered in weekly doses. Administering the drug every 2 weeks improved the histology, but not the signs and symptoms. This is where another interface comes into play. The IL-4Rα receptor subunit is involved in signal transmission within the dorsal root ganglia. Thus, a neuroimmune cycle was identified that regulates the allergic inflammation in the esophagus. The pathomechanism of EoE is highly complex and multifaceted, which explains the challenges related to therapy.

Good Monitoring Makes for Good Patient Care

Comprehensive monitoring can ensure that patients receive outstanding care, their symptoms improve, and that the efficacy of their therapy is not overshadowed by the side effects. But monitoring is always only as good as the methods used. In the case of EoE therapy, the main goal is to avoid strictures, but also to prevent food obstruction and malnutrition. This means that the symptoms and the histological and endoscopic activity of EoE must be recorded. A good way to capture endoscopic activity is with the established and validated **EREFS** endoscopic reference score. While the score measures **e**dema, the typical EoE **r**ing structure, **e**xudates, **f**urrows, and **s**trictures, the desired end point of the treatment is improvement in the furrows, exudates, and edema, **Prof. Glenn T. Furuta**, Aurora, Illinois (USA) noted. The EREFS endoscopic reference score is extremely reliable in assessing endoscopic disease activity. Furuta recommended taking biopsy samples from the esophagus regardless of the endoscopic appearance at the time of food impaction. EoE's histological features include an increased number of eosinophils, dilated intercellular spaces, basal cell proliferation, and lamina propria fibrosis.

To determine the severity of EoE, Furuta presented the **I-SEE** index, which was developed by the American Gastroenterological Association. The objective was to combine all disease-related elements to provide patients with information on the severity of their disease. Out of this process an innovative app has developed that can be downloaded from all regular app stores. The I-SEE app reflects the molecular and clinical disease activity in children very well, Furuta said. He recommended always carrying out the monitoring whenever modifying therapy and when there are clinical changes. For children, he recommended sedative-free transnasal endoscopy. The quality of images and samples gained this with method are comparable to conventionally collected samples. Tissue material can be collected using a cyto sponge, which was originally developed for treating suspected Barrett's esophagus or esophageal tumors. EndoFLIP technology can obtain information about the distensibility of the esophagus, Furuta reported.

Current and Future Therapy Options for EoE

The present guidelines enable doctors and patients in Europe to choose between diet-based therapy, proton pump inhibitors (PPIs, off label), topical corticosteroids, and a biologic (dupilumab) that may be used if the 3 aforementioned options do not effectively

control the disease. **PD Dr. Luc Biedermann**, Zürich (Switzerland), and **Prof. Arjan Bredenoord**, Amsterdam (The Netherlands), discussed the advantages and disadvantages of treatment with corticosteroids and biologics. The efficacy of orodispersible budesonide in induction therapy has been clearly demonstrated, Bredenoord said. One advantage of topical corticosteroid therapy is the outstanding histological response and good clinical results. Local fungal infections are rare, and the therapy does not impact morning cortisol levels. The orodispersable budesonide therapy has proved effective for long-term treatment. The complete remission rate after nearly 1 year of therapy was reported to be 16.1%.

A. Bredenoord: **"It requires significant effort on the part of doctors to educate patients about the importance of maintenance therapy and motivate them to adhere to it."**

One ongoing issue in the treatment of EoE is adherence, however. Adherence to both pharmacologic and dietary interventions is poor, with only around 40% of patients following either approach. Younger patients, who have often been managing the condition for years, are frequently less diligent with their therapy. This generally has consequences, since non-compliant patients require esophageal dilation twice as often.

He pointed out that there are significant differences among the different budesonide formulations. The orodispersible formulation available in Europe is highly effective for long-term use, whereas sprays and liquids that need to be swallowed are generally less effective. Additionally, orodispersible budesonide offers a cost advantage over biologics.

L. Biedermann: **"Many patients think that doctors underestimate the adverse effects of drugs."**

Dupilumab targets both the IL-13 and the IL-4 inflammatory route. In terms of histological remission and the DSQ, dupilumab is effective. However, patients prefer a topical medication they can take orally rather than drugs that must be administered subcutaneously or by infusion. The patients' greatest concerns are adverse effects.

When choosing the ideal treatment candidate, different criteria are considered. The guidelines already offer a preselection: Biologics should be used when other therapies are ineffective or are not tolerated. This situation is difficult to judge, however, because the residual symptoms are not always caused by EoE, but may have other causes, Biedermann said.

Other criteria may include costs and comorbidities. In Europe, the cost of daily budesonide in treatment is low, in contrast to that of the biologic. In the United States, the situation is different. The costs for the less effective budesonide solutions are quite high and the difference in costs for the biologic is not as great. However, comorbidities open up another perspective on the choice of treatment. For atopic comorbidities, the biologic may have a broader effect.

Biedermann and Bredenoord discussed pharmacologic developments for EoE therapy in the pipeline. Numerous biologics that target different sites of the inflammatory cascade are currently being investigated in clinical trials. Some potential drugs are derived from the field of inflammatory bowel disease (IBD), including etrasimod, which acts as a B-cell modulator. A drug targeting TSLP (tezepelumab) is also under development. These monoclonal antibodies can be used as alternative treatments when standard medications fail to achieve adequate results.

It All Comes Down to Diet

A diet-based treatment is an important component of EoE therapy in addition to pharmacologic therapy. In many cases, EoE can be successfully managed using elimination diets. However, according to **Prof. Alfredo J. Lucendo**, Tomelloso (Spain), these diets should not just be based on allergy tests, but should omit specific foods. These foods include milk and dairy products, wheat and other gluten-containing cereals, egg, soy/legumes, nuts, and fish/seafood. These items should be eliminated from the patient's diet for 6 to 8 weeks, because experience has shown that most patients react to them.

Once the 6 food groups have been eliminated, an endoscopic procedure can confirm whether the diet has been effective. Then, the food groups are reintroduced to the patient's diet, one by one, over a period of several weeks. This at least is the theory, and there is evidence that this procedure can be effective. On the other hand, considering the specific nutrients, it is obvious that following this diet demands a great deal from the patients. Lucendo discussed a 2-food elimination diet (milk and wheat) as an alternative with **Dr. Nirmala Gonsalves**, Chicago, Illinois (USA), concluding that it can be nearly as effective as the 6-food elimination diet while being better accepted by the patients. Less restrictive diets are not less successful, Lucendo said. Two out of 3 milk-triggered EoE patients also tolerate sterilized and heated milk.

Gonsalves did not agree with this tactic, preferring the approach of initially eliminating 6 foods in the patients in order to reward their patience by gradually adding food groups. If a 1- or 2-food elimination diet is unsuccessful, it means that patients will have additional foods taken away from them.

What should you do if the diet is not effective after 6 weeks?

- Check whether the diet was adhered to or whether there are hidden sources of allergens.
- Ensure that other factors are being treated.
- Check for reflux and aeroallergens and considered the role of seasonality.
- Depending on severity,
  - Undertake empirical elimination of additional foods
  - Switch to drug therapy with topical corticosteroids or dupilumab

Gonsalves added that 45% of the patients who failed to improve in response to the elimination of a single food group benefited from a 6-food elimination diet. Two-thirds of the patients with EoE have more than 1 food trigger. This should be clearly communicated to the patient from the very beginning.

Gonsalves stated that is important to show the patients that the 6-food elimination diet does not have to mean restriction. The elimination diet she presented largely aligns with standard recommendations for a healthy diet: lots of fruits and vegetables, rice and other gluten-free cereals, little meat, and low or unprocessed foods.

As with drug therapy, adherence to the elimination diet is low. One out of 3 patients does not adhere to the diet. More than half of them do not follow the combined recommendations of diet and medication. Younger patients living with the condition for a longer period are less often adherent.

EoE is Rarely the Only Condition

In many cases, EoE is not the only condition that patients with this type of type 2 inflammation suffer from. It is often associated with allergic rhinitis, as **Prof. Alain Schoepfer**, Lausanne (Switzerland), reported, sharing data to support this. Bronchial asthma and topical eczema are also commonly associated with patients who have EoE. Food allergens and airborne allergens, gastric acids, and primary barrier dysfunctions of the epithelium trigger type 2 inflammation, which can lead to broader systemic effects, explained **Dr. Seema S. Aceves**, San Diego, California (USA). Aceves stated that IgE-mediated food allergies and asthma often precede EoE, manifesting in childhood earlier on. The pathogenesis of a food allergy shares similarities with that of EoE, including having the same triggers. Aceves spoke about dust mite-induced EoE, highlighting complications similar to those associated with asthma. The predisposition may also be the same, with certain skin biomarkers linked to food allergies in early childhood.

When EoE occurs in association with other type 2 inflammation-related disorders, a multidisciplinary treatment approach is needed, Aceves continued. Good coordination between family physicians, allergy specialists, and GI specialists is also required to treat the patients holistically. The combined manifestation of atopic dermatitis, asthma, and EoE suggests that a biologic therapy should be considered to target multiple structures simultaneously.

For patients with an IgE-mediated food allergy, dietary treatment may require eliminating more than the 6 most common EoE food triggers. Good coordination among the healthcare professionals involved in the patient's care is essential here as well. Patients with EoE have higher rates of anxiety and depression than the general population. Aceves emphasized the importance of taking signs of these disorders very seriously. X urged attendees to consider the financial burden on patients, recommending a holistic approach to their care and advocated for intensive collaboration among all parties involved in the therapy process.

