EMJ GASTROENTEROLOGY

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UEG Week Virtual 2021

EDITOR'S PICK

Faecal Microbiota Transplant in the Treatment of *Clostridioides difficile* Infection: An Update

INTERVIEWS

EMJ spoke with Douglas Drossman about gut–brain interactions and his career in research; and with Helena Cortez-Pinto and Joost Drenth regarding their roles in United European Gastroenterology (UEG).

Contents

"In this eJournal, you will find the latest advancements in the field of gastroenterology through compelling peer-reviewed articles, exclusive interviews with key opinion leaders, and exciting abstract reviews from sessions presented at the United European Gastroenterology (UEG) Week Virtual 2021."

+ WEBINAR REVIEWS

+ ARTICLES

Editorial Board

VIEW IN FULL ←

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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.

EMJ is published quarterly and comprises review articles, case reports, practice guides, theoretical discussions, and original research.

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Front cover and contents photograph: Vienna, Austria, home of the UEG 2021. © rh2010 / 123rf.com

EMJ Gastroenterology 10.1

Welcome

Dear Readers,

We are delighted and proud to welcome you all to this year's issue of *EMJ Gastroenterology.* In this eJournal, you will find the latest advancements in the field of gastroenterology through compelling peer-reviewed articles, exclusive interviews with key opinion leaders, and exciting abstract reviews from sessions presented at the United European Gastroenterology (UEG) Week Virtual 2021.

Due to the ongoing restrictions faced as a result of the COVID-19 pandemic, the UEG decided once again to hold their congress week virtually. Despite this, it was ensured that each session was based around the concept of interactivity, offering real-time interaction from the audience through a question and answer tool. The virtual nature of this year's UEG Week also allowed those who were unable to attend the live sessions to access footage on-demand, ensuring that no one missed out on this exciting event. An independent, comprehensive review of the UEG Week Virtual, which took place between the 2nd and 5th October 2021, can be found in this issue of *EMJ Gastroenterology*, alongside reviews of abstracts presented, covering topics including ursodeoxycholic acid to treat gallstones, duodenectomy in patients with familial adenomatous polyposis, and genetic changes in oesophageal carcinoma during neoadjuvant treatment.

The fascinating peer-reviewed papers included in this issue cover a range of exciting topics. The Editor's Pick for this issue is an article by Moore-Gillion et al., which provides an update on faecal microbiota transplants in the treatment of *Clostridioides difficile*. Gonzalvez-Gasch et al. investigate factors associated with venous thromboembolism in acute pancreatitis. These feature alongside many more compelling, expertly written articles.

We were honoured to speak with Helena Cortez-Pinto, Vice-President of the UEG, and Joost Drenth, UEG Board Member. Both experts discussed their careers, research, and the impact of the UEG on professionals and patients. We were also delighted to interview Douglas Drossman, expert gastroenterologist and President of Drossman Gastroenterology, who spoke about his research interest of the brain–gut interactions and the future of the field.

We would like to express our thanks to the Editorial Board, peer-reviewers, authors, and interviewees for their continued efforts and brilliant work produced for this issue of *EMJ Gastroenterology*. All that remains is for us to do is to thank you, the reader, for your support and engagement in our previous and upcoming journals.

EMJ Editorial Team

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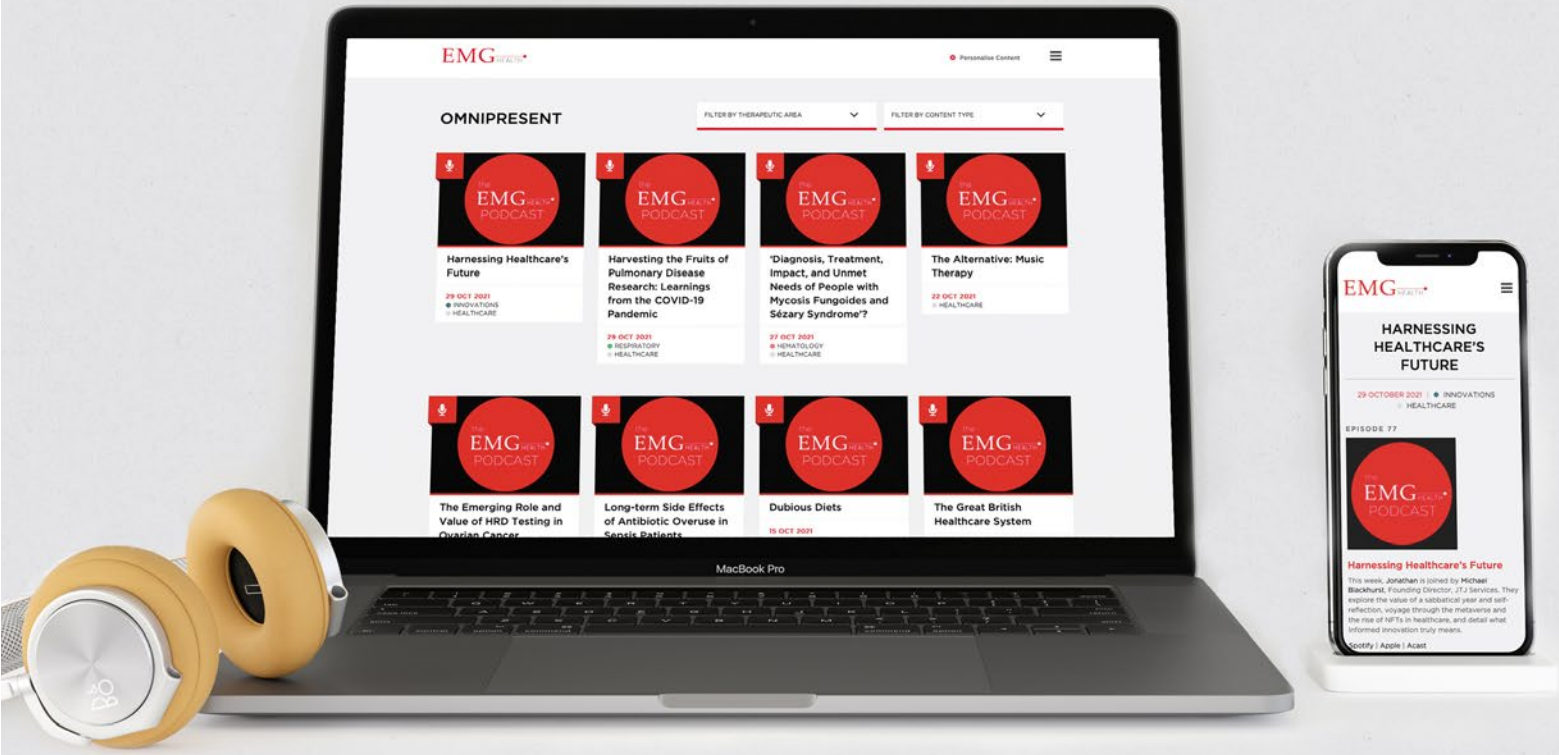

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Foreword

Dear Readers,

I am delighted to welcome you to the 10th edition of *EMJ Gastroenterology*, which delivers the latest clinical advances, expanding knowledge in the field of the digestive system, and associated disorders. This issue presents the highest-quality content and includes a scientific highlights package, summarising the most important content from United European Gastroenterology (UEG) Week Virtual 2021.

Broadcasted from Vienna, the virtual congress platform provided by the UEG facilitated superb dissemination of critical updates in the world of gastroenterology. The congress review within this eJournal summarises some of the ground-breaking abstracts presented, alongside an insightful feature.

Interviews with UEG Vice-President Helena Cortez-Pinto and Committee Member Joost Drenth provide first-hand insight into the inner workings of the UEG and suggest the directions that gastroenterology research might take in the near future. These are complimented by an in-depth conversation with Douglas Drossman, Founder of the Drossman Centre for Education and Practice of Biopsychosocial Care LLC, who is internationally renowned and influential in his field, about his illustrious career and published works.

Several peer-reviewed articles at the forefront of research are also enclosed in this edition; however, particular attention should be drawn to the Editor's Pick in this issue. Moore-Gillon et al. present an enlightening paper on faecal microbiota transplant, looking ahead to the next generation of faecal microbiota transplant products and summarising the recent developments observed in this evidence base. Another interesting article in this issue investigates the interaction between obesity and inflammatory bowel disease.

I hope you find this publication both interesting and thought-provoking, and that you enjoy engaging with the clinical research and medical expertise within this issue of *EMJ Gastroenterology*.

Sorin T. Barbu

Professor of Surgery, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

Congress Review

Review of the United European Gastroenterology (UEG) Week Virtual 2021

Location: UEG Week Virtual 2021

Date: 3rd–5th October 2021

Citation: EMJ Gastroenterol. 2021;10[1]:11-18. Congress Review.

"INGEST the best" was the catchphrase coined at the 29th Annual Meeting of United European Gastroenterology (UEG), hosted in the Austrian city of Vienna, the second congress of this speciality with a fully virtual attendance. Often called the 'City of Music' due to the influences of Mozart and Beethoven, UEG were able to orchestrate a sophisticated scientific programme over 3 days from a purpose-built TV studio alongside their global headquarters.

Attendees of UEG Week Virtual 2021 were comprised of colleagues from all continents, summating to near 8,500 delegates in 105 different countries. The scientific programme on offer was highly interactive, mitigating any barriers to disseminating knowledge imposed by a virtual congress. Faculty members from the Vienna studio encouraged their audience to engage and participate in discussions by utilising voting tools and question and answer functions. The learning platform was diverse, boasting a range of live sessions from abstract and poster presentations to webinars and case-based discussions. This was part of an initiative mentioned by the UEG President, Axel Dignass, who considers, along with his successor, Helena Cortez-Pinto, currently the UEG Vice-President, that it is "a constant necessity to innovate and to change the way in which we deliver our strategic plan."

UEG members can access on-demand recorded meetings from the 2021 congress, a definite benefit associated with the online shift in content delivery. In total, 782 presentations and 217 sessions, with contributions from 632 speakers, remain available. Highlights from these include symposia and webinars on the management of patients with obesity, nutritional approaches to managing gastrointestinal disorders, elimination of chronic viral hepatitis, and cutting-edge approaches to the treatment of rectal cancer. Alongside all this, Cortez-Pinto spoke in the closing ceremony about some of the abstracts she found of particular interest, describing the importance of maintaining strict

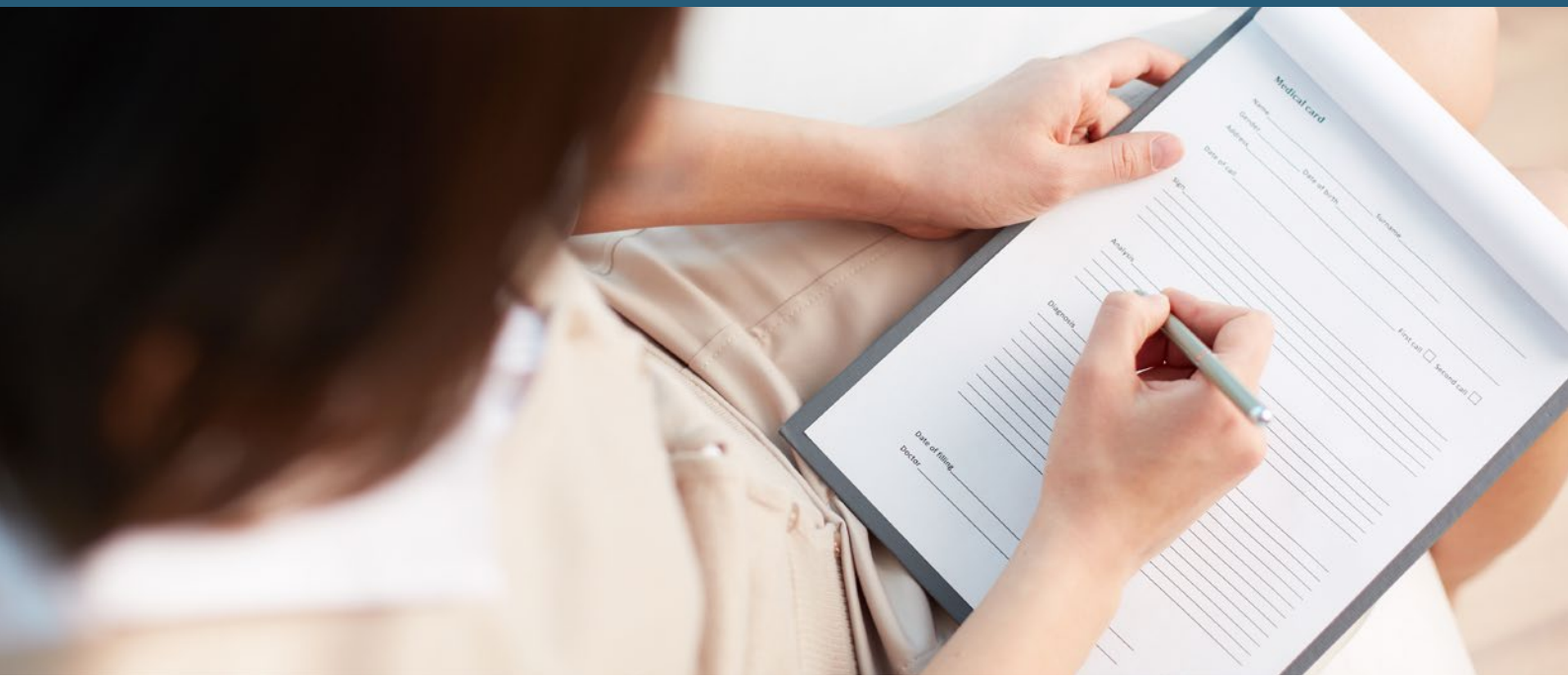
surveillance on patients with cirrhosis who have been treated with direct-acting antivirals. UEG Secretary General Magnus Simrén added to these highlights by spotlighting a multinational study investigating the presence of gastrointestinal symptoms in patients with COVID-19 who were hospitalised.

A selection of awards were handed out throughout the congress, recognising particularly significant contributions in the world of gastroenterology. The first of these went to Nicolas Richard, Rouen University Hospital, France, who received the Journal Best Paper Award for his winning article, entitled 'The Effectiveness of Rotating Versus Single-Course Antibiotics for Small Intestinal Bacterial Overgrowth'. The Research Prize was awarded by Luigi Ricciardiello, the Chair of the UEG Research Committee, who described the parameters for this honour as demonstrating "the best of the best in basic, translational and clinical research." For work on 'Repurposing Mitochondria Protective Targets for Adjuvant IBD Therapy', the awardee was Dirk Haller, Technical University of Munich, Germany, who will receive 100,000 EUR to fund his research. The most prestigious of the recognitions was the Lifetime Achievement Award, which was presented to Michael Farthing for outstanding contributions to the UEG and gastroenterology for over more than 30 years. Rebecca Clare Fitzgerald, University of Cambridge, UK, and a fellow of Farthing's, delivered his laudation by describing how he has "inspired a generation of researchers." Crediting the lasting contributions he has made to societies such as the UEG, where he served as President, Fitzgerald spoke about how Farthing has pioneered the modification of structures within organisations and acted as a timeless ambassador for gastroenterology internationally.

As part of the closing ceremony, Dignass revealed that planning for the 30th Anniversary UEG Week, hosted again in Vienna in October 2022, is very much underway, and hinted at inclusion of a hybrid model of attendance. Looking ahead to after he departs from his second year in office, he concluded with excitement that "we will engage as one connected community in this hybrid world." Whilst this shows there is light at the end of the tunnel for in-person interaction, the scientific highlights that follow will illuminate to those who could not attend the most-coveted information from UEG Week Virtual 2021. ■

"...a constant necessity to innovate and to change the way in which we deliver our strategic plan."

UEG 2021 REVIEWED →



Psychological Distress and Quality of Life Associated Gas-Related Intestinal Symptoms

RECENT findings from a new survey assessing the impact of gas-related symptoms on quality of life revealed a correlation between higher burden symptoms and increased stress and anxiety. These results from the Intestinal Gas Questionnaire (IGQ) were presented at this year's UEG Week, which took place from 3rd–5th October 2021.

The new IGQ survey is a 17-question validated questionnaire assessing the severity of seven key symptoms related to gas production over the last 24-hour period. The survey also measures the impact of these symptoms on patient quality of life (QoL) in the last 7 days. Scored from 0 to 100, the IGQ combines these aspects to evaluate the burden of each individual's gas-related symptoms. The study presented used the IGQ survey to evaluate the prevalence and QoL impact of these symptoms on the general population of the USA, UK, and Mexico. The research also aimed to assess the demographic associations of observed symptoms and their correlation with physical activity and BMI.

The study involved almost 6,000 individuals from the USA, UK, and Mexico, who all participated in the quality-assured, secure internet survey to assess these aims. Olafur Palsson, Professor of Medicine, University of North Carolina at Chapel Hill, USA, who was involved in the study, presented the survey results. The USA and UK saw similar IGQ scores of 14.5 and 13.7, respectively, with little disparity between the male and female groups. Mexico saw a significantly higher IGQ score throughout, with a total score of 26.0. Individuals from Mexico also consistently scored higher than those from the USA and UK in all seven assessed gas-related symptoms.

Palsson explained: "As we expected, gas-related symptoms are related to quality of life impairment and poorer wellbeing." The results clearly indicated a correlation between higher gas-related symptom burden and lower physical and mental QoL component scores, as well as increased anxiety and depression. Palsson went on to note that a relationship was not observed between these symptoms and BMI and physical activity. He concluded: "The most striking thing about our findings is that nearly all adults in the general population experience some daily gas-related symptoms." The significant differences between Mexico and the other countries involved strongly suggest that cultural, diet, or public health factors may influence gas-related symptoms, and future research will likely concentrate further on this observed result. ■

Meal-Related Abdominal Pain Frequently Experienced by 11% of the Population

ALARMING data from recent study has revealed that high rates of gastrointestinal discomfort are affecting the daily lives of multiple populations worldwide, and that meal-related abdominal pain affects one in 10 people. Research presented at UEG Week Virtual 2021, on 5th October, reported 40% of the global population experience recurrent gastrointestinal symptoms, and on routine check-up are reported as normal. Furthermore, 11% of the population experience abdominal pain while eating meals. Individuals who experience meal-related pain often suffer from other gastrointestinal symptoms as well, including bloating, diarrhoea, constipation, and feeling too full after eating. These disorders of the gut–brain interaction (DGBI) have substantial impact on society, categorised into over 20 subgroups. Although they are benign in not leading to serious complications or affecting life expectancy, patients experience a significant daily impact on their lives.

Incorporating information from 33 countries, each with more than 2,000 participants, this global epidemiology study, conducted by the Rome Foundation, consisted of a survey distributed via the internet or in some countries, door-to-door interview collection. The data presented at UEG Week was based on the approximate 55,000 who completed this online questionnaire. Fifty-two percent of the overall dataset experienced abdominal pain in 3 months prior to questioning, 18% of which was not meal-related, 23% occasionally meal-related, and 11% frequently related to meals. Thirty percent of those who reported frequent

meal-related abdominal pain suffer from lower gastrointestinal symptoms such as constipation and diarrhoea, which is 10% and 20% higher than those who occasionally have meal-related pain and those who rarely do, respectively. Individuals who suffer from frequent pain while eating meals are more likely to suffer from depression (35%) compared with the other groups (24% and 17%, respectively).

Lead author Esther Colomier, Katholieke Universiteit (KU) Leuven, Belgium, and the University of Gothenburg, Sweden, believes that meal-related symptoms should be considered in future diagnostic criteria. She reported: "In China, Singapore, and Italy prevalence rates were the lowest, whereas the prevalence rates were clearly higher in countries such as South Korea, Turkey, and Egypt." Researchers noted that it remains to be clarified why patients develop DGBI, but recognise there is a multifactorial profile of causation, with contribution from physiological, psychosocial, and early life factors. The main success of this study lies with identifying a relationship between food intake and gastrointestinal symptoms, achieving the over-arching aim of determining global prevalence of meal-related abdominal pain. Investigators were also able to characterise individuals experiencing meal-related abdominal pain in terms of DGBI diagnostics, physical burden, frequency, quality of life, healthcare utilisation, and psychological distress.

The sample size of this study is an obvious strength, and brings interesting comparison geographically. The researchers were able to assess meal-related symptoms in all patients with DGBI, which is of major importance for improving and individualising future treatment approaches. "In clinical practice, assessing meal association in all patients with DGBIs should be of major importance for improving and individualising treatment," were the words of Colomier. "Here, patients could benefit from a multidisciplinary care approach, including dietary and lifestyle advice, psychological support, and pharmacological therapy." ■

"In China, Singapore, and Italy prevalence rates were the lowest, whereas the prevalence rates were clearly higher in countries such as South Korea, Turkey, and Egypt."

Pandemic Delays Cause a Drop in Colorectal Cancer Diagnoses

DRAMATIC decline of colorectal cancer (CRC) rates since the beginning of the COVID-19 pandemic have been recorded in a recent study presented at the UEG Week Virtual 2021 Congress. CRC is Europe's second largest cancer killer, with 375,000 cases newly diagnosed annually.

Research conducted across multiple hospitals in Spain found that when data from the first year of the COVID-19 pandemic was compared to the previous year, cases of CRC identified fell by almost two-thirds. Of the total 1,385 cases identified across the 2-year period, 868 cases (62.7%) were identified in the pre-pandemic year compared with 517 cases (37.3%) diagnosed during the pandemic.

This trend was mirrored in the drastic drop in colonoscopies conducted, with 24,860 carried out pre-pandemic falling to 17,337 in the first year of COVID-19. Subsequent analysis also found that those diagnosed with CRC during the pandemic tended to be older, with more frequent symptoms, an increased number of complications, and presented at a more advanced disease stage than cases diagnosed in the previous year.

"These are worrying findings indeed," stated María José Domper Arnal, Service of Digestive Diseases, University Clinic Hospital, Aragón Health Research Institute, Zaragoza, Spain, and lead author of the study. "Cases of CRC undoubtedly went undiagnosed during the pandemic. Not only were there fewer diagnoses, but those diagnosed tended to be at a later stage and suffering from more serious symptoms."

Experts have suggested that the fall in diagnosis is due to the suspension of screening programmes and postponement of non-urgent colonoscopy investigations that occurred as a consequence of the pandemic. During the pandemic, more patients were diagnosed through symptoms instead of screening programmes: 81.2% of diagnoses compared with 69.0% in the previous year.

Diagnosis with serious complications, a sign of late-stage disease, increased significantly throughout the pandemic. Incidence of bowel perforation, abscesses, bowel obstruction, and bleeding requiring hospitalisation represented 10.6% of diagnoses pre-pandemic and 14.7% during the pandemic.

"CRC is often curable if it's caught at an early stage," explained Arnal. "Our concern is that we're losing the opportunity to diagnose patients at this early stage, and this will have a knock-on effect on patient outcomes and survival. We are likely to see this fall out for years to come." ■

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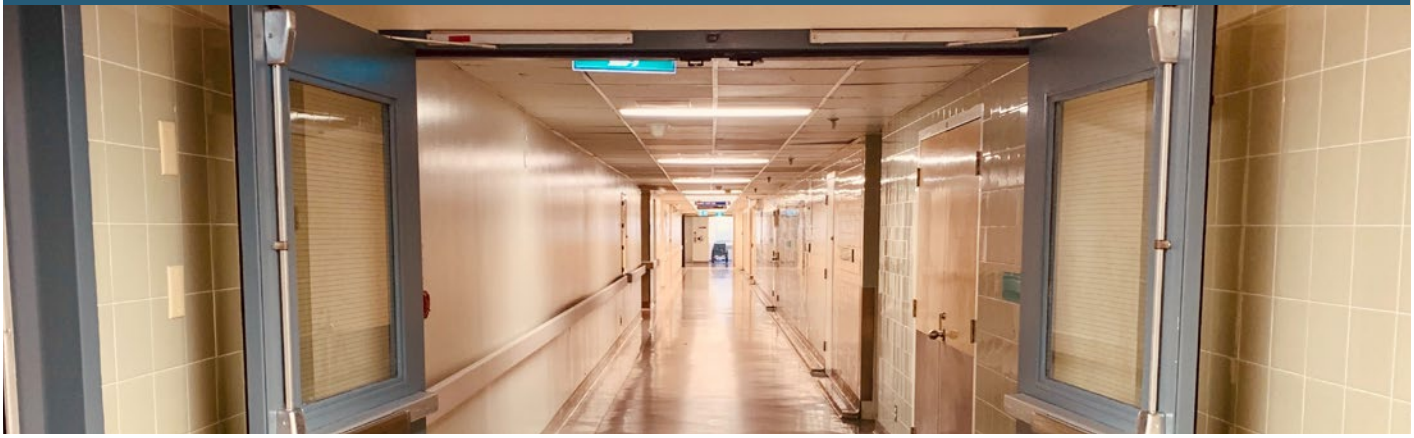
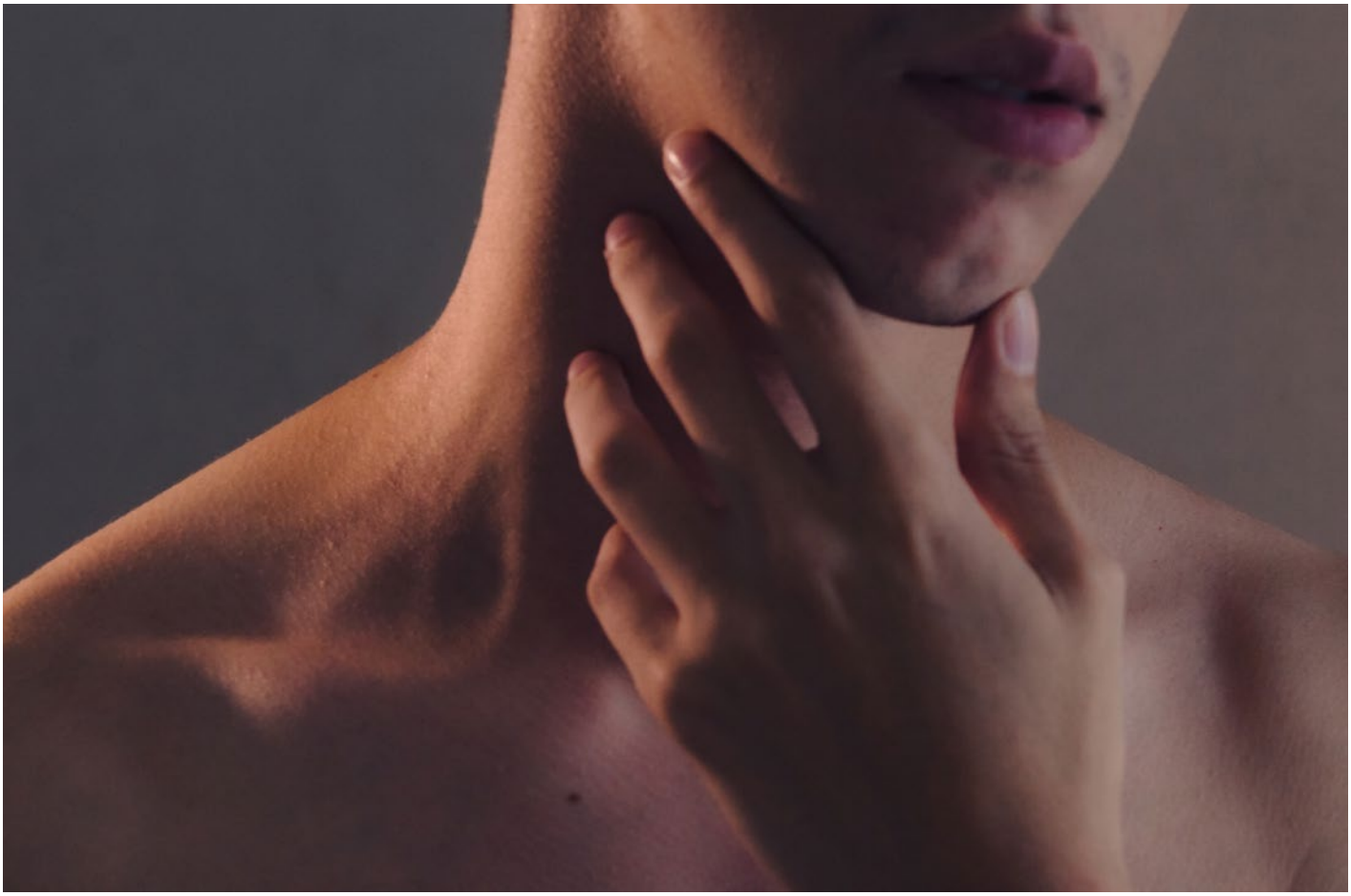
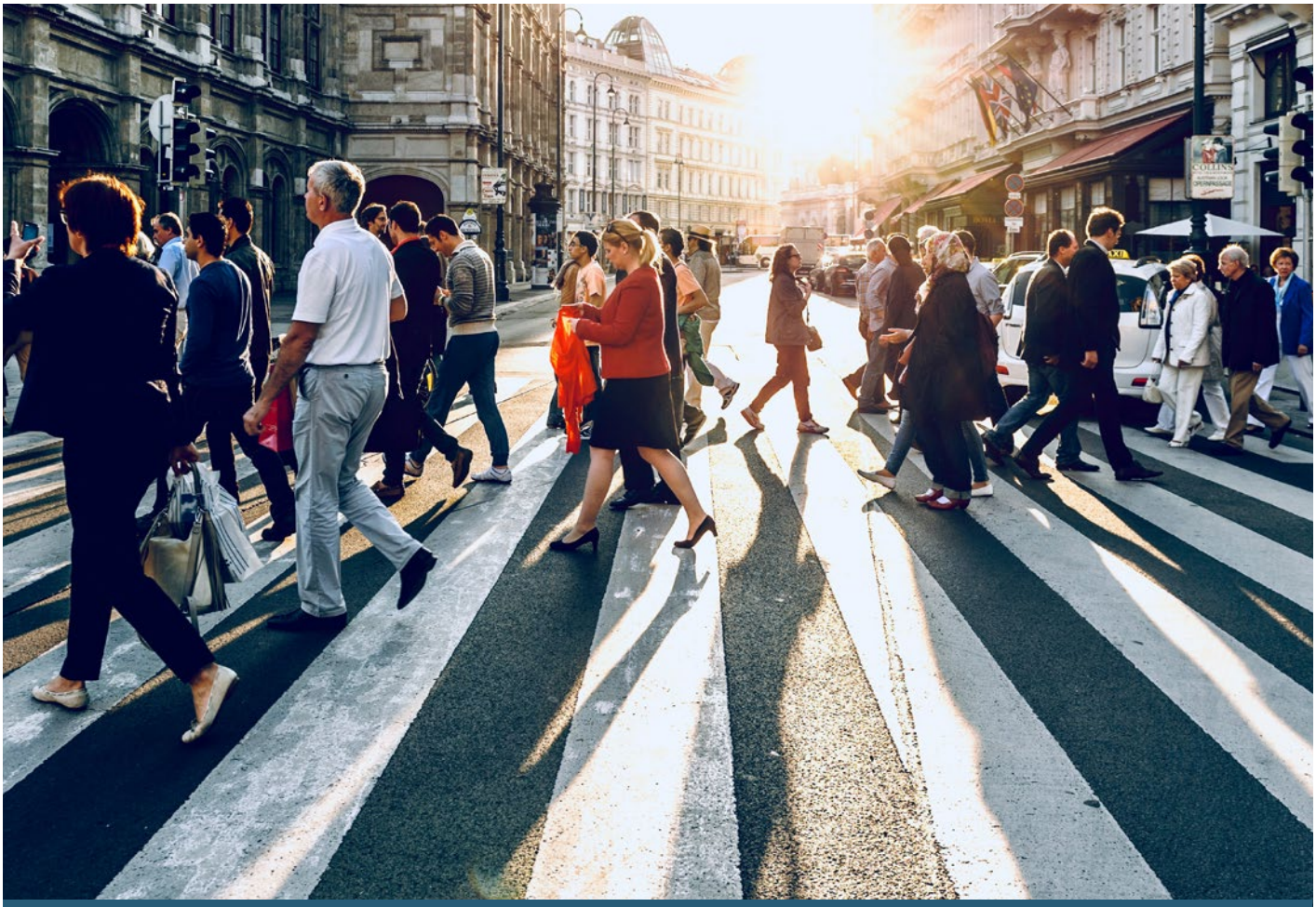




Increasing Incidence of Oesophageal Cancer in Dutch Adults

RESULTING in more than half a million deaths per annum, oesophageal cancer (EC) is the seventh leading global malignancy, with approximately 600 thousand new cases each year. The importance of this topic is emphasised by the World Health Organization (WHO) forecast for 2040, which predicts a further global increase. This presentation at UEG Week by Ali Al-Kaabi, Radboud University Medical Centre, Nijmegen, the Netherlands, discussed the associated burden of this increase, especially in young adults (under the age of 50 years). Analysing both of the most common forms of EC, oesophageal adenocarcinoma and oesophageal squamous cell carcinoma, the former is commonly associated with obesity and gastro-oesophageal reflux disease, whereas the latter is linked with alcohol and smoking.

