EMJ EUROPEAN MEDICAL JOURNAL

GASTROENTEROLOGY

ISSN 2054-6203 — Vol 8.1 • December 2019 • emjreviews.com

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Aims and Scope

The European Medical Journal (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.

EMJ also publishes 16 therapeutic area journals, which provide concise coverage of salient developments at the leading European congresses. These are published annually, approximately 6 weeks after the relevant congress. Further details can be found on our website: www.europeanmedical-journal.com

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- Invited contributors are recognised authorities from their respective fields.
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- An experienced team of editors and technical editors.

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All peer review is double blind.

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European Medical Journal Gastroenterology is published once a year. For subscription details please visit: www.europeanmedical-journal.com

Front cover and contents photograph: Barcelona, Spain, home of the UEGW 2019. © Olena Serditova / 123rf.com

EMJ Gastroenterol.

EMJ 4.3 2019

In this edition you will find a selection of peer-reviewed articles covering the latest developments across therapeutic areas including rheumatology, hepatology, plus more.

VIEW ALL JOURNALS ←

Welcome

To our readers and contributors, with great delight I welcome you to this year's edition of *EMJ Gastroenterology*, a marvellous collection of our finest hand-picked articles. Viewing *EMJ Gastroenterology 8.1* in its entirety provides me with a great deal of satisfaction and pride. As one of our longest running journals, the publication of this edition showcases our devotion to the quality and longevity of our brand. Having overcome and endured within the challenging open-access environment, it is important to reminisce and be proud of the many successes that have come, and to consider ways of improving in the future. This letter serves both as a thank you for your continued support and an invitation for your involvement in shaping the future of our journal content. Our editorial team is always delighted to receive ideas from our readers for making the content more compelling; therefore, should you have any suggestions or feedback then please contact them **here**.

This year's 27th United European Gastroenterology (UEG) Week truly lived up to its motto: sharing the future of digestive health. Our Congress Review provides an overview of the latest research trends of the field including frozen faecal transplant for irritable bowel syndrome, and how commonly used drugs affect the gut microbiota. You will also find a review of the abstract awards bestowed at the congress followed by exemplary abstract summaries. Furthermore, we provide a 'What's New' feature, summarising the newest updates within the fields of gastroenterology, hepatology, and endoscopy and another feature on algorithms in the management of Crohn's disease.

Make sure to give our interviews with the UEG Chair of Equality & Diversity Task Force and the Chair of the National Societies Committee a read. Both present insights into the operations of the committees to ensure a successful UEG congress each year and provide encouraging words which may be extremely valuable to the upcoming gastroenterologists among you.

Within these pages, you will also discover an assortment of truly intriguing articles and case reports. These span from refractory gastroesophageal reflux disease to exclusive enteral nutrition in children with Crohn's disease. Despite the continued research and efforts within the field of gastroenterology, an increased prevalence of digestive and hepatic disorders exists. We hope that this publication and future publications will spark new research ideas and challenging debates amongst colleagues contributing to advancements in the field. I would like to acknowledge all contributors for their input to this journal and extend great appreciation to my entire EMJ team. *Ad astra per aspera!*

Spencer Gore

Chief Executive Officer, European Medical Group

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Foreword

Dear Colleagues,

It is a pleasure to welcome you to *EMJ Gastroenterology 8.1*, which encapsulates the true spirit of the field at this time. The passion that EMJ has for this important area of study is evident in every page, and I am excited for you to join us by reading our journal to hear what you have to say about it.

This year's United European Gastroenterology (UEG) Week was a spectacular event, filled with exciting sessions, fascinating presentations, and challenging debates. Delegates joined from across the world, and the atmosphere was buzzing. In the Congress Review, EMJ report on the comings and goings of the event, highlighting the news stories that really matter, and giving a voice to researchers and presenters who regaled attendees with the results of studies and trials that will propel us forward in our understanding of the gastroenterological system. We are particularly excited to report on the awards that were received at the congress, recognising the exceptional work of a number of individuals.

The Congress Review features a selection of articles with renowned members of UEG Week, all of whom offer their thoughts and ideas about some exceedingly important topics. Alongside the hot topics of study, the interviewees discuss their experience in things like the National Societies Committee and the UEG Week Equality & Diversity Task Force. Adding a personal touch to our congress coverage, these interviews will prove valuable for readers at any stage in their medical career; I highly recommend them.

The articles included in the journal comment on some of the biggest topics from UEG Week and offer some interesting food for thought on them. In my Editor's Pick for this year, read Nabi et al.'s article about gastroesophageal reflux disease, its multifaceted pathophysiology, the different stages of evaluation that will lead to correct diagnosis, and the multidisciplinary nature of treatment. Additionally, the improvement of communication between pathologists and surgeons relating to resection margins in the surgical treatment of colorectal cancer is discussed by Salmo and Haboubi. Kangesu et al. present an interesting case study on a patient who, following multiple misdiagnoses and examinations, was diagnosed with severe systemic manifestations of rheumatoid arthritis. The diagnosis methods and treatment of the patient are detailed with precision, making this a valuable addition to the journal. All these plus more are included for your reading pleasure, and I hope that they will create debate and discussion among peers.

It is my pleasure to serve as Editor in Chief of EMJ Gastroenterology, and I am very proud to present this year's journal. I hope you will enjoy reading it as much as I did.

Professor Sorin T Barbu

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

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Congress Review

+ Review of the European Association for the Study of the Liver's (EASL) International Liver Congress (ILC) 2019, Vienna, 10th–14th April 2019

Congress Interview

+ Prof Dina Tiniakos

Abstract Reviews

Features

+ Management of Hepatitis C in People Who Inject Drugs: Some Practical Lessons from the Frontline of the Elimination Battle
+ Transjugular Intrahepatic Portosystemic Stent-Shunt (TIPSS) for Acute Variceal Bleeding: Has it Come of Age?

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+ Editor's Pick: The Overview of Alpha-1 Antitrypsin Deficiency-Mediated Liver Disease Esra Karatas et al.
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Congress Review

Review of the 27th United European Gastroenterology (UEG) Week Congress

Location: Fira Gran Via, Barcelona, Spain

Date: October 19th–23rd

Citation: EMJ Gastroenterol. 2019;8[1]:13-21. Congress Review.

One can walk in almost any direction through the bustling streets of Barcelona and be presented with constant reminders of the ingenuity and creativity that has for centuries sprouted from the Catalonian earth. Brilliant architectural minds such as Antoni Gaudi and Lluis Domènech i Montaner have graced the city with a unique aesthetic that to this day enamours visitors, while artistic contributions from innovators such as Joan Miró helped cement Barcelona as a cultural hub on the world stage. True and lasting innovation, however, comes through debate and co-operation, both ideals that Barcelona has built a reputation for through the facilitation of numerous annual congresses, a significant attention of which is given to different aspects of the medical landscape. This year, we have had the pleasure of attending a number of these meetings, making this review of the 27th United European Gastroenterology (UEG) Week Congress a fitting conclusion to our 2019 publication schedule.

Welcoming approximately 13,204 attendees from across 122 countries, UEG President Paul Fockens opened proceedings with news of this being the first time that >4,000 abstracts were submitted for consideration at the meeting, and that this same number of individuals attended the Postgraduate Teaching Programme. This is a sign of not only the growth of UEG Week as an institution, but of the growth the gastroenterological field is experiencing regarding the continual advancement of patient-tailored and effective therapies. "I believe we generated a hugely exciting programme and sincerely hope that attendees engaged in stimulating debates and enjoyed the latest science," concluded Herbert Tilg, Chair of the UEG Scientific Committee, following the Congress.

A number of highly informative abstract presentations were delivered at UEG, of which we have highlighted two that we believe deserve special mention. Metwaly et al. have graciously contributed a summary of their work into the metabolome and how it can

reveal functional signatures in Crohn's disease through a connection with sulphur metabolism. It is tremendously exciting to see how rapidly research into the metabolome is progressing, and undoubtedly the gastroenterological community is at the forefront of this investigation. Hassan et al. shift the conversation to Paneth cell lymphangiogenesis regulation, both in normal physiology and experimental portal hypertension, and in doing so identify a new function of this cellular niche. Also included within our review is a recap of the abstract award winner ceremony at this year's event; Drs Magdy El-Salhy, Lissy de Riddler, and Yang Wang among others were commended for their efforts in advancing the field, and collectively these achievements represent a very proud moment for the Congress and the field as a whole.

One of the most valuable benefits of medical congress attendance is the opportunity to hear the exciting breakthroughs in a given field for the first time, and UEG Week was no exception. In one press release, it was reported that nearly half of 41 commonly prescribed drugs considerably affect the gut microbiome, perhaps eluding to unexplained side-effects associated with medication use; alarming findings were presented suggesting a significant underestimation of inflammatory bowel disease prevalence in the UK, and how this can have impacts on factors outside of personal health; and faecal microbiota transplantation has shown highly encouraging results for the treatment for irritable bowel syndrome. The gastroenterological field can be defined as much by its unique challenges as it is by the innovative solutions being proposed for its betterment, however the passion this community brings to the table is ubiquitous. These stories and more are described in the following pages.

Complementary to these discoveries are informative interviews with members of two UEG Week committees: Prof Dan Dumitrascu and Prof Nurdan Tözün. Representing the views of the National Societies Committee and the Equality & Diversity Task Force, respectively, these key figures in the gastroenterological field

"I believe we generated a hugely exciting programme and sincerely hope that attendees engaged in stimulating debates and enjoyed the latest science,"

"The gastroenterological field can be defined as much by its unique challenges as it is by the innovative solutions being proposed for its betterment,"

provide an astute opinion regarding various aspects of the therapeutic area and the inner workings of a hugely influential society in UEG. It is a constant source of amazement to us hearing first-hand from committee members how meetings as successful as UEG Week come to fruition, and the commentary these pillars of the society give can most certainly enhance the mindsets of other aspiring researchers and clinicians.

This has been a fantastic year across all the therapeutic disciplines that EMJ covers however the advancements presented at UEG mark an explosive ending to the year. It is obvious that the congress has and will continue to grow from strength to strength, making next year's event in our home city of London a clear highlight to mark in your calendars. Until then, and from the entire EMJ family, we hope you enjoy getting stuck into this Congress Review.

Increased Rates of Digestive Diseases within the Last 30 Years

GLOBAL death rates for pancreatic cancer and incidence rates for colorectal cancer have increased by 10% between 1990 and 2017 according to a press release revealed at UEG Week 2019 in Barcelona, Spain. The results of the Global Burden of Disease Study which spanned across 195 countries is the first to provide an estimate of the worldwide burden, epidemiological features, and risk factors of a number of digestive diseases.

The study showed that the number of pancreatic deaths increased from 196,000 in 1990 to 448,000 in 2017. Some of the increases in the 27-year study period can be attributed to rising population numbers and life-expectancy; however, age-standardised incidence and death rates for pancreatic cancer increased by 12% and 10%, respectively. These increases are believed to be associated to the rise in the prevalence of diabetes and obesity, reflected in the risk factors of high BMI and hyperglycaemia which are two of the main risk factors for pancreatic cancer. According to Prof Reza Malekzadeh, Tehran University of Medical Sciences, Tehran, Iran, "pancreatic cancer is one of the world's deadliest cancers, with an overall 5-year survival rate of just 5% in high, middle, and low-income countries. Major risk factors for the disease, such as smoking, diabetes, and obesity, are largely modifiable and present a huge opportunity for prevention."

Globally, age-standardised incidence rates for colorectal cancer increased by 9.5% from 1990 to 2017; however, age-standardised death rates decreased by 13.5%. Colorectal cancer screening programme inductions are believed to be the catalyst for the decreased death rate, leading to earlier detection and increased survival rates. Results from the study also indicated that risk factors for colorectal cancer differ between males and females and should therefore be considered in national policy and prevention programmes. Risk factors for males include alcohol use, smoking, and diets low in calcium, milk, and fibre; for females, dietary risks, but not alcohol use or smoking, were found to be risk factors.

In the case of age-standardised gastric cancer death rates and incidence, a steady decrease was observed between 1990 and 2017, yet this decline did not lead to a lower burden on the health system in high-risk countries prompting experts to believe that local strategies should be tailored to each country's specific risk factor profile. Prof Malekzadeh concluded that "beyond the current decline in incidence and death rates, a decrease in the absolute number of cases and deaths will be possible if the burden in east Asia, where currently almost half of the cases and deaths occur, is further reduced."

"pancreatic cancer is one of the world's deadliest cancers, with an overall 5-year survival rate of just 5% in high, middle, and low-income countries."

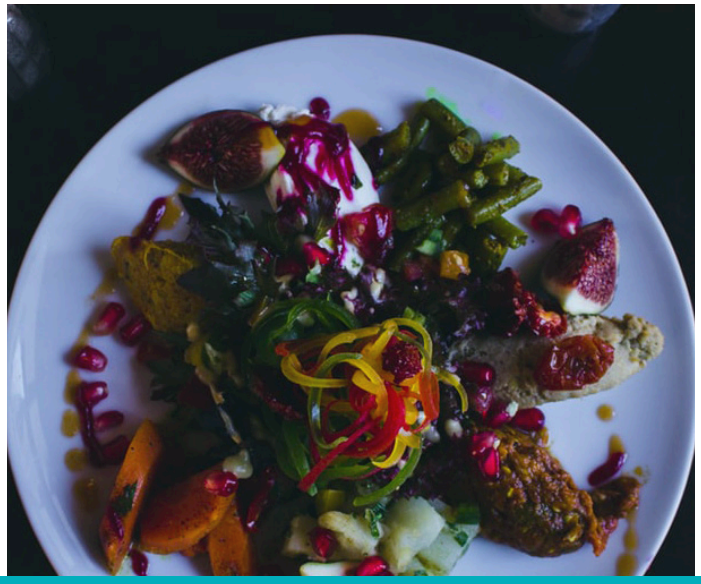
Rising Cases of Antibiotic Resistance to Clarithromycin

TREATMENT involving antibiotics is becoming a challenge with *Helicobacter pylori* bacterial infections because resistance to the commonly used antibiotic clarithromycin has almost doubled in the last 20 years. This is according to findings presented at the 27th UEG Week in Barcelona, Spain, and reported in a press release dated 21st October 2019. *H. pylori* causes inflammation of the stomach lining and can lead to harmful stomach conditions such as gastric ulcer, lymphoma, and gastric cancer. It is frequently treated with clarithromycin, as well as levofloxacin and metronidazole.

The study, led by the research team of Prof Francis Megraud, University of Bordeaux, Bordeaux, France, collected data from 1,232 *H. pylori*-infected patients across 18 European countries. Results indicated that between 1998 and 2018, resistance to clarithromycin increased from 9.9% to 21.6%. Trends were also spotted within countries: the highest resistance rates were reported in south Italy (39.3%), Croatia (34.6%), and Greece (30.0%). This correlates to previous findings that these countries overconsume antibiotics for common colds and flu and is further evidence of predictions that these countries will have highest death rates for antimicrobial resistance by 2050.

Resistance to antibiotics is considered to be one of the biggest threats to global health as resistance rates are climbing nearly 1% a year and causing over 750,000 deaths globally per annum. Resistance occurs when a bacterium acquires the ability to survive antibiotic treatments which have historically killed them. This research is especially poignant as *H. pylori* is thought to be present in half of the world's population, leading to the World Health Organization (WHO) naming clarithromycin resistance in the bacteria as a high priority for research and development in 2017. Professor Megraud expressed his concern as he declared, "treatment options for *H. pylori* will become progressively limited and ineffective if novel treatment strategies remain undeveloped."

Inflammatory Properties of Gut Microbiota Affected by Consumption of Certain Foods



CONSUMPTION of certain foods has been shown to have beneficial effects on gut microbiota, as observed by researchers from the University Medical Center Groningen in Groningen, Netherlands. This study was presented as part of a press release on 21st October at the UEG Week held in Barcelona, Spain.

The researchers found that the increased levels of gut bacteria, which aid the biosynthesis of essential nutrients and short chain fatty acids, were associated with consumption of certain foods. By including foods such as legumes, bread, fish, nuts, and wine in the diet, the gut could be provided with additional protection and to a certain extent, disease control. The lead researcher of the study, Dr Laura Bolte, commented, "we looked in depth at the association between dietary patterns or individual foods and gut microbiota. Connecting the diet to the gut microbiome gives us more insight into the relation between diet and intestinal disease. The results indicate that diet is likely to become a significant and serious line of treatment or disease management for diseases of the gut – by modulating the gut microbiome".

"Connecting the diet to the gut microbiome gives us more insight into the relation between diet and intestinal disease."

Research was obtained by collection and analysis of stool samples from participants in divided into four main study groups: patients with Crohn's disease, irritable bowel syndrome, ulcerative colitis, and the general population not suffering from any of these conditions. By analysing the samples provided by the patients, researchers were able to reconstruct the individual's microbiota and use this to compare with a food frequency survey to identify food patterns with microbial populations or groups.

From the food types tested, 61 individual items were shown to be associated with microbial populations and correlation between food patterns and microbial groups was identified in 49 instances. The researchers observed a decrease in harmful, aerobic bacteria and lower levels of inflammatory markers in the stool analysis of participants with a diet high in legumes, bread, fish, and nuts. Increased consumption of these foods, as well as red wine, fruit, and vegetables, was also associated with greater levels of bacteria with anti-inflammatory functions.

The study showed that increased consumption of meat, fast food, or refined sugar was associated with decreased function of beneficial bacteria and increased inflammatory markers, certain markers of which are known to rise during intestinal inflammation. There was a great contrast between the effects of animal and plant-derived protein on the gut microbiota to such an extent that entirely opposing associations were seen. A plant-based diet was associated with increased production of bacterial short chain fatty acids, increased biosynthesis of vitamins and amino acids, breakdown of sugar alcohols, and ammonium excretion.

The research showed that certain diets are risk factors to the incidence of intestinal disease. By ascertaining which foods are beneficial to the gut microbiota with anti-inflammatory properties, effective dietary decisions can be made to increase consumption of these foods and create management strategies to combat disease.

Commonly Used Drugs Affect the Gut Microbiome

THE GUT microbiome is impacted by nearly half of the drugs most commonly used, as found in a study and presented in a press release from EUG Week 2019 dated Wednesday 23rd October 2019. Of the 41 commonly used drugs studied, 18 were found to considerably impact the gut microbiome, both its taxonomic structure and metabolic potential.

Within the study, researchers studied 41 drugs that were categorised as common use. The patient cohort comprised people living with irritable bowel syndrome, people who have inflammatory bowel disease, and healthy controls. From these participants, 1,883 faecal samples were collected, and taxonomic and metabolic functions were measured. Comparisons were made for drug users versus non-drug users to identify the impact of both single and combined medication use.

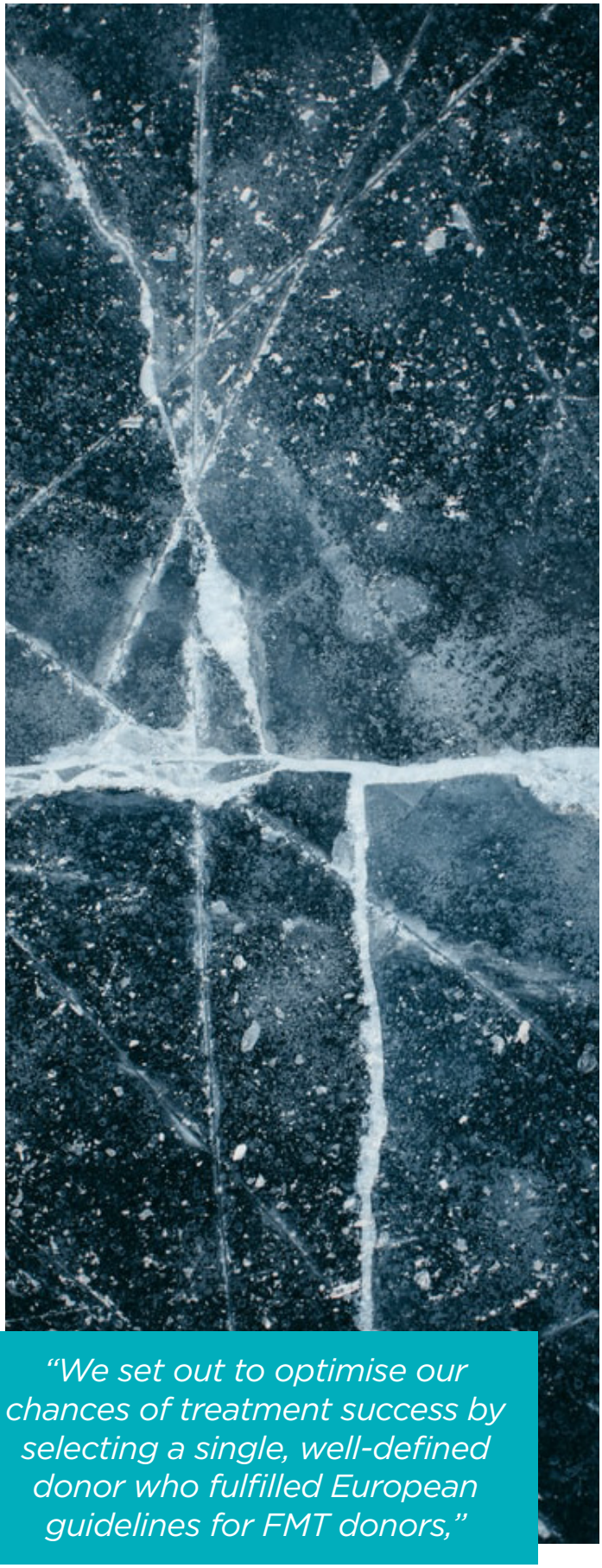
Results showed that identified changes could lead to a higher chance of obesity, intestinal infections, and other gut microbiome health conditions. Proton pump inhibitors, metformin, antibiotics, and laxatives were the four drug categories found to have the biggest effect on the gut microbiome. Participants who were using proton pump inhibitors displayed higher levels of upper gastrointestinal tract bacteria. Patients on metformin showed increased levels of *E.coli*: a potentially damaging bacteria.

Of the drug categories studied, seven were found to be associated with differences in the gut's bacterial population. Selective serotonin reuptake inhibitors were linked to an increase of the bacteria species *Eubacterium ramulus*, which is also potentially harmful. Steroid use was found to be associated with an increase of methanogenic bacteria: a bacteria linked to obesity and higher BMI.

Arnau Vich Vila, University Medical Center of Groningen, Groningen, Netherlands, concluded: "It is crucial to understand which are the consequences of medication use in the gut microbiome. Our work highlights the importance of considering the role of the gut microbiota when designing treatments and also points to new hypotheses that could explain certain side-effects associated with medication use."

"Our work highlights the importance of considering the role of the gut microbiota when designing treatments"

Frozen Faecal Transplant from Super-Donor Proves a Success for Irritable Bowel Syndrome



FAECAL microbiota transplantation (FMT) has been speculated as a potential treatment for inflammatory bowel disease (IBD) until now. Results presented in a UEG Week press release dated 21st October 2019 have now confirmed that FMT from a single 'super-donor' is well tolerated, effective, and shows marked IBS symptom improvement.

The large, randomised, double-blind, placebo-controlled study involved 164 individuals with IBS and moderate-to-severe IBS. Placebo consisted of a solution of the participants own faeces. Those not on placebo received either a 30 g or 60 g donor transplant solution containing faecal matter from a super-donor. In contrast to other studies, the transplant material had been stored at -80°C then administered into the proximal duodenum via gastroscope once thawed.

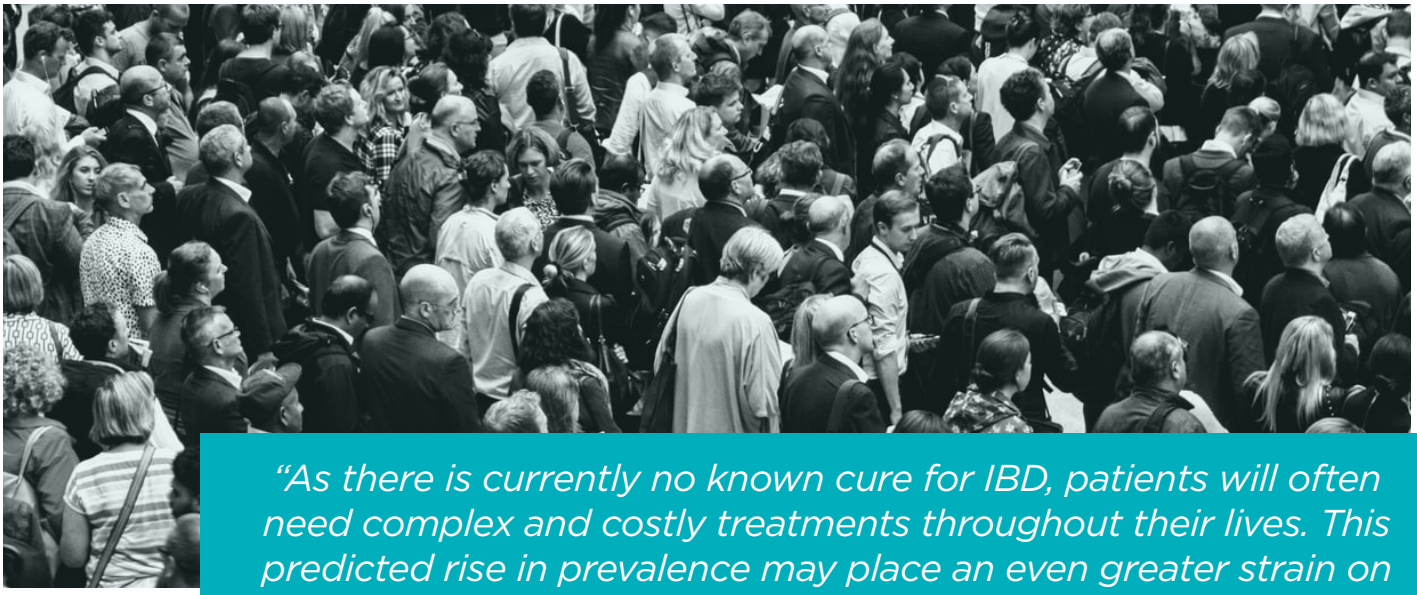
The super-donor chosen for this study was an athletic, 36-year-old, Caucasian male. He had no significant medical history and had only received three courses of antibiotics during his lifetime. "We set out to optimise our chances of treatment success by selecting a single, well-defined donor who fulfilled European guidelines for FMT donors, and who had a favourable faecal microbial profile," commented the study lead investigator Prof Magdy El-Salhy, Haukeland University Hospital, Bergen, Norway.

A response (≥50-point reduction in IBS-SSS [IBS severity scoring system] at 3 months after FMT) occurred in 23.6%, 76.9%, and 89.1% of patients who received placebo, FMT 30 g, and FMT 60 g, respectively. Furthermore, clinically significant improvements in symptoms (a ≥175-point reduction in IBS-SSS) was observed in 5.5%, 35.2%, and 47.3% of participants on placebo, FMT 30 g, and FMT 60 g, respectively.

The study investigators stressed the importance of the super-donor in the effectiveness of the treatment and Prof El-Salhy concluded: "The use of frozen faeces eliminates the logistical problems associated with FMT involving fresh faeces, making it possible to establish bio-banks for the routine use of FMT in clinical practice."

"We set out to optimise our chances of treatment success by selecting a single, well-defined donor who fulfilled European guidelines for FMT donors,"

New Estimates for Inflammatory Bowel Disease Prevalence in UK



"As there is currently no known cure for IBD, patients will often need complex and costly treatments throughout their lives. This predicted rise in prevalence may place an even greater strain on already overburdened healthcare systems."

FINDINGS have emerged from a press release dated October 21st at UEG Week Barcelona 2019 suggesting that assumptions the gastrointestinal clinical community had made regarding inflammatory bowel disease (IBD) prevalence in the UK were underestimating the problem, and that the number of IBD patients is three times higher than previously thought. The analysis also deduced that this demographic is at an increased risk of colorectal cancer development.