What Patients Wish For ...

EoE places a substantial burden on patients. The diagnosis, often made late in the disease progression, along with difficult-to-manage manifestations, atopic comorbidities, as well as anxiety and depression, all take a physical, emotional, and financial toll. Studies have shown that the stress caused by EoE impacts patients' medical care, social relations, and emotional well-being, **Dr. Evan S. Dellon**, Chapel Hill, North Carolina (USA), reported. Finding doctors who can offer treatment, arranging regular check-ups, and carrying out the therapy are just one part of the problem. The patients often feel isolated, stigmatized, and left alone with their disease.

Despite these challenges, progress is being made in addressing patients' needs. Patients express a desire for a focused view of their symptoms and their quality of life. According to Dellon, most patients are satisfied with their therapy in terms of managing their symptoms and inflammation. However, some of them wish for a more collaborative approach when it comes to finding the right therapy. Patients involved in selecting their therapy are significantly more satisfied with their treatment.

A key challenge in the treatment of EoE is the disconnect between histological remission and symptom relief. Patients also emphasize the importance of earlier diagnosis and better support for their emotional well-being. Dellon advocated for improved access to therapies and the development of new treatment options.

Celiac Disease – Time for a Pharmacologic Therapy

Celiac disease is inflammation of the bowel caused by gluten contained in wheat, rye, and barley. It affects around 0.9 to 2.5% of the global population. For years, the only therapy has been the gluten-free diet, which causes high living expenses that patients have to cover themselves.

The global prevalence of celiac disease is approximately 1% and is on the rise, as Dr. David S. Sanders, Sheffield (UK), reported in his talk on the epidemiology of celiac disease. Strict gluten intolerance occurs significantly more often in the Global North than in the Global South. Sanders suspects a high number of undetected cases, which could make a screening program worthwhile. What "red flags" suggest suspected celiac disease, and when is a serological test conclusive? The criteria are diverse according to Sanders (see infobox).

Celiac Disease: Who Should Be Tested and When?
Testing for celiac disease should be considered in the following situations:

- Persistent or unexplained abdominal gastrointestinal symptoms
- Failure to thrive in children
- Chronic fatigue
- Unplanned weight loss
- Severe or persistent mouth ulcers
- Unexplained iron, vitamin B_{12} or folic acid deficiency
- Presence of type 1 diabetes
- Diagnosis of autoimmune thyroid disorder
- Symptoms of irritable bowel syndrome

Sanders stated that while celiac disease is usually already diagnosed during childhood, adults are also occasionally diagnosed with the condition. Adults often develop refractory celiac disease, defined as malabsorption syndrome that continues in an adult despite a year of following a strict gluten-free diet. Histology reveals very flat epithelia. As Sanders explained, while this affects only a limited number of patients with celiac disease, it is still important to precisely examine whether they have type 1 or type 2 refractory celiac disease, because the classification is significant for the patient's therapy and outcome. Type 2 refractory celiac disease is linked to a reduced lifespan due to an increased risk of T-cell lymphoma. Patients with type 2 refractory celiac disease typically exhibit clinical signs and look sick. They are usually somewhat older, have experienced unplanned weight loss, have low albumin levels, anemia, and their capsule endoscopy has highly abnormal findings.

Celiac disease can also exert an effect on the central nervous system, Sanders reported. In these patients, notable symptoms are not gastrointestinal but rather cognitive impairment and slowed response time. These cases are difficult to detect. So does that justify setting up a screening program for celiac disease? The results of other screening programs for other conditions would suggest otherwise. Sanders has high hopes for a screening program in Italy evaluating the effectiveness of childhood screening. The high costs of the disease, which can already come about prior to the diagnosis, argues for the screening program. On the other hand, the screening itself is very expensive.

Sanders is also concerned about false-positive screening results. Celiac disease is a heterogeneous disorder. Does this mean that the diagnosis is the same for each patient? More likely than not, because in some cases it can be debated whether the diagnosis and the gluten-free diet, as the sole treatment option, might actually compromise the patient's quality of life compared to life without the diagnosis. So should we do screening or not? This question is still difficult to answer.

How Gluten Interacts with the Immune System

Celiac disease is a T_H1-T cell reaction that activates the cell-mediated immune response, resulting in characteristic small bowel lesions, including villous atrophy and crypt hyperplasia. The disease presentation varies widely, from no or very few signs and symptoms to severe diarrhea and malabsorption. The symptoms can be atypical. The condition can be unequivocally diagnosed through detection of TG2 autoantibodies in serum and a characteristic duodenal histology. One out of 3 adults with celiac disease have an additional autoimmune disorder, often inflammatory bowel disease.

The basis of the immune response to gluten is genetically encrypted. Patients with celiac disease exhibit alterations in the HLA genes, as well as epigenetic changes. Stress, the microbiome, and a diet high in gluten contribute to the development of the disease. While gluten is the primary trigger of celiac disease, it is not the only factor responsible for its development. Numerous cofactors are involved in the inflammation, including bacteria, viruses, and other dietary proteins.

According to **Prof. Detlef Schuppan**, Mainz (Germany), an exact identification of a microbiome contributing to celiac disease has not yet been achieved. Many studies are still needed to answer this question. One interesting discovery is the special peptides with a bacterial origin that mimic the structure of gluten and can trigger a comparable effect. This can cause cross-reactions with certain peptides from Pseudomonas fluorescens, archae, or yeast. This concept has yet to be validated, however, Schuppan said.

D. Schuppan:
"The time for drug therapy is overdue, because the gluten-free diet is costly for patients and significantly compromises quality of life."

He pointed out a long list of foods that can serve as hidden sources of gluten. A common characteristic of all these foods is their high degree of processing. This highlights the challenges of adhering to a strict gluten-free diet, which can result in a significant reduction in quality of life, comparable to the impact of hemodialysis, Schuppan continued. Transglutaminase-2 activity plays a crucial role in celiac disease and may serve as a key target for drug therapy. Currently, a highly specific transglutaminase-2 inhibitor is undergoing evaluation in a phase IIb trial, and the findings are eagerly awaited.

Still No Consensus on Celiac Disease Monitoring

While a good algorithm exists for diagnosing celiac disease, further post-diagnosis monitoring of the patients is not so straightforward. Monitoring must be carefully considered, because with the large number of cases, it ties up a great deal of resources said **Dr. Luca Elli**, Milan (Italy). The monitoring should be geared toward the results that can be achieved through the gluten-free diet. These may include:

- A decrease in symptoms
- A negative antibody status
- A recovery of the duodenal mucosa.

Long-term goals include preventing complications, inducing and maintaining remission, ensuring good quality of life, and improving the patient's overall health. The benefits of the gluten-free diet do not manifest simultaneously and certainly not immediately. Symptoms typically improve within weeks, but it takes months for antibody levels to decrease, and years for mucosal healing to occur. Elli emphasized the importance of monitoring therapy adherence and using histological evaluation to assess disease activity. It is well known that many individuals with celiac disease occasionally deviate from their strict diets despite understanding the consequences. As Elli demonstrated, however, this behavior is not reflected in histological findings. Patients who do not strictly adhere to their diets show no significant histological differences compared to those who follow a strict gluten-free diet. Elli noted that this indicates the high variability in disease activity.

A biopsy is recommended only when systems persist despite the gluten-free diet, when additional symptoms occur, when type 2 transglutaminase antibodies are found in the serum, and when patients request one. The titers of the type 2 transglutaminase antibodies should be regularly checked. If the gluten-free diet remains ineffective or there is suspicion of refractory celiac disease, a capsule endoscopy may be a good solution for monitoring. Elli shared the guideline recommendations for monitoring (see infobox).

Key Recommendations for Monitoring Patients with Celiac Disease:

- The type 2 transglutaminase antibodies (TG2Ab) titers should be regularly checked, because a persistent elevation is an indication of exposure to gluten; however, normal levels of TG2Ab are not a sensitive marker for mucosal damage.
- Nutritional tests for patients following the gluten-free diet should target deficiencies identified at diagnosis, with a particular emphasis on iron and vitamin D levels.
- Evaluating therapy adherence through assessments by specialized dietitians appears to be more effective than relying solely on adherence questionnaires. However, combining dietary evaluations, adherence questionnaires, and tests for gluten immunogenic peptides also appears to be more accurate than dietitians' evaluations alone.