The study was a population-based cohort design, including data on all newly diagnosed patients with EC in the Netherlands between 1989 and 2018. Adenocarcinoma and squamous cell carcinoma were both analysed. The overall participant count of 59,864 was split into age groups of <50, 50–74, and ≥75 years. Endpoints in the investigation were incidence as new cases/100,000 person-years, estimated annual percentage change (EAPC), and survival. Notably, 47% of the young adult group (aged 18–49 years) presented with incurable EC at the palliative treatment stage. Analysis of incidence discovered that oesophageal adenocarcinoma tripled in young adults over the 30-year period. Average annual increase in incidence began at 40 years of age in males, increasing at an average of 1.3%. Interestingly, increase began in the same age category of women (aged 40–49 years) but the average annual increase



"This discovery that EC has tripled over the course of three decades has been attributed by scientists to poor lifestyle choices such as an unhealthy diet, lack of exercise, and smoking."

was higher, with an average of 3%. This discovery that EC has tripled over the course of three decades has been attributed by scientists to poor lifestyle choices such as an unhealthy diet, lack of exercise, and smoking.

Al-Kaabi made a point to recognise that whilst the reasons are unknown for this escalating trend, the EC risk factors that most likely contribute include growing ageing populations, urbanisation, smoking, and alcohol use. This investigation aimed to provide age-specific incidence data for EC in order to increase awareness in healthcare professionals, re-evaluate existing practices, and support further research. Al-Kaabi also shared that the relative survival in younger individuals has improved compared with older individuals, and this could be due to the increased likelihood of younger patients being treated with chemoradiotherapy and surgery that might increase their survival.

A limitation to the study was that young adults only made up 6% of the total participants, 78% of whom were male. This restricts the applications of the data in drawing conclusions, but promotes further study in the field considering a larger proportion in the age-group under scrutiny and exhibiting a more even gender split. "As far as we know, this was the first study reporting age-specific incidence rates for EC in a European population," concluded Al-Kaabi, delivering the key takeaways from the current study, also noting there is an increasing survival gap between young adults and the elderly. He stressed the importance of being aware of the symptoms of EC, as well as maintaining healthy habits. This was seen in his remarks on how adults under 50 years need to be aware of the symptoms of EC such as problems swallowing, heart burn, and indigestion, in order to have an earlier diagnosis and increase chances of survival, especially in patients at high-risk. ■

Elimination of Chronic Viral Hepatitis: What's New in 2021

Robin Stannard
Editorial Assistant

Citation: EMJ Gastroenterol. 2021;10[1]:19-22.

RECENT breakthrough research was shared and debated on Day 2 of the United European Gastroenterology (UEG) Week Virtual Congress 2021 in the symposium session discussing the progress towards, and barriers to, the elimination of chronic viral hepatitis (HCV). The session featured experts in the field, including Sabela Lens, Division of Infection and Immunity, University College London, UK, and Jean-Michel Pawlotsky, National Reference Centre for Viral Hepatitis B, C and Delta, Department of Virology & INSERM U955, Henri Mondor Hospital, University of Paris-Est Créteil, France, who came together to share knowledge, challenge findings, and contribute to the fundamental goal of HCV elimination. The symposium looked at all aspects of eliminating HCV, from profiling the disease in the clinic to large-scale epidemiological characteristics of HCV within global populations.

THE ROLE OF ADAPTIVE IMMUNITY IN CHRONIC HEPATITIS B INFECTION

The presentation was opened by up-and-coming expert Lens who shared her recent research investigating the changes chronic hepatitis B (CHB) infection induces in immune cells, specifically changes to the memory B cell compartment. B cells are important both for preventing initial infection but also for ongoing control of CHB. Lens's study sought to investigate the differences in phenotype of antigen-specific B cells between adult and paediatric patients with CHB. Paediatric patients often present with less exhausted B cells, so the research aimed to discover whether this was due to shortened duration of exposure to the antigen versus fundamental defects in antigen-specific development due to an immature immune system or inadequacy of assistance from T follicular helper cells (cTfh).

The group performed flow cytometry for the *ex vivo* quantification of antigen-specific B cells, specifically *s* antigen-specific hepatitis B virus (HBV) B cells (sAgB) and *core* antigen-specific HBV B cells (cAgB), using stringent gating criteria to avoid non-specific binding. The study included groups of healthy children and adults alongside adults with CHB and paediatric patients with CHB. The study found circulating sAgB markedly reduced in children relative to adults with no significant difference in cAgB between the groups. Lens and her colleagues subsequently analysed HBV-specific B cells, classifying them into subsets based on the expression of markers CD27 and CD21. The absence of both markers

indicates an atypical memory B cell (atMBC) classification. Researchers found that this subtype was significantly expanded in sAgB cell population compared with cAgB cell population in children with CHB. Analysis on the global B cell stage of all study groups showed that this expansion of atMBC was only found in children with CHB and not in infected adults or either of the healthy control groups.

Further analysis of the atMBC cells, Lens explained, found increased expression of inhibitory marker CD22 and exhaustion marker PD-1 compared with classic memory B cell (cMBC) counterparts. Furthermore, chemokine CXCR5 and costimulatory molecules CD80 and CD40 expression was reduced in atMBC relative to cMBC in children with CHB. CXCR5 drives sequestration of B cells to the germinal centre in the lymph nodes where they interact with cTfh, and the costimulatory molecules drive this interaction. Notably, analysis of cTfh in children with CHB showed that CD40L, the counterpart costimulatory ligand to CD40, had reduced expression.

In her final remarks, Lens explained that low levels of sAgB and expanded atMBC in children represent a difference from CHB disease expression in adults. Furthermore, reduced expression of co-stimulatory molecules and relocation cytokines required for the B–T cell interaction suggest inadequate T cell assistance accounting for the exhausted B cells with minimal antibody production observed in patients with CHB. These findings in particular point to a need to boost B cell stimulation in children with CHB to rescue humoral immunity. In the question and answer session after the presentation, the experts debated the findings of increased PD-1 expression, suggesting that treatment with PD-1 inhibitors could rescue some humoral responses through reducing cell exhaustion. Lens agreed, highlighting the need for further research and future study to analyse HBV-specific B cells in the liver and the role that they play in CHB disease.

COVID-19: THE IMPACT ON ELIMINATING CHRONIC VIRAL HEPATITIS

The symposium also featured a presentation from Pawlotsky, who chose to speak on a more epidemiological level about methods to success and barriers to achieving the elimination of HCV. The World Health Organization's (WHO's) current target is the elimination of viral hepatitis as a major public health concern by 2030. They classify elimination as meaning "a world where viral hepatitis transmission is halted and everyone living with hepatitis has access to safe affordable and effective care and treatment."[1]

In coalition, representatives from global institutions, American Association for the Study of Liver Diseases (AASLD), the European Associations for the Study of the Liver (EASL), Asian Pacific Association for the Study of the Liver (APASL), and the Latin American Association for the Study of the Liver (ALEH) have given a joint call to action identifying four key areas to focus on to achieve HCV elimination. These include simplification of diagnostic treatment and algorithms with a move towards the goal of a one-stop 'test-and-cure' for HCV; integration of HCV treatment with primary care and other disease programmes, such as HIV and tuberculosis; decentralisation of HCV service from large urban referral hospitals to local level care; and finally, task sharing of HCV care for uncomplicated cases with primary care clinicians, nurses, pharmacists, and trained community health workers.[2]

Pawlotsky's presentation reflected on the impact that the COVID-19 pandemic has had upon the goal of HCV elimination by 2030. The pandemic brought with it disruption to healthcare services that inevitably impacted

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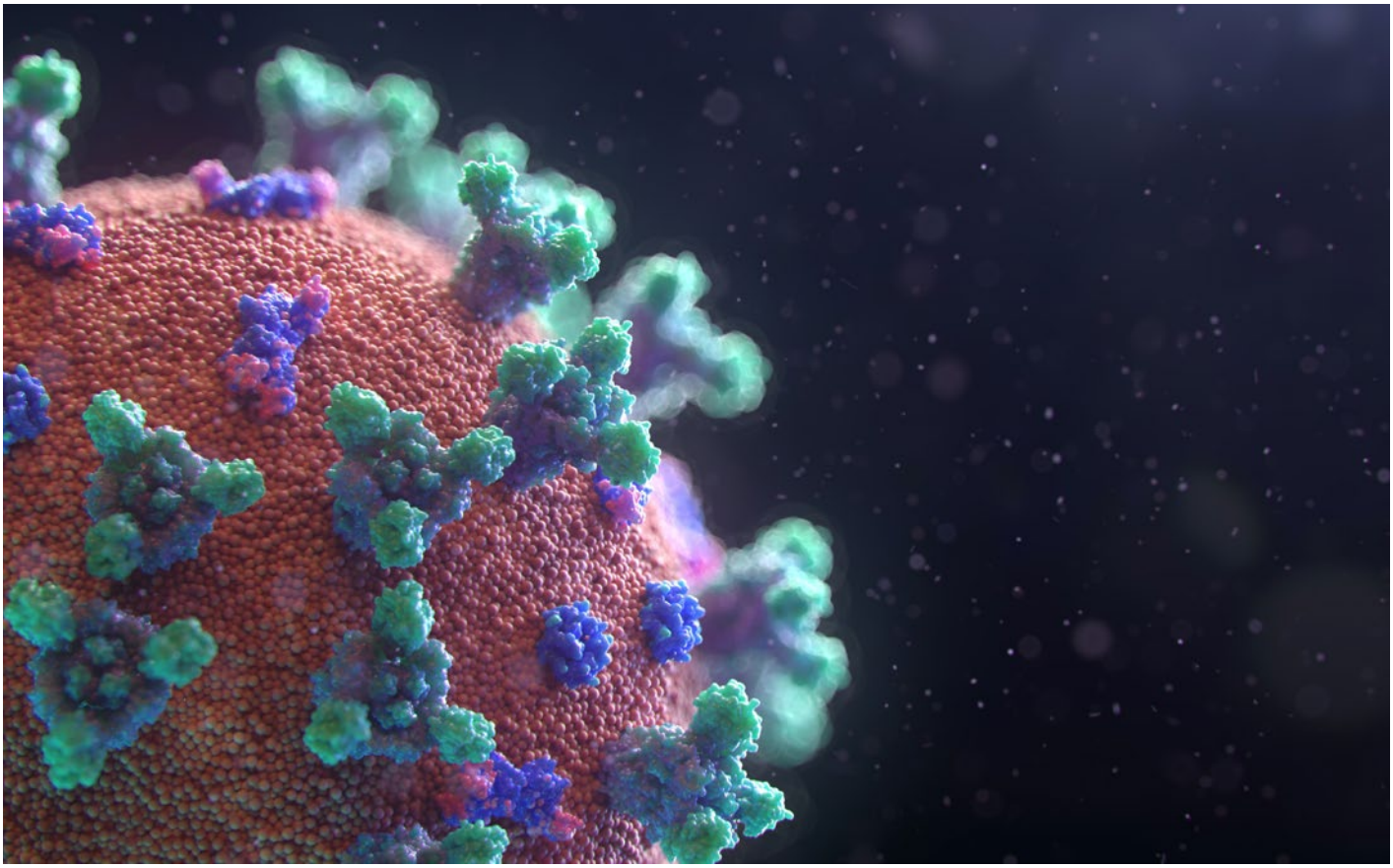

HCV treatment, through de-prioritisation of screening services, diversion of staff to COVID-19 response, and disruption to access for drug and harm reduction services. Overall, these changes to HCV care since March 2020 have led to a drop in the rates of screening, diagnosis, and linkage to care and treatment.

The impact of COVID-19 upon elimination goals has been examined in several studies as presented by Pawlotsky. A study analysing the use of ambulatory HCV testing at the Boston Medical Centre found a 50% drop in mean daily HCV antibody testing after 16th March 2020, compared to the previous year, with a 21% reduction in mean new cases identified.[3] Issues have also arisen with drug utilisation throughout the pandemic. A retrospective study of direct-acting antiviral use across a number of countries found that the majority of countries had experienced a significant decrease in direct-acting antivirals sold from March to August 2020 compared with the same period of 2019.[4]

These findings beg the question of what the global impact of a 1-year delay to HCV elimination programmes will be. Modelling studies have looked to the future to assess the fallout from changes to HCV healthcare provision. Pawlotsky communicated the findings of a study in which he participated that modelled for a 1-year delay in elimination programmes, finding that approximately 906,000 less diagnoses will be made between 2020 and 2030 as a result of COVID-19. The model suggested treatment commencement will diminish by 746,000, and there will be 623,000 additional viraemic infections that would not have happened if COVID-19 had never occurred. Pawlotsky also made the significant point that these models were based on 1 year of delays; however, as we have seen, the COVID-19 pandemic has persisted for much longer.

Pawlotsky closed his discussion by offering a contrasting point of view and drawing attention to the opportunities that the COVID-19 pandemic might offer for HCV elimination, emphasising the importance of not missing this moment to mitigate some of the consequential delays. The pandemic has brought with it increased awareness of infectious diseases, as well as an increased

usage and recognition of the value of telemedicine. There is also the potential to combine the testing, diagnosis, and treatment for COVID-19 and HCV. Opportunities for increased efficiency have been researched, with one team in Northern Italy analysing the potential for HCV detection through mass COVID-19 testing. Approximately 5,000 patients were tested for severe acute respiratory syndrome coronavirus 2, with half that number also being tested for HCV. Researchers identified 72 HCV antibody positive individuals who were subsequently linked to the necessary treatment.

Pawlotsky concluded his presentation with a call to action for researchers, funding bodies, and governments, emphasising that the tools and recipes were within reach to achieve the WHO goal of eliminating HCV as a public health threat. He summarised that "the COVID-19 pandemic has had, still has and will have a major negative impact on HCV elimination programmes." However, the pandemic may also offer new opportunities to accelerate aspects of HCV elimination in the coming years and these must be exploited.

CONCLUDING COMMENTS

HCV is an infectious disease that remains persistent within populations. Achieving the goal of elimination would contribute positively to nations worldwide, both socially and economically. This goal will only be reached by a combination of basic and clinical research combined with population-wide analysis of public health initiatives, treatment uptake, and mitigating environmental factors. Lens's and Pawlotsky's presentations both demonstrate a positive and hopeful look to the future. Lens's research provides an example of the necessary steps to understand the virus and the immune responses it initiates to develop new and effective therapies. Pawlotsky's summary of both the impact of the pandemic but also the potential opportunities it presents in helping to improve the future of HCV care demonstrates the holistic thinking needed to achieve elimination. ■

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Planning the Patient's Journey to Success in Crohn's Disease

This Janssen-sponsored satellite symposium took place on 3rd October 2021 as part of the United European Gastroenterology (UEG) Week Virtual 2021

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Meeting Summary

This Janssen-sponsored satellite symposium, entitled 'Planning the patient's journey to success in Crohn's disease', took place during the United European Gastroenterology (UEG) Week Virtual 2021. The symposium focused on the considerations for the selection of the first therapy for, and the dynamic management of, Crohn's disease (CD) using treat-to-target (T2T) and tight monitoring. Séverine Vermeire presented the advantages of intervening with biologics early in the disease course by looking at key studies, and underlined the role of a T2T and tight monitoring strategy in achieving long-term disease modification. The effectiveness, durability, and safety of ustekinumab are supported by both clinical studies and real-world evidence. Silvio Danese highlighted the SEAVUE study, which showed in a head-to-head setting that ustekinumab rivalled adalimumab as a first-line treatment choice for patients newly diagnosed with CD. He also reinforced the concept that early treatment with biologics allows patients to achieve high remission rates and robust endoscopic results. Joana Torres went on to illustrate the application of these principles using a patient case-based interactive discussion with the audience. During this she focused on assessing the patient's risk for progression

or complications, determining the long-term treatment goal, and choosing the right biologic based on these factors. A key takeaway was that no treatment fits all patients and physicians should tailor therapies to the individual patient's profile and needs.

The Evolution of Dynamic Management in Crohn's Disease

Séverine Vermeire

The journey of a patient with CD starts at diagnosis. A crucial step is to identify and capture the illness early in the disease course, thereby allowing physicians to swiftly start effective treatments and set appropriate treatment targets. Each patient is unique, and physicians should tailor the treatment based on factors such as age, comorbidities, risk of infections or complications, and patient preference (personal communication, Vermeire). The current evidence indicates that early intervention in CD, defined as ≤18 months disease duration and no previous disease-modifying drugs,[1] significantly decreases inflammatory activity[2] and prevents bowel damage, disability, and the need for intestinal resections.[3] These outcomes change the natural history of the disease[3] and reduce the risk of complications, while simultaneously increasing the time in remission.[4] More specifically, clinical trials and real-world studies have shown that the early use of biologics improves clinical outcomes in both adult and paediatric patients and is accompanied by lower relapse rates and improved mucosal healing.[5]

Once a treatment regime has been established, short- and long-term treatment goals need to be determined with the aim of modifying the disease course. According to the STRIDE-II and SPIRIT consensus, the primary target for which physicians should aim in the first 3 months of therapy should be symptom control through anti-inflammatory effects of treatment. This target then evolves into deep remission between 3 months and 1 year of treatment, in which the patient should display no clinical symptoms. Beyond 1 year, the goal shifts towards mucosal healing that will ultimately lead to disease modification.[6,7] Such a T2T strategy necessitates frequent monitoring to gauge the patient's progress and to adjust therapy as needed. Along with the treatment goals, clinical and patient-reported outcome responses such as reduction in diarrhoea and cramping pain are suitable for monitoring symptom control; the assessment of deep remission is best achieved using biomarkers, including the normalisation of C-reactive protein (CRP) and faecal calprotectin (fCal) levels. Furthermore, endoscopic healing, normal quality of life (QoL), and absence of disability reflect disease modification in the long term.[6,7]

The concept of tight monitoring was adopted in the CALM study, which demonstrated that clinical decisions driven by tight monitoring of objective biomarkers paired with clinical symptoms result in superior endoscopic and clinical outcomes in CD compared with symptom-driven care only.[8,9] In addition, data from the ongoing REACT2 study indicate that the intensification of treatment based on ileocolonoscopic findings leads to fewer CD-related complications than treatment escalation based solely on symptoms.[10] The STARDUST study is the first study to investigate the benefits of T2T in patients with CD by using endoscopy at Week 16 as a decision point for the dose-adjustment of ustekinumab. Additional dose adjustments were allowed based on symptoms as well as biomarkers.[11] Compared with a symptom-driven approach, T2T numerically improved the proportion of patients achieving endoscopic response, although other outcomes such as corticosteroid-free endoscopic response, endoscopic remission, and mucosal healing were comparable.[12] Achieving mucosal healing is linked to a reduction in surgery, hospitalisations, and treatment failure,[13] while simultaneously improving long-term clinical remission rates.[14] A more advanced outcome is transmural healing, which can, crucially, be easily monitored using non-invasive intestinal ultrasound (IUS) and is increasingly recognised as an indicator of deep remission that predicts even more favourable outcomes than mucosal healing.[15] The results from the STARDUST IUS sub-study suggest that ustekinumab induced transmural healing in 11.9% of patients at Week 16, which increased over time to 24.1% by Week 48.[16]

The efficacy of ustekinumab has been analysed with a follow-up of up to 5 years in the IM-UNITI study, which demonstrated that 28.7% and 34.4% of patients receiving ustekinumab every 12 weeks and 8 weeks, respectively, were in clinical remission at Week 252.[17] Furthermore, ustekinumab improved health-related QoL and maintained its known safety profile throughout the study.[18,19] The long-term clinical efficacy of ustekinumab is not only an outcome of clinical trials but is also reflected in the real world. National cohort studies have shown that 42.1–47.7% of patients achieved clinical response and 25.7–39.4% of patients achieved clinical remission by Week 52. Importantly, over 98% of patients had prior anti-TNF experience and most of the patients in clinical response or remission were also corticosteroid-free.[20,21]

In summary, the early diagnosis and start of effective treatment are critical for the long-term outcomes in patients with CD. Appropriate treatment goals paired with a tight monitoring strategy will result in good persistence and treatment success, which ultimately changes the disease course and allows the patient to achieve full remission and excellent QoL.

Selecting the First-Line Biologic in Crohn's Disease

Silvio Danese

A crucial step in the patient's journey is the selection of a first-line treatment. Anti-TNF therapies still dominate as the first-line biologic due to their long history of use in CD. With the appearance of biologics with other mechanisms of action in recent years, head-to-head studies are becoming increasingly important for physicians to compare therapies and make informed treatment decisions for their patients. The SEAVUE study is the first head-to-head study in CD comparing biologics, in particular the efficacy and safety of ustekinumab and adalimumab.[22,23]

The patients included in the study presented with moderately-to-severely active CD and were biologic-naïve but had previously failed, or were intolerant to conventional therapies, including corticosteroids and/or immunomodulators. The median disease duration in the study was 2.62 and 2.57 years in the adalimumab and ustekinumab groups, respectively, indicating a population with relatively early disease.[23] The primary endpoint was clinical remission at Week 52, which did not differ between the ustekinumab and adalimumab treatment arms; both treatments provided clinical remission in over 60% of patients, of whom the majority were corticosteroid-free Interestingly, the kinetics of clinical remission through Week 52 showed that ustekinumab matched adalimumab at every time point, suggesting that ustekinumab has an equally rapid onset of action. Adalimumab and ustekinumab also scored similarly well regarding the other endpoints, including clinical response, endoscopic response and remission, and reduction in corticosteroid dose; however, ustekinumab exhibited a significantly higher proportion of patients maintaining clinical response at Week 52 among patients in clinical response at Week 16 compared with adalimumab (88.6% versus 78.0%). The safety profiles of both drugs were consistent with previous experience, although administration of adalimumab resulted in more injection-site reactions (10.3% versus 1%) and adverse events leading to discontinuation (11.3% versus 6.3%) than ustekinumab.[23]

Collectively, the SEAVUE data show that ustekinumab is a comparably robust option as a first-line biologic for patients with early CD who have failed conventional treatment options.

Applying New Insights to Clinical Practice

Joana Torres

The insights presented by Vermeire and Danese were translated into clinical practice using a patient case-based discussion between the expert panel and the audience, moderated by Torres, illustrating the treatment journey in the real world.

The first patient case was a 31-year-old male who presented with diarrhoea, mild abdominal pain, and fatigue. He presented with increased bowel movements (up to 4 or 5 per day) and increased CRP and fCal levels. Ileocolonoscopy revealed deep ulcers in the terminal ileum and superficial erosions in the right colon, leading to a simple endoscopic score for CD (SES-CD) score of 11.

IUS also showed severely increased bowel-wall thickness (BWT) of 7 mm in a 30 cm section of the bowel, loss of bowel-wall stratification, and fat hypertrophy. Vermeire elaborated that this patient's disease features indicate that he is highly at risk of progression towards strictures and a need for surgery in the future. Danese reiterated that the short-term treatment goal should be control of symptoms, to enable the patient to feel better. Intermediate targets would be the normalisation of biomarkers with a final goal of achieving endoscopic and mucosal healing and change in the disease course in the long run. He noted that in his clinical practice he combines non-invasive monitoring such as IUS with biomarkers to assess disease control.

The patient in this case received infliximab combined with azathioprine as a first-line treatment and initially responded well but started to lose response by Week 32. Despite treatment optimisation, he developed anti-infliximab antibodies that resulted in treatment failure. The panel debated the next line of treatment options, including adalimumab, vedolizumab, ustekinumab, or surgery. Vermeire highlighted that switching to another anti-TNF agent such as adalimumab would be unfavourable due to the development of anti-drug antibodies and that surgery was also undesirable as a large section of the bowel was affected. Vedolizumab and ustekinumab are both outstanding options to discuss with this patient, although it would be important to consider the notable durability of ustekinumab. The patient was ultimately administered ustekinumab and exhibited clinical remission, with normalised biomarkers and BWT as well as an absence of ulcers (endoscopic remission) after 8 months. This patient case underscored the importance of risk stratification and early intervention, which should be paired with monitoring to optimise treatment. Importantly, newer biologics may be accompanied by higher drug persistence and less immunogenicity, aspects that were important to consider in this clinical case.

The second patient case presented a 55-year-old female primary school teacher with a history of breast cancer that had been treated with surgery. She had recently been diagnosed with CD with ileal and pancolonic involvement with an SES-CD score of 14 and achieved an incomplete response after 2 weeks of oral corticosteroids; she was still experiencing fatigue, 4 or 5 bowel movements per day, and abdominal pain paired with elevated biomarkers. Taking the patient's age and history of cancer into consideration, the panel discussed the possible therapeutic options. Danese further stressed the significance of the durability of ustekinumab over anti-TNF therapies as well as the fact that ustekinumab can be used as monotherapy without immunosuppressants,[24] which would be more suitable for this patient given the risk of cancer. Furthermore, the SEAVUE study has shown strong response rates when treating patients early in the disease course,[23] which is also reflected in real-world studies.[25] Other studies have shown that a disease duration of ≤2 years or ≤5 years with no disease-related complications were associated with a higher probability of achieving (corticosteroid-free) clinical and endoscopic remission with ustekinumab.[26] The panel emphasised that there is no one-size-fits-all treatment and that physicians need to consider factors such as speed of onset, sustained efficacy, safety, and convenience for the patient.

Biomarkers such as CRP and fCal as well as clinical symptoms are probably accessible to all physicians to use when applying tight monitoring. Vermeire pointed out that, in her clinical practice, these are measured at baseline and Week 4 and 8 to evaluate the response to therapy. Some studies have demonstrated that early reduction of fCal <250 mg/kg predicted long-term endoscopic healing.[27] In addition, IUS is non-invasive and can complement the current clinical examination strategies, with patients showing reductions in BWT as a response to treatment as early as Week 4.[16] In combination with biomarkers, IUS may be an equivalent to endoscopy in the future, with further refinement of the technique, although endoscopy is currently still the gold standard for assessing the mucosa between 6 and 12 months after treatment. Patient education may also improve compliance to tight-monitoring strategies, which some patients may experience as a heavy burden.

In conclusion, the first-line biologic choice is crucial for determining long-term outcomes, and physicians should aim to tailor therapy to the patient's profile. Additionally, the durability, safety, convenience of administration, and improvements in QoL advocate for ustekinumab as an appealing first-choice biologic in patients

with CD. And above all, we should remember that each journey is unique: no treatment fits all patients, and physicians should tailor therapies to the individual patient's profile and needs.

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Abstract Highlights

The following highlights spotlight the award-winning abstract presentations at United European Gastroenterology (UEG) Week 2021.

Dietitians Could Help with the Demand in Gastrointestinal Services

DIETITIANS could provide outpatient medical gastroenterology clinics for patients with irritable bowel syndrome (IBS). Evidence for this was presented on 3rd October 2021 at the virtual UEG Week by Christian Shaw, Sheffield Teaching Hospital NHS Foundation Trust, UK.

Currently, there is an unmet need for gastroenterologists in the UK, with 43% of new consultant appointments vacant. An ageing population with more complex needs leaves some patients waiting for long periods to see a clinician for the management of their symptoms. Private contractors are being used to meet the demand for gastrointestinal services, which has grown exponentially over the last 10 years.

After training two Band 6 dietitians to undertake outpatient gastroenterology clinics, patients with symptoms compatible with IBS were assessed by a physician (62%) and dietitian (38%). Patients were then asked how satisfied they were on a scale of 0–10. Their clinical notes were reviewed to assess the diagnostic outcome.

Of the 91 patients reviewed, the majority were diagnosed with IBS (73%), followed by bile acid diarrhoea (12%), functional diarrhoea (4%), and microscopic colitis (2%). The remaining 9% had different diagnoses. However, there was no significant difference in clinical satisfaction between physician- and dietitian-led clinics (mean: 9.2±1.5 versus 9.4±1.1, respectively; p=0.5).

Training dieticians to become advanced clinical practitioners is expensive, costing 40,500 GBP/year/dietitian. They must also enrol in an MSc in advanced clinical practice. However, a payment by results model suggests that the total income generated would be 68,200 GBP, on the basis that each dietitian will have 84 clinics, with three new patients and seven follow-ups. Subtracting the cost employ a Band 7 dietitian would lead to a 14,700 GBP surplus.

As there was no difference in clinical satisfaction between physician- and dietitian-led clinics, there is the potential for patients with IBS to attend the latter. This would lead to 14,700 GBP surplus and reduce the number of patients seeing premium-rated consultants. ■

Ursodeoxycholic Acid to Treat Gallstones in Bariatric Surgery Patients

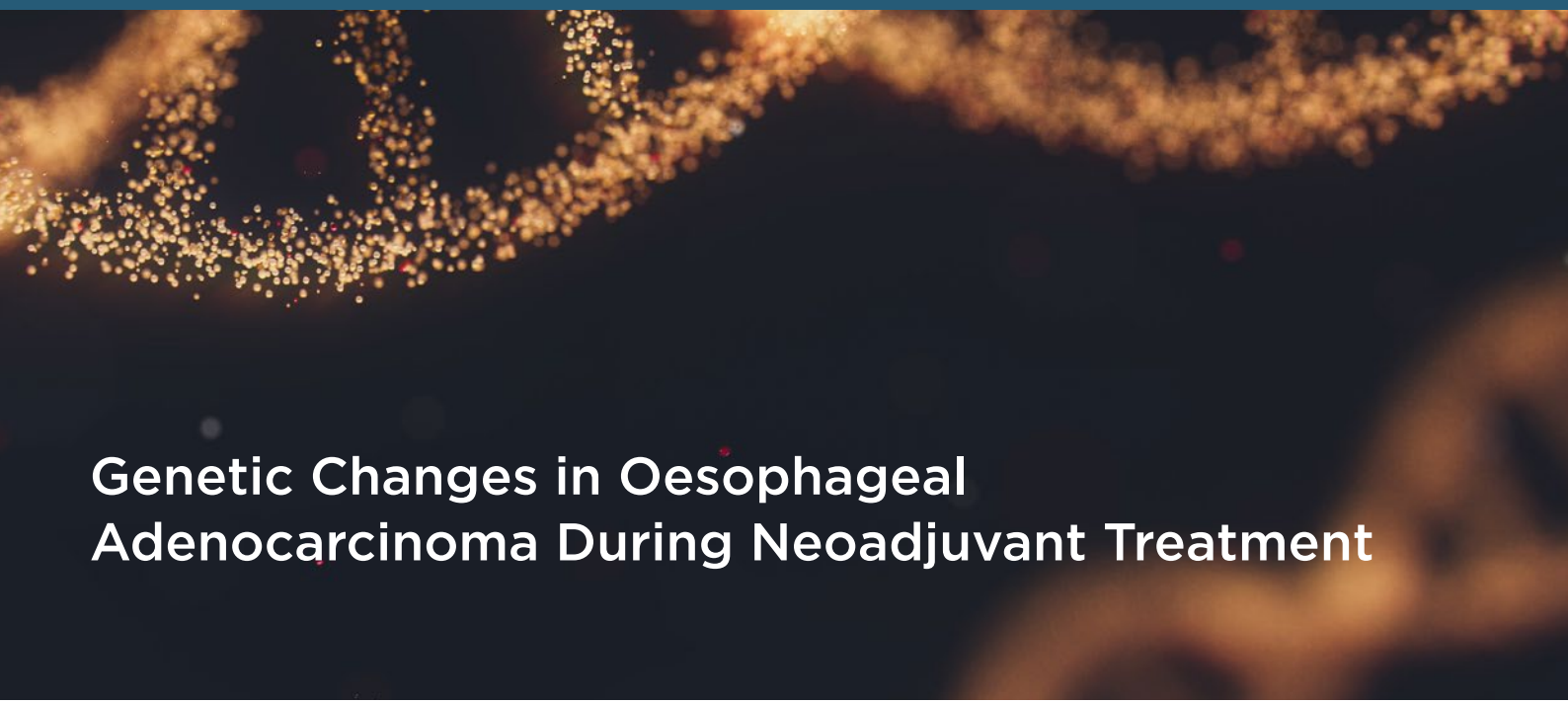
BARIATRIC surgery is a safe and long-term treatment for weight loss; however, the rapid weight loss it induces is a major risk factor for the formation of cholesterol gallstones. The causal link between weight-loss and gallstone formation is not fully understood, but an important factor is the consequential imbalance in biliary lipids. Cholecystectomy at the time of bariatric surgery is the current standard treatment for gallstones, the evidence for the use of ursodeoxycholic acid (UDCA) prophylaxis is still under debate. Research led by Sylke Haal, Amsterdam UMC, University of Amsterdam, the Netherlands, was conducted to provide evidence for whether UDCA reduces the occurrence of gallstone disease after bariatric surgery.

