

ECCO'22

FEATURES

2022 ECCO Guidelines for the Treatment of Ulcerative Colitis

What Is the Role of the Environment (Exposome) in Inflammatory Bowel Disease?



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Dear Readers,

Welcome to this supplemental issue to *EMJ Gastroenterology* covering the 17th Congress of the European Crohn's and Colitis Organisation (ECCO). This supplement spotlights insights shared at ECCO'22, alongside highlights from the top 10 prize-winning abstracts as well as our summaries of key presentations at the congress.

Read on to share in the latest research in inflammatory bowel disease, Crohn's disease, and ulcerative colitis presented at ECCO'22, ahead of our main issue of *EMJ Gastroenterology* later this year.



Koutsouki

Evgenia Koutsouki, PhD.

Editor

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Aims and Scope

EMJ is an online only, peer-reviewed, open access general journal, targeted towards readers in the medical sciences. We aim to make all our articles accessible to readers from any medical discipline.

EMJ allows healthcare professionals to stay abreast of key advances and opinions across Europe.

EMJ aims to support healthcare professionals in continuously developing their knowledge, effectiveness, and productivity. The editorial policy is designed to encourage discussion among this peer group.

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Congress Review

Review of the 17th Congress of the European Crohn's and Colitis Organisation (ECCO)

Location: ECCO'22 Virtual

Date: 16th-19th February 2022

Citation: EMJ Gastroenterol. 2022;11[Suppl 1]:5-16. Congress Review. DOI/10.33590/emjgastroenterol/22E0317. <https://doi.org/10.33590/emjgastroenterol/22E0317>

DIVING into the virtual programme available at the 17th Congress of the European Crohn's and Colitis Organisation (ECCO) saw attendees share in the latest updates to the field of gastroenterology. Aiming to 'navigate the oceans of IBD', this shaped the various informative sessions, stretching from the depths of developing environmental recipes for inflammatory bowel disease (IBD) to future applications of telemedicine in this area.

Hosted in the Austrian capital, Vienna provided a virtual experience this time around. Instead of negotiating the historic streets of the city to attend sessions, delegates were able to access the ECCO booth and interact with congress material online. Across the 4-day event, 5,901 attendees observed the scientific programme presented at ECCO'22, voyaging 17 virtual booths to witness major breakthroughs, highlights, and trends in the field of IBD. With engagement from 105 different countries, this international gathering of leading experts consisted of 12 different academic sessions and 31 talks. The scientific programme boasted 865

abstracts, with 90 of these presented orally, in addition to several satellite symposia and 735 exhibited e-posters.

In his welcome, Laurent Peyrin-Biroulet, ECCO President, spotlighted a short list of sessions to watch out for, including a lecture delivered by Séverine Vermeire, KU Leuven, Belgium, on 'A European IBD voyage'. Other noteworthy sessions he mentioned included 'From basic science to practical approach' and 'Aiming high with treatment goals in IBD: the modern Icarus?' All these sessions remain accessible, temporarily, on the congress portal, alongside presentations on minimising malignancy risks, which highlighted interesting clinical cases and modern monitoring methods related to managing IBD in clinical practice.

As is custom at each congress, ECCO recognised the outstanding contributions made by numerous individuals; these awards highlight the global diversity that was integral to the material shared at ECCO'22. ECCO Grants, acknowledging the promotion of innovative scientific research in IBD in Europe, were awarded to Silvia Cerantola and Ferdinando D'Amico



of Italy; Celia Escudero-Hernández in Germany; Danish Urs Mörbe; Joep van Oostrom and Elsa van Wassenaer from the Netherlands; Margarita Papatheodoridi from the UK; and Australian Robert Venning Bryant. ECCO Fellowships for promoting innovative scientific research and knowledge exchange in IBD in Europe were awarded to Vittoria Bellato of Italy and Sulak Anandabaskaran from Australia. ECCO Pioneer Awards, which are awarded to congratulate visionary interdisciplinary research projects in the field of IBD, were presented to the partnerships of Salomé Pinho and Harry Sokol, of Portugal and France, respectively, as well as Annemarie de

Vries and Alison Simmons, from the Netherlands and the UK. Finally, Swiss Marianne Spalinger and Raja Atreya of Germany shared the ECCO Multi-Year Research Grant. These researchers and clinicians received their prestigious awards alongside many others to congratulate their significant work as leading gastroenterologists.

Where ECCO'22 allowed attendees to 'navigate the oceans of IBD', the 18th Congress of ECCO will encourage participants to journey north to Copenhagen, Denmark, in March 2023, where preparations for the next annual meeting have already begun. ■

ECCO 2022 REVIEWED →

Long-Term Outcomes for Patients with Very Early Onset Inflammatory Bowel Disease

INFLAMMATORY bowel disease (IBD) is characterised by chronic inflammation of the gastrointestinal tract and is estimated to affect nearly 80,000 children in the USA alone. Very early onset IBD (VEOIBD) occurs when a patient receives an IBD diagnosis before they are 6 years old; if the patient is <2 years old, the condition is diagnosed as infantile IBD. Recently, a longitudinal, multicentre, retrospective cohort study of patients with VEOIBD was conducted using data from 21 international paediatric centres to determine the long-term outcomes for these populations, with findings shared at ECCO'22. The patients with VEOIBD included in the study were diagnosed between the years 2008 and 2018, with at least 2 years of follow-up.