Acknowledging limitations in existing data, researchers from Sandwell and West Birmingham hospitals NHS trust and the University of Birmingham conducted a new analysis into ulcerative colitis (UC) and Crohn's disease (CD) cases dating back to 2000. Incorporating additional data from the Health Improvement Network (THIN), an alarming realisation was made in the discovery of a three-fold increase in IBD prevalence: 55% and 83% increases were found for UC and CD, respectively, from 2000–2017. Furthermore, a 25% prevalence jump is predicted by 2025.

Speaking at UEG Week, researcher Dr Dominic King from the University of Birmingham elaborated on the findings: "As there is currently no known cure for IBD, patients will often need complex and costly treatments throughout their lives. This predicted rise in prevalence may place an even greater strain on already overburdened healthcare systems." Dr King also highlighted the association the team found with malignancy, in that CD patients exhibited a 23% increased risk of colorectal cancer development compared to matched controls; this risk was nearly doubled (43%) in patients with UC.

Given the European-wide scale of IBD (an estimated 3 million people affected), as well as the severity and duration of the symptoms associated with this group of disorders, the importance of these findings cannot be underestimated. IBD patients experience higher rates of depression and reduced workforce participation, meaning the challenges facing clinicians looking to treat IBD are shared by patients and policy makers nationwide. "The cost to society, either through direct medical costs or indirect costs such as lost days at work, lost educational opportunities, or caring for an affected family member, are enormous," commented President of the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA) Salvo Leone. However, whilst alarming, a new and more accurate appreciation of the epidemiological data and outlook for the future will undoubtedly help towards finding effective treatments for these patients.

What's New? A Year in Gastroenterology, Hepatology, and Endoscopy

Rachel Donnison
Editorial Administrator

Looking back on the last year, it is easy to be awestruck by the progression of clinical gastroenterology and hepatology research, one of the most notable developments being our greater understanding of the microbiome. UEG Week, speeding towards almost 30 years of congress, covered a host of material spanning last year's developments and cutting-edge research, summarised nicely in the 'What's New' sessions for gastroenterology, hepatology, and endoscopy. Additionally, lesser known aspects of the specialism such as gender equality and equal opportunity have experienced real growth. UEG Week have stepped up to play their part, taking direct action following the 2015 congress where data showed an under-representation of women, and leading to the implementation of the Equality and Diversity Task Force. Diversity and balance have been shown to have wide-reaching, positive implications, and is perhaps a reason that in the last year we have witnessed such a spike in revolutionary research.

WHAT'S NEW IN GASTROENTEROLOGY?

Gastroenterology has enjoyed a lot of time in the spotlight in 2019. Prof Emad El-Omar of the University of South Wales, Sydney, Australia, kickstarted this session with a debrief of the hottest topics this year, stating: "It is not a secret that perhaps the microbiome is the one that takes the lion's share."[1] The multi-omic approach is one that has been highlighted by several recent papers, including Zhou et al.[2] Involving an integrative biological analysis of transcriptomes, metabolomes, cytokines, and proteomes, multi-omics was used as tool to study host-microbe dynamics in prediabetes to create prediction models for insulin resistance. One multi-omics-based study that made the headlines this year involved an analysis of elite athletes that identified an increase of *Veillonella* in the gut 5 days post marathon.[3] The subsequent inoculation of this bacterial strain into mice significantly increased performance in the exhaustive treadmill test. The scope of the microbiome field is ever-expanding it seems, and partnered with multi-omics, is making waves across all specialities. According to Prof El-Omar, multi-omics is "an approach that should perhaps be followed by all of our research in the microbiome field."

Prof El-Omar proceeded to give a summary of other exciting papers that have been published in the last year, focussing attention firstly to the

Lamb et al.[4] paper. This featured a monumental systematic review of 88,247 publications alongside a Delphi consensus process involving 81 multidisciplinary clinicians and patients, generating 168 evidence and expert opinion-based intervention recommendations for those with ulcerative colitis and Crohn's disease. Concluding remarks concentrated on the latest pancreatic cancer research, specifically in reference to the link between high tumour microbial diversity and long term survival,[5] the role of the microbiome in adaptive immune suppression,[6] and promotion of pancreatic oncogenesis by the fungal microbiome via the mannan-binding lectin pathway.[7]

"it could well be that in 2020 we have the first approved drug for patients with advanced Stage 2 fibrosis NASH."

WHAT'S NEW IN HEPATOLOGY?

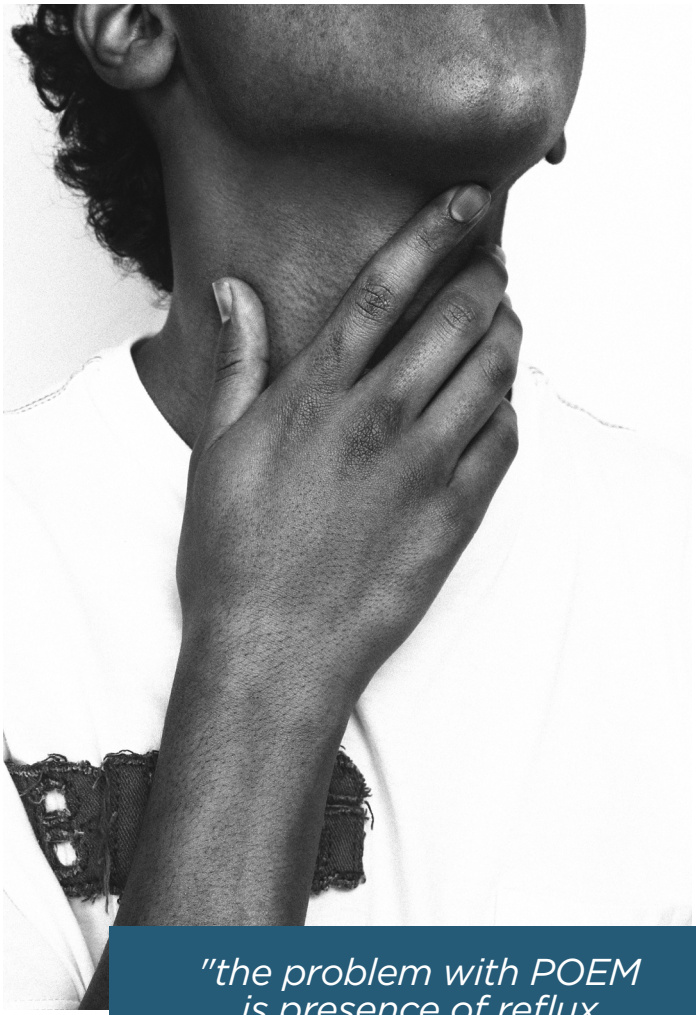
Popular research topics in hepatology this year include viral hepatitis, non-alcoholic fatty liver disease, cholestatic liver disease, and cirrhosis complication prevention. Dr Thomas Berg of the University Clinic Leipzig, Leipzig, Germany, shared his personal overview on upcoming treatment options, many of which are in Phase III clinical trials, as well as studies that could have important implications in clinical management strategies.[8] Regarding hepatitis C virus (HCV), real-world cohorts and large global datasets have confirmed clinical trial evidence for velpatasvir/sofosbuvir treatment, with incredibly high sustained virologic response (SVR) rates (PP: 98.5%; ITT: 92.7%).[9] Building on the research presented at the latest EASL ILC meeting analysing glecaprevir/pibrentasvir treatment,[10] more attention is being paid to lowered response rates seen in the HCV genotype 3. Patients who did not respond to first-line, direct-acting antiviral agents have responded well to the rescue treatment sofosbuvir/velpatasvir/voxilaprevir (Vosevi), with only 1–2% failing to rescue.[11] The next step, according to Dr Berg, is deciding "what to do now with patients we have cured," in terms of safe discharge and appropriate follow-up.

Another hot topic in the hepatology field is key drug targets in clinical trials for non-alcoholic steatohepatitis (NASH). Four examples from Phase III clinical trials are: selonsertib and cenicriviroc, targeting inflammation and fibrosis; and elafibranor and obeticholic acid, which both target lipid metabolism.[12] Of these four, obeticholic acid is currently showing most promise, especially concerning the results of a study by Younossi et al.[13] which demonstrated a primary endpoint of fibrosis improvement by ≥1 Stage, with no worsening of NASH in 23.1% of participants and a decline in all biochemical parameters. There is much excitement surrounding these results, and Prof Berg noted that "it could well be that in 2020 we have the first approved drug for patients with advanced Stage 2 fibrosis NASH."

WHAT'S NEW IN ENDOSCOPY?

Attempting to avoid the "haute cuisine" of endoscopy in 2019, Dr Maria Pellisé of the Hospital Clínic of Barcelona, Barcelona, Spain, centred her session[14] around three less-talked-about subjects: third space endoscopy, per-oral endoscopic myotomy (POEM), and artificial intelligence (AI). Focus was firstly aimed at achalasia, a rare disease that has an incidence rate of 5 in 1 million, and the use of the POEM technique as a first treatment option. In a randomised controlled trial conducted by Ponds et al.,[15] the success rate of POEM in achalasia was 92% compared to 54% with pneumatic dilation. Dr Pellisé does however acknowledge that "the problem with POEM is presence of reflux oesophagitis that comes after treatment, but in clinical practice almost half of

the patients can be controlled with proton pump inhibitors. This is something that will come in the next years."



"the problem with POEM is presence of reflux oesophagitis that comes after treatment, but in clinical practice almost half of the patients can be controlled with PPI. This is something that will come in the next years."

Endoscopy research has also benefitted from the escalating rise in machine learning technology. One of the most recent papers published by Ebigo and colleagues[16] instrumented the use of computer-aided diagnosis using deep learning. The AI technology accurately analysed still images of patients with Barret's oesophagus and early oesophageal adenocarcinoma, both of which are experiencing increased prevalence in the West, to improve endoscopic assessment. The machine learning technology was, however, based on very good quality images and hence the real-world validity is yet to be confirmed. Establishing the limitations of AI will be crucial to its long-term success as a tool, allowing health practitioners to have realistic expectations of the software. Another paper released this year by Luo et al.[17] utilised AI to detect upper gastrointestinal cancer using endoscopy with accuracy equivalent to that of expert endoscopists. These results highlight the usefulness of this software as a tool for community hospitals where often there are no experts, allowing effective diagnoses. Seemingly the strengths of AI are many, though Dr Pellisé is also fully aware of the associated challenges, such as "the need for large multi-centre video dataset collections, which is not easy."

CONCLUSION

With the number of significant leaps made in gastroenterology this year, it is no surprise that much of the discussions at UEG Week focussed on future developments and predicting the innovations coming to this specialty in 2020. There will be eager anticipation as to the next discoveries of the multi-omics approach in microbiome research, and its current popularity in the press can only be good for stimulating discussion and increasing funding. The large numbers of drugs at Phase III clinical trials to treat HCV and NASH tells us we are on the cusp of rolling out successful treatment options for patients of these conditions and, whilst AI has yet to make large breakthroughs in every-day endoscopy medicine, the potential of machine learning as a tool appears boundless.

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Moving Towards a New Era: Algorithms in the Management of Crohn's Disease

Lenos Archer-Diaby
Editorial Administrator

Successful, cost-effective, and efficient management of disease treatment is the driving factor behind many scientific studies, particularly for diseases such as Crohn's disease (CD), a disorder of unknown aetiology characterised by transmural inflammation of the gastrointestinal tract.[1] With no cure available, treatment paradigms have adhered to symptom control and remission; however, within the last 10 years the focus has shifted towards 'mucosal healing': the prevention of structural damage to the intestinal wall. Consequently, to achieve these new treatment goals more aggressive treatment and earlier use of immunosuppressants and biologics are required.[2] Some patients benefit from such early aggressive treatment; others, however, incur the disadvantages of immunosuppression, of which includes the increased risk of severe infections. As a result, a major question today is whether a 'top-down' or a 'step-up' treatment approach is better suited for CD management.

Top-down treatment starts with a combination of biological and immunosuppressant agents and is de-escalated if necessary, whereas step-up treatment commences with weaker topical steroids followed by a step up to systemic steroids and, if necessary, subsequent immunosuppression and biologic use.[2] Patient diversity, however, does not permit an all-encompassing treatment, and as we are gearing towards an era of precision medicine, over and undertreatment must be avoided at all cost, prompting the need of an algorithm delineating the best patient treatment path.

Top-down is proposed as an alternative approach to classical step-up treatment because some studies have shown that immunosuppression therapy is effective in the management of CD; it is, however, seen as overtreatment by several. In a therapy update session on CD at the United European Gastroenterology (UEG) Week 2019, Dr Gerhard Rogler, University of Zurich, Zurich, Switzerland, expressed his views on the algorithm of CD management. The session opened with data from a network meta-analysis on the comparative effectiveness of agents for the induction of remission in CD, demonstrating that high doses of aminosalicylates (5-ASA), budesonide, and corticosteroids are effective, contrary to earlier guidelines which stated that 5-ASA are not effective and should not be considered during therapy, fuelling the notion that step-up is still relevant.[3]

If 5-ASA are as effective as corticosteroids, then why have they been trivialised? This may be attributable to the lack of scientific evidence regarding the efficacy of 5-ASA in CD patients. The Epi-IBD cohort, a prospective European population-based cohort, revealed that the

majority of the patients who received 5-ASA required mild or no treatment during follow-up and experienced a quiescent disease course. This establishes that patient stratification at baseline to prevent not only undertreatment, but, more importantly, overtreatment is pivotal, with Dr Rogler stating: "Top-down for everybody with CD is overtreatment." In support of this, he presented a diagram exemplifying a potential algorithm to support the management of CD. Displaying that in all population cohorts of inflammatory bowel disease, 40% have mild CD and are sufficiently treated with 5-ASA or step-up , 40% have moderate CD requiring accelerated step-up treatment with some requiring biological therapy, while only 20% have severe disease symptoms and should receive top-down targeted treatment.[3] Before proceeding to talk about ways to optimise current treatment paradigms, he emphasised that he personally believes "the slogan T2T (treat-to-target) is M4M (marketing for morons)," expressing his opposing view on everyone receiving a top-down treatment.

Knowing that budesonide is as effective as systemic steroids, despite it only having a 10% bioavailability, is a driving reason to optimise standard therapy and avoid the side effects associated with systemic steroid use. Another class of drugs that require optimisation are immunosuppressants, including thiopurines. Current guidelines recommend 2.0–2.5 mg/kg/day of azathioprine (AZA) or 1.0-1.5 mg/kg/day of mercaptopurine (6-MP) for the management of CD, but these are not efficacious for all patients.[3] Dose-response treatment appears to be the next step forward according to a meta-analysis, showcasing a lower odds-ratio to achieve treatment response. Data also revealed that when AZA treatment is not tolerated, there is a potential to switch to the lower dosage treatment of 6-MP because over half of the patients who did not tolerate AZA tolerated 6-MP. To determine how to best optimise treatment, Dr Rogler presented an algorithm involving measuring 6-thioguanine nucleotide (6-TGN) and metabolite mercaptopurine (MMP). In this model, low or absent 6-TGN and MMP demonstrates non-adhering patients who could benefit from counselling. Low 6-TGN or low to normal MMP may signify underdosing and identify patients who may benefit from a dose increase, and patients that are thiopurine refractory should be recommended another drug.

When biological treatment is necessary, what should our first line biologic be? Dr Rogler revealed that infliximab is the most potent agent to induce clinical remission in moderate-to-severe CD, but it loses efficacy when maintaining clinical remission. Whereas, adalimumab has efficacy in the opposite manner, having a lower rate of inducing remission but is better at maintenance. The European Crohn's and Colitis Organisation (ECCO) e-Guide, a collection of algorithms based on the ECCO guidelines, provides an algorithm for the optimisation of anti-TNF therapy in CD. It emphasises that regular assessment is vital, and that after relapse therapy should be revaluated and optimised, rather than switching the drug.

In summary, Dr Rogler presented the 'Swiss Algorithm', a combination of all algorithms providing a potential new structure to treating CD. He expressed his concerns regarding the therapy target of mucosal healing, which has been shown to not be achievable in most patients; therefore, is this goal suitable? In some instances, mucosal healing has been demonstrated post-surgery, yet the first-line treatment choice after surgery is still unclear. A Cochrane network analysis on interventions for maintenance of surgically induced remission in CD has shown that 5-ASA is the only significantly effective drug in the post operation situation. Combined with the fact that 5-ASA is also a drug that can be used as the first step in mild-to-moderate CD, and is as effective as corticosteroids, we are left questioning whether we have jumped the gun with top-down treatment and should step up our therapy algorithm with step-up treatment.

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Congress Interviews

Prof Dr Nurdan Tözün

Chair of the Equality & Diversity Task Force (E&DTF) for United European Gastroenterology (UEG)
Head of Internal Medicine and Gastroenterology Departments, Acibadem University, Istanbul, Turkey

Q1 You are one of the founding faculty members of Acibadem University in Istanbul, Turkey, and founder of Turkey's first gastroenterology institute at Marmara University. Could you explain a bit about your journey to achieving this ground-breaking accomplishment?

Education, a mission which I inherited from my family, has always been my priority. I based all my life on education which is for me to spread the light you acquired to people following you. For this goal we need scientific knowledge, innovation, a perfect teaching medium, the right people to work with, and of course money. I had the dream of an institution where young people could develop their skills, make high quality translational research through a better collaboration of basic sciences with clinical work, and team up with similar international institutions for research and training. Marmara University Institute of Gastroenterology, which was the first of its kind in my country, cost me 5 years of hard work and struggle with bureaucratic hurdles before being approved by the Council of Ministers in 1992. The Institute served as a ground to outstanding publications and has been a nest for many physicians and basic scientists who did their MSc and PhD in this productive learning medium. It still keeps its prestige and credibility today.

The second big project was the Acibadem Mehmet Ali Aydinlar University which was the dream of my colleague Prof Necmettin Pamir, a brilliant neurosurgeon with whom I collaborated during all my academic career to create modern institutions with international standards. The idea was to open a new and top-quality University focussing mainly on health sciences, which again would be the first of its kind in the country. Mr Aydinlar and his foundation have been our benefactor. Nothing is more painful than a new idea, but perseverance is the key because after an intense work of 4 years, Acibadem University was born in 2008. This is a proof that chance favours only the prepared mind. The University now ranks among the top ten foundation universities in Turkey and welcomes students from all over the world. We dared to dream big and always moved forward. This is the only way to succeed and not be stationary. In summary, have an idea, find the right people and run 'ad Astra per Aspera' (through hardships to the stars). This has been my motto.

Q2 During your career you have achieved some impressive feats. What, or who inspired you to have made these sorts of changes?

The inspiration and spark to become an academician and a leader came from my family

first, my teachers at the French High School (Notre dame de Sion), and from Atatürk, the founder of modern Turkey who gave women immense power and exceptional rights. My father who was a professor of finance at the university advised me to always stay in the education field no matter what I do in my profession and my mother, a teacher of maths and physics has instilled in me a sense of perfection, idealism, and humanism. Most of all, I had excellent female role models, pioneers in their fields who inspired me and encouraged me during my career. Therefore, thanks to them, I remained a passionate learner and a tireless runner, ready to take challenges.

Q3 How does UEG encourage the opportunity to promote diversity, and how does it give individuals the platform to express their ideas?

From the very beginning UEG's vision has been to provide an umbrella for all scientific, social, and professional activities concerning gastroenterology. By doing this over the years, UEG has developed an exceptional medium promoting science through share of knowledge and solidarity in Europe and beyond. It is a platform open to everyone without discrimination of sex, region, religion, disability, and nationality. It is like a honeycomb where diverse bees come to depose their honey. It is a ground where each individual who wishes to share their experience with others are encouraged, each candidate who wants to cultivate their seeds on a fertile ground or to develop their skills are provided with countless opportunities. Diversity is within the core values of UEG and efforts are made to achieve utmost quality in this field.

Q4 The E&DTF for UEG supports equal opportunities and involvement for underrepresented groups. In which situations do you think inequalities experienced by these groups of people most commonly occur?

Like any other professional society in Europe, there are barriers and unconscious bias for women in gastroenterology. We have some statistics about women in gastroenterology attending UEG Week according to a survey carried out by the E&DTF. Women with small children experience difficulties in childcare while attending UEG Week. When questioned, 49.0% of the women said that they would attend the week if childcare facilities were provided at the congress site. This year this problem was solved by the UEG organisation. A second inequality lies in the inadequate number of female speakers and chairs at UEG Week; furthermore, the representation of females in various Committees and the Council is far from ideal. Only 20.0% of the UEG Week participants were women in 2018. Likewise, 25.9% of the faculty was female with a 4.0% increase compared to the previous year, so the female faculty at UEG Week is on the rise but it will take time. Apart from E&DTF, the percentage of women in UEG Boards and Committees varies between 16.7% and 44.4%, with the exception of the Young talent group (62.5%) and the E&DTF (100.0%). We still have a long way to go, but as I will explain further, thanks to the efforts and encouragement of the Council and E&DTF the number of female members in UEG Committees is also on the rise. It is not only the so-called 'glass ceiling' effect but women have to volunteer for these positions.

We should also mention inadequate regional representation regarding speakers and chairs at UEG Week which we expect to improve in the following years.

Q5 What are the greatest challenges faced by the members of the E&DTF who strive to achieve a discrimination-free environment?

One of the challenges faced by E&DTF members was to solicit the representation of the group within the Council and that was unanimously accepted. This opportunity enabled us to raise our voice within the top administrative body of UEG and get some of our objectives accomplished.

Our major achievements were as follows:

- The age limit for applications to grants was increased by 1 year for each child for women.

- Women, young gastroenterologists, and people from underrepresented groups were encouraged to apply for open positions in the boards and committees.

- The barriers, especially for women to attend

UEG Week and to take leadership positions were analysed via a survey.

• Our members endorsed mentoring programmes organised by the Young Talent Group.

• Career chat in the Young GI lounge with female leaders enabled young gastroenterologists to get insights for their future career and learn from the experience of experts.

• Two great challenges of this year were the nomination of a female candidate for the Vice President position and the "Women in GI networking/Making Equality a Reality" event.

Both initiatives were crowned with great success and for the first time in the history of UEG a female Vice President (Prof Helena Cortez Pinto) was elected at the Meeting of Members.

All these activities should not be interpreted as to consider the E&DTF as only a womens' club. We are to encourage and satisfy the needs of people from both sexes regardless of age, nationality, country, religion, economic state, and disability.

Q6 Does the E&DTF collaborate with other societies at UEG? Do you have any upcoming projects with any of these groups?

Until now all our efforts were concentrated on establishing a strong working plan for E&DTF so that it gains visibility and recognition within UEG and outside. We had very good collaboration with the Young Talent Group and worked together in different platforms. Because the Young GI is our future, we aimed to contribute to their development by sharing with them the experience of the masters. Now we will create close collaboration with the National Societies Committee to disseminate our messages to various countries and also with other Committees within UEG. Furthermore, we always try to recruit members from other Committees to share different views which will enrich our activities.

One of the great advantages we have is the UEG Journal, which provides an excellent platform to spread our ideas. The newsletters and the social media also help us to propagate our messages to everyone interested in gastroenterology and particularly in E&DTF events.

Q7 What are your opinions regarding the representation of women in gastroenterology? What tools or initiatives would women most greatly benefit from to thrive in this field?

Women are definitely underrepresented in gastroenterology. The survey of the European Section and Board of Gastroenterology and Hepatology (ESBGH) showed that women constitute only 34% of gastroenterologists in Europe. The percentage is even smaller in leadership positions and academic institutions. This is a general trend of the so-called 'leaky pipeline' effect which shows that women who make a good start in medical school can later succumb to different obstacles including difficulties in the work–life balance, family affairs, and parenting.

Apart from some exceptions, women are paid less, promoted slower, receive fewer honours, receive less grants for research, hold fewer leadership positions, and have difficulties in access to career.

A recent survey, which will be published in the UEG Journal, also showed that women face several barriers during training in endoscopy such as lack of flexible working hours, childbearing, lack of encouraging role models, and lower self-advocacy in addition to unconscious bias towards them. Women are not choosing therapeutic endoscopy unless they have a good role model and are provided with hands-on endoscopy at an early stage in their training. UEG statistics also show that >50% of the Classroom Courses participants at UEG Week are female.

To overcome this gender inequality in gastroenterology, especially in leadership roles, women have to be trained early in their career to become leaders. They should benefit from the experience of their seniors (male or female). They should be encouraged to apply to key positions within UEG, in their country, or elsewhere in accordance with their interest and talent. They should be thought of not being afraid from failing. Finally, women in the gastroenterology community need more networking and solidarity to achieve their goals.

Q8 Are there any differences between attitudes towards women in gastroenterology that you have experienced in Turkey and internationally in your career? Have these attitudes changed over time?

Being a woman would inevitably put you in a disadvantageous position in my time. In a male dominated speciality, the preferences would go for a male candidate when one woman and one man apply for the same position. But I was resilient and also lucky enough to have an excellent mentor (male), a guide who helped me to overcome the difficulties standing in my way. Now that recruitment of trainees in gastroenterology is done by a national entrance examination, there is practically no gender discrimination in Turkey at least at the start of the career. However, women in leadership positions are still insufficient. The proportion of female gastroenterologists is <30% and female leaders are even less. Nowadays, female gastroenterologists are more attracted to invasive procedures and are as successful as their male counterparts when they choose therapeutic endoscopy. In a recent survey done by the Women's Committee at the Turkish Society of Gastroenterology, 46.0% of the female gastroenterologists reported that they experienced difficulties at the beginning of their career or throughout their training because of their gender and 58.5% were exposed to mobbing. However, 77.5% were satisfied with their job whilst 60.0% reported they had family/career dilemmas. In addition, 5.0% of them had divorced and 20.0% were single because of their inability to manage the work–life balance. The statistics are similar in many countries although cultural differences may affect the outcome.

Q9 What are the biggest actions needed to be able to change the face of gastroenterology and achieve great and varied specialities?

Gastroenterology is a specialty that needs more diversity and inclusion. First to valorise the qualities of women and underrepresented people, second to be more effective in the prevention and management of diseases. Allow me to explain these statements:

Women have some qualities and leadership skills that can make medical service and administration 'smooth running'. These are empathy, communication skills, flexibility inclusiveness, resilience, and ability for building excellent teams. So, why not profit from them!

For the second argument: women prefer female gastroenterologists when they seek medical care, especially for colonoscopy.

With respect to pluralism and multinationalism, we need more people from underrepresented countries to know more about the epidemiology of the diseases, to collaborate for joint projects, to exchange ideas, to harmonise gastrointestinal training, to increase the quality of care across the countries, and perhaps to use academic diplomacy for peace and solidarity in Europe and beyond.

How to achieve these goals? Again, by networking, educating, collaborating, providing resources for research, and grants for training in specific areas.

Q10 What do you think was the most important session from UEG 2019?

In my opinion, UEG Week 2019 was overall very successful; in particular, the plenary session and the live endoscopy were the most interesting and well attended sessions of the week. I always find the opening session, the distribution of awards, and the subsequent presentations the most exciting part of UEG Week. This year's artificial intelligence session was also an exciting one. But many colleagues report that they find case presentations and case scenarios the most interesting sessions.

I may be biased, but the hotspot session on "professional risks and burnout among gastroenterologists" was also one of the important and special sessions of UEG Week.

Today as a whole, UEG has become an unmissable congress for gastroenterologists and other health professionals from all over the world who wish to update their knowledge in a competitive but friendly environment.

Prof Dan Dumitrascu

Chair of the National Societies Committee for United European Gastroenterology (UEG)
Professor of Medicine, University of Medicine and Pharmacy Head, 2nd Medical Department,"Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

Q1 With there being such a large collection of intriguing scientific fields, what drew your attention towards gastroenterology and prompted you to pursue a career in the field?

This is rather a personal history: my father was a gastroenterologist and I did not want to walk in his shoes. That is why I started out in a cardiology department, and even published some papers on cardiology in my youth, ready to become a cardiologist. But I was living in a communist state with a dictatorial regime: my brother in law defected, so I was not allowed to work in a university, only as a research fellow. Therefore, I became a research associate and moved to the gastroenterological department chaired by my father. Dare I say: I became a gastroenterologist against my wishes! After the fall of the iron curtain I had the liberty to train myself abroad and to enthusiastically develop my career in gastroenterology.