In this multicentre, double-blind, randomised, placebo-controlled, superiority trial, patients underwent a gallbladder ultrasound to determine the presence of asymptomatic gallstones. At study commencement, 985 patients were enrolled and randomly assigned to treatment with 900 mg of UCDA daily for 6 months or placebo. Primary endpoint was determined using a chi-squared test to quantify a significant difference between the two trial arms paired with a logistic regression to test for interactions between the subgroups.

After exclusion criteria were examined, 959 patients were included for analysis and 20% were found to have asymptomatic gallstones at baseline testing. The primary endpoint, symptomatic gallbladder disease, was found in 6.5% of the treatment group compared with 9.7% of the placebo arm. This equated to a relative risk of 0.67, which at 95% confidence interval was not statistically significant. The logistic regression analysis demonstrated a significant interaction between UDCA and the presence of asymptomatic gallstones at baseline. A beneficial impact from UDCA was observed in patients without gallstones at baseline. No significant safety concerns were noted throughout the trial.

The results from the trial suggested that in bariatric surgery patients with no gallstones prior to surgery, UDCA prophylactic treatment for 6 months led to a clinically relevant and significant reduction of symptomatic gallstone disease relative to the placebo. ■

"A beneficial impact from UDCA was observed in patients without gallstones at baseline."



Genetic Changes in Oesophageal Adenocarcinoma During Neoadjuvant Treatment

OESOPHAGEAL cancer (OAC) is the seventh most common cancer in the world. Patients with this cancer are commonly treated with neoadjuvant chemotherapy, radiotherapy, or surgery. Unfortunately, over half of tumours are resistant to neoadjuvant therapy and survival rates are poor. A novel study, shared at the UEG Week Virtual, aimed to understand the genetic and transcriptomic changes in OAC.

Melissa Schmidt, Centre for Genomics and Computational Biology, Barts Cancer Institute, Queen Mary University of London, UK, and her team investigated treatment response using a multi-omics study to evaluate the genetic and transcriptomic changes caused by neoadjuvant treatment in patients with OAC. Samples were taken from patients with OAC who responded to chemotherapy and from individuals who did not respond to chemotherapy at different stages of treatment (before, during, and after neoadjuvant therapy). Individuals who responded to chemotherapy were given platinum-based chemotherapy whereas patients who did not respond to chemotherapy were given radiochemotherapy instead.

The exons of the genome were sequenced from a total of 65 samples. Forty-two samples were taken from 13 chemotherapy-responding individuals and 23 samples were taken from nine non-responding individuals. In addition, blood samples were drawn and sequenced as a control. Finally, the researchers conducted RNA sequencing on an additional 78 samples: 17 samples from patients responding to chemotherapy and 25 samples from patients who did not respond to chemotherapy.

Fascinatingly, the scientists discovered significant changes in the cell signalling and immune pathways at the transcriptome level in neoadjuvant treatment. Samples taken after treatment showed there was significant enhancements in numerous signalling pathways, including the mitogen-activate protein kinase, phosphoinositide 3–protein kinase B, RAS, Wingless-related integration site, and Hedgehog signalling cascades, all of which are important in cancer development.

Furthermore, there were substantial changes in mutation signatures after a patient underwent neoadjuvant chemotherapy with FOLFOX (folinic acid, fluorouracil, and oxaliplatin). There were also key changes in single nucleotide variant profile, which indicated loss of subclones and spatial heterogeneity. Additionally, the phylogenetic tree analysis revealed there was plasticity in phenotypes due to resistance in treatment. Other insights included the revelation of non-silent mutations, namely, *KMT2D*, *SMARCA4*, *AXIN1*, *EGFR*, and *FAT1–4*. All these mutations were new in patients undergoing neoadjuvant treatment.

This novel study showed that major altering genetic and transcriptomic changes were caused in mutation signatures by chemotherapy and radiochemotherapy. Future research could involve studying how these genetic changes occur during neoadjuvant therapy and modifying patient treatments accordingly. ■

Outcomes Following Duodenectomy in Patients with Familial Adenomatous Polyposis

DETERMINING the timing of surgery remains a challenge for patients with adenomatous polyposis, an inherited autosomal dominant condition. This abstract was presented by Isabel Martin, St Mark's Hospital, London, UK, at UEG Week Virtual, who noted: "Ideally intervention takes place before cancer is diagnosed, as afterwards the outcomes are very poor." Upper gastrointestinal endoscopic surveillance was recommended following pancreaticoduodenectomy (PD) or pancreas-sparing duodenectomy (PSD). This review is of importance in a field where long-term data is lacking.

Data were taken from two of the largest polyposis registry databases, Amsterdam UMC, the Netherlands, and St Mark's Hospital, identifying and studying medical, surgical, and endoscopic reports for the patients who underwent endoscopic surveillance following PD or PSD between 1995 and 2020. The cohort of identified patients was 103, with a median follow up of 9 years. Ninety-one of this overall group underwent prophylactic surgery, three of whom experienced an unexpected cancer following surgery. Twelve of the large group had cancer surgery, most of which were ampullary cases. Endoscopic surveillance data was available in 74 patients. Forty-six gastric adenomas were diagnosed in 18 patients, with the median time from surgery to development of gastric adenoma 9 years. Three patients were diagnosed with gastric cancer, where median time from surgery to diagnosis was 13 years, and 473 jejunal adenomas were identified in 35 patients, where median time from surgery to development was 5 years. Causes of death were available for 24 of the 28 patients who died. Summarising the statistics produced, Martin revealed that in those who underwent surgery for ampullary and duodenal disease in adenomatous polyposis, 5% developed gastric cancer, of which 24% gastric adenomas and 7% high grade dysplasia. Furthermore, 3% developed jejunal cancer, 49% jejunal adenoma, with 6% high grade dysplasia.

Researchers were able to conclude based on their study that survival after diagnosis with duodenal cancer is poor, and clinicians should aim to operate in similar patients before cancer arises. Gastric and jejunal neoplasia is common after PD or PSD, highlighting the need for patients to have ongoing surveillance post-surgery. This was among the highlights of the abstracts presented at UEG Week this year, with the research adding novel and helpful information to guide practice in a field where it is highly sought-after. ■

"Ideally intervention takes place before cancer is diagnosed, as afterwards the outcomes are very poor."

Congress Interviews

EMJ spoke with Helena Cortez-Pinto and Joost Drenth about their influential roles in the United European Gastroenterology (UEG) and the impact this organisation has on wider practice. The following interviews also discuss their career highlights, challenges encountered, and what lies ahead in their respective research works.

Helena Cortez-Pinto

Vice-President, United European Gastroenterology (UEG);
Professor of Hepatology, Faculdade de Medicina de Lisboa,
Centro Hospitalar Lisboa Norte, Portugal

Q1 What led you to pursue a career in gastroenterology, and was there a particular person or event that helped shape your progression to where you are today?

I considered, at the time, and still consider, that gastroenterology is a very interesting and diverse specialty. In fact, it has a practical component (endoscopic techniques) and a clinical more reflexive component, mostly in the hepatology area. Altogether, it gives a myriad of opportunities and varied activities. Furthermore, it is in constant development, what represents a challenge, and makes it even more exciting. Regarding persons, several persons shaped my progression. My first mentor, Pinto Correia, was an outstanding scientist and educator in gastroenterology and was certainly my role model.

Q2 As an educator, we have seen your progress recently in raising awareness in critical health topics such as alcohol and sugar-sweetened beverage consumption. Is this an area where we can expect to see your focus lie in the near future and, if not, which other topics merit greater attention?

During my career, I became aware that disease prevention is, in fact, much more significant in the public outreach than treatment after disease is present. Consequently, I became progressively more interested in public health, and how simple and effective measures in this area can make such a huge impact. So, I am looking forward to work more in this area. Furthermore, I am also interested in contributing to the creation of large networks or consortiums, to foster research and attract financing from the Europe Union (EU),

Q3 Can you highlight some of the key challenges and successes you have experienced from the roles you have had as an EU Policy Councillor for the European Association for the Study of Liver (EASL) and as the United European Gastroenterology (UEG) Vice-President?

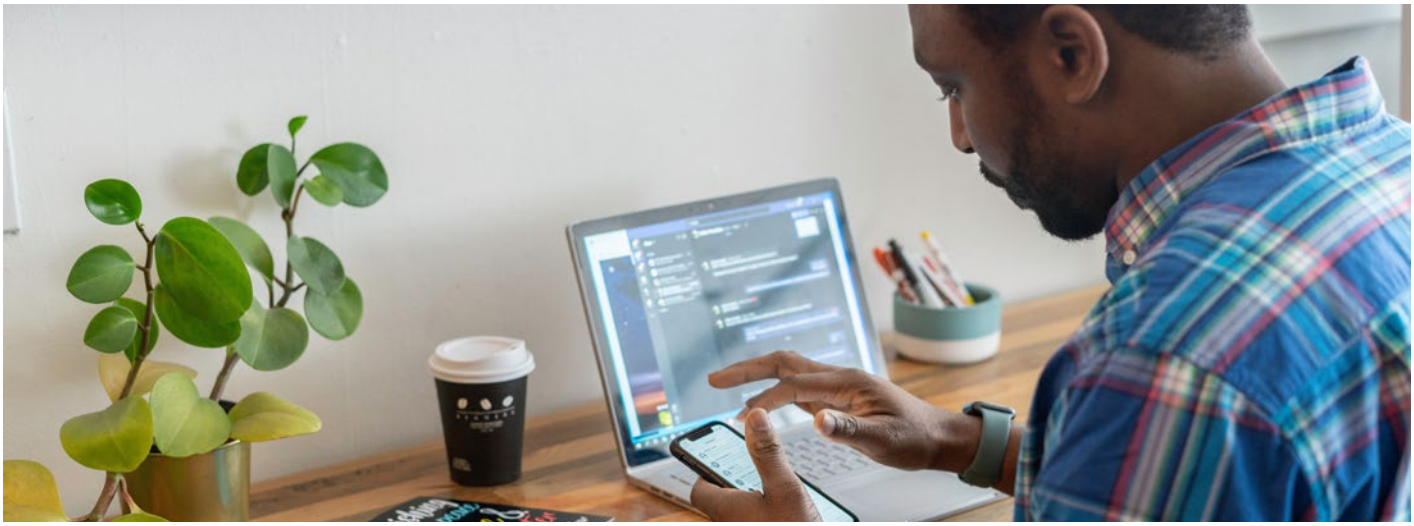
During my term as the EASL EU Policy Councillor, we were able to create and disseminate policy statements regarding topics such as obesity and non-alcoholic fatty liver disease, the burden of alcohol-related liver disease, and an action plan on eliminating hepatitis C among our associates. We developed a project entitled Hepahealth, which evaluated the actual panorama of liver disease in Europe and what are the more effective policy measures. We also created a Public Health Committee, incorporating patients in the board. In fact, we have tried hard to approach the patients, either as patient groups or individually, since we consider that their contribution in scientific medical societies is of great importance.

Q4 How much of an impact do you believe the UEG has on the clinical practice of gastroenterology directly and indirectly in improving the experience of patients?

I believe UEG has a strong impact in the clinical practice of gastroenterologists (GI), probably more so in the young GIs. In fact, through the education-related activities and the quality-of-care activities, GIs gain access to many educational activities, either during the UEG Week, or through webinars and master schools throughout the year. The recently developed app of GI guidelines is also extremely useful to GIs, and I'm sure improve their daily practice to the benefit of the patients. We are now creating a UEG Library that will make it even easier the access to all the pertinent information in a more organised fashion.

Q5 In the recently published article, 'A consensus integrated care pathway for patients with primary biliary cholangitis: a guideline-based approach to clinical care of patients', which you co-authored, what are the main findings you hoped to convey?

Firstly, information that it is possible and very useful to create a platform where doctors can register their patients and where we can retrieve information that can be worked with, published, and, in this way, increase knowledge in the area. I also wanted to highlight that although treatment with ursodeoxycholic acid significantly increases liver transplant-free time and is often enough to treat the primary biliary cholangitis patients, now that we have second line treatments available such as obeticholic acid or bezafibrate we need to be sure that patients achieved a complete response. If not, other lines of treatment must be considered and used.



Q6 What are the most exciting changes which have been implemented in this year's UEG Week?

The UEG Week 2021 is our second virtual meeting and, this time, it was planned as a virtual event from the beginning, which is an advantage. So, we had sessions like 'Gut Talk', which offer the ideal setting for clinicians to get a crash course on common, distinct topics of their daily clinical routine, or a 'Live Expert lunch'. All sessions had a lot of interactivity in order for participants to be as active as possible. Also, sessions like the Live Video Case Session showed unusual cases or new technologies based on diagnostic and therapeutic endoscopy.

Q7 Are there any innovations on the horizon in the field of gastroenterology that you think are particularly noteworthy?

I think the application of artificial intelligence to several fields of gastroenterology is going to make a great difference, as well as the concept and use of big data. Major advances are also being accomplished in endoscopy and ultrasound-guided endoscopy. It is mostly in advanced endoscopic therapeutic procedures that we are observing major developments, with the third-space concept in rapid evolution, including the management of gastrointestinal motility disorders. The area of bariatric related endoscopic procedures is also rapidly developing.

In the liver area, fatty liver disease has gained great importance in all aspects, and I believe we will soon have results from the many ongoing clinical trials. Also, techniques to evaluate liver fibrosis in easy and accessible ways are going to undergo major improvements. Inflammatory bowel disease is also an area of increasing interest and research, with increasing availability of effective oral delivery biological drugs.

> *"I believe UEG has a strong impact in the clinical practice of gastroenterologists (GI), probably more so in the young GIs."*

Q8 Looking back at your career, what has been your proudest achievement to date, and what advice would you give out to a younger-self or aspiring gastroenterologist aiming to establish themselves in the specialty?

Our group was one of the first to describe the association of non-alcoholic fatty disease with the metabolic syndrome and several of its aspects in 1999. Very early on, we recognised the importance that fatty diseases were going to have in the following years.

As advice, I would recommend dedicating to a particular area, although, of course, being aware of all the others, and be very focused on that area. There is often the temptation to do too many things at the same time, which is not good. I also recommend being patient and resilient, since you don't always get you want immediately. If it's worth it, don't give up. ■

Joost Drenth

Professor of Gastroenterology and Hepatology; Head of the Department of Gastroenterology and Hepatology, Radboud University Medical Centre, Nijmegen, The Netherlands.

Q1 What led you to pursue a career in gastroenterology, and with such an interest in polycystic liver disorders?

As a medical student I had keen interest in internal medicine and the challenge that comes with solving cases. That is why I really wanted to do a MD-PhD programme and I have been fortunate to do so. My PhD targeted hyper-IgD syndrome, which was, at that time, an ill-recognised inflammatory disorder, and it took me from phenotyping to assessing cytokine profiles to therapeutic trials. We rapidly recognised that the disease was inherited, and I spearheaded an effort that discovered the gene responsible for hyper-IgD syndrome. At the time, I had just finished my internal medicine training and was approached to start a fellowship in gastroenterology. I was drawn to gastroenterology because of the research opportunities, and it felt to me that the space was wide open. At one of my first outpatient clinics, my boss introduced me to a patient with polycystic liver disease. She gave an impressive family history with nieces and aunts suffering from huge livers with many, many cysts. There was no description in literature that fitted with this particular disease. This struck me as an opportunity. I was invited to visit the family. Blood samples were collected, and an onsite ultrasound of their liver was done. With the samples acquired, we went on a hunt and were lucky enough to discover it a few months later. This taught me the power of clinical investigation and has been my driving force ever since.

Q2 Do you think there are any misconceptions about your speciality and particularly in one of your research interests, the molecular background of inherited gastrointestinal diseases?

I believe that genes should be seen as a risk factor, just like other components that we assess as contributors to liver disease such as lifestyle (smoking, alcohol use, and an unhealthy diet leading to overweight). We are just beginning to appreciate the power of next generation sequencing and the wealth of data that it generates. We have just left the era where we were hyper-focused on discovering mendelian inherited disorders with clear distinguishable phenotype caused by a single genetic culprit. That is an oversimplification of the clinical reality. I see many patients with so-called cryptogenic liver disease where we have exhausted our conventional diagnostic armamentarium and failed to identify a cause. Genomic medicine can help us to distinguish new genes that contribute as risk factor to liver disease. That will require clinical acumen, and this is where gastroenterologists come in. Discoveries are being made by the prepared mind. Do not stop with telling yourself that this is cryptogenic, just go on travelling the uncharted sea and make your discovery.

"I believe that genes should be seen as a risk factor, just like other components that we assess as contributors to liver disease such as lifestyle"

Q3 Since your appointment as the Head of Department at Radboud University Medical Centre, Nijmegen, The Netherlands, what has been your proudest achievement?

I have worked hard to create a professional environment, injecting science into our clinical thinking, and creating space for clinical investigators. Three developments have made me particularly proud. We run a well-oiled

fellowship programme in close collaboration with our regional partners. Fellows are trained at secondary and tertiary referral centres in our region and are exposed to a wide range of gastrointestinal disorders, adding to their expertise. We have personalised the training programme so that it fits with the need of the individual fellow rather than the institute. We have also merged our clinical ward with that of the surgeons and share morning handovers. The shared expertise has benefited us both, and I realise that we should have done this much earlier. We train medical doctors in our department to become clinical investigators, and this has been very rewarding at a scientific and personal level.

Q4 You currently have more than 300 international publications to your name for your research in gastroenterology. What do you believe to be the current gaps in literature and which topics merit greater investigation?

It is not about the number of papers; it is the impact one can achieve. Many of my (best) publications have started with a question by a patient from the outpatient clinics. Simple questions such as "What can we do to prevent that this from happening again?" or "Where is this coming from?" may lead to a research programme. I have a pragmatic approach: solving the problem of the patient comes first. A strong personal impetus to do research is to challenge rusty dogma. For example, presence of abdominal pain in a patient with gallstones qualifies for cholecystectomy. We have designed clinical trials to assess the necessity of cholecystectomy and came with surprising answers. I will share one example of what we found. Whilst a cholecystectomy relieves a patient from their gallbladder, 40% of patients will continue to have the abdominal pain that led to surgery. With the abdominal surgeons, we discovered that many patients with gallstones actually have functional dyspepsia. We performed a clinical trial aimed at reducing the volume of cholecystectomies. This led to a large joint research programme supporting the concept that cross specialty collaboration is very valuable.

Back to your question on gaps in the literature and which topics merit greater investigation. Personally, I wish that we directed our efforts towards so-called undruggable disorders, i.e., diseases without a proper medical treatment. For example, the mere fact that we still lack a drug for primary sclerosing cholangitis upsets me. Seeing these patients being unable to change the natural course of the disease is very frustrating.

Q5 What does your involvement as a committee member for the United European Gastroenterology (UEG) constitute, and what are the aims of this association?

The UEG is a wonderful creative and professional environment, bringing healthcare professionals together. The UEG's aim is to improve digestive disease through prevention, research, diagnosis, and cure. As such, it is a driver for better awareness of digestive diseases, giving patients and physicians a voice. One of their flagships is the UEG Week, which is a yearly conference that brings together >10,000 professionals. It has grown to a global marketplace of knowledge exchange in gastroenterology. I like the inclusiveness of the organisation and the can-do mentality. Personally, I am the Editor-in-Chief of the *UEG Journal*, a relatively young (2013) scientific journal. We have established ourselves among the first tier of gastroenterology journals and I am convinced that there is more to come.

"I hardly see new patients with hepatitis C. In fact, we are running a national programme that promises (micro-) elimination of hepatitis C in my country by 2030."

Q6 Some of your most recent publications have investigated polycystic liver disease, post-endoscopic retrograde cholangiopancreatography pancreatitis, and cholecystectomy. Where can we expect your future research focus to lie?

Indeed, I am not so picky, and perhaps that stems from a remark that was made at the time of my re-evaluation as professor to expand my research efforts beyond rare diseases. I took that challenge and looking back to these efforts in gallstone

disease, endoscopy for dyspepsia, and post-endoscopic retrograde cholangiopancreatography pancreatitis. What they all have in common is that a clinical trial has been a central theme as well as multidisciplinary collaboration. I am a believer in networks and in my country in particular it is relatively easy to collaborate with people. Networking is a game of giving and taking and you should never be afraid to give more away than to expect back. The prize is a well-run clinical trial, with an outcome that has clinical implications. Your role is just to set the wheels in motion.

Q7 Over the course of your extensive career in research, what are the most noteworthy developments to the field of gastroenterology you can recall, and are there any exciting innovations on the horizon we should be aware of?

I would like to mention the developments in hepatitis C. When I entered gastroenterology, we could barely identify patients with hepatitis C because of the lack of a good molecular test. Once recognition became possible, we struggled to treat these patients. I recall running clinics where we offered the many patients a year-long treatment with a meagre chance of success and tonnes of side effects. That changed with the advent of direct antiviral agents. These drugs cured patients within weeks. I hardly see new patients with hepatitis C. In fact, we are running a national programme that promises (micro-) elimination of hepatitis C in my country by 2030.

Currently, we categorise disease on basis of conventional tests (primary biliary cholangitis), most dominant affected organ type (inflammatory bowel disease), time of onset (congenital liver fibrosis), or any combination of the above. I expect that genomic medicine will help us better diagnose, better categorise, and better treat patients. We have just begun to scratch the surface will most certainly be impactful in the years to come but on a clinical level of the patient. ■

Interview

Douglas Drossman

President, Drossman Center for the Education and Practice of Biopsychosocial Care, DrossmanCare; Drossman Gastroenterology, DrossmanCare; President, Drossman Consulting; Professor Emeritus of Medicine and Psychiatry, University of North Carolina (UNC) School of Medicine; President Emeritus and Chief of Operations, Rome Foundation; Former Co-director, UNC Center for Functional GI and Motility Disorders, North Carolina, USA

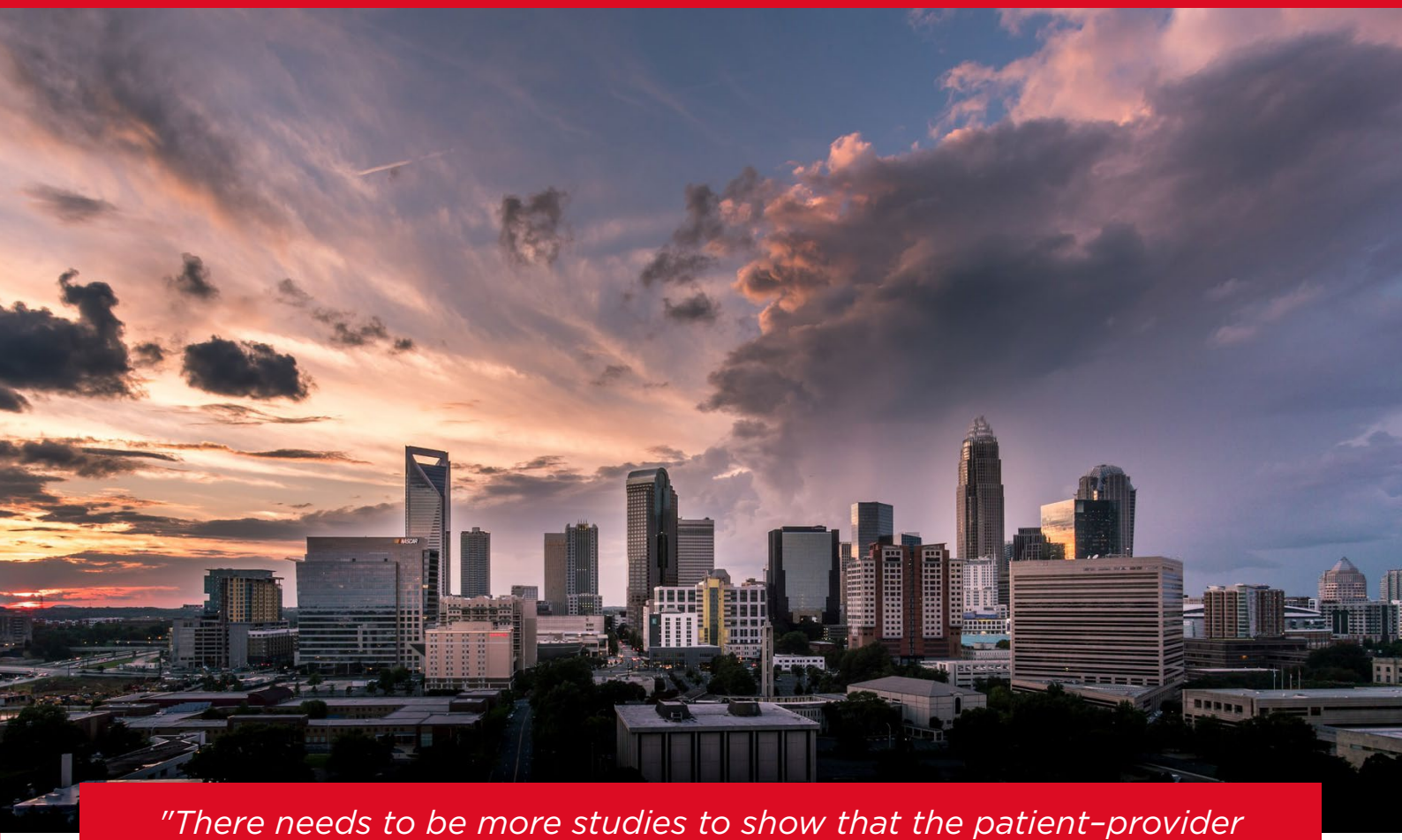
Q1

You have previously spoken about the brain–gut interactions that appealed to you, but was there a particular event or person that encouraged you to pursue a career in gastroenterology?

My interest in gastroenterology came because I always had an interest in the psychological aspects of medical illness and, unlike other subspecialties that are number driven (e.g., cardiac physiology, pulmonary function, electrolytes with renal disease), there are no numbers in gastroenterology. We take a history and assess symptom patterns, quality of life, and other psychosocial features. Of course, there is endoscopy and I always liked that. In fact, as a fellow I would interview the patient before the exam and try to predict who would have a normal endoscopy (*vis-à-vis* functional) and who would have an ulcer or IBD. But to truly understand the disorder you have to understand the patient and that relates to the history you hear from the patient. That fit well with my interest in mind–body interactions from my mentor, George Engel, who trained me and coined the term 'Biopsychosocial model'. So, it became a perfect combination because George was also an excellent interviewer. I trained with him in psychosomatic (biopsychosocial now) medicine and then went into gastroenterology. That was how I evolved the work in the functional gastrointestinal (GI) disorders (FGIDs) and brain–gut interactions (DGBI) very early on (in the 1970s), before anyone was really interested. Once I became a GI fellow, I was mentored by Don Powell, the GI Division Chief, who taught me how to 'play the game' of academics: how to publish, write grants, and give presentations. That convinced me to stay in academics and use my skills to help develop the field that led to the Rome Foundation and my work in communication skills.

Q2

In the recently published study you co-authored, entitled 'A survey of gastroenterologists in the United States on the use of central neuromodulators for treating irritable bowel syndrome', what



"There needs to be more studies to show that the patient–provider relationship improves health status, health outcomes, reduces unneeded procedures, and costs."

were the key messages you and the other researchers were trying to deliver?

First of all, I wanted to increase awareness of the value of using neuromodulators. That survey came after we did a Working Team report at the Rome Foundation in December 2018, which was a comprehensive review of the neuromodulators for GI problems, particularly painful conditions. That 2018 article has become a highly quoted publication. One of the major messages was to change the term from antidepressants, anti-anxiety, and antipsychotics to neuromodulators. We proposed that in the paper and that has rapidly taken hold because it avoids the stigma of using these medications for DGBI and not psychiatric problems. It's very analogous to how, in 2016, with *Rome IV* we changed the name functional GI disorders to disorders of brain–gut interaction. It's more scientifically based and avoids stigma. So, the key message is the awareness and legitimisation of using neuromodulators. As a side note, we call the GI drugs peripheral neuromodulators when they act on the enteric nervous system.

Another message is that these drugs are effective. There have not been sufficient studies in patients with GI disorders but enough empiric and consensus evidence to show benefit and we can borrow from other painful medical conditions where studies have been done.

The third message is that good clinicians can learn to broaden their repertoire from the usual 10 mg amitriptyline to higher doses and a wider spectrum of medications including the antipsychotics. It's the sense of dualism and stigma that leads to fear of learning how to use them. That was shown in the survey data. Personally, and throughout the Rome Foundation and my educational programme, DrossmanCare, I now run workshops to teach GI doctors how to use them.

Q3

You currently have more than 500 publications and over a dozen associated with your name for your research in the clinical, epidemiological, psychosocial, and treatment aspects of GI disorders.

What do you believe to be the current gaps in literature and what topics merit greater attention?

That's easy. There needs to be more studies to show that the patient–provider relationship improves health status, health outcomes, reduces unneeded procedures, and costs. That's the only way to convince the insurers to reimburse at least equally for face-to-face time compared to procedures. In the USA, the discrepancy is very large. Why spend an hour talking with a patient and make 250 USD when you can spend an hour doing 3 colonoscopies and make 3,000 USD! Patient centred care needs to be taught and reimbursed in the USA and the world. We have just released an article in *Gastroenterology* (online now); a Rome Working Team Report on communication skills and the patient–provider relationship. Part of that was an evidence-based review that demonstrated that good communication skills can improve patient and provider satisfaction, improve symptoms, and reduce costs. More studies like that may change medical school and residency curricula to teach communication skills and incentivise clinicians to learn more about these skills. Then, in time, unneeded procedures and reimbursement for services will fall in line. I also think we can develop good training programmes to teach doctors to communicate with patients better and then show that those courses are associated with patient and physician satisfaction and behavioural change in the practice. The Rome Foundation and DrossmanCare are doing these programmes now.

Another gap, as we noted above, would be to study the impact of central neuromodulators on improving the more severe DGBI.

Q4

What was the mission you set out to achieve when you founded the Rome Foundation?

At the time (the 1980s), functional GI disorders were not well understood, not well studied, not well taught, and were even trivialised. Diagnosis was made by exclusion of other disorders and the patients were thought to be psychiatric. So, my mission, personally and professionally, was to reverse all of that. Another mission was to put the FGIDs on the map, so to speak. The development and unique application of symptom-based criteria changed the way we diagnosed these disorders. Once it was accepted by the U.S. Food and Drug Administration (FDA) and other regulatory agencies, the Rome Foundation criteria were required for clinical trials and that opened the door to more research. Now patients can be studied around the world with the same symptom features, something that didn't exist before. We began by developing the criteria, but we had other goals: to educate clinicians on these disorders and our working teams, and subsequent editions of *Rome II*, *III*, and *IV* have done that. We wanted to encourage research and our research institute is doing that. Finally, we wanted to bridge the gap between doctors and patients and our communication skills programme is doing that. Ultimately, we want to help patients. The overall mission is: "To improve the lives of people with disorders of brain–gut interactions." There are four objectives: to promote global recognition and legitimise DGBIs; advance the scientific understanding of their pathophysiology; optimise clinical management for these patients; and develop and provide educational resources to accomplish these goals.

Q5

What are the most significant changes you have seen in the field of gastroenterology during your time working within the field?

First of all, I came into training in the 1960s and endoscopy was just beginning. Without question, diagnostic and therapeutic endoscopy has been a game changer for GI disorders. Then, for those who had negative studies, as I noted above, the use of symptom-based criteria gave the DGBIs (previously FGIDs) a home starting in the early 1990s. Prior to that everyone with GI symptoms and negative endoscopy were thought to have IBS. Now we have a classification system of 33 disorders and that has allowed for more specific treatments targeted towards patients. A third change over the last 10 years has been the more recent field of neurogastroenterology, or the science of brain–gut disorders. This evolved by blending the work of clinicians and scientists in motility with those working in FGIDs and then adding the work of epidemiologists, basic scientists, psychologists, and dietitians. This is a more integrated and effective way to study these patients.

Q6 In your preface of the book you co-authored, *Gut Feelings*, you mention an aim is to deliver a "learning experience" and to "optimize the patient–doctor relationship." What are the biggest challenges to this in clinical practice?

The biggest challenge to optimising the patient–doctor relationship begins with abrogating mind–body dualism and replacing it with the biopsychosocial model. Once we can teach the biopsychosocial understanding of DGBI and reduce the stigma attached to patients, both doctors and patients can partner to optimise the patient–doctor relationship. The next challenge is to teach clinicians and patients how to communicate with each other in a collaborative and patient-centred fashion. The third challenge, as I noted above, would be to incentivise this process by training doctors and rewarding them for doing it.

I believe that the uniqueness of this book is that it is a collaboration between a doctor and a patient. That can go a long way to meeting these challenges. The book gives a joint perspective on the patient–doctor relationship. I'm not sure that has ever been done before; at least not in gastroenterology. I was fortunate to have Johannah Ruddy as my patient. Her experience motivated her to clearly articulate in written and spoken word her transition from illness to wellbeing. From that, we began working together, doing communication training programmes and researching and writing peer-reviewed publications. So, the learning experience is for doctors to understand the patient's world and for patients to understand how doctors work. The book also contains an easy-to-read compendium of all the DGBIs, a mini *Rome IV*, So patients or healthcare providers can quickly learn about these disorders.