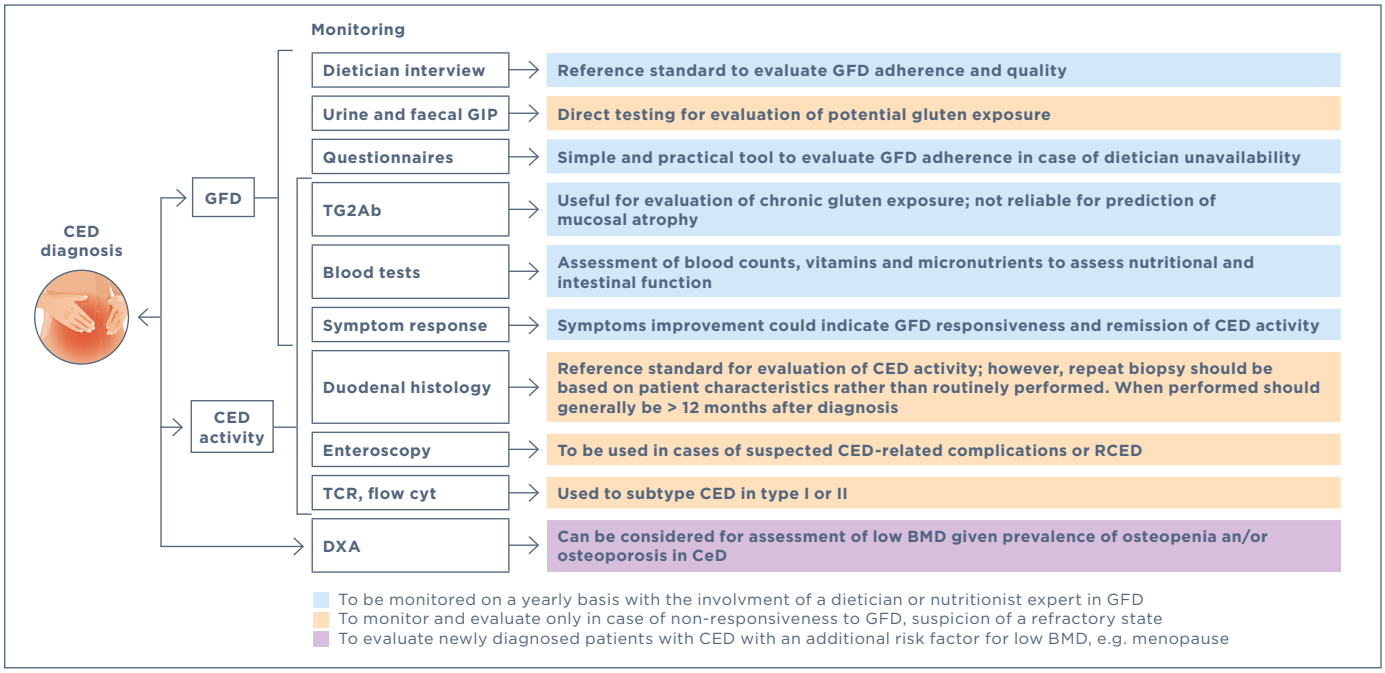


Fig. 3: Summary of the most important biomarkers, clinical parameters, and tests used to monitor celiac disease activity and the gluten-free diet (modified after Elli L. et al. Nat Rev Rev Gastroenterol Hepatol 2024;21:198–215)

The Quest for a Pharmacologic Therapy for Celiac Disease

For some patients, adhering to the gluten-free diet is very difficult. Adherence rates are between 23% and 98%. This is due to the incompatibility of the diet with many day-to-day situations, as well as the high costs of the diet. Despite adherence to the diet, only 60 to 80% of patients experience mucosal healing and in some cases, still develop complications. The gluten-free diet is not suitable for treating extraintestinal comorbidities. For this reason, the development of a pharmacologic therapy for celiac disease that can be used to complement the gluten-free diet is very important, **PD Dr. Michael Schumann**, Berlin (Germany), explained.

Endopeptidases may offer a potential treatment option. Gluten, a peptide that is difficult to digest, consists of 2 main components: gliadin, which is soluble in alcohol, and glutelin, which is not. The immune reaction is triggered by gliadin. Studies have shown that endopeptidases can degrade 97 to 99% of gluten in healthy volunteers. However, even this small remaining percentage may still be enough to trigger an immune response.

Additionally, transglutaminase inhibitors are under investigation. These inhibitors work by preventing the transglutaminase enzyme in the small intestine from deamidating the residual glutamine in gluten peptides, which prevents the stimulation of T cells. Final results from phase IIb trials are expected soon.

Another approach involves restoring gluten tolerance using gliadin nanoparticles. These nanoparticles are administered intravenously and are metabolized by macrophages and dendritic cells, a method that has already shown success in mice. Still other studies are exploring the use of anti-interleukin-15 antibodies. Research is also focused on mechanisms to induce mucosal healing and address T cells as part of the therapeutic approach.

The Gluten-free Mediterranean Diet – (Not) a Panacea

Patients with celiac disease have to be prepared for different systemic consequences of their condition. One notable sign is weight gain after they start following the gluten-free diet. Although the metabolic syndrome is typical, patients do not develop type 2 diabetes at a higher rate. However, the risk of cardiovascular disorders is significantly elevated. As a result of following the gluten-free diet, some patients do not reach the recommended daily doses of fiber, vitamin D, magnesium, calcium, and iron, **Nick Trott**, Sheffield (UK), said. Trott sees gluten-free foods as problematic, because they are often high in calories and contain too many carbohydrates and saturated fatty acids. The sodium content is also usually too high. On the other hand, they usually contain too little protein, folic acid, zinc, and iron.

Studies have shown that a Mediterranean diet significantly lowers the risk of cardiovascular incidents, Trott said. The diet also lowers the risk of diabetes and cancer. The Mediterranean diet is based on vegetables, fruit, whole-grain bread and cereals, along with extra virgin olive oil, nuts, legumes, seeds, herbs, and spices. Individuals following the Mediterranean diet should avoid highly processed foods as well as red meat and sweets. Trott explained how the Mediterranean diet can be adapted to a gluten-free Mediterranean diet. Cereals can be exchanged for pseudocereals, such as buckwheat, amaranth, quinoa, or chia, or for gluten-free cereals, such as teff, sorghum, rice, maize, or oats.

However, several challenges make implementing this diet difficult. Adopting a new way of eating affects the entire family. Access to suitable ingredients is not always guaranteed, and financial constraints can further hinder the transition to a new diet. Compounding this challenge are factors such as a lack of knowledge, insufficient support in implementing the diet, and inadequate ingredient labeling on food packaging. To address these issues, regular education and training for patients would be highly beneficial As Trott noted, up to 80% of the people with celiac disease in the United Kingdom lack access to follow-up examinations where such concerns could be discussed.

Trott therefore presented approaches for improving self-management in putting the gluten-free diet into practice (Fig. 4), focusing on ways to identify and assess gluten-free products. Meal planning and a certain amount of assertiveness when eating out are also important points. Additionally, evaluating the quality of food is essential, such as determining whether it provides adequate amounts of all necessary nutrients. Continuous self-education is crucial for patients with celiac disease, and engaging in this process alongside others with the same condition has proven particularly effective.

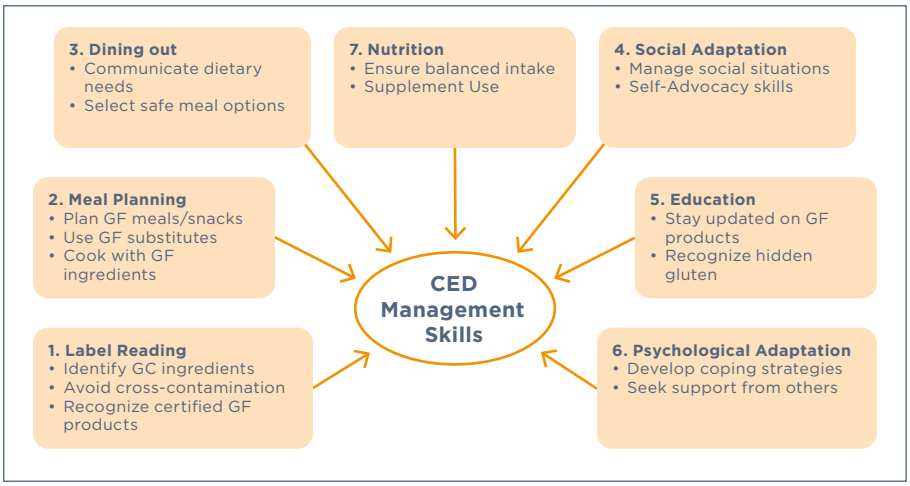


Fig. 4: Tips for self-management for following the gluten-free diet (modified after Lee AR et al.. Aliment Pharmacol Ther 2022;56(Suppl. 1):S38–S48)

Trott presented the findings of a study, reporting that it took around 6 months for patients with celiac disease to be able to reliably read food labels and assess whether a particular food is safe for them to consume. It often takes more than 3 years to become capable of explaining the importance of the gluten-free diet to others, for instance, when eating out. Individuals with celiac disease often need more than 5 years to clearly communicate their needs when traveling abroad. There is still a great deal of room for improvement regarding patient training, at least in the United Kingdom.

The Atypical Older Patient

In older patients with celiac disease, gastrointestinal complaints are often not the predominant sign of the disease. Instead, they often have anemia, generally due to iron and vitamin B12 deficiency, **Prof. Fabiana Zingone**, Padua (Italy), explained. For older patients with suspected celiac disease, Zingone recommended conducting serology, taking a duodenal biopsy, and performing a complete check-up, due to the elevated rate of osteoporosis in these patients. Men older than 40 with celiac disease have higher fracture rates than healthy individuals. In addition, the risk of metabolic syndrome in older patients with celiac disease is elevated.

Zingone explained that in patients with a strong suspicion of celiac disease but negative serology, seronegative celiac disease could be responsible for the symptoms, reporting that this was common among older individuals. She commented that in such cases other causes for the enteropathy should be ruled out, such as olmesartan-induced enteropathy.