The cohort was made up of 243 patients (52% male), 69 (28%) of which were diagnosed before the age of 2 years old. The median age at diagnosis was 3.3 years, with a median follow-up of 5.8 years. Of this population, IBD was classified as either Crohn's disease, ulcerative colitis, or IBD-unclassified in 30%, 59%, and 11% of patients, respectively. Within the population of patients with ulcerative colitis or IBDU, 75% presented with pancolitis, whereas in the cohort of patients with Crohn's disease, 62% presented with isolated colonic disease, 32% with ileocolonic disease, and 19% with perianal involvement. Genetic testing was performed in 96 (40%) patients, identifying a monogenic diagnosis in 23% of cases, mutations of the IL-10 receptor in 5 cases (23%), and structuring or penetrating diseases in 9 cases (4%).

First induction therapies used in the study were corticosteroids, 5-aminosalicylic acid, and nutritional therapy, which were utilised in 53%, 30%, and 11% of patients, respectively. Corticosteroids were used more commonly to treat patients with infantile rather than non-infantile IBD (64% versus 49%), and no significant differences between age groups were observed with the use of maintenance therapies.

Patients with infantile IBD presented with higher rates of IBD-unclassified, lower levels of haemoglobin and albumin, higher levels of C-reactive protein, lower weight z-scores, lower rates of response to first induction therapy, and a shorter time to hospitalisation during follow-up when compared with patients who were diagnosed after 2 years of age. A colectomy was performed in 11% of patients and diversion surgery in 4% of patients, with no significant differences observed between age groups. Furthermore, no malignancies or deaths were observed in the cohort, and 85% of patients were in corticosteroid-free clinical remission at the end of follow-up.

Overall, although patients with infantile IBD were observed as having more severe clinical features at presentation and a lower response to induction therapy than patients who were 2–6 years of age, it was found that all patients with VEOIBD had a fair long-term outcome with low rates of complications and surgical interventions. Moving forward, further steps could include replicating this study on a larger scale to confirm long-term clinical outcomes. ■



"there is no link between the disease activity of inflammatory bowel diseases (IBD) such as ulcerative colitis (UC) and Crohn's disease (CD) and COVID-19 severity and long-term outcomes."

Inflammatory Bowel Diseases Activity Is Not Linked with Severity of COVID-19 Outcomes



POPULATION-based study carried out in Denmark, presented at ECCO'22, stated that there is no link between the disease activity of inflammatory bowel diseases (IBD) such as ulcerative colitis (UC) and Crohn's disease (CD) and COVID-19 severity and long-term outcomes. The severity of COVID-19 in this study was defined as requiring admission to an intensive care unit, ventilation requirement, or death. Long-term COVID-19 outcome was defined as COVID-19 infection hospitalisation.

UC disease was measured by a clinical colitis, while CD was measured by the Harvey-Bradshaw Index (HBI). Other IBD measures such as biochemical and endoscopic activity of UC and CD were also considered. Either C-reactive protein >5 mg/L or faecal calprotectin >250 µg/g were used to determine the biochemical activity of CD and UC. Additionally, a Mayo Endoscopic Subscore (MES) of ≥2 defined the endoscopic activity of UC, while a Simple Endoscopic Score (SES) of ≥3 was used for CD.

The aim of the study was to understand whether the disease activity of UC and CD is correlated with the severity of COVID-19. The researchers utilised a Danish IBD database that collates and records the course of disease in patients with UC and CD and who have confirmed COVID-19. The inclusion period of the study was between 28th January 2020 and 1st April 2021, with 319 patients diagnosed with UC and 197 patients with CD. All the patients included in the study had positive confirmation of COVID-19 and results showed that the patients with UC had clinical activity: 83.1%; biochemical activity: 100.0%; and endoscopic activity: 20.7%. Patients with CD had clinical activity: 71.1%; biochemical activity: 66.5%; and endoscopic activity: 21.3%. In this population-based study it was concluded that the clinical, biochemical, and endoscopic activity in both CD and UC were not associated with adverse or severe COVID-19 or the long-term outcomes. ■