Q7 You have described your latest focus of research as "patient–provider communications." What are the latest advances in this field and where else can we expect to see your attention lie in the future?

In the last 2–3 years I've developed a collaboration between my educational programme, DrossmanCare, and the Rome Foundation to create a curriculum: 'What Do You Hear?'. This has seven components: production of videos to teach communication skills; presentations and symposia; full day workshops at medical centres and other educational venues; Train the Trainer programmes to teach key opinion leaders in the field to run communication skills workshops; publishing educational materials in peer-reviewed journals on patient–provider communications; having a visiting scholar programme so interested providers can observe our patient care methods on site; and having a research programme to demonstrate the effectiveness of this curriculum in improving outcomes. My goal is to not only to increase learning but to also create a legacy by training others to continue our goals and objectives

"Without question diagnostic and therapeutic endoscopy has been a game changer for GI disorders."

Q8 What advice would you give to a younger-self or aspiring gastroenterologist looking to establish themselves in the near future?

I've learned a few things along the way.

If you do research or teaching, search from within to find what turns you on. Learn what gives you meaningfulness and use the interest and energy that ensues to build your career. Too many young GI doctors rely too much on what they are being told to do. I know that is difficult because new GI fellows are often asked to start doing research and to publish before they know what they want.

Learn to network. Find collaborators, join the societies, and learn from others, e.g., young investigator programmes.

Get a mentor. Often the most productive clinicians, educators, and scientists had mentors to guide them and to be there when things were not going well; to help provide direction. I had two and it helped immensely in building my career.

Enjoy what you do. Find the gratification and go with it. Too many young gastroenterologists can burnout because they haven't found a satisfactory path. If you are having trouble, get advice. ■

Gut Microbiota and Probiotics in Health and Disease

This webinar took place on 23rd September 2021, as part of the 5th Global Microbiota Summit

Speakers: Mary Ellen Sanders,[1] Ana Teresa Abreu,[2] Karine Clément[3]

1. Dairy and Food Culture Technologies, Centennial, Colorado, USA
2. Hospital Ángeles del Pedregal, Mexico City, Mexico
3. Inserm/Sorbonne University, Pitié-Salpêtrière Hospital, Paris, France

Disclosure: Sanders has received consultancy and speaker fees from Bayer, Bloom Pharmaceuticals, The Chronic Disease Research Foundation (CDRF), Church & Dwight, PepsiCo, Kerry, Associated British Foods, Mead Johnson, Fairlife, GlaxoSmithKline, Trouw Nutrition, Allergosan OMNi-BiOTiC, Probi, Sanofi, Cargill, Danone North America, Danone Research, Winclove Probiotics, and Yakult. Abreu has received consultancy, speaker, or research fees from Sanofi, AB Biotics, Axon Pharma, Mayoly Spindler, Biocodex, Alfasigma, Tecnoquímicas, MD Pharma, Medix Healthcare, Menarini, Ferrer, Takeda, Carnot (Mexico), Adare Pharmaceuticals, Abbott, Faes Farma, Falk Institute, Instituto de Nutrición y Salud Kellogg's, and Danone Institute. Clément has received consultancy, speaker, or research fees from Danone Research, Ysopia, Confo Therapeutics, and Sanofi Consumer HealthCare.

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Meeting Summary

Mary Ellen Sanders opened the webinar by defining and differentiating the 'biotic' family, including probiotics, prebiotics, synbiotics, and postbiotics. She discussed the need for improved labels on commercial products in the biotics family and emphasised the research gaps in this field Ana Teresa Abreu expanded on a specific probiotic, *Bacillus clausii*, describing the evidence for health benefits associated with this bacterium and the potential mechanisms through which it might achieve these effects. Finally, Karine Clément discussed the role of the gut microbiome in cardiometabolic disease, suggesting that gut microbiota may represent a missing link between the environmental and genetic factors that impact these diseases. Clément described the evidence for a dysbiosis of gut microbiota in metabolic diseases and posited that a personalised approach to gut microbiome therapy might be the best way to leverage this association.

The Science of Probiotics and Related Biotics: How to Understand and Use Them

Mary Ellen Sanders

Mary Ellen Sanders introduced 'biotics' as a family of four microbiome-targeted substances: probiotics, prebiotics, synbiotics, and postbiotics. Each type of biotic has the potential to impact the resident microbes of a host, which have diverse physiological functions, including promotion of fat storage and angiogenesis, immune development, synthesis of vitamins and amino acids, drug metabolism, modification of the nervous system, breakdown of food, resistance to pathogens, protection against epithelial injury, and modulation of bone-mass density.[1]

Many human diseases and disorders are associated with an altered microbiome, including irritable bowel disease, colon cancer, diabetes, obesity, rheumatoid arthritis, and liver disease.[1–3] However, Sanders emphasised that it is not yet clear whether the altered microbiome is a cause or a result of these conditions.[1] This raises the question of whether restoring the microbiota in individuals with these conditions, to match that of healthy individuals, would affect the condition itself.

Biotics are intended to influence colonising microbiota to improve health, but understanding of what constitutes a healthy microbiome is still quite limited. Sanders explained that rather than focusing on the specific microbes present in the microbiome, a healthy microbiome may be better characterised by a high diversity of taxonomic units, high resilience (the ability to recover from perturbations such as antibiotic exposure), and functional redundancy (more than one ecosystem member can perform the same function).[4]

Sanders feels that although studying the microbiome is helpful to understand the mechanisms of biotics, the evidence of health benefits is more important. For example, probiotics have been shown to benefit health for various clinical endpoints, across the human lifespan, and in different organ systems, such as preventing antibiotic-associated or traveller's diarrhoea, treating ulcerative colitis, and reducing the incidence of infection gastrointestinal disease.[2] For most of these benefits, a microbiome-mediated mechanism has not been demonstrated yet.[4]

The International Scientific Association for Probiotics and Prebiotics (ISAPP) has published statements that include clear definition for each of member of the biotic family, based on consensus panels (Table 1). Importantly, these definitions are deliberately broad enough to support innovation; they do not restrict these substances by host (e.g., human, agricultural animals, etc), regulatory category (e.g., food,

Table 1: ISAPP Definitions of biotic substances.

Biotic substance	Definition
Probiotic	Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host[5]
Prebiotic	A substrate that is selectively utilised by host microorganisms, conferring a health benefit on the host[6]
Synbiotic	A mixture comprising live microorganisms and substrate(s) selectively utilised by host microorganisms that confers a health benefit on the host[7]
Postbiotic	Preparation of inanimate microorganisms and/or their components that confers a health benefit on the host[8]

Definitions are concise; for full understanding, see the full statements. All substances must be safe for their intended use.

ISAPP: International Scientific Association for Probiotics and Prebiotics.

drug, or supplements), site of action (e.g., gut, vaginal tract, skin, etc), or mechanism of action.[5-8]

Probiotics

A number of different microbes are used as probiotics, many of which are members of the *Lactobacillaceae* family or are species of *Bifidobacterium*, *Bacillus,* or *Saccharomyces.*[9] The range of probiotic species is rapidly expanding[10] as more is learnt about the microbes that reside in the healthy human body. Sanders emphasised the importance of recognising that probiotics are a heterogenous group; two products which contain the same microbial genus and species but differ by microbial strain may differ in function.

To be defined as a probiotic, a substance must be a properly identified (both sequenced and named). The microbe must be alive when administered, and studies need to have demonstrated a health benefit for a specific target host at the specific dose delivered by the product. In addition, the microbial strain and manufacturing process must be safe for the intended use, and the product must be correctly labelled with the strain and colony forming units (CFU) expected at the end of its shelf life.[5]

Ideally, probiotic product labels should detail health benefits (supported by evidence), suggested serving size, proper storage conditions, and contact details for consumer information.[11] However, a survey of refrigerated probiotic foods in grocery stores in the USA found that only one-half (22 of 45) of products listed the constituent microbial strains. Those that did, could be linked to evidence of health benefits, tended to contain fewer strains, and had a lower CFU per serving compared to other products.[12] A survey of probiotic supplements found similar results: most products could not be linked to evidence; 45% did not list constituent microbial strains; and 45% did not provide CFU at end of shelf life.[13] Sanders emphasised that similar problems exist outside of the USA.

Neither probiotics nor postbiotics are required to target the microbiome directly, whereas prebiotics and synbiotics should do so as part of their mechanism of action.[5-8] Despite these distinctions, Sanders explained that there is a common belief among both scientists and the general public that probiotics have an important impact on the gut microbiome. This belief is not fully substantiated by the available research data; a systematic review of clinical trials showed that probiotics did not have a global impact on the faecal microbial communities in healthy subjects.[14] Sanders suggested that this does not prove that probiotics have no effect; their effects may be limited to minor components of the microbiota, not evident in faecal samples or in healthy subjects, or only evident in the metabolites rather than the microbiome composition. However, she stressed that the evidence to date indicates that the effects of current probiotics on the microbiome are likely to be quite subtle.

In summary, Sanders reiterated that the healthy gut microbiome has not yet been defined by researchers, but that for probiotics, effects on the microbiome are probably less important than health benefits. There is a clear need for improved labels on commercial products in the biotics family so that healthcare practitioners and consumers know what they are buying, and the terms probiotics, prebiotics, synbiotics, and postbiotics should only be used when the scientifically accepted criteria are met. She emphasised the research gaps in this arena, including defining a healthy microbiome, robust trials to confirm health benefits, and identifying the best strains and doses for specific applications. Finally, Sanders emphasised that it will be important to understand the mechanisms that drive the clinical benefits of biotics in order to optimise these substances for future use.

Bacillus clausii: Mechanisms as Spore Probiotics in Gastrointestinal Disorders

Ana Teresa Abreu

Bacillus is one of the most studied bacterial genera[15] and its species can be found in soil, water, food, and in the human gut.[16] These aerobic bacteria can differentiate into a dormant endospore, allowing them to survive in stomach acid and bile salts in the gastrointestinal system.[16,17]

Most *Bacilli* are not pathogenic to humans or animals, and in the case of *B. clausii* (Figure 1),[18] an endosymbiotic relationship, where one organism lives inside the other, between

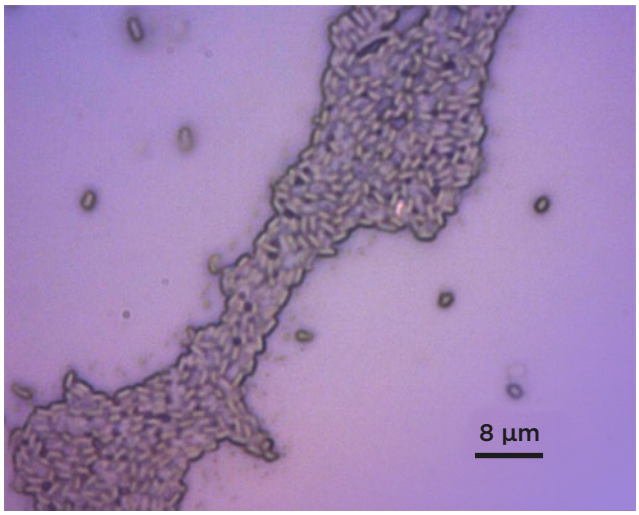

Figure 1: *B. clausii* (combined antibiotic resistant strains: O/C, SIN, N/R, T).
N/R: novobiocin and rifampicin; O/C: chloramphenicol; SIN: streptomycin and neomycin; T: tetracycline.

species and their hosts has been suggested.[17,19,20] Four strains of *B. clausii* are resistant to antibiotics, a property considered advantageous to restoring a healthy gut, and are named for their predominant antibiotic resistance: novobiocin and rifampicin (strain N/R), chloramphenicol (strain O/C), streptomycin and neomycin (strain SIN), and tetracycline (strain T).[19]

There are several properties of *B. clausii* that contribute to its probiotic effects:

- *B. clausii* spores can survive the hostile environment of the gastrointestinal tract and multiply to colonise the intestine.[21-23]
- The pan-genome of *B. clausii* (O/C, SIN, N/R, T) includes genes involved in carbohydrate metabolism,[19] and one strain, SKAL 16, has been shown to excrete butyrate in *in vitro* conditions.[24] Butyrate serves as the major energy source for enterocytes, exerts anti-inflammatory effects, and enhances gut barrier function.[25]
- The antibiotic resistance genes of *B. clausii* are stable and cannot be transferred to other bacteria.[26] Many strains of *B. clausii* are recommended for use along with antibiotics, and Abreu emphasised that it is important for clinicians to match probiotic strains to the prescribed antibiotic therapy.
- Some strains of *B. clausii,* particularly SIN and T, produce the essential vitamin riboflavin (vitamin B2) *in vitro*, suggesting that *B. clausii* has the potential to compensate for host deficits in riboflavin that can occur in clinical contexts such as chemotherapy.[27]
- *Bacillus* species produce a wide range of antimicrobial substances, including lantibiotics (post-translationally modified peptides) which are active against gram-positive bacteria such as *Clostridium difficile.*[20,28] One such lantibiotic, clausin, has been isolated from *B. clausii* and interacts with lipid intermediates in the bacterial envelope biosynthesis pathways,[29] suggesting that it could help to manipulate the constituents of the intestinal microbiota.

Immunomodulation

B. clausii has been shown to have immunomodulatory properties in preclinical studies. In a human enterocyte model of rotavirus infection, *B. clausii* strains (O/C, SIN, N/R, and T) induced the synthesis of bacteriocins, reduced enterocyte cell death, and inhibited the release of pro-inflammatory cytokines. They also increased mucin production and the synthesis of tight junction proteins, both important for the integrity of the gut mucosal barrier.[30] In addition, a small *in vivo* experiment has shown that *B. clausii* modifies the gene expression profile in the intestine in patients with mild oesophagitis, including genes involved in immunity and inflammation.[31] Finally, in an animal model of asthma, *B. clausii* reduced the numbers of eosinophils, neutrophils, and lymphocytes, and lowered IL-4 and IL-5 levels,

suggesting a potential use in reducing airway inflammation in clinical settings.[32]

Abreu explained that one potential mechanism for the immunomodulatory capacity of probiotic *B. clausii* strains could be the expression of extracellular compounds and/or immunostimulation via the cell wall. In murine cell lines, *B. clausii* MTC 8326 was shown to activate metabolic activity and innate immune responses in macrophages,[33] and *B. clausii* (O/C, N/R, SIN, and T) was also shown to stimulate the production of nitrite in peritoneal cells, IFN-γ in spleen cells, and CD4+ T-cell proliferation.[20] One route through which *B. clausii* may induce these immunomodulatory effects is through the secretion of lipoteichoic acid.[34]

Gut Homeostasis

Other studies have suggested that *B. clausii* contributes to gut homeostasis. In an *in vitro* simulation of the human gastrointestinal tract, *B. clausii* SC 109 spores (along with other probiotic bacteria and prebiotic ingredients) were shown to increase microbiome production of butyrate, and the overall diversity of gut microbiota.[35] The presence of *B. clausii* in patients with pancreatic adenocarcinoma has been associated with longer survival times,[36] and treatment with *B. clausii* UBBC07 has been shown to reduce serum urea levels in rats with acetaminophen-induced renal failure, suggesting a novel clinical use for probiotics in chronic kidney disease.[37]

Antimicrobial Properties

Abreu explained that *B. clausii* can produce antimicrobial peptides, including lantibiotics, that inhibit the growth of pathogenic bacteria *in vitro.*[20] This characteristic means that probiotics can be supportive when delivered alongside antibiotic therapy. *B. clausii* (O/C, N/R, SIN, and T) appears to be protective during *Escherichia coli* infection in mice, increasing protective mucus secretion and resulting in minimal mucosal damage and less sloughing of villus tips.[38,39]

Infection with *C. difficile* can result in symptoms ranging from diarrhoea to pseudomembranous colitis,[40] and infection with *B. cereus* can cause vomiting, diarrhoea, and haemorrhage.[41] *B. clausii* strain O/C has been shown to secrete a serine protease capable of inhibiting the cytotoxic effects of both *C. difficile* and *B. cereus in vitro.*[41]

Abreau explained that *B. clausii* has been efficaciously and safely used in humans for several decades. For example, in patients with dietary endotoxemia, believed to be caused by disruptions in gut permeability, administration of probiotic strains including *B. clausii* was associated with a 42% reduction in post-prandial serum endotoxin and reductions in pro-inflammatory markers.[42] In patients with recurrent aphthous stomatitis, a disease of the oral mucosa that results in ulcers and pain, local adjunct application of *B. clausii*, alongside glucocorticoid treatment, reduced oral pain and ulcer severity compared to glucocorticoid alone.[43]

In summary, Abreu reiterated that the physiological, antimicrobial, and immunomodulatory properties of *B. clausii* have been demonstrated both *in vitro* and *in vivo*; and antimicrobial activity against enteropathogens such as *C. difficile* and *B. cereus* has been demonstrated, providing one potential mode of action for the efficacy of this probiotic in gastrointestinal disorders. Further clinical studies using specific strains in targeted medical conditions are needed to validate these findings, and to increase the scientific credibility of *B. clausii*.

Gut Microbiota in Cardiometabolic Diseases

Karine Clément

Clément began by emphasising that there is a heavy societal burden from cardiometabolic and nutrition-related diseases and that the gut microbiota can be considered a 'super-integrator' for many of the risk factors for mortality.[44]

Obesity, the fourth highest risk factor for mortality in Western Europe,[44] is associated with altered inter-organ cross-talk involving the intestinal tract, brain, adipose tissue, muscles, and others (PRIEST 2019). In the adipose tissue, obesity is connected to perturbed endocrine secretions, immune or inflammatory imbalances, altered angiogenesis, organelle dysfunction, altered extracellular matrix, and adipocyte hypertrophy.[45-47] The development of obesity involves the pathogenic remodelling

of white adipose tissue, which may lead to the development of obesity-related cardiometabolic disease and compromised response to obesity treatment.[48] There is substantial heterogeneity in the clinical trajectory of subjects with obesity and their weight loss responses, for which gut microbiota-derived elements may be contributing factors.[49]

Clément explained that the role of the gut microbiota genomes in host biology should be considered: while it is accepted that both environmental and genetic factors play a role in the development of metabolic disease, gut microbiota may represent the missing link between them.

The key functions of the gut microbiota are in the digestion of food and the production of metabolites, the development and integrity of intestinal structure, immune system development, metabolism of toxic compounds, and synthesis of vitamins K and B.[50] However, several studies have suggested that gut microbiota also play a role in energy balance and our capacity to store fat. Clément described ground-breaking pre-clinical experiments that showed that germ-free rodents have decreased adiposity and are resistant to diet-induced weight gain, compared to conventionally raised rodents.[51] In addition, transplanting gut microbiota from mouse models of obesity into germ-free mice can partially transfer the obesity phenotype.[51] Similar experiments have been conducted to transfer microbiota from humans to mice, and these have shown that the receipt of gut microbiota from an obese human can result in increased adiposity in a mouse, even when a healthy diet is followed. In parallel, the receipt of gut microbiota from a lean individual (a twin of the obese individual) results in a lean mouse when a healthy diet is followed[52,53] (Figure 2).

Clément then discussed the importance of diversity in the gut microbiome in healthy individuals. Subjects living in westernised countries such as the USA have been shown to have a lower diversity of gut microbiota from an early age, compared to populations that are more isolated or live with an ancestral mode, such as Malawians or Amerindians.[54] Some studies have attempted to stratify individuals by their microbiotic gene richness. Across these studies, 20–30% of subjects were considered to have low gene richness, and this group was characterised by increased overall adiposity, dysmetabolism, and a more pronounced inflammatory phenotype than individuals with high gene richness.[55,56] Approximately 75% of patients with severe obesity (candidates for bariatric surgery) can be classified as having low gene richness.

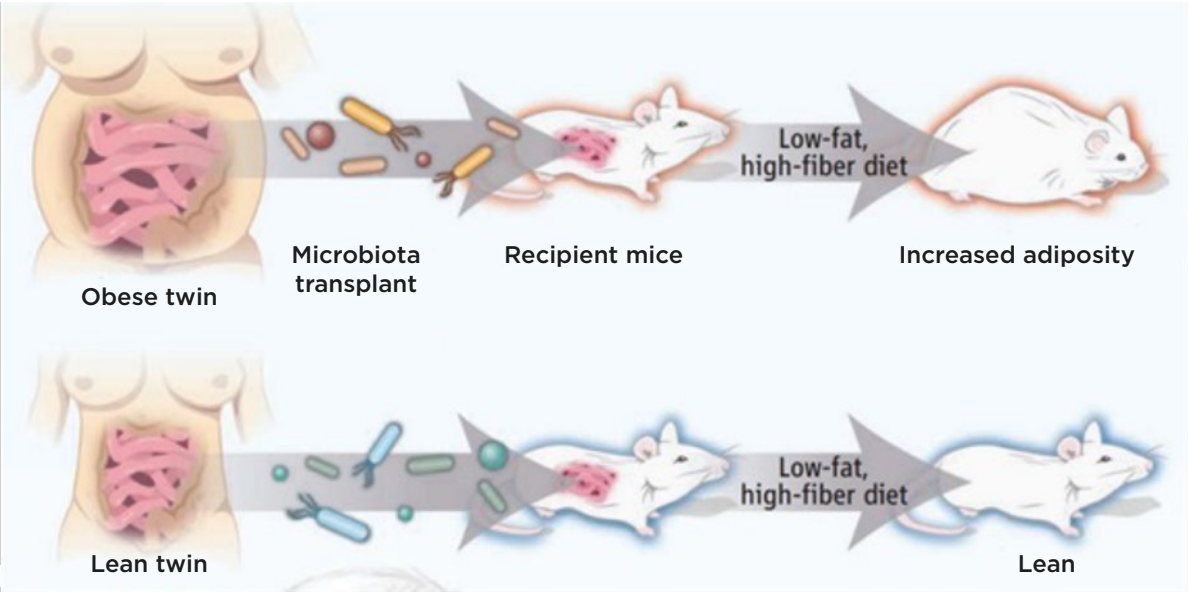

Figure 2: The protective role of gut microbiota from a lean donor in the presence of a healthy diet.

Reproduced with permission, Walker and Parkhill.[52]

This is important because a low gene count is associated with enrichment of pro-inflammatory bacteria, whereas a high gene count is associated with enrichment of anti-inflammatory bacteria.[55]

One of the important characteristics of 'healthy' gut microbiota is the production of short-chain fatty acids (SCFAs), including butyrate.[6,8,25,57] SCFAs act on enterocytes to stimulate the production of certain hormones, improving insulin sensitivity and glucose tolerance and modifying lipid metabolism.[8,25] Clément emphasised that there is considerable research effort focused on understanding the imbalance between the gut microbiota in healthy individuals and those with disease. Gut microbiota may also contribute to the health of the intestinal barrier in metabolic diseases.[58] For example, studies have shown that modification of the gut microbiota affects the thickness of the mucus barrier.[58]

The effects of gut microbiota on the host can be classified as metabolism-independent pathways, driven by components of the bacterial membrane such as lipopolysaccharide or peptidoglycan and impacting low-grade inflammation processes or modifying host biology; or metabolism-dependent pathways driven by microbial metabolites such as imidazole propionate, SCFAs, secondary bile acids, or trimethylamine. [59,60]

Clément described several studies that have attempted to stratify gut microbiomes into groups based on their genome. In a European study, Arumugam et al., described three distinct clusters of microbiomes, termed enterotypes, each characterised by a dominant gut microbial species: Type 1, enriched in *Bacteroides*; Type 2, enriched in *Prevotella;* and Type 3, enriched in *Ruminococcus.*[61] Subsequent studies have identified a subset of the Type 2 microbiome with a low proportion of *Faecalibacterium* and low microbial cell density, named Bact2, which is more prevalent in patients with inflammatory bowel disease versus the general population (78% versus 13%, respectively).[62] The prevalence of Bact2 also correlates with higher BMI and with low-grade systemic inflammation in the MetaCardis European cohort.[63]

Clément explained that interventions to increase microbial diversity, increase beneficial microbes, and change metabolite concentrations are intended to improve metabolism and the immune response, potentially reducing the burden of complications. Potential mechanisms to modify the gut microbiome include dietary changes, selective enrichment of gut bacteria, faecal transplant, and bariatric surgery.

One example of such an intervention is diet-induced weight loss in patients with obesity or overweight, which improved gut microbiotic diversity and clinical phenotypes in patients with a low microbial gene count at baseline.[56] Bariatric surgery also appears to increase microbial gene richness one-year post-surgery.[63] Administration of *Akkermansia muciniphila* to mouse models of obesity or Type 2 diabetes resulted in a reduction in fat mass, insulin resistance, and low-grade inflammation,[64] and *A. muciniphila* is associated with healthier metabolic status and greater insulin sensitivity in human subjects with obesity or overweight.[65] Finally, a study of faecal transfer from healthy individuals to patients with obesity and metabolic syndrome showed an improvement in insulin sensitivity, however, the effect was transient and mainly observed in patients with a low gut microbiota diversity at baseline.[66]

Clément concluded that there is evidence for a dysbiosis of gut microbiota in metabolic diseases, and that a personalised approach to the gut microbiome may be the best way to leverage this association. However, she stressed that further research is needed as the links between the changes in the gut microbiota and the expected clinical effects have yet to be fully elucidated.

Summary

In summary, the evidence to date supports the hypothesis that both probiotics and the gut microbiome have an impact on the health of humans and other animals. However, though potential mechanisms of action have been suggested experimentally, further research including well-designed trials is needed to fully understand how probiotics manipulate the gut microbiota to benefit the host.

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Solving the Puzzle of Recurrent Abdominal Pain: A Rare Liver Disease with Common Symptoms

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Speakers: Frank Tacke,[1] David Cassiman[2]

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Summary

Frank Tacke presented the hypothetical case of a 24-year-old female with a 10-year history of multiple emergency department (ED) visits for recurrent severe abdominal pain with weakness, fatigue, mental fogginess, and dark urine. Laboratory tests, imaging, and endoscopies were generally unremarkable, but urine analysis showed elevated porphobilinogen (PBG), 5-aminolevulinic acid (ALA), and uroporphyrin, leading to a diagnosis of acute hepatic porphyria (AHP).

Awareness of this rare disease is low, with misdiagnosis/delayed diagnosis common, therefore AHP should be considered in patients with the above-mentioned symptoms. David Cassiman outlined current management strategies for AHP, including the avoidance of attack triggers (e.g., fasting, smoking, alcohol, drugs); the treatment of acute attacks (e.g., haemin, glucose, analgesics); and the management of chronic symptoms. He also discussed a new treatment, givosiran▼ (Givlaari®▼, [Alnylam Pharmaceuticals Inc., Cambridge, Massachusetts, USA]). In the ENVISION study, 94 patients with AHP were randomised to givosiran▼ or placebo for 6 months, followed by a 30-month open-label phase. At a 24-month interim analysis, the median annualised attack rate (AAR) had fallen from 1.04 (double-blind givosiran▼) to 0.00 (open-label givosiran▼), and from 10.65 (double-blind placebo) to 1.35 (open-label givosiran▼). Secondary efficacy and quality of life results supported the sustained benefits of givosiran▼, which had an acceptable safety profile. The question and answer session elicited information about the diagnostic management of patients with unexplained abdominal pain episodes; which patients are most likely to benefit from givosiran▼; the reasons for misdiagnosis/delayed diagnosis, AHP symptoms and management, which patients can receive givosiran▼; the accuracy of PBG testing; and the importance of renal and liver function monitoring for patients on givosiran▼.

Mystery Diagnosis, Disease Overview, and Pathophysiology

Frank Tacke

Details of a hypothetical 24-year-old female with a longstanding history of recurrent abdominal pain were presented. Over the previous 10 years, she had presented at the ED once or twice yearly with episodes of severe abdominal pain. At her last ED visit, her abdominal pain was debilitating and overwhelming (9–10/10 in severity). Liver function tests were mildly elevated, but blood counts, inflammatory markers, renal function tests, and urine analysis were all normal. Abdominal imaging (ultrasound and CT) and gynaecological examination were also normal. She was discharged from the ED without a specific diagnosis, but was referred for oesophagogastroduodenoscopy and colonoscopy, which were normal.

Her severe abdominal pain began 10 years ago with the onset of menses. She recalls symptoms of weakness, fatigue, and mental fogginess preceding episodes of abdominal pain. The pain was usually localised to her lower abdomen, was crampy/colicky in nature, and 8–10/10 in severity, which prompted seeking medical attention. There were no identifiable precipitants, although it seemed to occur around the time of menses. Her pain usually required an ED visit, but generally improved over 3–5 days after receiving intravenous fluids and opiates. The episodes were associated with feeling dehydrated and producing darker (reddish) urine. She estimated eight discrete attacks from age 18 to 22 years but had months between attacks in which she was completely asymptomatic.

The hypothetical patient was also affected by anxiety, had a maternal history of hypothyroidism, and had her appendix removed 4 years ago for suspected appendicitis. She had no known drug allergies, and was taking fluoxetine, oral contraceptives, oxycontin, and analgesics as required. She was a radiology technician who does not smoke or use drugs and only drinks 1–2 glasses of wine 2–3 times per month.

Her most recent episode led to an ED visit for abdominal pain 3 weeks ago. She had severe abdominal pain (9/10) with nausea and fatigue and noted dark urine prior to the ED visit. She had radiating limb pain (mainly in her legs). Her heart rate was 110 bpm and her blood pressure was 154/92 mmHg. Physical examination showed severe diffuse abdominal pain that was non-localised. Laboratory tests revealed mild hyponatraemia (129 mEq/L) and elevated liver function tests (alanine aminotransferase: 65 U/L; aspartate aminotransferase: 50 U/L). Other tests (e.g., urine pregnancy, complete blood count, urine analysis, C-reactive protein, erythrocyte sedimentation rate) were normal.

Abdominal and pelvic CT with contrast were unremarkable, as was an ultrasound of her right upper quadrant. Her creatinine kinase was normal (120 U/L) and a hepatitis panel was negative. Analysis of her urine showed elevated PBG (79 mg/g of creatinine [reference range:[1] 0–4 mg/g]), ALA (35 mg/g [reference range:[1] 0–7 µg/g]) and uroporphyrin (98 µg/g of creatinine [reference range:[2] 0–30 µg/g]), resulting in a diagnosis of AHP.[2-4]

It is very important that porphyria is considered as a differential diagnosis in patients with recurrent abdominal pain with neurological symptoms, muscle weakness, or fatigue. The objectives of this webinar were to:

1. raise awareness of AHP and highlight the importance of achieving an earlier diagnosis;
2. discuss best practice for the diagnosis and management of AHP; and
3. present the latest clinical data supporting givosiran▾ (Givlaari▾), which is indicated for the treatment of AHP in adults and adolescents aged ≥12 years.[5]

Patients with acute porphyrias have altered haem biosynthesis, which results in toxic metabolites.[6] As AHP is a rare disease, it is often not considered in differential diagnosis when assessing for unexplained acute abdominal pain (and other characteristic symptoms).[4] AHP has a variable presentation, with many of the symptoms presenting as non-specific and mimicking other more prevalent conditions, leading to challenging disease identification and delayed diagnosis or misdiagnosis.[3,7,8]

Current management strategies for AHP focus on the avoidance of attack triggers (such as fasting, alcohol, smoking, and certain medications), the treatment of acute attacks

(with fluids, glucose infusions, pain medications, and haemin), and the management of pain and other chronic symptoms.[1,3] However, medications may have unanticipated deleterious effects.[1]

The toxic metabolites produced in AHP do not only affect the liver, but can also cause a myriad of other problems, including central nervous system (CNS),[9-11] peripheral nervous system (PNS),[9,10] and autonomic nervous system (ANS) manifestations[4,9] (Figure 1). Patients with variegate porphyria and hereditary coproporphyria can also have cutaneous manifestations (lesions on sun-exposed skin).[11] Furthermore, AHP can result in long-term complications, including hepatocellular carcinoma, chronic kidney disease (CKD), neuropathy, and hypertension.[9,12]

Patients with AHP can also experience chronic symptoms between attacks. In the prospective, multinational EXPLORE study,[13] 65% of patients with AHP and recurrent attacks experienced chronic symptoms, with 46% of patients experiencing them daily. The most common symptoms were abdominal pain (20%); tiredness, anxiety, and nausea (each 19%); headache, weakness, and trouble sleeping (each 14%); and back pain (12%).[13]

Patients with AHP are frequently misdiagnosed (e.g., non-specific abdominal pain, irritable bowel syndrome, depression, or fibromyalgia)[14] and can even undergo potentially unnecessary surgeries.[4] Frequent healthcare utilisation, reduced quality of life, and lost workdays all contribute to disease burden.[13,15,16] Further, the pain and the unpredictable nature of attacks (Figure 2) is a source of fear and anxiety for many patients.