Q2 You are actively engaged in various committees including the Romanian Society of Neurogastroenterology and the American Gastroenterological association. What do you believe to be the most rewarding aspect of being part of a committee and what is crucial for the activities to run smoothly?

Working in committees allows you to share experiences with many other colleagues, to progress in your personal development, and to represent an interface for those who are outside of the committees. Being a member and becoming chairman of the International Liaison Committee of the Rome Foundation was, and still is, very exciting for me.

Q3 As the chair of the UEG National Societies Committee (NSC), could you briefly describe the duties and responsibilities of the committee and how these contribute to the UEG vision of reducing the burden on digestive diseases and improving digestive health?

Of course, this is a great responsibility. We work and make decisions in a very democratic and transparent manner, whilst also aiming for a balanced representation in NSC. Therefore, our activity mirrors the purposes of the national societies and is integrated in the strategy of the UEG Council. We are also supported by the fantastic staff from the House of Gastroenterology in Vienna.

Q4 With >30,000 specialists from every field in gastroenterology within the 17 Ordinary Member Societies and the 47 National Gastroenterology Societies, how do you co-ordinate the collaboration between the societies and advocate the UEG vision on a European and national level?

We are now 48! We mainly respect the bottom-up principle, but sometimes suggestions are also processed and disseminated top-down. We create the conditions to offer each national society the possibility to express their wishes or present their agendas. Our cross-representatives in the other committees are an important interface between national societies and profile committees, with which we interact extremely well.

Q5 The aim of the NSC is to maximise communication and strengthen relationships between the National Societies and UEG. What challenges are you faced with in harmonising the societies and how are these trials overcome?

We are indeed a choir with many voices; but our choir sings very well!

Q6 In regard to the co-ordination of the large amounts of societies, is there any competition between the societies? Furthermore, how do you regulate the amount of input each society has towards the organisation of UEG Week?

Sometimes, as always, divergent interests may be expressed. We negotiate in harmony and find the best agreements.

Q7 In your expert opinion and with regard to your past experience as an internal medicine and gastroenterology consultant, what steps would you advise the public to take to personally prevent gastrointestinal diseases.

Lifestyle recommendations are the most important guidelines for prevention. To this I should add the need to stop reading pseudoscientific information on the internet. It is not easy to give general recommendations. In the era of personalised medicine, we should not disseminate general recommendations for healthy lifestyle, such as increase physical activity and eat less fat, as many see on TV. The dietary and behavioural recommendations should respect general principles but be individualised. The most concerning is when patients develop or are induced to develop radical attributions or convictions without scientific support and without proven benefit.

Q8 What particular session or topic from this year's UEG Week did you find the most captivating and what did you learn from it?

I can mention only those I attended. Many were very interesting, but I liked the plenary sessions for their synthetic approach to different fields of specialty.

Q9 Another aim of the NSC is to support all affiliated societies in their scientific and professional activities, what kind of support does the NSC offers its members and are there common scientific themes that you promote amongst them?

We disseminate the initiatives and opportunities offered by UEG to the member societies and to young trainees and specialists. We recommend the organisation of multidisciplinary educational events or programmes. We are committed to enlarging the number of society members as some are still missing from the European map.

Q10 In your opinion, what areas of gastrointestinal research merit increased attention and should be discussed at future UEG Week congresses?

On the one hand, precision medicine has been evolving well. On the other hand, there is a need to not neglect the patient behind the disease, and more attention to biopsychosocial medicine should be given by gastroenterologists.

‘Old but Gold’ – Insights About Anti-TNF-α Therapy in the Treatment of Inflammatory Bowel Disease

These interviews took place in October 2019 at the 27th United European Gastroenterology (UEG) Week in Barcelona, Spain

Interviewees: Remo Panaccione,[1] Thomas Ochsenkühn,[2] Stefan Schreiber,[3] Jonas Halfvarson[4]

1. Inflammatory Bowel Disease Clinic, University of Calgary, Calgary, Canada

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Disclosure: Prof Schreiber has served on advisory boards and clinical trials, as well as received grants from AbbVie, Allergan, Amgen, AMT, Arena, Biogen, BMS, Boehringer Ingelheim, Celgene, Celltrion, Falk, Janssen, Gilead, Lilly, Merck, Mylan, Pfizer, Roche, Sandoz, Takeda, and Tillots; and received speaker fees from AbbVie, Amgen, Arena, Biogen, BMS, Celgene, Celltrion, Falk, Ferring, Janssen, Gilead, Merck, Pfizer, Roche, Sandoz, Takeda, and Tilotts. Prof Ochsenkühn has received travel grants, honoraria for advisory activities, and lecture fees from Sandoz. Prof Panaccione has worked as a consultant for AbbVie, Abbott, Amgen, Aptalis, AstraZeneca, Baxter, Eisai, Ferring, Janssen, Merck, Schering-Plough, Shire, Centocor, Elan, GlaxoSmithKline, UCB, Pfizer, Bristol-Myers Squibb, Warner Chilcott, Cubist, Celgene, Gilead Sciences, Takeda Pharmaceuticals; he has worked on the Speakers’ Bureau for AbbVie, AstraZeneca, Janssen, Schering-Plough, Shire, Ferring, Centocor, Elan, Prometheus, Warner Chilcott, Takeda Pharmaceuticals; he has served on the advisory board for AbbVie, Abbott, Amgen, Aptalis, AstraZeneca, Baxter, Eisai, Ferring, Genentech, Janssen, Merck, Schering-Plough, Shire, Centocor, Elan, GlaxoSmithKline, UCB, Pfizer, Bristol-Myers Squibb, Warner Chilcott, Takeda Pharmaceuticals, Cubist, Celgene, Salix; he has received research/educational support from AbbVie, Abbott, Ferring, Janssen, Schering-Plough, Centocor, Millennium, Elan, Procter & Gamble, and Bristol-Myers Squibb.

Acknowledgements: Prof Schreiber, Prof Ochsenkühn, and Prof Halfvarson collected information at the UEG Week in Barcelona, Spain, 2019. Prof Schreiber acknowledges the support of Sandoz during UEG Week. Prof Halfvarson acknowledges the support of Sandoz in the preparations of the symposium that took place on 8th March 2019 as part of the 14th European Crohn's and Colitis Organisation (ECCO) Congress. Medical writing assistance was provided by David Jacobs, Lewis-Barned, Balcombe, UK.

Support: The publication of this article was funded by Hexal AG. The opinions and claims made in this article are those of the interviewees alone. They are not those of the writer, the publisher, or any other group including Sandoz International GmbH/Hexal AG or its affiliates. None of the aforementioned shall incur any liability in respect thereof. The purpose of these interviews is for educational purposes only; i.e., to inform readers of the views of the four interviewees.

Citation: EMJ Gastroenterol. 2019;8[1]:35-38.

Interview Summary

In these interviews, the experts clearly highlighted four key messages:

1) Too few patients with inflammatory bowel disease (IBD) are being treated with biologics, including anti-TNF-α therapies.

2) Some patients may also be receiving this treatment too late in the disease course, when structural damages have already occurred. This may be due to the high cost of originator biologics or a lack of awareness among physicians of the proven benefits of early anti-TNF-α therapy introduction. These therapies have been shown to decrease complications and disease progression.

3) The development of affordable anti-TNF-α biosimilars can facilitate greater access to these therapies and could extend their early use to more patients, with no detected safety issues in switched patients discerned to date.

4) Newer therapeutic options with other mechanisms of action are available, but for now at least, anti-TNF-α therapies are seen as 'old but gold'.

Professor Remo Panaccione

Prof Panaccione believed that biologic therapies are generally underutilised in patients with IBD; they are started too late and prescribed to too few patients. Some physicians still prefer conventional therapy and a slow step up to biologics; this means by the time their patients are started on biologic therapy, the biologic efficacy has been compromised.[1] However, he did acknowledge the challenges faced by doctors looking to treat IBD patients earlier with biologics. These include limited accessibility on the grounds of cost, as well as a lack of awareness among these physicians about the benefits of early intervention.[1] According to Prof Panaccione, there is also a lack of awareness among IBD patients about the benefits, and established safety profile, of the anti-TNF-α antibodies in particular. There are now two decades of experience supporting these benefits. Some physicians and patients also do not understand the severity of the disease and its progressive nature. Peoples' feelings towards their IBD and its severity not only relate to their symptoms but also the overall disease burden and the risk factors that predict poor outcomes.

Drawing on his extensive clinical experience, Prof Panaccione believed that all patients could benefit from early intervention with biologic therapy, particularly the paediatric population due to the associated growth problems.[2] In young patients, a 'top-down' strategy should be increasingly used to induce deep remission as an attempt to modify the clinical course of the disease.[1,2] He is also of the opinion that biologic treatment is most effectively used in early, uncomplicated disease.

Prof Panaccione was clear in his beliefs: "Shifting to these drugs earlier is associated with better outcomes, fewer complications, and slower disease progression." On the other hand, he also recognised that, in a real-world setting, limited access to these treatments means clinicians should focus on patients with a significant disease burden and unfavourable risk factors. These patients should be treated early, with clinicians adopting a pragmatic top-down approach.[1] He emphasised that newer modes of action (MoA) have yet to demonstrate the same benefit to IBD patients; currently the best outcomes from early treatment all point to anti-TNF administration.[1,3]

Professor Thomas Ochsenkühn

Prof Ochsenkühn focussed on long-term experience with anti-TNF. In his opinion, anti-TNF remain first-line biologics with a central role in the treatment of IBD; they are fast, effective, and have a low incidence of side effects. He recognised that anti-TNF-α biosimilars are driving down the cost of access and creating the opportunity for more patients to be treated with these therapies, even though newer MoA are available. For him, anti-TNF occupy a huge space in IBD treatment and will be used even more in the future.

Quoting 2016 data from German insurance companies, he pointed out that 6% of ulcerative colitis and 9% of Crohn's disease patients were treated with antibodies. He describes this as "a dramatic underuse of these drugs." Looking ahead, he expects this situation to change, affordable anti-TNF-α biosimilars being the catalyst.

According to Prof Ochsenkühn, anti-TNF are the first choice when immunomodulation becomes necessary. He bases this on their proven efficacy over 20 years, the speed of onset of action, their use in pregnancy, their postoperative impact, their low rates of side effects, and affordability. According to him, immunomodulators with other MoA can be used as a second-line treatment when anti-TNF-α therapies fail, if patients experience intolerance, or when side effects present following anti-TNF-α treatment.

Prof Ochsenkühn also believed that anti-TNF should be used early in the management of patients with high-risk factors for an aggressive course of IBD. These high-risk factors include severe flares, high inflammatory burden, long segment involvement in Crohn's disease, pancolitis in ulcerative colitis, fistulising disease, stricturing disease, and a high or ongoing need for steroids.

He stressed that anti-TNF have a preventive action which newer MoAs,[1] such as the anti-integrins (e.g., vedolizumab), ustekinumab (an antagonist of the p40 subunit of IL-12 and IL-23), and JAK-inhibitors (e.g., tofacitinib), have yet to demonstrate. And until more data are available, his view was that anti-TNF will remain the first-line biologic to prevent structural damage and functional losses in the long term. To date this preventive action has not been shown with newer MoA,[1] and hence the key player is anti-TNF therapy for most IBD patients.

Professor Stefan Schreiber

Prof Schreiber described the efficacy of anti-TNF therapies and how the introduction of biosimilars has changed the IBD landscape. He remarked that there is substantial evidence to show that higher dosages and early intervention with anti-TNF-α therapies improve outcomes in patients with IBD. He commented that affordable biosimilars will be an option for increasing access, permitting higher doses, and allowing earlier treatment. In addition, these cheaper biosimilars keep spending constant.

However, despite this body of evidence, he echoed the sentiment of Prof Panaccione and described an unmet need for the continuous medical education of some healthcare professionals, especially those not practising in specialist IBD centres, or those who are seeing more patients but not prescribing anti-TNF optimally in-line with the latest algorithms.

Asked whether he feels confident about using biosimilars, Prof Schreiber asserted: "I am confident to use biosimilars [...] At the moment we have an extremely high production quality for the biosimilars we are using. We have companies that are open to research and invest in data generation to support the best practice use of established molecules."

In this context, Prof Schreiber described the value of GIANT, the first prospective, global, noninterventional study to evaluate the effectiveness, safety, and cost-effectiveness of adalimumab and infliximab in Crohn´s disease under real-world conditions.

GIANT is a large observational study that bridges the evidence gap between a controlled study and the observation of clinical practice. Although it regards real-world patient access, GIANT is constructed in such a way as to generate prospective data that are quality-controlled and reusable for therapy optimisation, as well as for patient outcome improvement.

Prof Schreiber emphasised that GIANT will help to answer open scientific questions and increasing knowledge surrounding the effectiveness of adalimumab and infliximab in routine clinical care and will additionally evaluate the newly introduced IBD disease severity index under real-world conditions. Data on best practice usage with these established drugs are needed, stated Prof Schreiber: "I would foresee that in the next years anti-TNF therapy gets even stronger and will be the entry-level drug for most of our patients."

In a similar vein, Prof Schreiber contrasted the earlier placebo-controlled approval study of adalimumab, ULTRA, with the results derived from

the recently published head-to-head VARSITY study. Here, the efficacy and safety of adalimumab was assessed versus an active comparator (vedolizumab) in patients with moderate-to-severe ulcerative colitis. One important result is that, when compared with an active comparator, adalimumab showed greater efficacy than revealed through ULTRA, with high response rates and no attenuation.[4] This was explained by Prof Schreiber who believes we get both closer to the real world and discover better data about established drugs from an active comparator rather than placebo-controlled trials. In his opinion, the latter are typically not representative of real-world practice due to issues concerning patient extraction.

Professor Jonas Halfvarson

Prof Halfvarson from Sweden was asked to share his experience about biosimilar usage in Nordic countries. These countries have already amassed considerable experience of switching. Patients have been switched from an originator to a biosimilar and also between biosimilars, as well as from an originator to a first biosimilar and then to another second biosimilar. His reply couldn't have been clearer: "In Nordic countries, we haven't experienced any safety issues after switching patients from originator to biosimilar or from one biosimilar to another biosimilar." His conclusion was based on extensive clinical experience and the patient data routinely collected and included at a national level in the Swedish Quality Registry (SWIBREG) for IBD. SWIBREG was launched in 2005 and, as of April 2019, includes 46,400 patients with IBD.[5]

When it comes to managing a patient's move to biosimilars, Prof Halfvarson emphasised the importance of good communication. His advice is to implement a standardised switching regimen and let patients know the reasons for switching and exactly how the switch will be performed. It is also necessary to communicate with colleagues and nurses about the need and rationale for switching, and to let the patient organisation know. Beyond the switch, he advised tight monitoring of anti-TNF patients for proactive treatment adaptations.

Closing Remarks

Those expecting leaders in the field to be moving IBD patients to newer therapeutic options may have to wait, at least until further data are published. For now, it seems to our interviewees that biosimilars may extend, widen, and enable the early use of anti-TNF in the treatment of IBD and in doing so help improve patient outcomes. With no safety-related issues in switched patients to date, old is indeed gold.

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Burning Questions in Inflammatory Bowel Disease: Learnings from Emerging Drug Options and Clinical Cases

This symposium took place on 21st September 2019, as part of the United European Gastroenterology (UEG) Week 2019 in Barcelona, Spain

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Speakers: Julián Panés,[3] Laurent Peyrin-Biroulet,[1] Séverine Vermeire[2]

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Disclosure: Prof Panés has received research support and acted as a principal investigator for AbbVie, MSD, and Pfizer; acted as a consultant for AbbVie, Arena, Boehringer Ingelheim, Celgene, Ferring, Genentech/Roche, Gilead, GoodGut, GSK, Immunic, Janssen, MSD, Nestlé, Oppilan, Pfizer, Progenity, Second Genome, Shire, Takeda, Theravance, and TiGenix; and been part of Speaker's Bureau for AbbVie, Biogen, Falk Pharma, Ferring, Janssen, MSD, Pfizer, and Takeda. Prof Peyrin-Biroulet has received research support and acted as a principal investigator for AbbVie, Janssen, MSD, Pfizer, and Takeda; has been a consultant for AbbVie, Amgen, Biogaran, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Ferring, Genentech, H.A.C. Pharma, Hospira, Index Pharmaceuticals, Janssen, Lilly, Lycera, Merck, Norgine, Pfizer, Pharmacosmos, Samsung Bioepis, Sandoz, Takeda, Tillots Pharma AG, Vifor Pharma; and been part of Speaker's Bureau for AbbVie, Ferring, H.A.C. Pharma, Janssen, Merck, Takeda, Tillots Pharma AG, and Vifor Pharma. Prof Vermeire has received research support and acted as principal investigator for AbbVie, Janssen, MSD, Pfizer Inc., and Takeda; acted as a consultant for AbbVie, Celgene, Ferring, Galapagos, Genentech/Roche, Gilead, GSK, Hospira, Johnson & Johnson, MSD, Mundipharma, Pfizer Inc., Prodigest, Progenity, Second Genome, Shire, and Takeda; and been part of Speaker's Bureau for AbbVie, Dr. Falk Pharma, Ferring, Hospira, Johnson & Johnson, MSD, Pfizer Inc., Takeda, and Tillotts Pharma AG.

Acknowledgements: Medical writing assistance was provided by Megan Breuer of Excerpta Medica, Amsterdam, the Netherlands.

Support: Both the symposium and the publication of this article were funded by Janssen.

The views and opinions expressed are those of the authors and are not necessarily those of Janssen.

Citation: EMJ Gastroenterol. 2019;8[1]:39-44.

Meeting Summary

The symposium, entitled "Burning questions in IBD: Learnings from emerging drug options and clinical cases," took place during the 2019 United European Gastroenterology (UEG) Week annual congress in Barcelona, Spain. Distinguished experts Prof Peyrin-Biroulet, Prof Vermeire, and Prof Panés tackled several of the outstanding questions in inflammatory bowel disease (IBD) management, focussing the discussion on treat-to-target strategies and how these could be applied in IBD management; when to initiate biologic treatments, and the factors involved in making these treatment decisions; the use of ustekinumab in ulcerative colitis (UC) management; efficacy and safety of biologics; and whether monotherapy or combined treatment is the optimal treatment approach in IBD. The experts used informative patient cases and data from current clinical studies to help illustrate the possible solutions to each 'burning question', incorporating questions from the audience into each discussion.

What Should be the Treatment Target in Crohn's Disease and Ulcerative Colitis, and How Should the Treat-To-Target Strategy be Applied for Both Diseases?

Professor Laurent Peyrin-Biroulet

The treatment armamentarium is expanding for patients with UC and Crohn's disease (CD). The treatments currently available include anti-inflammatory, immunosuppressant, and corticosteroid therapies, as well as small-molecule treatments and several biologic treatments targeting TNFα, α4β7 integrins, and IL-23/12.[1,2]

Treatment targets can include factors such as improved quality of life, and clinical, biochemical, and endoscopic remission. Though perhaps not every goal can be achieved in an individual patient, applying a treat-to-target strategy could be useful for patients. Treat-to-target can be defined as "a treatment strategy in which the clinician treats the patient aggressively enough to reach and maintain explicitly specified and sequentially measured goals."[3] Treat-to-target is especially attractive in IBD management, as this strategy is proactive and offers a clear goal for patients.[3,4]

There is a current need for personalised and 'top-down' treatment in UC and CD; this is not solely to treat the symptoms, but to alter the disease course and improve disease burden to the point at which the patient can once again lead a normal life.[5] For patients with CD, the 2015 Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) recommendations state treatment targets that include resolution of abdominal pain, normalisation of bowel habits, and an absence of ulcerations within an approximated 6-month period. For patients with UC, treatment targets include resolution of rectal bleeding, normalisation of bowel habits, and a Mayo endoscopic subscore of 0 (0 is considered optimal, a subscore of 1 should be considered the minimum) within a 6-month period.[4] Patients should be closely monitored during the initial period, with possible 'step-up' of treatment dosing being implemented if necessary (Figure 1).

Currently, two clinical trials have examined the effect of 'tight monitoring' and treat-to-target strategies (CALM and STARDUST, respectively) on clinical outcomes in patients with CD.[6,7] The design of the CALM study aimed to examine the use of a tight monitoring algorithm on treatment outcomes in patients with CD, using biomarkers such as faecal calprotectin, C-reactive protein, and clinical symptoms as drivers for dose escalation or de-escalation during the 48-week trial period.[6] The landmark STARDUST treat-to-target study consisted of an induction phase, a maintenance phase, and a long-term extension, with a primary outcome of endoscopic response as the treatment target at Week 48, with endoscopies performed at baseline, Week 16 (treat-to-target arm only), and Week 48.[7]

Remission may not be achievable in every patient, according to Prof Panés. He noted that mild-to-moderate symptoms may persist even if there is complete endoscopic healing, and mild symptoms may be an indicator of the need to proactively intensify treatment.

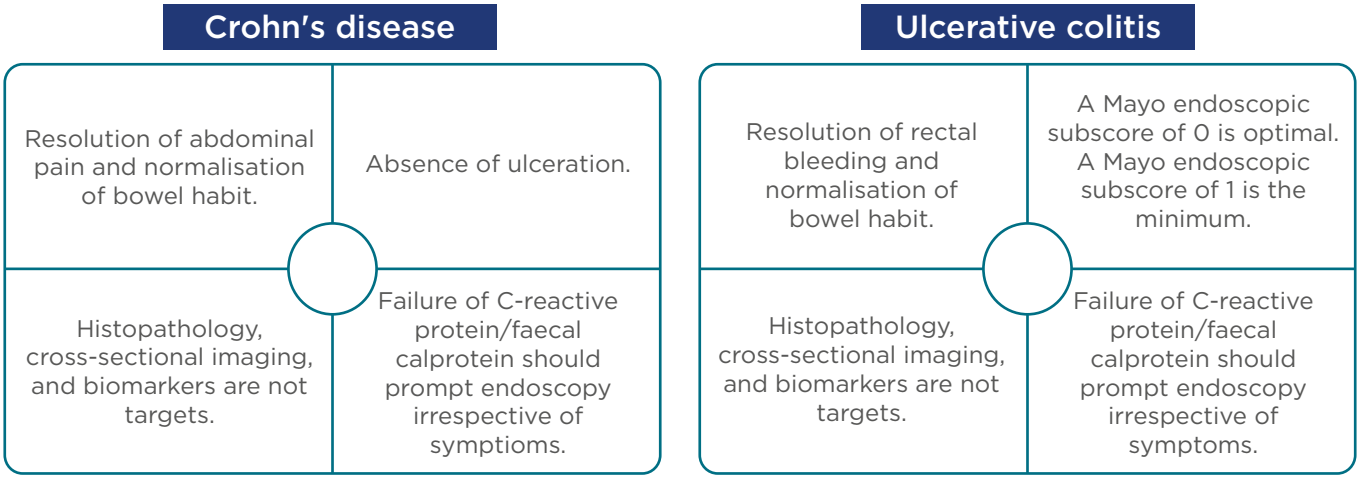

Figure 1: Current Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) recommendations for Crohn's disease and ulcerative colitis.

Adapted from Peyrin-Biroulet et al.[4]

Treat-to-target is beginning to be adopted in clinical practice, according to Prof Peyrin-Biroulet, although proper patient education is an important factor for acceptance of this strategy.

When is the Appropriate Time to Start Treatment, either with a Biologic or Small-Molecule Therapy, and What Factors Should be Considered when Making Treatment Decisions?

Professor Laurent Peyrin-Biroulet

Appropriate timing of biologic treatment initiation often represents a challenge for clinicians, because there are no specific recommendations for the initiation of biologic treatment for patients with IBD.

Moreover, current European Crohn's and Colitis Organisation (ECCO) guidelines do not offer guidance on choosing a biologic based on individual patient need, and delays in the representation of new treatments in the guidelines presents a further challenge when making treatment choices.

The results of the UNIFI study to evaluate the safety and efficacy of ustekinumab, a human monoclonal antibody against the p40 subunit of IL-23/12, showed that the primary endpoint of clinical remission at Week 8 of treatment versus placebo was met.[8] Of all randomised patients in the study, approximately 62% showed a clinical response with the single intravenous induction dose of ustekinumab.[8]

Ustekinumab treatment also resulted in rapid and high efficacy in patients who did not respond to the induction dose, but who received a subcutaneous dose of ustekinumab dose at Week 8 and reassessment at Week 16; a combined analysis of data from Weeks 8 and 16 showed that approximately 78% of all patients showed a clinical response with ustekinumab by following the recommended dose schedule.[9] Clinical response to ustekinumab was also observed in patients in whom disease had remained active on other biologic therapies.[8]

One of the most important treatment goals for patients with IBD is the achievement of steroid-free remission. The results from the UNIFI maintenance study indicate that, of those patients who were in remission at 1 year of treatment with ustekinumab, 97% were steroid-free (Figure 2).[8]

Importantly, the UNIFI study was the first to use histoendoscopic mucosal healing as an endpoint. This endpoint includes both endoscopic improvement (endoscopy end score of 0 or 1) and histological improvement (0–5% neutrophils in

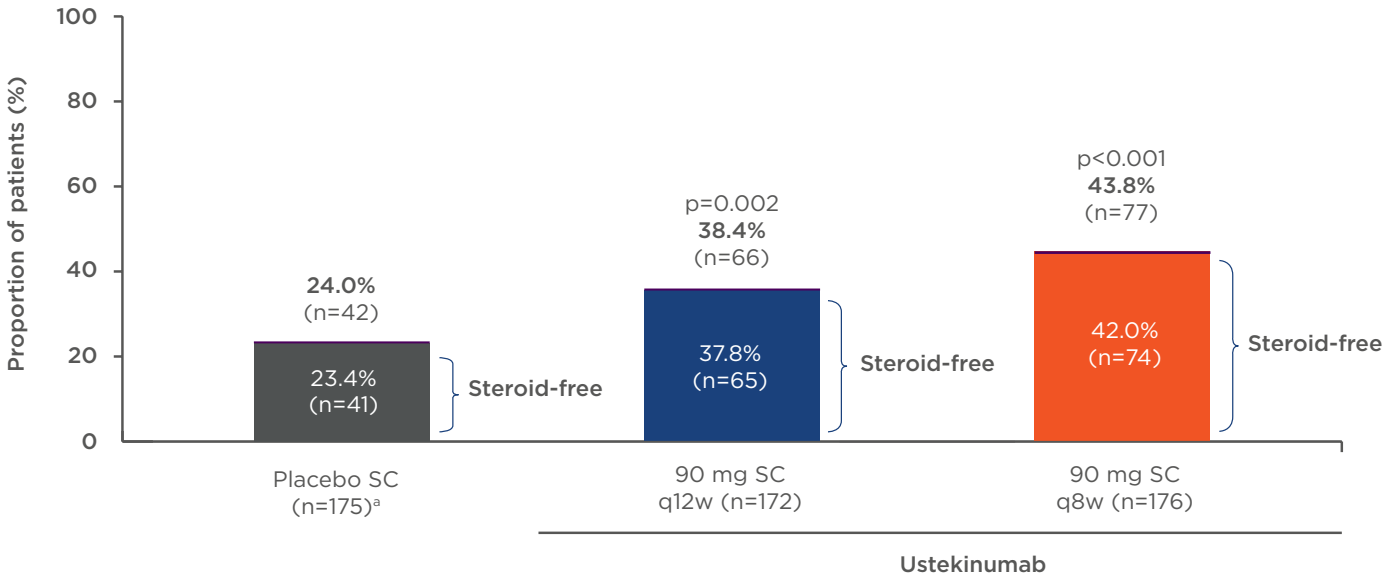

Figure 2: Patients in remission[b] at Week 44[c] of maintenance therapy.

[a]The maintenance placebo population includes patients who received and responded to intravenous ustekinumab induction before receiving subcutaneous placebo. [b]Mayo score ≤2; no individual subscore >1. [c]Week 44 in maintenance is 1 full year of ustekinumab treatment (8-week induction + 44-week maintenance = 52 weeks in total).
q8w/q12w: every 8/12 weeks; SC: subcutaneous.