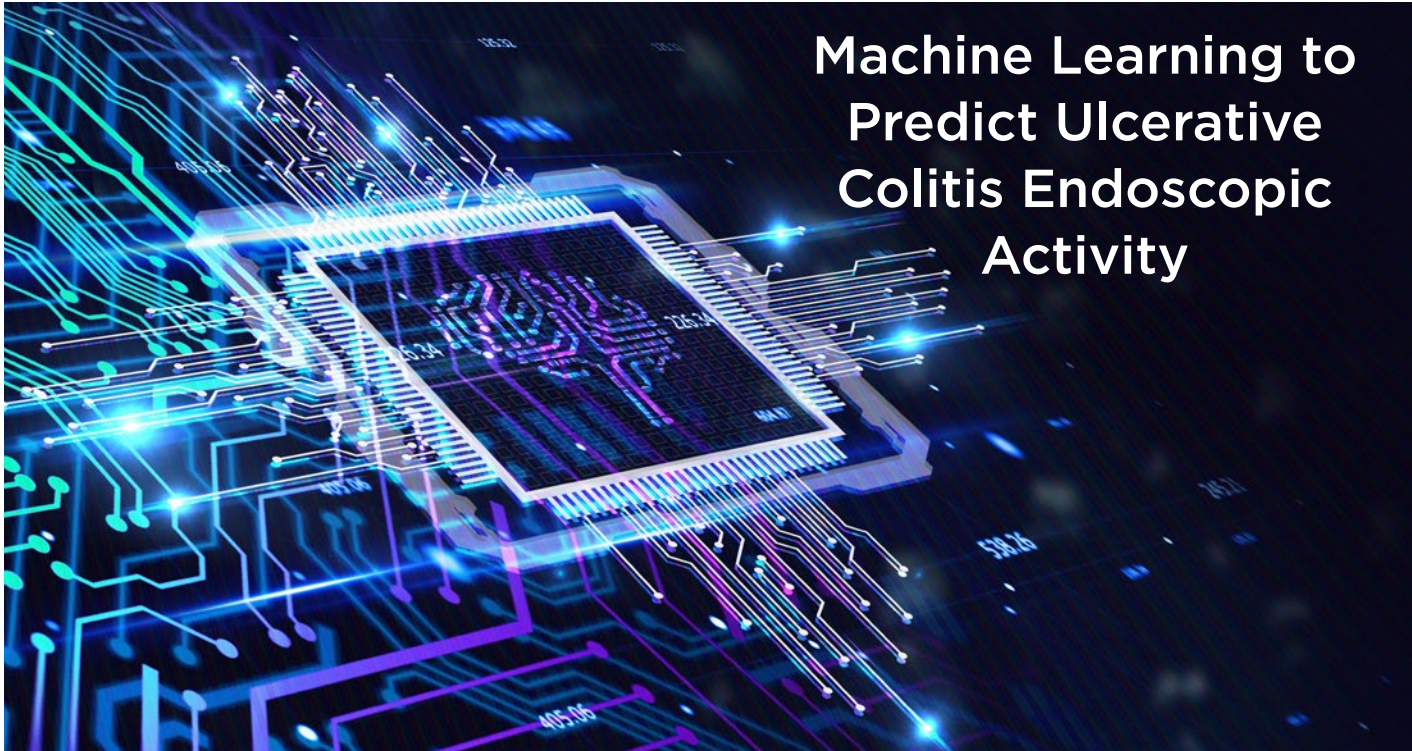
The Role of Adherent and Invasive *E. Coli* in Crohn's Disease

A STUDY presented at ECCO'22 supported the role of adherent and invasive *Escherichia coli* (AIEC) as a predictive factor in the re-occurrence ileal Crohn's disease (CD). The researchers used a post-operative recurrence model from the REMIND multicentre prospective cohort of patients with CD who had undergone an ileocolonic resection to examine rates of AIEC.

Surgical specimens were used to identify AIEC in 181 patients following the operation, whilst a colonoscopy of the neo-terminal ileum was carried out at 6 months in 119 of the 181 patients. The Rutgeerts' score, an endoscopic scoring system, was used to predict endoscopic post-operative disease recurrence, with a score ≥ 2 classed as post-operative endoscopic recurrence or ≥ 3 as severe recurrence. Additionally, the reappearance of the initial ileal lesions was classed as i_1 , from a pathophysiological point of view, and more progressive post-operative ileal recurrence was $i_2 + i_3$. Furthermore, the relative risks and/or odds ratios were modified based on potential confounding factors such as gender, smoking history, duration and phenotype of CD, preventative treatment, antibiotics, and prior bowel resection.

Of the 181 patients included in the study, 46.3% had not received any preventative treatment for endoscopic post-operative recurrence; however, 24.3% of the 181 study participants had been treated with an anti-TNF for preventative measures. According to the results, AIEC was two-fold more common in the neo-terminal ileum at Month 6 compared with the initial surgical specimen: 30.3% versus 14.9%, respectively ($p < 0.001$). Data from this study also demonstrated that AIEC colonisation was linked to a specific microbiota signature including higher levels of *Ruminococcus gnavus*. Based on the post-operative recurrence model, the data from this study supported the discovery of AIEC within the surgical specimen was a predictive factor recurrence of ileal CD. ■





Machine Learning to Predict Ulcerative Colitis Endoscopic Activity

"this machine learning approach to endoscopic evaluation could be used as an alternative to human central reading when conducting future clinical trials."

MACHINE learning algorithms have been described to predict how human readers would evaluate disease activity in ulcerative colitis using the endoscopic Mayo score (eMS). Advancing this field of research further, Jean-Frederic Colombel, Icahn School of Medicine at Mount Sinai, New York City, USA, and collaborators have now developed a machine learning predictive model that is trained on eMS features using centrally read endoscopies. The results were shared in an award-winning abstract presented at ECCO'22.

In total, Colombel et al. obtained 793 full-length videos from approximately 250 patients enrolled in a Phase II study that investigated mirikizumab for moderate-to-severe ulcerative colitis. Notably, these participants had a centrally read eMS. The machine learning workflow involved annotation, segmentation, and classification. A test set of 147 videos and a consensus set of 94 videos were used to assess the model.

Regarding the primary objective, the machine learning model was shown to categorically predict inactive disease versus active disease

with an accuracy, positive predictive value (PPV), and negative predictive value (NPV) of 84%, 80%, and 85%, respectively, in the test set. Moreover, in the consensus set, the model predicted inactive disease compared with active disease with an accuracy, PPV, and NPV of 89%, 87%, and 90%, respectively.

