# FALK GASTRO SCOPE

November 2023

## Congress news from Symposium 235 in Madrid



**THERAPEUTIC UPDATE IN GI DISEASE**
**Symposium 235 | Madrid | November 3–4, 2023**

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2023

# THERAPEUTIC UPDATE IN GI DISEASE
## Symposium 235 | Madrid | November 3–4, 2023

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# Gastroenterology shows itself to be innovative and progressive

**The latest trends and findings for all organs in the gastrointestinal tract were presented at Symposium 235 in Madrid. Not only can we now describe an impressive number of disease patterns much better, but – as in the case of eosinophilic esophagitis (EoE) – we can now also offer improved approaches to treatment. Artificial intelligence has the potential to advance gastroenterology – and above all endoscopy – a great deal. The richness and diversity of the presentations offered valuable insight into the dynamic world of gastroenterology.**

Scientific organizers:
**Prof. R. Bañares, Prof. F. Gomollón, Prof. C. Hassan, Prof. J. Mayerle**

In sessions that lasted almost two hours each, participants at the Symposium 235 event hosted by Falk Foundation e.V. in Madrid were offered a comprehensive overview of current issues in the field of chronic inflammatory intestinal disorders (IBD), liver diseases, pancreatitides, and other diseases of the upper and lower gastrointestinal tract.

Rare diseases like CMUSE or eosinophilic esophagitis (EoE), which it emerged is not actually all that rare after all, were important main topics at the event. EoE as an indicator for functional dyspepsia – this correlation was established, for example, by Prof. Jan Tack from Leuven (Belgium), this year's winner of the Herbert-Falk Award.

Much of the attention was directed toward endoscopies: When are they required? How much time remains? When and how will artificial intelligence (AI) be able to assist the trained eyes of gastroenterologists, and when would it be more likely to do harm? These are important questions for the future, where it will be necessary to tackle challenges relating to data protection legislation in particular. AI learns from patient data. Once it has processed this data, the question arises as to how the information can be taken away again from the AI if a patient decides to withdraw their consent for disclosure of the data.

Gastroenterology is evolving at a rapid rate – both in terms of diagnostics as well as in terms of the available treatments. This is why immune checkpoint inhibitors (ICI) were also an important topic in Madrid. They are now an indispensable part of treatment for a number of tumors in the gastrointestinal tract, and as such they are providing some patients with new hope of being cured.

The excellent selection of topics and the high-caliber experts who delivered the talks provided the perfect basis for a comprehensive, varied, and highly informative professional training event, where high-quality scientific insight was combined with a really practice-driven approach to deliver an impressive congress in Madrid.

# Gastroenterology reinvents itself

**Clear diagnostics form the basis for effective treatment – this is nothing new. However, it became apparent during Symposium 235 quite how bright the future is for gastroenterological diagnostics. Artificial intelligence (AI) can help to open up precision medicine using drugs that are already available. Brand new tips were also offered for diagnostics for biliary pancreatitis. Valuable innovations were also presented in relation to therapies – above all for eosinophilic esophagitis (EoE) and colorectal cancer.**

Artificial intelligence is neither artificial nor necessarily intelligent, but AI can emulate complex human tasks and interpretation skills and make diagnostics and therapy faster, better targeted, more cost-effective, and more environmentally friendly. **Dr. Alanna Ebigbo** from Augsburg (Germany) gave a talk on the use of AI in the upper gastrointestinal tract. In the context of esophageal cancer, he mentioned that the diagnostic error rate is 6.4%. The error rate in assessments of high grade dysplasia can even be as high as 25% – depending on the experience and expertise of the endoscopist. Small/flat dysplasia poses the greatest challenge to the human eye. The expert presented data that demonstrates how a video-based, computer-assisted detection system was able to significantly improve the detection of Barrett's neoplasia. Although experts in esophageal endoscopy did not benefit from the technology, detection rates among general endoscopists improved by 12%.

## Important to be aware of potential pitfalls

According to Ebigbo, the potential pitfalls of AI in gastroenterology include human-to-machine interactions and the generation of data to enable machine learning. Endoscopists need to learn to trust the "assessment" of the AI system, but they must not accept it blind. Finding a healthy middle ground will be a challenge for the future. Ebigbo also spoke about more far-reaching applications for AI, for example a GastroGPT. This is the first discipline-specific AI language model, and it outperforms general models on important clinical tasks.

## AI – an environmental topic

One important benefit of the use of AI is savings in terms of CO2 consumption. AI in gastroenterology helps to save resources and allows physicians to operate more environmentally friendly. Every histological sample results in CO2 consumption that is comparable to one kilometer driven by an average car. So, 10 samples already mean 10 kilometers. If AI can be used to lower the number of samples that need to be taken, this is a valuable contribution to climate protection.

## CADe and CADx – detection and characterization in the lower gastrointestinal tract

In the lower gastrointestinal tract, AI is used for detection (CADe) and characterization (CADx) of polyps and tissue changes. **Prof. Cesare Hassan** from Milan (Italy) reported that AI can increase the adenoma detection rate – regardless of the properties of the polyps and the expertise of the endoscopist. With computer-based detection, more polyps are being discovered, and this is pushing up the costs of treatment. However, early detection and the associated prevention of tumors in turn lead to significant cost savings. The same also applies to computer-assisted characterization, which permits a visual assessment and requires fewer polypectomies. All in all, costs can therefore be potentially lowered with the aid of AI. As a projection for the USA, Hassan estimates a savings potential of $300 million per year. Nonetheless, his summary is that only synergy between humans and AI will lead to improved quality in healthcare. Working with AI needs to be learned and practiced in order to be able to make effective use of the advantages it offers.

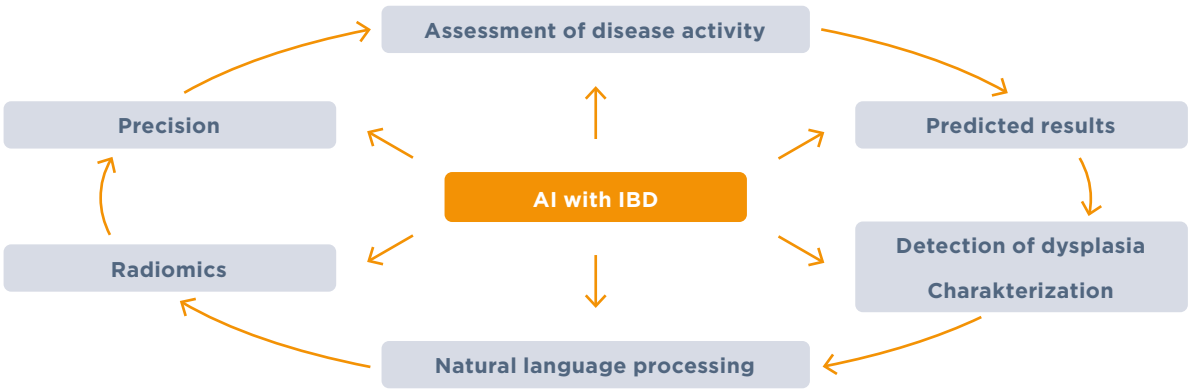


Figure 1: Options for use of artificial intelligence (AI) in chronic inflammatory intestinal disorders (IBD)

## Major progress thanks to AI in chronic inflammatory intestinal disorders

**Prof. Marietta Iacucci** from Cork (Ireland) spoke about the use of AI in chronic inflammatory intestinal disorders (IBD). The target for IBD therapy is precision medicine. However, the large volumes of data from thousands of individuals cause problems. Interpretation of the data is a non-trivial exercise and requires an approach that allows hidden patterns to be identified in the complex data sets. AI could be used for IBD in various areas (Figure 1).