Adapted from Sands et al.[8]

the epithelium, no crypt destruction, and no erosions, ulceration, or granulation tissue).[10] Patients receiving ustekinumab also showed endoscopic improvement at Weeks 8 and 44; significantly more patients treated with ustekinumab experienced histoendoscopic mucosal healing through 1 year versus placebo.[8] Patients also reported improvements in Inflammatory Bowel Disease Questionnaire (IBDQ) scores through 1 year of treatment with ustekinumab versus placebo.[11]

In conclusion, the UNIFI trial data showed that induction and maintenance therapy with ustekinumab is associated with steroid-free remission, endoscopic improvement, histoendoscopic mucosal healing, improved quality of life, and early symptomatic improvement in patients with UC.[8,12]

Focus on Emerging Treatment Options in Ulcerative Colitis: How Should Ustekinumab be Used in the Treatment of Ulcerative Colitis?

Professor Séverine Vermeire

Ustekinumab is indicated for the treatment of adult patients with moderately to severely active UC who have had an inadequate or lost response, were intolerant to either conventional therapy or a biologic, or who have medical contraindications to such therapies.[13] Prof Vermeire illustrated how ustekinumab treatment was used in the case of a male patient with UC and psoriasis who also developed synovitis.

The patient was initially treated with corticosteroids and continued to receive these during flares; he was eventually started on golimumab therapy and was later switched to infliximab in combination with azathioprine. Re-evaluation of the patient revealed no improvement; he was therefore enrolled in the

UNIFI study and began receiving ustekinumab. The patient's ustekinumab dose was escalated to every 8 weeks 2 years into the study; his faecal calprotectin levels began decreasing when he started showing clinical improvement and continued to decrease after a short stressful period when these levels temporarily increased. At this time, the patient has been receiving ustekinumab for almost 4 years, and is considered to be in clinical, biochemical, and endoscopic remission.

The faculty also discussed how optimising the dose of the current treatment can sometimes be a more effective strategy than switching to a different therapy. They also concluded that early treatment of inflammation with appropriate dosing is a necessary factor for treat-to-target strategies.

Efficacy and Safety Aspects: What is the Best Approach?

Professor Julián Panés

Prof Panés described the efficacy and safety aspects of biologic therapies. He began by discussing the clinical case of a 55-year-old male patient with colonic CD; the patient had showed some improvement with prednisone treatment, but remission had not been achieved at 4 weeks of treatment. The patient was subsequently started on adalimumab as monotherapy and tapered off corticosteroid treatment. The patient showed sustained improvement following initiation of adalimumab, but still had persistent mild-to-moderate symptoms. In the 6-month period following adalimumab initiation, the patient experienced several infections, after which he stopped adalimumab therapy and switched to ustekinumab. He achieved clinical remission at Week 8 of treatment, and sustained remission through the next 5 years of treatment with no serious infection-related adverse events (AE).

Data from the UNITI-1 and UNITI-2 trials in patients with CD showed that ustekinumab treatment is associated with similar rates of AE, severe AE, and infections through Week 8 of treatment versus placebo.[14] The safety profile for ustekinumab remained consistent through Week 156 of treatment in the IM-UNITI trial.[15,16] Furthermore, data from the UNIFI trial in patients with UC show that through 1 year of treatment, rates of key safety events remained similar between patients who received placebo and those who received ustekinumab.[8] The safety profile of ustekinumab remained consistent through 1 year of treatment across other indications (including psoriasis and psoriatic arthritis), and was comparable to placebo in registrational trials including approximately 6,000 patients.[17]

The Use of Treatment Monotherapy Versus Combination Therapy

Professor Julián Panés

Compared with monotherapy, the use of combination therapy in IBD has been associated with an increased risk of AE;[18,19] however, data from the IM-UNITI trial showed that rates of antidrug antibody formation remained low through Week 156 in patients with CD treated with ustekinumab.[15] Furthermore, data from the UNIFI induction and maintenance trials revealed that antidrug antibody formation rates were low through Week 8 in patients with UC who were treated with ustekinumab.[20,21]

In patients with IBD, data from the IM-UNITI and UNIFI trials also showed that concomitant use of immunomodulators does not appear to affect the efficacy of ustekinumab treatment in patients with IBD, suggesting that, with ustekinumab, there is no need for combination therapy. Remission efficacy in patients with CD was maintained through Week 92 of treatment, regardless of whether patients were receiving concomitant immunomodulators.[13,22] Furthermore, immunomodulator use did not affect serum ustekinumab concentrations in patients with CD though Week 92 of treatment.[23]

Prof Vermeire noted that monitoring of drug levels may not be necessary if patients are still showing a clinical response, though patients who are losing response may require monitoring for possible dose optimisation. In conclusion, Prof Vermeire reiterated the importance and application of treat-to-target strategies in UC

and CD management, stressing the importance of the current data regarding safety and efficacy with biologic treatments, and the lack of added outcome benefits with combination therapies.

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Practical Management of Anaemia After a Gastrointestinal Bleed

This symposium took place on 21st October 2019, as part of the United European Gastroenterology Week (UEGW) 2019 Congress in Barcelona, Spain

Chairpeople: Ian M. Gralnek,[1,2] Angel Lanas[3,4,5]

Speakers: Ian M. Gralnek,[1,2] Angel Lanas[3,4,5]

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Disclosure: Prof Gralnek has received grants and/or honoraria as a consultant, speaker, and/or advisory board member from Astra Zeneca, Boston Scientific, Endo Aid, GI View, Intect Pharma, Motus GI, Taro Pharma, Simbionix, 3D Matrix Medical Technology, and Vifor Pharma. Prof Lanas has received honoraria as a consultant, speaker, and/or advisory board member from Bayer A.G., Reckitt Benckiser, and Vifor Pharma.

Acknowledgements: Writing assistance was provided by Stefan Amisten, Amisten Consulting, London, UK.

Support: The symposium and publication of this article were funded by Vifor Pharma.

Citation: EMJ Gastroenterol. 2019;8[1]:45-51.

Meeting Summary

Prof Gralnek presented a clinical case on the management of gastrointestinal bleeding (GIB) as a result of *Helicobacter pylori* infection, and the role of intravenous (IV) ferric carboxymaltose (FCM) as a treatment option for iron deficiency anaemia (IDA) was discussed. IV iron is suitable for patients who have intolerance or limited or no response to oral iron, haemoglobin (Hb) <10 g/dL, or Hb >10 g/dL with cardiovascular or respiratory comorbidities. Prof Gralnek stressed that IDA is common, often underdiagnosed and undertreated, and that the choice between oral or IV iron therapy depends on the degree of anaemia, presence of inflammation, and adherence to oral iron therapy. The main objective of iron treatment is to normalise Hb and iron parameters, and gastroenterologists need to be more aware of anaemia beyond the acute GIB episodes.

Prof Lanas presented a clinical case on the management of patients taking anticoagulants (AC) or antithrombotics (AT) who have anaemia due to GIB, and highlighted challenges associated with reducing the risk of bleeds while avoiding thrombotic events. Prof Lanas highlighted clinical dilemmas arising from stopping, restarting, and switching AC in patients with anaemia and GIB, as well as Hb management at discharge. He also stressed that GIB, and especially anaemia or iron storage depletion, are frequently encountered in patients taking AT, and may have a direct impact on mortality, morbidity, and quality of life (QoL). Anaemia and iron deficiency affect mortality, recovery, and QoL in patients who need a rapid restoration of Hb levels and iron stores to decrease the risk of cardiovascular events. Prof Lanas concluded by explaining that FCM therapy has a favourable safety profile, and is more effective, faster, and cost-effective compared to oral iron therapy, and therefore represents a good therapeutic option for anaemic GIB patients with elevated risk of thrombosis.

Clinical Case: Acute Gastrointestinal Bleed in a *Helicobacter Pylori* Positive Patient

Professor Ian M. Gralnek

Case Presentation

Prof Gralnek opened the symposium with a clinical case: a 52-year old woman presented with dizziness and explained that she had had bloody stools (melena) for 48 hours. A year prior to this, she had seen her doctor for indigestion (dyspepsia), and a urea breath test returned positive, indicating that she had an active *H. pylori* infection, for which she was treated with antibiotics. She was then lost to follow-up. In the emergency department, the patient said that she had not been taking any long-term medications. She had a normal blood pressure (102/64 mmHg), but her pulse was moderately tachycardic (112 beats per minute). Upon palpation, her abdomen was soft, and she only complained of mild epigastric pain. A rectal exam revealed melena, and she was anaemic (Hb: 8.2 g/dL). One year prior, her Hb was 10.3 g/dL, iron 12.0 µM/L, ferritin 6.0 ng/mL, and transferrin saturation index 9.0%. Gastroscopy revealed a small bleeding ulcer, which was treated with clipping to stop the GIB. A rapid urease test at endoscopy revealed a persistent *H. pylori* infection. The patient was transfused with 2 units of red blood cells (RBC), which increased her Hb to 9.6 g/dL. Next, she was treated with IV proton pump inhibitor (PPI), and re-treated with antibiotics for *H. pylori*. Finally, she was given oral PPI and discharged home.

At a clinic follow-up 2 weeks later, the patient was feeling better, and her Hb was 9.1 g/dL. She mentioned that she had always had anaemia and low iron, and she has had heavy menses since she was a teenager. She also told the treating physician that she does not like oral iron supplements because they give her abdominal pain and constipation. Furthermore, she has no family history of GI malignancies, and has had no prior colonoscopy for colorectal cancer screening. At a clinic follow-up 8 weeks later, a colonoscopy to the terminal ileum was negative, as was a follow-up post-gastric ulcer gastroscopy. Duodenal and gastric biopsies were also negative, and her repeat Hb was 9.4 g/dL.

Prof Gralnek concluded the case presentation by highlighting the importance of investigating the cause of the underlying IDA and the need to consider treating underlying IDA on top of acute GIB.

What the Science Tells Us about How to Treat Gastrointestinal Bleeding in Patients with Underlying Iron Deficiency Anaemia

A retrospective study from Denmark identified that 80% of acute nonvariceal upper GI haemorrhage patients were discharged with anaemia, and that only 16% had oral iron recommended at discharge. This may be partly because no standardised follow-up protocols were in place for patients with anaemia at the time.[1] It has since become evident that the gastroenterologist must not only treat the acute GIB event but also the underlying anaemia and iron deficiency. Anaemia is associated with disability, poorer physical performance, and lower muscle strength,[2] and a prospective study on women aged 65 years or older reported that the 5-year all-cause mortality increased when Hb was below the World Health Organization (WHO) low-normal cutoff of 12 g/dL.[3]

Little attention has been paid to the health-related QoL of patients with GIB because this aspect requires contact to be maintained with patients and actions to be implemented after the hospital discharge. The appropriate management of anaemia and iron deficiency has the potential to directly affect the QoL and performance of most patients. Implications for physical health, mobility, performance of daily activities, pain, discomfort, anxiety, and depression following hospital admission and discharge have not been adequately investigated but are as important to patients and families as the bleeding itself. These aspects need to be featured within the physician's agenda when considering the appropriate management of patients with GIB.[4]

Oral iron preparations are the mainstay for the treatment or prevention of IDA, and numerous oral preparations and dosing regimens are available.[5] IV iron preparations with improved toxicity profiles have been used for cases in which rapid therapy was useful in reducing the need for RBC transfusion.[6] As a general rule, iron supplementation therapy should be continued

until the anaemia is resolved and the iron stores are replenished.[7,8] Oral administration of iron sulphate is viewed as the first-line treatment for IDA patients; however, oral iron shows substantial limitations for patients with GI disorders because of insufficient absorption, slow course of action, and severe GI side effects that may exacerbate existing symptoms.[9] Due to this intolerance, oral iron treatment is discontinued in up to 50% of IDA patients.[10]

Ferric carboxymaltose (FCM) is one of several IV iron formulations[11] available and was first approved in Europe in 2007.[12] The FCM formulation consists of a complex carbohydrate shell that tightly binds the elemental iron, which allows a large dose of supplemental iron to be administered IV in a short time period.[12,13] In a 42-day clinical trial (N=71 patients) comparing FCM with oral iron (ferrous sulphate), FCM was more efficacious and faster to normalise Hb levels (Figure 1a) and transferrin saturation index (Figure 1b) than oral iron.[9] No treatment-related adverse events, withdrawals, or dose reductions were reported for the FCM group, whereas treatment-related adverse events (mainly constipation) were reported by 30% of oral iron treated-patients.

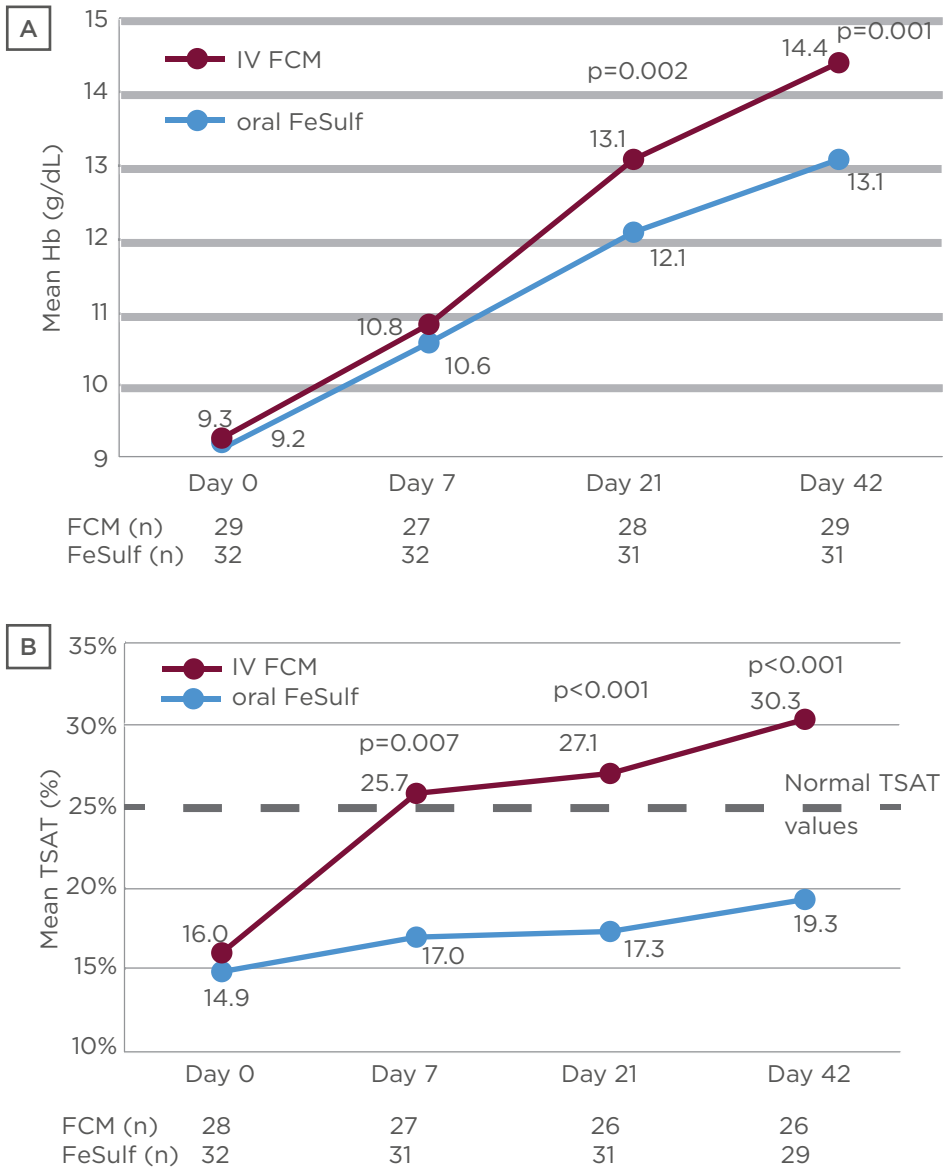

Figure 1: Mean Hb levels (a) and mean transferrin saturation index (b) of patients treated with IV FCM or oral iron (FeSulf).[9]

FCM: ferric carboxymaltose; FeSulf: ferrous sulphate; Hb: haemoglobin; IV: intravenous; TSAT: transferrin saturation index.

Table 1: Advantages and limitations of oral iron and IV iron formulations. Courtesy from Spanish Association of Gastroenterology (AEG).[14]

Iron formulation	Advantages	Limitations
Oral iron	At the right dose, it is effective in many patients.	GI side effects are common.
	The risk of serious adverse effects is practically nonexistent.	Adherence may be low.
	The cost is very low.	Unsuitable for iron replacement in cases of severe bleeding or continuous occult blood loss.
		Replenishment of iron stores may take several months.
		Total costs may be high when absenteeism and presenteeism costs are combined.
IV iron	It is effective in most cases.	IV infusion requires monitoring.
	Faster correction of anaemia and its symptoms.	Although uncommon, infusion-related reactions and allergies have been reported.
	Possibility of administering high doses (≤1,000 mg of elemental iron) in a single infusion.	Special equipment and trained staff are required to treat potential infusion-related reactions.
	Adherence is guaranteed.	The initial cost is higher.
	No GI side effects.	

GI: gastrointestinal; IV: intravenous.

At Day 42, 77% of FCM-treated patients repleted their iron deposits compared with only 24% of patients treated with oral iron, with a significant difference (p=0.04) between the two treatments observed already at Day 7. Patients treated with FCM also had a significantly better (p=0.02) subjective state of health (measured using the EuroQol-visual analogue scale) versus patients treated with oral iron.[9] A summary of advantages and limitations of oral or IV iron replacement therapies are summarised in Table 1.[14]

Prof Gralnek argued that IV iron is suitable for patients with intolerance or limited or no response to oral iron, a Hb <10 g/dL, or with a Hb >10 g/dL in conjunction with cardiovascular or respiratory comorbidities. IV iron therapy has a favourable safety profile, as reported by a systematic review and meta-analysis of 103 trials. This study concluded that although IV iron is associated with infusion reactions, it is also associated with reduced rates of GI adverse events, and it is not associated with an increased risk of serious adverse events or infections.[15]

Furthermore, IV iron is cost-effective compared to other anaemia therapies such as RBC transfusion,[16-18] which is a leading indication for acute upper GI bleeding, although the optimal Hb thresholds for transfusion are poorly defined. A meta-analysis of five randomised trials found that restrictive RBC transfusion results in lower all-cause mortality and lower re-bleeding compared with liberal RBC transfusion.[19] Additionally, FCM therapy in patients with chronic GIB reduces the need for RBC transfusions and improves Hb and iron indices.[17]

Prof Gralnek concluded his case-based presentation on IDA in patients with GIB by stressing that IDA is common, often underdiagnosed, and undertreated. The decisions on whether to treat with RBC transfusion should be made individually, depending on the origin and extent of the bleeding and the existence of

patient comorbidities. The choice between oral versus IV iron therapy will depend on multiple factors such as the degree of anaemia, presence of inflammation, and adherence to oral iron therapy. The main objective of iron treatment is to normalise Hb and iron parameters, and gastroenterologists need to be more aware of anaemia beyond the acute GIB episode. Furthermore, future GIB guidelines should consider recommendations on iron therapy.

Acute Gastrointestinal Bleeding in Patients Taking Anticoagulants or Antiplatelets

Professor Angel Lanas

Case Presentation

Prof Lanas opened his presentation by introducing a typical clinical case: a 74-year old woman with Type 2 diabetes mellitus, hypertension, and atrial fibrillation. She was taking metformin, candesartan, and warfarin, and had noticed the presence of red blood in the rectum for several days and had been feeling weak. Her primary care physician detected Hb 6 g/dL and an international normalised ratio (INR) of 4. The patient was hospitalised and diagnosed with colonic diverticular bleeding. Prof Lanas highlighted important clinical considerations associated with stopping the AC, and if so, for how long. Other considerations included whether to change the AC to a different type if resumed, as well as challenges associated with Hb management at discharge in anaemic GIB patients that are taking AC or antiplatelet (AP) drugs.

What the Science Tells Us About How to Treat Anemia in Acute Gastrointestinal Bleeding Patients Taking Anticoagulant or Antiplatelet Drugs

More than 5,700 severe bleeding episodes linked to AC occur in Spain every year. The largest proportion of these bleeding events linked to AC therapy due to atrial fibrillation is digestive system bleeds (43.6%), followed by brain bleeds (30.6%), and urogenital bleeds (14.5%).[20,21] Patients with IDA of unknown aetiology are usually referred to a gastroenterologist because GI conditions are likely to be the cause of the bleed.[22] Nonvariceal upper GIB is a type of bleeding that develops in the proximal duodenum, stomach, or oesophagus. Peptic ulcers, caused by *H. pylori* infection or use of nonsteroid anti-inflammatory drugs (NSAID) and low-dose aspirin, are the most common causes of nonvariceal upper GIB.[4]

Prof Lanas pointed out that in nonvariceal upper GIB in patients taking vitamin K antagonists such as warfarin, it is important to determine the INR once the vitamin K antagonist has been stopped. If the INR is <2.5, the patient should be referred for endoscopy, and if the INR is >2.5, the treatment plan depends on whether or not the patient is haemodynamically compromised.[4] The timing for when to restart AC therapy depends on the clinical context. An observational cohort study of patients who developed GI bleeding while on AP or AC therapy found that with AP/AC, the cardiovascular risk is reduced at the expense of an increased risk of recurrent GIB.[23] There is no firm evidence for when AP or AC therapy should be resumed. European Society of Gastrointestinal Endoscopy (ESGE) guidelines recommend restarting AC therapy following nonvariceal upper GIB in patients with an indication for long-term anticoagulation.[24] The timing for resumption of anticoagulation should be assessed on a patient-by-patient basis: within 7–15 days following the bleeding event for most patients, and within the first 7 days for patients at high thrombotic risk.[24] Importantly, early resumption of AT therapy is not associated with poorer outcomes, and appears beneficial.[23]

Should the Gastroenterologist be Concerned with the Patient's Haemoglobin Levels at Discharge?

In the illustrative clinical case, the patient received three units of RBC and was discharged after the GIB stopped spontaneously. She is now treated with a new oral direct AC and oral iron, and her Hb at discharge was 9.5 g/dL. A frequent clinical scenario after an acute GIB event at hospital discharge is that the GIB is controlled, the patient has comorbidities, and remains anaemic (Hb between 7 and 10 g/dL) either after receiving blood transfusion or no blood at all. In the clinical case, the patient felt weak and physically limited, and was prescribed oral iron, without clear

instructions given to their primary care physician. Many patients also need aspirin or AC, as in the case presented by Prof Lanas, which puts them at risk of rebleeding or maintaining occult blood loss. Importantly, there are data suggesting that patients leaving the hospital with low Hb have an increased risk of death,[25] but patients who receive IV iron are less likely to reattend hospital within 30 days, are more likely to reattend electively, and tend to have a shorter length of stay in hospital compared with patients who receive oral iron therapy.[26] Treatment with FCM for acute GIB is associated with a good erythropoietic response and anaemia correction after hospitalisation, even in severe episodes or when transfusion is needed. Favourable outcomes (Hb increase of 3–6 g/dL) of FCM treatment were observed also in patients that were aged ≥75 years, had a high Charlson Comorbidity Index ≥3, or who had low Hb (≤10 g/dL) at admission. Additionally, FCM has a favourable safety profile, is well-tolerated, and may support a restrictive blood transfusion policy.[27]

Prof Lanas brought a question to the audience: **What Happens to those Patients that did not have a Previous Gastrointestinal Bleed but were Receiving Drugs Potentially Toxic for the Gastrointestinal Tract, such as Aspirin, Antiplatelet, Anticoagulant, or Nonsteroidal Anti-Inflammatory Drugs?**

Anaemia and iron deficiency are common in patients with cardiovascular disease,[28] and a retrospective observational cohort study of patients who started dual AP therapy (DAPT, i.e., clopidogrel plus aspirin) after percutaneous coronary intervention reported that anaemia and iron deficiency were the most commonly reported GI events. After 1 year of follow-up, almost 50.0% of patients taking dual AP therapy developed anaemia or iron deficiency and only 3.6% developed a major GI event. This data is important because most of the patients (90%) were receiving PPI, even though a majority (72%) of the lesions responsible for the anaemia were found in the lower GI tract.[29] GIB have also been associated with NSAID therapies. The CONDOR study investigated the risk of GIB in patients with osteoarthritis or rheumatoid arthritis that were treated with either celecoxib (a cyclo-oxygenase-2-selective NSAID) or diclofenac (a nonselective NSAID) plus a PPI, with clinically significant GI events through the GI tract as primary endpoint. The authors concluded that the risk of developing clinically significant GI events was lower in patients treated with a cyclo-oxygenase -2-selective NSAID than in patients treated with a nonselective NSAID plus a PPI. Importantly, 92 of the 101 reported GI events were not major bleeds, but anaemia cases with a Hb decrease of ≥2 g/dL due to GI origin bleeds.[30] This Hb decrease may be countered by FCM therapy, because patients with chronic GIB that are treated with FCM have a reduced need of RBC transfusion and improved Hb and iron parameters.[17]

Conclusion

In summary, upper and lower GIB, and especially anaemia or iron storage depletion, are frequent in patients taking AT agents, and occur in patients with comorbidities such as cardiovascular disease, which have a direct impact on mortality, morbidity, and QoL. Anaemia after hospital discharge is common in patients who have developed a GIB event, and in patients taking AP or AC drugs. These patients are at the highest risk of remaining anaemic, since most will need to maintain their medication, and many will develop anaemia without presenting with a major GIB event. Anaemia and iron deficiency affect mortality, recovery, and QoL in patients who need a rapid restoration of haemoglobin levels and iron stores to decrease the risk of new and recurrent cardiovascular events. FCM therapy is more effective, faster, has a favourable safety profile, and is cost-effective compared to oral iron therapy, and represents a good therapeutic option for this type of patient.

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Abstract Awards

UEG Week Awards 2019

The United European Gastroenterology (UEG) Week was initially launched as a communicative meeting about gastrointestinal research and practice in Europe and has now flourished into a large-scale influential global congress and mainstay in the world of digestive health. In its 27th year, UEG Week was hosted in Barcelona, Spain, and saw an influx of high-calibre abstracts from leading experts in the field. A total of 4,021 abstracts were submitted by researchers and 2,443 abstracts were accepted for presentation at the meeting. The impressive volume and standard of abstracts received by UEG is testimony to the significance of this annual congress as a platform upon which research is hailed. As is convention, the abstracts are assessed by the Scientific Committee for their quality and relevance to the meeting ensuring the greatest quality of research is maintained for delegates to reap from. UEG honours its contributors for their scientific research and dedication in many ways. One of these acknowledgments is the prestigious ''Top Abstract Prize'' awarded to the best five abstracts submitted to UEG, some of which are summarised here.

Kicking things off on the morning of Monday October 21st, Dr Lissy de Ridder, Erasmus MC, Rotterdam, the Netherlands, presented the abstract entitled ''Top-down infliximab superior to step-up in children with moderate-to-severe Crohn's disease – a multicenter randomized controlled trial.'' The abstract discussed the results of the first randomised controlled study to compare early initiation of anti-TNF treatment with the guideline-recommended 'step-up' (SU) treatment for paediatric patients newly diagnosed moderate-to-severe Crohn's disease (CD). Traditional therapy for paediatric CD includes exclusive enteral nutrition (EEN), oral prednisolone, and immunomodulators. The SU strategy taken by clinicians is the administration of infliximab (IFX) suggested to have extremely positive results in overcoming refractory disease. The authors commented on the latest evidence that the earlier this treatment is given to patients, the greater effect it will confer. They suggested 'top-down' (TD) treatment of IFX in moderate-to-severe paediatric patients, of which would be directly administered after diagnosis, would achieve increased long-term remission rates. To compare efficacy of the 2 treatment types, researchers collated data from 100 patients who were aged between 3 and 17 years old in this randomised controlled trial. Preliminary analysis revealed that there was sustained clinical

remission for patients who received TD treatment compared to SU treatment (18/37 [49%] versus 5/38 [13%]; p=0.001), and more patients in the TD group were in clinical remission (24/41 [59%] versus 15/42 [36%]; p=0.037) in Week 10. Additionally, there was a significantly greater proportion of patients with low faecal calprotectin level in the TD set compared to the SU set (n=44; 9/23 [39%] versus 4/21 [19%]; p=0.005). This randomised controlled trial by de Ridder et al. was the first to directly compare TD IFX to SU treatment in paediatric CD patients. The results showed that TD treatment was more beneficial to patients than traditional SU therapy in sustained clinical remission without the need for additional therapy or surgery.