Older patients with celiac disease also need to follow a strict gluten-free diet. A slow histological response to the diet, persistent histological damage, and symptoms are all not positive signs. A score has been developed to identify patients who respond poorly to the diet. Patients who are older than 45 at diagnosis, exhibit clinical signs, and fail to respond to the gluten-free diet, are at higher risk of a poor outcome. Poor adherence to the diet significantly compounds the risk. Individuals older than 60 at diagnosis have an 18-fold higher risk of developing complications. In contrast, 40- to 60-year-old patients have a 9-fold higher risk of developing complications. Zingone demonstrated that older patients may be able to be diagnosed without undergoing biopsy. However, experts are debating whether this may lead to tumors being overlooked. Zingone stated that that causes of a poor outcome have not been sufficiently investigated in older individuals with celiac disease, adding that the disease is underdiagnosed.

Patients' Goals Not the Same As Those of Doctors

When doctors consider what patients with celiac disease want, they assume it is the freedom from symptoms. Quality of life is important, along with feeling secure that gluten-free food is available. They may also desire medication for treating the disease, as well as psychological and financial support with the therapy, **Prof. Carolina Ciacci**, Baronissi (Italy), suggested. Knowing what patients want is important, because it can impact recommendations for their treatment.

Celiac disease is associated with a number of other symptoms, including fatigue and osteoporosis, Ciacci said. Celiac disease-related symptoms and the consequences of the disease and its treatment pose a considerable burden for patients. However, not all patients experience them to the same extent. Many of them report that their quality of life is good. At first glance, the number of sick days taken by patients with celiac disease seems alarming, totaling 42.5 sick days on average, which is 49% higher than the control population. However, a closer look shows that only 7% of the patients with celiac disease take around 60% of the sick days. This means that most patients feel well and are not sick more frequently than average.

The quality of life of the patients with celiac disease appears to be largely dependent on the care they receive from their doctors and nutritionists, Ciacci stated, citing a UK study. Most patients wish to have annual follow-up examinations. They consider blood tests to be an important diagnostic tool. In addition, they would like to talk about their supply of vitamins and their symptoms. Patients less commonly reported that they desire to ask questions about the gluten-free diet or have it monitored. The higher the patients' adherence to the diet, the lower their tendency to have more frequent follow-up examinations.

The gluten-free diet poses a huge challenge for patients. They report that adhering to the diet is an enormous burden that can lead to mental health issues. Many patients admit that they are unable to adhere to the diet at all times, especially when traveling. They often seek information on restaurants in advance. They take a (translated) description of their condition with them, along with a list of foods they do not tolerate, that they can present when ordering food.

Ciacci reported that the responses to questions regarding research on new medications for treating celiac disease were surprising when it came to things the patients did not want: 60% of them wished for an alternative therapy, and 40% said they would prefer a vaccine. Only 38% of the parents of children with celiac disease said that they would consent to their children participating in a study. Only just over 20% said they would be in favor of having an endoscopic procedure as part of a study.

When Italian patients with celiac disease were asked to state their greatest wish, they responded, "Better availability of gluten-free foods while traveling," followed by "a diet containing gluten," and "monitoring of restaurants offering gluten-free food." The diet is expensive and is generally not eligible for reimbursement. For this reason, patients wish for financial support for the diet or more affordable prices for gluten-free products.

Improving Prediction, Support, and Treatment for IBD

Inflammatory bowel diseases (IBDs) are detectable in the blood well before clinical manifestations occur. The talks on IBD focused on the potential therapeutic benefits of detecting the condition early on. The speakers also presented current recommendations on monitoring and therapy, diet, and on sharing decision-making in the treatment of these chronic conditions.

For many years, research on Crohn's disease (CD) and ulcerative colitis (UC), both IBDs, has investigated whether its pathogenesis could be predicted and whether there are any predictive biomarkers for the disease course. If this were the case, therapy could be initiated early on. The talk by **Prof. Tine Jess**, Copenhagen (Denmark), was devoted to this topic. Jess began by stating that in most cases, there is not enough data to identify connections between the diverse factors playing a role. Molecular markers linked to both CD and UC have been identified, but they are not enough to predict the disease course.

In Denmark, all medical data for the country's nearly 6 million inhabitants are stored in a central registry. This resource provides Jess access to laboratory values for more than 50,000 individuals with CD and UC. Jess's working group discovered a correlation between the very early onset of one of these conditions and elevated interleukin-17 (IL-17) levels. Conversely, interleukin-4 (IL-4) is a predictor for a low risk of IBD. In patients with late-onset IBD (up to age 18), no cytokine correlations were identified.

It is now clear that CD can be predicted up to 9 years before clinical manifestation based on leukocyte, neutrophil, and platelet levels, offering a significant window for early intervention. For UC, these same markers are predictive, with the addition of eosinophil levels. However, these markers only change up to 4 years prior to the onset of clinical signs. The disease course may be determined by genetic factors.

IBD – A Question of Balance

In IBD, not only are the bowel epithelium and immune system involved, but the mucus layer, microbiome, nervous system, and mesenteric fat layer also play crucial roles. An imbalance in any of these factors can trigger inflammation, said **Prof. Britta Siegmund**, Berlin (Germany). Siegmund presented data comparing mucus in healthy individuals and patients with IBD.

Rheological measurements showed significantly more viscose mucus in patients with IBD. When viewed under an electron microscope, the mucus network shows a tighter mesh compared to the mucus of healthy individuals.

In order for the epithelial layer to remain intact, it is essential for the mucus to be subjected to a dynamic movement. The flow and the movement in the intestinal lumen maintain the layer thickness. The immune cells in the mucosa secrete cytokines in damaged epithelium, which can lead to additional epithelial damage. Thus, blocking the cytokines can promote epithelial repair. Studies have shown that extracting regulatory T cells from patients, multiplying them, and reintroducing them into the patients can be particularly beneficial for individuals with ulcerative colitis (UC), especially those with refractory disease, Siegmund stated.

Siegmund discussed the role of the mesentery in IBD. Animal models have demonstrated that mice without fat do not develop IBD. However, when fatty tissue was transplanted into these mice, IBD was able to develop. Despite these findings, removing parts of the mesentery during bowel surgery in human patients with IBD does not provide any therapeutic benefit Siegmund explained, emphasizing the importance of other determinants, such as the microbiome and the nervous system.

Adapting IBD Monitoring to Reflect the New Findings

Treatment objectives for IBD patients have traditionally focused on managing symptoms. However, there is increasing evidence that many patients with persistent disease activity do not manifest symptoms. Subclinical inflammation increases the risk of flare-ups and long-term complications. For this reason, there is consensus about the need to treat patients beyond their symptoms and define clear treatment objectives for patients with IBD, which must then also be monitored, explained **Prof. Alessandro Armuzzi**, Milan (Italy), and **Hagar Banai-Eran**, Petah Tikva (Israel), in their tandem talk.

It is important to use a combination of endoscopic and biochemical markers to monitor patients in order to assess the degree of inflammation and manage the

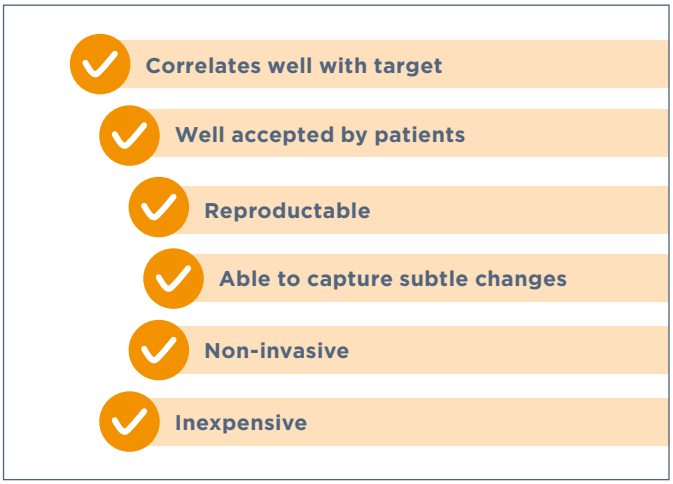


Fig. 5: Conditions that a good monitoring tool must meet (modified after the talk by Armuzzi and Banai-Eran, slide 4)

disease early on. Armuzzi presented conditions that a good monitoring tool needs to meet (Fig. 5). Both experts focused on the following tools for monitoring CD and UC:

- Endoscopy → Gold standard
- Biomarkers: C-reactive protein (CRP), fecal calprotectin
- Patient-reported outcome (PRO)
- Intestinal ultrasound

Patients in an early phase of CD have a significantly lower risk of the IBD progressing if there is endoscopic remission after 48 weeks. This is particularly evident in patients who achieve deep remission. A treatment that aims to bring about remission can thus be more effective in patients with signs of active inflammation than a symptom-oriented treatment, Armuzzi said. He called for proactive monitoring using capsule endoscopy and colonoscopy-guided therapy.

At the same time, apart from a capsule endoscopy, an endoscopy is generally an invasive measure, Banai-Eran said. Her talk focused on the benefits of biomarkers. C-reactive protein (CRP) appears not to be a reliable marker for either UC or CD, as it cannot confirm endoscopic remission in UC or predict the course of disease. CRP also fails to make reliable predictions for CD. Fecal calprotectin is a more reliable biomarker for assessing the endoscopic condition of the intestinal epithelium. However, this does not apply to the proximal small intestine. Therefore, while biomarkers are important, they are not sufficiently reliable on their own to guide patient therapy.

According to patient reports, symptoms like defecation urgency have the greatest impact on quality of life, followed by abdominal pain and fatigue. However, the correlation between symptoms and endoscopic lesions is not particularly high, for UC even less so than for CD. Be this as it may, monitoring the symptoms is still meaningful, Armuzzi said, because they are highly relevant for patients.