AI could help improve the quality of reporting and prevent avoidable medical errors. It plays a role in real-time detection of characteristics that are difficult to spot, and can also help improve patient trust in the results of the examination and any investigations carried out. Iacucci presented the AI approaches that are currently available for IBD diagnostics, including the PICaSSO AI tool developed by the working group itself.

They believe that these developments still have a long way to go. In the future, it will be necessary to look at the entire intestine in order to make precision medicine possible. At present, too often efforts tend to focus only on smaller sections of the intestine. Details are often missing here. AI has the potential to uncover new therapy options, take well-founded treatment decisions, and identify sub-groups of diseases. The increasing availability of data, particularly from large cohorts, can help drive the development of algorithms forward. Nonetheless, important challenges remain – in particular the question of how such data sets can be used in practice.

## Data protection is needed wherever data is generated

Data utilization also throws up ethical and legal questions that have still not been dealt with adequately, explained **Dr. Omer Ahmad** from London (UK). This is a highly topical issue, with strong efforts under way both in the USA and in Europe to draw up binding regulations for working with AI. Nonetheless, gastroenterologists can be proud that the field of endoscopy is one of the driving forces that has pushed forward the use of AI in medicine the most. One major concern is who can be held responsible for incorrect diagnoses caused solely by AI. This is a relevant issue, as the future is set to be one where AI is allowed to make decisions autonomously and to produce results that are trusted. While this is not yet possible, AI will at least be used as an aid during diagnoses. As a result, we already need legal clarification today as to what should happen if damages result from the use of AI. At the moment, it is highly recommend that the decision-making process is well documented. It needs to be discussed whether the doctors who use AI should be held responsible for any errors in diagnosis or treatment, or whether the this responsibility should instead be laid at the feet of the hospital, the AI developers, or whoever provided the AI training images.

## Problematic: labeling requirements and the right to data erasure

Ahmad assumes that, in the future, regulatory bodies will require something like a package leaflet for all types of AI. The purpose of this will be to disclose how the KI has been programmed, which patients it is suitable for, and what the resulting limitations are. An important point in this context is also the data used to train the AI. For example, if there is a failure to cover all ethnic groups, then this poses the risk that the results might be unusable for certain people. This also leads to another point: What is the situation with regard to data privacy? On the one hand, we need to protect personal data. However, on the other hand the principle on which the AI model is founded depends on having access to ideally large data sets. So who does the medical data belong to? And what happens with the patient data and the right to have it erased if the AI has already processed the data as part of training its algorithm? There are many unanswered questions that need to be dealt with urgently.

## Current diagnostics for biliary pancreatitis: ERCP is rarely necessary

Around one in five people can expect to have gallstones at some point in their life. Biliary pancreatitis occurs in 8% of cases with symptomatic gallstones. Looking at this the other way around, up to 75% of patients with biliary pancreatitis also have gallstones. In nine out of ten patients with biliary pancreatitis, gallstones can be detected in feces. It is already known that gallstones trigger biliary pancreatitis through transient obstruction of the pancreatic duct. However, it is a relatively new finding that Piezo1 receptor activation occurs as a result of a build-up of pancreatic secretions. This is followed by a transient intracellular rise in calcium, trypsin activation, and damage to the cells of the pancreas. Decompression due to widening of the restricted ducts should lead to a reduction in symptoms.

However, the difficulties start with the diagnosis of biliary pancreatitis, for which there is presently no specific blood marker. However, as **Prof. Julia Mayerle** from Munich (Germany) explained, an ultrasound investigation is completely sufficient for the identification of gallstones. He added that although it is often difficult to image the pancreas, in the majority of cases gallstones can be found in the gall bladder. Magnetic resonance cholangiopancreatography (MRCP) is a contender for more far-reaching diagnostics. This diagnostic method is a way to potentially reduce the need for endoscopic retrograde cholangiopancreatography (ERCP). However, small gallstones are a problem. These can be imaged more successfully with endoscopic ultrasound – a method that is preferable to ERCP according to the expert from Munich.

| Individual components | ERC with sphincterotomy Y (n = 117) | Conservative treatment (n = 113) | Risk ratio (95% confidence interval) | p value |
|---|---|---|---|---|
| Death | 8 (7%) | 10 (9%) | 0.77 (0.32–1.89) | 0.57 |
| Newly occurring organ failure | 22 (19%) | 17 (15%) | 1.25 (0.70–2.23) | 0.45 |
| Bacterial infection | 17 (15%) | 25 (22%) | 0.66 (0.38–1.15) | 0.14 |
| Pneumonia | 9 (8%) | 10 (9%) | 0.87 (0.37–2.06) | 0.75 |
| Pancreatic parencymal necrosis | 17 (15%) | 18 (16%) | 0.91 (0.50–1.68) | 0.77 |
| Pancreatic insufficiency | 9 (8%) | 3 (3%) | 2.90 (0.81–10.43) | 0.09 |
| **Cholangitis** | **2 (2%)** | **11 (10%)** | **0.18 (0.04–0.78)** | **0.01** |

Table 1: Early endoscopic retrograde cholangiopancreatography with biliary sphincterotomy vs. conservative treatment

## ERCP not always necessary within 24 hours

Mayerle questioned whether an ERCP is always necessary within 24 hours in the case of acute biliary pancreatitis. It does not seem to be necessary for mild pancreatitis. If the disease takes a milder course then the stone will certainly have already been passed, rendering ERCP unnecessary. But current investigations also show that the rationale for early ERCP should be questioned even for severe pancreatitis (Table 1). It only makes sense if cholangitis is present at the same time. Early ERCP often leads to patients spending time in an intensive care unit.

In patients with mild biliary pancreatitis, prompt removal of the gall bladder is recommended. In cases of severe pancreatitis, cholecystectomy should not be performed within the first 14 days of diagnosis. Investigations have now shown that the best time for this is around 8 - 10 weeks after the patient is discharged from hospital.

## EoE – no longer rare and now well treatable

Eosinophilic esophagitis (EoE) is a recent disease. It was first described around 35 years ago. But it is nothing like as rare as is often assumed. This was the topic that **Prof. Alfredo J. Lucendo** from Tomelloso (Spain) and **Prof. Javier Molina Infante** from Cáceres (Spain) discussed in a tandem talk. A disease is classed as rare if there are fewer than 50 cases per 100,000 people (prevalence). This is the case for EoE in some regions around the world. However, in countries like Spain and the USA there are far more cases than this.

According to the two experts, one reason why there might have been more diagnoses in the last five years could be the update to the guidelines in which new diagnostic criteria have been defined. Nonetheless, it is likely that only a very small proportion of children and adults will be diagnosed promptly with EoE. “We only see the tip of the iceberg,” explained the two Spanish gastroenterologists. Many patients do not take their symptoms seriously and refuse medical advice. They often avoid the pain and difficulties swallowing by adapting their food intake to the symptoms.

**Prevalence of EoE:**
Utah (USA): 118 cases per 100,000 people
Spain: 80–100 cases per 100,000 people
Denmark: 70 cases per 100,000 people

EoE can take a mild course and is not a life-threatening disease. This is potentially another reason why it is often overlooked and under-diagnosed. Up to 50% of cases display this mild phenotype. In around 10% of patients the disease progression is severe, with the remainder experiencing a moderate form of the disease. With EoE, inflammation of the esophageal epithelium occurs initially (Figure 2). If the disease progresses, fibrosis of the tissue occurs and eventually the diameter of the esophagus becomes narrowed. This makes passage of food more difficult. Although EoE is chronic in all cases, its development is not always progressive.