The next author granted with a prestigious award was Dr Magdy El-Salhy, University of Bergen, Bergen, Norway, for the abstract entitled ''FMT using a 'super-donor' effective and well tolerated in irritable bowel syndrome.'' There is an acknowledged difference between intestinal microbiota of the healthy population with dysbiosis, and in patients living with intestinal bowel syndrome (IBS), a condition in which the prevalence of microbiota dysbiosis is said to have a major contribution to its clinical manifestations. The team of researchers explored ways to improve IBS symptoms in this study by exploring the effect of faecal microbiota transplantation (FMT) from a single donor with a more diverse microbiota profile. In this randomised, double-blind study, 164 patients were treated with either a 30 g or 60 g transplant, or placebo, in a ratio of 1:1:1. The primary outcome of the trial was a reduction of the symptoms of IBS ascertained 3 months after FMT by an Irritable Bowel Syndrome Severity Scoring System (IBS-SSS) score ≥50. The secondary outcome was a reduced Dysbiosis Index (DI) and favourable difference in the intestinal bacterial profile in the IBS patients 3 months after FMT. The trial assessed abdominal symptoms, fatigue, quality of life, and gut bacterial analysis in the patients. For each of the placebo, 30 g and 60 g transplant groups, response to FMT occurred in 23.6%, 75.9%, and 87.3% of patients, respectively. Fatigue and quality of life was significantly improved in these patients. Clinical improvements in symptom remission, fatigue, and quality of life was shown increase from placebo, to 30 g, and increase further in the 60 g transplant group. There were no significant differences in DI between the groups and intestinal bacterial profiles changed in both FMT groups only. The results of this study suggested that FMT is a beneficial treatment option for IBS patients, and response to treatment is more favourable with increased dosage. The difference in intestinal bacterial profiles between responders and nonresponders indicated that this may be useful criteria to identify those eligible for FMT. A donor must have a normal DI and a specific microbial signature.

Dr William Waddingham, University College London, London, UK, was the first author for another exceptional abstract presented at UEG Week awarded with the Top Abstract Prize. The abstract was entitled, ''Defining the clonal origin, expansion rate and clonal diversity of intestinal metaplasia in the *Helicobacter*-infected human stomach.'' Gastric intestinal metaplasia (GIM) is a pre-cursor lesion to gastric cancer (GC) with unknown origins and can be caused by chronic infection with *Helicobacter pylori*. Development of targeted endoscopic surveillance in those for whom the risk of GC is highest may be possible following greater understanding of stem cell dynamics and clonal diversity in GIM. The authors aimed calculate quantitative measures of clonal diversity of GIM in patients with chronically inflamed stomachs by comparison with participants who had normal gastric mucosa and were undergoing sleeve gastrectomy weight loss surgery. The results from the study showed that GIM originates from a single stem cell within a single gastric gland and that the mutation burden of GIM can be compared to mature GC. With their data, they determined that *H. pylori* promotes selection and expansion of mutant lineages by initiation of adaptive radiation of metaplastic cellular clones. The metaplastic phenotype has a fitness advantage at the level of the individual stem cell and the rate of expansion of GIM throws light on time-dependent transformation of the gastric mucosa into a competitive field of cancer precursor lineages. The authors concluded that the GC progression risk could be addressed by assessment of clonal genetic diversity as a potential marker in chronic gastritis patients.

It is abundantly clear that the quality of abstracts submitted to UEG continues to rise exponentially and no less is expected next year at UEG 2020 in Amsterdam, the Netherlands!

Abstract Reviews

The following pages provide summaries of exemplary abstracts presented at this year's United European Gastroenterology (UEG) Week, written by the authors themselves.

Integrated Microbiota and Metabolite Profiles in Human and Mice Identified Functional Signatures in Crohn's Disease with a Link to Sulphur Metabolism

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Disclosure: The authors have declared no conflicts of interest.

Acknowledgements: This work was supported by the Helmsley Charitable Trust (IBD overtime consortium).

Keywords: Crohn's disease (CD), functional signatures, gut microbiota, humanised mice.

Citation: EMJ Gastroenterol. 2019;8[1]:54-55. Abstract Review No: AR1.

BACKGROUND AND AIMS

Crohn's disease (CD) is a chronic, remitting relapsing inflammatory disease of the gastrointestinal tract. Disease pathogenesis is suggested to be driven by complex interactions of genetic,[1,2] environmental, immune, and microbial factors.[3] This inherent complexity of the disease, manifested in a widely variable clinical course,

makes it difficult to dissect disease mechanisms or to predict disease progression based on the patient's status at initial diagnosis. Metabolic activities of the microbiome play a central role in maintaining vital physiological processes of the host, including energy harvest,[4] protection against pathogens,[5] and modulation of host immunity.[6] Alterations in metabolite profiles are indicative of functional changes in the microbiome and the development of CD. The aim of this study was to identify functional signatures associated with disease outcome and response to therapy in patients with CD, and to mechanistically characterise their pathogenic potential using humanised gnotobiotic mice and an integrative multiomics approach.

METHODS AND RESULTS

A total of 29 CD patients were studied for a period of 5 years after autologous haematopoietic stem cell transplantation therapy. Faecal samples were collected both at baseline and at different time points during follow-up. To characterise changes in gut microbiome and metabolome, 16S ribosomal RNA gene sequencing was performed, alongside global 16S predicted metagenomes, shotgun metagenomic sequencing, and untargeted metabolomics. To address the functional impact of microbial dysbiosis, a humanised inflammatory bowel disease mouse model was established by colonising germ free IL-10-/- mice with selected faecal samples from CD patients at different disease states. Temporal fluctuations in gut microbiota composition and metabolite profiles reflected individual patient-related variations and differences in disease activity. The faecal microbiome of patients with active disease was enriched in microbial taxa involved in sulphur metabolism such as *Eschericia Shigella* and *Fusobacterium*, as well as a high proportion of sulphate-reducing bacteria such as *Desulfovibrio* and *Campylobacter.* Faecal metabolic profiling confirmed an increased abundance of sulphated metabolites (bile acids, polyphenols, and biogenic amines). Predicted metagenomes from 16S ribosomal RNA gene profiling revealed enrichment of functional genes associated with sulphate and ion transport system metabolism in CD patients with active disease. In contrast, increased abundance of several basic biosynthetic processes correlated with remission. Transplantation of microbiota from patients with active or inactive disease was reproducibly sufficient to recreate disease phenotypes in recipient IL-10-/- germ-free mice. Humanised mice reflected the dysbiotic features of their respective human donors and inflammation was driven by a variety of individual community profiles of different community configurations. Using a machine learning algorithm, a panel of 10 taxa was identified that could discriminate between humanised mice via their inflammatory status. For instance, it was found that a microbial signature characterised by an overabundance of *Bacteroides fragillis* and *Desulfovibrio* classified humanised mice by inflammation with high accuracy. In accordance with the signature identified in humans, enrichment of sulphated metabolites was indicative of an inflamed phenotype, together with an abundance of genes mapping to sulphate metabolism and Type II, IV, and VI secretion systems.

CONCLUSIONS

The present data provide evidence that despite the heterogeneity of CD patients' gut microbiome at the taxonomic level, shared functional signatures correlate with disease severity. Integration of microbiota and metabolite profiles from both human and mice improved the predictive modelling of disease outcome significantly and identified a network of functionally relevant bacteria–metabolite interactions linked to disease activity in CD.

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Regulation of Lymphangiogenesis by Paneth Cells in Normal Physiology and Experimental Portal Hypertension

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Disclosure: This work was supported by a grant from Foundation Johanna Dürmüller-bol to Sheida Moghadamrad and from the Swiss National Science Foundation (grant 31003A_129842) to Dr De Gottardi.

Acknowledgements: The authors would like to thank United European Gastroenterology (UEG) Week for the opportunity to present and *EMJ Gastroenterology* for publishing this abstract review.

Keywords: Lymphatic vessels, Lyve-1, Paneth cells.

Citation: EMJ Gastroenterol. 2019;8[1]:56-57. Abstract Review No: AR2.

INTRODUCTION

In parallel to the blood vascular system, an extensive network of lymphatic vessels circulates throughout the entire body. The lymphatic system plays an important role in maintaining tissue fluid homeostasis, immune cell trafficking, and in particular facilitates dietary lipid uptake in the intestine.[1] Paneth cells are a part of the intestinal innate immune system and have a central role in regulation of intestinal angiogenesis.[2] It has been previously reported that a decrease in intestinal vascularisation and number of Paneth cells occurs alongside lymphangiogenesis in the absence of intestinal microflora.[3] However, the association between Paneth cells and the regulation of lymphatic vascular development is currently unknown. The aim of this study was therefore to investigate the regulatory role of Paneth cells in the development of intestinal and mesenteric lymphangiogenesis and portal hypertension.

METHODS

The experiment involved inducing Paneth cell depletion in *Math-1 Lox/Lox Villcre^{ERT2}* mice by injecting three consecutive doses of tamoxifen and performed partial portal vein ligation (PPVL) to induce portal hypertension. After 14 days, portal pressure was measured. Intestinal and mesenteric lymphatic vessels were assessed by immunohistochemistry using lymphatic vessel endothelial hyaluronic acid receptor 1 (Lyve-1) antibody. The lymphatic vessels were quantified using MetaMorph® (Molecular Devices, San Jose, California, USA) software to calculate pixel percentage ratio. Expression of genes involved in the regulation of lymphatic vessels was evaluated by RT^2 Profiler™ PCR array (Qiagen, Hilden, Germany) in intestinal tissue. Intestinal organoids from controls and Paneth cell depleted mice (Figure 1) were exposed to various bacterial derived products. Proteomic analysis of conditioned media was performed using MaxQuant software to analyse differentially regulated proteins associated with lymphangiogenesis in the absence or presence of Paneth cells or in portal hypertension.

RESULTS

Portal pressure was significantly attenuated in Paneth cell depleted mice compared to control mice after PPVL (n=11/group, 9.78±1.23 cm H_2O versus 11.45±1.41 cm H_2O, respectively; p<0.002). Depletion of Paneth cells resulted in a significantly decreased density of lymphatic vessels compared to controls as assessed by immunohistochemistry (n=5, pixel ratio), in the intestine (0.176%±0.12 versus 0.367%±0.15; p=0.01), and in the mesentery (0.160%±0.06 versus 0.404%±0.20; p=0.001). Quantitative PCR showed a decreased expression of genes involved in the regulation of lymphangiogenesis, including *VEGF-C*, *VEGF-D*, *VEGF-A*, *Nrp2*, *Angpt-2*, *Tie-1*, *Tie-2*, *TGF-α*, *HGF*, and *CXCL-1* in Paneth cell depleted mice.

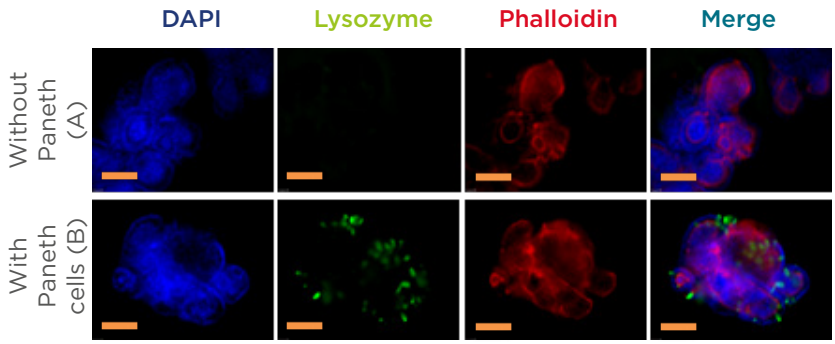

Figure 1: Organoids with (green) or without Paneth cells.

Representative immunofluorescent images of small intestinal organoids cultured from **A)** Paneth cell depleted mice small intestine **B)** control mice small intestine with Paneth cells. Nuclei (blue), Paneth cells (Green), F-actin (Red). F-actin is endogenously expressed and is stained with phalloidin, Paneth cells are detected using a polyclonal rabbit antibody lysozyme in combination with a secondary antibody Alexa Fluor®488 (Thermo Fisher Scientific, Waltham, Massachusetts, USA) F(ab')2 fragment of goat anti-rabbit IgG. Nuclei are labelled with DAPI. Images of organoids were obtained using a Leica DMI4000 B (Leica Microsystems, Wetzlar, Germany) fluorescence system. The yellow line represents 100 µM and 50 µM magnification in both **A** and **B**, respectively.
DAPI: 4`,6-diamidino-2-phenylindole.

Moreover, the expression of specific markers of lymphangiogenesis, such as transcription factor Prox-1, growth factor VEGFR3, or protein FOXC2, were significantly decreased in Paneth cell depleted mice after PPVL. In the absence of Paneth cells, proteomic analyses showed a significant downregulation of several proteins involved in lymphatic vessel development and morphogenesis, as well as in lipid metabolism and transport processes.

CONCLUSION

In the absence of Paneth cells, portal hypertension was attenuated significantly in association with a decreased density of intestinal and mesenteric lymphatic vessel. These findings suggest that Paneth cells not only play an antimicrobial role in the intestine, but also contribute to the regulation of lymphatic vessels and portal pressure.

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Making the Invisible Visible: The Hidden Cost of Paediatric Inflammatory Bowel Disease

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Disclosure: For the last 3 years Dr Turner has received consultation fees, research grants, royalties, or honorarium from Janssen, Pfizer, Hospital for Sick Children, Ferring, Abbvie, Takeda, Atlantic Health, Shire, Celgene, Lilly, Neopharm, Roche, and ThermoFisher.

Received: 27.11.2019

Accepted: 28.11.2019

Keywords: Disability, disease burden, health costs, paediatric inflammatory bowel disease.

Citation: EMJ Gastroenterol. 2019;8[1]:58-60.

Abstract

This year, the European Society for Gastroenterology Hepatology and Nutrition (ESPGHAN) joined forces with the European Federation of Crohn's & Colitis Associations (EFCCA) to drive awareness of the hidden costs of paediatric inflammatory bowel diseases (IBD) and make the invisible visible. This feature puts the hidden cost of paediatric IBD in the spotlight and the author makes the case for policy makers to recognise the invisible cost of paediatric IBD. He pledges to take four key steps to reduce the burden of the diseases on society and improve the lives of children and their families.

INTRODUCTION

Europe has the leading prevalence rates of inflammatory bowel diseases (IBD) in the world. It is estimated that 2.5–3.0 million people on the continent bear the condition,[1] and the associated costs are on the rise. Up to 20% of IBD cases develop during childhood which equates to a pan-European figure of 500,000–600,000 children affected by IBD. This has led to substantial direct costs, such as medications, admissions, surgeries, and various healthcare expenses. To make matters worse, indirect costs of IBD include lost working and school days as well as reduced productivity of the child and the immediate family circle. Moreover, the 'invisible' costs such as anxiety, depression and loss of motivation, as well as lost family time are often left unnoticed but heavily exacerbate the issue.

THE PROBLEM

The direct healthcare costs of IBD are posing a significant challenge with reports of €5.6 billion across Europe each year. With pan-European prevalence rates of IBD on the rise, this figure is expected to further increase.[1] Park et al.[2] showed that IBD patients incurred a direct cost of care bill that was over three times higher than that of non-IBD patients,[2] and for paediatric IBD patients the cost is on average even higher than for adults.[3] Furthermore, while incidence rates are declining in adults, they are rising amongst children.[4] This is reflected in healthcare services, where the utilisation of adult gastroenterologists and surgeons for IBD is decreasing but their use in paediatrics is increasing. In the extreme

context, it has been reported that the risk of death amongst children with IBD when followed through adulthood is up to three times greater when compared with the general population.[5]

In short, IBD is associated with a substantial strain on the healthcare of western countries, but perhaps the biggest burden is associated with the tremendous indirect and 'invisible' costs to the individual, families, and society. It is noteworthy that the costs of IBD, in children and in adults, are not exclusively rooted in a healthcare setting. Studies have suggested that the economic burden of IBD per patient on society (indirect costs) account for up to 68% of the total cost, with the annual direct cost to the patient of around €750 being dwarfed by the €2,300 cost to society per year.[6] Based on this calculation it may be speculated that the true cost of IBD is in the region of tens of billions of euros per year. On average, parents and carers of children with IBD take an additional week off from work to provide care for their child,[7] and people with IBD lose up to 20 days of recreational time every year due to their condition. Indeed, IBD patients are sick approximately 4 weeks a year on average and are 50% more likely to take sick leave.[1]

Multiple studies indicate that IBD frequently leads to issues associated with work or school absence, in addition to social life and psychological problems such as anxiety and depression. This is often a consequence of the burdens of IBD, such as flares, admissions, surgeries, emotional and body image challenges, issues around growth, and osteopenia. The ramifications of these costs may be more significant in children given the additional age-specific considerations. The impact on children, living with the condition at such a key stage of their physiological, social, physical, mental, and educational development, can be detrimental. In a recent study, 52% of IBD patients indicated that their condition negatively affected their education.[1] Many paediatric patients find the symptoms of IBD embarrassing and humiliating, which in turn can cause psychological issues.[8] These form part of the invisible costs that are difficult to quantify but exist on top of both the direct and indirect costs. When it is considered that 72% of patients report that they are worried about their IBD, even when in remission,[9] we can begin to understand not just the physical, but the psychological battle that many children with IBD face, and how this struggle can spill over into their education and every day life. It is thus intuitive to grasp how important effective management of those children is, in the goal of achieving complete and sustained deep remission.

POSSIBLE SOLUTIONS

Solving the issue is not a quick or easy process but it is realistic if policy makers commit to taking swift and appropriate action. To achieve this, four key steps are suggested to help reduce the burden of IBD on society and improve the lives of children and their families. Firstly, policy makers must recognise the true cost of paediatric IBD and also incorporate the indirect and invisible costs into economic modelling and public health decision-making. Acknowledging the real disease burden will undoubtedly justify more investments into paediatric IBD and actively facilitate improved management of the condition in childhood.[10] Optimal paediatric treatment has been proven to reduce both the direct and indirect costs of IBD.[11]

Secondly, implementation of education and workplace policies that better consider the needs of children with IBD and their caregivers. Schools could play a central role in this motion by providing flexible food options, cleaner and readily accessible bathrooms, and a secure environment where children are comfortable with their disease, such as when asking to exit the class to go to the bathroom or going home as needed. Moreover, schools should provide extra examination time to children with IBD to account for the associated multi-level burdens that they experience. Similarly, workplaces should be educated about the disease to provide parents with the necessary flexibility for managing their child's chronic disease.

Gradual transitional arrangements between paediatric and adult care should be a key stage of the care pathway. Policies that build on this will ensure and foster an effective and the least disruptive transition and long-term management. This is particularly important given the concerning statistic that as many as half of adolescents are non-compliant with the recommended treatment and that the transition period is especially vulnerable for disease flares.[12]

Finally, children with IBD must be treated by a competent multidisciplinary paediatric IBD team,[13] and the healthcare community should play an active role in accomplishing this. Patients with the condition should be managed at the very least by a paediatric gastroenterologist trained in the care of paediatric IBD, a paediatric IBD nurse, dietitian and psychologist, and more paediatric IBD referral centres should be established to provide comprehensive treatment. While a substantial proportion of children are not treated in referral paediatric IBD centres, even the most specialised paediatric IBD centres in Europe and North America do not offer all necessary services to provide comprehensive care to children with IBD.[14] Multidisciplinary teams and being part of quality improvement programmes that monitor disease severity and provide tailored treatment plans, could facilitate clinically important outcomes including remission and mucosal healing.[15] In addition to providing dietary, social and physiological care, offering support groups and other easily accessible psychosocial interventions in the community are mandatory to enhance coping skills and improve quality of life.

CONCLUSION

The burden posed by paediatric IBD across Europe is becoming an increasingly alarming issue, and a significant proportion of this burden concerns the indirect and 'invisible' societal costs; however, overcoming the problem is achievable. A concerted action towards strengthening paediatric IBD centres and training community paediatric gastroenterologists, as well as facilitating more IBD-friendly environments, are key foundations for making the invisible visible.

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Refractory Gastroesophageal Reflux Disease: Pathophysiology, Diagnosis, and Management

EDITOR'S PICK

My Editor's Pick for this edition is Nabi et al.'s review on the topic of refractory gastroesophageal reflux disease in the context of its pathophysiology, diagnosis, and treatment. The authors explore these elements in great detail, offering a timely and helpful update on this common gastrointestinal complaint.

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Disclosure: The authors have declared no conflicts of interest.

Received: 10.05.19

Accepted: 02.07.19

Keywords: Antireflux surgery, endoscopy, gastroesophageal reflux, proton pump inhibitors (PPI).

Citation: EMJ Gastroenterol. 2019;8[1]:62-71.

Abstract

Gastroesophageal reflux disease (GERD) is one of the most commonly encountered gastrointestinal diseases in clinical practice. Proton pump inhibitors (PPI) remain the cornerstone of the treatment of GERD. Up to one-third of patients do not respond to optimal doses of PPI and fall into the category of refractory GERD. Moreover, the long-term use of PPI is not risk-free, as previously thought. The pathophysiology of refractory GERD is multifactorial and includes reflux related and unrelated factors. It is therefore paramount to address refractory GERD as per the aetiology of the disease for optimal outcomes. The management options for PPI refractory GERD include optimisation of PPI, lifestyle modifications, and the addition of alginates and histamine-2 receptor blockers. Neuromodulators, such as selective serotonin reuptake inhibitors or tricyclic antidepressants, may be beneficial in those with functional heartburn and reflux hypersensitivity. Laparoscopic antireflux surgeries, including Nissen's fundoplication and magnetic sphincter augmentation, are useful in patients with objective evidence of GERD on pH impedance studies with or without a hiatal hernia. More recently, endoscopic antireflux modalities have emerged as an alternative to surgery in patients with PPI-dependent and PPI-refractory GERD. Long-term data and randomised comparison studies, however, are required before incorporating endoscopic therapies in the management algorithm for refractory GERD.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common gastrointestinal (GI) disorder worldwide. Proton pump inhibitors (PPI) are the mainstay of treatment for GERD and achieve symptom relief in the vast majority of patients. However, approximately one-third of patients continue to experience symptoms of GERD on once daily

Table 1: Causes of proton pump inhibitor refractory gastroesophageal reflux disease.

Reflux related	Nonreflux related
• Drug compliance and improper dosing. • Residual acid reflux. • Nonacidic or weakly acidic reflux. • Acid pocket. • Oesophageal hypersensitivity. • Nocturnal acid breakthrough. • Duodenogastric reflux. • PPI metabolism and CYP2C19 polymorphism.	• Functional chest pain. • Functional heartburn. • Oesophageal motility disorders (achalasia, scleroderma). • Eosinophilic oesophagitis. • Impaired gastric emptying. • Extraoesophageal symptoms (chronic cough, asthma, hoarseness of voice).

CYP2C19L: cytochrome P450 2C19; PPI: proton pump inhibitor.

PPI therapy and 10% of patients on twice daily PPI therapy.[1,2] While on long-term PPI therapy, approximately 50–60% of patients complain of persistent or breakthrough symptoms.[3] Refractory GERD is associated with poor health-related quality of life (HRQoL), low work productivity, greater absenteeism from work, psychological impairment, and poor sleep quality.[4] Moreover, recent studies and guidelines report significant health risks associated with long-term PPI therapy.[5] Considering the significant burden of GERD on the healthcare system and a sizeable proportion of patients with suboptimal response to medical therapy, it is crucial to understand novelties in the field of refractory GERD. In this review, the authors discuss the pathophysiology, diagnosis, and various treatment options for PPI refractory GERD.

DEFINITION

Heartburn and regurgitation are the two cardinal symptoms of GERD. The most accepted and pragmatic definition of refractory GERD is the persistence of typical symptoms, heartburn and/or regurgitation, that do not respond to a standard double dose of PPI for a treatment period of at least 12 weeks.[2] In clinical practice, the diagnosis of refractoriness can usually be established after 8 weeks of PPI therapy.

Pathophysiology of Refractory Gastroesophageal Reflux Disease

The causes of refractory GERD can be classified as reflux related and nonreflux related (Table 1). In the majority of the cases, refractoriness to PPI can be attributed to residual acid reflux, nonacidic or weakly acidic reflux, acid pocket, oesophageal hypersensitivity, and functional heartburn.

Drug Compliance and Improper Dosing

One of the most important factors that contributes to refractory GERD is poor drug compliance and improper dosing. In a large population-based survey, strict adherence to PPI treatment was observed in only 38.7% and 30.6% of patients over 6 months and 1 year, respectively.[6] Improper timing of PPI intake is another important factor resulting in suboptimal acid suppression and refractoriness to PPI. Administration of PPI 30–45 minutes before a meal is crucial because gastric proton pumps are activated following food intake; however, there is no systematic study or direct

evidence to suggest symptom improvement with strict drug adherence.

Weakly Acidic or Nonacidic Reflux

Weakly acidic reflux is defined as a fall in oesophageal pH by at least 1 unit; however, the pH remains between 4–7 and does not fall below 4. A pH cut-off value of 7 is used to differentiate between weakly acidic and nonacidic reflux.[7] In some studies, nonacidic reflux episodes have been found in 60–80% of patients with symptoms on double dose PPI therapy.[1,8] The proposed mechanisms of symptom generation include stretching of the oesophageal wall attributable to volume reflux, and sensitisation of the oesophagus because of increased acid exposure.[9,10] In addition, duodenogastroesophageal reflux may generate symptoms in a small subset of patients by impairing oesophageal mucosal integrity, producing dilated intercellular spaces, and even inducing epithelial apoptosis.[11]

Acid Pocket

The acid pocket is an area of unbuffered acid compartment that forms in the proximal part of the stomach after meals and serves as a potential reservoir for acid reflux in healthy subjects as well as GERD patients. Patients with GERD are predisposed to upward migration of proximal margin of the acid pocket when compared with healthy controls.[12] The acid pocket is also a potential therapeutic target and can be attenuated by PPI or alginates that form a pH neutral raft at the gastroesophageal junction and displace the acid pocket distally.[13]

Nocturnal Acid Breakthrough

Nocturnal acid breakthrough (NAB) is defined as the persistence of intragastric pH <4 for >60 minutes during the night. NAB was initially thought to be responsible for PPI refractory symptoms and could be abolished by either doubling the dose of PPI or adding an H2 receptor antagonist at night.[14] However, the clinical significance of NAB is not clear and some of the latter studies revealed that oesophageal acid reflux and symptoms were independent of the occurrence of NAB.[15,16]

Protein Pump Inhibitor Metabolism and CYP2C19 Polymorphism

PPI are predominantly metabolised in the liver by CYP2C19 and, to a lesser extent, CYP3A4. Rapid metabolisers show decreased gastric acid suppression with PPI, which may result in reduced efficacy and sustained symptomatic response compared to intermediate or poor metabolisers.[17]

Functional Heartburn

Functional heartburn is defined as burning retrosternal discomfort or pain that is refractory to optimal antisecretory therapy in the absence of objective evidence of GERD or major oesophageal motility disorder. Nearly one-third of the patients with reflux symptoms may have functional heartburn.[18,19] These patients are more refractory to antireflux therapy than those with erosive oesophagitis, and may have other coexistent functional disorders such as functional dyspepsia or irritable bowel syndrome.[20-22]

Oesophageal Hypersensitivity

Oesophageal hypersensitivity is defined as the presence of typical reflux symptoms without evidence of pathological reflux on endoscopy or pH impedance monitoring, but with demonstration of positive symptom correlation with physiological reflux. Oesophageal hypersensitivity may contribute to symptoms in approximately 30–35% of patients with nonerosive reflux disease.[23] Various pathophysiological mechanisms of symptoms have been proposed in these patients including peripheral or central sensitisation, altered central processing of peripheral visceral stimuli, autonomic and psychological abnormalities, and increased permeability of oesophageal mucosal barrier.[24,25] Upregulation of acid sensitive receptors, such as TRPV1 and protease-activated receptor 2, has been demonstrated in patients with oesophageal hypersensitivity.[26]

Eosinophilic Oesophagitis

The symptoms of eosinophilic oesophagitis, including heartburn, chest pain, and dysphagia, can mimic those of GERD; however, the actual prevalence of eosinophilic oesophagitis is very low among patients with refractory GERD.[27] Therefore, an oesophageal biopsy may be cost-effective if the prevalence of eosinophilic oesophagitis is high (>8%) in the general population.[28]

DIAGNOSIS

A detailed evaluation of refractory GERD includes a thorough clinical evaluation, upper GI endoscopy, oesophageal motility assessment using high definition manometry, and reflux monitoring, preferably with a multichannel intraluminal pH-impedance monitor.