For the secondary objectives, it was revealed that, in the full test set, the model predicted endoscopic healing with an accuracy, PPV, and NPV of 90%, 44%, and 95%, respectively. In this same set, the model predicted severe disease with an accuracy of 80%, a PPV of 86%, and a NPV of 86%. In the consensus set, the model predicted endoscopic healing with an accuracy of 95%, a PPV of 86%, and an NPV of 95%. Additionally, severe disease was predicted with an accuracy, PPV, and NPV of 85%, 82%, and 87%, respectively.

Based on these results, it has been proposed that this machine learning approach to endoscopic evaluation could be used as an alternative to human central reading when conducting future clinical trials. ■

Targeting Hedgehog Signalling Pathway to Treat Inflammatory Bowel Disease

*"inhibiting the hedgehog signalling pathway with the small inhibitor vismodegib or genetic ablation of *Ihh* led to a significant decrease in clinical disease severity and decrease in IL-17a+ Th17 cells."*

INFLAMMATORY bowel disease (IBD) affects approximately 1 in 210 people in the UK. The aetiology is poorly understood and there is no cure. Therefore, understanding what is occurring at a cellular level could be useful in discovering novel therapeutic drug targets for IBD. Hedgehog signalling has an important role in tumorigenesis, development, and tissue homeostasis and is targetable using approved small molecule inhibitors. Presenters from the University of Cambridge, UK, among other institutions, worked together to understand the role of hedgehog signalling in Th17 differentiation in an award-winning abstract and original study shared at ECCO'22.

Th17 cells play a vital role in protecting the gastrointestinal tract but are also key pathological drivers of IBD. In this study, researchers analysed the signalling pathways that regulate the differentiation of Th17. Firstly, the team created two knock-out mouse models that targeted Indian hedgehog (*Ihh*) and its receptor smoothed in the hedgehog signalling pathway. Using techniques such as flow cytometry and gene expression analysis, they were able to study Th17 differentiation. Other methods conducted by the researchers included *in vivo* studies such as T cell adoptive transfer colitis using knockout T cells or controls, histological analysis, colon length, and weight measurements. Bioinformatic analyses of gene expression data of human rectal biopsies was also carried out to reinforce the translational relevance of the findings from mouse models.

Results showed that hedgehog signalling, in the absence of *Ihh*, selectively drives differentiation of Th17 cells. Further to this, the speakers were able to show that inhibiting the hedgehog signalling pathway with the small inhibitor vismodegib or genetic ablation of *Ihh* led to a significant decrease in clinical disease severity and decrease in IL-17a+ Th17 cells. This study opens doors for scientists to investigate small molecules to inhibit the hedgehog pathway and consequently Th17 differentiation, which can drive the pathology of IBD. Next steps could include conducting a larger study in humans and testing approved small inhibitors of the hedgehog signalling pathway to treat IBD. ■

Corticosteroid-Free Remission in Patients with Ulcerative Colitis

JAK inhibitor upadacitinib (UPA) has proven effective in corticosteroid (CS)-free remission in patients with moderate-to-severe active ulcerative colitis in a Phase II clinical programme. Presented at ECCO'22, this programme comprised of two induction trials and the U-ACHIEVE maintenance study.

Patients were randomised 2:1, using UPA 45 mg once daily (QD) or placebo for 8 weeks. After the initial 8 weeks, patients who achieved clinical response were randomised again 1:1:1, receiving UPA 15 mg QD, UPA 30 mg QD, or placebo for 52 weeks. Despite the CS use among patients, disease characteristics of the participants were well balanced.

Results indicate that clinical remission for patients receiving UPA 45 mg did not differ from the use of baseline CS. In fact, treatment-emergent adverse events increased in the group taking UPA 45 mg plus baseline CS, including the risk for serious and opportunistic infections, compared

with the placebo and UPA without baseline CS groups. However, CS-free remission (defined by the Adapted Mayo Score as being CS-free for ≥ 90 days) was significantly increased with UPA 30 mg QD and UPA 15 mg QD, compared with placebo ($p < 0.001$).

Rates of adverse events as a result of treatment with UPA with baseline CS versus UPA without baseline CS were 33% versus 39% and 27% versus 35% for UPA 30 mg and UPA 15 mg groups, respectively. Adverse events such as malignancy and major adverse cardiovascular events were not frequently reported by patients receiving UPA.

This clinical programme indicates that UPA is superior to placebo in conferring CS-free remission in patients with moderate-to-severe active ulcerative colitis, while baseline CS use did not have any efficacy benefit. Therefore, disease control with UPA without CS use is an optimal treatment strategy. ■



"Adverse event such as malignancy and major adverse cardiovascular events were not frequently reported by patients receiving UPA."

Online Training Platform to Improve Dysplasia Detection in Inflammatory Bowel Disease

"training using the new OPTIC-IBD learning platform improved the confidence of endoscopists to accurately diagnose dysplasia despite their previous experience."

PATIENTS with inflammatory bowel disease (IBD) are at a significantly greater risk of developing colorectal cancer. To treat patients with IBD timely and effectively, healthcare professionals conduct endoscopy to detect dysplasia. This technique helps doctors characterise lesions accurately; however, the speakers of the prize-winning abstract shared at ECCO'22 discussed how there was a gap in training, particularly in ability to recognise and accurately diagnose dysplastic lesions in IBD. In their presentation, the speakers discussed how they created an online training platform called OPTIC-IBD to help overcome this issue for healthcare professionals old and new.