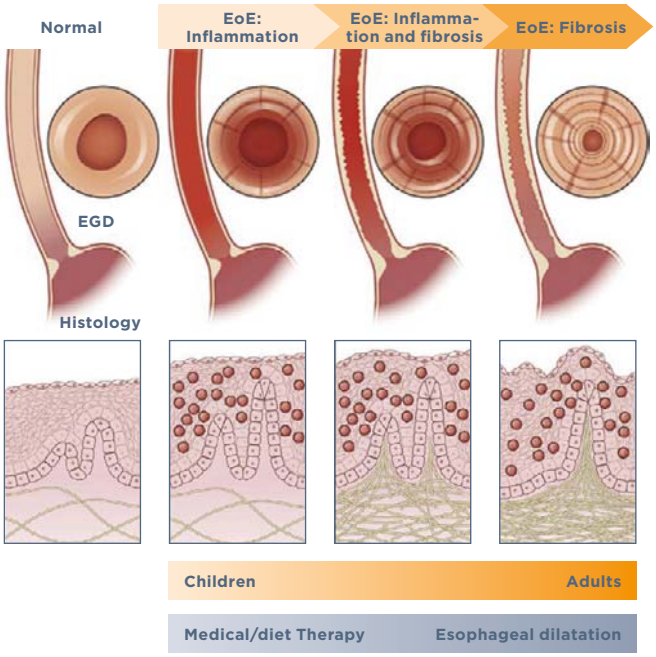


Figure 2: Development of EoE (Dellon ES, Hirano I. Epidemiology and natural history of eosinophilic esophagitis. Gastroenterology. 2018;154(2):319-32.e3. Fig. 4, © Elsevier 2018)

The goal of therapy is to get the patients into remission to prevent further inflammation. However, in milder cases there are not yet any indications that long-term anti-inflammatory treatment is necessary. It is possible that acute therapy is sufficient in these milder cases.

## Therapy options for EoE

There are currently three main options available for the treatment of EoE:
- Proton pump inhibitors (PPI), off-label
- Elimination diets
- Topical corticosteroids

In the event of clinical and histologic remission, patients should be offered a maintenance therapy. If symptoms persist with histologic remission then the possibility of esophageal stricture should be considered. If patients do not go into remission then the next option is to review and adjust the therapy. Only in rare cases is it advisable to deviate from the principle of monotherapy. Dual therapy with PPI could be an option for example if this is required to treat symptoms of gastroesophageal reflux disease but the PPI fails to adequately address the EoE symptoms. In such cases the treatment with PPI cannot be abandoned. However, in this case the treatment of the EoE will require a dietary intervention or the use of topical corticosteroids. In isolated cases a therapy strategy will not lead to an improvement in symptoms. Here again, a combination therapy may be appropriate.

**PPIs** are a cost-effective therapy option. Their efficacy has been demonstrated in multiple studies. Induction therapy should be administered over a 12-week period. Patients who go into remission with this can be given a halved dose as maintenance therapy. 70% of patients manage to remain in remission with this, but the therapy is not yet officially approved for treatment of EoE.

**Elimination diets** are often a challenge for the patients concerned. As a rule, milk protein cannot be tolerated. Similarly, wheat and eggs also cause problems for the patients. This already underlines the difficulties involved, as it is almost impossible to eliminate these food groups. Nonetheless, there is an established "2-4-6" approach to elimination diets. In the first step, two foods are eliminated, then four, and then six food groups in the final step. This is because the list of "suspect" foods also includes soy, nuts, and fish/seafood. The two speakers recommended stopping the dietary intervention when four food groups are eliminated. If this does not alleviate the symptoms then there is not much hope for achieving better results by eliminating further foods. One interesting experiment is to "provoke" the patients with sterilized milk. Here, the patient should initially cut out milk before then being given sterilized milk twice a day over a period of eight weeks. After this provocation, around two thirds of the patients can expect a lactose intolerance.

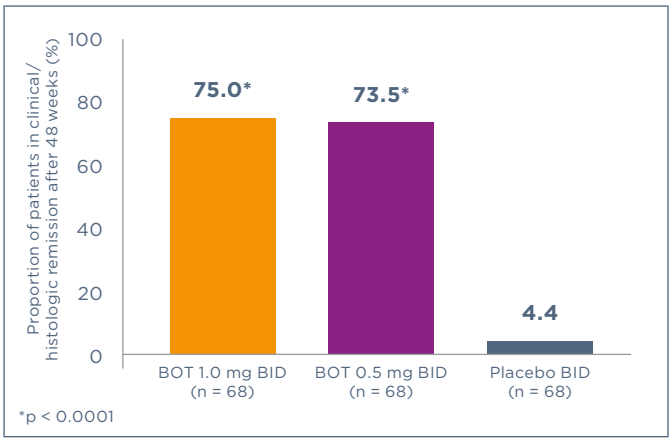


Figure 3: Proportion of patients (%) in clinical/histologic remission after 48 weeks of treatment with budesonide orodispersible tablets (BOT)

**Budesonide orodispersible tablets** are the first and currently only approved corticosteroid therapy for topical induction and maintenance therapy in adults with EoE. The mucoadhesive saliva in which the active substance is dissolved provides long exposure to the budesonide on the esophageal mucosa. As investigations have shown, after 6-week induction therapy 93% of trial participants given a dose of 1 mg orodispersible budesonide twice a day achieved histologic remission along the entire esophagus. After a year of treatment with budesonide orodispersible tablets (identical or halved dose), 75% and 73.5% respectively of the affected patients were kept in clinical/histologic remission (Figure 3). In fact, in a 96-week open study 80% of the affected were identified as being in clinical, histologic, and endoscopic remission.

**Biologics** are also an interesting new therapy option for treatment of EoE. However, the costs are relatively high when compared with treatment with PPI and corticosteroids, which are recommended as standard therapies in the guidelines. The only currently approved preparation is Dupilumab, a monoclonal antibody that binds to the receptors of the inflammatory mediators IL-4 and IL-13 and thus prevents them from forming a bond. The antibody is injected subcutaneously once a week. 82% of patients achieved histologic remission as a result (< 15 eosinophils per high power field [HPF]). This biologic drug can also be given to children from the age of one. As well as for EoE, it is also approved for treatment of bronchial asthma, atopic dermatitis, and nasal polyps. However, in terms of their significance Lucendo and Molina Infante regard biologics as a second-line therapy based on the high costs of the treatments. Biologics make sense particularly if other therapies fail to achieve success, or if additional diseases such as asthma, atopic dermatitis, or nasal polyps are present that can be treated at the same time.

**Endoscopic dilatation** is a co-therapy for patients with a narrowed esophagus. According to the two speakers, this method must be performed in small steps but is a low-risk and important option. "Start low, go slow" is the motto. The goal is to achieve a lumen diameter of at least 15 mm.

## Between dream and reality: ICI for colorectal cancer

Colorectal tumor cells have various mechanisms at their disposal that are capable of disabling the immune system in order to secure their own survival. They do this by addressing two different receptors on T-cells, namely the PD-1 receptor and the CTLA receptor. The bond between the tumor cell and the receptors causes the immune system to turn a blind eye to the tumor, explained **Prof. Thomas Seufferlein** from Ulm (Germany). This is why antibodies that are targeted against these receptors or an antibody that targets the ligands of the PD-1 receptor on the tumor cell (PD-L1 inhibitor) are used to overcome this "blindness" and mobilize the immune system. Colorectal tumors that respond particularly well to immune checkpoint inhibitors (ICI) are ones that display a deficient mismatch repair system (dMMR) and high microsatellite instability (MSI-H). This treatment promises to be successful if there are a high number of PD-1 and CTLA-4 receptors on the T-cells and of PD-L1 receptors on the tumor cells. Up to 15% of patients with colorectal cancer have a dMMR/ MSI-H tumor. Metastatic colorectal tumors only display this advantageous constellation for ICI in up to 4% of cases.