Banai-Eran assessed intestinal ultrasound as a valuable monitoring tool, because it allows statements about bowel peristalsis to be made. It also allows for effective detection of extramural complications, such as small bowel dilation or abscesses. Patients prefer ultrasound to endoscopy. Banai-Eran demonstrated that ultrasound examination achieves similar accuracy to endoscopy for both CD and UC. However, the quality of the examination can be impaired by the patient's build. Ultrasound is of limited value for assessing the severity of the IBD and is unsuitable for evaluating the mucosa and for distinguishing between active and chronic IBD.

Ulcerative Proctitis, An Often Underestimated Form of UC

Ulcerative colitis often begins in the rectum as ulcerative proctitis, but exhibits fewer symptoms and is often excluded from clinical trials, **Dr. Ferdinando D'Amico**, Milan (Italy), reported. Unlike left-sided colitis or pancolitis, patients with ulcerative proctitis typically do not experience left-sided abdominal pain, loss of appetite, or weight loss. However, ulcerative proctitis can progress to left-sided colitis or pancolitis over time and is associated with a significant disease burden. For this reason, D'Amico emphasized that ulcerative proctitis should not be regarded as merely a minor form of UC, but as a genuine form of UC deserving equal access to effective therapies. Poorly managed ulcerative proctitis increases the risk of disease progression.

According to guidelines, the treatment of mild to moderate ulcerative proctitis should be initiated with 5-aminosalicylate (5-ASA) as a suppository, and for moderate cases also orally. Severe ulcerative proctitis requires treatment with a combination of oral and topical steroids. If remission is not achieved, a sigmoidoscopy is advised. In severe cases, a biopsy and potential escalation of therapy should be considered. D'Amico commented that randomized, controlled clinical trials for immunosuppressives and biologics have not yet been conducted.

F. D'Amico:
"So far, the recommendations for treating ulcerative proctitis have been based on the duration and activity of the disease, the disease course, extraintestinal manifestations, and on the efficacy and safety of the drug. But the focus should be on symptomatic and endoscopic remission."

For long-term treatment of refractory ulcerative proctitis, azathioprine and biologics have proven effective, D'Amico said. However, the evidence for this is based on retrospective study data with low case numbers. However, tumor necrosis factor α (TNF-α) antibodies have demonstrated clinical efficacy and endoscopic improvements. Tofacitinib can induce a clinical response in patients who have become resistant to TNF-α antibody therapy. Etrasimod induces and maintains clinical remission. Ozanimod and vedolizumab have also achieved comparable efficacy. For cases in which treatment with 5-ASA and/or topical and oral steroids – depending on the type of disease progression – has failed, D'Amico strongly recommended immediately escalating treatment with TNF-α antibodies, etrasimod, or other biologics or small molecules.

Dealing with Strictures in Patients with Crohn's Disease

In patients with Crohn's disease, strictures can be purely fibrotic or can be mixed with an inflammatory component, said **Prof. Willem A. Bemelman**, Amsterdam (The Netherlands). It is difficult to distinguish whether strictures are caused by fibrosis or rather by muscular hypertrophy. Regardless, it is clear that strictures reduce the diameter of the small bowel and cause reduced segmental motility. Strictures are diagnosed endoscopically, via MRI, or via ultrasound. With endoscopy, the length of a stricture can be underestimated, Bemelman said. He also addressed the topic of secondary strictures, which may result from surgical errors or the healing of bowel perforations. Strictures can be treated with drugs or physical means (balloon dilation) or surgically.

Bemelman and co-presenter **Dr. Charlotte Hedin**, Solna (Sweden), presented a case study to discuss the use of a strict enteral formula diet (liquid diet) for 4 to 6 weeks before surgery for a stricture to induce remission and counteract the weight loss experienced by the patients beforehand. They observed that this led to a reduction in the C-reactive protein (CRP) levels. The length of surgery was shorter and there were fewer complications. The patients were able to stabilize their weight prior to the surgery. In 25% of cases, following the liquid diet eliminated the need for surgery, Hedin reported.

The biologics adalimumab and infliximab have been demonstrated to be beneficial for the treatment of strictures in prospective studies, Hedin added. Data on other anti-inflammatory therapies is still missing. However, endoscopic techniques such as balloon dilation, stricturotomy, and stents have become more significant as therapy options. Balloon dilation is recommended in the following cases:

- When the stricture is short (< 5 cm)
- When there is only minor inflammatory activity
- When no fistulas or tumors are present
- When there are no angles and endoscopic access is good.

Hedin stated that the risks of enteral balloon dilation included bleeding and perforation. Endoscopic stricturotomy involves the use of an electrocautery needle knife to make radial, circumscribed, or horizontal incisions in the stricture, allowing it to expand. The primary complication of this procedure is bleeding. For refractory strictures, stents are a potential treatment option, though risks include migration, impaction, and the formation of fistulas or abscesses, Hedin explained. Balloon dilation has been shown to be more effective than stents. Bemelman compared the outcomes of stricturotomy with surgery, stating that up to 45% of patients required revision surgery within 5 years of stricturotomy, compared to 62% within 10 years following the endoscopic procedure. In 90% of cases, strictures recurred at a different site.

Both Bemelman and Hedin emphasized that the choice of treatment depends on the characteristics of the stricture, including its length, origin (primary or secondary), association with abscess or fistula, and location (in the colon or elsewhere). They also recommended that patients seriously consider an enteral diet prior to surgery. Despite the variety of available treatments, both experts acknowledged the high recurrence rates associated with all options. Future solutions are expected to focus on developing drugs that prevent fibrosis from occurring in the first place.

IBD and PSC: One Disorder or 2 Separate Ones?

IBD and primary sclerosing cholangitis (PSC) often occur concomitantly. **Nora Cazzagon**, Padua (Italy), presented the question as to whether the 2 entities should be considered to be separate conditions or just 1. The prevalence of IBD in patients with PSC is very high, affecting up to 88% of these patients in Europe. However, only 2.2% of individuals with IBD have PSC. In most cases, IBD develops before PSC, although the 2 conditions are diagnosed simultaneously in about 25% of cases.

The genetic correlation between CD and PSC is low, while the correlation between UC and PSC is somewhat higher. The close interaction between the bowel and liver, such as through bile exchange, may explain the concurrent occurrence of PSC as an extraintestinal manifestation of IBD. Alterations in bile composition and dysbiosis of the intestinal microbiome are also under investigation as contributing factors. Additionally, a permeable intestinal epithelium and abnormalities in lymphocyte function may also play a role in the development of both conditions. Clinically, the simultaneous occurrence of PSC in IBD typically involves the entire colon. When only part of the colon is affected, it is generally the right (ascending) colon. Patients with both conditions have an elevated risk of colorectal neoplasia. Recently identified mechanisms underlying the coexistence of these disorders may provide opportunities for targeted therapeutic interventions.

The close relationship between the 2 conditions is also reflected in their management. Studies have shown that a colectomy performed before the diagnosis of PSC is associated with a lower risk of requiring a liver transplant. The type of colectomy also appears to influence outcomes, with restorative protocolectomy with construction of an ileal pouch anal-anastomosis being associated with a reduced risk of liver transplant. In terms of pharmacologic treatment, azathioprine has been shown to reduce the risk of liver transplant in PSC patients. Conversely, biologics have not demonstrated efficacy in PSC. However, the Janus kinase (Jak) inhibitor tofacitinib has shown promise, with safety studies reporting a reduction in alkaline phosphatase levels. The therapeutic relevance of this finding, however, remains unclear.

When IBD Affects the Skin

Skin lesions are significantly more common in Crohn's disease than in ulcerative colitis, except for pyoderma gangrenosum, which is more frequently associated with UC. In approximately 25% of cases, extraintestinal manifestations of the IBD occur before a diagnosis of CD or UC is made. **PD Dr. Pascal Juillerat**, Fribourg and Berne (Switzerland), noted that the interval between the onset of IBD and the development of skin lesions typically ranges from a few months to years.

Although bowel and skin lesions associated with IBD share common immunopathegenic mechanisms, they exhibit distinct histopathological characteristics, Juillerat said. The associated inflammation involves altered neutrophil function which makes TNF-α antibodies effective for both types of lesions. However, the precise underlying mechanisms remain unclear.

Skin lesions in patients with IBD may have different causes. Some, such as aphthous stomatitis, erythema nodosum, or pyoderma gangrenosum, occur reactively or independently of the bowel disease. Others are secondary lesions resulting from malabsorption, malnutrition, or medication side effects.

Juillerat reported that the prevalence of reactive skin lesions is approximately 15%. Topical steroid therapy may be considered for treating aphthous stomatitis or erythema nodosum. Pyoderma gangrenosum. which affects up to 8% of patients, can be treated with agents such as infliximab.

Secondary skin lesions may be drug-induced. For example, antibiotics or contraceptives may affect the skin of patients with IBD. In addition, biologics such as TNF-α or IL-23 antibodies may also contribute. Juillerat stated that treating skin lesions in patients with IBD is complex and requires close collaboration with dermatologists. Some conditions can be treated with topical therapies, while others may necessitate temporarily discontinuing treatment with biologics.

Future Treatment Options for IBD

A number of pharmacologic treatment options are available to treat IBD, including TNF-α and IL-12 targeted antibodies, S1P receptor modulators, and Jak inhibitors. Despite these options, there is still a need for new mechanisms of action and effective drugs. **Prof. Silvio Danese**, Milan (Italy), provided an overview of promising new developments for treating CD and UC.