Potential long-term complications of AHP include liver and kidney disease, hypertension, and chronic neuropathy.[1,17-22] AHP has been identified as a risk factor for primary liver cancer, especially hepatocellular carcinoma.[17] In a Norwegian cohort study, the annual incidence of primary liver cancer was 0.35% in individuals with AHP, over 100 times higher than the 0.003% in a reference population.[18] Porphyria has also been linked to CKD.[19] In a French study, 59% of patients with symptomatic acute intermittent porphyria (AIP) had CKD.[20] In a Spanish study, patients with sporadic AIP (<4 attacks/year) had a significantly higher risk of CKD than patients with latent AIP (30% versus 0%; p=0.018).[21] Patients with AHP may also be at increased risk of chronic sustained hypertension,[1,22] although as the risk of

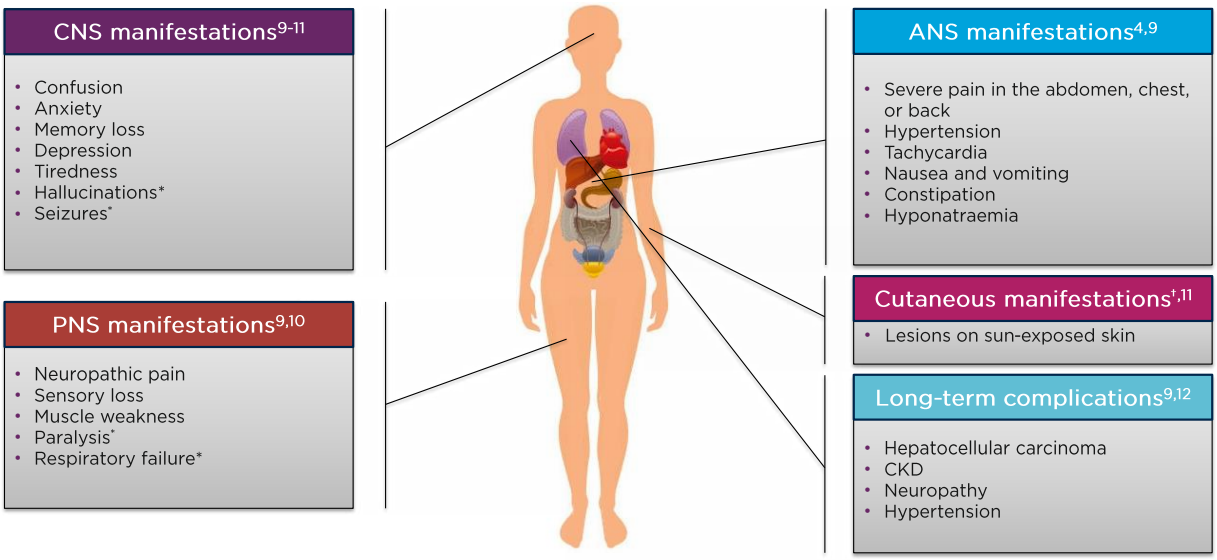

Figure 1: Clinical characteristics of acute hepatic porphyria and associated conditions.

*Only occurs in severe cases.

†Only occurs in variegate porphyria and hereditary coproporphyria.

ANS: autonomic nervous system; CKD: chronic kidney disease; CNS: central nervous system; PNS: peripheral nervous system.

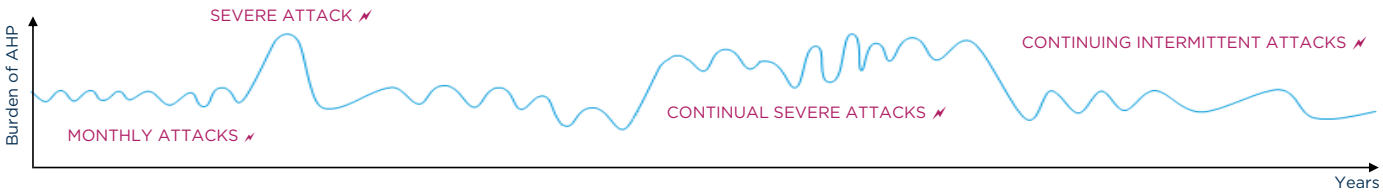

Figure 2: Illustrative patient experience with acute hepatic porphyria.
AHP: acute hepatic porphyria.

hypertension is high in the general population, further research is required to ascertain the true excess risk associated with AHP.[22] Patients with AHP can also develop chronic pain associated with axonal motor polyneuropathy.[1] Chronic pain symptoms can lead to severe depression and anxiety, which may necessitate psychiatric care,[1] and suicidality has been observed in patients with AHP.[23] Lastly, severe attacks can even result in permanent quadriplegia.[12]

Many different medical specialists may be variably involved in the diagnosis and management of patients with AHP.[7] AHP commonly presents with acute neurovisceral attacks that manifest as severe abdominal pain and debilitating chronic symptoms.[13] Prompt diagnosis and treatment is beneficial as this may improve prognosis and prevent severe or chronic neuropathic symptoms.[4] Therefore, gastroenterologists play a vital role in identifying the hallmark symptoms of AHP in order to obtain an earlier diagnosis and improve the management of these patients.

AHP can be diagnosed with a random (spot) urine test for PBG, ALA, and porphyrins, normalised to creatinine.[11,24] The ideal time to take a urine sample for diagnosis is during a suspected attack.[25] Genetic and biochemical testing can then be used to confirm the diagnosis and ascertain the type of AHP.[6,26] Sequencing and deletion testing detects approximately 95–99% of mutations in the genes associated with AHP.[26] However, due to a lack of awareness, incorrect tests are often ordered when AHP is suspected.[27] Testing for porphyrins alone cannot diagnose AHP, as levels can be elevated in various disorders.[11]

Disease Management and Givosiran▼ Treatment

David Cassiman

Current management strategies for AHP focus on the avoidance of attack triggers (e.g., smoking, alcohol, drugs, and hormonal therapy), the treatment of acute attacks, and the management of pain and other chronic symptoms.[3]

Acute attacks can be treated with haemin, which decreases ALAS1 activity and urine and plasma ALA and PBG.[1,3] Glucose and carbohydrate loading can also be used to downregulate the haem biosynthesis pathway,[1,3] and may be most effective in patients who are malnourished or where dietary restrictions have contributed to an attack.[24] Pain is generally managed using opioid and non-opioid pain medications.[1] For women who experience acute attacks related to their menstrual cycle, gonadotropin-releasing hormone agonists may be used to suppress ovulation.[1] Patients with AHP may also benefit from treatment for their other symptoms, e.g., nausea, hypertensive crises, neuropathy, seizures, metabolic changes, anxiety, and depression. For severely affected patients, liver transplantation may be considered as a last resort.[1]

Givosiran▼ has recently become available as a treatment option for AHP.[1,3] This small interfering RNA (siRNA) therapeutic reduces ALAS1 messenger RNA, thus lowering ALA and PBG accumulation, which have been linked to attack frequency and symptoms.[5,28] Givosiran▼ is indicated for the treatment of AHP in adults and adolescents aged ≥12 years.[5]

In the ENVISION study, 94 patients (aged ≥12 years) with AHP (≥2 attacks in the previous 6 months) were enrolled at 36 sites in 18 countries.[29] Patients were randomised to monthly subcutaneous givosiran▾ 2.5 mg/kg or placebo.[29] The primary endpoint was the AAR (i.e., attacks that required hospitalisation, urgent healthcare, or at-home haemin administration per year) among 89 patients with AIP.[29] Secondary endpoints included urinary ALA and PBG, haemin use, pain, fatigue, nausea, and quality of life among 89 patients with AIP; and AAR among all 94 patients with AHP.[29]

Among the 94 patients with AHP, the median age was 38 years, 89% were female, and the median time since diagnosis was 7 years.[29,30] The median historical AAR was 8.0, 40% had prior haemin prophylaxis, 52% had symptoms most/every day between attacks, and 29% regularly used opioids.[29,30] Baseline median urinary ALA and PBG were 16.4 and 39.6 mmol/mol creatinine, respectively.[30]

After the 6-month double-blind period, 93 eligible patients entered a 30-month open-label extension, during which patients received monthly givosiran▾ 2.5 or 1.25 mg/kg, although this was later increased to 2.5 mg/kg for all patients.[30] At a 24-month interim analysis (at which time all patients had ≥18 months of follow-up), the median AAR had fallen from 1.04 during the double-blind period to 0.00 during the open-label period among patients who received givosiran▾ throughout, and from 10.65 to 1.35 (i.e., an 87% reduction) among those who received placebo followed by givosiran▾ (Figure 3).[30]

The proportions of patients free from attacks during each 3-month interval increased among those randomised to givosiran▾, from 0% (baseline) to 67% (Months 3–6, i.e., the second half of the double-blind period) to 83% (Months 21–24) to 95% (Months 27–30) and among those originally randomised to placebo, from 2% to 24% to 76% to 94%, respectively.[30] Patients who were randomised to givosiran▾ had median annualised days of haemin use of 0.0 during the double-blind and open-label periods, while those randomised to placebo had 15.0 annualised days of haemin use during the double-blind phase, which fell to 0.7 during the open-label phase, a reduction of 95%.[30]

Givosiran▾ was also associated with clinically important (based on data from patients with other chronic diseases[31-34]) improvements in quality of life.[30] Mean increases in the Short-Form 12 physical component summary score were 5.1 during the double-blind period and 8.1 during the open-label period among those randomised to givosiran▾, and 1.7 and 9.0, respectively, among those originally randomised to placebo.[30] Similarly, mean changes in EuroQol-Visual Analogue Scale (EQ-VAS) scores were +5 and +14 at Months 6 and 24, respectively, among those randomised to givosiran▾, and –1 and +9, respectively, among those originally randomised to placebo.[30] Likewise, results from the Porphyria Patient Experience Questionnaire (PPEQ), which was designed for this study, also showed improvements in quality of life, much more so with givosiran▾ versus placebo during the double-blind phase and somewhat more so for those who had received givosiran▾ for 24 months versus those who received placebo for 6 months then givosiran▾ for 18 months.[30] These included improvements in "overall satisfaction with treatment", "convenience of treatment", "planning for future events", "traveling >1 day for work or pleasure", "doing household chores", "participating in social activities", "exercising moderately", and "study drug helping more normal life". Taken together, these results imply that quality of life improves gradually over time with givosiran▾.

Among all patients combined, adverse events (AEs), serious AEs, and severe AEs occurred in 96%, 30%, and 29% of patients, respectively.[30] The most common treatment-related AEs were injection-site reactions (29%), nausea (20%), and fatigue (13%).[30] Serious AEs included increased homocysteine, CKD, device breakage, pyrexia, and urinary tract infection (each 2%).[30] AEs led to treatment discontinuation in 3% of patients, and there were no deaths by the 24-month interim analysis. Hepatic AEs, which were reported in 18% of patients, were mild to moderate in severity.[30] Renal AEs (mostly increased blood creatinine and/or decreased estimated glomerular filtration rate [eGFR]) were reported in 22% of patients, but none led to treatment discontinuation.[30] Small decreases in eGFR observed early in therapy stabilised over Months 12–24.[30] However, patients on givosiran▾

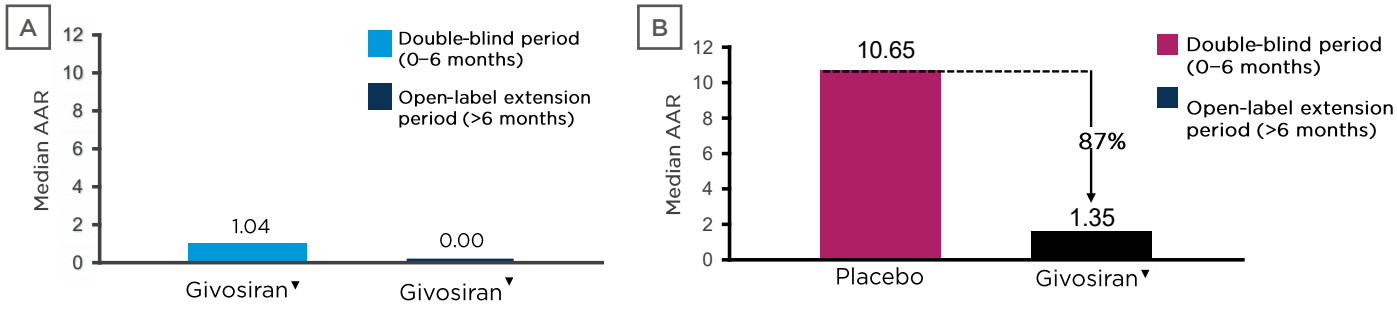

Figure 3: Reductions in annualised attack rate* with givosiran among A) patients who received givosiran during the double-blind and open-label periods and B) those who received placebo during the double-blind period and givosiran during the open-label period (descriptive analyses).[30]

*Attacks that required hospitalisation, urgent healthcare, or at-home haemin administration per year.

†Placebo crossover patients receiving givosiran 2.5 mg/kg (n=29) or 1.25 mg/kg (n=17).

AAR: annualised attack rate.

should be monitored for transaminases and creatinine/eGFR.[5,28]

Overall, these long-term results from ENVISION show that givosiran▾ treatment provided sustained reductions in attack rates for up to 24 months, with reductions in haemin use and improvements in quality of life. The safety of givosiran▾ during the open-label phase[30] was consistent with that during the double-blind phase.[29]

In summary, AHP remains challenging due to low disease awareness,[4] delayed or misdiagnosis,[3,7,8] and limited treatment options,[1,3] meaning that there is an unmet medical need in patients with AHP. Gastroenterologists can play a vital role in the diagnosis and management of AHP, making them well positioned to identify the hallmark symptoms of AHP and facilitate diagnosis and management. Lastly, the long-term management of AHP with givosiran▾ has been shown to lead to a sustained reduction in porphyria attacks and improve quality of life.[30]

Questions and Answers

Is urinary ALA and PBG a test that is standardised and available in all university hospital laboratories?

These tests are usually available in university hospitals, but are not necessarily available in primary care or outpatient gastroenterology. These urine tests are very important for the differential diagnosis of abdominal pain, but it is vital to keep the urine sample away from light. If physicians cannot find a laboratory to run these tests, the European Porphyria Network (EPNET) website has a list of diagnostic centres that can run the tests and to which patients with AHP can be referred. Of note, spot urine tests are easier for patients, but many laboratories use 24-hour urine testing. Similarly, quantitative testing is more reliable, but some laboratories only offer qualitative testing.

When should a patient with AHP start receiving givosiran▾?

This largely depends on local reimbursement criteria and the relevant givosiran▾ label.[5,28] However, the inclusion criteria for the studies indicate that patients with >2–3 attacks per year who require emergency treatment (e.g., with haemin) should be considered for givosiran▾. Patients who are recurrently hospitalised with abdominal pain are most likely to benefit. However, those with more chronic symptoms may also benefit, so could be considered for givosiran▾ treatment, depending on local reimbursement criteria. Currently, more evidence is needed to ascertain which patients are most likely to benefit from givosiran▾, and how long to continue treatment.

Can you discuss the reasons why patients are misdiagnosed or experience delayed diagnosis?

The main reason is the non-specific nature of AHP symptoms. Various diseases can cause recurrent abdominal pain and neurological symptoms in the CNS, PNS, or ANS (Figure 1). However, recurrent abdominal pain that warrants an ED visit and occurs with neurological symptoms, paraesthesia, muscle weakness, and dark (reddish) urine should raise suspicion for AHP. However, as AHP is very rare, many patients get misdiagnoses of endometriosis or gastrointestinal motility issues. Awareness of AHP therefore needs to be improved, and if imaging, endoscopies, and blood tests all come back negative, porphyria should be considered.

What are the most common symptoms besides abdominal pain, and is abdominal pain also present when patients are not experiencing acute attacks?

Severe abdominal pain is common during acute attacks, but not otherwise. Additional symptoms can include autonomous neuropathy, neuropathic pain, and muscle weakness. Patients may also develop chronic renal insufficiency, liver lesions, hypertension, paraesthesias, and neuropathy. Of note, patients without acute attacks may also develop these chronic problems. Patients with AHP often go through phases of symptom severity (Figure 2), and this should raise suspicion of AHP, especially when pain is combined with neurological manifestations.

How are patients with a lower frequency of attacks managed?

Patients with an acute attack are treated with haemin, analgesics (e.g., morphine), and/or glucose infusions/supplements. Patients are also advised to avoid triggers (e.g., fasting, alcohol, menses, certain medications, and infections). Those with frequent attacks (every month or more) may also require other treatments, e.g., givosiran▾. Regarding medications to avoid, these tend to include those that are metabolised by enzymes that require haem. Drugs can be checked on websites such as the American Porphyria Foundation.

Can you treat pregnant females with givosiran▾?

There are not yet any data on givosiran▾ use during pregnancy, but this will likely become available over time.

How often can you get a false negative diagnosis?

Urine testing for PBG and ALA is very specific, so highly elevated levels can be used to diagnose AHP with a high degree of certainty. Patients with only slightly elevated levels should have the test repeated during an attack. Errors in sample handling (e.g., urine not kept protected from light) could also affect the measurement. False negatives are very unlikely if urine is collected during an attack, but can occur between attacks. In patients with AIP, if the interval between the attack and the test is too long, the cut-off of 3–5 times the upper limit of normal may not be seen.

Would you prescribe givosiran▾ to a patient with kidney disease?

Renal function declines over time in patients with AHP, so kidney disease is somewhat inherent, making it challenging to assess whether there is any renal toxicity related to givosiran▾. Patients with kidney disease can be treated with givosiran▾, but their renal function should be monitored even though there are no data to show that givosiran▾ worsens the normal renal function decline seen in patients with AHP. However, patients with eGFR <30 mL/min/1.73 m^2 were excluded from the ENVISION study,[29] so data in such patients are not available.

During the ENVISION study, did any patients drop out? If so, what was the reason?

One patient dropped out during the double-blind period as their alanine aminotransferase increased to >8 times the upper limit of normal while on givosiran▾. Some patients had smaller rises in transaminases (approximately 3–5 times the upper limit of normal), which resolved spontaneously over time. However, it is important to monitor the renal and liver function of patients on givosiran▾. Of note, porphyria can cause elevated liver enzymes, with abnormalities visible on ultrasound. It would be interesting to see whether givosiran▾ can help to avoid this.

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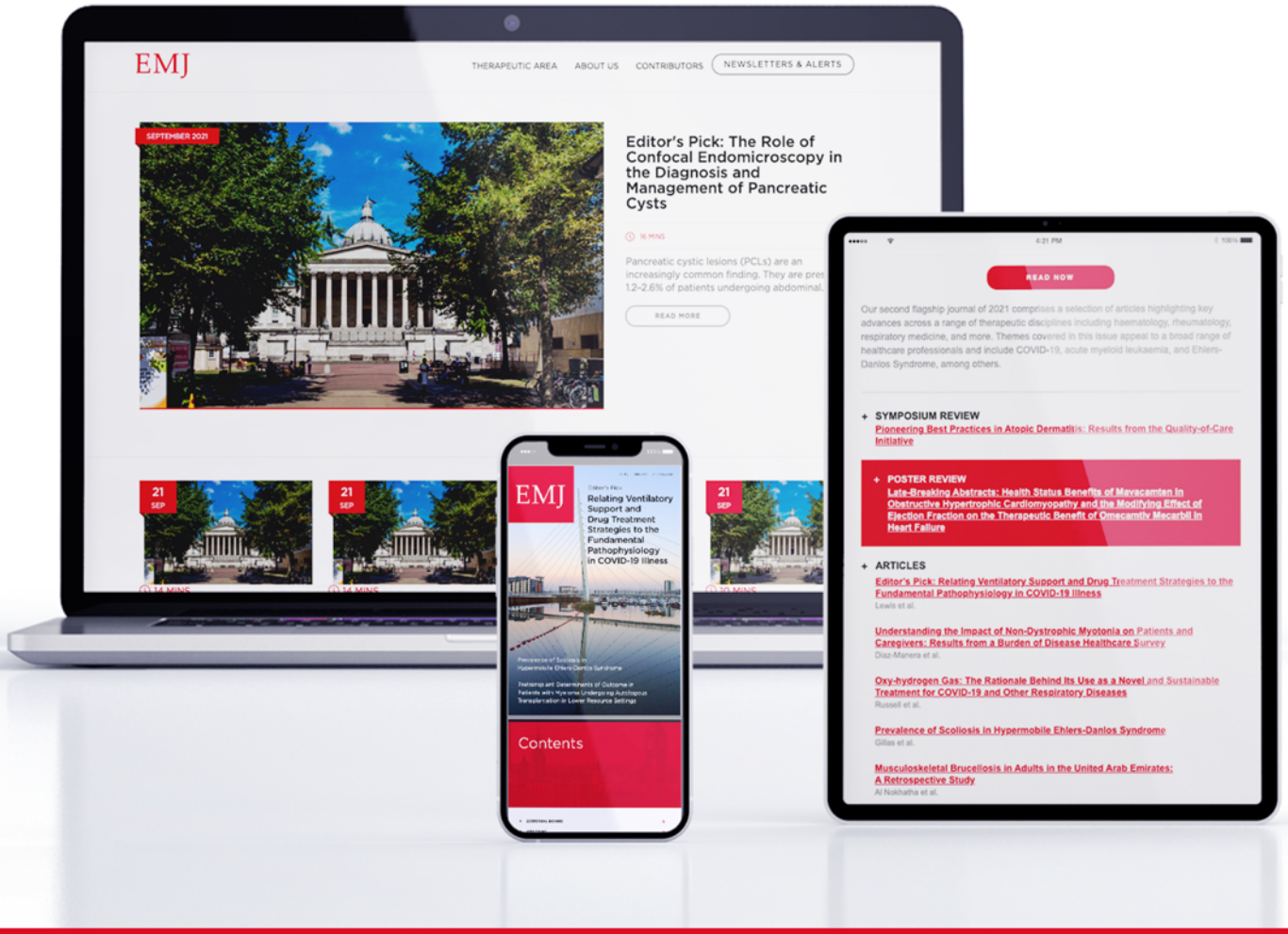

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Faecal Microbiota Transplant in the Treatment of *Clostridioides difficile* Infection: An Update

EDITOR'S PICK

The Editor's pick, by Moore-Gillon et al. delivers an insightful update on the evidence base studying the utilisation of faecal microbiota transplant (FMT) in the treatment of *Clostridioides difficile* infection. Discussing capsulised FMT and the 'next-generation' of FMT products, this study provides a forward-thinking approach towards the latest initiatives on offer and the associated challenges within this specialty.

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Abstract

Clostridioides difficile infection (CDI) presents a major global healthcare challenge. Recurrent/refractory disease is particularly hard to manage, and novel therapeutic strategies have recently been adopted. In particular, within the past decade, faecal microbiota transplant (FMT) has rapidly progressed from a 'potential' treatment option of fringe interest to one of the global mainstays of therapy for recurrent/refractory CDI. The first randomised study of its use for this indication was published as recently as 2013, but the emergence of subsequent randomised studies has led to its rapid adoption into guidelines and treatment algorithms. Very rare but serious reports of infection transmission from donor to recipient have resulted in ongoing refinements to donor screening, including the adoption of routine screening for intestinal carriage of multidrug resistant bacteria and severe acute respiratory syndrome coronavirus 2 status. Developments in the evidence base have given new insights into optimal recipient selection and preparation. Upper and lower gastrointestinal administration of FMT slurry are safe and effective in treating recurrent or refractory CDI, although the newer option of capsulised FMT has recently grown in popularity. The 'next generation' FMT products of defined microbial communities derived from donor stool are in late phase clinical trials and may become licensed for use in the near future. While different regulatory structures for FMT use have been adopted in different countries, the development of international networks of FMT-interested specialists has helped to harmonise best practice.

INTRODUCTION

Clostriodioides difficile infection (CDI) remains globally one of the major causes of hospital-acquired infection,[1] with almost half a million cases occurring annually in the USA alone.[2] Over the past two decades, several interrelated global changes in the pattern of CDI have made it particularly challenging to treat, including rising rates of metronidazole failure,[3] the emergence of hypervirulent strains (particularly B1/NAP1/027),[4] and rising rates of CDI recurrence. Specifically, the risk of recurrence within 8 weeks following treatment for primary CDI is up to 25% and rises as high as 65% for patients experiencing further recurrences.[5]

As such, there has been a major need for the development of novel therapeutic approaches to the condition, particularly for recurrent or refractory CDI (rCDI). While a vancomycin taper has been a well-established standard of care for this, there is also now evidence for the use of fidaxomicin (a novel macrocyclic antibiotic)[6] and bezlotoxumab (an anti-toxin B monoclonal antibody),[7] both of which reduce recurrence risk compared with vancomycin. However, neither of these treatments completely fill the therapeutic gap. For instance, concerns exist with fidaxomicin regarding its expense, limited evidence in treating CDI with severe colitis, and apparent limited efficacy in treating B1/NAP1/027 disease.[6]

Antibiotic use is well-established as the major risk factor for CDI, with antibiotic-mediated perturbation of the gut microbiome facilitating the colonisation of the distal gut by *C. difficile*, from which it can undergo growth, toxin production, and cause disease.[4] If such disruption of the gut microbiome precipitates CDI, then restitution of the microbiome back to pre-morbid composition and functionality is an attractive therapeutic strategy. The first randomised trial investigating the use of faecal microbiota transplant (FMT) in the treatment of rCDI was reported in 2013, comparing rates of disease resolution in patients treated with fresh FMT administered via nasoduodenal tube compared with those receiving either vancomycin alone or vancomycin and bowel lavage.[8] This trial was stopped prematurely on ethical grounds as rates of resolution at an interim analysis were significantly higher in those in the FMT arm than those in the vancomycin arms; reported side effects consisted principally of self-resolving gastrointestinal (GI) or systemic symptoms.[8] Other randomised studies that quickly followed demonstrated similarly impressive safety and efficacy profiles when donor FMT was used to treat rCDI via nasogastric tube,[9] enema,[10] and colonoscopy.[11,12] Subsequent studies demonstrated improved efficacy rates when healthy donor FMT was used compared with 'autologous' FMT,[13] and that FMT produced higher remission rates than vancomycin.[14] Systematic review and meta-analysis has been helpful for collating the published clinical data on FMT for rCDI, with a recent study estimating a number needed to treat compared with vancomycin of 2.9 for a single FMT and 1.5 for repeat FMT.[15]

In the UK, these randomised trials and other supportive studies have led to the adoption of FMT as a recognised treatment for rCDI in guidelines from Public Health England (PHE),[16] the National Institute for Health and Care Excellence (NICE),[17,18] and joint guidelines from the British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS).[19,20] European, American, and other international consensus guidelines have also been published.[21-23]

The authors present an overview of current best practice in the use of FMT for the treatment of rCDI.

FAECAL MICROBIOTA TRANSPLANT DONOR RECRUITMENT AND SCREENING

The recruitment and retention of donors of healthy stool is central to a safe and effective FMT pathway. A recent multicentre study found that both social norms and logistics may be significant barriers to donation.[24] Education on the benefits of FMT to others has been shown to encourage donation. Remuneration is also a motivating factor, a practice that is common in certain settings (including North America) but not currently in the UK and Europe.[24,25]

Potential donors are initially screened via either interview or a questionnaire, which covers basic demographic information. If they remain eligible, the next step is a more detailed medical assessment, looking at personal and family

history in particular; this focuses on the wide range of both GI and non-GI conditions related to the gut microbiome, as well as risk factors for transmissible diseases (e.g., risk factors for blood-borne viruses). In general, donors should be between 18–60 years old and have a BMI within the healthy range; however, the recent use of antibiotics (typically within 3 months) is a common reason for exclusion.[20] There is also a low threshold for exclusion of potential donors with a history of medical conditions clearly related to the gut microbiome, such as inflammatory bowel disease (IBD). Furthermore, given the association between a growing number of non-GI diseases (including metabolic, rheumatological, and neurological conditions) and perturbation of the gut microbiota, potential donors with a history of any such conditions are also excluded.[22] Further health questionnaires are normally used at the point of each donation (e.g., regarding recent acute illness or travel to areas with endemic GI infection that may contraindicate donation).

There has been some debate about the use of related versus unrelated donors. While it is generally accepted that both may be safe and effective,[26,27] most guidelines suggest that the use of a healthy, unrelated donor is preferable.

A significant risk related to FMT is the transmission of potential pathogens from donor to recipient. There are strict guidelines on laboratory screening of potential donors, though these may vary between regions (Table 1).[20] With certain blood tests, such as Epstein-Barr virus and cytomegalovirus serology, some authorities recommend that these are only strongly indicated if the likely recipient is immunocompromised.[20]

The frequency of re-testing potential donors depends on the FMT method. As discussed below, the use of banked frozen samples over fresh samples is now strongly recommended in most territories, in part due to the need for fewer and less frequent donor screenings, increasing convenience for donors and reducing cost for centres. With frozen FMT, donors will typically donate regularly for a defined period of time, with health questionnaires and full serology and stool screening at the start, and repeated at the end, of the donation period ('bookending'). FMT prepared during these periods of screening is held in 'quarantine' until both screens are clear and the FMT can be safely released for clinical use. In centres still using fresh FMT, regular donor laboratory screening (with a further health questionnaire at the time of each donation) has been suggested; however, this clearly has an inferior safety profile compared with frozen FMT, as the material is likely to be administered before the extensive laboratory screen can be completed.

A number of clinical reports of FMT-related transmission of infection have been described, which have resulted in adaptation and modification of FMT donor screening protocols.[28] There have been recent concerns about FMT-related transmission of multidrug resistant bacteria, with two cases of extended-spectrum β lactamase (ESBL)-producing *Escherichia coli* bacteraemia occurring in separate clinical trials, albeit both from the same stool donor.[29] One of these cases was fatal. At the time of donation, screening for ESBL-producing organisms was not mandated by the U.S. Food and Drug Administration (FDA), although screening for these (as well as other multidrug resistant bacteria) was subsequently advised.[30] Consistent with this, guidelines produced since 2018 have recommend ESBL and carbapenemase-producing *Enterobacteriales* CPE stool screening universally.[20] In 2020, four cases of Shiga toxin-producing *E. coli* infections were reported in the USA, again from a single donor.[31] The stool had been screened for Shiga toxin-producing *E. coli* with enzyme immunoassay, with a negative result, but was later found to be positive on nucleic acid amplification testing (NAAT), a more sensitive method.[32] The FDA now mandates NAAT for future screening, and BSG and HIS guidelines already specify the use of PCR, a form of NAAT.[20]

Furthermore, the COVID-19 pandemic has introduced new challenges to donor recruitment and screening. Collection of FMT donor samples was postponed in many regions at the height of the pandemic, with the 'shelf life' of previously frozen samples being extended to enable continued treatment. As FMT has been deemed a vital procedure, rapid updates and adjustments to guidelines have been made to adapt to the pandemic.[33,34] Risk assessment has been updated to assess for exposure to COVID-19, and nasopharyngeal swabbing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was also recommended.[33] However,

Table 1: Laboratory screening protocol for faecal microbiota transplant donors.[20,22,23,24]

Category	Laboratory tests	Comments
Blood screening	• Full blood count with differential	• Epstein-Barr virus and cytomegalovirus testing is more strongly recommended if the likely recipient is immunosuppressed and at risk of severe infection.
	• Renal profile	
	• Liver enzymes	
	• C-reactive protein	
	• HIV-1 and HIV-2 antibodies	
	• Hepatitis A, B, C and E screening	
	• HTLV-1 and HTLV-2 antibodies	
	• *T. pallidum* antibodies	
	• *S. stercoralis* IgG	
	• *E. histolytica*	
	• Epstein-Barr virus	
	• Cytomegalovirus	
	• SARS-CoV-2 serology	
Stool screening	• Typical enteral pathogens – *Campylobacter*, *Salmonella*, *Shigella*, Shiga toxin-producing *E. coli* PCR	• PCR testing, rather than EIA, is used due to higher sensitivity where possible, e.g., for Shiga toxin-producing *E. coli* • CPE and ESBL screening are mandatory; VRE and MRSA screening may also be appropriate, depending on local prevalence
	• *C. difficile* PCR	
	• *H. pylori* antigen	
	• Multidrug resistant bacteria, including CPE and ESBL	
	• *Cryptosporidium*, *Giardia*, *Cyclospora*, and *Isospora*: options include PCR, antigen, or microscopy	
	• Norovirus and rotavirus PCR	
	• SARS-CoV-2	
	• Ova, cyst, and parasite analysis	
Other tests	• SARS-CoV-2 nasopharyngeal swab	

Adapted from previously published guidelines.