T. Seufferlein:
**"In order for immune checkpoint inhibitors (ICI) to be sufficiently effective, the tumor microenvironment must also be suitable."**

## ICI treatment during the early stages of a tumor

During the early stages of a tumor, a neoadjuvant therapy consisting of a single dose of Ipilimumab, which is an antibody that targets the CTLA-4 receptor, and two doses of the antibody Nivolumab, which targets PD-1, can bring about a pathological response. Pathological complete response (pCR) was achieved by 60% of patients in the group with a dMMR/ MSI-H tumor. In the group of patients with a proficient mismatch repair system (pMMR) this was only around a quarter. ICI has also been shown to be effective with locally advanced tumors with dMMR/MSI-H. Here, the immunotherapy is well tolerated.

## Effective even in locally advanced tumors

Very good results can also be achieved with a combination of the antibody Nivolumab to target PD-1 and the antibody Relatlimab to target LAG3 in patients with locally advanced dMMR/MSI-H tumors. A pCR of 79% gives cause to hope that surgery can be carried out with greater protection for the organs.

With locally advanced rectal cancer (dMMR/MSI-H) the antibody Dostarlimab, which targets PD-1, demonstrated good efficacy. 14 patients achieved clinical complete remission (cCR). To date, with ICI it has been possible to avoid chemotherapy. The long-term observations will show whether therapy with Dostarlimab is a curative treatment approach.

## ICI can be used even for metastatic tumors

In the guidelines of the European Society for Medical Oncology, Pembrolizumab is recommended as first-line treatment for inoperable, metastatic (stage IV) colorectal cancer if the tumor is a dMMR/MSI-H tumor. Pembrolizumab is also a PD-1 inhibitor. In studies, better results were obtained with ICI than with chemotherapies, specifically with regard to progression-free survival rate (PFS), side effects, and quality of life. The combination of Ipilimumab and Nivolumab is now also recommended for the second-line treatment. In long-term trials with a low dose of Ipilimumab combined with Nivolumab, it was also shown that, with this type of tumor, metastatic colorectal cancer also displays a very long-lasting response to this therapy. The median PFS was not yet reached after 48 months. The ICI combination is regarded as the new standard in this area.

Nonetheless, ICI has also proven to be effective for patients with pMMR. In the case of therapy-naive patients with inoperable metastatic colorectoral cancer, the PD-L1 inhibitor Atezolizumab in combination with chemotherapy with FOLFOXIRI and Bevacizumab led to an improvement in PFS in comparison to treatment with FOLFOXIRI and Bevacizumab alone. In patients with stable microsatellites (MSS), the immunoscore is a predictor for the efficacy of ICI treatment. In an immunoscore, a tumor-independent method for determining the immune response of a particular tumor and for predicting and stratifying patients who might potentially benefit from immunotherapies, the density of CD3 and CD8-positive T-cells is measured in two different tumor regions (tumor center and invasive margin). A high immunoscore (high density of CD8+/ PD-L1-positive cells in the tumor) is an argument in favor of ICI. As Seufferlein emphasized in his closing remarks, it is important to note that not all MSI-H tumors are the same. MSI-H1 tumors are characterized by low BRAF mutation and by an enrichment of M2 macrophages. They lead to a worse outcome than MSI-H2 tumors.

**Who can benefit from ICI?**
For some patients with colorectal cancer, based on the latest study data we can conclude that ICI is a dream come true. These patients are being given the chance of organ preservation (MSI-H colon and rectal cancer). For some patients with metastatic MSI-H colorectal cancer, healing is a possibility. However, for other patients the reality is unfortunately harsh: with pMMR, only a small subgroup of patients has benefited to date.

## Tricky cases in gastroenterology

Attempts at locating gastrointestinal bleeding can feel like looking for the proverbial needle in a haystack. One such case was presented by **Prof. Cesare Hassan**. A 72-year-old woman with diabetes and high blood pressure presented herself in 2015. Over the course of a 5-year period prior to this, she had suffered multiple episodes with low hemoglobin levels and melena. Each time, the problems resolved themselves spontaneously. However, the patient did require clinical treatment on multiple occasions. Colonoscopies and CT scans revealed nothing. A capsule endoscopy was then performed in 2015, as part of which bleeding in the colon was found. However, a colonoscopy was unable to localize the bleeding. A repeat of the capsule endoscopy one year later then led to the following result: angiodysplasia of the terminal ileum, which does not bleed during the investigation procedure, was discovered in connection with nodular and edematous mucosa. On patients with cardiovascular disease, increased risk of enteric angiodysplasia should be considered. Repeating an endoscopy of the lower or upper gastrointestinal tract is not helpful. Performance of a capsule endoscopy prior to an enteroscopy is the method of choice.

**Prof. Julia Mayerle** presented two case studies that are linked to the pancreas. The first related to a 64-year-old male with chronic pancreatitis with pancreatic calcifications associated with alcohol abuse. The endocrine and exocrine functions of the pancreas were adequate. He presented himself to the clinic due to an acute episode of pancreatitis. In the endoscopic ultrasound, a 7 mm stone was found in the pancreatic duct, which had caused an obstruction. Ten days later he suffered a painful skin rash and subcutaneous nodules on both legs below the knee. The participants in the session suspected fat necrosis. After removal of the stone from the pancreatic duct via extracorporeal shock wave lithotripsy (ESWL) and implantation of a stent the painful skin reactions receded. It was a case of pancreatic panniculitis, a rare diagnosis in connection with a stone in the pancreatic duct.

In a second case of chronic pancreatitis with pancreatic calcifications, the patient in question was a female with a hereditary condition (PRSS1 mutation). Magnetic resonance imaging showed clear indication of a dilated pancreatic duct and a stone, which it was subsequently possible to remove. Three months later the patient presented with the same problems again. She was then given a metal stent. Mayerle derived the justification for a repeated endoscopic approach instead of surgical treatment of the patient on the basis of study data. However, the key reason for choosing the endoscopic procedure was the age of the patient: she was just 8 years old.

**Prof. Fernando Gomollón** from Zaragoza (Spain) presented a talk about difficulties in the choice of therapy for a young patient with early diagnosis of Crohn's disease. The 23-year-old student was suffering from merely minor signs of inflammation in the ileum and displayed strongly increased CRP levels and a high CRP level. All other indicators pointed toward a mild disease. Based on the 2020 guidelines the patient was a candidate for steroid treatment. However, Gomollón argued that the long-term therapy strategy should also be considered in addition to the guidelines. From his point of view, steroids should be avoided wherever possible. He discussed with the audience his choice of the TNF-α blocker Adalimumab as a monotherapy.

**Expert tip**
Latest information about treatments for inflammatory intestinal disorders can be found on the website www.ibd-eii.com, which is managed by Dr. Beatriz Gros from Edinburgh (UK).