Very good study results have been obtained with MORF-057, an orally administered small molecule inhibitor of the α4β7 integrin. According to Danese, regular infusions and reactions to the drug can be avoided by tailoring the form of administration to the patient. A comparable candidate is GS-1427, which is also an α4β7 integrin inhibitor, for which the results of a phase II trial are now anticipated.

Danese commented that a new mechanism of action is anticipated through the regulation of leukocyte trafficking, addressing S1P1 receptor modulation as a mechanism of action. While ozanimod has been shown to be ineffective in the treatment of CD, data on the efficacy of estrasimod are still in the pipeline. Danese expects that the third drug in this class, VTX002, may prove to be the most effective. VTX002 is a third-generation S1P1 receptor modulator.

Danese has high expectations for anti-cytokine therapies, particularly new drugs that specifically target interleukin-23 (IL-23). The dilemma is that while 4 drugs are currently available, the specific differences between the individual preparations remain unclear. The method of administration is likely to impact their practical use. Orally administered medications are becoming increasingly popular.

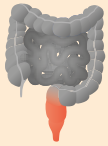
Danese also foresees strong efficacy for anti-TL1A antibodies, which enhance proinflammatory signaling by stimulating cytokine production through T cells, natural killer cells, and innate lymphocytes. RO7790121 is currently being studied in a phase IIb trial. The phase IIa trial indicated clinical remission in 25% of patients. Good results have also been reported for PRA023, which Danese values for its antifibrotic mechanism of action.

According to him, a further option is the target molecule tyrosine kinase 2 (TyK2), a member of the Jak family involved in transmitting inflammatory signals. The results of a phase II trial with deucravacitinib indicate a numerically better endoscopic response and clinical remission in patients pretreated with biologics. VTX958 is a drug that inhibits the TyK2 pathway and does not influence the Jak 1, 2 and 3 pathway Results of a phase II have shown that while VTX958 could improve the SES-CD endoscopic score compared to placebo, the primary end point, improvement in the Crohn's disease activity index (CDAI) was not achieved. Other TyK2 inhibitors have been the subject of studies.

Obefazimod is a small molecule that highly regulates the microRNA miR-124 in immune cells selectively, which reduces the translation of specific proteins. One outcome is the lower cytokine production. A phase IIb trial showed better clinical response. Another exciting mechanism of action may be present on the mitochondrial membrane, where the NLRX1 signaling pathway occurs, Danese explained. NX-13 is the drug of its class that is orally effective and limited to the bowel that selectively targets this signal path. The drug activates the signaling pathway to effect immunometabolic changes. NX-13 thus most likely reduces inflammation in IBD. Looking ahead, the RIPK1 signaling pathway may emerge as another therapeutic target. RIPK1 is an intracellular serine threonine protein kinase, a key protein for different proinflammatory pathways. Small molecules such as SAR443122 could block this pathway. RIPK1 regulates not only inflammation, but also cell survival and cell death.

S. Danese:
The immune metabolism in the cell appears to be a key factor in overcoming the therapeutic ceiling of current IBD treatments."

New Treatment Options for Acute Severe Ulcerative Colitis



According to **Prof. David Laharie**, Bordeaux (France), about 1 in 4 patients with UC experiences at least 1 episode of acute severe ulcerative colitis during their lifetime. Of these, up to 70% are treated with IV corticosteroids 1% of the patients die and 15% need to undergo a colectomy. If IV corticosteroids prove ineffective, second line therapy typically involves IV cyclosporine or infliximab. Currently, there are no established recommendations for a third-line treatment. Laharie discussed the possibility of predicting corticosteroid efficacy and introduced the ADMIT-ASC score for this purpose. This score incorporates CRP, albumin, and UCEIS scores.

Laharie spoke about different aspects of maintenance therapy after initiation of corticosteroid treatment. One option is combining infliximab and azathioprine, rather than using azathioprine with oral corticosteroids. If corticosteroids fail, both infliximab and cyclosporine have shown roughly comparable efficacy. Administering infliximab at higher doses or at shorter intervals has not produced better outcomes. Consequently, new therapeutic strategies are needed, with vedolizumab and ustekinumab as 1 option, and tofacitinib also showing promise. Laharie recommended treating the patients at specialized centers to detect treatment failure early on and intervene promptly. A salvage colectomy should always be considered at each treatment step and not unnecessarily delayed. There remains a pressing need for more effective drug options.

Current Dietary Recommendations for IBD

Nutritional counseling for patients with IBD has evolved rapidly in recent years, reported **Rotem Sigall-Boneh**, Tel Aviv (Israel), in her tandem talk with **Julie van der Stappen**, Leuven (Belgium). They emphasized that a diet should be tailored to disease severity, patient preferences, lifestyle, and cultural habits. Because each person's microbiome and its metabolism are unique, an individualized approach is warranted. In fact, microbial signals and diet-related metabolites in the stool may help predict the success of a nutritionally complete liquid diet, which remains the first-line therapy for children despite increasing use of biologics.

An important question is whether IBD diets can be personalized to align with patients' microbiomes and inflammatory activity. To investigate this, the Nutri-IBD app is being developed to identify specific food triggers. In general, a high intake of ultra-processed food is linked to an increased incidence of Crohn's disease (CD), while a diet rich in fiber and vegetables appears to lower CD risk.

Sigall-Boneh compared the role of a specific carbohydrate diet (SCD) with the Mediterranean diet. While the SCD resulted in somewhat higher rates of symptomatic remission and slightly lower CRP levels than the Mediterranean diet, the overall benefit was modest. The Mediterranean diet is more familiar, reduces disease activity and inflammatory markers—including fecal calprotectin—and has been shown to enhance quality of life.

The Crohn's Disease Exclusion Diet, which eliminates wheat, dairy products, animal fats, additives, processed foods, and red meat, is also highly effective. In contrast, van der Stappen noted that evidence for dietary treatment in UC remains limited.

Another new approach is the "Tasty and Healthy Diet," which aims to eliminate diarrhea and lower CRP. Once those goals are met, patients gradually reintroduce possible trigger foods to determine their impact. A study of this diet found that gluten significantly worsened IBD symptoms, whereas other foods, such as milk and cheese, did not trigger these effects. While fiber is generally recommended, there appear to be differences among different types of fiber. Sigall-Boneh stated that unfermented β fructans drive inflammation.

Most patients say they would prefer a dietary approach to manage IBD, but few actually adhere to such regimens because of the lifestyle constraints. Diets only work if they are adhered to, which makes it challenging. The more restrictive the diet, the harder it is to follow, van der Stappen explained. Both experts agree that the Mediterranean diet is a good option during remission (while a liquid diet is used in the progression phase), at least until more successful and more personalized intervention become available.

IBD from the Perspective of Patients and Doctors

Patients may view their medical condition differently than their doctors do. This discrepancy is also evident in IBD, as discussed by **Prof. Fernando J. Magro Dias**, Porto (Portugal), and **Ciara Drohan**, Brussels (Belgium), discussed in their tandem talk. According to Drohan, patients tend to prioritize symptom relief, wishing to have less pain, fatigue, and defecation urgency, rather than mucosal healing.

Magro Dias pointed out, however, that managing symptoms alone is not enough for an optimal clinical outcome. An improvement in symptoms does not necessarily indicate lower disease activity. Mucosal healing and, ideally histological remission, are associated with more favorable long-term outcomes. Achieving mucosal healing within the first year of treatment

is a predictor of success, Magro Dias said. Managing symptoms should be regarded only as a short-term objective. Over the long term, the goal should be to achieve histological healing.

From the patient's perspective, physicians often underestimate the importance of defecation urgency. Drohan explained that it is the second most commonly reported symptom in moderate to severe UC, yet doctors do not typically rank it among their top 3 concerns. In fact, 80% of patients with UC experience defecation urgency, with 50% of them facing it at least once a day. It poses a greater burden on daily life than abdominal pain, blood in the stool, or frequent bowel movements. For most patients, reducing defecation urgency is their top priority, while fatigue, pain, and stool frequency matter only most during active inflammatory phases.

Patients would prefer for therapy to focus more on quality of life, including maintaining independence and freedom from worrying about immediate access to a bathroom. They would like to be able to manage their chronic condition without always feeling stressed by it. Physicians often underestimate the impact of these factors on a patient's quality of life.

For patients, concerns about adverse effects of their medication are less important, Drohan said. This is particularly the case when they have the feeling that their symptoms are under control. They also have difficulty assessing the long-term consequences, leading some patients to request that their physician allow them discontinue the diet and wait to see what happens, knowing full well that it could trigger disease activity. Patients additionally desire treatments that provide rapid and lasting relief. A pronounced gap exists between patients and doctors regarding corticosteroid use: nearly 50% of patients outright reject steroids, whereas only 25% of doctors are similarly critical.

Patients often find disease monitoring burdensome and stressful, particularly when they are asymptomatic. Nonetheless, doctors and patients frequently have differing perceptions of disease severity. Patients would like their care to be holistic, encompassing psychological support, nutritional counseling, and social assistance, for example, at the workplace. They view medical care as only one facet of overall disease management.

Drohan and Magro Dias agreed that shared decision-making is the best approach to patient care (see infobox). This approach fosters communication, strengthens patients' understanding of their condition, and is likely to encourage greater adherence in the long run.