C. difficile: *Clostridioides difficile*; CPE: carbapenemase-producing *Enterobacteriales*; *E. coli*: *Escherichia coli*; ESBL: extended-spectrum β-producing lactamase; *E. histolytica*: *Entamoeba histolytica*; EIA: enzyme immunoassay; *H. pylori*: *Helicobacter pylori*; HTLV: human T-lymphotropic virus-1; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; MRSA: methicillin-resistant *Staphylococcus aureus*; *S. stercoralis*: *Strongyloides stercoralis*; *T. pallidum*: *Treponema pallidum*; VRE: vancomycin-resistant *Enterococci*.

recognising that SARS-CoV-2 may be detectable in stool,[35] guidelines were updated further, to strongly recommend that molecular stool testing should be carried out where possible. There is some evidence that this may be the best way of reducing the risk of transmission,[36] and validated assays have recently been approved,[37] facilitating the resumption of FMT services. The response to the COVID-19 vaccination programme is not yet entirely clear, but as the current validated vaccines do not use a live attenuated virus, it has been suggested there is no risk of transmission from vaccinated donors.[38]

WHEN TO CHOOSE FAECAL MICROBIOTA TRANSPLANT AS A TREATMENT FOR *CLOSTRIODIOIDES DIFFICILE* INFECTION

Despite some small studies investigating the use of FMT as a treatment for primary

episodes of CDI,[39,40] it is widely accepted that antimicrobial therapy remains the mainstay of treatment in this scenario.

As outlined above, current guidelines recommend that the major indication for FMT is in recurrent or refractory CDI, provided that there has already been previous treatment with 'standard of care' therapies (i.e., vancomycin or fidaxomicin).[20,22] There are no data definitively stating how many recurrences after treatment with antimicrobials are required before FMT merits consideration in CDI, but UK guidelines recommend considering FMT after two recurrences or one recurrence with risk factors for further episodes.[20] While there is no uniform definition of success or failure after FMT for rCDI, published guidelines have strongly recommended that repeat FMTs are indicated where a single FMT alone does not cause disease remission.[20,22]

There are few absolute contraindications to FMT, although anaphylaxis or severe allergic food allergy is often included in this list. One option in this scenario may be patient-directed selection of a stool donor on a diet avoiding any potential food allergens; similarly, a donor on a gluten-free diet may be appropriate for a recipient with coeliac disease.[20] Pregnancy and lactation may be viewed as relative contraindications. While earlier small retrospective studies had suggested a risk of an IBD flare when FMT was administered to patients with IBD and super-added CDI, a recent prospective study of FMT in this scenario did not corroborate this.[41,42] Despite initial concerns about bacterial translocation and risk of sepsis when FMT was administered to patients with cirrhosis and CDI, more recent data demonstrate that it is safe and effective in this setting.[43] There appears to be no additional risk associated with the use of FMT to treat rCDI when administered to patients who are immunocompromised.[44,45]

The largest study reported on FMT in children to date is from a multicentre retrospective cohort study of 372 patients receiving FMT for CDI.[46] CDI resolution after one or two FMTs was >80%, and adverse events were, overall, comparably modest to those occurring in adults who receive FMT. In a joint position paper from North American and European paediatric gastroenterologists, the use of FMT was recommended in children with CDI for similar indications to those in adults.[47]

ROUTES OF FAECAL MICROBIOTA TRANSPLANT ADMINISTRATION

Conventionally, FMT administration routes were principally categorised into upper GI (nasoduodenal/nasogastric tube, or gastroscopy) or lower GI (colonoscopy, flexible sigmoidoscopy, or enema). Systematic review and meta-analysis has demonstrated that enema appears to be the least efficacious route for a single administration; lower GI and upper GI administration appear to be of comparable efficacy, with colonoscopy being the single most effective route of administration.[15] The potential discrepancy in efficacy between upper and lower GI routes is less relevant in the context of multiple infusions, where efficacy rates of different routes are comparable.[15] Other considerations for a preferred route of administration may be practical. For instance, colonoscopy may be desirable in particular circumstances for allowing endoscopic assessment of the large bowel, while nasogastric tube may be more pragmatic for patients who are older and frailer, and who may not tolerate endoscopic procedures.

An alternative route of delivery to these conventional methods is capsulised FMT, whereby the faecal matter is delivered via oral capsules; this can either be in the form of capsulised frozen slurry or as lyophilised material. In the largest randomised controlled trial exploring capsulised FMT in the treatment of rCDI to date, capsules demonstrated similar efficacy to colonoscopy in terms of successful prevention of rCDI (>95%) in both patient groups.[48] Capsule administration eliminates the need for invasive procedures and potential complications secondary to these. However, different centres using capsules have prepared them using different methodologies, and a 'dose finding' exercise might be required to find the balance between a threshold number of capsules to successfully treat most cases of CDI versus an acceptable capsule burden to ingest.

Depending on which route is used, patient preparation varies prior to the procedure. Irrespective of route of delivery, a further course of anti-CDI antibiotics (with a washout period just prior to FMT administration) is recommended. Bowel lavage (e.g., with polyethylene glycol) may help to reduce *C. difficile* burden further and remove residual antimicrobials. For upper

GI administration, many centres recommended proton pump inhibitors and pro-kinetics prior to administration.[20] Anti-motility drugs (i.e., loperamide) may be considered after lower GI administration to aid retention.

STOOL BANKING AND REGULATION

An evolution in FMT protocols has been the widespread use of frozen faecal material that can be prepared from screened donors in advance of a planned FMT and thawed, transported, and administered when treatment is required (commonly using glycerol as cryopreservative). A non-inferiority randomised controlled trial demonstrated no significant difference in safety or in efficacy between fresh and frozen FMT, and frozen FMT[10] confers a number of logistical advantages as discussed above. This has resulted in a trend towards a shift from FMT services operating as small, local centres towards centralised stool banks, where expertise, traceability, and standardised procedures translates into increased safety and quality control of the production.[49] This ultimately has allowed the development of 'hub and spoke' FMT network arrangements, allowing FMT treatment to be available at centres that would otherwise have been limited due to lack of facilities and resources.[22]

The development of stool banks has also been helpful from the perspective of developing standardised pathways for co-ordinating an FMT service, from which clinical experience can be shared between interested parties internationally. However, challenges still remain with regard to aspects related to FMT regulation and governance of FMT services. In the UK, FMT is regulated as an unlicensed medicinal product by the Medicines and Healthcare Products Regulatory Agency (MHRA), and best practice regarding manufacturing, production quality control, and donor screening governance has been defined in national guidelines.[20] In contrast, in other countries, FMT has been regulated as a tissue or transplant material.[22,23] Within certain regions, national FMT registries have been established, providing a useful tool for audit and research.[50,51]

The largest stool bank globally has been OpenBiome, based in Boston, Massachusetts, USA. Recently, the large stool bank in Birmingham, UK (Microbiome Treatment Centre), published their FMT methodology, which received licensing in accordance with the MHRA guidelines for the production and distribution of FMT as a medicinal product. This has been fundamental in extending the reach of this treatment within the UK National Health Service (NHS), as well as providing a validated framework for implementation across other countries.[52]

OUTSTANDING ISSUES, NEXT STEPS, AND CONCLUSIONS

Despite the clear efficacy of FMT in the treatment of rCDI, there are several remaining uncertainties related to its use. For example, concerns have been raised about the relatively small size of randomised trials published and limited follow-up before FMT reached widespread adoption, especially when this therapy lacks standardised dosing or formulation and well-defined mechanism of action, which are required for the introduction of other therapeutics.[53] The emergence of longer-term patient follow-up data after FMT for rCDI has helped to alleviate some of these concerns.[54] There remain gaps in knowledge related to mechanism of action, although progress has been made in this area too (Figure 1).[55,56] There is also a theoretical concern about gut microbiota 'traits' being transmitted from donor to recipient (e.g., an increased risk of developing IBD in the future), although there has been no conclusive demonstration of such an occurrence.

While the development of capsulised FMT has helped to avoid some of the drawbacks associated with FMT use (e.g., invasive administration of slurry), it does not avoid all of the drawbacks. There is considerable interest in 'microbial therapeutics' and 'next generation' FMT products. Recently, there have been reports of initial results of two microbiome-based therapeutic products used in clinical trials for rCDI, including a Phase III study of a spore-based therapy (SER-109) undertaken by Seres Therapeutics (ECOSPOR III study; Cambridge Massachusetts, USA), and a Phase II study of a 'whole microbiome' investigational product from Finch Therapeutics (CP101; PRISM3 trial; Somerville, Massachusetts, USA).[57] Both products met efficacy endpoints. Should these products reach clinical endpoints

Figure 1: Mechanisms of efficacy of faecal micriobiota transplant in the treatment of recurrent *Clostridioides difficile* infection.

C. difficile: *Clostridioides difficile*; FMT: faecal microbiota transplant.

in larger studies, it seems likely that there will be a strong case for consideration of their licensing, which may require further evaluation of their cost, accessibility, and other issues.[58]

Another challenge for FMT more generally is its use beyond the remit of rCDI. Given the increasing number of medical conditions associated with perturbation of the gut microbiome, there is great enthusiasm for trialling FMT in the management of a range of different conditions.[55] While there are signals of clinical interest for the use of FMT for non-CDI indications (including for the induction of remission in mild to moderate ulcerative colitis, or transient improvement in insulin sensitivity in metabolic syndrome),[28,55] there has not been a comparable level of durable clinical benefit observed as that seen in rCDI. As understanding of the contribution of the gut microbiome to these conditions expands, there may be an opportunity for more nuanced application of FMT or other microbial therapeutics, taking into consideration donor and recipient factors in more detail.[59]

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Factors Associated with Venous Thromboembolism in Acute Pancreatitis: A Population-Based Cohort Study

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Abstract

Background: There is limited literature and a lack of practical guidelines regarding venous thromboembolism (VTE) in patients with acute pancreatitis (AP). The aim of this report is to estimate the prevalence and risk factors of deep vein thrombosis and pulmonary embolism in hospitalised patients with pancreatitis and to evaluate its impact on clinical outcomes.

Methods: A retrospective chart review of patients admitted with AP between 2005 and 2015 was performed. Patients with a secondary diagnosis of VTE were identified. Prevalence and risk factors for VTE development were recorded. The in-hospital mortality rate and length of stay of patients with AP and coexistent VTE was compared with their counterparts without thrombosis. Descriptive statistics and univariate and multivariate analyses were applied where appropriate; $p<0.05$ was considered statistically significant.

Results: The medical records of 50,564 patients with AP were analysed, with 258 patients (0.5%) presenting concurrent VTE. Factors associated with the development of VTE were length of stay, peripheral arterial disease, malnutrition, and Atlanta systemic complications. Patients with AP and coexistent venous thrombosis showed a significantly higher risk of death (odds ratio: 2.4; 95% confidence interval: 1.51–4.10) and length of stay (22.4 days versus 10.0 days; $p<0.001$) compared with subjects without thrombosis.

Conclusions: Patients with AP and concurrent thrombosis stay longer in the hospital and have more than a two-fold increase in mortality when compared to the non-thrombotic group.

INTRODUCTION

Acute pancreatitis (AP) is an inflammatory condition of the pancreas that represents one of the most common gastrointestinal cause for hospital admission in high-income countries.[1,2] Many European and North American studies have reported a median hospital cost of nearly 7,000 USD per hospitalisation[3,4] and 2.6 billion USD per year.[5,6] The annual incidence has gradually increased during the past decade. Recent data show that AP incidence varies between 4.9 cases and 73.4 cases per 100,000 worldwide.[7,8] Gallstone disease (45%) and a history of excessive alcohol consumption (20%) are the two leading causes of AP.[9-11] Pancreatitis clinical outcome is often unpredictable. According to the revised Atlanta classification,[12] the severity of AP can be defined as mild, moderately severe, or severe. Most patients run a benign self-limited course and can be discharged within 1 week of admission. However, up to 20% develop local (peripancreatic fluid collections, pseudocysts, pancreatic, or peripancreatic necrosis) and/or systemic inflammatory disease (respiratory, cardiovascular, or renal failure), resulting in complications that pose potential serious problems.[13] The overall mortality in patients with AP is 3.5%, while patients with severe AP have a substantial mortality rate of 14–40%.[1,2,14,15] Some authors claim that the incidence of early death (within 14 days after admission) does not significantly differ from that of late death (>14 days), organ failure being the cause of death in the early phase (regardless of the presence of necrosis) and infection of pancreatic or peripancreatic necrosis being responsible for mortality in the late phase.[16]

Vascular disturbances account for 25% of systemic complications in patients with AP, including haemorrhage following an arterial erosion, pseudoaneurysms, and venous thrombosis.[17] Although splanchnic vein thrombosis is frequently related to pancreatitis,[18-20] deep vein thrombosis (DVT), with or without concurrent pulmonary embolism (PE), in the setting of AP is a rare complication, where incidence remains unknown. As a preventable condition, venous thrombosis prompts a growing interest in AP. The aim of this study is to estimate the prevalence and risk factors of venous thromboembolism (VTE) in AP and to evaluate its impact on clinical outcomes in hospitalised patients with pancreatitis.

MATERIALS AND METHODS

A retrospective chart review of consecutive patients with AP as the primary reason for discharge was performed. The authors identified every patient discharged from an internal medicine department from hospitals in the Spanish Public Health Service (SPHS) between 1st January 2005 and 31st December 2015.

Hospital discharge data were obtained from the Basic Minimum Data Set (BMDS), which is a compulsory registry for each patient admitted to a hospital in the SPHS, a system that cares for more than 90% of the country's population. As these data are neither identifiable nor private, no institutional review board approval was required. All centres are requested to submit this information to the Spanish Health Ministry. BMDS contains socio-demographic and clinical data for every hospital discharge including gender, age, and, primary and secondary diagnoses, according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code, primary and secondary procedures, admission and discharge status, inpatient stay from the time of admission to discharge, and hospital characteristics (<200 beds, 200–500 beds, 500–1,000 beds, and >1,000 beds).

Patients were selected if they were discharged with the principal diagnosis of AP (ICD-9-CM: 577.00). Patients who had a secondary diagnosis of thromboembolic disease (PE ICD-9-CM: 415.10, 415.11, 415.19; deep venous thrombosis ICD-9-CM: 451.20, 451.81, 451.90, 453.40, 453.41, 453.42, 453.80, 453.90) were analysed.

The following exclusion criteria were used: patients with a previous diagnosis of cancer (ICD-9-CM: 140.00–172.90, 174.00–195.80, 200.00–208.90, V10.00–V10.90), inflammatory bowel disease (ICD-9-CM: 555.00–556.xx), cirrhosis (ICD-9-CM: 572.20–578.00, 456.00–456.29), and a median length of stay less than 2 days.

Definitions

Aetiological factors for acute pancreatitis

Cholelithiasis or choledocholithiasis (gallstone related): ICD-9-CM 574.x0 and 574.x1. Alcohol related: ICD-9-CM 291.xx, 303.xx; 305.0x; 760.71. 980.00, 357.50, 425.50, 535.30, 535.31, 571.00–571.30.

Complications

The grading of the severity in AP has undergone significant recent changes.[12,21] In the present study, disease severity was stratified as described in the Atlanta classification[22] because it reflects the criteria used in the medical reports and discharge files during the period of the study. Severe AP was defined by the presence of local complications (fluid collections or pancreatic necrosis) and/or organ failure including shock, renal or respiratory failure, or digestive haemorrhage. In the authors' study, other conditions linked to a poor outcome were also considered as complications during admission.

In order to describe the complications as mentioned above, the authors identified the following ICD-9-MC codes that presented in any secondary diagnosis field in the discharge medical reports: acute respiratory failure (ICD-9-CM: 518.82–518.84), acute renal failure (ICD-9-CM: 403.11, 403.91, 404.12, 585.00–586.00), pneumonia (ICD-9-CM: 480.00–486.00; 003.22, 507.00, 510.00, 510.90, 513.00), bronchoaspiration (ICD-9-CM: 507.00), hypoglycaemia (ICD-9-CM: 251.00–252.00, 250.30–251.00, 250.80–251.00, 249.80–249.81), decubitus ulcer (ICD-9-CM: 707.xx), urinary tract infection (ICD-9-CM: 599.00, 590.xx, 646.60–49, 601.00), sepsis (ICD-9-CM: 531.00–536.00, 537.83, 530.20, 530.82, 038.xx, 995.91, 995.92), gastrointestinal bleeding (ICD-9-MC: 530.21, 530.82, 531.00–535.00, 531.00–535.01, 531.00–535.20, 531.00–535.21, 531.00–535.40, 531.00–535.41, 531.00-535.60, 531.00-535.61), shock (ICD-9-CM: 785.50–785.59), and malnutrition (ICD-9-CM: 260.00–263.90). The presence or absence of complications has been shown in three different ways. Firstly, a composite item including 'Complications', if any complication is present. Secondly, a composite variable named 'Atlanta', which includes two or more complications linked to severe AP according to the 1992 Atlanta consensus (namely, acute kidney failure, acute respiratory failure, gastrointestinal bleeding, and shock), and finally, every complication in a separate display.

Comorbidity

The Charlson Comorbidity Index (CCI)[23] was computed for each patient. This index illustrates the number and relevance of comorbid diseases. It has been used in the present study to adequately depict the presence of additional co-occurring disorders, and thus appropriately adjust the results for the presence of diseases coexisting with AP and VTE that may affect mortality. CCI predicts the 10-year mortality for a patient who may have a range of comorbid conditions. Each condition is assigned a score of 1, 2, 3, or 6, depending on the risk of dying associated with each one. Results provide a total score of 0–37 to predict mortality. A grade higher than 2 is related to a mortality rate >50% per year. Clinical conditions and associated scores are as follows:

- 1 each: myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, ulcer, chronic liver disease, or diabetes.
- 2 each: hemiplegia, moderate or severe kidney disease, diabetes with end organ damage, tumour, leukaemia, or lymphoma.
- 3 each: moderate or severe liver disease.
- 6 each: malignant tumour, metastasis, or AIDS.
- Length of hospital stay: mean hospital stay was defined as the number of days that each patient spent at the medical centre.
- In-hospital mortality: patients who died during admission were recorded. Deaths that might have occurred after a patient's discharge were not measured as these data were not available for the investigators.

Statistical Methods

A descriptive analysis was carried out in patients with AP. The demographic variables among patients with or without thromboembolic disease were compared. The authors used the chi-square test for categorical variables with the Yates correction, the Fisher's exact test for dichotomous variables when the expected value of a cell was less than 5, and Student's t-test or analysis of variance (ANOVA) for quantitative variables. All

the univariate analyses were accomplished after having adjusted for age and gender. The odds ratios (OR) and 95% confidence intervals (CI) were estimated from the regression coefficients.

Univariate analysis was performed to identify variables associated with VTE in patients with PA and with mortality. A multivariate logistic regression analysis was performed to determine the independent effect of diagnosis of VTE on in-hospital mortality. Stratified analyses were performed to examine confounders and interactions. All statistical analyses were carried out with the Statistical Package for the Social Sciences (SPSS, version 16; IBM, Armonk, New York, USA).

RESULTS

There was a total of 50,564 discharges with a primary diagnosis of AP from 2005 to 2015. The average age was 63.4 years (standard deviation [SD]: 18.7 years; range: 17–104 years). Men accounted for 57.3% of the patients. The median hospital stay was 98 days (SD: 10.5 days; range: 2–357 days). A CCI >2 was present in 5.4% of the cases. The average cost was 4,519.8 EUR (SD: 5,049.9 EUR; range: 1,944.4–119,417.0 EUR). During admission, 7.3% of patients developed a severe AP as described in the Atlanta classification. All-cause mortality in patients with AP was 2.9%. A total of 258 patients (0.5%) were diagnosed as having concurrent VTE. Among patients with VTE, isolated DVT was found in 198 (76.7%), while PE alone was diagnosed in 54 (21%). Both DVT and PE presented simultaneously in 6 (2.3%) patients.

Within the study period, an increasing temporal tendency was seen in AP prevalence, from 3,926 (7.8%) cases in 2005 to 4,929 (9.7%) cases in 2015, although the statistical analysis failed to show a trend significance. VTE prevalence showed an irregular pattern throughout the period of study, varying from 0.2% to 1.0%, depending on the year. Similarly, variation in mortality prevalence ranged from 2.5% to 3.3% throughout the study interval, both without a significant trend.

In the univariate analysis, patients with AP and concurrent VTE had a significantly higher length of stay (22.4 days versus 10.0 days; p<0.001), There was also a higher percentage of peripheral arterial disease (9.3% versus 3.4%; p<0.001), and chronic obstructive pulmonary disease (21.7% versus 12.8%; p=0.002). Furthermore, the following complications were more frequently reported in patients who developed VTE: sepsis (5.0% versus 1.2%; p<0.001), pneumonia (3.1% versus 1.1%; p=0.014), malnutrition (7.7% versus 1.3%; p<0.001), acute renal failure (10.0% versus 5.2%; p=0.002), acute respiratory failure (10.8% versus 2.5%; p<0.001), systemic inflammatory response syndrome (1.5% versus 0.2%; p<0.005), and the presence of more than one systemic complication as defined in the Atlanta criteria (23.2% versus 11.0%; p<0.0001). In the multivariate logistic regression analysis, the demographic and clinical factors that were independent predictors of occurrence of VTE in patients with AP were length of stay, peripheral arterial disease, malnutrition, and the combination of two or more Atlanta systemic complications (Table 1).

Table 2 shows the covariates that were significantly associated with mortality in the univariate analysis. Patients who died were more frequently women (59.2% versus 42.1%; p<0.001) and older (82.8 years versus 62.4 years; p<0.001). Higher in-hospital mortality was also observed in patients with more comorbid conditions (CCI>2: 14.5% versus 5.1%; p<0.001), in participants with VTE (1.6% versus 0.04%; p=0.001), and in those who presented more AP-related complications such as shock (7.4% versus 0.4%; p<0.001), acute kidney failure (31.6% versus 4.5%, p=0.02), and acute respiratory failure (24.1% versus 1.9%; p=0.001).

A multivariate logistic regression analysis was performed to further assess which variables were independently associated with mortality (Table 3). The factors that remained as independent predictors of mortality in patients with AP were female gender (OR: 1.21; 95% CI: 1.08–1.36), age (10 years) (OR: 4.47; 95% CI: 4.06–4.93), CCI (OR: 1.50; 95% CI: 1.27–1.78), two or more Atlanta complications (OR: 5.06; 95% CI: 1.27–1.78), pneumonia (OR: 2.36; 95% CI: 1.78–3.11), systemic inflammatory response syndrome (OR: 6.14; 95% CI: 3.97–9.49), sepsis (OR: 4.76; 95% CI: 3.82–5.93), and VTE (OR: 2.48; 95% CI: 1.50–4.10). Overall, mortality in patients with AP was 2.9%; however, when analysed separately according to the presence of VTE, the results revealed that 7.5% of patients with AP and coexistent VTE compared with 2.9% of their counterparts without VTE died.

Table 1: Multivariate analysis of factors associated with venous thromboembolism in acute pancreatitis.

	OR	95% CI		p value
LOS	1.022	1.018	1.027	0.000
Peripheral arterial disease	2.452	1.573	3.822	0.000
Malnutrition	3.709	2.271	6.055	0.000
Atlanta*	1.602	1.165	2.203	0.004

*At least two systemic complications
CI: confidence interval; LOS: length of stay; OR: odds ratio.

Table 2: Univariate analysis of factors associated with mortality in acute pancreatitis.

	Death (n=1,471)	Non-death (n=49,093)	OR (95% CI)	p value
Gender (% female)	872 (59.2%)	20,705 (42.1%)	1.9 (1.7–2.2)	<0.001
Age, years (SD)	82.8 (10.7)	62.4 (18.6)		0.000
Comorbidity				
Hepatopathy (%)	48 (3.2%)	6,434 (13.1%)	0.22 (0.16–1.2)	<0.001
Diabetes (%)	343 (23.3%)	1,986 (18.7%)	1.3 (1.1–1.4)	<0.001
Dementia (%)	179 (12.1%)	1,106 (2.2%)	6.0 (5.0–7.1)	<0.001
CKD (%)	239 (16.2%)	2,407 (4.9%)	3.7 (3.2–4.3)	<0.001
COPD (%)	525 (35.6%)	5,997 (12.2%)	3.9 (3.5–4.4)	0.002
Alcohol intake (%)	73 (4.9%)	12,131 (24.7%)	0.15 (0.12–0.20)	<0.001
Obesity (%)	110 (7.5%)	4,532 (24.7%)	0.79 (0.65–0.96)	0.023
CCI>2 (%)	214 (14.5%)	2,530 (5.1%)	3.1 (2.6–3.6)	<0.001
Complications				
Biliary procedure (%)	55 (3.7%)	1,328 (2.7%)	1.3 (1.0–1.8)	0.020
Sepsis (%)	156 (10.6%)	466 (0.9%)	12.3 (10.2–14.9)	<0.001
Pneumonia (%)	82 (5.5%)	528 (1.0%)	5.4 (4.2–6.8)	<0.001
Broncho-aspiration (%)	73 (4.9%)	124 (0.2%)	20.6 (15.3–27.6)	<0.001
Malnutrition (%)	51 (3.4%)	654 (1.3%)	2.6 (1.9–3.5)	<0.001
Hypoglycaemia (%)	22 (1.4%)	324 (0.6%)	2.2 (1.4–3.5)	<0.001
Acute renal failure (%)	466 (31.6%)	2,217 (4.5%)	9.8 (8.7–11.0)	0.020
Acute respiratory failure (%)	355 (24.1%)	958 (1.9%)	15.9 (13.9–18.3)	0.001
Shock (%)	110 (7.4%)	223 (0.4%)	17.7 (14.0–22.3)	<0.001
Atlanta* (%)	722 (49.0%)	4,874 (9.9%)	8.74 (7.8–9.7)	<0.001
VTE (%)	24 (1.6%)	234 (0.04%)	3.46 (2.26–5.28)	<0.001

*At least two systemic complications.
CCI: Charlson Comorbidity Index; CI: confidence interval; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; OR: odds ratio; SD: standard deviation; VTE: venous thromboembolism.

Table 3: Multivariate analysis evaluating variables independently associated with in-hospital mortality in all patients with acute pancreatitis.

	OR	95% CI		p value
Gender (female)	1,216	1,083	1,366	0.001
Age (10 years)	4,478	4,064	4,935	0.000
CCI>2	1,506	1,273	1,781	0.000
Atlanta*	5,068	4,507	5,698	0.000
Pneumonia	2,369	1,786	3,115	0.000
SIRS	6,140	3,970	9,497	0.000
Sepsis	4,761	3,820	5,934	0.000
VTE	2,489	1,510	4,103	0.000

*At least two systemic complications
CCI: Charlson Comorbidity Index; CI: confidence interval; OR: odds ratio; SIRS: systemic inflammatory response syndrome; VTE: venous thromboembolism.

DISCUSSION

Despite improvements in diagnostic techniques, antibiotic therapy, surgical treatment, and critical care, AP is an unpredictable condition that continues to be associated with high mortality rates in severe cases, mainly related to organ failure and infection of pancreatic or peripancreatic necrosis.[14,15] Among vascular systemic complications, venous thrombosis is also associated with adverse outcomes in hospitalised patients with AP.[17,24] Following close anatomical ties with the pancreas, the most common venous vascular complication in pancreatitis involves the splanchnic veins including portal vein, splenic vein, and superior mesenteric vein, either separately or in combination.[19,20]

Portosplenomesenteric vein thrombosis may lead to portal hypertension, with high risk of gastrointestinal bleeding, bowel ischaemia, intra-abdominal haemorrhage, ascites, splenomegaly, and splenic infarction, among other complications[25-27] While splanchnic vein thrombosis is a well-known phenomenon in pancreatitis, VTE is a rare complication and is less commonly reported. To date, very little data is available on the prevalence of pulmonary and deep veins thrombosis in hospitalised patients with pancreatitis. Prior publications of VTE in the setting of AP are mostly case series reports[28-33] and two population-based analyses including information of inpatient databases similar to the authors' cohort study.[35,35]

In general population, both PE and DVT have an overall incidence of 0.1% per year, while PE and DVT inpatient incidence increases up to 0.4% and 1.3%, respectively.[1] In the present report, the prevalence of VTE among patients with AP was 0.5%. Previous analyses have stated different results depending on the patient selection. Studies including only patients suffering with necrotising pancreatitis have noted a significantly higher prevalence of DVT (16%)[37] while reports with all degrees of pancreatitis severity show a similar VTE prevalence as the one described in the authors' study and are in concordance with the prevalence in other hospitalised patients.[34]

The potential specific mechanisms that may account for the development of VTE in patients with pancreatitis remain unclear. Immobilisation in prolonged hospitalised patients, regardless of the reason for admission, is a recognised mechanism for venous stasis.[38] This condition has also been reported in patients with pancreatitis for, even in its mildest clinical presentation, patients admitted with AP stay up to 5 days in the hospital.[39,40] Several specific explanations have been proposed to elucidate the development of VTE in patients with AP. The systemic inflammatory response associated with pancreatitis induces endothelial damage at a microvascular level, resulting in a

pro-thrombotic state and making vascular events more likely.[33] Besides, the release of pancreatic proteolytic enzymes into the vessels may provoke a procoagulant state leading to venous thrombosis.[41] Furthermore, the mass effects from the surrounding inflamed pancreas may also contribute to a prothrombotic milieu, especially in splanchnic veins.[26]

In this analysis, several parameters have been identified as independent predictors for VTE among hospitalised patients with AP, namely median hospital stay, peripheral arterial disease, malnutrition, and systemic organ dysfunction. These findings agree with previous studies and are consistent with the fact that sicker patient profiles develop more frequently into thrombotic events.[42] Similarly, it has been reported that patients with more complicated pancreatitis are more prone to present simultaneous VTE.[34] It is not surprising that in the authors' study, patients with serious comorbid conditions such as peripheral arterial disease and those who run a complicated pancreatitis course with organ failure present more frequently concurrent venous thrombosis.

The authors' results show that VTE is adversely associated with mortality. Patients with pancreatitis and coexistent VTE die approximately twice as much as their counterparts without VTE (7.5% versus 2.9%). Likewise, the current study reveals that length of stay is significantly higher in patients with AP and concurrent VTE (22.4 days versus 10.0 days). Prior retrospective studies also point out that VTE in patients with AP is associated with adverse outcomes.[34]

The major strength of the authors study is the fact that it includes a large nationwide population (more than 50,000 patients), allowing statistically precise estimates of the prevalence and relationship of VTE with adverse disease course in patients with pancreatitis. Administrative databases provide massive information not only for reimbursement purposes but also for clinical research[43-45] and, despite some methodological limitations, databases are increasingly used in public health research.[46] Compared with previous reports, this is a population-based analysis involving a large cohort of patient records and thus adequately powered to detect differences between thrombosis and non-thrombosis groups.

There are, however, certain caveats that may affect the results. First, the main limitation is its retrospective nature. Data have been fully obtained from the BMDS administrative database and, therefore, the authors' findings are subject to information bias. Erroneous clinical documentations can lead to misclassification. However, this system has long been accepted in many different countries in the authors' environment. Many authors have examined in previous reports data from large national and multinational databases including information on patients' discharge records.[34,47-49] A second limitation is that the relationship between the occurrence of a venous thrombotic event and the presence of pancreatic necrosis has not been evaluated. Little data is available regarding DVT and PE and necrotising pancreatitis; however, some studies on the association between venous thrombosis and pancreatitis show that splanchnic vein thrombosis is significantly higher in patients with pancreatic necrosis.[50-52] Administrative data use codes to identify diagnosis or procedures. Based on ICD-9-CM 577.0, a 'grouper' programme assigns a DRG 204 to all patients with AP, irrespective of the presence of necrosis. Therefore, this administrative classification does not allow adjustment for oedematous or necrotising pancreatitis. The third limitation is that no information is available regarding patients who developed VTE despite the use of prophylactic anticoagulation or those who were under pro-thrombotic treatments.

Finally, another weak point is that the diagnostic means of VTE have not been recorded (doppler ultrasonography or contrast-enhanced CT scanning), which can significantly change the incidence of VTE in patients with AP.[53]

The following conclusions can be drawn from the present report. Firstly, it is known that VTE is a frequent condition in hospitalised patients. Nearly 25% of all thromboembolic events occur during or are related to a recent hospitalisation.[54,55] Thromboembolic complications are associated with high mortality and morbidity and with an increased consumption of healthcare resources, leading to significant associated costs.[65] These findings in medical hospitalised patients have been confirmed in the authors' report: the development of VTE increases both mortality and median hospital stay in patients with pancreatitis. Secondly, VTE is a potentially

avoidable complication and is responsible for approximately 10% of deaths within the hospital. It has become the leading cause of preventable death in hospitalised patients. The present study may help to recognise patients who might benefit from mechanical or pharmacological thromboembolic prophylaxis. Several VTE risk factors in hospitalised patients with pancreatitis have been identified, such as length of stay, peripheral arterial disease, malnutrition, and systemic organ dysfunction. The authors' data show that sicker patients with pancreatitis present higher prevalence of thrombotic events; thus, management strategies to decrease and control organ dysfunction in pancreatitis may reduce the development of VTE and, therefore, may help improving healthcare resource utilisation.