The case of a 22-year-old woman with asthenia, anorexia, and various abnormal blood test results was presented by **Prof. Rafael Bañares** from Madrid (Spain). The patient was suffering with changes to her liver morphology, splenomegaly, retroperitoneal lymphadenopathy, and minimal ascites. Severe anemia initially led to the suspicion of a hematological disorder. However, the ratio of aspartate transaminase to alanine transaminase was conspicuous, instead steering attention toward the possibility of liver disease – and here specifically to Wilson's disease. With Wilson's disease, the body is unable to remove extra copper via the gall bladder due to a genetic defect. As a result, copper accumulates in the liver and in other organs, such as the brain, and subsequently it is also washed out into the bloodstream. However, the patient did not display increased levels of copper in her blood or urine. Nonetheless, the diagnosis remained unchanged because the patient met all the other criteria for the disease. With Wilson's disease confirmed, the patient would be a candidate for a liver transplant. A genetic analysis confirmed the suspicion. Bañares recommended that all exons should be analyzed both for chronic and acute cases of Wilson's disease. Acute cases of Wilson's disease are rare. They primarily affect women at an age of around 18. For this reason, the expert reminded the audience of the importance of considering the possibility of Wilson's disease during diagnosis. Most commonly, the disease is already advanced at the point of diagnosis. This makes precise and fast diagnosis all the more important. It also makes things easier in terms of being able to offer patients prompt treatment.

# XXVII. INTERNATIONAL BILE ACID MEETING: BILE ACIDS IN HEALTH AND DISEASE 2024

July 5–6, 2024

Symposium 237

EDINBURGH (UNITED KINGDOM)

Registration:
www.falkfoundation.org/de/veranstaltungen

# IMMUNO-MEDIATED DISEASES OF THE GI TRACT: WHERE DO WE STAND?

November 8–9, 2024

Symposium 238

FLORENCE (ITALY)

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# Latest news about the pancreas, liver, and intestine

**Among the wide range of gastrointestinal topics covered in Madrid, discussions of (emergency) endoscopy always played a leading role. But the subject of diet-based approaches to therapy was also addressed, for example for chronic inflammatory intestinal disorders and celiac disease. The focus was also on latest news on a range of topics from steatosis to decompensated cirrhosis, pancreatitis, and tumors in the gastrointestinal tract.**

## IBD: We will soon be able to predict the efficacy of biologics

In the future, the goal of endoscopy for chronic inflammatory intestinal disorders will not only be to provide an endoscopic assessment of remission, but also to judge histologic remission, as was explained by **Prof. Marietta Iacucci**. New options for optical magnification and immediate biopsy diagnosis directly on-site should help with diagnosis. In future, it will be possible to characterize and evaluate lesions of the colon. Ultrastructural and functional imaging will enable predictions of disease progression and thus help to improve outcomes. However, there are hurdles here that need to be overcome. The costs of state-of-the-art ultra-high-resolution endoscopy and probes are huge. In addition, the procedure will require additional time investment because the new techniques demand new learning. However, it is likely that AI will change endoscopic interpretation in clinical practice and in clinical studies. Evaluation of the permeability of the intestinal barrier will open up brand new options for IBD diagnostics. The ENDO-OMICS approach is also very promising: Here, fluorescent-labeled biologics are applied in the intestine in order to assess their bonding via confocal laser endomicroscopy. This investigation provides information about the efficacy of a biologics-based therapy.

## The microbiome as a therapeutic goal for IBD

The gut microbiome has been adapting to changing environmental conditions for centuries, explained **Dr. Gianluca Ianiro** from Rome (Italy). A regular diet of often the same types of food, as are consumed in industrial nations, generally has a strong influence on the microbiota of bacteria, fungi, and viruses in the intestine. While people in African countries still have a microbiome that is identical to the one people had centuries ago, first changes are now being observed in Asia and South America. One of the main differences in people's microbiomes in Europe and the USA is the reduced level of diversity. The consequence of this is a number of different diseases like IBD. Fortunately it is possible to modify the microbiome. New drugs like microbial consortia could capture the market. However, the associated costs for this are huge and exceed the prices for biologics. Stool transplants are another option. However, it has been shown that the success of a stool transplant depends on many factors.

In addition, not all donors are equally well suited. Transplant recipients need to be prepared for the treatment. As part of this, bacteria that are not helpful should preferably be removed beforehand. Stool transplantation is a long-term therapy. This is something that therapists should consider.

## Opportunities for IBD thanks to new therapeutics

In the early 2000s, the drugs for IBD therapy were ineffective. Patients suffered from poor quality of life, and the number of surgical interventions was high. The situation changed once biologics became available, in particular the TNF-α blockers. However, the biologics were expensive and working with them was untested. The drugs that were effective were rarely prescribed, in addition to which they did not offer long-lasting effects. Thanks to numerous new drugs and also to the development of small molecules and active substance combinations, IBD treatment with biologics has now gained momentum, explained **Prof. Charlie W. Lees** from Edinburgh (UK). Although the prevalence of IBD is on the rise, surgery on the intestine is needed less frequently. Complications are rarer. Nonetheless, even today it can still be difficult to prescribe the right drug at the right time to a suitable patient. Patients need to be stratified based on their disease characteristics (aggressive or mild case), their response, and the expected complications. The objective is to keep them permanently in remission. A number of new biologics are expected in the future. But studies on useful combinations of active substances are also on their way. Therapies are already being tailored to the individual, but they are still a long way away from precision medicine.

## Surgery will continue to play an important role for IBD

Despite the major progress being made in drug-based IBD therapy, surgery still plays a major role particularly for Crohn's disease. Around 50% of patients will require surgical treatment within 10 years of diagnosis. In the case of ulcerative colitis, this number is 10-15% of patients within a time frame of five to ten years. Here, surgery is not necessarily a last resort: It has been shown only recently that ileocecal resection at an early stage can offer advantages for patients, emphasized **Dr. Monica Millan Scheiding** from Valencia (Spain). Half of the people who were operated on at an early stage required no treatment with drugs for a period of five years afterwards. Discussions about new surgical techniques are currently under way. The goal is to minimize not only the post-operative complication rate, but to also avoid long-term effects, in particular recurrent events. Surgeons are currently talking about a new antimesenteric functional end-to-end anastomosis. In the case of Crohn's disease, this is intended to prevent anastomotic recurrences. The role of the mesentery is currently being intensively researched as part of this. It appears to play a key role in the pathogenesis of Crohn's disease. There is still no ideal treatment available for perianal fistula therapy, a common complication with Crohn's disease. The therapeutic results are better in patients with combined therapies and a shorter duration of illness.

**Main goals for surgery in ulcerative colitis:**
- Alleviation of symptoms
- Minimized cancer risks
- Attainment of good functional outcomes
- Improved quality of life

## When a gluten-free diet is not enough for celiac disease

In some patients with celiac disease, the symptoms and/or the duodenal lesions can persist despite a strict gluten-free diet. If the mucosa has recovered and only the symptoms persist, then comorbidities such as microscopic colitis, IBD, or pancreatic insufficiency should be considered, reported **Dr. María G. Esteve** from Barcelona (Spain). However, if the atrophy of the mucosa persists, then non-responsive celiac disease should be assumed, which is not actually all that rare. In investigations, around 50% of patients continued to display lesions of the intestinal mucosa. Over 70% of these are symptom-free. Under closer consideration, it is noticeable that the age of the patient plays an important role for the efficacy of a gluten-free diet. People aged 30 or older should expect a poorer response. The duration of illness does not appear to play a role.