The team created an online multi-modality learning module, which included key aspects of detecting dysplasia in IBD from surveillance principles to classifications, examples, and optical diagnosis methods. Researchers conducted a study to test the efficacy of their new interactive training platform by recruiting 77 participants from Canada, Italy, and the UK. Participants included a mix of intermediate and experienced endoscopists who completed training that included 24 endoscopic videos of

IBD colonic lesions. All those taking part in the study had to classify lesions, predict histology, provide feedback, and rate their confidence. Finally, participants were randomised to receive feedback and extra training in a 1:1 ratio and had a final assessment at 60 days.

Impressively, the online learning platform had positive results and diagnostic accuracy was improved largely for new and intermediate endoscopists. Moreover, experienced endoscopists also benefitted from using OPTIC-IBD as sensitivity for dysplasia increased from 50.3% to 59.1%. Most importantly, the speakers had succeeded in executing the aim of their learning platform as specificity and accuracy for diagnosing dysplasia was the most improved outcomes from 44.9% to 70.3% and 55.0% to 64.6%, respectively.

Optical online training using the new OPTIC-IBD learning platform improved the confidence of endoscopists to accurately diagnose dysplasia despite their previous experience. Future work for the team will include studying the training approaches to improve the platform and make it available to endoscopists treating patients with IBD. ■





Novel Study Compares Effectiveness of Vedolizumab Versus Ustekinumab in Crohn's Disease

"a significant number of patients with CD following anti-TNF failure were able to maintain ustekinumab or vedolizumab on a medium-long-term basis"

PATIENTS with Crohn's disease (CD) can maintain ustekinumab or vedolizumab in medium-to-long-term clinical practice after failure or intolerance of anti-TNF therapy, said a comparative study presented at ECCO'22. The aim of this study was to compare the retention rate, short- and long-term efficacy, and the safety of both treatments following anti-TNF failure.

A total of 755 patients with CD from the ENEIDA registry from 30 centres, following failure or intolerance of anti-TNF agents and who had received either vedolizumab or ustekinumab as an alternative, were included in the study. Clinical activity, both in short- and long-term duration, was classified based on Harvey-Bradshaw Index (HBI). The predictive factors for effectiveness and durability of both treatments were analysed by Kaplan-Meier curves, Cox regression models, inverse probability weighting, and propensity matching score. There were 195 patients in the vedolizumab cohort and 560 patients in the ustekinumab cohort.

Following a 20-month follow-up, the survival rate for vedolizumab therapy was lower than ustekinumab. Additionally, the clinical response, steroid-free remission, and short-term clinical remission proportion of patients was greater in the ustekinumab cohort compared with the vedolizumab cohort. Following a 2-year period after starting both treatments, significant differences were discovered in both cohorts. Vedolizumab and ustekinumab were discontinued due to primary non-response in 142 patients (52%) and 185 patients (58%), respectively. Adverse events were observed in 12% of patients, mainly infections and skin lesions; however, this was not distinguishable in either treatment. The results concluded that in clinical practice, a significant number of patients with CD following anti-TNF failure were able to maintain ustekinumab or vedolizumab on a medium-long-term basis; however ustekinumab had a higher retention rate in these patients compared to vedolizumab. ■

Using Monoclonal Antibody Clearance to Predict Treatment Response in Inflammatory Bowel Disease

PREDICTING treatment outcomes in patients with inflammatory bowel disease is a long-term goal for clinicians. A recent study presented at ECCO'22 investigated the benefits of monitoring monoclonal antibody clearance in patients with Crohn's disease (CD). Using data from clinical trials, the researchers investigated two monoclonal antibodies: infliximab and ustekinumab.

The study recruited patients with moderate-to-severe CD who were treated with either infliximab (n=108) or ustekinumab (n=80). Disease was assessed at Week 12 and 24 by endoscopic remission, which was judged to be a CD Endoscopic Index Score of <3, and endoscopic response, $\geq 50\%$ decrease from baseline in simple endoscopic score for CD. Predictions were made using previously built pharmacokinetic models, with faecal calprotectin, albumin, CD activity index, and antibodies towards infliximab all

used to estimate infliximab clearance. Albumin and body weight were used to estimate ustekinumab clearance.

Researchers found that patients with endoscopic remission at Week 12 had lower infliximab clearance and higher infliximab serum concentration at both Week 2 and 6 of treatment. Most patients with early clearance of infliximab did not reach endoscopic endpoint. Contrastingly, the serum concentrations at Week 4 and 8 of ustekinumab treatment were similar between patients with and without endoscopic response.

The research concluded that lower infliximab and ustekinumab clearance predicted more favourable endoscopic outcomes. In patients treated with ustekinumab, the researchers further concluded that clearance monitoring may better predict endoscopic response than standard therapeutic drug monitoring. ■



"Researchers found that patients with endoscopic remission at Week 12 had lower infliximab clearance and higher infliximab serum concentration at both Week 2 and 6 of treatment."



Contributing Factors for Chronic Abdominal Pain in Inflammatory Bowel Disease

CHRONIC abdominal pain is a common symptom in patients with inflammatory bowel disease (IBD), yet the aetiology is not well understood. Scientists believe an altered gut-brain interaction as well as persistent histologic inflammation contribute to chronic abdominal pain in IBD. In an award-winning abstract presented at ECCO'22, scientists aimed to identify lifestyle, psychosocial, and clinical factors in patients with IBD with abdominal pain to fill in gaps in the research in IBD aetiology.