Prospective studies have shown that DVT and PE incidence in hospitalised patients who do not receive thromboprophylaxis can reach 15.0% and 1.5%, respectively.[58-60] Pharmacological prophylaxis with heparins is safe and effective, with reductions in DVT and PE relative risk of 40–70%.[61,62] The American College of Chest Physicians (CHEST) guide for the prevention of VTE in non-surgical patients recommends the use of low-molecular-weight heparin, unfractionated heparin, or fondaparinux, unless contraindicated.[63] However, thromboprophylaxis may also increase haemorrhagic complications in acutely ill patients with pancreatitis undergoing invasive procedures. Lacking a standard of care in the current clinical practice, the decision to use pharmacological prophylaxis is made on a case-by-case basis. Further research is needed to determine the specific recommendations for VTE prophylaxis in patients with pancreatitis deemed high risk.

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Interactions Between Obesity and Inflammatory Bowel Diseases: The Pandemic Promoting 'Civilisation' Diseases

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Abstract

The end of the 20th and the beginning of the 21st centuries witnessed a change in human nutritional status, from malnutrition to an obesity pandemic. During a similar time period, many Western-type, non-communicable diseases increased globally in previously low-incidence areas. One group, inflammatory bowel diseases (IBD), is particularly noteworthy because its treatment does not eliminate the disease. Its current pan-global rise in incidence and prevalence seems to follow regions with more recent increases in prevalence of obesity. Obesity, which has now been redefined as a chronic disease, seems to share some pathogenic features with IBD. These include the promotion of a pro-inflammatory state via fat-derived hormones and oxidative stress induced by insulin resistance. In addition, the intestinal microbiome in obesity and IBD may also contribute to mutual disease development. Finally, the merger of these two diseases impacts the clinical course of IBD. This review explores these relationships.

INTRODUCTION

The end of the 20th and the beginning of the 21st centuries witnessed a remarkable change in human nutritional status. Prior to this period, a large portion of the world's population experienced malnutrition; however, the subsequent four decades witnessed global increases in body weight. While poor nutrition and being underweight are associated with poor health, being overweight and obesity are also associated with multiple health issues. The National Institute of Health (NIH) recognised obesity as a chronic disease rather than a behavioural disorder in 1998.[1] Specific biochemical, physiological, and microbiomial abnormalities have been described. Furthermore, the pathogenic importance of the intestinal microbiome (bacteria, archaea, fungi, and viruses) has emerged as an important factor in many diseases.[2,3] It is then plausible that obesity can merge and promote diseases linked with disturbances in the microbiome.

Inflammatory bowel diseases (IBD), consisting of Crohn's disease (CD) and ulcerative colitis (UC), are immunologically mediated conditions in conjunction with disruptions of the microbiome.[4] More recently, IBD has been reported to be associated with comorbidities found in obesity.[5] In addition, the geographic expansion of IBD, to some extent, follows the obesity pandemic. This review will outline reported relations between these two diseases.

OBESITY: THE PANDEMIC

Obesity is generally defined by the World Health Organization (WHO) with a formula relating body weight in kg to height in m^2.[6] By this definition, overweight is defined as 25–29 kg/m^2; Grade I obesity as 30–<35 kg/m^2 (in Asia it is considered ≥27 kg/m^2); Grade II obesity as 35–<40 kg/m^2; and Grade III obesity (morbid obesity) as ≥40 kg/m^2. Progressive increase in weight adds additional risks, which are also modified by the distribution of body fat. A central location of abdominal fat (android distribution, which is more common in males) confers higher risk for complications than a more diffuse distribution (pear-shaped obesity and gynoid fat distribution, which is more common in females).[7]

Obesity promotes the metabolic syndrome consisting of diabetes, hypertension, sleep apnoea, dyslipidaemia, and chronic fatty liver. In turn, these conditions lead to complications of the cardiovascular system, renal disease, advanced liver dysfunction, as well as hepatocellular carcinoma.[8] In addition, obesity is associated with a number of gastrointestinal disorders and cancers.[9]

The pandemic of obesity began in Western countries, primarily in the USA, towards the end of the 20th century[10] and is predicted to continue to spread globally well into the first third of the 21st century.[11]

The causes for obesity are linked to excess caloric intake with reduced energy utilisation. However, dietary factors do not completely explain the difficulties with weight reduction and resistance. An increasing body of information has been compiled on the role of environmental polluting compounds in industrialised societies, 'obesogens', which alter energy homeostasis.[12] Furthermore, approximately 300 polymorphisms have been discovered by genome-wide association studies to be operational in obesity.[13] These are thought to interact with environmental variables (e.g., diet, which is the easiest to change, lack of exercise, or other factors).[13]

Once obesity is established, a pro-inflammatory reaction is induced. This state is achieved by interactions between fat cell-derived and other hormones and the promotion of insulin resistance. Among several hormones, subcutaneous-derived leptin, which also controls appetite, is increased in obesity and promotes the release of inflammatory cytokines. Adiponectin, from visceral fat cells, counteracts leptin but control is diminished as this hormone secretion is reduced.[14] These hormones induce insulin resistance. Additional hormones, such as resistin derived from the r eticulo-endothelial system, also contribute.[15] In the pro-inflammatory response, TNFα inhibits tyrosine kinase at insulin receptors, conferring resistance and leading to enhanced oxidative stress.[16]

Additional nutrient-derived energy is provided to the host by the intestinal microflora.[17] Alterations in distribution, diversity, and richness from normal, or dysbiosis, is a term describing bacterial changes that can lead to or are a result of host disease.[2,18] The microbiome is responsive to external effects related to human culture, diet, antibiotics, and the changing local environment, much of which is related to industrialisation.[19]

As outlined above, pathogenic factors that underpin obesity also have profound effects on numerous diseases that have been labelled as 'Western' civilisation diseases.[20] Among these, of note is the global spread of IBD into areas previously devoid of or reporting only very low incidence rates. Figure 1 outlines possible pathogenic mechanisms that might mutually interact to produce diseases.

INFLAMMATORY BOWEL DISEASES AND EXPANDING INCIDENCE

UC and CD are two related, yet different, immune-mediated diseases of the colon and intestines. Both diseases have been associated with progressive Western industrialisation.[21] There is no cure for IBDs and, although they are associated with relatively low mortality, IBDs are generally lifelong conditions with relapsing clinical flares.

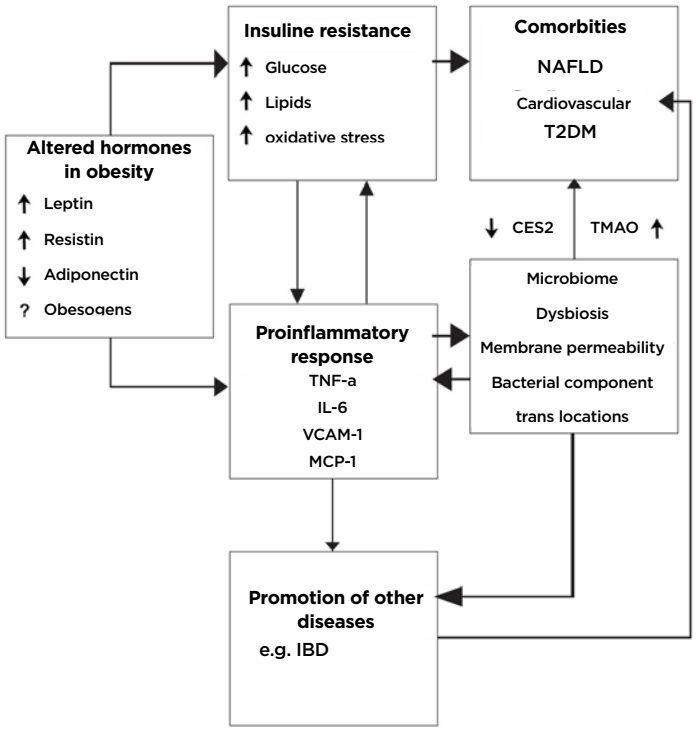

Figure 1: Pathogenic relationships of obesity with comorbidities and the potential for complicity in other illnesses such as inflammatory bowel diseases.

Obesogens are compounds polluting the environment and altering metabolic homeostasis (e.g., polycyclic aromatic hydrocarbons, polybrominated diphenyl ethers, and others).[12] Pro-inflammatory cytokines, TNFα, IL-6, VCAM-1, MCP-1, CES2[43] promote NAFLD, TMAO[55] through diet, and bacterial metabolism promotes atherosclerosis and increases risk for cardiovascular disease.

CES2: carboxylesterase-2; IBD: inflammatory bowel diseases; MCP-1: monocyte chemoattractant protein-1; NAFLD: non-alcoholic fatty liver disease; T2DM: Type 2 diabetes mellitus; TMAO: trimethylamine N-oxide; VACM-1: vascular cell adhesion molecule-1.

Adapted from Szilagyi A.[22]

UC, limited to the colon, was recognised earlier, while CD, potentially involving the entire gastrointestinal tract, was described in detail in the first half of the 20th century. The causes of IBD are complex. While there are differences between UC and CD the current paradigm is the interaction of the role of host genetic factors, which lead to inappropriate immune responses in conjunction with a disturbed balance in host microbial flora. A variety of environmental factors are considered related to IBD development.[23]

These IBDs were also initially described in Western societies. Incidence rose somewhat in the second half of the 20th century. Subsequently, from the early 1950s to the end of the 20th century, IBD expanded in Western cultures and began to stabilise, except in paediatric populations.[24]

The incidence of UC and CD began to increase in regions of the world previously free of IBD by the end of the 20th century and has risen progressively since. There are some epidemiological differences in IBD in different parts of the world (such as Asia, South America, and Africa).[25,26] Based on the accumulated tracking of IBD from various regions, Kaplan and Windsor[21] hypothesised a four-stage evolutionary development of IBD: an early stage of emergence; accelerated incidence followed by a balance between incidence and prevalence; compounding incidence; and, finally, when a balance between incidence and prevalence is reached, prevalence equilibrium.[21]

RELATIONS BETWEEN OBESITY AND INFLAMMATORY BOWEL DISEASES

Epidemiology

Although both obesity and IBD emerged from Western industrialised societies, geographic expansion of IBD and obesity diverge. IBDs, like several other Western civilisation diseases,[19] were observed to follow diminishing latitudes toward the equator.[27,28] This was initially ascribed to increasing exposure to sunshine and, hence, vitamin D skin synthesis. In turn, new research showed that vitamin D has pleiotropic anti-inflammatory and anti-neoplastic functions.[29] As many of these diseases were associated with low serum vitamin D, the lack of sunshine exposure was hypothesised to be the cause for higher incidence rates at higher latitudes. Although obesity was also observed to be associated with low vitamin D,[30] its trajectory included a geopolitical West to East direction.[11]

Perhaps co-incidentally, the incidence of some of Western civilisation diseases including IBD also inversely correlated with increasing population proportions who were unable to digest lactose.[31] Lactose digestion in adulthood is a dominant genetic trait that occurred in human evolution some 7–10x10^3 years ago.[32] The genetic trait divides humanity mainly into two phenotypes of lactase-persistent and lactase-non-persistent people (LNP).

On a global scale, obesity is modestly and inversely correlated with LNP status and more weakly but positively with latitude. This relationship of obesity with IBD may interfere with previously observed north–south (south–north) relations with IBD,[33] a topic that was of interest in the late 20th century.

The second epidemiological variation is the relationship of economic growth with increasing rates of IBD. Initially, both obesity and IBD were associated with wealthy countries. Obesity was found more in rural communities but, with time, obesity became associated with poorer economic areas in crowded urban locations.[10] Similarly IBD is associated with more urban crowding but generally higher socioeconomic standards.[23,26]

This association with national economic growth and industrialisation, as defined by the Gross National Product (GDP), has also been reported.[26,34] Globally, GDP correlates positively with latitude and negatively with LNP distributions, similar to IBD. However, correlation of obesity diverges from IBD and GDP.[34] Regional relationships, as in China, retain the close associations of IBD with GDP but are more evident in a south- to north-west direction from coastal areas.[26] Overall, in Asia all these relationships are negligible.

These findings could suggest that obesity is more dependent on adoption of a Western-type diet, which may precede independently from national economic growth.[10,35] It also suggests that IBD is associated with other features of acquisition of national wealth besides diet.

Mutual Pathogenic Influences

As described above, obesity promotes a pro-inflammatory milieu through insulin resistance and adipokine-mediated imbalance. Hypothetically, this state could favour any disease where pro-inflammatory cytokines contribute to pathogenesis.

In addition to physiological parameters, as pointed out, intestinal microbial changes likely contribute to obesity, IBD, and other diseases. The microbiome is intimately affected by diet. High fats such as saturated, monosaturated, polyunsaturated, and linoleic acids play roles in modulating the immune system. Western-type diets lead to obesogenic and pro-inflammatory patterns of the microbiome.[34] Although there is no clear evidence that a low-fat diet leads to more weight loss than a high-fat diet,[36] similar high-fat diets play a probable role in inducing and possibly causing relapses in IBD.[37,38] High carbohydrates, especially refined sugars, also contribute to a pro-inflammatory state, through the contribution to insulin resistance. However, fibres from vegetables and, to an extent, fruits are considered beneficial in IBD.[23] In obesity, fibres are helpful but fructose may be harmful. Proteins, particularly in dairy foods, may be protective against cardiovascular events, helping to maintain better weight control and reducing the risk of IBD before overt disease development.[39] Some similar effects of diet are shown in Table 1.

Consumption of pro-inflammatory nutrients could lead to alterations in gut barrier tight junctions, with bacterial access to the host immune system.

Table 1: Summary of current hypotheses related to dietary promotion and prevention of obesity and both forms of inflammatory bowel diseases.[23,34,36-39]

Variable	Obesity	Pre-IBD	Crohn's disease	Ulcerative colitis
Fats	All animal fats are pro-inflammatory; Dairy may be less obesogenic	High animal fat promotes IBD; Dairy may be protective for both forms of IBD	High fat could precipitate CD and UC flares; Pro-inflammatory diet promotes CD	High fat could precipitate CD and UC flares; Pro-inflammatory diet could be less offensive
Carbohydrates	Excess carbohydrates, especially refined sugars, are pro-inflammatory; Fibres, vegetables are anti-inflammatory; Fructose in excess can damage the liver and is obesogenic	High carbohydrates, especially refined sugars, may promote IBD; High fibre: vegetables>fruits reduces the risk for CD; Fruit may protect against UC	Low fibre increases CD flares; High fibre protects against CD	Low fibre increases UC flares; High fibre protects against UC
Proteins	Processed and red meats are pro-inflammatory; Fish, on the whole, is anti-inflammatory; Dairy, e.g., casein and whey, may promote satiety	Processed and red meats are linked with increased CD and UC risk; Dairy could protect against IBD	Processed and red meats may precipitate flares; Dairy role is unclear	Processed and red meats may precipitate flares; Dairy role is unclear

CD: Crohn's disease; IBD: inflammatory bowel disease; UC: ulcerative colitis.

A microbiome pattern that is altered is referred to as dysbiosis.[2,18] Although microbiome findings vary in different studies, recently described bacterial milieu in IBD shares a number of similarities with obesity as described in Table 2.[22] In IBD, strictly anaerobic microflora are replaced to an extent by facultative bacteria. The similar sharing of bacterial characteristics could, hypothetically, lead to mutual predisposition between diseases. Indeed, the long-term follow-up of patients, especially with CD, show increasing weight gain over time.[40]

Shared Comorbidities

The apparent shared pathogenic similarities between obesity and IBD also lead to increasing shared comorbidities. Among these, non-alcoholic fatty liver disease (NAFLD) is the best described. This condition, defined as >5% of liver fat, is largely attributed to insulin resistance, which leads to altered lipid metabolism and transport out of the liver. The role of TNFα interfering with insulin receptors is thought to lead to resistance and hence connect pro-inflammatory-dependent disease on predisposition to NAFLD.[16] This mechanism is thought to be similar in individuals who are both overweight and normal- or underweight.[41] A recent study showed that reduced carboxylesterase 2, which affects diglyceride and monoglyceride metabolism in the intestine and liver, could contribute to NAFLD in patients with obesity and CD alike.[42]

Table 2: Comparison of bacterial abundance in the microbiome of patients who are obese, with Crohn's disease, or with ulcerative colitis.

Bacterial taxa	Obesity	CD	UC
Similar distributions			
Proteobacteria (P)	Increased	Increased	Increased
F. prausnitzii (G and S)	Decreased	Decreased	Decreased
Clostridium leptum (G and S)	Increased or decreased, study depending	Decreased	Decreased
Bifidobacteria (G)	Decreased	Increased or decreased, study depending	Increased or decreased, study depending
E. coli (G and S)	Increased	Increased	Increased
Ruminococcus gnavus (G and S)	Increased	Increased	Increased
Different distributions			
Firmicutes (P)	Increased	Decreased	Decreased
Bacteroides (P)	Decreased	Decreased	Increased or decreased, study depending
Actinobacter (P)	Decreased	Increased	Increased
Roseburia (G)	Increased	Decreased	Decreased
Akkermansia muciniphila (G and S)	Decreased	Decreased	Stable compared with healthy controls
Desulfovibrio (G)	Decreased	Increased	Increased

CD: Crohn's disease; *E. coli*: *Escherichia coli*; *F. prausnitzii*: *faecalibacterium prausnitzii*; G: genus; P: phyla; S: species; UC: ulcerative colitis.

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World rates of NAFLD are reported to be 9–43%. In the USA, 27% of the population is reported to have NAFLD. The risk of NAFLD is reported to be 3.5 times higher in people who are obese.[43] In IBD, a systemic review found that 39.5% of patients with CD and 23.0% of patients with UC had NAFLD compared with 20.0% (range: 6.0–33.0%) of controls.[44] In a prospective study of 321 patients with CD, followed for 3 years, one-third developed NAFLD, although <1.0% were considered obese. Of these, 2.2% developed more advanced liver disease over time, such as non-alcoholic steatohepatitis, inflammation, ballooning degeneration, or degrees of fibrosis.[45] Another study of patients with IBD reported a prevalence of 32.8%, of which 12.2% were advanced; in this case, 30.4% of patients were overweight and 13.8% were obese (BMI: ≥30kg/m^2).[46] The impact of the microbiome on altered intestinal barrier and bacterial translocations are also thought to play an important role in NAFLD development.[47]

Another shared comorbidity between obesity and IBD is cardiovascular complications. However, the risk factors in IBD differ somewhat from those observed in obesity. The types of vascular problems are summarised in a recent review and include venous and arterial thromboembolism; heart failure; arrhythmias; valvulopathies, with or without endocarditis; and Takayasu arteritis.[48] The

occurrence of ischaemic stroke or myocardial infarction is somewhat controversial. An earlier meta-analysis did find increased episodes of myocardial infarction in IBD,[49] while another reported study reported inverse association of cardiovascular disease (CVD) with IBD.[50]

However, a more recent meta-analysis did find an increased, albeit modest, risk for cardiovascular events in both CD and UC, interestingly more frequently in women aged <50 years. These events were unaffected by smoking and controlling for obesity.[51]

In obesity, traditional risk factors related to adipocytes and insulin resistance promote atherosclerosis[52] and cardiovascular complications. It is of note that in Class I obesity (but less so in Classes II and III), prognosis for cardiac event outcomes is better than in patients who are of normal weight or lean and with CVD. This has been called the 'obesity or lean paradox'.[53]

The role of microbial contributions to CVD comorbidities in obesity have been evaluated by examining plasma metabolites in a cohort of patients who are obese and compared with controls who are not obese. In this study, 48 metabolic microbial pathways were linked with CVD risks.[54] In addition, dietary intake of choline and carnitine (found in animal products) are metabolised by bacteria to produce trimethylamine, which is oxidised in the liver to become trimethylamine N-oxide. This compound increases platelet adhesiveness and promotes atherosclerosis.[55] A similar effect could contribute to CVD in IBD, depending on diet.

The recent increasing association of Type 2 diabetes mellitus (T2DM) with IBD adds another measure of overlap between obesity and IBD. In obesity, insulin resistance leads to T2DM via the promotion of a pro-inflammatory state. It is suggested that the inflammatory milieu of IBD contributes to insulin resistance as well. One study reported a modest 26% increase in T2DM in UC after an 11-year follow-up compared with healthy controls.[56] A more recent report from Korea, however, found that T2DM was more frequent in CD (hazard ratio: 1.677; 95% confidence interval: 1.408–1.997), but not in UC. The occurrence was also more common in younger patients.[57]However, a recent Danish study, based on more than 6 million persons followed for 37 years, found increased risk (by 54–57%) for T2DM in both CD and UC. Notably the risk increased after 2003 compared to the time period from 1977.[58] This time difference is of note because the obesity pandemic is hypothesised to have begun around the 1980s.[10]

CLINICAL IMPACT OF OBESITY ON INFLAMMATORY BOWEL DISEASE

If these two diseases collide in time and geography, what effects of obesity can be seen on the clinical course of IBD? The influence of obesity on IBD location is not well defined. A population-based study of 488 patients found a trend in favour of colonic involvement,[59] while another study found increased perianal disease and more hospitalisations in CD,[60] the previous study[58] did not substantiate this.

Obesity was reported to increase risk of surgery in UC but decreased in CD,[61] and was reported to be more frequently associated in women with UC.[62] In that study, metabolic syndrome and C-reactive protein were increased but were not related to BMI.[63] However, in another report, the presence of metabolic syndrome was found to increase the risk of hospitalisation two-fold.[63] This contrasted with another study that found that obesity was associated with a more mild course of CD.[64] A meta-analysis of 7 studies (5 UC and 2 CD), reported that patients who were obese were less likely to undergo IBD-related surgery, receive hormonal therapy, or require hospitalisation than patients who were not obese.[65] The presence of obesity and traditional associated comorbidities may increase perioperative complications, although not all reports agree; these are reviewed by Johnson and Loftus Jr.[66]

There is also a debate over whether patients with IBD who are obese respond as effectively to biologic therapy as patients who are not obese. In the case of TNFα inhibitors, reduced clinical outcome was reported in patients with IBD who were obese.[67] However, another study failed to support therapeutic failure, and a meta-analysis of therapeutic response to biologics in a number of autoimmune diseases found a 60% higher failure rate but not in IBD.[68] In addition, a report suggested that the α4β7 integrin

inhibitor vedolizumab trough levels were lower in patients with IBD who were obese.[69]

EVIDENCE THAT OBESITY PROMOTES INFLAMMATORY BOWEL DISEASE

Despite the theoretical similarities in pathogenesis between obesity and IBD, the literature is conflicting on a clear evolution between the two diseases. There are emerging hypotheses suggesting an interchange between these two diseases, despite the presence of malnutrition in IBD in the past.

Mendall et al.[70] initially suggested that obesity may promote CD. In a cohort of 524 patients, obesity at diagnosis was linked more with CD than UC or healthy controls.[70] More recent studies showed that obesity at the age of 18 years increased the risk for CD but not UC in the Nurse's Health Study II.[71] These reports were similar to previous findings.[70] In two other Danish studies, one found that increasing BMI in children between the ages of 7 and 13 years increased the risk for CD until age 30 years, but there was an inverse relationship with UC.[73] In the second study of young military conscripts, there was a 'U'-shaped risk profile for CD up to the age of 60 years. However, only a low BMI (<18.5 kg/m^2) was statistically significantly associated with CD. This study also showed an inverse association with UC.[73]

As stated above, the reverse observations have also been reported, that patients with CD enrolled in clinical trials gain weight with time over follow-up.[39]

SUMMARY AND CONCLUSIONS

In this review, the obesity pandemic has been examined together with the coincidental extension of both forms of IBD, UC and CD, into areas of previous low incidence. Both diseases, with differences in detail, are linked with a pro-inflammatory state. A large part is related to the functions and alterations in the intestinal microbiome. In addition, adipocytes in obesity contribute to the pro-inflammatory pattern. Although genetic predispositions differ, the internal milieu in each disease leads to similar development of comorbidities such as NAFLD, some cardiovascular complications, and T2DM. As such, there are suggestions that some features of obesity and IBD are interchangeable. That is, the pathogenic changes in IBD can lead to weight gain and, under some circumstances, obesity may promote IBD. These interactions favour CD more than UC.

The consequences of these interactions could lead to variations in clinical outcomes in IBD. It is not yet clear whether a 'paradoxical' effect in IBD occurs as it has been described in CVD. On an epidemiological level, it is hypothesised that the geographic distribution of obesity impacts on patterns of IBD, which is best seen in Europe. This impact may partly have led to the disruption of previously observed north–south disease distributions there. Secondly, although obesity and IBD both emerged in Western societies, often in wealthier, industrialised regions, the two diseases diverge in their expansion somewhat. In areas where obesity is evident and not accompanied by increased economic wealth, IBD rates are proportionately lower. However, IBD may be closely following areas affected by increased obesity. Thus, there may be a subtle interaction evident that promotes both conditions. While 'Western' diets may precede economic growth, chemical pollutants may affect these interactions in ways that are not yet clear. Seen in this light, obesity may be a marker for impending regional development of IBD (and some other civilisation diseases).

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Jejunojejunal Intussusception as Initial Presentation of Coeliac Disease: A Case Report and Review of Literature

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Abstract

Intussusception as the initial presentation of coeliac disease has been rarely reported, with an incidence of 1% in all coeliac disease presentations. Furthermore, intussusception requiring surgical reduction as the primary presentation for coeliac disease in adults is even rarer. Presented here is a case of a 37-year-old female Asian patient who presented with abdominal pain and distension; she was diagnosed with small bowel obstruction due to jejunojejunal intussusception and required surgical reduction as the initial presentation of coeliac disease.

INTRODUCTION

Coeliac disease is a disorder of the small intestine, which is characterised by mucosal inflammation, villous atrophy, and crypt hyperplasia, and occurs upon exposure to dietary gluten; the disease eventually shows improvement after cessation of gluten in the diet. Adult coeliac disease is now considered to have a prevalence of 0.5–1.0%.[1,2] A classic presentation in patients with coeliac disease is diarrhoea with stool that is floating, bulky, and foul-smelling due to steatorrhoea. Historically, intussusception in association with adult coeliac disease is considered to be transient and asymptomatic.[3] Willingham et al.[4] were the first to suggest that intussusception in adults with coeliac disease may result in symptoms. Intussusception is defined as the invagination or telescoping of a part of the intestine into itself. Intussusception is unusual in adults (approximately 5% of all cases) and is thought to be due to structural lesions in more than 80–90% of cases, a retrospective series of surgical cases reports.[5,6] In the majority of adult cases, a pathologic cause is identified.[7] Conversely, reviews analysing radiologically diagnosed intussusception reported that only 30% of

patients had an identifiable lead point, while >50% were without one and were therefore considered to have idiopathic or non-lead intussusception.[8,9] Furthermore, the location of adult intussusception in surgical literature[6,10] and radiologic series[5,9,11,12] was found to be enteroenteric or ileocolic, with the majority of non-neoplastic cases being enteroenteric intussusception. Moreover, non-lead intussusceptions are mostly inflammatory in nature: pancreatitis, cholecystitis, appendicitis, Crohn's disease, cystic fibrosis, adhesions, scleroderma, and coeliac disease.[5] In the medical literature, a well-established relationship has been made between transient intussusception and known coeliac disease; however, intussusception requiring surgical reduction appearing as the primary presentation for coeliac disease in adults is a rare entity.

CASE REPORT

Initial Presentation

A 37-year-old female Asian patient, with no previous medical or surgical history, presented with acute onset of diffuse abdominal pain associated with nausea, two episodes of vomiting, and increased abdominal girth for the past day, and the inability to pass any flatus for the past 12 hours. The patient denied fever, chills, change in bowel habits, history of diarrhoea, and weight loss, nor any previous episodes of similar complaints. On physical examination, the patient had tachycardia, with a pulse rate of 117 beats per minute, and her blood pressure was haemodynamically stable at 120/80 mm Hg. On abdominal examination there was abdominal distension, very faint bowel sounds, tenderness on deep palpation, and no rebound tenderness.

Laboratory Findings

Laboratory work-up showed leukocytosis, with a white blood cell count of 15,000 cells/mm^3 and neutrophil shift with 80% neutrophils, and elevated inflammatory markers, with normal electrolytes, creatinine, amylase, and lactate dehydrogenase.

Imaging

Consequently, an abdominal and pelvic CT scan with intravenous contrast was performed, which showed jejunojejunal intussusception 6 cm in length with wall thickening (Figure 1); no lead point could be identified nor any signs of compromise in blood supply, and there was minimal free intraperitoneal fluid.

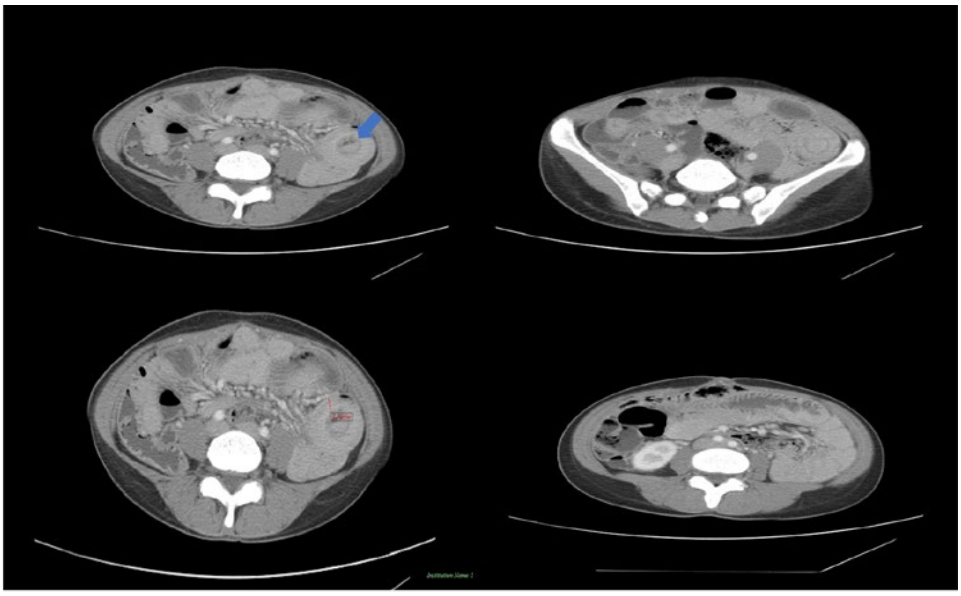

Figure 1: Abdominal and pelvic CT scan with intravenous contrast.

Target sign (blue arrow), extending 6 cm, suggests intussusception between ileo-ileal loops. There is prominent wall thickening of the intussuscepted bowel, measuring 11 mm in thickness with surrounding fat streaking.

Therefore, a nasogastric tube with a low pressure Gomco® suction machine (Allied, St Louis, Missouri, USA) was inserted. Due to the aforementioned, the patient was scheduled for diagnostic laparoscopy.

Surgery

In the operating theatre, the patient was given general anaesthesia, positioned in the modified lithotomy position with both hands adducted, and a urinary Foley catheter was inserted. A 10 mm trocar was inserted into the infraumbilical area and two additional 5 mm trocars were inserted into the left side of the abdomen under direct vision. The ileocaecal valve was identified and small bowel inspection was performed, starting at the ileocaecal valve until the ligament of Treitz was reached. The intussusception was identified (Figure 2A), which was reduced with no signs of ischaemia; however, the oedematous bowel wall was identified, with no tumourous growth detected.

Inpatient Stay and Further Analysis

The patient had a smooth in-hospital stay. Oral feeding resumed and flatulence passed on Day 1 post-surgery. The patient was discharged on Day 2 post-surgery. The patient also completed the necessary laboratory work-up (gastroscopy, colonoscopy, and possible capsule endoscopy) in order to identify the aetiology of intussusception. Further blood work-up showed increased levels of IgA and anti-transglutaminase, suggesting the diagnosis of coeliac disease. This was followed by a gastroscopy that showed scalloped duodenal mucosa, which too suggested the identification of coeliac disease. Duodenal biopsy showed mild to moderate villous atrophy (Figure 2B), increased intraepithelial leukocytosis (Figure 2C), and positive CD3 staining (Figure 2D). This led to the diagnosis of adult coeliac disease, with primary presentation of jejunojejunal intussusception requiring surgical reduction as the first manifestation.

Long-Term Follow-Up

The patient was started on a gluten-free diet. There was one reported episode of abdominal pain with transient intussusception, which was likely caused by non-adherence to the advised diet, 6 months post-diagnosis. Following this, the patient lived 1-year symptom-free with strict adherence to a gluten-free diet.