Adults often display a slow response to the change in diet. The inadequate response to a gluten-free diet can have serious consequences: depression, fatigue, and cognitive complaints are some of the knock-on effects, but diabetes and osteoporosis are also part of the spectrum. Various drugs are currently undergoing trials in order to prevent this. Orally administered glutenase is already available and being widely used. Results on the use of IL-15 antibodies, inhibitors for tissue transglutaminases, or immunotherapies, which are hoped will raise tolerance to gluten, are not yet available in sufficient quality. A proportion of patients with non-responsive celiac disease has refractory celiac disease. Two different types can be distinguished here: Fewer than 10% of people with non-responsive celiac disease have type 1 refractory celiac disease, and around 1% have type 2. They are normally older than 50 and display signs of persistent or recurrent malabsorption with villous atrophy despite following a strict gluten-free diet for 1 year. Differential diagnosis is not a straightforward matter. Type 1 is treated with a strict diet, budesonide, and azathioprine. For type 2, in addition to the diet and budesonide, the purine inhibitor Cladribine or a JAK inhibitor can be considered. In severe cases, autologous stem cell transplantation should be considered.

## A rare disease among enteropathies: CMUSE

**PD Dr. Helga-P. Török** from Munich (Germany) opened her presentation on the topic of CMUSE with the observation that the small intestine is known as the dark area of the gut. The name CMUSE stands for cryptogenic multifocal ulcerous stenosing enteritis. Diseases like this are extremely rare. The literature contains only individual case descriptions, but no systematic investigations. Disease progression is usually chronic. Patients often display symptoms for many years before the diagnosis is confirmed. Unfortunately, despite medical and surgical therapies patients often suffer clinical relapses. Investigations of the small intestine should begin with abdominal imaging, followed by balloon enteroscopy for assessment of superficial ulcers and strictures. Capsule enteroscopies should be used only with great caution if there is suspicion of CMUSE, as the probability of capsule retention is high. The diagnosis must be genetically confirmed (prostaglandin transporter defect). In terms of treatment, surgery is usually the first option. Steroids and immunomodulators can be considered as drugs for treatment. Endoscopic balloon dilatation can offer relief. As supporting therapy, enteral or parenteral feeding with iron and vitamin supplements is required.

**CMUSE criteria:**
- Unexplained small intestine strictures
- Superficial ulcerations limited to the mucosa and submucosa
- Chronic and recurrent ulcerative stenosis
- Abdominal pain
- Persistent occult blood in the gastrointestinal tract
- Absence of inflammations

## Emergency endoscopies are rarely justified

Emergency endoscopies – during the night or at the weekend – are requested in hospitals for a wide range of very different diseases, but often they are not justified. **Prof. Alexander Meining** from Würzburg (Germany) spoke about absolute emergencies in which urgent action is essential. He spoke of cases where objects or food have been swallowed that could cause an obstruction. Whether or not a swallowed object demands an immediate endoscopy depends to a large degree on the object itself, the symptoms, and the time of swallowing. Small, smooth objects are usually not dangerous. The situation is different with sharp or very large objects. Symptoms that indicate perfusion result in a different urgency and need for action than non-specific complaints. 90% of patients do not require an urgent endoscopy according to Meining. What is really relevant is fast endoscopies after swallowing batteries, objects with sharp edges, or magnets. In these cases the endoscopy should be performed within six hours. If food causes an obstruction of the esophagus then very fast action is required again, and an endoscopy should be performed within two hours. The bolus should be pushed into the stomach. The reason for the obstruction must be clarified as a matter of urgency.

**Prof. Ian M. Gralnek** from Haifa (Israel) spoke about the necessity for an urgent endoscopy after gastrointestinal bleeding. On the basis of numerous studies, he was able to show that, in the case of bleeding in the upper gastrointestinal tract, there is no advantage in performing the endoscopy within the first 6 hours of admission of the patient. As a rule, there is a time window of up to 24 hours. He explained that it is often better to ensure that hemodynamic therapy is provided to the patients first and to then initiate management of further comorbidities. More urgency is needed if varices bleed. These should be investigated endoscopically within 12 hours. In the lower gastrointestinal tract there is even less time pressure to perform an endoscopy. It should only be performed during the stay in hospital.

Chronic intestinal pseudo-obstruction (CIPO) is a rare motility disorder of the gastrointestinal tract with recurrent episodes that resemble mechanical obstruction without organic, systemic, or metabolic disruptions being present and without an obstruction being detectable. CIPO is often induced by opioid therapy. Inflammation can also be the cause. As a general rule, the symptoms improve after up to 72 hours, explained **Dr. Antonio Capogreco** from Milan (Italy). An endoscopy is only necessary if the symptoms persist. In terms of treatment it is possible to implant a stent if the dilatation of the colon is more than 12 cm. Alternatively, fixation of the intestine to the abdominal wall can also be considered. Another form of obstruction is called volvulus. Here, a loop of intestine twists around itself and the mesentery that supplies it. In an image, this resembles what looks like a coffee bean. It is usually younger women who are affected by this. In these cases, an endoscopy is the first choice of therapy. Surgery is required if the problem occurs again.

With obstructive cholangitis, alongside the availability of the necessary resources, the severity also determines the urgency with which an ERCP needs to be performed. However, it should be taken into account for cholangitis that the disease can very quickly transition from an inflammation with moderate severity to a severe case. **Dr. Andrea Anderloni** from Pavis (Italy) reported on this using a recent case from his hospital and raised awareness among the audience for keeping a close eye on the progression of the disease. Antibiosis should be initiated prior to an ERCP. An emergency ERCP is associated with high risks. The mortality rate is 10%. The expert said that it is important to be able to accurately assess both the specifics of the case and one's own capabilities. In this way, in an emergency it is acceptable to initially only provide drainage and to then remove the cause – i.e. the gallstones – in a second step.

## Steatosis, fibrosis, cirrhosis – the liver in distress

Steatosis is one of the most common chronic forms of liver disease. Excess weight and lack of exercise are contributing factors. Based on a case study, **Prof. Manuel Romero-Gómez** from Sevilla (Spain) explained how a simple case of steatosis can turn into liver fibrosis. As has been shown in studies, minor steatosis can deteriorate in around 40% of patients. The reasons as to why this progression takes place are not easily explained. It is a dynamic and complex process in which genetic factors and the microbiome are both involved. The transition is determined by a range of different factors. For example, the PIDDOsome protein complex plays an important role. But the patient's aerobic capacity, i.e. their fitness, also helps determine the progression. Inflammation genes, MicroRNA profiles, and extracellular vesicles also modulate the tendency to develop liver fibrosis. A reduction in body weight and increased exercise can reverse the development.

While the life expectancy with compensated cirrhosis is around ten years, with decompensated cirrhosis this is reduced to around 24 months. Drivers for the decompensation are the portal hypertension, liver failure, and inflammation of the liver. **Prof. Cristina Ripoll** from Jena (Germany) stressed that great therapeutic importance should be placed on treatment of the portal hypertension.

The expert presented studies in which the betablockers Carvediol and Propanonol were used for treatment of portal hypertension, whereby Carvediol is more effective. Ripoll explained that treatment of the underlying disease, for example hepatitis, is very promising in order to treat cirrhosis. By contrast, no antifibrotic therapy is available. There are difficulties with identifying clinically significant portal hypertension. Ripoll recommended combining measurements of liver and spleen stiffness with a determination of platelets.

## Reducing mortality for acute pancreatitis

**Prof. Vinciane Rebours** from Paris (France) observed that incidences of acute pancreatitis have been rising for years. 80% of cases are mild, but the progression is moderate to severe in 20% of cases. Morbidity and mortality rates are significantly increased in these patients and can be as high as 13% for sterile necrosis and 35% for infected necrosis. The risk of severe progression is higher in older people, in patients with comorbidities such as chronic kidney failure or diabetes, as well as in people with obesity, particularly if the amount of visceral fat tissue is increased.

Various therapeutic approaches can be considered in order to reduce the mortality. They can be used in particular during the initial phase of the disease, which consists of two phases with an increased risk of mortality.