Researchers conducted a multicentre study involving a real-world cohort of patients with IBD in remission between January 2020 and July 2021. Patients used 'myIBDcoach', a patient-centred app for smartphones, which monitors IBD, quality of life, and symptoms of anxiety and depression. The study monitored these outcome measures in 3-month intervals in a total of 559 patients, 76.7% of whom were in remission. Additionally, the researchers assessed chronic abdominal pain in

patients with IBD in remission, characterised by an abdominal pain score of ≥ 3 .

Results showed that 46.4% of those patients in remission had a pain score that met the criteria for chronic abdominal pain.

Patients with IBD in remission with chronic abdominal pain had significantly greater levels of stress, fatigue, depression, difficult life events, and anxiety compared to patients in remission without chronic abdominal pain. Using a multivariable logistic regression, the research team were able to link clinical and psychosocial factors with the presence of chronic abdominal pain in patients with IBD in remission.

"Patients with IBD in remission with chronic abdominal pain had significantly greater levels of stress, fatigue, depression, difficult life events, and anxiety compared to patients in remission without chronic abdominal pain."

The authors shared their concluding remarks stating that quality-of-life, fatigue, anxiety, and psychosocial factors could contribute to the presence of abdominal pain in IBD in patients in remission and that this association could be exacerbating the abdominal pain via perceived levels of stress. ■

2022 ECCO Guidelines on the Treatment of Ulcerative Colitis

Natasha Meunier-McVey

Editorial Assistant

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KEY UPDATES to the European Crohn's and Colitis Organisation (ECCO) Guidelines on the Medical and Surgical Treatment of Ulcerative Colitis (UC) were presented in an engaging session at the 17th Congress of ECCO, which took place from 16th-19th February 2022. Chaired by Konstantinos Karmiris, ECCO Education Committee member and consultant gastroenterologist, Venizeleio General Hospital, Heraklion, Greece, and Henit Yanai, Head of the Inflammatory Bowel Disease Center, Rabin Medical Center, Petah Tikva, Israel, the session took place on the penultimate day of the congress and explored therapeutic and surgical options for the treatment of UC.

KEY OBJECTIVES OF THE ECCO GUIDELINE UPDATE

The session was opened by Timothy Raine, ECCO Guidelines Committee member and consultant gastroenterologist at Addenbrooke's Hospital, Cambridge, UK. Raine began by highlighting the key objectives of the updates to the ECCO Guidelines on the Medical Treatment of UC.

The goal of the 2022 update was to establish transparent and reproducible guidelines that are clinically relevant, whilst also recognising the lack of available data that is inevitable in some scenarios. Raine gave a clear explanation of the methodology used by experts in this year's update, a nod to the initiative for more transparency in guidelines for healthcare professionals. The guidelines were drafted using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process, prompting the formation of clinically relevant questions and meta-analyses of the quality of

existing evidence, ensuring a high standard of consensus recommendation. In areas where data lacked, the panellists employed the Oxford Levels of Evidence; this pragmatic approach involved a discussion of relevant papers following systematic review. These discussions took place in a face-to-face meeting of consensus group members with a panel of six expert patient representatives.

Raine went on to stress the importance of the outcomes measured by panellists for the medical section of the ECCO Guidelines on UC, in terms of what matters to patients and clinicians. Evidence supporting these outcomes was established through meta-analyses of data to accurately confirm treatment effects and risks associated with certain medications. Key areas of importance established for the medical treatment of UC included clinical response and remission for maintenance and induction therapies, as well as steroid-free clinical remission.



“The goal of the 2022 update was to establish transparent and reproducible guidelines that are clinically relevant, whilst also recognising the lack of available data that is inevitable in some scenarios.”

CHANGES TO THE MEDICAL TREATMENT OF ULCERATIVE COLITIS

Raine highlighted the key changes, referred to as ‘surprises’, in the update of the 2022 ECCO Guidelines on the Medical Treatment of UC. A notable shift from the 2017 guidelines is the recommendation of considering treatment options based on patient disease severity. Previously, guidelines advised treatment according to the site of the disease and its activity, whereas revised guidelines recommend treatment under sections labelled ‘Medical Management of Mildly-to-Moderately Active UC’ and ‘Medical Management of Moderately-to-Severely Active UC’. The decision to change this particular section aims to ensure that patients with limited disease who are displaying active symptoms have access to appropriate treatment options. A statement from the expert ECCO Guidelines Committee explained: “We feel that addressing the treatment choice to the clinical activity of a patient is appropriate.”

A notable change to the ECCO Guidelines on the Medical Treatment of UC is in regard to new data and treatments. Following the recent MERIT-UC trial conducted by Herfarth et al.,¹ which took place in 2018 and concluded that methotrexate was not superior to a placebo in maintaining steroid-free response or remission in UC, the drug has been removed from the guidelines.¹ New data for vedolizumab, ustekinumab, and tofacitinib have been included in the updated ECCO Therapeutic Guidelines on UC, which have purposefully been written in a way that allows for new updates to therapeutics to be included.