Benefits of Shared Decision-making:

Actively involved patients become more engaged and satisfied.

Involving patients better can bring about the following results:

- Communication improves.
- Trust is strengthened.
- Health outcomes are better.
- Adherence increases.
- Satisfaction with care rises.
- Fewer doctor's visits and lower costs.










Microscopic Colitis: Learning from Patients

To put it in a nutshell: microscopic colitis is a condition that cannot be diagnosed without a biopsy and poses a great burden to patients with the disease. As with the IBDs, the term "microscopic colitis" encompasses at least 2 disorders: lymphocytic and collagenous colitis. While the disease mechanisms have already been studied in detail, when it comes to therapy, there is still a great deal to explore. One thing that is clear: Patients have to be brought on board.

Like Crohn's disease and ulcerative colitis, microscopic colitis (lymphocytic and collagenous colitis) are inflammatory bowel diseases. However, they cannot be detected endoscopically and can only be confirmed through biopsy. To generate reliable epidemiological data for Europe, the European Microscopic Colitis Group (EMCG) and United European Gastroenterology (UEG) have established an electronic registry. With the help of the registry, patients with microscopic colitis (MC) will be monitored for 5 years to study the disease course and generate prognostic factors, **Dr. Andreas Münch**, Linköping (Sweden), reported. The registry collects data on the duration of therapy and patients' quality of life, among other things.

The estimated worldwide incidence of MC is 11.4 cases per 100,000 patient years. In Denmark, the incidence is 24.3 per 100,000 patient years. Compared to Crohn's disease (18.6/100,000) and ulcerative colitis (9.1/100,000), the incidence of MC in Denmark is thus higher. After 5 years, 394 cases of MC in Europe were included in the registry. Now, 220 datasets have already undergone a complete 5-year follow-up. According to Münch, 73% of patients with MC are women and the median age is 66. Approximately equal numbers of patients had lymphocytic and collagenous colitis. Around 25% of patients already had symptoms more than 12 months prior to diagnosis, in particular watery stools and high stool frequency. Stool consistency has a greater impact on quality of life than increased stool frequency, Münch said. Around half of the registered patients exhibited intermittent disease activity or ongoing persistent disease activity at the follow-up check-ups after 1 year. After 5 years, 40% of patients had persistent disease activity (intermittent and continuous). Defecation urgency was the most common symptom, followed by abdominal pain, nightly defecation, and fecal incontinence at the time of inclusion in the registry. All of the symptoms had significantly improved over the course (Fig. 6).

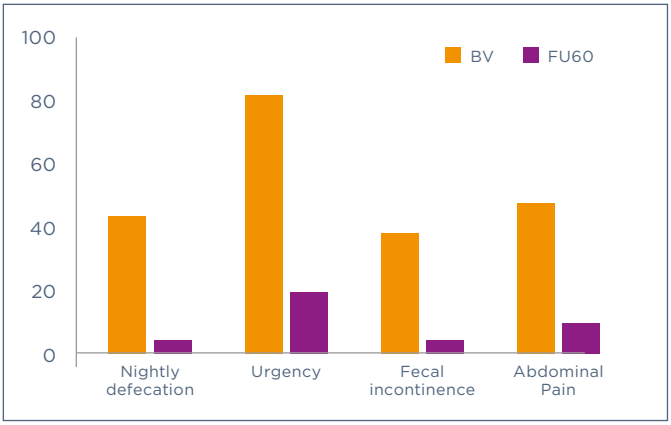


Fig. 6: Symptoms of MC at the beginning of inclusion in the registry and at follow-up (modified after slide 14 of Münch's presentation; no source)

The registry findings show that achieving remission within 1 year is a good indication that the disease will remain in remission. Significantly more individuals in the group of patients who failed to achieve remission within 1 year had a chronic disease progression. Stool frequency and consistency at inclusion in the registry did not correlate with the disease progression.

Approximately 25% of patients were still receiving oral budesonide therapy after 5 years, most of them patients with chronic disease progression. Seven percent of patients kept a similar drug on hand as needed. Biologics played a more minor role for the therapy.

One Name, Two Conditions

Although lymphocytic colitis and collagenous colitis are both covered by the name "microscopic colitis" and have the same disease presentation, there are significant histological distinctions between the 2 conditions. They share the following aspects:

- Persistent watery stools
- Abdominal pain
- Weight loss
- Nausea
- Fecal incontinence

Approximately 20% more lymphocytes are found in lymphocytic colitis. The epithelial regression is characterized by a loss of mucin and goblet cells, elevated mitosis, more vacuoles, and enlarged cell nuclei. Collagenous colitis shows a subepithelial fibrotic band, moderately elevated leukocytes, plasma cells, and mast cells, as well as variable eosinophils and neutrophils. Genetic aspects suggest that the two conditions are actually two different diseases. Transcriptomics confirms an immune reaction to bacteria in collagenous colitis. For its part, lymphocytic colitis can be divided into two different groups based on the transcriptome: channelopathic and inflammatory. According to **Dr. Celia Escudero-Hernández**, Kiel (Germany), however, collagenous colitis has a stronger overall immune response.

In MC, a proinflammatory immune response of the epithelium occurs. Reduced levels of IL-37 may trigger overexpression of chemokines in microscopic colitis, causing recruitment of mixed immune cell populations (eosinophils). Fecal biomarkers for this are the eosinophilic cationic protein and the eosinophilic protein X. The immune reaction in collagenous colitis and lymphocytic colitis differs in other ways as well. In MC, the immune response is weakened and the mucosa remains intact microscopically, but the epithelia no longer function, Escudero-Hernández continued. She explained that the dysfunction in the barrier is caused by hyperproliferation of the crypt cells. Claudin is internalized, which reduces the functionality of the tight junctions. In collagenous colitis, this leads to poor water absorption, which triggers diarrhea, watery stools, and defecation urgency. In lymphocytic colitis, both water absorption and sodium uptake are impaired. Collagenous colitis is essentially a disorder of pericryptic fibroblasts.

Triggers of MC and Disease Monitoring

Dr. Hamed Khalili, Danvers, Massachusetts (USA), endeavored to provide answers to questions about the pathogenesis of MC and the influence of cohort studies on monitoring and the management algorithm. The following are suspected triggers of MC:

- Smoking
- Diet
- Medications
- Infections.

However, common medications such as drugs for cardiovascular conditions or PPIs are not responsible for MC. Nor is gluten, which is responsible for celiac disease, associated with MC, while alcohol and smoking are indeed connected to the condition.

Khalili explained that data for etiological studies is lacking. Prior to 2017, no ICD code had been assigned for MC. In addition, a histological examination is required for diagnosis and very few samples exist. To date, very little data exists on the change in risk factors in the management of MC.

Compared with age- and sex-matched controls, patients with MC have a slightly higher mortality rate. This may be associated with the increased burden of comorbidities in this population. There is no indication of elevated risk of colorectal polyps or colon cancer. However, several studies have reported a slight increase in the risk of lymphoma and lung cancer, which may be associated with the higher share of smokers in this population. MC also appears to be associated with an increased risk of CD and UC, Khalili said. The data do not suggest a higher colon cancer screening frequency, however.

To assess the risk of MC, a clinical scoring system and biomarkers could be interesting, Khalili added. The following characteristics are relevant for the scoring system:

- Female
- Age over 50
- Use of PPIs
- Use of NSAIDs
- Weight loss
- Abdominal pain
- Celiac disease
- Nocturnal diarrhea

Although several clinical scoring systems have been developed to diagnose microscopic colitis (MC), they are not widely used in practice, despite their ability to help rule out MC.

Khalili discussed fecal calprotectin and other stool markers as biomarkers (see infobox). Fecal calprotectin can be used to establish a differential diagnosis with IBD. In microbiome and metabolome studies, new biomarkers for monitoring the disease have been identified.

Stool Markers for MC:

- Lactoferrin
- Eosinophilic protein X
- Eosinophilic cationic protein

When Budesonide is No Longer Effective: Treatment Strategies for MC

Budesonide has been used successfully for short-term treatment of patients with collagenous colitis, enabling 81% of patients to achieve remission, **Dr. Andreas Münch**, Linköping (Sweden), reported. Long-term treatment with budesonide has also shown promising results. However, some patients are not successful with budesonide. Indications for extended treatment for patients with MC include lack of response, diminished response, the risk of long-term adverse effects, intolerance, and unacceptable adverse effects. According to Münch, approximately 20% of patients do not respond to budesonide. These patients should be given loperamide and cholestyramine, either alone or combined. Only 2% of the patients receive a biologic, although biologics have demonstrated good efficacy. Antibiotics or prebiotics, 5-ASA, and methotrexate are all not options for therapy. Azathioprine often takes a long time to take effect and is often not tolerated in the long term.

Take-aways

- When budesonide is not effective, treat your patients as though they have an IBD.
- Personalize the therapy and take comorbidities into account, especially with older people.
- Inform your patients if you use an off-label drug and explain why you are suggesting it.
- Anti-TNF or vedolizumab are the biologics of choice.
- Increase the dosage of the anti-TNF drug if its efficacy diminishes.
- Drug-monitoring is not necessary.

The Burden of MC: Learning from Patients

Patient-reported outcome measures (PROMs) should be determined when patients notice the effects of their condition in their daily lives, serving as an important metric in clinical trials. So far, there have been 2 validated PROMs for MC, the Hjortswang criteria (collagenous colitis) and the Microscopic Colitis Disease Activity Index (MCDAI).