In the first step the blood volume should be regulated. A prompt infusion is recommended for hypovolemia. Here, an aggressive infusion with a bolus of 20ml/kg body weight followed by continuous infusion of 3 ml per kg and hour offers no advantage over a standard dosage according to Rebours – at least not in mild cases. However, the expert did see advantages in using Ringer's lactate solution rather than a saline solution. In one study, the rate of hospitalization was reduced by use of Ringer's lactate solution. Antibiotics and probiotics offer no advantage unless infected necrosis is present. With regard to early nasoenteric feeding, Rebours referred to the presentation by **Prof. Markus M. Lerch** from Munich (Germany).

Lerch explained that, in contrast to earlier textbook opinions, withdrawal of feeding for acute pancreatitis is not advised. If no nutrients are fed into the intestine then this will cause a reduction in microvilli. The risk of bacterial translocation increases.

And, on the other hand, an adequate calorie intake lowers the mortality rate. Enteral feeding offers many advantages over parenteral feeding – certainly in severe cases. Patients with severe acute pancreatitis benefit from enteral feeding in terms of the risks of mortality and multiple organ failure. The effectiveness of a gastric tube is comparable to that of a jejunal feeding tube. Trials have now shown that it is even preferable for patients to feed themselves. However, in the case of a gastric tube it should be ensured that feeding takes place intermittently, which is not important for jejunal feeding. The administration of probiotics is contraindicated. Pancreatic enzymes offer no advantage.

**Prof. Marianna Arvanitaki** from Brussels (Belgium) spoke about dealing with necroses. She explained that the first step is to use computer tomography to identify the necrosis. Then it needs to be determined whether or not the necrosis is infected. Antibiotics are only indicated for confirmed infected necrosis. An intervention is generally less urgent and does not need to happen within the first four weeks after stationary admission. The first option to be considered here is drainage. This can be done both with metal and plastic stents, whereby replacement of a metal stent is easier. The choice depends on how often it is forecast that the stent will need to be changed. In 50-60% of cases drainage is an adequate treatment for the necrosis. In the remaining cases, the next steps are endoscopic or subsequently also minimally invasive surgery.

## Immune checkpoint inhibitors in tumor therapy

The prognosis is good for very early tumor stages in the liver. Overall survival is high as a result of resection, transplantation, or local ablation therapy. Subsequent intermediary stages and advanced tumors usually require systemic therapy and result in limited life expectancy, explained **Prof. Christoph Roderburg** from Düsseldorf (Germany). However, the situation has dramatically improved for patients in the last 15 years. For a long time, the tyrosine kinase inhibitor (TKI) Sorafenib was the default treatment option. However, modern combinations with immune checkpoint inhibitors (ICI) have been able to extend the median overall survival (mOS) from around 12 to 24 months. Roderburg presented recent study findings in relation to this. According to these, combinations of the PD-L1 inhibitor Atezolizumab with Bevacizumab, which targets the VEGF, and of the PD-1 inhibitor Sintilimab with Bevacizumab were both able to significantly extend the mOS. Combinations of different ICIs that target PD-(L)1 and CTLA4 demonstrated advantages at the four-year follow-up stage, with 25% of the patients taking part in the trial surviving instead of 15%. Combinations of other TKIs and ICIs have not yielded any positive outcomes to date. ICI therapy is becoming more important in early lines of therapy and is used at earlier stages. Many trials are currently under way that are designed to yield more information about suitable sequences. Results are also expected for the combination of transarterial chemoembolization (TACE) with ICI.

**Why is ICI potentially superior to other existing therapy approaches?**

This is the question that was asked by **Prof. Enrico De Toni** from Munich (Germany) in his presentation. TKIs address complex signal paths. They are non-selective and display high toxicity. By contrast, ICIs interact only with few target structures. Their toxicity is lower and they are more easily tolerated. They also offer another advantage: patients who are to be given a systemic therapy often ask whether the treatment will merely add a few months to their life expectancy, i.e. whether it is a palliative approach. The answer is "yes" for TKIs. TKIs improve the median overall survival and, after a certain amount of time, lead to the same result as older comparable therapies. The situation is different with ICIs. Here, the focus is on the long end of the curve. Very many more patients can survive for a very long period of time – which means that, generally speaking, this is a curative approach.

However, the side effects of ICIs in relation to the immune system are a problem. Early administration of steroids can counter the efficacy of ICIs. New, tailor-made approaches are needed here. In the future, it will also be interesting to look at potential combinations with further drugs: triple therapies involving the addition of an ICI could bring about further progress.

The prognosis is poor for tumors in the upper gastrointestinal tract. Survival rates after 5 years are up to 30%. The median overall survival is up to 30 months. There is great variety in the tumors. For example there are four different types of gastric tumor alone. Adenocarcinomas offer better outcomes in terms of overall survival than squamous cell carcinomas. Stomach cancer has a better prognosis than esophageal cancer. As is already known from trials, patients who carry the Epstein–Barr virus or who have tumors with microsatellite instability (MSI-H) can benefit from treatment with ICIs, which is combined with chemotherapy. This subject was covered by **Prof. Tamara Matysiak-Budnik** from Nantes (France). In patients with a squamous cell carcinoma, the PD-1 inhibitor Tislelizumab proved effective. Patients also benefited from the addition of an ICI to their chemotherapy in the case of HER2-positive tumors. The microenvironment of the tumor also appears to be significant for the efficacy of ICIs. Further studies are due to clarify the role of the gut microbiome.

# Herbert-Falk Award goes to Professor Jan Tack


Left-to-right: Prof. Dr. Markus M. Lerch, Dr. Martin Falk, Prof. Dr. Jan Tack, Carola Falk, Julius Rüther

This year's **Herbert-Falk Award**, which is given out by the Falk Foundation e.V. and is endowed with a prize of €40,000, went to the recognized intestine specialist **Prof. Jan Tack** from Leuven (Belgium). "In the field of neurogastroenterology and motility he is now the leading researcher in the world," emphasized Prof. Markus M. Lerch in his speech of praise.

Tack was born in Leuven in 1962 and left the city between 1989 and 1990 for a research post at Ohio State University (USA). Tack has a passion for traveling and a strong drive to always be active. As the Head of the Gastroenterology and Hepatology Department at the University Hospital in Leuven and the founder of TARGID (Translational Research in Gastrointestinal Disorders), he can look back on over 1500 publications and 900 peer-reviewed articles. He has contributed to 45 book chapters whilst being clinically active at the same time. To date he has mentored 45 PhD students and 20 postdoctoral researchers from all around the world. His patients come from far and wide to be treated by him.

In his role of Associate Editor of the specialist publication "Gut" he has done a great deal to move forward the topic of functional diseases of the gastrointestinal tract. He is also in charge of the two publications "Neurogastroenterology & Motility" and "UEG Journal". The researcher has already been the recipient of numerous prizes and awards.

In his acceptance speech, Tack presented research results for functional dyspepsia, a field he has been working in for over 20 years. Although convincing therapeutic approaches are still lacking, the researcher has been able to establish a link between the symptoms and inflammatory events that take place in the duodenum – comparable with EoE. The Herbert-Falk Award can help to advance this research so that new therapy options can be developed here as well for patients with functional dyspepsia.