Clinical Evaluation

The following details should be obtained from the patient's history and physical examination:

1. Presence of typical and atypical symptoms of GERD.

2. Proper dosing and timing of PPI.

3. Presence of other functional GI disorders such as functional dyspepsia and inflammatory bowel syndrome.

4. Time of occurrence of troublesome symptoms i.e., nocturnal or post meals.

5. Presence of alarming symptoms such as weight loss, anorexia, dysphagia, odynophagia, and upper GI bleeding.

6. Coexistence of psychological comorbidity.

Endoscopy

Patients with typical GERD symptoms who fail to respond to initial PPI therapy despite optimisation of dose should undergo an upper GI endoscopy. Unfortunately, the diagnostic yield of endoscopy in refractory GERD is limited.[29] In the absence of erosive oesophagitis, random oesophageal biopsies can be obtained to examine dilated intercellular spaces and to rule out eosinophilic oesophagitis. The presence of dilated intercellular spaces and higher intercellular space diameter favours nonerosive reflux disease (NERD) and oesophageal hypersensitivity over functional heartburn.[30] Narrow-band imaging (NBI) with magnification endoscopy may help in identifying ongoing acid reflux in patients with NERD in the absence of obvious erosions or ulcerations on white light endoscopy. Increased and dilated intrapapillary capillary loops at the lower oesophagus, increased vascularity at the squamo–columnar junction, and tubular and villous pit patterns below the Z line are observed with NBI, and are more frequently seen in NERD compared to controls.[31]

Reflux Monitoring

Patients who are refractory to PPI therapy and have a normal endoscopy should undergo reflux monitoring. Currently, there are four available options for reflux monitoring: 1) catheter-based pH monitor; 2) wireless capsule pH assessment (Bravo™, Medtronic plc, UK); 3) combined multichannel intraluminal pH impedance monitor; and 4) oesophageal Bilitec™ (Bilitec™ 2000, Medtronic plc, Denmark). Extended recording times (48–96 hours) using wireless pH recording systems increase the diagnostic yield and may be especially useful in those with high suspicion of GERD but negative pH results. The commonly measured variables using pH testing include acid exposure time, number of reflux episodes, symptom index, and symptom association probability. Acid exposure time is qualified as normal (<4%), abnormal (>6%), and inconclusive (4–6%). Similarly, number of reflux episodes are classified as normal (<40/24 hours), abnormal (>80), and inconclusive (40–80). The decision to perform pH-monitoring 'off' or 'on' PPI is dependent upon the clinical scenario. Reflux monitoring 'off' PPI is performed when the diagnosis of GERD is unproven with no prior positive pH testing, or preoperatively before definitive surgical or endoscopic antireflux therapy. Whereas, reflux monitoring 'on' PPI is performed in patients with proven GERD in form of severe oesophagitis, long segment Barrett's, and prior abnormal pH result. These patients are typically on double dose PPI and pH-impedance testing is meant to establish the relation between reflux episodes and symptoms.

Nonacidic reflux, rather than acid reflux, appears to be the main driver of symptoms in PPI refractory cases.[32] Therefore, the diagnostic yield of traditional catheter-based or wireless (Bravo) pH monitoring is limited in PPI refractory GERD patients because of their inability to measure nonacidic reflux.[33] Combined multichannel intraluminal impedance pH monitoring is considered as the gold standard in the evaluation of PPI refractory GERD.[34]

Symptom association metrics including symptom index and symptom association probability

provide analysis of temporal association between symptom occurrence and reflux episodes, and help in assessing the cause of patients' symptoms. These parameters have major clinical implications in diagnosis and prediction of response to medical and surgical antireflux therapy. In the absence of pathological reflux, a positive symptom index (>50%) and symptom association probability (>95%) suggests oesophageal hypersensitivity. On the other hand, a negative symptom association implies functional heartburn.[35]

In addition to the above parameters, two novel impedance metrics, post reflux swallow induced peristaltic wave (PSPW) and mean nocturnal baseline impedance (MNBI), improve the diagnostic yield of pH-impedance testing and differentiate patients with pathological reflux from those with functional heartburn. The PSPW index is the proportion of reflux episodes followed by a PSPW and is a marker of integrity of primary peristalsis and oesophageal contraction reserve. A lower PSPW index helps to differentiate erosive oesophagitis from functional heartburn with high sensitivity (99–100%) and specificity (92%).[36] Similarly, low MNBI has been reported in erosive oesophagitis, PPI responsive NERD, and oesophageal hypersensitivity compared to PPI refractory cases and functional heartburn.[37-39] In addition, low MNBI (<2,292 ohms) independently predicts symptomatic improvement following antireflux surgery.[40]

Oesophageal Manometry

Oesophageal high-resolution manometry is performed to localise the lower oesophageal sphincter (LES) before placement of a pH probe. In addition, the assessment of oesophageal peristaltic function using the distal contractile index is crucial before definitive antireflux surgery. Up to 40% of patients with preoperative ineffective oesophageal motility (IEM) (distal contractile index <450 mmHg/cm/s in >50% swallows) might experience postoperative dysphagia.[41] In patients with IEM, multiple rapid swallows (MRS) can help further identify contraction reserve in the oesophagus. Absence of post MRS augmentation in patients with IEM predicts poor response to prokinetic drugs, higher oesophageal acid exposure in NERD, and dysphagia following antireflux surgery.[42] The Lyon consensus recently proposed routine incorporation of MRS into HRM protocols for establishing the contraction reserve in IEM, especially before antireflux surgery.[43]

TREATMENT

Treatment of PPI refractory GERD should be stepwise with multidisciplinary approach targeting ≥1 of the aforementioned mechanisms.

Lifestyle Modification

Lifestyle modifications such as weight loss; head elevation during sleep; and avoidance of tobacco, alcohol, caffeine, and high fat and spicy foods are frequently prescribed by the treating physicians. It is notable that weight loss and head of bed elevation are the only lifestyle interventions that have been found to be effective for GERD.[44]

Medical Management

Medical management of refractory GERD is targeted against a specific GERD phenotype established following a thorough examination including a pH-impedance study. The limitations of conventional PPI include short plasma half-life (1–2 hours) and strict adherence to dosing 30–45 minutes before meals. Novel PPI have the potential to largely overcome these limitations. These include stereoisomers with greater bioavailability (esomeprazole and dexlansoprazole), extended release formulations (dexlansoprazole modified release and rabeprazole extended release), long acting PPI with alternate metabolic pathways (tenatoprazole andilaprazole), and potassium competitive acid blockers (revaprazan and soraprazan).

Alginates decrease gastroesophageal reflux by forming a pH neutral raft on the postprandial acid pocket on top of the intragastric food. In a recent multicentre, placebo-controlled, randomised trial, the addition of alginates to PPI produced significant improvement in overall reflux and heartburn scores compared to placebo in patients with persistent symptoms.[45]

Prokinetics

Prokinetic drugs increase LES pressure, enhance oesophageal clearance of refluxed material, and stimulate gastric emptying rate;[46] however, the data on the utility of prokinetics in patients

with refractory GERD is not impressive. A meta-analysis found that the addition of prokinetics to PPI had no significant effect on symptom or endoscopic response to GERD but quality of life partially improved.[47] In a recent randomised control trial, acotiamide improved symptoms in patients with an overlap of GERD and functional dyspepsia who had persistent symptoms once daily PPI for >8 weeks.[48]

Reflux Inhibitors

Reflux inhibitors reduce gastroesophageal reflux by inhibiting transient LES relaxations (TLESR). Baclofen, a $GABA_B$ agonist, has been shown to decrease acidic and nonacidic reflux episodes and improve symptoms in refractory GERD, both as monotherapy and as an add-on therapy to PPI.[49] A recent metanalysis concluded that baclofen reduces the number of reflux events per person, the average length of reflux episodes, and the occurrence of TLESR.[50] However, baclofen is often not tolerated well because of neurological side effects. Moreover, there is currently a lack of long-term data on its use in patients with refractory GERD. Lesogaberan and arbaclofen placarbil are peripherally acting $GABA_B$ agonists with minimal central actions; however, they are probably less efficacious compared to baclofen.[51]

Neuromodulators

Tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors reduce heartburn and oesophageal pain in patients with oesophageal hypersensitivity and functional heartburn. In a randomised trial, only 38.5% of patients in the citalopram group continued to report reflux symptoms compared to 66.7% in the placebo group.[52] Similarly, fluoxetine has been shown to reduce the percentage of heartburn-free days compared to the use of omeprazole and placebo in patients with functional heartburn.[53]

Table 2: Outcomes of antireflux surgery in refractory gastroesophageal reflux disease.

Study	Number of participants	Study design	Follow-up	Outcomes
Hatlebakk et al., 2015[55]	116 rGERD	Randomised trial, open label (versus PPI)	5 years	Similar ↓ GERD symptoms and ↓ AET at 5 years
Spechler et al., 2019[56]	336 rGERD (78 with true GERD randomised)	Randomised trial, (versus medical)	1 year	Surgery superior to medical treatment (67% versus 28%; p=0.007)
Campos et al., 1999[57]	139 rGERD with small hiatus hernia	Prospective	15 months	86% good response predictors: abnormal AET, typical symptoms, clinical response to PPI
Wilkerson et al., 2005[58]	233 PPI responders versus 91 poor PPI responders	Prospective	1 year	Similar ↓ GERD symptoms (94% versus 87%)
Hamdy et al., 2014[59]	296 PPI responders versus 74 poor PPI responders	Prospective	1 year	↓ heartburn and regurgitation in good PPI responders
Anvari et al., 2003[60]	274 PPI responders versus 445 poor PPI responders	Prospective	5 years	Similar ↓ GERD symptoms and ↓ AET at 5 years poor physical HQoL and higher persisting PPI use in poor responders

AET: acid exposure time; GERD: gastroesophageal reflux disease; rGERD: refractory gastroesophageal reflux disease; PPI: proton pump inhibitor; HQoL: health related quality of life.

Although TCA reduce visceral hypersensitivity, the results of trials evaluating the use of nortriptyline do not favour their routine use in patients with functional heartburn.[54]

Surgical Management

Laparoscopic fundoplication or antireflux surgery (LARS) is effective in patients with typical GERD symptoms with acidic or nonacidic reflux. In the long term, LARS provides greater reductions in oesophageal acid exposure after 5 years when compared to PPI therapy;[55] however, the results of LARS in refractory GERD are conflicting. In a recent randomised trial, antireflux surgery (laparoscopic Nissen fundoplication) was found to be superior to medical treatment in a highly selected subgroup of patients with truly PPI refractory and reflux related heartburn (67% versus 28%; p=0.007).[56] The response to LARS appears to be superior in PPI responders compared to PPI nonresponders (Table 2).[55-60] The predictors of favourable outcome following LARS include objective evidence of abnormal oesophageal acid reflux and the presence of typical symptoms of GERD. A recent systematic review evaluated the outcomes of LARS in patients with partial response to PPI. Although heartburn and regurgitation improved immediately after surgery, the symptoms recurred and acid suppressive medication use increased at 10-years follow-up.[61] LARS might be considered as a treatment option in patients with refractory GERD with ongoing acid or nonacid reflux, but should be avoided in cases of oesophageal hypersensitivity and functional heartburn. A recent randomised controlled trial of laparoscopic magnetic sphincter augmentation showed promising results in patients with moderate-to-severe regurgitation on once daily PPI. Patients in the laparoscopic magnetic sphincter augmentation group experienced significantly greater improvement in GERD-HRQoL score and resolution of regurgitation compared to those receiving twice daily PPI.[62]

ENDOSCOPIC MANAGEMENT OF GASTROESOPHAGEAL REFLUX DISEASE

Endoscopic management options for GERD include radiofrequency application (the Stretta® procedure [UCI Health, California, USA]), endoscopic fundoplication, and antireflux mucosectomy. In recent years, these treatment modalities have resurfaced because of potential adverse events associated with PPI and antireflux surgery.

Radiofrequency application, or the Stretta procedure, involves delivery of thermal energy to the muscle of gastroesophageal junction and gastric cardia. The mechanism of action is still unclear; however, multiple studies have shown Stretta to be an effective therapy in patients with GERD.[63] In a long-term follow-up study including 217 patients, 72% of patients had significantly improved GERD-HRQoL and 64% of patients achieved >50% reduction in the use of PPI after 10 years of follow-up.[64]

Endoscopic plication devices that are currently available include transoral incisionless fundoplication EsophyX® device (EndoGastric Solutions, Washington, USA), GERDx™ device (G-SURG, Germany), and Medigus Ultrasonic Surgical Endostapler (MUSE™) (MediGus Ltd., Israel).[65] Of these, the largest body of evidence is available for transoral incisionless fundoplication using the EsophyX device.[66] Whereas, the data is still emerging for the other two plication devices.

The basic principle is similar for endoscopic plication and involves re-enforcement of the gastroesophageal junction using multiple plications or fasteners. In a systematic review and meta-analysis, transoral incisionless fundoplication was found to be safe and effective in patients with refractory GERD. Overall, the adverse event rate was 2%, and PPI therapy could be discontinued in 89% of patients after the therapy.[66] Ideal candidates for endoscopic antireflux therapies include those with mild oesophagitis, small hiatal hernia (<2 cm), endoscopic Hill's Grade II-III, absence of Barrett's oesophagus, and nonmorbid obesity.[65]

Besides radiofrequency ablation and endoscopic fundoplication, some of the recent studies have evaluated the efficacy of endoscopic band ligation and cap or multiband assisted antireflux mucosectomy for the management of GERD.[66-69] The basic mechanism of these endoscopic techniques is the tightening of gastric cardia as a result of scarring after band ligation or endoscopic mucosal resection. It should be noted

that these techniques need to be standardised and evaluated in randomised trials to conclude their efficacy.

CONCLUSION

PPI have revolutionised the treatment of GERD; however, a sizeable proportion of patients are refractory to PPI therapy. Most common aetiologies of refractory GERD include ongoing residual acid reflux, nonacid reflux, oesophageal hypersensitivity, and functional heartburn. Management of refractory GERD should be based on GERD phenotypes after thorough clinical assessment and reflux testing, preferably with combined pH-impedance monitoring (Figure 1). Patient selection for antireflux surgery or endoscopic therapy should be guided by a meticulous examination after excluding oesophageal hypersensitivity and functional heartburn. Treatment of patients with functional heartburn includes proper patient counselling, addressing concomitant psychiatric morbidities and associated functional gastrointestinal disorders, and neuromodulators such as TCA and selective serotonin reuptake inhibitors. Endoscopic antireflux therapies appear to be promising in appropriately selected patients with refractory GERD. Long-term follow-up studies are required before incorporating them into routine clinical practice.

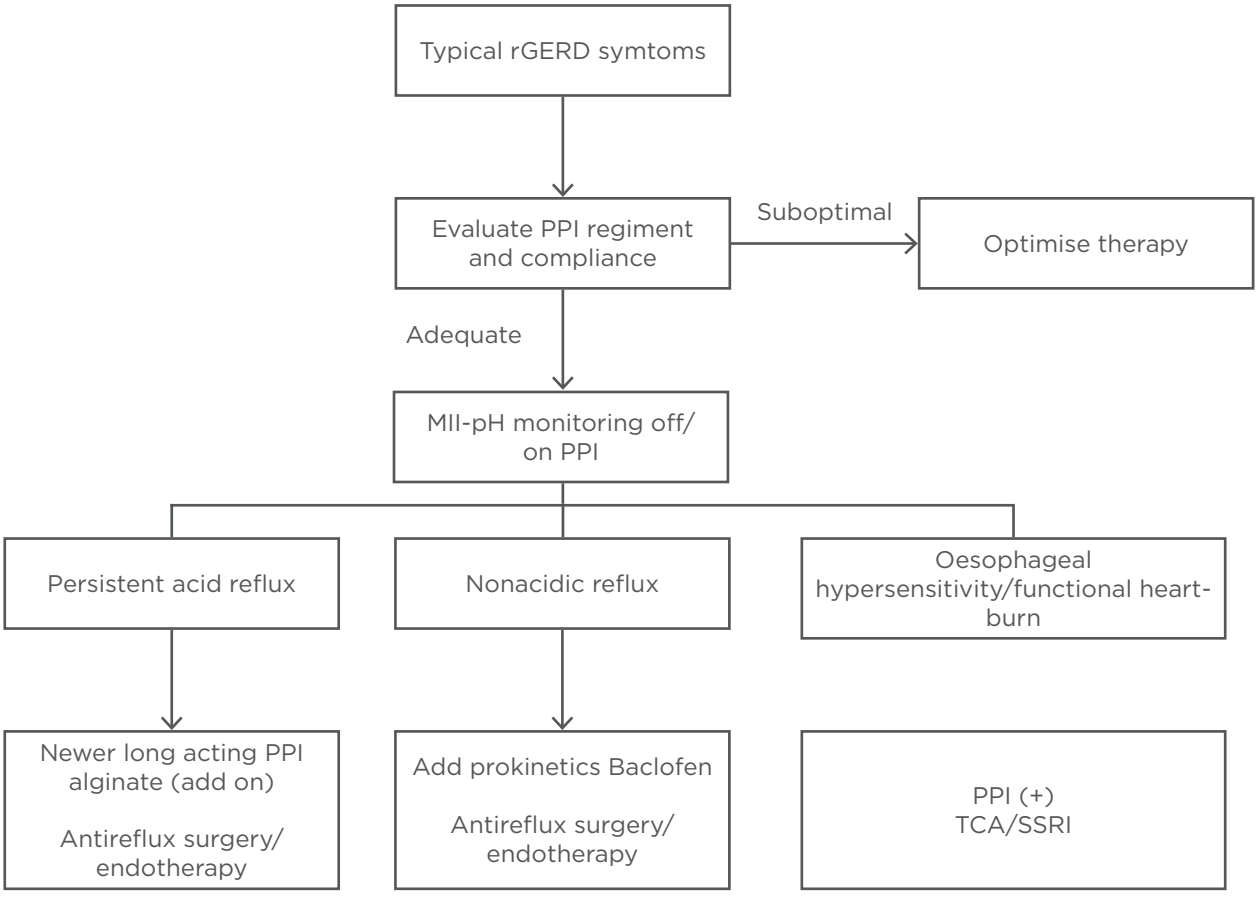

Figure 1: An approach to the management of refractory gastroesophageal reflux disease.

MII-pH: multichannel intraluminal impedance-pH; PPI: proton-pump inhibitor; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants.

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Who Audits Who Using Resection Margins: The Surgeon, or the Pathologist?

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Disclosure: The authors have declared no conflicts of interest.

Received: 01.09.2019

Accepted: 14.11.2019

Keywords: Colorectal cancer, polyp, resection margin (RM), surgery.

Citation: EMJ Gastroenterol. 2019;8[1]:72-79.

Abstract

Clear or involved resection margins have significant bearings on the outcome of colorectal cancer cases. There are two aspects of resection margins: longitudinal and circumferential. Pathological staging for rectal and colonic tumour specimens is a useful tool for providing continuous feedback to surgeons and may serve to improve the quality of surgery and pathology reporting. It is expected that a good pathology report will evaluate and audit the quality of other services such as radiology, surgery, and oncology. The aim of this paper is to outline how this parameter can be audited by surgeons and pathologists to improve both communication and standards.

INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignancies in the developed world and with the 'westernisation' of diets, other parts of the world are coming to bear a similar burden. Worldwide, CRC ranks third in terms of incidence,, behind lung and breast cancer, but second in terms of mortality.[1] Surgery is still the most successful treatment in the vast majority of cases. However, not all surgical specimens have clear resection margins (RM), which is an important parameter in terms of treatment outcome. Advancements in surgery, radiology, oncology, and pathology compel researchers to critically analyse the evidence.[2] This paper is designed to review the literature and present the findings on this important topic. To that aim, the longitudinal and circumferential RM (CRM) have been examined.

SPECIMEN PREPARATION[3,4]

The specimen should preferably be received fresh and intact, i.e., it should not be opened in theatre as this interferes with the assessment of both the CRM and the serosal involvement. The mesorectal and mesocolic planes of the surgical resection were then evaluated and photographed to keep a permanent record of the assessment, and to facilitate discussion at multidisciplinary team meetings (MDT) (Figure 1a and 1b). The non-peritonealised CRM was inked to facilitate histopathological assessment of margin involvement (Figure 1b, 1c, and 1d [blue arrow]). This is not limited to rectal cancers and should include colon cancers with associated circumferential colonic (non-peritonealised) RM, such as caecal and ascending colon tumours. After fixation, when the specimen was left for

at least 24–48 hours, the bowel was opened anteriorly above and below the tumour. The neoplasm was then sectioned at 3–4 mm transversely to produce whole (large) mount slices that include the tumour, adjacent lymph nodes, serosa, and CRM. Photography of these slices is recommended to provide a permanent record and to complement the verbal pathology report at the MDT meeting. Blocking the specimen should be according to The Royal College of Pathologists minimum dataset (RCPath MDS), and every effort should be made to retrieve as many lymph nodes as possible (minimum of 12).

LONGITUDINAL RESECTION MARGINS

Traditionally, radical surgery for CRC has included a significant removal of uninvolved parts of the colon. A paper by Miles in 1908[5] contains a reference to abdominoperineal excision for sigmoid cancer; this practice carried with it an unnecessary compromise of the sphincter, leaving patients with left sided, sigmoid colon with a permanent stoma and the associated morbidity and mortality.

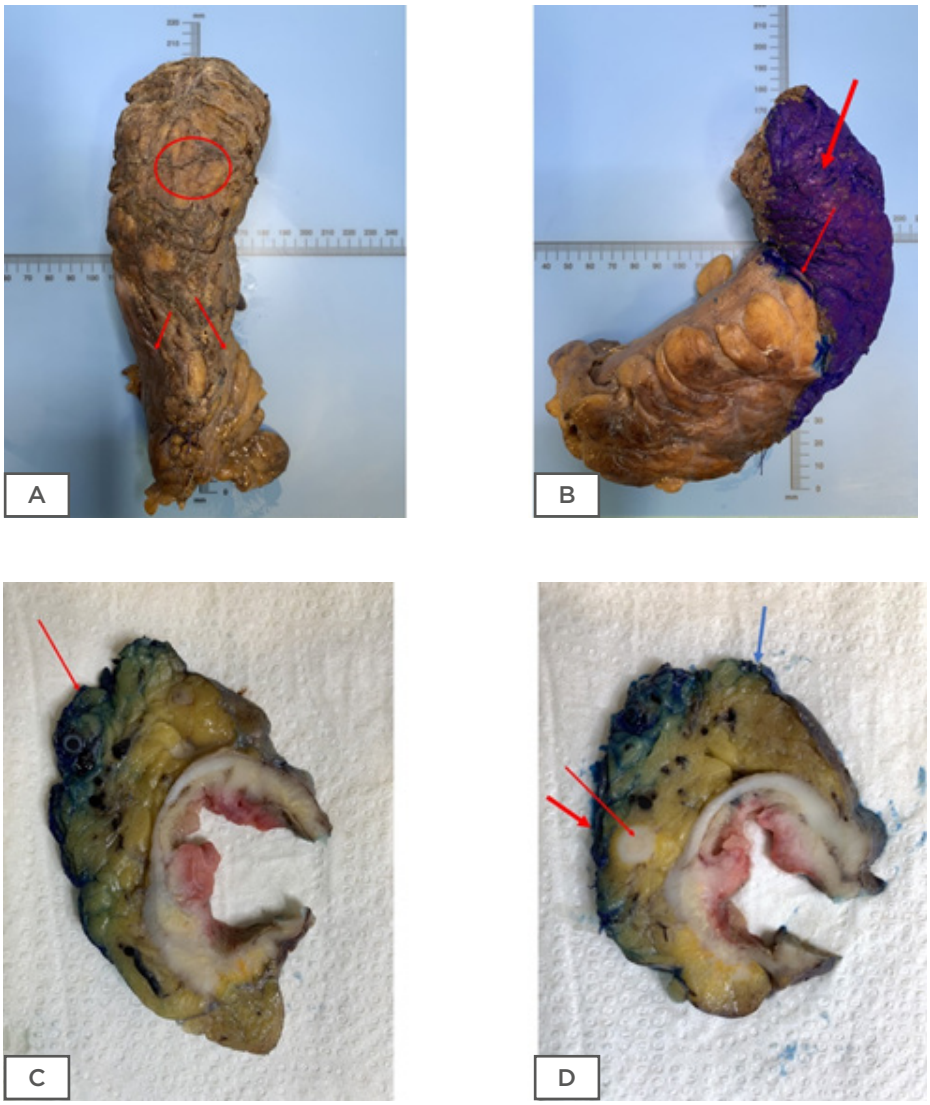

Figure 1: Colorectal resection specimens.

Mesorectal surface with no defects indicating good quality surgery (**A**: circle, **B**) which is inked prior to dissection (**B**). The peritoneal reflection is also shown (**A**: two arrows and **B**: thin arrow). Cross section of rectal tumour showing the CRM (**C**: red arrow and **D**: thick red arrow) and the peritoneal reflection (**D**: blue arrow). An involved lymph node near the circumferential resection margin (**D**: thin red arrow).

Subsequently, a 5 cm rule was introduced to minimise the huge morbidities associated with removal of long sections of healthy colon. The rule remained until Williams et al.[6] challenged the concept and concluded their paper with this statement: "The application of the 5 cm rule of distal excision may cause patients with low rectal cancer to lose their anal sphincter unnecessarilly."

At a similar time, the St Marks group[7] suggested that 2 cm was a safe margin after analysing a cohort of 334 patients who survived radical restorative operations for rectal adenocarcinoma. The length of rectum below the tumour measured on fixed, pinned-out pathologic specimens was ≤2 cm in 55 patients (Group 1), 2–5 cm in 177 (Group 2), and ≥5 cm in 102 (Group 3). The Dukes' classification, histologic grade, and extent of local tumour spreading was similar in the three groups. Overall crude 5-year survival rates for Groups 1, 2, and 3 were 69.1%, 68.4%, and 69.6%, respectively. Corresponding cancer-specific death rates were 25.5%, 23.2%, and 21.6%. These rates were also similar in matching pathologic subgroups of the three main groups. Of 23 observed or suspected local recurrences, there were 4 recurrences in Group 1 (7.3%), 11 in Group 2 (6.2%), and 8 in Group 3 (7.8%). They suggested that a margin <2 cm below a rectal carcinoma did not affect survival or local recurrence adversely.

Subsequently, Kirwan et al.[8] suggested that 1 cm was a safe margin and the follow-up paper from the same group showed the effect of their original work on sphincter saving.[9] The proposed safe distal RM became even smaller with the paper by Karanjia et al.,[10] when the authors suggested that the reduction of RM provided total mesorectal excision (TME) and properly performed washout, without increasing local recurrence or compromising survival. Twenty years later a published validation of the work by Karanjia et al.[10] came from the Cleveland Clinic, entitled 'Does sub-centimetre distal resection margin adversely influence oncological outcome,'[11] as they concluded that <1 cm longitudinal resection margin (LRM) does not influence outcome.

All of the above papers indicate that sphincter preservation surgery is now more achievable than 40 years ago due to an understanding of rectal cancer's biological behaviour, and also the significant advances in technology. Pathologists audit the closeness of the distal RM and gauge the frequency of anterior resection (AR) versus abdominoperineal resection (APR). It is anticipated there will be more AR than APR in most practices; however, this is a regular clinically audited schedule, because clinical situations like sphincter function play a major role in determining whether the patient is better served with AR or APR.