DISCUSSION

Coeliac disease is a chronic, inflammatory disease of the small intestine, with an incidence in the general population of 1–2%.[13,14] If undiagnosed and thereby untreated, the inflammation can lead to bowel wall oedema,[15] intestinal lymph node swelling,[16] dysmotility in the small intestine,[16] ulcers, and strictures in the small intestine,[17] all of which are predisposing factors for intussusception; therefore, patients with undiagnosed coeliac disease may present with intussusception. However, intussusception as the initial presentation leading to the diagnosis of coeliac disease has been rarely reported in the medical literature. Adult intussusception is a rare entity (5% of all cases) and is much more common in children,[18] being the most common cause of bowel obstruction (whereas it is responsible for only approximately 1% of adult cases).[10,19] Three main aetiologies have been identified: idiopathic, benign, and malignant.[20] Among the widely available imaging modalities, CT scanning is a sensitive test for diagnosing adult intussusception.[10,18,20] Furthermore, CT can further identify a lead point, the size of intussusception, detect vascular compromise, and predict the likelihood of self-resolution.[12,21] Although less sensitive than CT, ultrasound sonography has the ability to detect the pathognomonic target sign in some cases.[18] As a result, the more frequent use of cross-sectional imaging modalities in recent years has increased recognition of intussusceptions in adults.[22] With regards to the site of intussusception, enteroenteric intussusceptions account for the majority of cases in adults, although gastroenteric, ileocolic, and colocolonic intussusceptions can also occur.[11] A wide spectrum of symptoms are associated with adult presenting intussusception: non-specific abdominal pain, nausea, vomiting, change in bowel habits, abdominal distension, haematochezia, and surgical abdomen when venous blood flow is compromised followed by arterial compromise, making the diagnosis a challenge. However, intussusception as the initial manifestation of coeliac disease in adults is rare, and even rarer is intussusception requiring surgical reduction as the primary presentation.

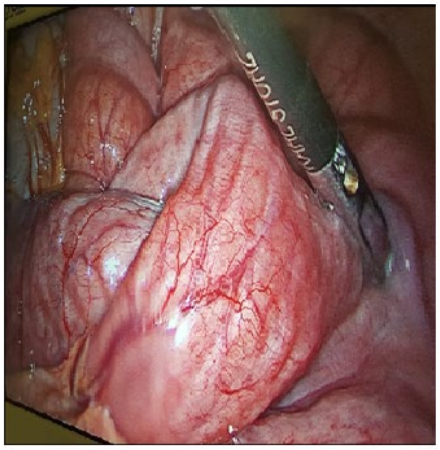

Figure 2A

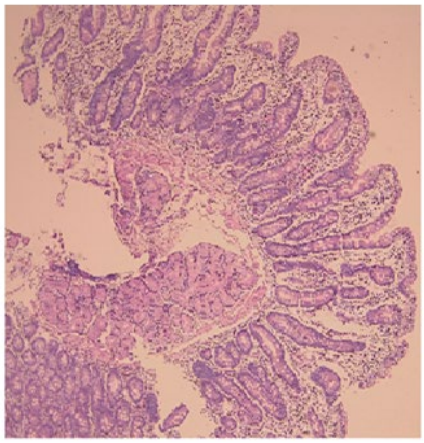

Figure 2B

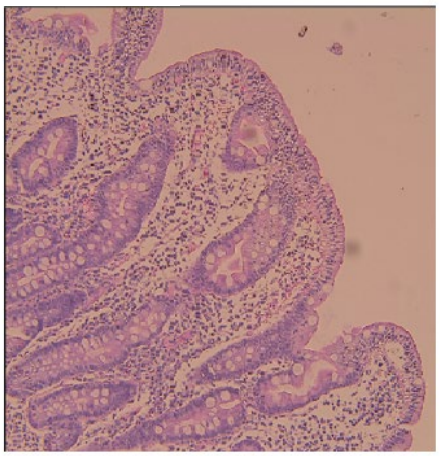

Figure 2C

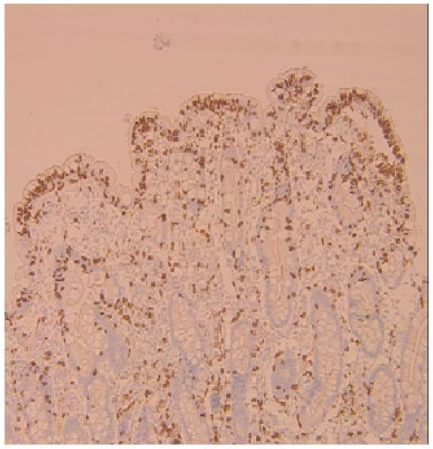

Figure 2D

Figure 2: Intraoperative findings and histologic appearance.

A) Intra-operative picture of the intussuscepted bowel loop, with no signs of ischaemia or necrosis noted; **B)** section of duodenum showing mild to moderate villous atrophy; **C)** increased intraepithelial lymphocytosis; **D)** CD3 immunohistochemistry stain confirming the increase in intraepithelial lymphocytes.

Only nine cases in the medical literature have reported intussusception as the initial presentation for coeliac disease (Table 1).

On the other hand, Warshauer et al.[11] suggested that transient intussusception of the small intestine be advocated as the sole finding in coeliac disease diagnosis, most likely due to intestinal motility disorders. Historically, surgical treatment was argued to be universally appropriate for adult intussusceptions; however, recent literature suggests that a more selective approach is warranted, whereby intussusception usually remits spontaneously in the majority of cases and surgery is deemed necessary only in a small subset of patients. Indeed, Lvoff et al.,[20] in an analysis of 37 cases of adult intussusception identified by CT, found a significant difference between the length of the intussusception between surgically and conservatively managed cases, with a length of <3.5 cm likely to be self-limiting. In general, recent studies favour a conservative approach to cases of adult intussusception, where the probability of malignancy, lead point, and ischaemia are low and the likelihood of spontaneous resolution is high. However, in patients presenting with recurrent intussusceptions, a diagnosis of inflammatory bowel disease or coeliac disease must be ruled out. Nonetheless, coeliac disease must be taken into consideration in cases of unexplained intussusception in adult patients, allowing for early diagnosis and hence early treatment to decrease the morbidity and mortality associated with delayed diagnosis.

Table 1: Previously reported cases of coeliac disease with intussusception as the initial presentation.

Reference	Age/ sex	Clinical presentation	Site	Management	CD diagnosis: later versus concomitant	Follow-up
Dodds et al.,[23] 2008	45/F	Abdominal pain, distension, SBO	Double intussusception: distal ileo-ileal, distal jejuno-jejunal	Surgical reduction	Later	Few days post-op recurrence of 3 intussusception: radiologic reduction No recurrence at 1 year after diagnosis: gluten-free diet
Quera et al.,[24] 2010	49/F	Abdominal distension, SBO	Jejuno-jejunal	Conservative	Later	No recurrence on gluten-free diet
Malamut, Cellier[25] 2010	38/F	Abdominal pain, weight loss, intermittent, diarrhoea lasting >12 months	N/A	Laparotomy (intra-operative enteroscopy)	Concomitant	Recurrence of intussusception: manual reduction No recurrence up to 18 months post-op on gluten-free diet
Grados et al.,[26] 2011	41/M	Right-sided iliac fossa abdominal pain, weight loss (BMI: 17)	US: Ileo-ileal CT: resolved spontaneously	Laparotomy	Later (on same admission)	Recurrence after 4 months due to non-compliance to gluten-free diet: spontaneous reduction Currently on close surveillance with gluten-free diet
López Redondo et al.,[27] 2012	50/M	Transient episodes of abdominal pain, weight loss	Jejuno-jejunal + ileo-ileal	Conservative	Concomitant	No recurrence on gluten-free diet
López Redondo et al.,[27] 2012	32/F	Diarrhoea, anaemia, weight loss	Ileo-ileal	Conservative	Concomitant	No recurrence on gluten-free diet
López Redondo et al.,[27] 2012	31/F	Abdominal pain, diarrhoea, weight loss, anaemia	Jejuno-jejunal	Conservative	Concomitant	No recurrence on gluten-free diet
Mitchell et al.,[28] 2014	39/F	Weight loss, epigastric discomfort, nausea, vomiting	Jejunojejunal intussusceptions x3	Laparotomy	Later (on same admission)	No recurrence on gluten-free diet
Pérez-Cuadrado-Robles et al.,[29] 2015	31/F	Chronic anaemia, abdominal pain	Jejuno-jejunal	Conservative	Later (on same admission)	N/A
Saad et al., 2021 (presented case)	37/F	Abdominal pain, obstipation, SBO	Jejuno-jejunal	Laparoscopic surgical reduction	Later (1 week post-op)	Recurrence at 6 months post-op due to non-compliance with gluten-free diet No recurrence after compliance to gluten-free diet

CD: coeliac disease; F: female; M: male; N/A: not available; post-op: post-operatively; SBO: small bowel obstruction; US: ultrasound.

CONCLUSION

Intussusception as initial manifestation of coeliac disease in adults is rare. Even rarer is intussusception requiring surgical reduction as the primary presentation for coeliac disease. CT and barium studies are the gold standard for diagnosis of intussusception. Coeliac disease must be taken into account in cases of unexplained intussusception in adult patients. Compliance with a strict gluten-free diet is greatly important as this will decrease the rate of emergency admissions and consequently hospital admissions.

Written informed consent was obtained from the patient to publish the case, as well as any associated images.

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Perforated Isolated Jejunal Diverticula due to Enterolith: A Case Report and Review of Literature

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Abstract

Jejunal diverticula is a rare condition quoted to affect between 0.5% and 7.0% of the population. Usually, it is clinically silent and becomes symptomatic only when complications develop. Perforation of a jejunal diverticulum secondary to enterolith formation leading to generalised or localised peritonitis is extremely rare; even rarer is an isolated perforated jejunal diverticulum. Herein, the authors present a case of perforated isolated jejunal diverticula due to enterolith in a 60-year-old female patient managed by small bowel resection and primary anastomosis.

INTRODUCTION

Small bowel diverticula are sac-like pouchings of the small bowel wall that can occur throughout the small bowel. Small bowel diverticula are most often found in the duodenum, followed by jejunum and ileum. In fact, Akhrass et al.,[1] in their retrospective review of 208 patients with symptomatic small bowel diverticulosis, found that diverticula were located in the duodenum in 79% of cases, in the jejunum or ileum in 18% of cases, and in all three segments in 3% of cases. The incidence of jejunoileal diverticula is variable, reported to occur in 0.5–2.3% of individuals in radiographic series and up to 7% in autopsy studies.[2] Furthermore, 77% of cases demonstrate multiple, as opposed to solitary, diverticula.[3] They are more commonly reported in males, with the highest incidence in the sixth and seventh decades of life.

Small bowel diverticula are usually asymptomatic, with a spectrum of presentation ranging from non-specific abdominal pain, dyspepsia, and bloating and reaching presentations with life-threatening complications. In fact, Tsiotos et al.[4] analysed 112 cases of jejunoileal diverticulosis where 42% of cases were asymptomatic; in the remaining patients, symptoms of diarrhoea were reported in 58% of patients, chronic abdominal pain in

51%, and bloating in 44% of cases. Furthermore, complication rates as high as 46% for jejunal diverticulosis have been reported and are known to be fatal at times.[5] Among the complications is perforation with localised or generalised peritonitis. Herein, the authors report a case of perforated isolated jejunal diverticula due to enterolith in a 60-year-old female patient, managed by small bowel resection and primary anastomosis.

CASE REPORT

This is a case of a 60-year-old female patient with previous history of laparoscopic cholecystectomy, presenting with a 2-day history of non-specific epigastric pain associated with decreased food intake. The patient denied having a fever, nausea, vomiting, obstipation, or change in bowel habits. The patient also denied weight loss and personal or family history of malignancy.

Upon arrival to the authors' emergency department, the patient's vitals were stable and a physical examination of the abdomen was within normal limits, with hypoactive bowel sounds and minimal tenderness upon deep palpation of the left upper and left lower quadrants. Laboratory work-up, including complete blood count, inflammatory markers (C-reactive protein), liver function tests, amylase, and lipase, and urine analysis were within normal limits. A CT scan of the abdomen and pelvis with intravenous (IV) contrast was negative for any pertinent signs except for segmental enteritis, with no evidence of bowel suffering and no signs of ischaemia.

The patient was admitted for further management of enteritis by IV hydration and IV antibiotics (ciprofloxacin and metronidazole) for 7 days in total. Two days after the admission, the patient reported acute worsening of her abdominal pain that was associated with one episode of fever of 39 °C and chills. On physical examination of her abdomen, there was diffuse four-quadrant tenderness and rebound tenderness, more so over the left side of the abdomen.

Consequently, another CT scan with IV contrast showed diffusely thickened and enhancing jejunal loops (Figure 1A). A dilated jejunal loop up to 4.5 cm filled with bezoar or enterolith (Figure 1B), significantly increased, and surrounding fat streaking were noted, in addition to free fluid in the pelvis and along the left paracolic gutter that had not been noted on the initial CT scan 2 days previously. In view of worsening pain, the new onset of fever, and the new findings on imaging despite IV antibiotics, the authors opted for a diagnostic laparoscopy.

In the operating theatre, the patient was given general anaesthesia, a urinary Foley catheter was inserted, and the patient was placed in the modified lithotomy position. An infraumbilical incision, an open technique

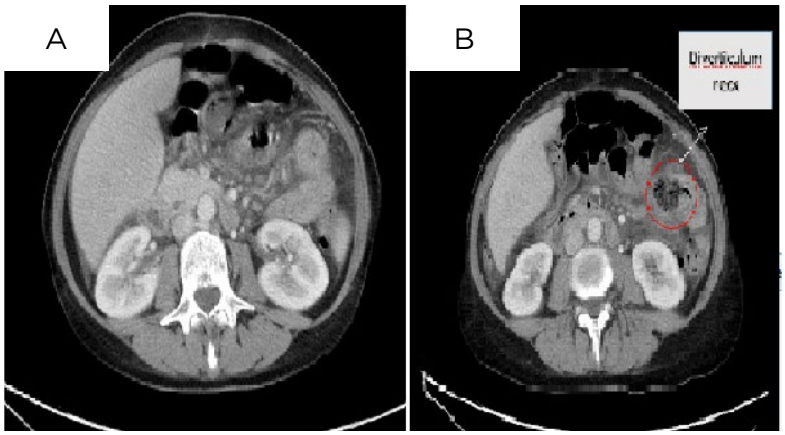

Figure 1: A) Diffuse jejunal wall thickening; and B) highlighting an enterolith or bezoar.

to access the abdominal cavity, insufflation, and the insertion of two 5 mm trocars were performed under direct vision in the suprapubic and left lower quadrant area. Sharp lysis of adhesions was done up until reaching the area of inflammation, whereby it was dissected using blunt dissection. A large jejunal diverticula on the mesenteric border measuring approximately 7 cm in diameter was identified, located 40 cm distal to the ligament of Treitz. Further blunt dissection of the diverticula from the jejunal mesentery identified an enterolith (Figure 2A). Furthermore, a jejunal perforation measuring approximately 3 cm was identified (Figure 2B). This was followed by a left paramedian 5 cm incision and placement of Alexis retractor. A small bowel segment was exteriorised and segmental resection with primary side-to-side anastomosis performed, followed by closure of the mesenteric defect (Figure 2C). Running of the small bowel from the ileocaecal valve until reaching the ligament of Treitz, the authors did not identify any other diverticula and no colonic diverticula were identified intra-operatively. Final histopathology studies confirmed the diagnosis of perforated false diverticulum with signs of necrosis and gangrene at the edges of perforation (Figure 2D). The patient's post-operative course was smooth and the patient was discharged home on Day 4 post-operation.

DISCUSSION

Small bowel diverticulosis was first reported by Sommering in 1794.[6] Its aetiology is thought to be related to a combination of intestinal dyskinesia and abnormal peristalsis, causing high segmental intraluminal pressures.[7] In fact, the current hypothesis focuses on abnormalities in the smooth muscle or myenteric plexus. Having said this, microscopic evaluation of jejunal specimens with diverticulosis has shown that there are three different abnormalities: fibrosis and decreased numbers of normal muscle cells, fibrosis and degenerated smooth muscle cells, and neuronal and axonal degeneration.[8] The presence of any of the above-mentioned abnormalities will consequently lead to distorted smooth muscle contractions of the affected small

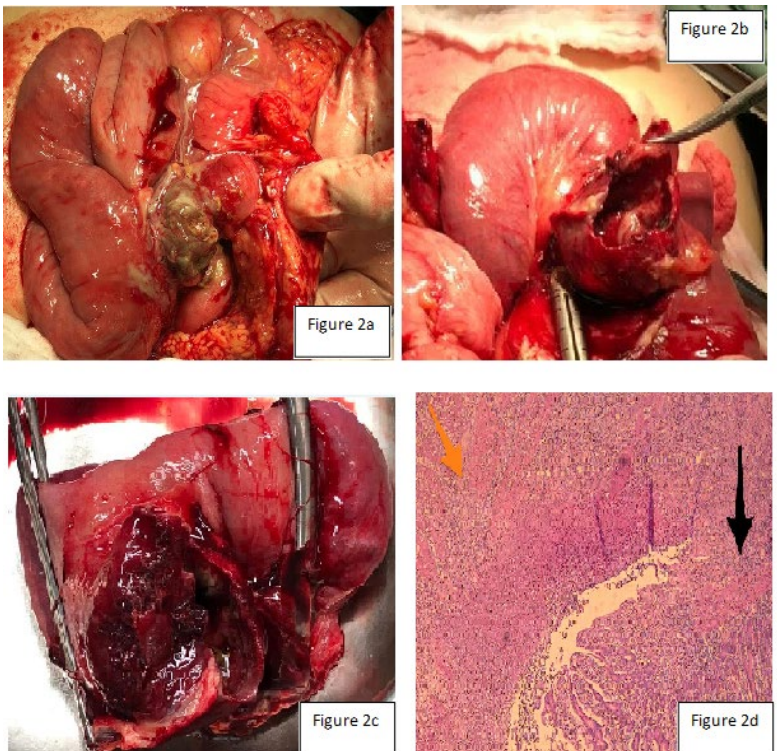

Figure 2: A) An enterolith, seen intra-operatively; B) diverticular perforation of the small bowel; C) the resected small bowel; and D) the transition from diverticular mucosa to bowel rupture, inflammation, and gangrenous formation. The black arrow represents normal mucosa while the orange arrow shows the rupture.

bowel, generating areas of increased intraluminal pressure, which in turn will lead to herniation of the bowel mucosa and submucosa through the weakest point in the bowel wall, the mesenteric border at the site of entry of the vasa recta, leading to the formation of small bowel diverticula.

Small bowel diverticula are usually clinically silent and discovered incidentally or once they become complicated. However, they may have a wide spectrum of presentation, ranging from non-specific abdominal pain, dyspepsia, and bloating and reaching presentations with life-threatening complications. Life-threatening complications include massive gastrointestinal bleeding, volvulus, diverticulitis, and perforation with localised or generalised peritonitis. Furthermore, jejunal diverticulosis complicated by enteroliths is a rare entity. The enterolith, formed within small bowel diverticula, can be either *de novo* or secondary to a piece of undigested food. Those that form *de novo* are comprised of cholic acid, the end-product of bile salt metabolism, as their primary constituent. It is theorised that cholic acid enteroliths form within small bowel diverticula due to an acidic pH shift within the diverticula.[9] Enterolith in jejunal diverticula can result in enterolith ileus or lead to perforation if it becomes impacted. The synergistic effect of intestinal dyskinesia with the abnormal peristalsis leads to the enterolith being stagnated due to this abnormal transit. This may eventually lead to perforation due to pressure necrosis or acute necrotising inflammation.[10,11] Presentation varies widely depending on the severity of perforation. For instance, patients where the enterolith has been sitting within the diverticulum for an extended period of time, resulting in progressive erosion into the bowel wall and consequently bowel wall perforation, usually present with a localised abscess without causing the patient to become acutely ill. This is either due to the perforation into the mesentery, hence a contained perforation, or due to the walling off by the adjoining small bowel mesentery so that only localised peritonitis will occur. On the contrary, patients with acute perforation present in an acutely ill situation with gross contamination of the abdomen and generalised peritonitis. For patients with localised peritonitis and clinically stable patients, non-surgical management by IV antibiotics and CT-guided aspiration of collections may be appropriate for some patients. On the other hand, for patients with generalised peritonitis or haemodynamic instability, resection of the affected segment should be done.

Reviewing the English literature regarding perforated isolated jejunal diverticula due to enterolith has revealed only few reported cases. In fact, in the authors' review of the medical literature, they identified a total of 23 cases of perforated jejunal diverticula (Table 1), of which five patients had isolated jejunal diverticula; their patient is the sixth reported in literature. The mean age of presentation was 71 years, with a male to female ratio of 2:1. Abdominal pain was the most frequent initial presentation.

All reported cases were managed surgically by laparotomy. The authors' case was the first to

Table 1: A review of medical literature where 23 cases of perforated jejunal diverticula were identified.

	Author/ year	Age (years)/sex	Clinical presentation	Radiologic finding	Surgical approach	Intra-operative finding	Multiple/ isolated jejunal diverticula	Treatment
1	Cegla et al.,[12] 2007	65/F	Localised peritonism in left iliac fossa	CT: free fluid in the abdominal cavity; free air in the retroperitoneum; small bowel perforation detected	Laparotomy	Mesenteric abscess; perforated diverticula	Multiple	Segmental resection with primary anastomosis

Table 1 continued

2	Kassahun et al.,[13] 2007	85/M	Fever, diffuse abdominal pain, and abdominal distension	CT: normal findings	Laparoscopy converted to open	Jejunal diverticulitis and abscesses in the mesentery/ sigmoid diverticulitis	Multiple	Resection of the entire diverticula-bearing segment of jejunum with primary anastomosis and Hartmann's procedure
3	Lempinen et al.,[3] 2009	78/M	4 days of right upper abdominal pain and chills	US: No free air; no fluid collections	Laparotomy	Extensive jejunal diverticulosis; adjacent mesenteric abscess	Multiple	Jejunal resection with primary anastomosis
4	Lempinen et al.,[3] 2009	75/F	1 day of abdominal pain (RLQ)	AXR: no free air	Laparotomy	Single jejunal diverticula with adjacent mesenteric abscess	Isolated	Jejunal resection with primary anastomosis and appendectomy
5	Lempinen et al.,[3] 2009	83/F	Increasing abdominal pain and signs of peritonitis	CT: free air	Laparotomy	Perforated diverticula and faecal peritonitis	Multiple	Segmental resection with primary anastomosis/lysis of adhesions
6	Lempinen et al.,[3] 2009	77/M	4 days of abdominal pain and melaena	CT: 5x10 cm solid tumour	Laparotomy	Large, bleeding jejunal diverticulum impacted with haematoma	Isolated	Jejunal resection with primary anastomosis
7	Lempinen et al.,[3] 2009	75/M	Acute abdominal pain and fever	CT: Normal	Laparotomy	Perforated jejunal diverticula, 30 cm from ligament of Treitz	Isolated	Jejunal resection with primary anastomosis
8	Lempinen et al.,[3] 2009	78/M	1 week of abdominal pain, nausea, vomiting, and fever; increased intensity of abdominal pain	CT: intra-abdominal abscess US: thickened, slow peristaltic colonic bowel loops	Laparotomy	Intra-abdominal abscess	Multiple	Segmental resection with primary anastomosis
9	Lempinen et al.,[3] 2009	72/M	1 day of abdominal pain and obstipation	NA	Laparotomy	Adhesions	Multiple	Adhesiolysis

Table 1 continued.

10	Lempinen et al.,[3] 2009	59/M	Chronic symptoms of abdominal pain, occasional fever	Gastro/colon normal CT: normal Enteroclysis: jejunal diverticulosis	Laparotomy	Turbid fluid in abdomen/ large impacted small bowel stone (enterolith) in mid-jejunum	Multiple	Segmental resection with primary anastomosis
11	Chugay et al.,[10] 2010	79/M	Abdominal pain, nausea, and vomiting	CT: extensive inflammation of a small bowel segment on left; free air; pneumatosis of mid-jejunum	Laparotomy	Turbid fluid in abdomen/ large impacted small bowel stone (enterolith) in mid-jejunum	Multiple	Segmental resection with primary anastomosis
12	Chugay et al.,[10] 2010	89/F	Abdominal pain and constipation; SBO	CT: pan-colic diverticulosis/ dilated small bowel loops	Laparotomy	Multiple diverticula and dilated SBO loops; impacted stone (3 cm enterolith) in distal jejunum	Multiple	Segmental resection with primary anastomosis
13	Butler et al.,[14] 2010	82/F	Generalised abdominal pain and vomiting	AXR: multiple dilated small bowel loops CT: thickening of duodenum/ dilatation of proximal jejunum; multiple diverticula with air surrounding	Laparotomy	2 pinhole jejunal perforations associated with faecal contamination	Multiple	Primary repair of the 2 sites of perforation with abdominal washout
14	Akbari et al.,[15] 2013	74/M	2 days of constipation, anorexia, fever, and left-sided abdominal pain	AXR: prominent but not dilated bowel loops	Laparotomy	Multiple jejunal diverticula, one of which perforated (40 cm distal to ligament of Treitz)	Multiple	Segmental resection with primary anastomosis
15	Webster et al.,[16] 2014	54/M	Diarrhoea, vomiting, and abdominal pain	CXR: air under the diaphragm	Laparotomy	Generalised purulent peritonitis due to perforation jejunal diverticula, containing impacted faecalith 20 cm from DJ flexure	Isolated	Segmental resection with primary anastomosis

Table 1 continued.

16	Kavanagh et al.,[7] 2014	63/M	RLQ pain	CT: contained perforation with central calcification within diverticula	Laparotomy	Perforated jejunal diverticula	Multiple	Segmental resection with primary anastomosis
17	Chaudhery et al.,[17] 2014	84/F	Abdominal pain and vomiting	CT: Locules of free gas; picture of SBO	Laparotomy	4-quadrant purulent peritonitis; micro-abscesses; isolated perforated jejunal diverticula due to enterolith (12x6 cm)	Isolated	Segmental resection with primary anastomosis
18	Baksi et al.,[18] 2014	55/F	Diffuse abdominal pain, constipation, and fever	AXR: free air under the diaphragm	Laparotomy	Isolated jejunal diverticula 50 cm from DJ flexure, with 1 cm perforation	Isolated	Segmental resection with primary anastomosis
19	Hubbard et al.,[19] 2015	Unknown/M	Abdominal pain	CT: large, calcified mass within the lumen of the small bowel; enterolith within the lumen of the small bowel; mesenteric twist	Laparotomy	Multiple jejunal diverticula; perforated diverticula with a 4x5 cm enterolith	Multiple	Segmental resection with primary anastomosis
20	Natarajan et al.,[20] 2015	56/M	Abdominal pain, vomiting, and low-grade fever	CT: multiple small-bowel diverticula; air under the diaphragm	Laparotomy	Purulent exudate with perforated jejunal diverticula	Multiple	Segmental resection with primary anastomosis
21	Sehgal et al.,[21] 2016	82/M	Abdominal pain, nausea, and low-grade fever	CT: hollow viscus perforation; pneumoperitoneum	Laparotomy	Multiple diverticula; single perforated jejunal diverticula	Multiple	Segmental resection with primary anastomosis
22	Gupta and Kumar,[22] 2017	50/M	Abdominal pain, nausea, and fever	N/A	Laparotomy	Multiple diverticula; sealed perforated diverticula	Multiple	Segmental resection with primary anastomosis

Table 1 continued.

23	Alvez Martins et al.,[23] 2018	74/F	Abdominal pain, nausea, and vomiting	CXR: free air under the diaphragm	Laparotomy	Multiple diverticula; perforated jejunal diverticula, 20 cm from ligament of Treitz	Multiple	Segmental resection with primary anastomosis
24	Authors' case	60/F	Abdominal pain, fever, and chills	CT: thickening and enhancing jejunal loops; enterolith within the jejunum with fat streaking	Laparoscopy	Isolated perforated jejunal diverticula due to enterolith, 40 cm distal to ligament of Treitz	Isolated	Segmental resection with primary anastomosis

AXR: abdominal x-ray; CXR: chest radiograph; DJ: duodenojejunal; F: female; M: male; N/A: not applicable; RLQ: right lower quadrant; SBO: small bowel obstruction; US: ultrasound.

utilise the laparoscopic approach and hence minimally invasive surgery in the treatment of such a rare entity. Due to its rarity, diagnosis is usually delayed. The authors' case report highlights the importance of maintaining a high clinical suspicion of a perforated small bowel diverticulum in any patient presenting with an acute abdomen with localised signs of peritonitis. Furthermore, although non-operative management has been shown to be beneficial in stable patients, surgical exploration with segmental resection and primary anastomosis remains the mainstay of management. The authors believe that the acute onset of pain in absence of gross contamination of the abdomen was due to ischaemia, caused by the stagnated enterolith. Furthermore, the authors opted for laparoscopic approach as the patient was haemodynamically stable and this decreased the post-operative morbidity.

CONCLUSION

Jejunal diverticula is a rare entity, and their perforation is a challenge to the unaware. A delay in the diagnosis can be fatal, especially as this disease is more common in the elderly population with multiple comorbidities. Early surgical intervention when indicated is the key for successful treatment. While there is emerging evidence for the role of conservative management, the concern for progression to free perforation, especially in the setting of large, perforated diverticula, makes segmental resection the preferred intervention. Surgical approach, being laparoscopic or open, depends on the surgeon's expertise and available resources.

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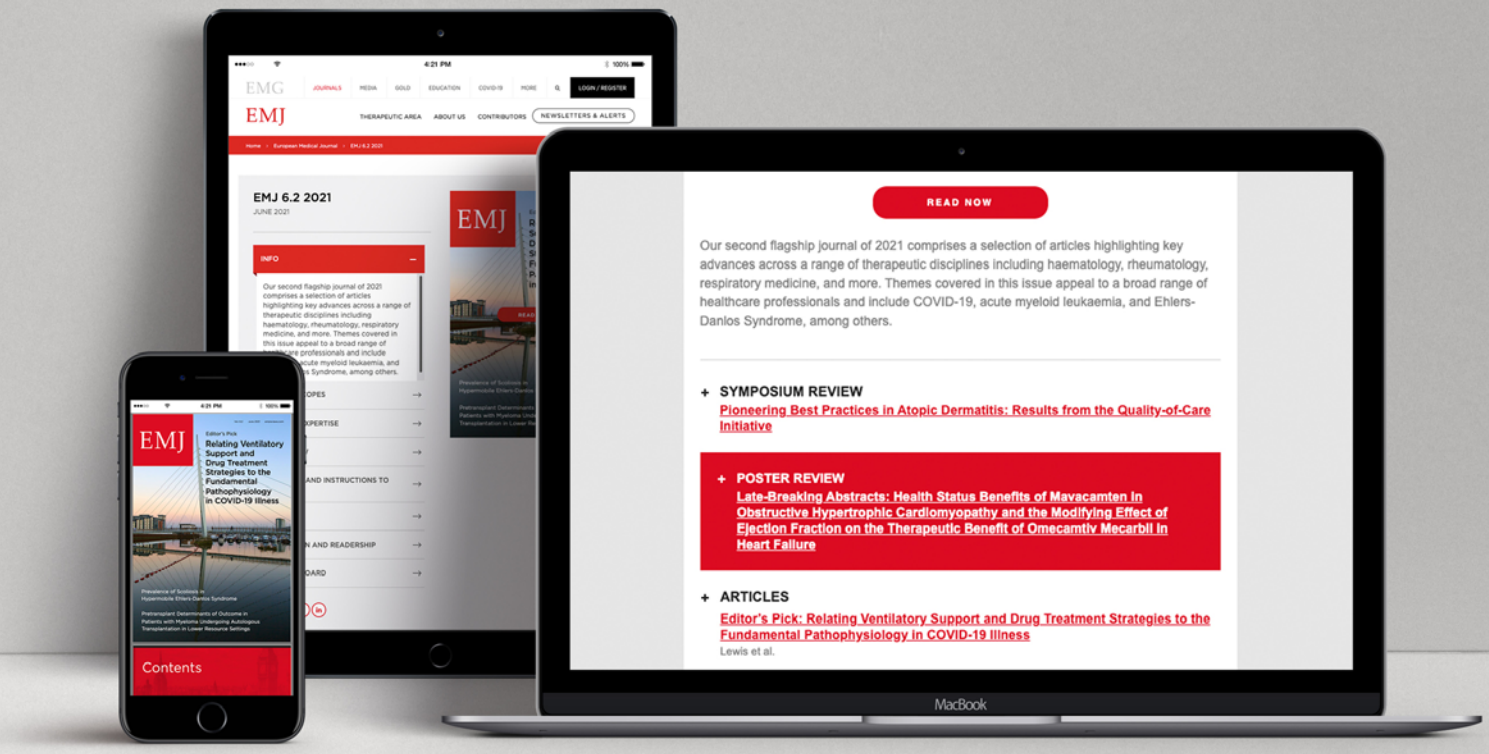

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