# Poster prizes: Awards for young scientists

**At the symposia of the Falk Foundation e.V., it is a longstanding tradition that young scientists are recognized for their outstanding research work. The following won awards at Symposium 235:**

**1st prize: Aline Pesi**, Mainz (Germany):
*The oral tissue transglutaminase inhibitor ZED1227 prevents gluten-induced enteropathy in the humanized NOD-DQ8 mouse model of celiac disease*

**2nd prize: Tanja Martina Müller**, Erlangen (Germany):
*Improved functional fitness of engineered ex vivo expanded Tregs for in vivo gut homing*

**3rd prize: Josiah Carter**, Bath (UK):
*Difficult to swallow: The one-stop dysphagia clinic*


Left-to-right: Adrian Rüther, Prof. Julia Mayerle, Tanja M. Müller, Aline Pesi, Josiah Carter, Dr. Martin Falk

# “AI is only useful if it has been trained properly”

**Prof. Dr. Julia Mayerle** is a medical specialist for internal medicine, gastroenterology, hepatology, endocrinology, and diabetology at the University Hospital of Ludwig Maximilian University of Munich, where she also heads up the Pancreas Working Group. In addition, she is also a member of Falk Foundation e.V.

**Professor Mayerle, what was your personal highlight at the Symposium in Madrid?**

**Prof. Mayerle:** We had some very high-caliber speakers in Madrid who covered the full scope of topics relating to gastroenterology. In addition, by streamlining the topics in the individual sessions we were able to immerse ourselves very deeply in the latest developments. The broad spectrum ranged from artificial intelligence in endoscopy to rare diseases of the small intestine such as CMUSE, a disease many of the participants were perhaps not even aware of yet. I believe we were able to reach out to a very wide group of people as a result. Personally, I greatly enjoyed the interdisciplinary approach and the opportunity to think outside of one’s own particular field.

**An entire session was dedicated to artificial intelligence (AI). Gastroenterology seems to have taken on a pioneering role here in medicine. What do you personally see as the advantages and disadvantages of AI?**

**Prof. Mayerle:** I can confirm this sense of a pioneering role. In the sessions on AI, we realized that there are now quite a lot of studies that have attempted to address the issues around the usefulness and limits of AI, and some of them have been very well done in terms of methodology. I think we can assume that assistance from artificial intelligence will enable us to see more intestinal lesions for example. However, we also have a duty to demonstrate that seeing and potentially removing these lesions will actually offer a benefit for patients.

It is a very complex challenge to choose the study design in such a way that it can demonstrate whether artificial intelligence really does add value. In fact, we should really perform each colonoscopy twice, once with and once without AI. But of course, this is not something we could expect our patients to put up with. This is why the study design suggested in Madrid is so interesting, in which one colleague performs the colonoscopy while the other sits with the AI system in the next room and tracks the colonoscopy at the same time with assistance from the AI. AI is only useful if it has been trained properly. This is a point we really need to address now. What I find really fascinating is the fact that we can assemble an AI system ourselves with simple means. It does not require any expensive commercial developments.

**The expansion of diagnostic options, above all the endoscopic ones, has helped improve the definition of clinical pictures in recent years. We are thinking here of EoE, which played a role at the Symposium. Do you also have the feeling that a lot is happening right now in the field of gastroenterology?**

**Prof. Mayerle:** Yes, there have been many advancements, and it is indeed the case that we have seen a lot of developments recently both in therapies for inflammatory disorders and also in the treatment of tumor diseases. For example, immune checkpoint inhibitors or CAR T cell therapy – these are areas in which things are really moving forward. But JAK inhibitors and IL23 antibodies also represent major breakthroughs that can be measured in terms of therapeutic success. There really is a lot happening.

Apart from new drugs, there are also other issues that are helping us to move forward. I am thinking here of the topic of biliary pancreatitis. We have now systematically investigated the therapy options in studies and worked through open questions. The outcome is not that we are doing something new, but that we are actually doing less as a result. Intervening too much or too quickly – this has probably ended up doing more damage than good to patients in the past. This is something that needs to slowly sink into our heads. This is also an innovative outcome.

**The pancreas is your specialist area. Which topics do you feel have not yet been properly addressed, and in which areas or on what topics would you like to see more research and development taking place in the future?**

**Prof. Mayerle:** If we look at the pancreas then I think there are two big questions that still need to be answered in relation to pancreatitis. At the moment we are treating both acute and chronic pancreatitis purely symptomatically. We are not doing anything to address the cause. We need to find out more about the inflammation processes in acute pancreatitis and how they are modulated. We still have an unmet medical need here, and this is something we should urgently address. With chronic pancreatitis, which is

the consequence so to speak, the same thing applies. It is not clear to what extent we need to delay or influence organ destruction. We do not yet know in detail whether fibrosis is good or bad. I think that this is not a phenomenon that is easy to pin down from an academic point of view. We will probably need to start by jointly defining end points in order to make progress with studies here. For example, we need to define what the study objective should be in relation to pain. How do we measure therapeutic success? I don't think it is sufficient to consider patients as healed just because they no longer have symptoms. The goal must be to secure healing histologically, for example.

**Your presentation covered biliary pancreatitis. How common is this form of pancreatitis, and how do you judge the importance of this disease? Would a prophylactic cholecystectomy help patients with gallstones?**

**Prof. Mayerle:** Around one in five people in Germany has gallstones. However, not all of them will develop biliary pancreatitis. Nonetheless, it is true that in 40% of cases asymptomatic gallstones first become symptomatic in the form of biliary pancreatitis. However, if we look at the overall picture then the incidences of biliary pancreatitis amount to around 1%. If we were to remove the gallstones from everyone who has them then this would represent an unnecessary, excessive treatment in around 99% of cases. This cannot be justified. What we have learned is that not everyone who comes into hospital with biliary pancreatitis needs an ERCP. One exception is if the patient also presents with cholangitis. Otherwise it is more likely to cause harm to the patient if they are given an ERCP within the first 24 hours of hospital admission or within 72 hours of pain onset. We do not know the reason for this. To date we have only seen theories, but these have not yet been proven. This is a relevant fact for hospitals though, because ERCP is a highly specialized procedure. It is complex and difficult to ensure that it is always available. In the future, we can probably do without emergency ERCPs.

**The topics of lifestyle and diet play an important role in many areas of gastroenterology. To what extent does this also shape your day-to-day work?**

**Prof. Mayerle:** We also have a nutrition advice center, an interdisciplinary center for dietics and nutrition. This is affiliated to my clinic. Here there are around 350 Standard Operating Procedures for the different diseases. And we also offer dietary advice. Some of these recommendations are evidence-based, while others tend to be more what you would call a common sense approach. One example: In the case of chronic inflammatory intestinal disorders, it is known that significant therapy successes can be achieved through dietary interventions such as elemental diets. This is very welcome particularly in pediatric care, because immunosuppressive drugs can be avoided as a result. Dietary recommendations are therefore an important element in our range of therapeutic tools. However, we regularly encounter problems with compliance.

**Pancreatic carcinoma is a real passion of yours. Overall survival time is still short with these tumors. What is current research looking at, and are there any developments in the pipeline that can give us hope?**

**Prof. Mayerle:** One area we could mention here would be cancer vaccines. It has been shown that a significantly increased chance of survival can be achieved with an mRNA vaccine in adjuvant therapy. However, there are still technical problems with the realization. In comparison to CAR T cell therapy in hematology, it is proving a challenge to implement the therapy. But it is going to be exciting in future to see whether and how the concept can be realized. In addition to this, there are also further approaches in the area of precision medicine that could deliver promising results soon.

**For you, what is the importance of the professional training events held by the Falk Foundation?**

**Prof. Mayerle:** I think they are tremendously important. In Madrid we had 1300 people taking part. This number included many international and highly renowned colleagues, even if many came just to listen and not to speak. I think that was fantastic.

**Professor Mayerle, thank you very much for taking the time to talk to us!**

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