Longitudinal spread of rectal cancers is very unlikely; thus, it is not essential to assess the longitudinal margins histologically if one of the tumour margins is ≥30 mm. The only piece of information missing from these surgical papers is that the submucosal spread of poorly differentiated CRC can spread >1 cm without being 'intraoperatively' noticeable. For this reason, it is recommended that with poorly differentiated adenocarcinoma it is mandatory to examine the resection end, otherwise it is not essential.[3] In a recent paper by Lee et al.,[12] 1,343 primary colonic cancer patients were reviewed and designated LRM to <3 cm, ≥3, and <5 cm. The results showed that with increasing length of LRM, the number of retrieved lymph nodes tend to increase (19.5 ± 12.0, 22.1 ± 12.8, and 30.0 ± 16.2; p<0.001). However, the study showed that the 3-year disease-free survival and 5-year overall survival were not significantly different between the groups.

RECTAL CIRCUMFERENTIAL RESECTION MARGIN

Currently, for patients with mid and lower rectal cancer, TME is regarded as the standard of surgical treatment.[13] The pioneering work of Heald et al.[14] showed the importance of TME in lowering the risk of regional recurrence by applying sharp dissection along the embryological plane. This approach aimed to produce a specimen with complete mesorectal excision, ensuring completeness of excision without disturbing the 'holy plane'.[15] Subsequently, Quirk et al.[16] complemented the work of Heald and colleagues to show that involvement of the CRM is associated with a high percentage rate of local recurrence and low survival. Therefore, it was suggested in a series of papers that positive CRM could be due to one, or any combination of factors: poor

standard of surgery, aggressive disease, tumour location, and male sex.

The association between a patient's outcome and the assessment of the intact mesorectum has been analysed by Nagtegaal et al.,[13] using the following grading system:

A (3) (Good). Complete. Mesorectal (MRR):

The mesorectum should be smooth and with a good bulk to the mesorectum both anteriorly and posteriorly. The distal margin should appear adequate with no coning. Any defect should not be >5 mm deep.

B (2) Nearly complete. Intramesorectal (IMR):

There should be a moderate bulk to the mesorectum with minor irregularity of the mesorectal surface with a moderate degree of coning of the specimen distally and the muscularis propria (MPR) should not be visible. There could be moderate irregularity of the CRM.

C (1) (Poor). MPR:

There should be significant defects in the mesorectal tissue with deep cuts into the MPR. The CRM will be very irregular and formed by the MPR in places.

The Nagtegaal et al.[13] paper showed conclusively that significant breach of the mesocolon is associated with worse outcomes, as seen in Table 1.

The group went further by stating that only Grade A was associated with good prognosis.[17] The quality of mesorectal excision in the 1,382 patients in a Belgian multidisciplinary improvement project who underwent elective resection for mid or low rectal carcinoma was assessed. The results showed that a 2-Grade score distinguishing MRR from the others (IMR and MPR) was found to predict distant metastasis rate, disease-free survival, and overall survival.

Quirke et al.[18] showed that the quality of rectal cancer surgery is an important factor in predicting local recurrence and survival. Results showed that high quality TME surgery reduced the incidence of local recurrence and improved the 5-year survival rate from 48% to 68%. Hence, pathologic assessment of the resection specimen has been shown to be a sensitive indicator to the quality of rectal surgery by grossly assessing the surgical planes of dissection and the CRM as a means of quality control.[19]

In the UK, the national recommendation suggests that CRM positivity in rectal cancer should be below 15%.[20] The pathologist is required to measure the tumour beyond the MPR, recorded in mm, as it relates to prognosis. Extramural extension of the tumour into the mesorectum in rectal cancer of ≥5 mm is associated with worse prognosis. This is specifically pertaining for T3 tumours, which form the majority of rectal cancers. A study performed in Erlangen, Germany,[21] demonstrated that the division into pT3a (≤5 mm spread into the mesorectum) and pT3b (>5 mm) carries a risk of locoregional recurrence rates of 10.4% for pT3a and 26.3% for pT3b. The cancer-related 5-year survival rates were 85.4% for pT3a and 54.1% for pT3b. A paper recently published on the importance of accurate measurement of extramural spread in rectal cancer argued that it should be included in any TNM classification as it has a direct influence on outcome.[22] This study confirmed that the pT3a has a 30% advantage over pT3b. Subsequently, the European Society for Medical Oncology (ESMO) published guidelines recommending the subclassification of the category T3 using MRI in the assessment of extramural invasion.[23] However, despite the data presented, the American Joint Committee on Cancer (AJCC) has not yet included the proposal into TNM version 8.

Table 1: Outcomes associated with significant breach of mesocolon.

Grade	Grades A and B	Grade C
Local recurrence	8.7%	15.0%
Local recurrence and distant metastasis	20.3%	36.1%
2-year survival	90.5%	76.9%

By convention, the CRM is considered positive if the distance between any tumour cells and the CRM is ≤1 mm.[4,24]

A positive CRM can be due to a direct tumour extension or a tumour within lymph nodes, veins, lymphatics, or around nerves[4] (Figure 1c and 1d).

However, not all types of positive margins carry the same risk for local recurrence. For example, Nagtegaal and Quirke[25] showed that a positive CRM due to an involved lymph node (Figure 1d) was associated with a lower risk of local recurrence than a positive CRM due to direct extension (12.4% versus 22.1%, respectively), and no greater risk than that of CRM-negative tumours. Therefore, the type of affected tissue leading to a positive CRM should be specified in the pathology report and its significance discussed in local MDT meetings.[4] In the case of a positive CRM based solely on an intra-nodal tumour contained by the lymph node capsule, it is recommended to leave a comment indicating that the risk of recurrence might not differ significantly from that of CRM-negative tumours.

THE NEW CONCEPT OF COMPLETE MESOCOLIC EXCISION

The assessment of non-peritonealised RM in colonic tumours similar to rectal cancers was popularised initially by Bokey et al.[26] in their study of patients undergoing a potentially curative, elective colonic resection at Concord Hospital from 1971–1995. By applying the same principle to rectal cancer dissection, the results showed improved survival after adjustment for other known prognostic factors. Subsequently the paper by Hohenberger et al.[27] showed that by undertaking CME, the local 5-year recurrence rates in colon cancer reduced from 6.5% in the period from 1978–1984, to 3.6% from 1995–2002. Additionally, the 5-year survival rates increased from 82.1% to 89.1%. Bateman et al.[28] later showed that retroperitoneal surgical margin (RSM) tumour involvement occurs within a considerable number of distal caecal and proximal ascending colon carcinomas. The rate of RSM tumour involvement identified here is similar to a previously published local recurrence rate of 10% in caecal carcinoma, suggesting that RSM tumour involvement may be a predictor of recurrence in these tumours. They further suggested that patients with distal caecal or proximal ascending colon carcinoma and RSM tumour involvement may benefit from postoperative radiotherapy.

West et al.[29] have produced a series of excellent work in this area and showed that with high vascular ligation, the surgeon achieves larger surface area of mesentery that includes more lymph nodes. The protocol devised is identical to rectal cancer and includes:

- Specimen ideally received fresh.
- Open, but leave the area around the tumour intact.
- Fix for at least 48 hours.
- Photograph anteriorly and posteriorly.
- Serial sectioning through the tumour at 3–5 mm intervals.
- Further photographs of the cross sections.

The grading is similar to rectal cancer and falls into three categories:

- Mesocolic plane (MCP): Smooth serosal/mesocolic mesentery or only small minor defects.
- Intramesocolic plane (IMCP): The defect is present but not revealing the MPR.
- Muscularis propria plane (MPP): Major defect(s) in the mesocolon reaching the MPR are present.

The study looked retrospectively at 399 cases in which every specimen followed the above protocol. Results showed 15% overall survival benefit comparing MCP over MPP specially in Stage III.

In a recent study comparing 364 patients in the CME group, with 1,031 patients in the non-CME group, the disease-free survival was significantly higher after CME, with 4-year disease-free survival of 85.8% after CME and 73.4% after non-CME.[30]

Table 2: Risk factors for residual disease and suggested management plans in a malignant colorectal polyp.

1) Scoring the risk of residual disease in malignant colorectal polyp 2) Risk stratification based on sum of risk factors		
1) Histological data	**Degree of risk**	
Resection margin less than 1 mm	++++	
Resection margin 1–2 mm	+	
Haggitt level 4	++++	
Kikuchi level 2	++	
Kikuchi level 3	++++	
Poor differentiation	+++	
Mucinous tumour	+	
Tumour budding	+	
Lympho-vascular invasion	++	
2) Risk stratification based on sum of risk factors	**Grading of risk and potential % risk of residual cancer**	**Suggested management**
Score 0	Risk very low <3%	Follow up
Score +	Low risk <5%	Assess other factors, careful follow up
Score ++	Medium 5–10%	Discussion on the risks and benefits of surgery
Score +++	High 8–15%	Discuss risk with patients in favour of surgery
Score ++++	Very high >20%	Recommend surgery

Adapted from Williams et al.[32]

POLYP CANCER (PT1 ADENOCARCINOMA) RESECTION MARGIN AND RISK OF RESIDUAL DISEASE

The status of the RM in a malignant colorectal polyp is important in predicting the potential for an adverse outcome.

It is important to specify whether the margin is the deep stromal or the mucosal margin, as more extensive surgery is usually indicated when the stromal margin is involved and further local excision may be necessary if the mucosal margin is involved.[20] In the literature, there has been considerable discussion on the degree of margin clearance and what is regarded as acceptable to classify the tumour as completely excised. The agreement is that a clearance of 0 mm and distance of <1 mm is an indication for further surgery due to incomplete excision; however, other investigators would use <2 mm as a cut-off. Currently, the European Guidelines recommend that clearance of ≤1 mm signifies a positive margin.[20] In a study of 1,900 patients, residual disease was more frequent in patients with a positive rather than a negative margin (30% versus 3%).[31] Margin positivity on its own, in the majority of studies, did not appear to be an independent risk factor for lymph node metastasis, with the risk of lymph node metastasis being similar in patients with and without margin involvement (9.2% versus 7.2%).[31] Further treatment may be taken when other high-risk factors are present. If there is uncertainty about margin involvement in cases with no other high-risk features, endoscopic follow-up looking for local recurrence is reasonable and is considered good practice. The ACPGBI position statement stratified the risk factors for malignant polyps and the authors advise following this recommendation (Table 2).[32]

An accurate measurement of the tumour to the closest deep margin should be recorded. However, diathermy artefact creates a false plane which can hamper assessment of the distance between the tumour cells and the RM. The zone of this artefact could be several millimetres and this measurement of clearance should not be present in the inner aspect of the diathermy zone. However, any infiltration by malignant glands into the diathermy zone is regarded as margin involvement (0 mm; R1 status), as it is not possible to confidently determine the true extent of infiltration in this situation.[33]

CONCLUSION

Pathologists play a key role in the modern multidisciplinary management of patients with CRC. Pathological assessment of the resected specimen not only provides key prognostic information, but also allows evaluation of the quality of the surgery, accuracy of radiology, and an assessment of response to neo-adjuvant therapy. A useful component in facilitating feedback on the quality of surgical specimens is keeping a permanent record of each specimen using digital photography. These images should be stored in a departmental archive and should be actively used in MDT meetings for feedback to clinical colleagues. In addition, they can be used for education, research, and audit purposes.[19] In essence, the pathologist assesses the quality of surgery and the surgeon assesses the quality of the pathologist's report.

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Dysphagia and Bone Marrow Failure: A Rare Neoplastic Mimic

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Disclosure: The authors have declared no conflicts of interest.

Received: 23.05.2019

Accepted: 12.09.2019

Keywords: Dysphagia, malignancy, rheumatoid arthritis.

Citation: EMJ Gastroenterol. 2019;8[1]:81-85.

Abstract

A 54-year-old male with a history of multiple autoimmune arthritides was admitted following a 3-week history of progressive dysphagia with odynophagia to solids and liquids, with significant weight loss, night sweats, and exertional dyspnoea. Oesophagogastroduodenoscopy revealed an obstructing oesophageal stricture. Blood tests showed neutropaenia and high levels of inflammatory markers, suggestive of primary oesophageal malignancy. Oesophageal and bone marrow biopsies demonstrated inflammatory change not suggestive of malignancy. PET showed highly active nodules in the left lung and sigmoid colon, but the oesophagus was clear. Following a clinical rheumatology review, a differential diagnosis of inflammatory lesions, most likely secondary to systemic rheumatoid, was considered. The patient responded well to high-dose intravenous steroid therapy. Subsequent outpatient interval high-resolution CT demonstrated complete resolution of the lung nodule. He was maintained on oral prednisolone and methotrexate, having no further symptoms of dysphagia or neutropenia. A literature search revealed no published reports or case studies outlining a similar history to the reported patient: rheumatoid arthritis presenting to hospital as potential oesophageal malignancy.

INTRODUCTION

A 54-year-old male with a history of multiple autoimmune arthritides was admitted following a 3-week history of progressive dysphagia with odynophagia to solids and liquids, associated with significant weight loss, night sweats, and exertional dyspnoea. Oesophagogastroduodenoscopy (OGD) revealed a malignant-looking stricture, thus promoting a working diagnosis of oesophageal malignancy.

Subsequent histological analysis from biopsies of the lesion demonstrated inflammatory change only, with no evidence of malignancy. The patient became repeatedly neutropenic; however, subsequent bone marrow biopsies and repeat oesophageal biopsies did not demonstrate malignant cells. PET-CT revealed an active lesion in the left lower lobe of the lung, but not the oesophagus. Following a clinical rheumatology review, a differential diagnosis of inflammatory lesions, most likely secondary to systemic rheumatoid, was considered. The patient's symptoms responded well to high-

dose intravenous steroid therapy. Subsequent outpatient interval high-resolution CT scans demonstrated complete resolution of the lung nodule. He was maintained on oral prednisolone and methotrexate, having no further symptoms of dysphagia or neutropaenia.

BACKGROUND

Rheumatoid arthritis is a chronic autoimmune symmetrical inflammatory condition of the joints, manifesting with progressive joint swelling and pain. It is associated with significant long-term morbidity and the necessity for lifelong medication (starting with nonsteroidal anti-inflammatories and ending with expensive and experimental monoclonal antibodies).[1,2] These long-term medications are not without side effects. This case demonstrates the challenges in diagnosis when systemic arthritides mimic the classic, and far more common, presentation of malignancy.

Following OViD and PubMed literature searches, the authors found no published literature of similar cases.

This report highlights the atypical features of autoimmune inflammatory conditions which is important because raising awareness can help to avoid misdiagnosis of malignancy and the subsequent psychosocial implications such a diagnosis entails.

CASE PRESENTATION

A 54-year-old Caucasian male was admitted under gastroenterology following a 3-week history of dysphagia, odynophagia, weight loss, night sweats, and exertional dyspnoea. His medical history included strongly positive anticyclic citrullinated peptide rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis. He was prescribed 15 mg methotrexate once weekly, 5 mg folic acid once weekly, 60 mg acemetacin twice daily, 15 mg lansoprazole once daily, and 100 mg tramadol as required for pain. He reported noncompliance with medications (never taking acemetacin or methotrexate), and did not attend routine general practitioner c heck-ups or rheumatology clinics. He had a 30 pack-year smoking history, minimal alcohol intake, and an unremarkable travel, sexual, or family history. He described no skin changes.

INVESTIGATIONS

1. **Admission blood tests:**

A) Full blood count: neutrophils 0.52x10^9/L (1.80–7.50x10^9/L), white blood cells 2.50x 10^9/L (3.60–11.00x10^9/L), haemoglobin 124 g/L (130–180 g/L), mean cell volume 76.0 fL (80.0–100.0 fL), hypochromic red cell 12.9%.

B) C-reactive protein 157 mg/L (<2 mg/L), erythrocyte sedimentation rate 67 mm/hour (<20 mm/hour).

C) Albumin 19 g/dL (35–50 g/dL), liver function otherwise unremarkable.

D) Urea 10.3 mmol/L (1.8–8.2 mmol/L), renal function otherwise unremarkable.

E) HIV screen: negative.

F) Rheumatoid arthritis investigations: strongly positive anticyclic citrullinated antibody 2,776.8 U/mL (<20 U/mL).

2. **OGD plus biopsy**: likely malignant stricture seen at 27 cm from incisors, impeding progression of endoscope (Figure 1).

A) The oesophageal biopsy microscopic conclusion was that morphological and immunohistochemical appearances favoured an inflammatory process. Ulcerated and severely inflamed squamous mucosa, showing polypoid granulation tissue, presented. Sheets of lymph plasmacytic cells expanded the lamina propria and obscured glands in places. The squamous epithelium that persisted showed atypia. No viral inclusions were seewwwn, and no epithelial malignancy presented. In view of lymphoplasmacytic cells, immunohistochemical staining was performed. Lymphoid population comprised of reactive B and T cells. There was no light chain restriction. Ki67 showed a low proliferation factor.

3. **CT chest/abdomen/pelvis**: dilated oesophagus shown at the level of the carina with an air-fluid level. No obvious oesophageal wall thickening was apparent. Several subcarinal and

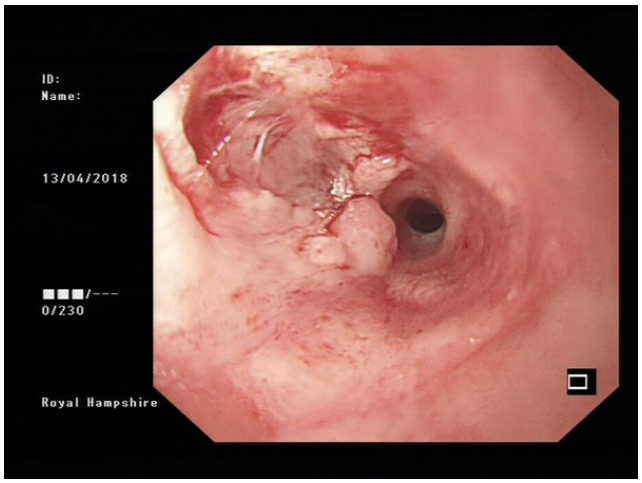

Figure 1: Oesophagogastroduodenoscopy appearances suggestive of malignant stricture.

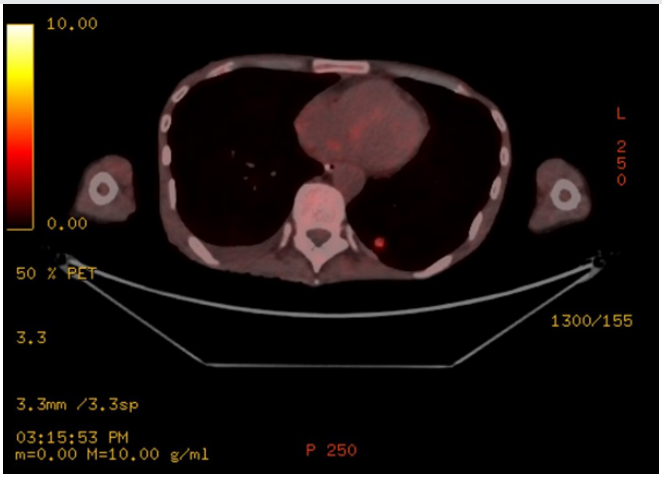

Figure 2: Left lower lung lesion as seen on PET.

para-aortic enlarged lymph nodes were revealed (≤1 cm).Lungs: panacinar emphysema. Left lower lobe subpleural inflammatory changes.

Liver: no definite lesion.

Spleen: unremarkable, normal size.

4. **PET-CT**: highly active speculated nodule in left lower lung lobe and sigmoid colon identified, concerning for malignancy. Diffuse low-grade activity along the oesophagus, presumably physiological, and no evidence of malignancy (Figure 2).

5. **Bone marrow biopsy**: inflammatory myelopathy only.

6. **Connective tissue disease screen** including antinuclear antibodies, immunoglobulins (IgG, IgA, IgM), scleroderma antibody antitopoisomerase I antibody (SCL-70), antiribonucloprotein and centromere antibody: all unremarkable.

7. **Reviewed by haematology due to recurrent neutropaenia**; differential diagnosis of lymphoma was considered and excluded based on oesophageal immunohistopathology and bone marrow findings.

TREATMENT

1. **Nasogastric feeding** via endoscopically placed nasogastric tube.

2. Initially high dose of **intravenous dexamethasone**

(0.6 mg/kg) advised by rheumatologist to treat oesophageal swelling.

3. **Oesophageal dilatation** for symptomatic relief.

A) **Repeat OGD biopsy post steroid therapy**: lymphoblastocytoid cells and generalised oesophagitis. Consistent with inflammatory change.

4. **Maintenance therapy** with prednisolone alone as methotrexate, azathioprine, and sulfasalazine contraindicated with neutropaenia.

DISCUSSION, OUTCOME, AND FOLLOW-UP

Throughout the course of his admission the patient had a number of potential diagnoses and was seen by four different subspecialty medical teams (gastroenterology, haematology, respiratory, and rheumatology). Primary oesophageal carcinoma was initially the working diagnosis, with a differential of lymphoma. Oesophageal and bone marrow biopsy showed inflammatory changes only. PET-CT further disputed oesophageal malignancy but raised the new possibility of lung malignancy. Following a lung multidisciplinary team meeting discussion, the lung nodule was initially considered to be an incidental lung primary carcinoma. Flexible sigmoidoscopy revealed no sinister lesion to corroborate the PET scan findings.

With all investigations taken into consideration, he was reviewed by a rheumatologist who diagnosed severe systemic manifestations of rheumatoid arthritis. Felty's syndrome was excluded based on normal splenic appearances and size on cross-sectional imaging. His 'hot-spots' on PET-CT and the oesophageal stricture were considered inflammatory nodules, which increase the misdiagnosis of malignancy using thoracic PET-CT.[3]

The patient has been followed up in the rheumatology clinic and was maintained on prednisolone alone. At follow-up, he was experiencing Cushingoid side effects, but neutrophils and inflammatory markers were within normal limits and his symptoms of dysphagia and odynophagia had resolved entirely. Neutropenia was likely a result of systemic inflammation as noncompliance with methotrexate rules out this as a cause. He has not had any infections and was managed in the outpatient setting with a reducing course of prednisolone and omeprazole. High-resolution chest CT showed complete resolution of the suspicious lung nodule. Given his ongoing rheumatological joint pain, he awaits a haematological opinion to advise on further methotrexate or disease-modifying antirheumatic drugs management given his history of bone marrow suppression.

A literature search revealed no published reports or case studies outlining a similar history to this patient: rheumatoid arthritis presenting to hospital as potential oesophageal malignancy.

Oesophageal manifestations have been reported in Behcet's disease.[4] The patient had previously undergone investigation and Behcet's had been excluded at the time of initial rheumatoid arthritis diagnosis. There are also reported cases of drug-associated oesophageal strictures (particularity nonsteroidal anti-inflammatory drug).[5] However, these patients did not suffer complete dysphagia, but had significant odynophagia. In addition, there are no published cases of acemetacin-associated oesophageal strictures, which the patient was prescribed (and was not compliant with) making this a less likely diagnosis.

LEARNING POINTS: SHEDDING NEW LIGHT ON RARE PRESENTATIONS OF A COMMON CONDITION

- Concerning clinical features suggestive of malignancy can be explained by other conditions, even if investigations are initially supportive of malignancy.
- Oesophageal strictures and 'hot spots' on PET-CT can be associated with inflammatory conditions, such as rheumatoid arthritis.

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Switching off Inflammation with Diet: A Review of Exclusive Enteral Nutrition in Children with Crohn's Disease

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Disclosure: The author has declared no conflicts of interest.

Received: 18.10.2019

Accepted: 13.11.2019

Keywords: Children, Crohn's disease (CD), exclusive enteral nutrition (EEN), inflammatory bowel disease (IBD), insulin growth factor 1 (IGF-1), IL-6, nutrition, nutritional therapies, polymeric formulae (PF), TNF-α.

Citation: EMJ Gastroenterol. 2019;8[1]:86-94.

Abstract

The specific dietary intervention known as exclusive enteral nutrition (EEN) is well-established as the preferred treatment to induce remission in children with active Crohn's disease. The majority of children managed with EEN respond well to this intervention, with high rates of mucosal healing, improved nutrition, and enhanced bone health, with few side effects. This dietary therapy, utilising a complete nutritional liquid product, is generally well-tolerated over the short period of induction of remission, but does require substantial changes to routine oral intake and daily patterns. After a period of exclusive use of this therapy, ongoing use of the same formulae (as maintenance enteral nutrition) may prolong remission and prevent relapse. Over the last few years, new reports have advanced our understanding of the mechanisms by which EEN acts: these include modulation of the intestinal microbiota and direct anti-inflammatory effects upon the epithelium. This review highlights key outcomes of EEN in children with Crohn's disease and highlights the current understanding of the mechanisms of action.

INTRODUCTION

The inflammatory bowel diseases (IBD) are a group of conditions characterised by chronic, incurable inflammation in the gastrointestinal (GI) tract.[1,2] The diagnosis of IBD is based upon endoscopic and histologic features, along with altered inflammatory markers, and radiology results.[1] The two main classifications of IBD are termed Crohn's disease (CD) and ulcerative colitis. These conditions are generally defined by their location in the gut, the pattern of inflammation, and disease behaviour.

At present the exact cause of IBD is not known definitively. The currently most-accepted hypothesis is that IBD begins in an individual with genetic risk (>240 genes are now linked to IBD) when various environmental factors trigger changes in the intestinal microbiota, prompting

innate and acquired immune responses that are then dysregulated.[3-6] The role of genetic factors may be more pronounced in younger children than in adults; this is paramount in the increased identification of monogenic forms of gut inflammation, as seen in children aged <6 years of age (very-early onset IBD).

Given the incurable nature of IBD, the focus of management is firstly upon the induction of remission, and then on the subsequent maintenance of remission. Establishment of mucosal healing is identified as a key outcome of management, with pronounced impact upon the subsequent disease course. Nutritional interventions, especially exclusive enteral nutrition (EEN), provide an important and safe method to induce remission and establish mucosal healing, particularly in children with CD. This review aims to outline the key aspects of CD, with a particular focus on children, and to overview the role EEN can play in children with CD, highlighting the putative mechanisms of this nutritional intervention.

CROHN'S DISEASE

CD is characterised by the presence of discontinuous inflammatory changes in any section of the GI tract.[1,2] Inflammation is typically transmural, with disease defining features of skip lesions and non-caseating granulomata. CD begins with an inflammatory phenotype which can then be complicated by the development of either fistulising (penetrating) or stricturing disease. Although some children will present with disease complications, most will have purely inflammatory luminal disease at diagnosis.[7,8] CD can also be accompanied by the presence of various extra-intestinal manifestations, which include peri-oral or oral findings, joint disease, eye changes, or skin manifestations.[9]

Children can be diagnosed with CD at any age, but it is more common in the second decade.[1] Although typical symptoms include the combination of weight loss, diarrhoea, and abdominal pain, other children may have atypical symptoms such as isolated linear growth failure, or weight loss without associated GI symptoms. Atypical symptoms may impede the recognition of CD, leading to diagnostic delay.

Almost all children diagnosed with CD will have weight loss, or impeded weight gains, which is mostly mediated by early satiety, post-prandial pain, or diarrhoea and consequent reduced dietary intake.[10,11] In addition, malabsorption may contribute. The anorexic effects of circulating inflammatory mediators, such as TNF-α, contribute to these outcomes. Reduced dietary intake and altered weight gains may then result in impaired linear growth, especially in peri-pubertal children, due to interrupted pubertal growth spurt.[12] A further consequence of active CD is delayed onset of puberty: this is more commonly observed in adolescent boys. These nutritional changes may reflect disease severity and may lead to significant psychological adverse effects. Furthermore, interruption of normal adolescent developmental processes may lead to reduced final adult height.