The committee took the deliberate decision to include head-to-head studies in the evidence review process. The first head-to-head biologic trial, the VARSITY study, was included in the updated guidelines. This showcases the importance of head-to-head trials, whilst ensuring that the outcomes included reflect those established as valuable by the committee. Indirect comparisons, such as references to external network meta-analyses, have also been

included in the ECCO guideline update to allow for nuanced discussion of treatment hierarchies to take place in the supporting text. Raine wrapped up the therapeutic section of the session by emphasising the importance of clinicians referring to this supporting information for the most practical advice.

ECCO GUIDELINES ON SURGICAL TREATMENT OF ULCERATIVE COLITIS

Opening up the second part of the update on the ECCO Guidelines on the Surgical Treatment of UC, Yves Panis, Professor of Digestive Surgery, Beaujon Hospital, Paris, France, provided key updates to surgery in cases of moderate-to-severe UC. The first statement update outlined that reconstructive ileal pouch-anal anastomosis surgery can be offered to refractory and corticosteroid-dependent patients following evidence that this improves patient quality of life. Panis also touched on the importance of pre-operative optimisation in patients with moderate-to-severe UC. The key update focuses on the use of steroids pre-operatively, which should be markedly avoided or weaned off before restorative surgery. The new guidelines advise that where weaning is not possible, surgery should be postponed. Prophylactic anticoagulation therapy is also advised in adult patients with active UC to reduce the risk of venous thromboembolism, and systemic nutrition is advised despite a lack of evidence.

Variations on total colectomy procedures were also discussed, which can be performed in modified two- (with temporary stoma) or three-stage methods. The updated guidelines state that the modified two-stage procedure may be associated with fewer complications, as patients are subjected to less surgery, but more evidence is needed to confirm this.

For patients with medically refractory UC, laparoscopic ileal pouch-anal anastomosis surgery is the advised choice. Panis explained that the guideline statements of lower intra- and post-operative morbidity and faster recovery come from a wider pool of reliable evidence. This technique is also an ideal option for young females, as it is associated with improved fecundity compared to open surgery. Ileo-rectal anastomosis (IRA) remains an option for patients

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with UC who have a minimally affected rectum. Panis went on to present data from the GETAID trial, the largest IRA follow-up study to date. This multivariate analysis study highlighted that patients with UC by severe acute colitis who have short-lived disease, are naïve to biologics, and do not present with chronic pruritis have the best chance of a good IRA outcome.

Panis closed the surgical update by drawing attention to the following statement from ECCO: "In addition to the clinical questions addressed in these guidelines, we recognise that many other topics would have been worthy of discussion." The statement lists areas such as the early post-operative management of patients with UC and acknowledges that the committee drafting process identified gaps in current knowledge, paving the way for future research.

CONCLUDING REMARKS

Bringing the session to a close, Raine explained that although uncertainty remains in some areas of the guidelines, the update has provided healthcare professionals with robust and pragmatic advice, once again emphasising the importance of referring to the supporting text for practical advice from more specific clinical presentations. Overall, Raine explained that the 2022 ECCO Guidelines on the Treatment of UC have been designed to guide and complement clinical judgement, whilst leaving room for the patient perspective. These guidelines will undoubtedly optimise patient care through advising clinical decision-making and allowing for further research and developments in the field of UC.

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What Is the Role of the Environment (Exposome) in Inflammatory Bowel Disease?

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OPENING Day 2 of the 17th Congress of European Crohn's and Colitis Organisation (ECCO), James Lindsay, Professor of Inflammatory Bowel Disease, Barts Health NHS Trust, London, UK, and The London School of Medicine, Queen Mary University of London, UK, discussed the influence of the environment on the risk of developing inflammatory bowel disease (IBD). The presentation discussed the pathways that mediate environmental impact on IBD as well as the limitations of presently available research, giving a valuable insight into what future studies could be conducted to ultimately determine the role of environmental factors in IBD.

The present understanding of IBD, an inflammatory disease, which includes Crohn's disease (CD) and ulcerative colitis (UC), is that the condition arises from an immune response to micro-organisms of the intestinal flora in genetically susceptible individuals. In addition to disease pathogenesis, other important aspects such as progression, extraintestinal manifestations, and immunogenicity to therapies, are yet to be well understood. While the genetics base is clear, it does not account for the discordance of disease in monozygotic twins, the increased incidence in second generation immigrants, or the rapid increase in IBD cases in the last 50 years. In light of these observations, Lindsay expressed the importance of examining the role of the environment, which, he stressed,

does not comprise a single factor, but a multitude of factors that are likely to impact disease onset and natural history.

INFLUENCE OF ENVIRONMENTAL EXPOSURE ON DISEASE ONSET

Lindsay presented a range of epidemiological studies that have proven fundamental when examining the impact of environmental factors on disease onset. An umbrella review, which examined over 71 environmental factors in 53 separate meta-analyses, found that breastfeeding had a protective effect on both CD and UC.¹ Additionally, Lindsay shared the findings of a study assessing the effect of



"An interesting new report revealed that antibiotic exposure over time might change the risk of developing antidrug antibodies with anti-TNF therapy in animal models, displaying a clear link between environment and disease natural history."

ultra-processed foods consumption in a cohort of nurses. In a total of 245,112 participants, there was incidence of both CD (369 cases) and UC (488 cases), with a median age of onset of 56 years, demonstrating that the intake of ultra-processed food was associated with an increased risk of incident CD but not UC, when corrected for a range of confounding factors.² The presentation also included an overview of a mechanistic introductory research that examined the dietary intake of foods linked to markers of inflammation. Such foods, termed empirical dietary inflammatory pattern (EDIP) foods were linked to an increased risk of CD.³ Lindsay highlighted the significance of the study in demonstrating the effect of dietary changes: individuals who started with a low intake of EDIP foods but moved to a high intake of EDIP foods had the same risk of developing CD as those who always had a high intake of high EDIP foods.