The Hjortswang criteria were developed to distinguish between disease activity and remission. The criteria are based on only 2 variables: stool frequency and stool consistency. According to the criteria, patients with a stool frequency of less than 3 stools a day and less than 1 watery stool a day are defined as being in clinical remission.

MICROSCOPIC COLITIS DISEASE ACTIVITY INDEX (MCDAI) SCORECARD

ITEM	SCORE	WEIGHTED COEFFICIENT	TOTAL ITEM SCORE
Average number of unformed stools daily over past week		x 0.31	
Nocturnal stools over past week (0 = absent, 1 = present)		x 0.78	
Maximum abdominal pain over past week (score 1 – 10)		x 0.22	
Average weight loss per month (lbs*)		x 0.11	
Fecal urgency over past week (0 = absent, 1 = present)		x 0.93	
Number of episodes of fecal incontinence over past month		x 0.01	
		6 ITEM SCORE	
			+ 1.1
*Kg x 2.2 = lbs		MCDAI SCORE	

Fig. 7: Score card of the Microscopic Colitis Disease Activity Index (MCDAI) (Source: https://gut.bmj.com/content/67/3/441.long)

The Microscopic Colitis Disease Activity Index (MCDAI) takes 6 criteria into account and is also validated (Fig. 7). However, the goal was now to develop a PROM to assess disease activity in microscopic colitis that met the requirements of the US Food and Drug Administration (FDA). The European Microscopic Colitis Activity Index was developed in 4 steps. First, a group of experts in this area created a list of symptoms associated with active MC. The validity of the symptoms was verified by 79 patients. Questions and response alternatives were created for each symptom, and the new index was then evaluated with interviews with patients and by the experts. Seven symptoms were included in 6 categories in the index: stool consistency, stool frequency, stools at night, feel a need to pass more stools shortly after a bowel movement, urgent need to empty the bowel, leakage of stool, and abdominal pain.

For some items, the ranking of the symptoms among experts and patients varied widely, as **Katarina Pihl Lesnovska**, Linköping (Sweden), described. Despite the differences, the new score was validated. In the evaluation phase, patients were asked to respond to the questions on 7 consecutive days. Currently, investigations are underway to see whether a shorter survey period is sufficient. The current MCS score is a compromise between "easy to use" and "accuracy of prediction." The very time-consuming creation and validation of the score gave experts the opportunity to learn a great deal from the patients about the truly relevant symptoms that most severely compromise quality of life and best characterize the disease activity, Pihl Lesnovska said.

“Networking and a holistic view bring us gastroenterologists together”

Prof. Dr. Axel Dignass is the Head of the Department of Medicine I at the Agaplesion Markus Hospital in Frankfurt am Main (Germany). He has a special interest in inflammatory bowel disease and is also interested in the use of artificial intelligence in the field of gastroenterology. Dignass is well known as the author of guidelines and is the chairperson of various national and international professional and medical associations.

Prof. Dignass, you helped plan this symposium. What is your personal event highlight?

Prof. Dignass: For me, the highlight is not one particular outstanding aspect of the symposium, but rather the entire event. We succeeded in linking four different conditions in such a way that each session featured one presentation on each of the four conditions, so that we could contribute to the discussion on EoE, celiac disease, IBD, and microscopic colitis. In other settings, we typically meet up with the experts on one specific topic and discuss the latest developments. This symposium was quite different. All participants had the opportunity to listen to experts working in various areas and compare similarities and differences. We covered all areas, from epidemiology to pathophysiology, medical and surgical management as well as diet. We covered the management of simple cases and also complicated and refractory patients. The format offered a great opportunity for seeing what is happening in other fields and for benefiting from other specialists. But for me there was another highlight. Our guests included leading experts from all over the world, Prof. Detlef Schuppan, to name just one. He is responsible for discovering the autoantibody for celiac disease and participated in developing many of the treatments. I am also pleased that Prof. Silvio Danese from Milan (Italy), participated. He is a world leader in IBD research. I would also like to touch on the very underrated topic of microscopic colitis. We received input from the European working group on MC (Microscopic Colitis).

An entire session was dedicated to dietary therapy and the patients’ perspective. What role do these topics play in practice?

Prof. Dignass: Dietary therapy and the patients’ perspective are two extremely important topics and are underrepresented in clinical practice. From my point of view, there is a huge need for education. Our goal is to continue to advance the concept of shared decision-making, which can help us improve adherence to clinical management including better adherence to medical management. Currently, only around 40% of patients with EoE adhere to therapy. Many people with celiac disease take a day off from their therapy every week, which has long-term consequences. What health care professionals (HCPS) may consider to be burdensome symptoms is often different than what patients experience. For patients, for instance, urgency is a critical factor. And yet only 1 out of 3 doctors considers urgency to be an important therapy objective. Doctors often describe undesired effects to be less relevant than our patients do. These are good reasons to focus more closely on this topic, as well as on dietary therapy.

The different preferences for therapy objectives are an interesting topic. Patients often prioritize relief from their symptoms, while physicians typically focus on achieving histological remission. Why is it so hard to align these 2 objective?

Prof. Dignass: It’s true that for example for Crohn’s disease the CDAI score often does not correlate with the endoscopic findings. But that has to do with the fact that the symptoms not only correlate with current inflammation, but often have to be attributed to previous damage resulting in strictures, fistula or scarring. Inflammation promotes tissue scarring. Motility may be disturbed even though the mucosa is currently in histological remission. But patients only notice the symptoms. That’s why for inflammatory disorders of the GI tract, it is important to take a holistic view of the situation. In this perspective, symptoms play a role, as do endoscopic, histological, and ultrasound findings.

You have a special interest in inflammatory bowel disease. Where do you see some unsolved mysteries?

Prof. Dignass: Inflammatory bowel diseases like ulcerative colitis and Crohn’s disease have been studied for many years, and we have learned a lot about them.

But there are always topics that require more investigation. From my point of view, one such topic is time-dependent treatment of IBDs. In many cases, we fail to keep this in mind. It should be clear to everyone involved in the therapy that patient-related outcomes need to be achieved in a timely manner. However, subjective, patient-reported improvement of symptoms needs to be confirmed by more objective tests like biochemical blood and stool tests such as calprotectin and CRP. Ultimately, we aim to achieve mucosal healing assessed by endoscopic assessment as a long-term goal. And last but not least, the therapeutic ceiling is very important to me. We have to find new ways to improve the long-term outcomes of our patients beyond our current success rate. Efficacy has to increase, for instance, with new drugs or through intelligent combinations of biological drugs, earlier inititiation of effective treatments and regular monitoring of treatment success.

There is no lack of pharmacologic options for IBD, is there?

Prof. Dignass: Compared to other disorders, like celiac disease, that is true. We have a number of biologics available. But we still too often fail to achieve the treatment objective of long-lasting remission. I am hoping that we will have solutions created with the help of artificial intelligence to improve diagnosis and, in particular, improve our treatment algorithms. We have a lot of medications, but we struggle with how to use our options in the most optimal way: sequential or combination therapy, which sequences and which combinations? With AI, we can evaluate our findings more quickly and hopefully answer the unanswered questions better. To address these questions, we are also still missing biomarkers. So far, all our attempts to identify them have failed. But there is a lot of research in this area, and I am sure that we will find a solution to this problem in the near future. Although we already have a lot of drugs available, in the near future we might be in the favorable position of being able to address additional mechanisms of IBD. For now, we can improve patient outcomes by treating patients according to medical guidelines and evidence-based recommendations for the use of the currently available drugs. Implementing a therapy currently requires a significant amount of specialized knowledge. I hope and wish that AI will help us create a tailored treatment that each and every colleague can implement based on clear guidance. So you see, there is still a lot to do when it comes to IBD.

What do you like about the international symposia like this one, and about the Falk Foundation symposia in particular?

Prof. Dignass: This is not the first symposium I have helped organize for the Falk Foundation. I always enjoy becoming involved, because the organizers have complete freedom to design the program and to select the speakers. The topics and formats are geared to the pressing issues of today and not to what is in a company pipeline. That does not go unnoticed by the many participants from all over the world. The events also attract experts who do not hold a presentation but come because they are interested. They all value the interactive exchange and the high quality of the events.

Professor Dignass, thank you very much for taking the time to talk to us.

Poster prizes: Awards for Young Researchers

In keeping with its good tradition, the Falk Foundation e.V.'s 238th Symposium honored young researchers for their outstanding research publications. The following young researchers were recognized at the symposium entitled "Immuno-mediated Diseases of the GI Tract: Where Do We Stand?" in Florence:

Chiara Amoroso, Milan (Italy): *Development of an algorithm to identify the best donor-recipient match for FMT in IBD patients based on immune system/microbiota interactions*

Luisa Bertin, Padua (Italy): *Efficacy of orodispersible budesonide in eosinophilic esophagitis: A comprehensive analysis of clinical, endoscopic, and histological outcomes*

Mariam Mohamed Abdou, Erlangen (Germany): *Vascular Leakage as an Early Diagnostic Marker for Inflammation in IBD: Insights from a Multiphoton Endomicroscopy Study in Mice*

Left-to-right: Edoardo Vincenzo Savarino, Iris Dotan, Flavio Caprioli, Chiara Amoroso, Luisa Bertin, Mariam Mohamed Abdou, Nicola de Bortoli, Martin Falk, Axel Dignass

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