In addition to the adverse impacts upon nutrition and growth in children diagnosed with CD, the patterns of CD present in children also differ in other regards from the same disease presenting in adult years. As illustrated in two large cohorts from France and Scotland, paediatric CD is typically more severe and extensive, with pan-enteric disease distribution seen commonly.[7,8] For example, both cohorts described higher rates of upper gut involvement in children with CD.[7,13]

EPIDEMIOLOGY OF CROHN'S DISEASE

Numerous studies have shown increasing rates of IBD in the last few decades.[14] From around the start of the 21st century, there have been particular increases in diagnoses in Asian countries.[15] In addition to these broad changes in IBD patterns, there have been continued increases noted in children and adolescents; for example, high rates of IBD (and especially CD) were noted in 2004 in the Canterbury region of New Zealand (NZ).[16] A subsequent study 10 years later showed an increase of almost two-fold within the same region.[17] Furthermore, a longer-term study focussing on children diagnosed in the same region of NZ demonstrated almost a five-fold increase in incidence over two decades until 2015.[18] In addition, high prevalence was also demonstrated in another study that determined the numbers of children diagnosed across the entirety of NZ.[19]

The reasons for high rates of IBD in various parts of the world, including NZ, and for the recent increased incidence, are unclear. Environmental factors are likely the most important drivers of these changes.[20] While vitamin D and sunlight exposure appear to explain some regional differences (with increasing rates with increasing latitude), dietary factors appear most important. Several reports indicate that breastfeeding and childhood pet ownership are protective. Westernised diets (high fat, high sugar foods), urbanisation, and dietary additives or preservatives are also implicated in higher rates of IBD.[20] Other early life events (for example birth method and antibiotic exposure) may further contribute to increased risk.

THE NUTRITIONAL IMPACT OF CROHN'S DISEASE IN CHILDREN

Many children with CD have a history of weight loss or poor weight gains prior to diagnosis. Some will also have impaired linear growth and others may have delayed pubertal development.[1,10,11] Micronutrient deficiencies can also occur in children with CD.

Poor weight gains are most commonly secondary to decreased oral intake, with early satiety and pain limiting intake. The circulating pro-inflammatory cytokines, such as IL-6, have been shown to induce anorexia, which contributes to these changes. While poor diet and weight gains may have a role, impaired linear growth is primarily a result of uncontrolled inflammation, including elevated IL-6, resulting in lower production of insulin growth factor 1 (IGF-1) and related proteins, which in turn abrogate the effects of growth hormone.[12]

Further to the adverse effects of reduced caloric intake and macronutrients, micronutrient deficiencies are also common in children with CD.[10,21-23] While low levels of iron and vitamin D are seen most often, zinc, selenium, and vitamin B12 may also be low. Low iron stores, consequent to reduced intake, impaired absorption, or increased enteric losses, result in anaemia, and present as fatigue, lethargy, and disrupted learning in children. Numerous reports indicate that children with CD typically have lower vitamin D levels than control children.[24,25] In an Australian report, more than half of a group of 78 children were deficient at diagnosis.[24] Vitamin D is critical for bone health but also contributes to innate immune function.[26] Correction of vitamin D levels has been associated with reduced inflammatory activity;[27,28] however, the ideal required level is unknown.

In view of the various nutritional impacts of CD in children, this needs to be a central aspect of management goals, in which nutritional therapies play a critical role.

EXCLUSIVE ENTERAL NUTRITION

A Typical Exclusive Enteral Nutrition Protocol

EEN involves the use of a liquid formula providing all nutritional requirements for a defined period, commonly 8 weeks, along with exclusion of usual solid foods.[29,30] Case reports and series published more than three decades ago described reduced inflammatory activity in adults taking intensive nutritional supplementation.[31-35] These observations were supported in an Irish randomised controlled trial that showed that EEN had similar outcomes to corticosteroids.[36] In more recent years, a large body of data has demonstrated that EEN has tremendous benefits to children with CD,[30,37] such that it is now recommended by European and North American organisations as the best therapy to induce remission in a child with active CD.[38-40] However, the utilisation of EEN and the specific EEN regimens vary between regions and countries.[41,42]

EEN is generally well-tolerated with few side effects expected. Refeeding syndrome has been reported in a handful of cases.[43,44] Although one group showed transient elevation of serum transaminases during EEN, this finding was not replicated in a second report.[45,46]

Exclusive Enteral Nutrition and Induction of Remission

The primary role of EEN is the induction of remission in children with active CD, especially at diagnosis. Numerous paediatric reports and meta-analyses of paediatric data clearly show that EEN has similar efficacy to corticosteroids;[47] however, not only does EEN avoid steroid-related side effects, which include impaired linear growth, EEN also leads to enhanced rates of mucosal

healing, which is a key treatment target.[48] EEN appears to have optimal benefits at the time of diagnosis,[49] with lower remission rates in those with long-standing disease. Generally, paediatric studies indicate remission rates of 80–85% with mucosal healing seen in up to 75% of those entering remission.[30,39]

A recent meta-analysis focussing on the outcomes of EEN in children with CD did not delineate any difference in efficacy to that seen in children managed with corticosteroids.[37] This report included 18 studies, 4 of which were prospective randomised controlled trials. Although efficacy between the two interventions was found to be similar, EEN resulted in much greater rates of endoscopic mucosal healing (odds ratio: 5.4; p=0.0005) and histological healing (odds ratio: 4.78; p=0.0009). Furthermore, weight gain was greater with EEN.[37]

As a further assessment of response to EEN, a number of earlier publications have evaluated various stool-based noninvasive markers such as calprotectin, S100A12, and osetoprotegerin during and following EEN in children.[50-52] Gerasimidis et al.[52] showed that faecal calprotectin decreased in children who entered clinical remission during EEN, but levels fell to the normal range in only one child. The level of reduction at 30 days correlated with response at the end of the EEN course. In contrast, Copova et al.[53] did not demonstrate any association between early reduction in calprotectin at 2 weeks and clinical response at 6 weeks. More recently, Logan et al.[54] reported that the reduction in calprotectin seen during EEN was not maintained after the recommencement of standard solid diet at the end of the EEN course.

Nutritional Benefits of Exclusive Enteral Nutrition

EEN also has benefits on nutritional status, including growth parameters, micronutrients, and bone health. Weight gain is expected during a course of EEN, especially in those with malnutrition prior to diagnosis.[30,39] The impact of EEN upon linear growth is less clear. One retrospective report showed that height increments over 24 months from diagnosis were greater (p=0.01) in 31 children treated with EEN than in 26 children managed with corticosteroids.[55] In contrast, a more recent report evaluating height outcomes 18 months after diagnosis in an inception cohort of Canadian children did not show any difference between those managed with EEN or corticosteroids.[56]

Nutritional changes occur early after starting EEN, as illustrated by prompt increases in markers such as IGF-1.[57,58] Children with active CD have altered bone health (reduced new bone formation and increased breakdown) compared to their age-matched peers. In an Australian study, bone health improved within 6–8 weeks of EEN, with enhanced new bone formation and reduced breakdown evident.[59] Other reports indicate improved bone mineral density in children with CD after treatment with EEN.[60]

Ongoing Enteral Nutrition to Maintain Remission

After induction of remission with EEN, some reports indicate benefit from ongoing use of enteral nutrition in conjunction with normal diet to maintain remission (i.e., maintenance enteral nutrition). This strategy may also work well in combination with medical therapies, enhance growth, and prevent relapse after surgically induced remission.

Early studies conducted in Canada showed that intermittent periods of EEN (such as given for 1 month every 3 months) or overnight feeds (given in conjunction with normal diet during the day) resulted in prolonged remission.[61,62] Remission may also be maintained with the addition of day-time sip feeds along with normal diet.[63] The ideal volume and caloric intake delivered in this fashion is not clear.

Further, a recent Scottish report noted that a small group of children who received minimal enteral nutrition were able to maintain lower levels of faecal calprotectin, suggesting enhanced mucosal control.[54] Despite this, minimal enteral nutrition in this group of 15 children was not associated with longer duration of remission.

Several Japanese studies have shown that on going feeds given overnight prevents disease relapse. In one of these reports, a group who received half their recommended caloric intake as an elemental feed overnight were half as likely to relapse than a comparative group who did not receive overnight feeds.[64] Other studies from Japan have demonstrated lower

rates of recurrence after surgical resection with maintenance nutrition.[65-68]

Recent reports have shown that nutritional support may work in concert with biologic therapies to augment response and prevent secondary loss of response.[69,70]

Given that EEN and anti-TNF-α inhibitors are the most effective interventions to result in mucosal healing, further work on such combined regimens may lead to important enhanced outcomes.[71-73]

Exclusive Enteral Nutrition and Complicated Crohn's Disease

Studies evaluating EEN have typically focussed on individuals with inflammatory CD alone. However, a number of reports have indicated that EEN may also have a role in the management of patients with complicated CD (penetrating or stricturing disease).

Two earlier publications described the inclusion of EEN in the management of a teenager with an entero-vesical fistula and three children with fistulising perianal disease.[74,75] More recently, EEN was beneficial in the management of two teenagers who presented with an ileal fistula and associated collection (phlegmon).[76] After an initial short period of gut rest, parenteral nutrition, and antibiotics, both children entered remission with an uncomplicated period of EEN. EEN may also be helpful in other manifestations of CD: for instance, 1 group reported that 19 out of 22 children with peri-oral changes had improvement after 8 weeks of EEN.[77]

This paediatric experience has been followed by a number of reports of EEN having a role in adults for the management of internal fistula with phlegmon, enterocutaneous fistula, and stenotic disease.[78-81] For example, a report from China described that 12 weeks of EEN resulted in healing of enterocutaneous fistulae in 30 out of 48 adults treated with EEN alone for 12 weeks.[82]

MECHANISMS OF ACTION OF EXCLUSIVE ENTERAL NUTRITION

A number of publications in the last decade have focussed upon the mechanisms of action of EEN in CD.[83] While gut rest and avoidance of one or more dietary triggers has been considered in the past, the more recent findings indicate that active effects of EEN are likely more important. Overall, this work has focussed on the effects of EEN upon the intestinal microbiota, improved barrier function, increased production of innate defence proteins, and direct anti-inflammatory activity.

Many reports have clearly shown that substantial changes are seen in the intestinal microbiota during and following the administration of EEN.[84-91] The application of advanced molecular tools such as 16S rRNA high-throughput sequencing and whole genome or shot-gun sequencing, have enabled researchers to show early and profound alterations in the microbiota. For example, one of these publications examined the flora before EEN, after 2 weeks, and then at the completion of EEN in 15 children with active CD.[90] The proportion of bacteria belonging to the *Bacteroidetes* phylum reduced while those in the *Firmicutes* phylum were increased. Further to the changes in the intestinal microbiota, this article showed concurrent changes in regulatory T lymphocytes. Although the authors did not delineate the exact connection between these separate processes, they did propose that these events may also contribute to the benefits of EEN.

Another recent report on the intestinal microbiota changes consequent to EEN demonstrated that initial changes in microbial diversity were linked with the outcome of a subsequent sustained remission.[91] This finding was used to predict the outcome with 80% accuracy.

These paediatric studies are complemented by two studies examining alterations in diversity in adults managed with EEN: both showed similar patterns.[92,93] In addition to the various reports that have focussed on the intestinal microbiota after EEN in individuals with CD, one report has evaluated the impact of EEN in children with rheumatologic disease managed successfully with EEN.[94] Similar changes in the microbiota were shown, suggesting that the alteration in the bacterial patterns reflect the dietary change. The precise reasons that these events abrogate inflammation have not yet been elucidated.

A series of *in vitro* and animal studies has demonstrated that the polymeric formulae (PF) used for EEN generates several changes in key components of intestinal barrier function.

Complementary evaluations of barrier function (such as trans-epithelial electrical resistance, short circuit current, para-cellular permeability, and tight junction protein patterns) in an epithelial cell line model of gut inflammation demonstrated that PF reversed the detrimental effects of pro-inflammatory cytokines.[95] Furthermore, these corrections of intestinal tight junction activity were mediated by inhibition of myosin light-chain kinase. Experiments conducted using an animal model of colitis showed consistent findings.

Further to these data, other reports using intestinal epithelial cell lines and animal models of IBD show direct anti-inflammatory effects consequent to PF.[96,97] These appeared to be modulated by interruption of NF-κB signalling. Further work demonstrated that these effects were mediated by arginine, glutamine, and vitamin D3; all present within the PF. Glutamine and arginine directly modulated components of the NF-κB and p-38 signalling pathways.[98]

In addition, recent work has shown that PF leads to carcinoembryonic antigen-related cell adhesion molecule (CEACAM)-6 and intestinal alkaline phosphate, two separate innate defence proteins.[99,100] The first of these reports demonstrated that PF exposure of epithelial cells resulted in increased production of CEACAM-6, which then functioned as a soluble decoy by binding bacteria thereby preventing bacterial interactions with the epithelial cells.[99]

While these reports have focussed on models of gut inflammation and do not include human studies, they do provide important and consistent support for the direct anti-inflammatory effects of EEN. In addition, the relationship(s) between these separate findings have not yet been ascertained.

CONCLUSION

EEN is recommended in several international guidelines as the preferred primary therapy for the induction of remission in children with active CD. These recommendations are based on the evidence that this therapy is safe and effective in children and adolescents.

Although there have been numerous studies focussing on the mechanisms of EEN, the precise mechanism of action has not yet been fully ascertained. It is most likely that these effects are direct and do not just reflect gut rest. In addition, it also appears feasible that the effects of EEN upon the intestinal microbiota might mediate some of the observed anti-inflammatory effects.

While the benefits of EEN are clear and unquestionable, EEN does not cure CD. In addition, EEN is not feasible to maintain indefinitely due to the onerous requirements to avoid solid food and the consequent disruption of normal dietary habits. Other interventions are consequently needed to maintain remission and prevent relapse. Maintenance enteral nutrition is one potential way to achieve this, but the optimal regimen to undertake this on an ongoing basis has not been demonstrated. Optimisation of EEN regimens, with enhanced provision of active components such as glutamine, may be beneficial.

Despite these reservations, it is clear that EEN has a role in switching off the inflammation seen in CD. Further understanding of the mechanisms of these events may also provide clues to the aetiology of CD.

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A Rare Case of an Inflammatory Myofibroblastic Tumour of the Colon as a Probable Result of Tumour Recurrence after Hemicolectomy

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Disclosure: The author has declared no conflict of interest.

Received: 17.09.2019

Accepted: 13.11.2019

Keywords: Haematochezia, inflammatory myofibroblastic tumour (IMT), nonspecific symptoms, tumour recurrence.

Citation: EMJ Gastroenterol. 2019;8[1]:95-99.

Abstract

Inflammatory myofibroblastic tumour (IMT) is a very rare mesenchymal solid tumour commonly found in children and young adults, but also found to be present in older population groups. This case report presents a 33-year-old male patient who was pathologically confirmed to have an IMT of the colon after hemicolectomy and biopsy. The patient presented with abdominal pain and vomiting along with lower gastrointestinal tract bleeding. Colonoscopy of the patient revealed a fungating annular growth in the descending colon. CT also showed annular mass and inflammation of neoplastic process in the entire descending colon and mid-to-transverse colon after hemicolectomy, which may be a result of recurrence of the tumour. Surgical histopathological reports showed infiltrates of polymorphous cells consisting of lymphocytes, eosinophils, and plasma cells.

The aim of this case report was to course through the history, pertinent laboratory test, and plans of management for a case of a young male with an IMT presenting with symptoms of abdominal pain and vomiting.

INTRODUCTION

Inflammatory myofibroblastic tumour (IMT) is a rare mesenchymal solid tumour commonly documented in children and young adults, but also found to be present in older population groups. It is histopathologically characterised by spindle-shaped cells with myofibroblastic proliferation and inflammatory infiltration. Although the common site is primarily in the lung, IMT occurs in many organs including the stomach, small intestine, large intestine, liver, mediastinum, retroperitoneum, and bladder. The clinical presentation of the disease solely depends on the occurrence site of the tumour and the organ involved; however, sometimes the clinical presentation is different with nonspecific features making the diagnosis difficult and challenging. IMT has often been synonymously characterised as a pseudotumour or plasma cell granuloma.

Presented here is an uncommon case of a 33-year-old male Filipino who presented with the primary complaint of abdominal pain and vomiting. He was histopathologically diagnosed

with an IMT, suspected through radiological findings to be a result of tumour recurrence.

Learning Objectives

In this case, readers have an opportunity to:

Learn about the history, pertinent laboratory test, and plans of management for a case of a young male with IMT.

Build knowledge of a rare disease with symptoms of abdominal pain and vomiting, and to increase awareness for when dealing with similar kinds of presentation in the future.

Become aware regarding the tumour recurrence even after hemicolectomy, which is the gold standard procedure.

CASE REPORT

A 33 year-old-male presented to the emergency department with symptoms of abdominal pain and vomiting. During the first week of May 2017, the patient started to have abdominal pain on the left lower quadrant (pain scale: 5/10) which was described as nonradiating, sharp in character, and not relieved by position change. There was no associated fever, nausea or vomiting, loose bowel, or constipation, for which consultation had been done in the district hospital. The patient was given some unrecalled medications and was sent home. On May 16th, 2017, the patient had an estimated 2 episodes of haematochezia, approximately 1.0 cup each time. The patient was immediately brought to the emergency room where he passaged 4 episodes of bloody stool, each time approximately 0.5 cup and associated with 1 episode of vomiting containing food particles (nonbilious and nonbloody). The patient was therefore admitted to the hospital.

After the third hospital admission, colonoscopy and biopsy were performed. The colonoscopy revealed a fungating annular growth in the descending colon (approximately 10 cm long), occupying roughly 40% of the colon and displaying ulcerations and small bleeding points. The biopsy showed necrotic tissue with acute and chronic inflammation, and gross findings revealed a few small pieces of tan-coloured tissue with a volume of 1.0 cm^3, and all tissues embedded. Microscopic findings revealed small fragments of necrotic tissue and a few fragments of colonic tissue exhibiting normal glands, as well as inflammatory cells in the stroma. On the fifth hospital day, CT of the whole abdomen showed annular mass lesions or inflammatory changes in the distal transverse colon, distal descending colon, and proximal sigmoid colon along with gall bladder polyp (2 mm intraluminal), bilateral nephrolithiasis (1–2 mm), urinary bladder cystitis, and retroperitoneal lymphadenopathies with a normal-sized prostate gland.

The patient then signed a waiver and went home against medical advice on the seventh hospital day (May 25th, 2017) and failed to follow up to the hospital for further planning and management. In June 2017, the patient underwent an exploratory laparotomy with hemicolectomy and the resected part was sent for pathological assessment in another district hospital. The surgical pathological report showed a transmural IMT with irregular defects and positivity for malignant mesenteric lymph nodes. Gross findings showed that the colon section measured 21.1 cm in length and was 8.2 cm wide. Three defects were noted along the entire length measuring up to 2.0 cm and located about 3.1 cm and 8.1 cm from 1 surgical margin. The cut section showed a thickened wall covered by grey white mass measuring about 5 cm in diameter and located near the third and fourth defect. A huge node was noted nearby measuring about 3 cm in diameter. Microscopic findings showed infiltrates of polymorphous cells consisting of lymphocytes, eosinophils, and plasma cells involved transmurally. After the surgical resection, the patient was apparently well and regularly followed up in the same district hospital. In October 2017, the patient started to have recurrences of intermittent fever and abdominal pain again. No medications were taken, and no consultation was given for 2 days. A few hours prior to consultation, the patient presented with haematochezia and anorexia with undocumented weight loss, nausea, and vomiting, and was therefore brought to the emergency department of the hospital. In the emergency room, the patient still had persistent abdominal pain in the left lower quadrant, and had also experienced 4 episodes of haematochezia (about 0.5 cup each time). Despite this, he had no associated vomiting, fever, or difficulty breathing. Consequently, the patient was admitted for further evaluation and management.

The patient did not have any remarkable past medical or family history; however, he was an 18 pack a year smoker and was alcohol-dependent, reporting that he that had drunk bottles of beer 3–4 times a week since his teenage years. The patient worked as an air condition technician. During physical examination, the patient was alert, awake, engaged in conversation, and displayed no signs of cardiorespiratory distress. However, the patient was using a wheelchair for mobility, pale looking, exhibited pale palpebral conjunctiva icteric sclera, had no bipedal oedema, had feeble pulse extremities, and no neck vein engorgement was present. On examination of the chest, there was a symmetrical chest expansion, and no retractions with clear breath sounds. Upon cardiovascular system examination there was a dynamic precordium, normal rate regular rhythm, and no heart murmurs. Abdominal examination showed normoactive bowel sounds; a centrally placed umbilicus; no fullness of flanks; tenderness on palpation of the left lower quadrant; and no palpable spleen, liver, or kidney. Digital rectal examination displayed stool mixed with a reddish tinge of blood on the examining finger, no palpable mass, and no fissures or haemorrhoids. Initial laboratory results showed haemoglobin 70 g/L with thrombocytosis of 564 cm^3, total bilirubin 10.26 mg/dL, and direct bilirubin of 8.30 mg/dL.

During the hospital stay, repeated CT was performed showing annular mass, infectious tuberculosis, and inflammation of neoplastic process in the entire descending colon and mid-to-transverse colon (Figure 1). To rule out carcinomatosis along with bilateral nephrolithiasis, the patient was also referred to the surgery department for further evaluation. They were advised for surgery, however the patient was noncompliant.

DISCUSSION

IMT of the colon is also known as fibrosarcoma, inflammatory pseudotumor, and plasma cell granuloma. This is a rare mesenchymal tumour originally described in the lungs, which is also the most common site among other body parts. Many cases are reported to be found in other parts of the body such as in the mesentery and omentum, stomach, small intestine, large intestine, liver, mediastinum, retroperitoneum, and bladder;[1] however, the most common site is the lung, with the most common extrapulmonary sites being the mesentery and omentum.[2] An IMT occurs primarily in children and young adults (mean age 10 years), but in more recent years it has been seen that it can occur in any age group and there appears to be no difference in incidence between males and females. It is an aggressive tumour and can occur anywhere in the body.

The cause of an IMT is not yet known, but some believe that its aetiology is multifactorial; this could be as an occurrence following surgery or trauma, or infection with Epstein–Barr or human herpes viruses attributable to reactive inflammatory mediators, mainly cytokines. New studies suggest that it is also associated with gene mutation. In approximately 50% of the cases an *ALK* gene mutation has been reported. A chromosomal rearrangement in *2p23*, the site of *ALK* gene, is present in a subset of these tumours.[2] Some studies have shown that this chromosomal abnormality may be attributable to a clonal origin, and is not necessarily a reactive process; therefore, an IMT should be considered as a true neoplasm.

Many cases of IMT of the colon have been reported, some with recurrence either after surgery or chemotherapy. The patients present with common gastrointestinal symptoms similar to other common disease conditions such as abdominal pain, vomiting, melena, or haematochezia, and sometimes with positive faecal occult blood and features of malignancy such a weight loss and night sweats. Patients can also present with unknown cases of anaemia, fever, and intussusception, mimicking appendicitis and bowel obstruction. The location of the lesion is mainly found in the sigmoid colon, mid-transverse colon, ileum ascending colon, appendix, left colon, and the proximal descending colon.

Differential diagnosis of IMT includes malignancy, submucosal tumour, lymphoma, solitary fibrous tumour, and fibromatoses or desmoid tumour. The diagnosis of an IMT includes complete evaluation of family medical history along with thorough physical examination. The diagnostic tools also include screening colonoscopy and lower gastrointestinal series;[3] however, examination of biopsy specimen under microscopy is the gold standard for arriving at a conclusive diagnosis.

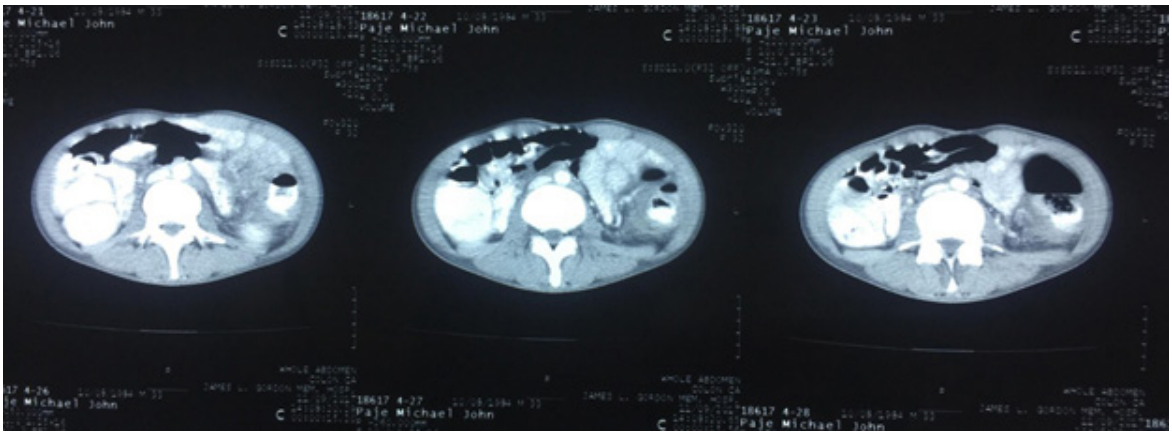

Figure 1: Whole abdominal CT scan with contrast.

This image was taken 4 months after the hemicolectomy when the patient presented with the same symptoms and the presence of an annular mass suggested the recurrence of an IMT of the colon. It shows the neoplastic process in the entire descending colon and mid transverse colon.

IMT: inflammatory myofibroblastic tumour.

Inflammatory fibroid polyp, fibromatoses (desmoid tumour), gastrointestinal stromal tumours, leiomyoma, leiomyosarcoma, and schwannoma have similar pathological findings with IMT.

Inflammatory fibroid polyp is typically submucosal and consists of a mixture of small granulation tissue-like vessels, spindle cells, and inflammatory cells, mainly eosinophils. Fibromatoses are composed of spindled or stellate cells, arranged in parallel with evenly spaced blood vessels and a collagenous background. Immunohistochemistry also gives valuable information regarding the tumours such as gastrointestinal stromal tumour stains for CD34 and CD117 (c-kit).[1] Leiomyoma and leiomyosarcoma stain positively for desmin and actin, and negatively for CD117 and CD34. IMT stains smooth muscle actin and vimentin for >90%, for desmin approximately 10–70%, for keratin 30–77%, and ALK 35–60%. However, ALK positivity is not specific for IMT because it also stains with CD68 and CD34 to variable degrees. In general, immunohistochemistry does not play a major role in confirming a diagnosis due to variable expression and lack of specificity of myofibroblastic markers. ALK positivity is helpful if present but its absence does not exclude the diagnosis of IMT.[2]

Chemotherapy, radiation treatment, nonsteroidal anti-inflammatory drugs, and steroids have been used as treatment modalities, but surgical resection is considered as the treatment of choice. Chemotherapy using cyclosporine A, crizotinib in *ALK* rearrangement, and infliximab have shown to be successful.[3] Chemotherapy may also help if the condition recurs, if there is local invasion, or a distant metastasis presents, yet chemotherapy is generally administered following surgery. There are no reports solely on radiotherapy treatment, but researches have shown that radiation can shrink the tumour prior to surgery for easy removal. In young children, if the tumour cannot be surgically removed, then corticosteroid administration can be beneficial. Orally administered nonsteroidal anti-inflammatory drugs may be effective as anti-inflammatory medication along with other treatment tools. Occasionally some tumours are known to disappear over time without any treatment.[4]

An early diagnosis and prompt treatment of IMT of the colon generally yields a better outcome than a late diagnosis and delayed treatment. The prognosis on timely surgical removal of the tumour is generally good. Some tumours are known to spontaneously regress and disappear but upon complete excision and removal they are generally not known to recur; in some instances, however, they can recur and even metastasise. It

is unclear what kind of factor is associated with prognosis,[3] and it is unclear what the best way of treatment of recurrence or metastasis is during long-term follow-up. It is important to follow-up on patients diagnosed with an IMT, even if they have undergone surgical resection.

CONCLUSION

The clinical presentation of the disease solely depends on the site of occurrence of the tumour and organ involved and the variability in presentation. Most of the cases are benign; however, these tumours also have malignant potential and some even metastasise. Therefore, being complacent with one diagnosis, typically with nonspecific features, can predispose to misdiagnoses. Complete surgical excision is the mainstay of treatment and the prognosis is generally good, with only rare reports of malignant transformation, recurrence, or distant metastases. Follow-up with long-term clinical and radiological review is advised to ensure early detection of recurrence or metastases.

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