Despite the obvious value of epidemiological studies, Lindsay emphasised the importance of recognising their limitations and having a solid understanding of the methodologies used. Firstly, timing is essential when analysing results. For instance, the positive effect of breastfeeding is not observed in a cohort with an average age of >30; however, in a cohort of children, such protective effect is evident.⁴ Secondly,

Lindsay said that definitions are pivotal. This is particularly obvious when analysing diet as an impact factor, particularly regarding the ability of questionnaires to define ultra-processed foods versus other refined foods.

PATHWAYS LINK EXPOSOME TO DISEASE AETIOLOGY AND NATURAL HISTORY

The determination of the mechanistic pathways that might drive the impact on the mucosal immune system is critical. Lindsay suggested such pathways would include changes in intestinal permeability, signalling through “environmental sensors,” and modifying the epigenetic control of gene transcription.

It is widely known that factors such as pregnancy, breastfeeding, and diet influence disease through changes in the microbiota. However, this begs the question of whether such changes are a causative factor or a result of disease. One of the largest sibling cohort studies, involving thousands of siblings of patients with CD followed up over time, looked to address this question. The results showed that people who subsequently developed CD were more likely to have antimicrobial antigens.⁵ This result highlighted the role of alterations in intestinal microbiota

“Environmental exposure has a major impact on the risk of developing IBD. There are well-defined pathways that mediate this impact.”

prior to disease onset, suggesting an aetiological impact. The study also emphasised the effect of permeability changes in disease onset: patients who had increased gut permeability and siblings who had increased gut permeability were significantly more likely to develop disease than those who did not.

There might also be environmental factors that have an impact on the mucosal immune system, independently to gut microbiota. There are many environmental sensing molecules, of which the most well described is the aryl hydrocarbon receptor (AHR), which has a range of ligands present in our diets. The presence of these AHR ligands is associated with protective immune responses, including protective intraepithelial lymphocytes and innate lymphoid cells. Research in animal models demonstrates that mice deficient in AHR develop more severe disease and that mice fed an AHR ligand-free diet also develop more severe IBD.⁶

A large study looking at modifications in the epigenome of patients with IBD compared with controls showed the effect of methylation on disease onset. The report found that IBD-associated hypermethylation in a key promoter (*TXK*) region negatively correlates with gene expression in cluster of differentiation 8+ T cells, which subsequently drives disease.⁷

IMPACT OF EXPOSOME ON NATURAL HISTORY OF INFLAMMATORY BOWEL DISEASE

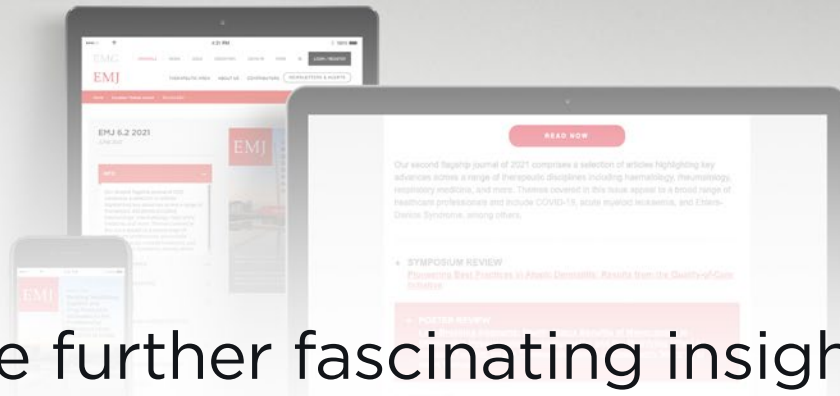
According to Lindsay, the impact of the exposome on IBD natural history is much harder to investigate due to the debate of cause versus association. The best studied factor that influences natural history of disease is smoking. Smoking increases the risk of a CD flare, increases risk of first surgery, and increases risk of disease recurrence after first surgery. On the contrary, quitting smoking improves the outcomes from the perspective of inflammatory

flares and risk of subsequent surgeries. An interesting new report revealed that antibiotic exposure over time might change the risk of developing antidrug antibodies with anti-TNF therapy in animal models, displaying a clear link between environment and disease natural history.⁸

In his closing remarks, Lindsay explained that: “Environmental exposure has a major impact on the risk of developing IBD. There are well-defined pathways that mediate this impact.” However, special attention needs to be paid to the evaluation of epidemiological studies to understand the exact methodology and whether the results are pointing to cause or association. According to Lindsay: “It will be through robust intervention studies that we will get the assessment of the true impact of the exposome.” ■

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Emerging Treatments for Crohn’s Disease: Cells, Surgery, and Novel Therapeutics

Meade et al. provide an update in this review on the advanced therapies for Crohn’s disease that are under investigation and could provide alternative to existing treatments. Novel non-pharmacological strategies are explored, alongside cellular therapies, and both surgical and dietetic interventions that could change the landscape of Crohn’s disease management.

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